

From: [BioCentury Weekly](#)
To: [Commissioner FDA MH](#)
Subject: BioCentury 2014 Year-End Stock Roundup
Date: Wednesday, January 07, 2015 10:58:30 PM
Attachments: [010815bc.pdf](#)



Good Morning,

Attached is the BioCentury 2014 year-end stock roundup.

Best regards,
BioCentury Subscriber Services

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From: [Immergut, Steven](#)
To: [Hamburg, Margaret](#)
Cc: [Hoague, Angela](#)
Subject: DMD- Sarepta
Date: Thursday, October 30, 2014 3:08:33 PM
Attachments: [Duchenne Muscular Dystrophy - Moms Fight for FDA Approval of Sarepta Drug - Businessweek.pdf](#)
[image001.gif](#)

Hi- yes at a few big stories on DMD/Sarepta this week. The announced earlier in week an update from their preNDA meeting. The one today from BusinessWeek sounds like the one you heard about - though strangely not in our clips this morning. Will need to check on that. First link below and attached pdf in case you want to print and bring home It's a really tough story on us. We didn't know was coming today but did work with reporter. This is a very difficult situation for us but need to think about how come off better than this.

<http://www.businessweek.com/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug>

The second and third one are more on the announcement - from Matt Herper at Forbes and Joe Walker at WSJ. Matt calls for CEO to resign.

<http://www.forbes.com/sites/matthewherper/2014/10/27/sarepta-needs-fda-expertise-stat/>

<http://online.wsj.com/articles/sarepta-therapeutics-sees-setback-in-eteplirsen-drug-application-1414414412>

here's the press release.

Sarepta Therapeutics Announces Regulatory Update on Eteplirsen

Updated and additional guidance received from FDA on specific data requirements for NDA;

FDA states further discussion needed to determine what constitutes a “complete” NDA submission;

NDA submission planned for mid-year 2015;

Company to hold teleconference today at 8:00 a.m. EDT

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 27, 2014-- Sarepta Therapeutics, Inc. (NASDAQ:SRPT), a developer of innovative RNA-based therapeutics, today provided an update on its discussions with the U.S. Food and Drug Administration (FDA) regarding its planned New Drug Application (NDA) submission for the approval of eteplirsen for the treatment of Duchenne muscular dystrophy (DMD).

In meeting minutes received last week from a Type B Pre-NDA meeting that took place in September 2014, the FDA provided updated guidance regarding the specific data to be included as part of, or at the time of, Sarepta's NDA submission. The guidance states

that additional data are now required as part of the NDA submission, including the results from an independent assessment of dystrophin images and the 168-week clinical data from study 202. Additionally, the guidance requests more specific data including a minimum duration of safety in new patients exposed to eteplirsen, patient-level natural history data to be obtained by Sarepta from independent academic institutions, and MRI data from a recent study conducted by an independent academic group. The FDA indicated that further discussion with Sarepta “will be necessary to determine what would constitute a complete NDA.” Based on these requests, Sarepta plans to submit an NDA by mid-year 2015, pending any additional requests from further discussions with the FDA.

"We are committed to satisfying the FDA's updated requests for these specific data to be included as part of an NDA submission and will continue to work with the Agency toward the goal of a complete and acceptable NDA filing," said Chris Garabedian, president and chief executive officer of Sarepta Therapeutics. "We believe all of the data requests and additional FDA discussions that have currently been outlined can be completed in time for an NDA submission by mid-year 2015. Obtaining an FDA approval of eteplirsen for the DMD patients who may benefit from the drug continues to be our highest priority."

Excerpts from the Pre-NDA Meeting Minutes related to information that the FDA is requesting as part of an NDA submission included:

"The sponsor should include 3-month data from at least 12 to 24 newly exposed patients at the time the NDA is submitted."

"Available data from the other patients enrolled in the new eteplirsen studies (studies 301, 203, 204) should also be included at the time the NDA is submitted, even if exposure is less than 3 months in duration."

"Additional data from later time points and from newly enrolled patients should be submitted in the 120-Day Safety Update."

"FDA strongly advises the sponsor to obtain and submit patient-level natural history data. FDA is prepared to appeal to the academic groups holding the data to allow the sponsor a means to acquire the data."

"The study 201/202 clinical site inspection conducted in May, 2014, after the issuance of the April 15, 2014, guidance letter, uncovered marked disparities in the immunohistochemistry methodology and concerns about the reproducibility of the data. The lack of confirmation of robust dystrophin measurement during the site visit necessitates including the independent assessment of dystrophin-positive fibers and 168-week efficacy data from study 201/202 in the NDA."

"FDA strongly urged the sponsor to submit the MRI data with appropriate natural history controls."

The FDA also stated that “[a]dditional discussion between the sponsor and the FDA will be necessary to determine what would constitute a complete NDA.”

Conference Call Information

Sarepta will hold a conference call to discuss this update today at 8:00 a.m. EDT (5:00 a.m. PDT). The conference call may be accessed by dialing 800.708.4539 for domestic callers and 847.619.6396 for international callers. The passcode for the call is 38376370. Please specify to the operator that you would like to join the "Sarepta Regulatory Update Call." The conference call will be webcast live under the investor relations section of Sarepta's website at www.sarepta.com and will be archived there following the call for 90 days. Please connect to Sarepta's website several minutes prior to the start of the broadcast to ensure adequate time for any software download that may be necessary. An audio replay will be available through November 3, 2014 by calling 888.843.7419 or 630.652.3042 and entering access code 38376370.

About Duchenne Muscular Dystrophy

DMD is an X-linked rare degenerative neuromuscular disorder causing severe progressive muscle loss and premature death. DMD affects approximately one in every 3,500 boys born worldwide. A devastating and incurable muscle-wasting disease, DMD is associated with specific errors in the gene that codes for dystrophin, a protein that plays a key structural role in muscle fiber function. Progressive muscle weakness in the lower limbs spreads to the arms, neck and other areas. Eventually, increasing difficulty in breathing due to respiratory muscle dysfunction requires ventilation support, and cardiac dysfunction can lead to heart failure. The condition is universally fatal, and death usually occurs before the age of 30.

About Eteplirsen

Eteplirsen is Sarepta's lead drug candidate and is designed to address the underlying cause of DMD by enabling the production of a functional dystrophin protein. Data from clinical studies of eteplirsen in DMD patients have demonstrated a broadly favorable safety and tolerability profile and restoration of dystrophin protein expression.

Eteplirsen uses Sarepta's novel phosphorodiamidate morpholino oligomer (PMO)-based chemistry and proprietary exon-skipping technology to skip mutations affecting exon 51 of the dystrophin gene. Approximately 13 percent of the total DMD population is amenable to exon 51 skipping. By skipping exon 51, eteplirsen may restore the gene's ability to make a shorter, but still functional, form of dystrophin from messenger RNA, or mRNA. Promoting the synthesis of a truncated dystrophin protein is intended to stabilize or significantly slow the disease process and prolong and improve the quality of life for patients with DMD. Sarepta is also developing other PMO-based exon-skipping drug candidates intended to treat additional patients with DMD.

About Sarepta Therapeutics

Sarepta Therapeutics is focused on developing first-in-class RNA-based therapeutics to improve and save the lives of people affected by serious and life-threatening rare and infectious diseases. The Company's diverse pipeline includes its lead program eteplirsen, for DMD, as well as potential treatments for some of the world's most lethal infectious diseases. Sarepta aims to build a leading, independent biotech company dedicated to translating its RNA-based science into transformational therapeutics for patients who face significant unmet medical needs. For more information, please visit us at www.sarepta.com.

Forward-Looking Statements and Information

This press release contains forward-looking statements. These forward-looking statements generally can be identified by the use of words such as “believes or belief,” “anticipates,” “plans,” “expects,” “will,” “intends,” “potential,” “possible,” “advance” and similar expressions. These forward-looking statements include statements about Sarepta’s planned timing for an NDA submission for eteplirsen in the treatment of DMD; Sarepta’s plans to work with the FDA towards the goal of a complete and acceptable NDA filing; Sarepta’s ability to satisfy the additional FDA requests; the timing and submission of additional data, analysis and other information to the FDA necessary for the FDA to make regulatory determinations; the timing of and ability to initiate additional studies for eteplirsen and other follow-on exons; and the potential regulatory approval of eteplirsen.

Each forward-looking statement contained in this press release is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statement. Applicable risks and uncertainties include, among others: we

may not be able to comply with all FDA requests; the FDA may determine that substantial additional data is required for accelerated or other approval of eteplirsen or that our NDA submission for eteplirsen does not qualify for filing, even with additional information; the results of our ongoing and new clinical trials may not be positive; there may be delays in timelines relating to an NDA submission, initiating clinical trials, or making a product commercially available for regulatory or internal reasons; we may not be able to manufacture sufficient supply for clinical trials or commercialization; agency or court decisions with respect to our patents or those of third parties may negatively impact our business and those identified under the heading “Risk Factors” in Sarepta’s Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 filed with the Securities and Exchange Commission (SEC), and Sarepta’s other filings with the SEC.

Any of the foregoing risks could materially and adversely affect Sarepta’s business, results of operations and the trading price of Sarepta’s common stock. For a detailed description of risks and uncertainties Sarepta faces, you are encouraged to review the Company’s filings with the SEC. We caution investors not to place considerable reliance on the forward-looking statements contained in this press release. Sarepta does not undertake any obligation to publicly update its forward looking statements based on events or circumstances after the date hereof.

Source: Sarepta Therapeutics, Inc.

**Sarepta Media Contact:
Tony Plohoros, 908-591-2839
tplohoros@6degreespr.com**

or

**Sarepta Investor Contact:
Stephanie Ascher, 212-362-1200
stephanie@sternir.com**

Bloomberg Businessweek

Technology

<http://www.businessweek.com/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug>

Moms, Regulators, Biotech Startups, and the Battle Over a Potentially Life-Saving Drug

By Paul M. Barrett October 30, 2014



Photograph by Ryan PflugerLeffler's son Aidan was diagnosed with Duchenne in 2006

The 2014 World Cup elevated soccer to the top of Aidan Leffler's roster of obsessions, rivaled only by endangered big cats—especially jaguars, “the coolest”—and *Star Wars* spaceships. In recognition of his new interest, he's set up a miniature soccer field with 4-foot-wide goals in his backyard in suburban Bellevue, Wash. “Watch this!” he shouts, preparing to fire a penalty kick.

Small for his age, Aidan, 11, moves awkwardly, shoulders high and hunched. He uses a lightweight plastic beach ball, not a regulation leather soccer ball. He begins his approach, pulls back his right foot, and ... collapses to the grass.

Mitch Leffler, the sole spectator, moves toward his son. “I'm OK,” Aidan says. “I can do it.” He struggles onto his hands and knees, raises his butt, places his hands one at a time on his thighs, and slowly pushes himself into an upright position. “My leg just wasn't there,” he says matter-of-factly. His father nods, and the game resumes.

Aidan has Duchenne, the deadliest strain of muscular dystrophy. It's inherited maternally on the X chromosome and mostly afflicts boys. Parents typically sense something is wrong when their sons at 3 or 4 don't run around or they start falling for no obvious reason. Beginning in the legs, Duchenne destroys muscle, which is replaced by fat and scar tissue. Victims lose the ability to walk by adolescence. Eventually the disease causes cardiac and/or respiratory complications that lead to death by the mid-20s. One in 3,500 newborns has Duchenne, which translates to around 15,000 cases in the U.S. There's no cure.

“Aidan doesn't really understand yet,” his mother, Mindy, says, “but it's basically a slow-motion death sentence.”

There's reason to hope—not for a miracle, but for a reprieve. Three small biotech companies are competing to develop drugs designed to address the cellular defects that cause some cases of Duchenne. If proven safe and effective, the drugs would turn Duchenne into a less devastating form of muscular dystrophy. Clinical trials, however, have yielded uneven results, and the U.S. Food and Drug Administration has made equivocal pronouncements about which of the drugs, if any, have a shot at approval. Even a marginally effective drug would likely command an astronomical price, making the winning company a billion-dollar sensation.

The hunt for a Duchenne treatment has generated a collision of commerce, cutting-edge science, and Wall Street speculation. The FDA, though, seems flummoxed over how to evaluate the experimental drugs, especially given a lack of large, clearly successful randomized studies. That's left the Lefflers confused and increasingly desperate.



Photograph by Ryan PflugerMcSherry with her son, Jett, who began college this fall

Mindy believes that one experimental treatment—eteplirsen, made by a company called Sarepta Therapeutics (SRPT)—has shown sufficient promise in a tiny trial to warrant wider availability. If approved, eteplirsen might help 13 percent of Duchenne boys who have certain genetic flaws. Mindy's son is among the 13 percent. “I want Aidan on that drug,” she says, “and I want it to happen before he's in a wheelchair or worse.”

She and a group of similarly minded moms are pressuring the FDA to give provisional approval to eteplirsen while Sarepta proceeds with confirmatory studies. Taking to Twitter, Facebook, YouTube, and Instagram, they've got the attention of top FDA officials. They've also encountered resistance from career FDA staff members and some rare-disease advocates alarmed by their assertiveness.

"What's hard to understand," says Mindy's friend Jennifer McNary, "is why the whole Duchenne community and the FDA aren't pulling together behind eteplirsen." McNary, who lives south of Boston, has two sons with the disease. Maternal genetic predisposition sometimes results in such sibling pairs. Max McNary, 12, gets eteplirsen in the small Sarepta trial; over the past two-and-a-half years, his symptoms have eased remarkably. Max's older brother, Austin, 15, didn't qualify for the study because he was already in a wheelchair when it started. He's declining physically, losing the use of his arms and having trouble feeding himself.

"Why doesn't the government let me have eteplirsen?" Austin asks when we meet. He waits for an answer, which I don't have. His mother joins the conversation: "The FDA's inaction," she says. "is killing my son."

Mindy agrees with Jennifer and Austin. "Aidan doesn't have time to wait for a perfect placebo-controlled trial with hundreds of subjects," she says. "The benefits outweigh any risks."

In 1986 researchers at Harvard isolated the gene responsible for making the protein dystrophin, a "shock absorber" that surrounds muscle cells. Boys with Duchenne have one of several genetic defects that inhibit production of dystrophin. Without it, ordinary physical exertion causes progressive muscle breakdown. The disease is named for Guillaume Duchenne, a French neurological pioneer who described the symptoms in the 1860s.

For generations, physicians reacted passively to Duchenne. Patricia Furlong's sons, Christopher and Patrick, were diagnosed in 1984. Her doctor told her to "take them home and love them, because there was nothing medicine could do." A former nurse with a stubborn streak, she began traveling the country from her home in central Ohio, pleading with researchers to look for a cure. "She was at NIH [National Institutes of Health]. She was on Capitol Hill. She was in my office," recalls Eric Hoffman, a genetic researcher at Children's National Medical Center in Washington. "Pat would not be denied." She couldn't save her sons, however, who died in the mid-1990s.

Angered by what she describes as the fatalism she encountered at the Muscular Dystrophy Association—sponsor of the long-running Labor Day telethon hosted by actor Jerry Lewis—Furlong formed a breakaway nonprofit: Parents Project Muscular Dystrophy, dedicated strictly to Duchenne. In 2001, largely because of her agitation, Congress passed the Muscular Dystrophy CARE Act, which over the following decade provided more than \$400 million in funding, much of it for Duchenne research. The federal backing, says Hoffman, "got the biotech companies thinking maybe there's money to be made with a Duchenne drug."

"What's hard to understand is why the whole Duchenne community and the FDA aren't pulling together behind eteplirsen"

A startup in New Jersey called PTC Therapeutics (PTCT) focuses on mutations that block dystrophin production. These "nonsense mutations" are akin to a period mistakenly placed in the middle of a sentence, which makes the genetic code incomprehensible. In 2008, Genzyme (SNY), a much larger biotech, gave credibility to PTC's research by paying the tiny company \$100 million upfront to secure future marketing rights to its drug outside North America.

Prosensa (RNA), a Dutch biotech, targets a different type of flaw in the exons, or segments, of the dystrophin gene. By "skipping" a defective exon, Prosensa's compound is supposed to allow the formation of a truncated version of dystrophin. In 2009 the pharmaceutical giant GlaxoSmithKline (GSK) added momentum to exon-skipping research by paying Prosensa \$25 million upfront for development and marketing rights and promising hundreds of millions more in future compensation.

In the U.S., Sarepta was also angling to get into the Duchenne chase. Choosing to work without a larger corporate partner, it began testing eteplirsen, an exon-skipping compound that relies on a different biochemical recipe from Prosensa's drug.

The proliferation of potential treatments gave the Lefflers reason for optimism after years of mounting apprehension. Aidan had first been diagnosed in 2006, at the age of almost 3, after breaking his leg while playing on a slide. As he lost strength, his parents installed an elevator at home so he could avoid stairs, but for the most part he remained ambulatory.

Mindy dug into the science of Duchenne, finding solace in genetics and chemistry, subjects she'd avoided as an English major in college. She works part-time developing software for a tech company and time-and-a-half seeking care for Aidan. Mitch—she met her husband in the early 1990s when they were Seattle-area high school track stars—teaches gym and takes a lot of responsibility for Aidan's two younger siblings. In 2010, the Lefflers felt inspired when the *New Yorker* published an article titled "Mother Courage" that described how the death of Furlong's sons propelled her campaign against Duchenne. "I thought, wow, Pat really got a lot done," says Mindy, "and now we're going to take the next step and actually find a treatment for Aidan, so he doesn't end up like Pat's boys."

In 2011, Mitch took Aidan to a hospital in Columbus, Ohio, where Sarepta was beginning a trial for eteplirsen. Then 7, Aidan was showing such ominous symptoms as knotty, seemingly overdeveloped calves—evidence of scar tissue swiftly replacing muscle. He performed well on a baseline walking test. Too well, it turned out: He was rejected for the study because he was much healthier than most other subjects whose disease was more advanced.

As a fallback, Mindy hustled to get Aidan enrolled in a 180-person Prosensa-GlaxoSmithKline trial at a test site in Vancouver. The trial proved to be an ordeal. Multiple muscle biopsies to check dystrophin levels required Aidan to undergo surgery with general anesthesia. And almost immediately, Leffler suspected he was receiving a saline-solution placebo, rather than injections of Prosensa's drug. She figured this out when he didn't have the swelling and pain other moms said their sons experienced.

For 48 weeks, Aidan's parents took him by plane or car to Vancouver every week for stays ranging from a few hours to several days, depending on the protocol, all the while suspecting he wasn't actually receiving medication. "This may be good for science," Leffler says she thought at the time, "but how's it good for my son?"



Photograph by Ryan Pfluger McNary with her sons, Max (left), who is receiving treatment, and Austin, who isn't

In late 2012, researchers switched all of the subjects on placebo over to treatment with Prosensa's compound, drisapersen. Aidan began to suffer the side effects from getting the drug, but Leffler couldn't tell whether his Duchenne symptoms were easing. "He fluctuated: sometimes better, sometimes worse," she says.

Over time, Leffler became jealous of moms with sons in the Sarepta study—the one from which Aidan had been rejected—because the company was reporting solid results. In October 2012, Sarepta announced that, after 48 weeks, boys receiving eteplirsen had stabilized, with statistically significant improvement in a standardized six-minute walking test. Moreover, unlike the Prosensa drug, which at higher doses creates risks that could lead to kidney damage, the Sarepta study didn't show any dangerous side effects.

The weakness of the Sarepta trial was that it had enrolled only 12 boys. Started in 1980 at the dawn of the biotech era, the company had gone public in 1997 but never put a drug on the market. After a series of management shake-ups, a newly hired chief executive officer, Chris Garabedian, decided in 2011 to bet Sarepta's few remaining chips on eteplirsen. The company simply couldn't

afford a larger trial. "We had a limited amount of drug and no capacity to make more," Garabedian says. "So we took what we had and did the best small trial we could design." Sarepta's shortage of eteplirsen also precluded providing the drug to individual applicants under the FDA's "compassionate use" program.

Despite the skimpy sample size, Sarepta's results ignited a stock market frenzy. The company's shares rose threefold on Oct. 3, 2012, to \$45. CNBC stockpicker Jim Cramer raved about Sarepta on his *Mad Money* show and interviewed Garabedian on camera. In June 2013, PTC announced an initial public offering that raised \$144 million. In their enthusiasm, investors were willing to overlook that PTC's drug, ataluren, had failed to show statistically significant improvement in subjects' walking ability in a clinical trial three years earlier. Prosensa soon followed with its own IPO, raising \$90 million, even though it hadn't yet reported results from its main ongoing clinical study. In July, Sarepta added to the bullishness by announcing that the FDA had provided guidance that it was open to considering eteplirsen for regulatory approval. (The agency routinely communicates with companies as they move toward a "new drug application.")

"It felt like a lot of good stuff was coming together," Leffler recalls.

Then the bubble burst. In September 2013, only three months after its IPO, the Prosensa-GSK trial in which Aidan was enrolled failed to show meaningful improvement on the six-minute walk test. The study was shut down, and Prosensa's stock plummeted 70 percent in a day. "No one called us," says Leffler. "We learned that the trial was over from a GSK investor conference call. . . . There's no safety net. You just crash." London-based GSK and Prosensa later terminated their partnership.

More bad news followed in November: After encouraging Sarepta to apply for approval of eteplirsen, the FDA reversed itself and called such a move "premature." Explaining its turnaround, the agency cited Prosensa's and PTC's trial failures. The FDA expressed "considerable doubt" that dystrophin production—the goal set out by all three companies—could be linked to meaningful clinical benefits. Sarepta's stock fell 64 percent that day.

The Lefflers received word about the FDA about-face on Sarepta while at Walt Disney World on a vacation with Aidan and his younger brother and sister. After the Prosensa-GSK trial failure, "it was a double blow," Mindy says. "I felt like I couldn't breathe."

After collecting herself, Leffler decided to fight. She'd already been communicating with two other moms she'd met via Facebook and at Duchenne conferences: McNary, who had the exquisitely painful situation of one son doing well in the Sarepta trial while his older brother, denied the drug, declined, and Christine McSherry, whose son, Jeti, then a wheelchair-bound high school senior, struggled to sit up straight.

"The three of us, the 'Three Musketeers,' had a lot of the same questions," McSherry says. Why had Prosensa's and PTC's setbacks influenced the FDA to shun Sarepta? After all, the companies used different types of chemistry. The moms also didn't understand why the incipient scientific consensus on the importance of dystrophin production had suddenly become clouded. "We began to realize that the FDA was confused," says McSherry, a former nurse who is now 49. "Eteplirsen, a drug that appeared to work, was in danger of becoming a victim to the shortcomings of other drugs and other trials."

The moms had begun in 2012 demanding personal attention from FDA officials. Remarkably, they got a meeting—then another, and another. In a law enacted that year, Congress instructed the FDA to entertain more flexible paths to provisional approval of rare-disease drugs. Under the aegis of that statute, the trio became self-appointed consultants at FDA headquarters in Silver Spring, Md.

McNary organized an online petition demanding "accelerated approval" of eteplirsen. The 2012 FDA reform statute encouraged the agency to grant accelerated approval based on relatively small trials that achieve a "surrogate" goal—such as dystrophin production—with the burden left on the manufacturer to conduct broader research. The FDA can rescind accelerated approval if follow-up studies don't demonstrate efficacy. McNary swiftly gathered 180,000 signatures for her petition, and she and other moms bombarded the FDA with tweets, Instagrams, and YouTube videos showing boys in Sarepta's 12-person trial climbing rocks, dancing, and diving into swimming pools.

McNary's heart-rending tale became a centerpiece of the lobbying campaign. "I could possibly be the mother of the last child to die from Duchenne and first child to survive it," she said in a video that zinged around the Internet.

Following its standard policy, the FDA didn't respond publicly to the lobbying drive. But the agency's ambivalent reactions could be discerned from private communication with the three moms, who used blogs and websites to report on the back-and-forth. According to the moms, senior FDA leaders sought to reassure the Duchenne parents, while rank-and-file staff members tended to express more skepticism.



In July 2013, McSherry recounted on her blog a conference call with Janet Woodcock, the director of the FDA's Center for Drug Evaluation and Research. "As always, Dr. Woodcock was warm, compassionate, and extraordinarily supportive of our position," McSherry wrote. "We are one step closer to getting this drug [eteplirsen] to our boys."

Four months later, though, evaluators working under Woodcock's supervision told Sarepta not to bother applying for approval. Asked for comment, Sandy Walsh, an FDA spokeswoman, says: "Under the law, we are not able to discuss any investigational new drug or any drug application." She adds that the agency "has been working with Sarepta to provide guidance on various clinical and regulatory issues related to eteplirsen."

In February 2014, the three moms joined forces with a fourth, Tracy Seckler, to ratchet up the pressure on the FDA by organizing a two-day summit in Washington that included a visit to the agency by several leading Duchenne researchers. The next day, a bipartisan briefing on Capitol Hill sponsored by Representatives William Keating (D-Mass.) and Spencer Bachus (R-Ala.) drew an audience of dozens of congressional staff members.

Louis Kunkel, the Harvard Medical School professor who headed the team that isolated the dystrophin gene in 1986, told the gathering that boys receiving eteplirsen were making dystrophin and called this success "amazing." Steve Wilton, a leading neuromuscular researcher from Australia, was even more emphatic about eteplirsen's promise. "In Australia," he told attendees, "we'd say it's bleeding obvious."

Leffler added the moms' sense of impatience: "The FDA," she said, "is standing in the way." Not so, says the agency's Walsh: "The FDA is fully committed to make safe and effective drugs available for patients with Duchenne as soon as possible and is actively engaged with all drug companies developing new drugs for Duchenne."

Notably absent from the Washington event was Furlong. She'd held her own Washington round table two months earlier, one that was far more deferential to the FDA's authority.

In an interview, Furlong, 68, says she was traveling on business in Europe at the time of the February summit and sent a representative from her organization. She decries what she describes as a splintering of "the Duchenne community" she has spent two decades building. Now a stateswoman rather than a firebrand, she criticizes younger mothers such as McNary, 34, who publicly describe their sons as dying. "What must those boys think?" she asks. More broadly, she adds, "It's just not smart strategy to chain yourself to the gates of the FDA in protest," an allusion to a tactic once used by AIDS activists.

While the more aggressive Duchenne moms haven't actually chained themselves to anything, their tone at times is abrasive. In March 2014, McNary appeared on John Stossel's government-bashing Fox Business News television show. A subscript running across the screen morphed from "Government Medicine Bullies" to "FDA Regulations Can Kill!" Stossel asked McNary whether her son Austin is "angry" because he couldn't get eteplirsen.

"Fifteen-year-olds in general are angry," McNary responded. "Fifteen-year-olds who are being betrayed by their government are even angrier." Stossel's other guest, Darcy Olsen of the libertarian Goldwater Institute, added: "What the FDA is doing here is an abomination."

In April, without public explanation, the FDA once again reversed its position on eteplirsen, saying Sarepta could move ahead toward regulatory approval. Given the absence of new data, the only plausible reason for the switch was escalating pressure from the three moms and their backers. Five months after rebuffing Sarepta, the FDA laid out a detailed "path forward" for eteplirsen to receive accelerated approval.

The agency's revised guidance—conveyed privately to Sarepta, then disclosed by the company—stressed government evaluators' continuing uneasiness regarding the data on eteplirsen. The company would have to conduct larger placebo-controlled studies before provisional approval would become permanent. Still, a closed door had cracked open.

Sarepta immediately said it would seek accelerated authorization by the end of 2014 and launch confirmatory studies. From April 17 to April 22, the company's stock rose 59 percent.

In June, the regulatory door opened further. Prosensa announced that the FDA would entertain an accelerated-approval application for drisapersen, even though the Dutch company's drug had failed its main clinical trial in 2013. Regulators' sudden receptivity struck some observers as peculiar, given the lack of fresh evidence of effectiveness. "It sure looks like the FDA wants to give itself cover and say, 'See, we're giving everyone a chance to apply, so parents, stop attacking us,'" says Steve Brozak, president of WBB Securities and a longtime analyst of the biotech industry.

Prosensa's CEO, Hans Schikan, disagrees with Brozak. The unsuccessful 2013 study was devised and run by GSK, he says. "Based on our reanalysis of our data, we strongly believe it was the trial that failed the drug, not the drug that failed the trial." Flaws in GSK's study design, he claims, muddied the results.

Adding yet another level of ambiguity to the situation, PTC, which had seemed out of the running for a Duchenne treatment, has reentered the race. "We shot ourselves in the foot" by conceding defeat after the failed 2010 ataluren trial, says Stuart Peltz, PTC's co-founder and chief executive. After reanalysis of its data, PTC concluded its drug actually works. "In biotech, you're building the airplane while you're trying to fly it at the same time," Peltz continues. "It took us a while to realize that when you focus on the boys with the most severe symptoms, ataluren does show a robust efficacy." In August the European Union's equivalent to the FDA granted conditional approval to ataluren, and PTC is beginning to sell the drug in Europe. After completing more clinical trials, Peltz says, his company will apply for full approval in Europe, the U.S., and elsewhere.

Furlong has faith the FDA will sort out which Duchenne drugs are effective. "Ideally," she says, "we'd like to see all of the drug candidates move forward in the regulatory process."

The three moms, in contrast, say the FDA's one-step-back, one-step-forward routine has them feeling unnerved, not reassured. "The boys on eteplirsen are walking when the natural history of the disease says that they should be in wheelchairs," says Leffler. Why, she wants to know, don't industry and government cooperate to get as many boys on eteplirsen as quickly as possible?

"That's not the way medical science works," says Hoffman, the Duchenne researcher at Children's National Medical Center. The FDA, Hoffman continues, "is doing the best it can, moving cautiously and looking skeptically at Sarepta's data, and all of the data from all of the companies." On Oct. 27, Sarepta announced that as a result of a new round of FDA data requests, the company would have to postpone its application for approval of eteplirsen until mid-2015. Hoffman, who for years has had a close working relationship with Furlong and her organization, expresses sympathy for moms like Leffler, McNary, and McSherry who are impatient for faster action. "They must mean well—their boys are sick," he says, "but their pressure tactics on the FDA seem like bullying more than anything else."

Leffler, 42, doesn't care anymore what anyone calls her tactics. Her determination to get Aidan on eteplirsen became more urgent in August when he fell and fractured the femur in his left leg while kicking a ball in the backyard. Doctors told Aidan's parents he had a 50-50 chance of ever getting back on his feet. He had surgery the next day to have a steel rod placed in his leg. Two weeks later, to his doctors' surprise, but not his parents', he started hobbling around with a walker. With some effort, he can even get in and out of the family minivan more or less on his own. "He's an amazing kid," Leffler says.

Soccer, even in modified form, is probably over forever. Aidan, now in sixth grade, has redoubled his attention to big cats. He's writing fundraising letters and passing along the money to a conservation group called Panthera.

He's not oblivious to his medical predicament. If anything, he's growing more worried. The other day, Leffler found a piece of paper in her bathroom with a question written in Aidan's neat block letters: "Does muscular dystrophy make you die sooner?"



Barrett is an assistant managing editor and senior writer at *Bloomberg Businessweek*. His new book, *Law of the Jungle*, tells the story of the Chevron oil pollution case in Ecuador.

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To: [Fritsch, Beth F. \(Beth.Fritsch@fda.hhs.gov\)](#); [Marchand, Heidi \(Heidi.Marchand@fda.hhs.gov\)](#)
Subject: for stakeholder search
Date: Thursday, February 05, 2015 1:43:00 PM
Attachments: [Commissioner Hamburg Resignation Boston Business Journal FDA head Margaret Hamburg says she will step down after 6 years.msg](#)
[Commissioner Hamburg Resignation CNN FDA chief to step down in March.msg](#)
[Commissioner Hamburg Resignation Coverage Reuters Fierce Pharma Medcity News.msg](#)
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Subject: Commissioner Hamburg Resignation Coverage: Bloomberg, Fierce Biotech, Pharmacy Times
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[Bloomberg: FDA Commissioner Hamburg to Step Down After Six Years](#)

By: Anna Edney

(Bloomberg) -- Margaret Hamburg will step down as U.S. Food and Drug Administration commissioner next month after almost six years at the regulatory agency.

Stephen Ostroff, the FDA's chief scientist, will be acting commissioner when Hamburg leaves, she said in an e-mail to staff. Hamburg, a 59-year-old Harvard Medical School graduate, had been the senior scientist at the Nuclear Threat Initiative before joining the FDA.

Under Hamburg, the agency sped up drug approvals by introducing a breakthrough therapy designation for experimental medicines, giving pharmaceutical companies expedited help during the development process.

"As you can imagine, this decision was not easy," said Hamburg. "While there is still work ahead (and there always will be), I know that I am leaving the agency well-positioned to fulfill its responsibilities."

Robert Califf, a Duke University researcher who was named as the FDA's deputy commissioner for medical products and tobacco last month, is expected by agency watchers to succeed Hamburg. Califf led Duke's translational research effort and was founding director of the Duke University Clinical Research Institute, the world's largest academic research organization, according to the FDA statement announcing his appointment.

Califf didn't immediately respond to a request for comment.

Hamburg Initiatives

Hamburg's tenure included a range of initiatives from phasing out trans fats in food to requiring calorie counts on restaurant menus. She also spearheaded an overhaul of how the agency regulates pharmacies that compound drugs into formulations or dosages that are otherwise unavailable after 64 people died from meningitis following use of tainted steroid injections.

"Her dedicated service leaves a legacy of incredible, historic accomplishment at FDA," Sylvia Mathews Burwell, the U.S. health secretary, said in an e-mailed statement. Burwell, like others close to Hamburg, calls the commissioner Peggy.

“From keeping our food supply safe to significant advancements in biomedical innovation to the quickly facilitating the availability of critical products to help fight Ebola, Peggy’s tireless leadership has impacted millions of people across this country,” Burwell said.

###

Fierce Biotech: FDA chief Hamburg is stepping down. Is Califf the next commissioner?

By: Damian Garde

FDA Commissioner Margaret Hamburg is set to step down, according to Reuters, weeks after appointing a deputy many believe to be her hand-picked successor.

Hamburg, who has held the agency's top spot for nearly 6 years, will announce her resignation Friday, Reuters' sources say, with FDA Chief Scientist Stephen Ostroff filling her position until a permanent replacement comes in. Robert Califf, a Duke cardiologist slated to begin his tenure as deputy commissioner this month, is widely viewed as the likely candidate for that position, and his January appointment may have been Hamburg's attempt to get an amenable party in place before a new administration takes over in 2017.

Hamburg, a former head of the New York City Health Department, will leave behind a legacy of working closely with the industries she regulates. Under her watch, the FDA instituted a slew of programs designed to speed up the review process for new drugs, and 2014 saw the agency approve a 20-year-record 51 novel therapies.

That's a testament "not just to our expanding understanding of human biology, the biology of disease and the molecular mechanisms that drive the disease process, but also to FDA's innovative approaches to help expedite development and review of medical products that target unmet medical needs," Hamburg wrote in a blog post earlier this week.

Califf, if appointed commissioner, would seem to share her vision of an agency engaged with its subjects. He has straddled the line between academia and industry throughout his career, serving as the founding director of the Duke Clinical Research Institute, a school-funded CRO that employs more than 1,000 people and has an annual budget of more than \$100 million. He later went on to run the Duke Translational Medicine Institute, which works with the National Institutes of Health to turn lab discoveries into actionable medicines.

Naming him deputy commissioner last month, Hamburg said in a statement that Califf's "deep knowledge and experience in the areas of medicine and clinical research will enable the agency to capitalize on, and improve upon, the significant advances we've made in medical product development and regulation over the last few years."

In an email to FDA staff obtained by CNN, Hamburg confirmed her resignation, saying it is with "mixed emotions" that she steps down from her post.

"As you can imagine, this decision was not easy," Hamburg wrote. "My tenure leading this agency has been the most rewarding of my career, and that is due in no small part to all of you--the dedicated and hard-working people that make up the heart of this agency. While there is still work ahead (and there always will be), I know that I am leaving the agency well-positioned to fulfill its responsibilities to the American public with great success."

###

Pharmacy Times: FDA Commissioner Hamburg Stepping Down

By: Laura Joszt

After nearly 6 years overseeing public health initiatives, Margaret Hamburg, MD, commissioner of the FDA will be stepping down, according to various sources.

Reuters is reporting that Dr. Hamburg's resignation will be announced on Friday, although as of right now a new commissioner has not been named. Until then, Stephen Ostroff, MD, the FDA's chief scientist, will fill the position.

The *Wall Street Journal* conjectured that Robert Califf, MD, from Duke University, who was recently appointed as FDA deputy commissioner for medical products and tobacco, will likely become the next FDA commissioner.

On January 27, when Dr. Califf's appointment was announced, experts began speculating that he was part of an FDA succession plan because he would quickly be confirmed.

"Dr. Califf's deep knowledge and experience in the areas of medicine and clinical research will enable the agency to capitalize on, and improve upon, the significant advances we've made in medical product development and regulation over the last few years," Dr. Hamburg had said in a statement upon Dr. Califf's appointment.

Dr. Hamburg is one of the longest-serving FDA commissioners. During her time as commissioner, she relaxed age restrictions on the Plan B contraceptive and faced the challenge of hundreds of deaths caused by compounded drugs mixed at a local pharmacy.

Under her leadership, the FDA also introduced measures to speed the development and review of new drugs and the agency gained regulatory authority over tobacco products.

Fallon Smith

Press Officer

Office of Media Affairs

Office of External Affairs

U.S. Food and Drug Administration

Tel: 301-796-8632

Fallon.Smith@fda.hhs.gov



From: [Smith, Fallon](#)
To: [Esquea, Jim \(OS\)](#); [Hamburg, Margaret](#); [Quinn, Kathleen](#); [Kraus, Tom](#); [Rebello, Heidi](#); [Yao, Stephanie](#); [Riley, Karen](#); [Zawisza, Julie](#); [Ostroff, Stephen](#); [Hoague, Angela](#)
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[Medscape: FDA Commissioner Dr Margaret Hamburg to Step Down](#)

By: Lisa Nainggolan

UPDATED February 5, 2015 // Margaret Hamburg, MD, commissioner of the US Food and Drug Administration (FDA), is to resign this week, after almost 6 years in her post, according to government officials.

Dr Hamburg is one of the longest-serving FDA commissioners in recent times. Stephen Ostroff, MD, the FDA's chief scientist, will fill the commissioner's position until a new appointee is named.

Sylvia Burwell, secretary of the Department of Health and Human Services, said the American people have been "well served" by Dr Hamburg.

"Her dedicated service leaves a legacy of incredible, historic accomplishment at FDA," Burwell said in a news release. "From keeping our food supply safe to significant advancements in biomedical innovation to the quickly facilitating the availability of critical products to help fight Ebola, Peggy's tireless leadership has impacted millions of people across this country."

One possible contender for the "top job" will undoubtedly be Dr Robert Califf, of Duke University Medical Center, who was named FDA deputy commissioner for medical products and tobacco.

Long synonymous with cardiovascular medicine, Dr Califf is scheduled to join the FDA later this month. He could not be reached for comment.

FDA Has Been "Enormously Rewarding"

Under Dr Hamburg's tenure, the FDA has approved many new drugs, including 51 in 2014, the highest number for almost 2 decades. Dr Hamburg has also overseen the effort to limit trans fats in foods and to legislate for restaurants to post calorie counts on menus.

Prior to her FDA appointment, Dr Hamburg had an extensive background in US public service, government, and in health and human services at different levels, including at the National Institutes of Health, and she spent 6 years as the New York City commissioner of health.

In November, Dr Hamburg told Medscape Medical News that the FDA "has been a terrific opportunity and it is an inspiring place to work."

She discussed some of the challenges of her career there, which have included trying to regulate rogue compound pharmacies, finally getting the Plan B emergency contraceptive approved for over-the-counter use, and navigating the fine line between making opiates available for pain relief while attempting to prevent their abuse.

The agency has also faced major public health issues on Dr Hamburg's watch, including, most recently, the outbreak of Ebola and other infectious diseases.

"Most of the real problems that underlie medical care and our desire to promote health are not going to be resolved simply in a doctor's office or in a hospital setting. We have to step back and look at all of the determinants of health," she told Dr Topol.

Nevertheless, "Public service is enormously rewarding, and you feel that every day you are making a difference," she added.

"Being engaged in health policy has made me look at things in a much more textured way. All of the problems before us are complex and multidetermined, and the solutions have to be multifaceted."

###

[The Hill: FDA Commissioner Hamburg to step down](#)

By: Elise Viebeck 10:31 a.m.

Food and Drug Administration (FDA) Commissioner Margaret Hamburg will step down after nearly six years as one of the Obama administration's top public health officials.

Hamburg oversaw drug approvals, food safety, tobacco control and other health initiatives during a tenure that made her one of the longest-serving FDA chiefs in modern history.

Dr. Stephen Ostroff, the agency's chief scientist, will temporarily fill the position when Hamburg departs at the end of March.

The commissioner wrote in a note to staff that her tenure had been "the most rewarding of my career" and that she has "very mixed emotions" about her decision to leave the FDA. No future plans were announced.

A former health commissioner of New York City, Hamburg is a graduate of Harvard Medical School who previously worked for the National Institutes of Health.

Her tenure at the FDA was marked by new public health challenges, including rising obesity, an increase in prescription drug abuse, heightened risk from antibiotic resistant bacteria and the unprecedented Ebola epidemic in West Africa.

The agency gained authority to regulate tobacco for the first time in 2009, under Hamburg's

leadership. The FDA is now moving to impose rules on e-cigarettes.

A non-controversial figure, Hamburg largely avoided political fights with Republican lawmakers that bogged down leaders like former Health and Human Services Secretary Kathleen Sebelius.

Nonetheless, her tenure did not come without its challenges, including a deadly outbreak of meningitis tied to compounded drugs and a slew of food safety scares.

Hamburg was also involved in the controversy over whether Plan B emergency contraception should be sold over the counter to young teenagers.

Her decision to make the medication available was initially overruled by Sebelius. The FDA later approved prescription-free Plan B for all ages.

A leading House Republican offered praise for Hamburg in a statement Thursday.

"Peggy has been a great partner and participant in the 21st Century Cures initiative," said Energy and Commerce Committee Chairman Fred Upton (R-Mich.), referring to a legislative effort to accelerate cures.

"I am grateful for her support of this important initiative and look forward to continuing to work with leaders at the FDA and in the administration as the legislative process continues this year."

Hamburg's decision comes about three weeks after another top administration health official — Medicare-Medicaid chief Marilyn Tavenner — announced she was stepping down.

###

[**AP: Head of FDA stepping down, chief scientist to take over**](#)

By MARY CLARE JALONICK and MATTHEW PERRONE 26 minutes ago

WASHINGTON (AP) — Food and Drug Administration Commissioner Margaret Hamburg is resigning in March after six years in the position.

Hamburg told employees of the FDA in an email Thursday that the agency's chief scientist, Stephen Ostroff, will serve as acting commissioner.

She is among the longest-serving commissioners to head the agency and helped oversee the creation of a new food safety system, reforms in how drugs are reviewed and new tobacco regulations.

President Barack Obama named Hamburg to the post in 2009, following a series of high-profile safety problems at the agency ranging from contaminated blood thinners to salmonella-tainted peanut butter that required one of the largest food recalls in U.S. history.

Under Hamburg's tenure, the FDA was more active on food policy than it had been since nutrition labeling rules were first written in the early 1990s. The agency has worked to put new food safety rules in place, phased out artery-clogging trans fats from the food supply, proposed updates to nutrition facts on the backs of food packaging and required restaurants and retailers to label calories on menus.

In her goodbye note to staffers, she emphasized the importance of science in these decisions and other reforms aimed at speeding up drug reviews and overseeing tobacco products.

"At the heart of all of these accomplishments is a strong commitment to science as the foundation of our regulatory decision-making and of our integrity as an agency," Hamburg said.

She took control of the agency at a time when its reputation had been tarnished by accusations that agency officials were allowing politics to influence their decisions. A federal judge ruled that in 2006 the agency deliberately delayed making a decision on the Plan B morning-after pill at the behest of the Bush administration.

Before joining the FDA, Hamburg, 59, was primarily known as a bioterrorism expert who served as New York City health commissioner

News of Hamburg's departure comes just a week after the agency announced that Robert Califf, a prominent cardiologist from Duke University, would take on the agency's No. 2 leadership position. Califf was considered for the agency's top job under the administrations of President George H.W. Bush and George W. Bush. Many FDA observers expect him to eventually move into the commissioner position.

###

[Politico: Alexander praises outgoing FDA chief](#)

By: Rachana Pradhan

Senate HELP Committee Chairman Lamar Alexander praised departing FDA Commissioner Margaret Hamburg for her leadership and said he hopes the president nominates a new agency head who will work closely with Congress.

"I hope the president nominates an FDA Commissioner who will work closely with Congress on finding ways to get safe medical treatments, devices and drugs to patients more quickly," the Tennessee Republican said in a statement.

Alexander and Sen. Richard Burr last week published a paper on plans to reform the role the NIH and FDA play in medical research and product development. The paper identified broad challenges that the agencies face but did not include specific policy recommendations.

Hamburg announced in an email to staff today that she will leave the agency at the end of March.

Fallon Smith

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-8632
Fallon.Smith@fda.hhs.gov



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To: [Esquea, Jim \(OS\)](#); [Hamburg, Margaret](#); [Quinn, Kathleen](#); [Kraus, Tom](#); [Rebello, Heidi](#); [Yao, Stephanie](#); [Riley, Karen](#); [Zawisza, Julie](#); [Ostroff, Stephen](#)
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[NPR: FDA Commissioner Margaret Hamburg To Step Down](#)

By: Scott Neuman February 05, 2015 8:39 AM ET

Updated at 10:23 a.m. ET

FDA Commissioner Dr. Margaret A. Hamburg — who has been at the center of controversial decisions such as relaxing age restrictions on the Plan B contraceptive — has decided to step down after six years in the job.

In a letter to FDA staff, Hamburg called the tenure "the most rewarding of my career." She cited, among other things, the agency's record in improving food safety, advancing the safety and effectiveness of medical products, reducing the time for pre-market reviews of medical devices as highlights of her six years at the FDA's helm.

Hamburg said FDA Chief Scientist Dr. Stephen Ostroff will serve as acting commissioner when she steps down at the end of March.

The Wall Street Journal reports that Dr. Robert Cahill, who was recently selected by Hamburg to become the agency's deputy commissioner for medical products and tobacco, is regarded as her likely successor for the top job.

News reports say the White House will announce Hamburg's departure on Friday.

Hamburg, 59, was approved by the Senate in 2009 and is among the longest-serving FDA commissioners the modern era.

###

[NYT: Margaret Hamburg, F.D.A. Commissioner, Stepping Down](#)

By: Sabrina Tavernise Feb. 5, 2015

Dr. Margaret Hamburg, the commissioner of the Food and Drug Administration, who led the agency for nearly six years through a period of rapid change in medical science, announced Thursday that she is stepping down.

Dr. Hamburg, 59, told agency colleagues in an email that she would depart at the end of March. "As

you can imagine," she wrote, "this decision was not easy. My tenure leading this agency has been the most rewarding of my career."

One of the longest-serving commissioners at the agency, Dr. Hamburg was nominated by President Obama and confirmed by the Senate in 2009. She had a behind-the-scenes leadership style that some criticized as not tough enough but others praised as the best way to be effective in an era of intensely partisan politics.

The F.D.A. is an immense agency. Its officials like to say that it regulates about 20 cents on every dollar spent by American consumers, and its authority extends from drugs and food to medical devices and tobacco. Dr. Hamburg has grappled with some of the biggest public health issues of the day: the opioid painkiller abuse epidemic, obesity and the rise of electronic cigarettes.

"She has really done a terrific job," said Dr. Thomas Frieden, director of the federal Centers for Disease Control and Prevention. "In virtually every issue that arises, she grasps it quickly and deeply and asks questions that force people to see a different dimension of it."

Dr. Hamburg has said the agency is making strides in an era that has brought a burst of new individualized treatments for small populations of patients based on genes. In a blog post earlier this week, she said the F.D.A. approved 51 drugs in 2014, the most in almost 20 years. She called that a testament to its "innovative approaches to help expedite development and review of medical products that target unmet medical needs."

While some have criticized the agency for speeding up approvals too much, others say the pace is justified.

Nancy Goodman, executive director of Kids V. Cancer, a nonprofit advocacy group, praised Dr. Hamburg in an email. Ms. Goodman, who lost a son to cancer, said she was grateful for the pace of pediatric cancer drug development, "including simpler faster and cheaper trials and the implementation of the Creating Hope Act pediatric rare disease priority review program."

Daniel Carpenter, a Harvard University political scientist who studies the F.D.A., noted the drug-safety problems that plagued the agency in the years before she took over. "She led the agency out of crisis," he said. "She got the funding. There's a steadiness there. A sense that the agency is growing."

Dr. Hamburg leaves as some in Congress are pushing for change in the regulation of food and drugs. A group of legislators has recently proposed combining the F.D.A.'s food safety capabilities with those of other agencies, such as the Department of Agriculture. There is also a proposal to streamline the agency's drug approval authority.

Dr. Hamburg has a long background in public health. She was New York City's health commissioner in the 1990s, at a time when tuberculosis had become increasingly resistant to standard drugs and long-term adherence to medicine was critical. She sent health care workers to patients' homes to help them manage their drug regimens. Under her leadership, New York City increased cure rates

and reduced tuberculosis significantly.

She comes from a family of prominent doctors. Her father was a renowned psychiatrist, and her mother was the first black woman to attend Vassar College and to graduate from the Yale University School of Medicine. Dr. Hamburg was the first New York City health commissioner to give birth while in office, and her children's birth certificates bear her name in two places: as their mother and as health commissioner.

###

[Washington Post: FDA head Margaret Hamburg to resign in March; Ostroff to be acting chief](#)

By: Brady Dennis Feb. 5, 2015 8:41a.m.

Margaret Hamburg, who as commissioner of the Food and Drug Administration over the past six years has presided over new initiatives on food safety and tobacco regulation and has worked to fast-track new breakthrough drugs, plans to resign from her post in March, the agency said Thursday.

"As you can imagine, the decision was not easy," Hamburg said in a statement. "While there is still work ahead (and there will always be), I know that I am leaving the agency well-positioned to fulfill its responsibilities to the American public with great success."

Stephen Ostroff, the FDA's chief scientist and a former official at the Centers for Disease Control and Prevention, will take over in the top post until President Obama names a successor for Hamburg.

Hamburg, 59, is among the longest-serving commissioners at the agency. A Harvard Medical School graduate, she previously worked as New York City's health commissioner, as well as at the National Institutes of Health.

"I think she's done a terrific job," said Anthony Fauci, a former boss and mentor of Hamburg's and head of the National Institute of Allergy and Infectious Disease at NIH. "She's intelligent. She's very measured and analytical."

Hamburg's tenure was not without controversy. She and the agency have been criticized for not doing more to curb the nation's epidemic of prescription drug overdoses. She faced tough questions on Capitol Hill in 2012 after a devastating outbreak of fungal meningitis killed scores of people who received unsterile injections made at largely unregulated "compounding" pharmacies.

The previous year, against Hamburg's objections, Health and Human Services Secretary Kathleen Sebelius overruled the FDA and said the controversial contraceptive "Plan B" could not be sold over the counter to young teenagers. The Obama administration later agreed to allow over-the-counter sales of the morning-after pill for women of all ages.

In a blog post earlier this week, Hamburg wrote proudly about the more than 40 drugs the agency

approved in 2014, many of which were to treat previously unmet conditions or otherwise considered “breakthrough” therapies.

The agency in recent years also has rolled out new regulations to include calorie listings on restaurant menus, limit harmful trans fat in food and improve the overall safety of the food supply. The FDA also for the first time announced its intention to regulate the booming market of e-cigarettes.

Fallon Smith

Press Officer

Office of Media Affairs

Office of External Affairs

U.S. Food and Drug Administration

Tel: 301-796-8632

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[Reuters: FDA Commissioner Margaret Hamburg to step down](#)

By: Toni Clarke

WASHINGTON, Feb 5 (Reuters) - Dr. Margaret Hamburg, who as commissioner of the U.S. Food and Drug Administration (FDA) for almost six years has overseen public health initiatives ranging from tobacco control and food safety to personalized medicine and drug approvals, is stepping down, the agency said on Thursday.

Hamburg, 59, is one of the longest-serving FDA commissioners in the modern era. She was nominated by President Barack Obama and confirmed by the U.S. Senate in May 2009 and last year was named the world's 51st most powerful woman by Forbes magazine.

In a note to staff, Hamburg said it was "with very mixed emotions" that she planned to step down at the end of March and that her tenure as FDA chief "has been the most rewarding of my career."

Dr. Stephen Ostroff, the FDA's chief scientist, will fill Hamburg's position until a new commissioner is named.

Late last month, the agency named Dr. Robert Califf, a prominent cardiologist and researcher from Duke University, to oversee its drug, medical device and tobacco policy. Califf is viewed by many as a potential successor to Hamburg.

A long-time public health official with extensive experience fighting AIDS and tuberculosis, Hamburg, who graduated from Harvard Medical School, previously served at the National Institutes of Health before becoming New York City's health commissioner. That public health focus endeared her to patient advocates.

"Commissioner Hamburg, from day one, has been committed to being a champion for patients," said Ellen Sigal, founder and chair of Friends of Cancer Research. "She has fostered the growth of science and innovation across the agency and really changed how FDA and industry collaborate."

Hamburg's resignation comes as the FDA prepares for what could be a significant transformation, spurred on the one hand by initiatives in Congress to speed new drug development, and on the other by food safety advocates, backed by the president, who would like to see the creation of a separate agency combining the food safety functions of the FDA and the U.S. Department of Agriculture.

MORE ENGAGEMENT

Under Hamburg's leadership the FDA, which oversees products representing more than 20 cents of every dollar spent by U.S. consumers, has proposed measures to improve nutrition by limiting dangerous trans-fats in food and requiring restaurants to post calorie counts on menus. It also has beefed up inspections of food and drugs from overseas and increased patient engagement in the drug development process.

The agency has introduced multiple measures to speed the development and review of new drugs. In 2014, the FDA approved 51 new therapies, the most in almost 20 years. In a blog post on Wednesday, Hamburg called the achievement "a testament ... to FDA's innovative approaches to help expedite development and review of medical products that target unmet medical needs."

During her tenure the FDA has confronted major public health issues, including the rise of antibiotic-resistant bacteria, the abuse of opioid painkillers, the emergence of electronic cigarettes and the outbreak of Ebola and other infectious diseases.

Her ride has not always been smooth. She faced hostile questioning by Republicans in Congress following a fungal meningitis outbreak in 2012 that killed dozens of people and sickened hundreds more. She also has been caught up in some controversial political battles.

In 2011, then Health and Human Services Secretary Kathleen Sebelius overruled the FDA's decision to allow an emergency contraceptive known as Plan B to be sold over the counter to young teenagers. Hamburg insisted Plan B was safe for use and it was approved two years later.

The health department's current secretary, Sylvia Burwell, said in a statement that Hamburg "leaves a legacy of incredible, historic accomplishment at FDA."

Hamburg was never a crusading commissioner in the way of one of her predecessors, Dr. David Kessler, who fought to bring tobacco under FDA regulation. But she has made her mark on multiple issues, including the use of targeted therapy to tailor medicines to an individual's genetic makeup. The FDA gained regulatory authority over tobacco products for the first time on her watch, in 2009.

Hamburg comes from a distinguished medical family. Her mother was the first African-American woman to attend Vassar College and to earn a degree from Yale University School of Medicine. (Editing by Ian Geoghegan, Bill Trott and Meredith Mazzilli)

###

[**Fierce Pharma: FDA chief Hamburg to step down, with new deputy a potential successor**](#)

By: Emily Wasserman

Dr. Margaret Hamburg is stepping down as FDA commissioner in March after 6 tumultuous years in the job, government sources say.

As The Wall Street Journal reports, FDA chief scientist Dr. Stephen Ostroff will serve as commissioner until President Obama appoints--and Congress confirms--a replacement. The news is not as surprising as it might have been before last month, when Hamburg selected Dr. Robert Califf of Duke University as deputy commissioner for medical products and tobacco. Industry watchers see Califf as a potential successor.

Since she took the FDA helm in 2009, Hamburg has juggled many contentious issues. She came under fire after a deadly meningitis epidemic was traced to a New England compounding pharmacy, and then led a crackdown on the compounding business. She stepped up plant inspections in the U.S. and abroad, expanding the agency's international reach to keep tabs on quality shortfalls. And Hamburg was forced to defend approvals of powerful painkillers amid worries about rampant opioid abuse--not to mention calls for her resignation over the issue

But Hamburg's reign as commissioner hasn't been all doom and gloom. The FDA stepped on the gas in drug approvals, speeding up the process for potentially life-saving drugs. As Hamburg pointed out in a recent FDA blog post, the agency approved 51 novel drugs and biologics in 2014--the most in almost 20 years--including 17 "first in class" treatments.

"These developments are a testament not just to our expanding understanding of human biology, the biology of disease and the molecular mechanisms that drive the disease process, but also to FDA's innovative approaches to help expedite development and review of medical products that target unmet medical needs, while adhering to the established standards for safety and efficacy," Hamburg said in the blog post.

Hamburg has also focused on quality issues in emerging markets. Early last year, Hamburg made her first trip to India to inspect conditions at manufacturing plants. In November, she traveled to China to meet with the country's top regulatory officials about working together on drug food and safety.

Meanwhile, the FDA could face an uphill battle in naming Hamburg's successor. The post requires congressional approval, which is often difficult to obtain in a polarized political climate. But Califf, widely respected in the scientific community and the industry, may encounter fewer roadblocks than other candidates might, the WSJ reports.

###

[**Medcity News: FDA Commissioner to resign after 6 years on the job**](#)

By: Nicole Oran

Dr. Margaret Hamburg will be stepping down from her position as commissioner of the U.S. Food and Drug Administration after being appointed by President Obama nearly six years ago.

Hamburg has overseen initiatives including personalized medicine, disease control, medical device

and drug approval, food safety and tobacco control. Reuters reported that the news comes from a person briefed on the matter and that a formal announcement from The White House will be made Friday. FDA spokeswoman Stephanie Yao reportedly declined to comment.

It isn't clear who would replace her yet, but Dr. Robert Califf, cardiologist and researcher from Duke University, was recently appointed by the agency to oversee drug, medical device and tobacco policy. He could be a likely contender.

For now, the FDA's chief scientist, Dr. Stephen Ostroff, will temporarily fill her spot, according to a second Reuters source.

Hamburg has had a significant influence on things like improving nutrition by requiring restaurants to label calories and limiting trans-fats, as well as having a major focus on increasing patient engagement with the FDA patient network.

Under her leadership the FDA also dealt with health issues like the rise of antibiotic-resistant bacteria, the emergence of electronic cigarettes, the abuse of opioid painkillers and the Ebola outbreak, among other things.

Many things could be changing soon for the FDA following her resignation as Congress looks to speed up new drug development even more and the potential for a new agency combining the food safety aspects of the FDA with the U.S. Department of Agricultural could be in the future.

Fallon Smith

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-8632
Fallon.Smith@fda.hhs.gov



From: [Smith, Fallon](#)
To: [Hamburg, Margaret](#); [Quinn, Kathleen](#); [Kraus, Tom](#); [Rebello, Heidi](#); [Yao, Stephanie](#); [Riley, Karen](#); [Zawisza, Julie](#); [Ostroff, Stephen](#); [Hoague, Angela](#); [Esposito, Denise](#); [Pennington, Caitlin](#)
Subject: Commissioner Hamburg Resignation: Boston Business Journal, "FDA head Margaret Hamburg says she will step down after 6 years"
Date: Thursday, February 05, 2015 1:22:40 PM
Attachments: [image001.png](#)
[image002.jpg](#)
[image003.jpg](#)
[image004.jpg](#)
[image005.jpg](#)
[image006.jpg](#)

[FDA head Margaret Hamburg says she will step down after 6 years](#)

By Don Seiffert

[Margaret Hamburg](#), commissioner of the U.S. Food and Drug Administration for six years, said today she is stepping down as of March, [according to the New York Times](#).

Hamburg, [who came to Boston last April](#) to speak at the MassBio annual meeting, has attracted both praise and criticism for her job overseeing the nation's top agency that oversees drug approvals. The past few years have seen more drug approvals in more than a decade as the biotech sector has enjoyed an explosion of innovation. She's overseen the implementation of new designations to help further speed up the approval process for certain kinds of drugs, particularly antibiotics and those which have promise to substantially improve treatment for life-threatening diseases.

At the same time, the agency has attracted significant criticism from patient advocates for not acting quickly enough on promising drugs to treat some diseases, such as Duchenne muscular dystrophy. [Christine McSherry](#), a Pembroke mother of a 19-year-old with DMD and head of the Jett Foundation, a patient advocacy group, said that while Hamburg laid the foundation for the precision medicine initiative announce last week by President [Barack Obama](#), she "hasn't done enough" to speed approval of rare diseases like DMD.

"We hope to have more focus going forward and implementation of faster processes across all the divisions... but would like to see all of these endeavors translated into action which would mean quicker access to drugs and faster approvals," said McSherry in an interview today.

While Hamburg has touted the agency's work to use accelerated approval in reviewing drugs for diseases which have not treatments, McSherry said that during Hamburg's tenure, the agency continues to burden small drug development companies with requirements that take months or years to fulfill. As a result, she said it still takes an average of seven years from when clinical trials start for a drug for a rare disease before that drug is approved. McSherry cited the example of Cambridge-based Sarepta Therapeutics (Nasdaq: SRPT), which has suffered numerous delays due to FDA's requirements in developing its DMD drug, despite the fact that no safety issues have surfaced in a trial of 12 boys that's lasted more than three years.

"The only thing that's happened in that time is more boys have died (from the disease)... and more safety data has accumulated," she said. McSherry said she's met with Hamburg three times in recent years and has found her empathetic, but says, "I don't believe she has full control over her agency."

[Jim Greenwood](#), head of BIO, the world's largest trade association representing biotechnology companies, [has also criticized the agency](#) for not using post-marketing data in some cases to get life-saving drugs on the market sooner, while former FDA Commissioner [Andrew von Eschenbach](#) went

so far last year as to say of the biotech industry, "[the business model is basically falling apart](#)" due to the FDA's increasing demands.

While there has reportedly not been a successor named, The Wall Street Journal reported that the FDA's chief scientist, Dr. Stephen Ostroff, will temporarily fill in. One likely successor could be Dr. Robert Califf of Duke University, who Hamburg recently recruited as the agency's deputy commissioner for medical products and tobacco.

Fallon Smith

Press Officer

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U.S. Food and Drug Administration
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From: [Smith, Fallon](#)
To: [Hamburg, Margaret](#); [Quinn, Kathleen](#); [Kraus, Tom](#); [Rebello, Heidi](#); [Yao, Stephanie](#); [Riley, Karen](#); [Zawisza, Julie](#); [Ostroff, Stephen](#); [Hoague, Angela](#); [Esposito, Denise](#); [Pennington, Caitlin](#)
Subject: Commissioner Hamburg Resignation: CNN, "FDA chief to step down in March"
Date: Thursday, February 05, 2015 12:09:36 PM
Attachments: [image001.png](#)
[image002.jpg](#)
[image003.jpg](#)
[image004.jpg](#)
[image005.jpg](#)
[image006.jpg](#)

[FDA chief to step down in March](#)

By Jim Acosta and Jeremy Diamond, CNN

*Washington (CNN)*The head of the Food and Drug Administration announced Thursday in an email to staff that she is stepping down after six years leading the agency.

FDA Commissioner Margaret "Peggy" Ann Hamburg has overseen a slew of public health regulations ranging from food safety improvements to tobacco control since the Senate confirmed her to the agency's top post in May 2009 in Obama's first months in office. Stephen Ostroff, the agency's chief scientist, will serve as acting commissioner once she leaves her post in March, Hamburg said in the email to staff obtained by CNN.

Hamburg called her tenure at the helm of the agency a "privilege" and said she made her decision to resign with "mixed emotions."

"As you can imagine, this decision was not easy. My tenure leading this Agency has been the most rewarding of my career, and that is due in no small part to all of you - the dedicated and hard-working people that make up the heart of this Agency," Hamburg wrote. "While there is still work ahead (and there always will be), I know that I am leaving the agency well-positioned to fulfill its responsibilities to the American public with great success."

Hamburg also ticked off the FDA's successes in her six years leading the agency: modernizing food safety, improving the review process for medical drugs and strengthening anti-tobacco efforts.

"As Commissioner, my goal has been to shape and support an FDA that is well-equipped to meet the challenges posed by scientific innovation, globalization, the increasing breadth and complexity of the products that we regulate, and our new expanding legal authorities," Hamburg said. "We can honestly say that our collective efforts have improved the health, safety and quality of life of the American people."

Secretary of Health Sylvia Burwell praised Hamburg for her "dedicated service" in a statement Thursday and lauded her accomplishments as "incredible" and "historic."

"From keeping our food supply safe to significant advancements in biomedical innovation to the quickly facilitating the availability of critical products to help fight Ebola, Peggy's tireless leadership has impacted millions of people across this country," Burwell said. "The American people and this Department have been well served by Peggy's tenure at the FDA."

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Press Officer

Office of Media Affairs
Office of External Affairs

U.S. Food and Drug Administration

Tel: 301-796-8632

Fallon.Smith@fda.hhs.gov



From: [Hamburg, Margaret](#)
To: [Pennington, Caitlin](#)
Subject: Fw: "The Pink Sheet" DAILY | Today's News & Analysis
Date: Tuesday, October 28, 2014 3:04:06 PM

[Print Zohydro story and Sarepta story](#)

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

From: The Pink Sheet DAILY [mailto:info@pharmamedtechbi.net]
Sent: Tuesday, October 28, 2014 06:11 AM
To: Hamburg, Margaret
Subject: "The Pink Sheet" DAILY | Today's News & Analysis



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Top Stories

Turning the Page on Zohydro? New Formulations, New Division Leadership Should Help FDA Move Forward in Opioids

The long-time head of FDA's pain drug review group, Bob Rappaport, has retired after 20 years at FDA. The new acting Division Director is Sharon Hertz - suggesting continuity in the substance of reviews, but perhaps a symbolic change in moving beyond the controversy over Zohydro.

In Brief: Sarepta Filing Delay; Baxter Hemophilia Approval; Valeant To Increase Allergan Offer

Sarepta says NDA submission for its muscular dystrophy treatment will be delayed until mid-2015 due to "new" and "updated" FDA requirements; agency approves Baxter's porcine-sourced Obizur for acquired hemophilia A.

As Merck's Keytruda Gains Momentum, Investors Look To The Future

Keytruda, already the first anti-PD-1 drug to market for melanoma, received FDA breakthrough therapy designation for an indication in lung cancer. The drug's long-term potential - and upcoming data on a two-drug hepatitis C combo - helped to offset a decline in Merck's third quarter sales.

Legacy Devices The Weak Link In Cybersecurity Fence Device companies, hospitals and

federal agencies are slowly moving towards adoption of a government framework to guide cybersecurity designs and safeguard newer products, but legacy devices are still vulnerable to hackers and may supply entry into secure systems, cybersecurity experts warn at a joint agency summit.

Remoxy Development Not 'Unmitigated Disaster,' CEO Reassures; Hunt Begins For New Partner Pfizer terminates agreement with Pain Therapeutics after reviewing top-line results of five studies done to address FDA complete response letter; Pain says data supports refiling of NDA for its abuse-deterrent long-acting oxycodone formulation by mid-2015.



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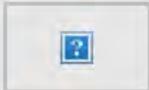
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From: [Hamburg, Margaret](#)
To: [Pennington, Caitlin](#)
Subject: Fw: DMD- Sarepta
Date: Thursday, October 30, 2014 3:26:53 PM
Attachments: [Duchenne Muscular Dystrophy Moms Fight for FDA Approval of Sarepta Drug - Businessweek.pdf](#)
[image001.gif](#)

Print. Folder: Sarepta/DMD
Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

From: Immergut, Steven
Sent: Thursday, October 30, 2014 03:08 PM
To: Hamburg, Margaret
Cc: Hoague, Angela
Subject: DMD- Sarepta

Hi- yes at a few big stories on DMD/Sarepta this week. The announced earlier in week an update from their preNDA meeting. The one today from BusinessWeek sounds like the one you heard about - though strangely not in our clips this morning. Will need to check on that. First link below and attached pdf in case you want to print and bring home It's a really tough story on us. We didn't know was coming today but did work with reporter. This is a very difficult situation for us but need to think about how come off better than this.

<http://www.businessweek.com/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug>

The second and third one are more on the announcement - from Matt Herper at Forbes and Joe Walker at WSJ. Matt calls for CEO to resign.

<http://www.forbes.com/sites/matthewherper/2014/10/27/sarepta-needs-fda-expertise-stat/>

<http://online.wsj.com/articles/sarepta-therapeutics-sees-setback-in-eteplirsen-drug-application-1414414412>

here's the press release.

Sarepta Therapeutics Announces Regulatory Update on Eteplirsen

Updated and additional guidance received from FDA on specific data requirements for NDA;

FDA states further discussion needed to determine what constitutes a “complete” NDA submission;

NDA submission planned for mid-year 2015;

Company to hold teleconference today at 8:00 a.m. EDT

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 27, 2014-- Sarepta Therapeutics, Inc. (NASDAQ:SRPT), a developer of innovative RNA-based therapeutics, today provided an update on its discussions with the U.S. Food and Drug Administration (FDA) regarding its planned New Drug Application (NDA) submission for the approval of eteplirsen for the treatment of Duchenne muscular dystrophy (DMD).

In meeting minutes received last week from a Type B Pre-NDA meeting that took place in September 2014, the FDA provided updated guidance regarding the specific data to be included as part of, or at the time of, Sarepta's NDA submission. The guidance states that additional data are now required as part of the NDA submission, including the results from an independent assessment of dystrophin images and the 168-week clinical data from study 202. Additionally, the guidance requests more specific data including a minimum duration of safety in new patients exposed to eteplirsen, patient-level natural history data to be obtained by Sarepta from independent academic institutions, and MRI data from a recent study conducted by an independent academic group. The FDA indicated that further discussion with Sarepta "will be necessary to determine what would constitute a complete NDA." Based on these requests, Sarepta plans to submit an NDA by mid-year 2015, pending any additional requests from further discussions with the FDA.

"We are committed to satisfying the FDA's updated requests for these specific data to be included as part of an NDA submission and will continue to work with the Agency toward the goal of a complete and acceptable NDA filing," said Chris Garabedian, president and chief executive officer of Sarepta Therapeutics. "We believe all of the data requests and additional FDA discussions that have currently been outlined can be completed in time for an NDA submission by mid-year 2015. Obtaining an FDA approval of eteplirsen for the DMD patients who may benefit from the drug continues to be our highest priority."

Excerpts from the Pre-NDA Meeting Minutes related to information that the FDA is requesting as part of an NDA submission included:

"The sponsor should include 3-month data from at least 12 to 24 newly exposed patients at the time the NDA is submitted."

"Available data from the other patients enrolled in the new eteplirsen studies (studies 301, 203, 204) should also be included at the time the NDA is submitted, even if exposure is less than 3 months in duration."

"Additional data from later time points and from newly enrolled patients should be submitted in the 120-Day Safety Update."

"FDA strongly advises the sponsor to obtain and submit patient-level natural history data. FDA is prepared to appeal to the academic groups holding the data to allow the sponsor a means to acquire the data."

"The study 201/202 clinical site inspection conducted in May, 2014, after the issuance of the April 15, 2014, guidance letter, uncovered marked disparities in the immunohistochemistry methodology and concerns about the reproducibility of the data. The lack of confirmation of robust dystrophin measurement during the site visit necessitates including the independent assessment of dystrophin-positive fibers and 168-

week efficacy data from study 201/202 in the NDA."

"FDA strongly urged the sponsor to submit the MRI data with appropriate natural history controls."

The FDA also stated that "[a]dditional discussion between the sponsor and the FDA will be necessary to determine what would constitute a complete NDA."

Conference Call Information

Sarepta will hold a conference call to discuss this update today at 8:00 a.m. EDT (5:00 a.m. PDT). The conference call may be accessed by dialing 800.708.4539 for domestic callers and 847.619.6396 for international callers. The passcode for the call is 38376370. Please specify to the operator that you would like to join the "Sarepta Regulatory Update Call." The conference call will be webcast live under the investor relations section of Sarepta's website at www.sarepta.com and will be archived there following the call for 90 days. Please connect to Sarepta's website several minutes prior to the start of the broadcast to ensure adequate time for any software download that may be necessary. An audio replay will be available through November 3, 2014 by calling 888.843.7419 or 630.652.3042 and entering access code 38376370.

About Duchenne Muscular Dystrophy

DMD is an X-linked rare degenerative neuromuscular disorder causing severe progressive muscle loss and premature death. DMD affects approximately one in every 3,500 boys born worldwide. A devastating and incurable muscle-wasting disease, DMD is associated with specific errors in the gene that codes for dystrophin, a protein that plays a key structural role in muscle fiber function. Progressive muscle weakness in the lower limbs spreads to the arms, neck and other areas. Eventually, increasing difficulty in breathing due to respiratory muscle dysfunction requires ventilation support, and cardiac dysfunction can lead to heart failure. The condition is universally fatal, and death usually occurs before the age of 30.

About Eteplirsen

Eteplirsen is Sarepta's lead drug candidate and is designed to address the underlying cause of DMD by enabling the production of a functional dystrophin protein. Data from clinical studies of eteplirsen in DMD patients have demonstrated a broadly favorable safety and tolerability profile and restoration of dystrophin protein expression.

Eteplirsen uses Sarepta's novel phosphorodiamidate morpholino oligomer (PMO)-based chemistry and proprietary exon-skipping technology to skip mutations affecting exon 51 of the dystrophin gene. Approximately 13 percent of the total DMD population is amenable to exon 51 skipping. By skipping exon 51, eteplirsen may restore the gene's ability to make a shorter, but still functional, form of dystrophin from messenger RNA, or mRNA. Promoting the synthesis of a truncated dystrophin protein is intended to stabilize or significantly slow the disease process and prolong and improve the quality of life for patients with DMD. Sarepta is also developing other PMO-based exon-skipping drug candidates intended to treat additional patients with DMD.

About Sarepta Therapeutics

Sarepta Therapeutics is focused on developing first-in-class RNA-based therapeutics to improve and save the lives of people affected by serious and life-threatening rare and infectious diseases. The Company's diverse pipeline includes its lead program eteplirsen, for DMD, as well as potential treatments for some of the world's most lethal infectious diseases. Sarepta aims to build a leading, independent biotech company dedicated to translating its RNA-based science into transformational therapeutics for patients who face significant unmet medical needs. For more information, please visit us at www.sarepta.com.

Forward-Looking Statements and Information

This press release contains forward-looking statements. These forward-looking statements generally can be identified by the use of words such as “believes or belief,” “anticipates,” “plans,” “expects,” “will,” “intends,” “potential,” “possible,” “advance” and similar expressions. These forward-looking statements include statements about Sarepta’s planned timing for an NDA submission for eteplirsen in the treatment of DMD; Sarepta’s plans to work with the FDA towards the goal of a complete and acceptable NDA filing; Sarepta’s ability to satisfy the additional FDA requests; the timing and submission of additional data, analysis and other information to the FDA necessary for the FDA to make regulatory determinations; the timing of and ability to initiate additional studies for eteplirsen and other follow-on exons; and the potential regulatory approval of eteplirsen.

Each forward-looking statement contained in this press release is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statement. Applicable risks and uncertainties include, among others: we

may not be able to comply with all FDA requests; the FDA may determine that substantial additional data is required for accelerated or other approval of eteplirsen or that our NDA submission for eteplirsen does not qualify for filing, even with additional information; the results of our ongoing and new clinical trials may not be positive; there may be delays in timelines relating to an NDA submission, initiating clinical trials, or making a product commercially available for regulatory or internal reasons; we may not be able to manufacture sufficient supply for clinical trials or commercialization; agency or court decisions with respect to our patents or those of third parties may negatively impact our business and those identified under the heading “Risk Factors” in Sarepta’s Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 filed with the Securities and Exchange Commission (SEC), and Sarepta’s other filings with the SEC.

Any of the foregoing risks could materially and adversely affect Sarepta’s business, results of operations and the trading price of Sarepta’s common stock. For a detailed description of risks and uncertainties Sarepta faces, you are encouraged to review the Company’s filings with the SEC. We caution investors not to place considerable reliance on the forward-looking statements contained in this press release. Sarepta does not undertake any obligation to publicly update its forward looking statements based on events or circumstances after the date hereof.

Source: Sarepta Therapeutics, Inc.

**Sarepta Media Contact:
Tony Plohoros, 908-591-2839**

tplohoros@6degreespr.com

or

Sarepta Investor Contact:
Stephanie Ascher, 212-362-1200

stephanie@sternir.com

Bloomberg Businessweek

Technology

<http://www.businessweek.com/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug>

Moms, Regulators, Biotech Startups, and the Battle Over a Potentially Life-Saving Drug

By Paul M. Barrett October 30, 2014



Photograph by Ryan PflugerLeffler's son Aidan was diagnosed with Duchenne in 2006

The 2014 World Cup elevated soccer to the top of Aidan Leffler's roster of obsessions, rivaled only by endangered big cats—especially jaguars, “the coolest”—and *Star Wars* spaceships. In recognition of his new interest, he's set up a miniature soccer field with 4-foot-wide goals in his backyard in suburban Bellevue, Wash. “Watch this!” he shouts, preparing to fire a penalty kick.

Small for his age, Aidan, 11, moves awkwardly, shoulders high and hunched. He uses a lightweight plastic beach ball, not a regulation leather soccer ball. He begins his approach, pulls back his right foot, and ... collapses to the grass.

Mitch Leffler, the sole spectator, moves toward his son. “I'm OK,” Aidan says. “I can do it.” He struggles onto his hands and knees, raises his butt, places his hands one at a time on his thighs, and slowly pushes himself into an upright position. “My leg just wasn't there,” he says matter-of-factly. His father nods, and the game resumes.

Aidan has Duchenne, the deadliest strain of muscular dystrophy. It's inherited maternally on the X chromosome and mostly afflicts boys. Parents typically sense something is wrong when their sons at 3 or 4 don't run around or they start falling for no obvious reason. Beginning in the legs, Duchenne destroys muscle, which is replaced by fat and scar tissue. Victims lose the ability to walk by adolescence. Eventually the disease causes cardiac and/or respiratory complications that lead to death by the mid-20s. One in 3,500 newborns has Duchenne, which translates to around 15,000 cases in the U.S. There's no cure.

“Aidan doesn't really understand yet,” his mother, Mindy, says, “but it's basically a slow-motion death sentence.”

There's reason to hope—not for a miracle, but for a reprieve. Three small biotech companies are competing to develop drugs designed to address the cellular defects that cause some cases of Duchenne. If proven safe and effective, the drugs would turn Duchenne into a less devastating form of muscular dystrophy. Clinical trials, however, have yielded uneven results, and the U.S. Food and Drug Administration has made equivocal pronouncements about which of the drugs, if any, have a shot at approval. Even a marginally effective drug would likely command an astronomical price, making the winning company a billion-dollar sensation.

The hunt for a Duchenne treatment has generated a collision of commerce, cutting-edge science, and Wall Street speculation. The FDA, though, seems flummoxed over how to evaluate the experimental drugs, especially given a lack of large, clearly successful randomized studies. That's left the Lefflers confused and increasingly desperate.



Photograph by Ryan PflugerMcSherry with her son, Jett, who began college this fall

Mindy believes that one experimental treatment—eteplirsen, made by a company called Sarepta Therapeutics (SRPT)—has shown sufficient promise in a tiny trial to warrant wider availability. If approved, eteplirsen might help 13 percent of Duchenne boys who have certain genetic flaws. Mindy's son is among the 13 percent. “I want Aidan on that drug,” she says, “and I want it to happen before he's in a wheelchair or worse.”

She and a group of similarly minded moms are pressuring the FDA to give provisional approval to eteplirsen while Sarepta proceeds with confirmatory studies. Taking to Twitter, Facebook, YouTube, and Instagram, they've got the attention of top FDA officials. They've also encountered resistance from career FDA staff members and some rare-disease advocates alarmed by their assertiveness.

"What's hard to understand," says Mindy's friend Jennifer McNary, "is why the whole Duchenne community and the FDA aren't pulling together behind eteplirsen." McNary, who lives south of Boston, has two sons with the disease. Maternal genetic predisposition sometimes results in such sibling pairs. Max McNary, 12, gets eteplirsen in the small Sarepta trial; over the past two-and-a-half years, his symptoms have eased remarkably. Max's older brother, Austin, 15, didn't qualify for the study because he was already in a wheelchair when it started. He's declining physically, losing the use of his arms and having trouble feeding himself.

"Why doesn't the government let me have eteplirsen?" Austin asks when we meet. He waits for an answer, which I don't have. His mother joins the conversation: "The FDA's inaction," she says. "is killing my son."

Mindy agrees with Jennifer and Austin. "Aidan doesn't have time to wait for a perfect placebo-controlled trial with hundreds of subjects," she says. "The benefits outweigh any risks."

In 1986 researchers at Harvard isolated the gene responsible for making the protein dystrophin, a "shock absorber" that surrounds muscle cells. Boys with Duchenne have one of several genetic defects that inhibit production of dystrophin. Without it, ordinary physical exertion causes progressive muscle breakdown. The disease is named for Guillaume Duchenne, a French neurological pioneer who described the symptoms in the 1860s.

For generations, physicians reacted passively to Duchenne. Patricia Furlong's sons, Christopher and Patrick, were diagnosed in 1984. Her doctor told her to "take them home and love them, because there was nothing medicine could do." A former nurse with a stubborn streak, she began traveling the country from her home in central Ohio, pleading with researchers to look for a cure. "She was at NIH [National Institutes of Health]. She was on Capitol Hill. She was in my office," recalls Eric Hoffman, a genetic researcher at Children's National Medical Center in Washington. "Pat would not be denied." She couldn't save her sons, however, who died in the mid-1990s.

Angered by what she describes as the fatalism she encountered at the Muscular Dystrophy Association—sponsor of the long-running Labor Day telethon hosted by actor Jerry Lewis—Furlong formed a breakaway nonprofit: Parents Project Muscular Dystrophy, dedicated strictly to Duchenne. In 2001, largely because of her agitation, Congress passed the Muscular Dystrophy CARE Act, which over the following decade provided more than \$400 million in funding, much of it for Duchenne research. The federal backing, says Hoffman, "got the biotech companies thinking maybe there's money to be made with a Duchenne drug."

"What's hard to understand is why the whole Duchenne community and the FDA aren't pulling together behind eteplirsen"

A startup in New Jersey called PTC Therapeutics (PTCT) focuses on mutations that block dystrophin production. These "nonsense mutations" are akin to a period mistakenly placed in the middle of a sentence, which makes the genetic code incomprehensible. In 2008, Genzyme (SNY), a much larger biotech, gave credibility to PTC's research by paying the tiny company \$100 million upfront to secure future marketing rights to its drug outside North America.

Prosensa (RNA), a Dutch biotech, targets a different type of flaw in the exons, or segments, of the dystrophin gene. By "skipping" a defective exon, Prosensa's compound is supposed to allow the formation of a truncated version of dystrophin. In 2009 the pharmaceutical giant GlaxoSmithKline (GSK) added momentum to exon-skipping research by paying Prosensa \$25 million upfront for development and marketing rights and promising hundreds of millions more in future compensation.

In the U.S., Sarepta was also angling to get into the Duchenne chase. Choosing to work without a larger corporate partner, it began testing eteplirsen, an exon-skipping compound that relies on a different biochemical recipe from Prosensa's drug.

The proliferation of potential treatments gave the Lefflers reason for optimism after years of mounting apprehension. Aidan had first been diagnosed in 2006, at the age of almost 3, after breaking his leg while playing on a slide. As he lost strength, his parents installed an elevator at home so he could avoid stairs, but for the most part he remained ambulatory.

Mindy dug into the science of Duchenne, finding solace in genetics and chemistry, subjects she'd avoided as an English major in college. She works part-time developing software for a tech company and time-and-a-half seeking care for Aidan. Mitch—she met her husband in the early 1990s when they were Seattle-area high school track stars—teaches gym and takes a lot of responsibility for Aidan's two younger siblings. In 2010, the Lefflers felt inspired when the *New Yorker* published an article titled "Mother Courage" that described how the death of Furlong's sons propelled her campaign against Duchenne. "I thought, wow, Pat really got a lot done," says Mindy, "and now we're going to take the next step and actually find a treatment for Aidan, so he doesn't end up like Pat's boys."

In 2011, Mitch took Aidan to a hospital in Columbus, Ohio, where Sarepta was beginning a trial for eteplirsen. Then 7, Aidan was showing such ominous symptoms as knotty, seemingly overdeveloped calves—evidence of scar tissue swiftly replacing muscle. He performed well on a baseline walking test. Too well, it turned out: He was rejected for the study because he was much healthier than most other subjects whose disease was more advanced.

As a fallback, Mindy hustled to get Aidan enrolled in a 180-person Prosensa-GlaxoSmithKline trial at a test site in Vancouver. The trial proved to be an ordeal. Multiple muscle biopsies to check dystrophin levels required Aidan to undergo surgery with general anesthesia. And almost immediately, Leffler suspected he was receiving a saline-solution placebo, rather than injections of Prosensa's drug. She figured this out when he didn't have the swelling and pain other moms said their sons experienced.

For 48 weeks, Aidan's parents took him by plane or car to Vancouver every week for stays ranging from a few hours to several days, depending on the protocol, all the while suspecting he wasn't actually receiving medication. "This may be good for science," Leffler says she thought at the time, "but how's it good for my son?"



Photograph by Ryan PflugerMcNary with her sons, Max (left), who is receiving treatment, and Austin, who isn't

In late 2012, researchers switched all of the subjects on placebo over to treatment with Prosensa's compound, drisapersen. Aidan began to suffer the side effects from getting the drug, but Leffler couldn't tell whether his Duchenne symptoms were easing. "He fluctuated: sometimes better, sometimes worse," she says.

Over time, Leffler became jealous of moms with sons in the Sarepta study—the one from which Aidan had been rejected—because the company was reporting solid results. In October 2012, Sarepta announced that, after 48 weeks, boys receiving eteplirsen had stabilized, with statistically significant improvement in a standardized six-minute walking test. Moreover, unlike the Prosensa drug, which at higher doses creates risks that could lead to kidney damage, the Sarepta study didn't show any dangerous side effects.

The weakness of the Sarepta trial was that it had enrolled only 12 boys. Started in 1980 at the dawn of the biotech era, the company had gone public in 1997 but never put a drug on the market. After a series of management shake-ups, a newly hired chief executive officer, Chris Garabedian, decided in 2011 to bet Sarepta's few remaining chips on eteplirsen. The company simply couldn't

afford a larger trial. "We had a limited amount of drug and no capacity to make more," Garabedian says. "So we took what we had and did the best small trial we could design." Sarepta's shortage of eteplirsen also precluded providing the drug to individual applicants under the FDA's "compassionate use" program.

Despite the skimpy sample size, Sarepta's results ignited a stock market frenzy. The company's shares rose threefold on Oct. 3, 2012, to \$45. CNBC stockpicker Jim Cramer raved about Sarepta on his *Mad Money* show and interviewed Garabedian on camera. In June 2013, PTC announced an initial public offering that raised \$144 million. In their enthusiasm, investors were willing to overlook that PTC's drug, ataluren, had failed to show statistically significant improvement in subjects' walking ability in a clinical trial three years earlier. Prosensa soon followed with its own IPO, raising \$90 million, even though it hadn't yet reported results from its main ongoing clinical study. In July, Sarepta added to the bullishness by announcing that the FDA had provided guidance that it was open to considering eteplirsen for regulatory approval. (The agency routinely communicates with companies as they move toward a "new drug application.")

"It felt like a lot of good stuff was coming together," Leffler recalls.

Then the bubble burst. In September 2013, only three months after its IPO, the Prosensa-GSK trial in which Aidan was enrolled failed to show meaningful improvement on the six-minute walk test. The study was shut down, and Prosensa's stock plummeted 70 percent in a day. "No one called us," says Leffler. "We learned that the trial was over from a GSK investor conference call. . . There's no safety net. You just crash." London-based GSK and Prosensa later terminated their partnership.

More bad news followed in November. After encouraging Sarepta to apply for approval of eteplirsen, the FDA reversed itself and called such a move "premature." Explaining its turnaround, the agency cited Prosensa's and PTC's trial failures. The FDA expressed "considerable doubt" that dystrophin production—the goal set out by all three companies—could be linked to meaningful clinical benefits. Sarepta's stock fell 64 percent that day.

The Lefflers received word about the FDA about-face on Sarepta while at Walt Disney World on a vacation with Aidan and his younger brother and sister. After the Prosensa-GSK trial failure, "it was a double blow," Mindy says. "I felt like I couldn't breathe."

After collecting herself, Leffler decided to fight. She'd already been communicating with two other moms she'd met via Facebook and at Duchenne conferences: McNary, who had the exquisitely painful situation of one son doing well in the Sarepta trial while his older brother, denied the drug, declined, and Christine McSherry, whose son, Jeti, then a wheelchair-bound high school senior, struggled to sit up straight.

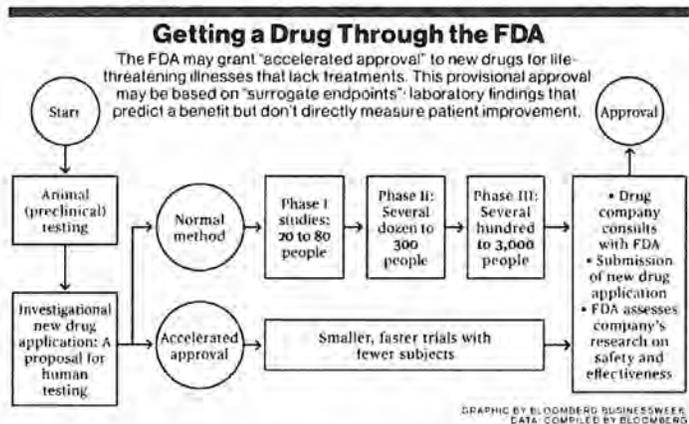
"The three of us, the 'Three Musketeers,' had a lot of the same questions," McSherry says. Why had Prosensa's and PTC's setbacks influenced the FDA to shun Sarepta? After all, the companies used different types of chemistry. The moms also didn't understand why the incipient scientific consensus on the importance of dystrophin production had suddenly become clouded. "We began to realize that the FDA was confused," says McSherry, a former nurse who is now 49. "Eteplirsen, a drug that appeared to work, was in danger of becoming a victim to the shortcomings of other drugs and other trials."

The moms had begun in 2012 demanding personal attention from FDA officials. Remarkably, they got a meeting—then another, and another. In a law enacted that year, Congress instructed the FDA to entertain more flexible paths to provisional approval of rare-disease drugs. Under the aegis of that statute, the trio became self-appointed consultants at FDA headquarters in Silver Spring, Md.

McNary organized an online petition demanding "accelerated approval" of eteplirsen. The 2012 FDA reform statute encouraged the agency to grant accelerated approval based on relatively small trials that achieve a "surrogate" goal—such as dystrophin production—with the burden left on the manufacturer to conduct broader research. The FDA can rescind accelerated approval if follow-up studies don't demonstrate efficacy. McNary swiftly gathered 180,000 signatures for her petition, and she and other moms bombarded the FDA with tweets, Instagrams, and YouTube videos showing boys in Sarepta's 12-person trial climbing rocks, dancing, and diving into swimming pools.

McNary's heart-rending tale became a centerpiece of the lobbying campaign. "I could possibly be the mother of the last child to die from Duchenne and first child to survive it," she said in a video that zinged around the Internet.

Following its standard policy, the FDA didn't respond publicly to the lobbying drive. But the agency's ambivalent reactions could be discerned from private communication with the three moms, who used blogs and websites to report on the back-and-forth. According to the moms, senior FDA leaders sought to reassure the Duchenne parents, while rank-and-file staff members tended to express more skepticism.



In July 2013, McSherry recounted on her blog a conference call with Janet Woodcock, the director of the FDA's Center for Drug Evaluation and Research. "As always, Dr. Woodcock was warm, compassionate, and extraordinarily supportive of our position," McSherry wrote. "We are one step closer to getting this drug [eteplirsen] to our boys."

Four months later, though, evaluators working under Woodcock's supervision told Sarepta not to bother applying for approval. Asked for comment, Sandy Walsh, an FDA spokeswoman, says: "Under the law, we are not able to discuss any investigational new drug or any drug application." She adds that the agency "has been working with Sarepta to provide guidance on various clinical and regulatory issues related to eteplirsen."

In February 2014, the three moms joined forces with a fourth, Tracy Seckler, to ratchet up the pressure on the FDA by organizing a two-day summit in Washington that included a visit to the agency by several leading Duchenne researchers. The next day, a bipartisan briefing on Capitol Hill sponsored by Representatives William Keating (D-Mass.) and Spencer Bachus (R-Ala.) drew an audience of dozens of congressional staff members.

Louis Kunkel, the Harvard Medical School professor who headed the team that isolated the dystrophin gene in 1986, told the gathering that boys receiving eteplirsen were making dystrophin and called this success "amazing." Steve Wilton, a leading neuromuscular researcher from Australia, was even more emphatic about eteplirsen's promise. "In Australia," he told attendees, "we'd say it's bleeding obvious."

Leffler added the moms' sense of impatience: "The FDA," she said, "is standing in the way." Not so, says the agency's Walsh: "The FDA is fully committed to make safe and effective drugs available for patients with Duchenne as soon as possible and is actively engaged with all drug companies developing new drugs for Duchenne."

Notably absent from the Washington event was Furlong. She'd held her own Washington round table two months earlier, one that was far more deferential to the FDA's authority.

In an interview, Furlong, 68, says she was traveling on business in Europe at the time of the February summit and sent a representative from her organization. She decries what she describes as a splintering of "the Duchenne community" she has spent two decades building. Now a stateswoman rather than a firebrand, she criticizes younger mothers such as McNary, 34, who publicly describe their sons as dying. "What must those boys think?" she asks. More broadly, she adds, "It's just not smart strategy to chain yourself to the gates of the FDA in protest," an allusion to a tactic once used by AIDS activists.

While the more aggressive Duchenne moms haven't actually chained themselves to anything, their tone at times is abrasive. In March 2014, McNary appeared on John Stossel's government-bashing Fox Business News television show. A subscript running across the screen morphed from "Government Medicine Bullies" to "FDA Regulations Can Kill!" Stossel asked McNary whether her son Austin is "angry" because he couldn't get eteplirsen.

"Fifteen-year-olds in general are angry," McNary responded. "Fifteen-year-olds who are being betrayed by their government are even angrier." Stossel's other guest, Darcy Olsen of the libertarian Goldwater Institute, added: "What the FDA is doing here is an abomination."

In April, without public explanation, the FDA once again reversed its position on eteplirsen, saying Sarepta could move ahead toward regulatory approval. Given the absence of new data, the only plausible reason for the switch was escalating pressure from the three moms and their backers. Five months after rebuffing Sarepta, the FDA laid out a detailed "path forward" for eteplirsen to receive accelerated approval.

The agency's revised guidance—conveyed privately to Sarepta, then disclosed by the company—stressed government evaluators' continuing uneasiness regarding the data on eteplirsen. The company would have to conduct larger placebo-controlled studies before provisional approval would become permanent. Still, a closed door had cracked open.

Sarepta immediately said it would seek accelerated authorization by the end of 2014 and launch confirmatory studies. From April 17 to April 22, the company's stock rose 59 percent.

In June, the regulatory door opened further. Prosensa announced that the FDA would entertain an accelerated-approval application for drisapersen, even though the Dutch company's drug had failed its main clinical trial in 2013. Regulators' sudden receptivity struck some observers as peculiar, given the lack of fresh evidence of effectiveness. "It sure looks like the FDA wants to give itself cover and say, 'See, we're giving everyone a chance to apply, so parents, stop attacking us,'" says Steve Brozak, president of WBB Securities and a longtime analyst of the biotech industry.

Prosensa's CEO, Hans Schikan, disagrees with Brozak. The unsuccessful 2013 study was devised and run by GSK, he says. "Based on our reanalysis of our data, we strongly believe it was the trial that failed the drug, not the drug that failed the trial." Flaws in GSK's study design, he claims, muddied the results.

Adding yet another level of ambiguity to the situation, PTC, which had seemed out of the running for a Duchenne treatment, has reentered the race. "We shot ourselves in the foot" by conceding defeat after the failed 2010 ataluren trial, says Stuart Peltz, PTC's co-founder and chief executive. After reanalysis of its data, PTC concluded its drug actually works. "In biotech, you're building the airplane while you're trying to fly it at the same time," Peltz continues. "It took us a while to realize that when you focus on the boys with the most severe symptoms, ataluren does show a robust efficacy." In August the European Union's equivalent to the FDA granted conditional approval to ataluren, and PTC is beginning to sell the drug in Europe. After completing more clinical trials, Peltz says, his company will apply for full approval in Europe, the U.S., and elsewhere.

Furlong has faith the FDA will sort out which Duchenne drugs are effective. "Ideally," she says, "we'd like to see all of the drug candidates move forward in the regulatory process."

The three moms, in contrast, say the FDA's one-step-back, one-step-forward routine has them feeling unnerved, not reassured. "The boys on eteplirsen are walking when the natural history of the disease says that they should be in wheelchairs," says Leffler. Why, she wants to know, don't industry and government cooperate to get as many boys on eteplirsen as quickly as possible?

"That's not the way medical science works," says Hoffman, the Duchenne researcher at Children's National Medical Center. The FDA, Hoffman continues, "is doing the best it can, moving cautiously and looking skeptically at Sarepta's data, and all of the data from all of the companies." On Oct. 27, Sarepta announced that as a result of a new round of FDA data requests, the company would have to postpone its application for approval of eteplirsen until mid-2015. Hoffman, who for years has had a close working relationship with Furlong and her organization, expresses sympathy for moms like Leffler, McNary, and McSherry who are impatient for faster action. "They must mean well—their boys are sick," he says, "but their pressure tactics on the FDA seem like bullying more than anything else."

Leffler, 42, doesn't care anymore what anyone calls her tactics. Her determination to get Aidan on eteplirsen became more urgent in August when he fell and fractured the femur in his left leg while kicking a ball in the backyard. Doctors told Aidan's parents he had a 50-50 chance of ever getting back on his feet. He had surgery the next day to have a steel rod placed in his leg. Two weeks later, to his doctors' surprise, but not his parents', he started hobbling around with a walker. With some effort, he can even get in and out of the family minivan more or less on his own. "He's an amazing kid," Leffler says.

Soccer, even in modified form, is probably over forever. Aidan, now in sixth grade, has redoubled his attention to big cats. He's writing fundraising letters and passing along the money to a conservation group called Panthera.

He's not oblivious to his medical predicament. If anything, he's growing more worried. The other day, Leffler found a piece of paper in her bathroom with a question written in Aidan's neat block letters: "Does muscular dystrophy make you die sooner?"



Barrett is an assistant managing editor and senior writer at *Bloomberg Businessweek*. His new book, *Law of the Jungle*, tells the story of the Chevron oil pollution case in Ecuador.

SPONSOR CONTENT

From: [Hamburg, Margaret](#)
To: "(b) (6) [redacted].net"
Subject: Fw: HHS position
Date: Friday, October 17, 2014 10:32:43 PM
Attachments: [HHSpositiondraftEVDTherapies v2.docx](#)

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

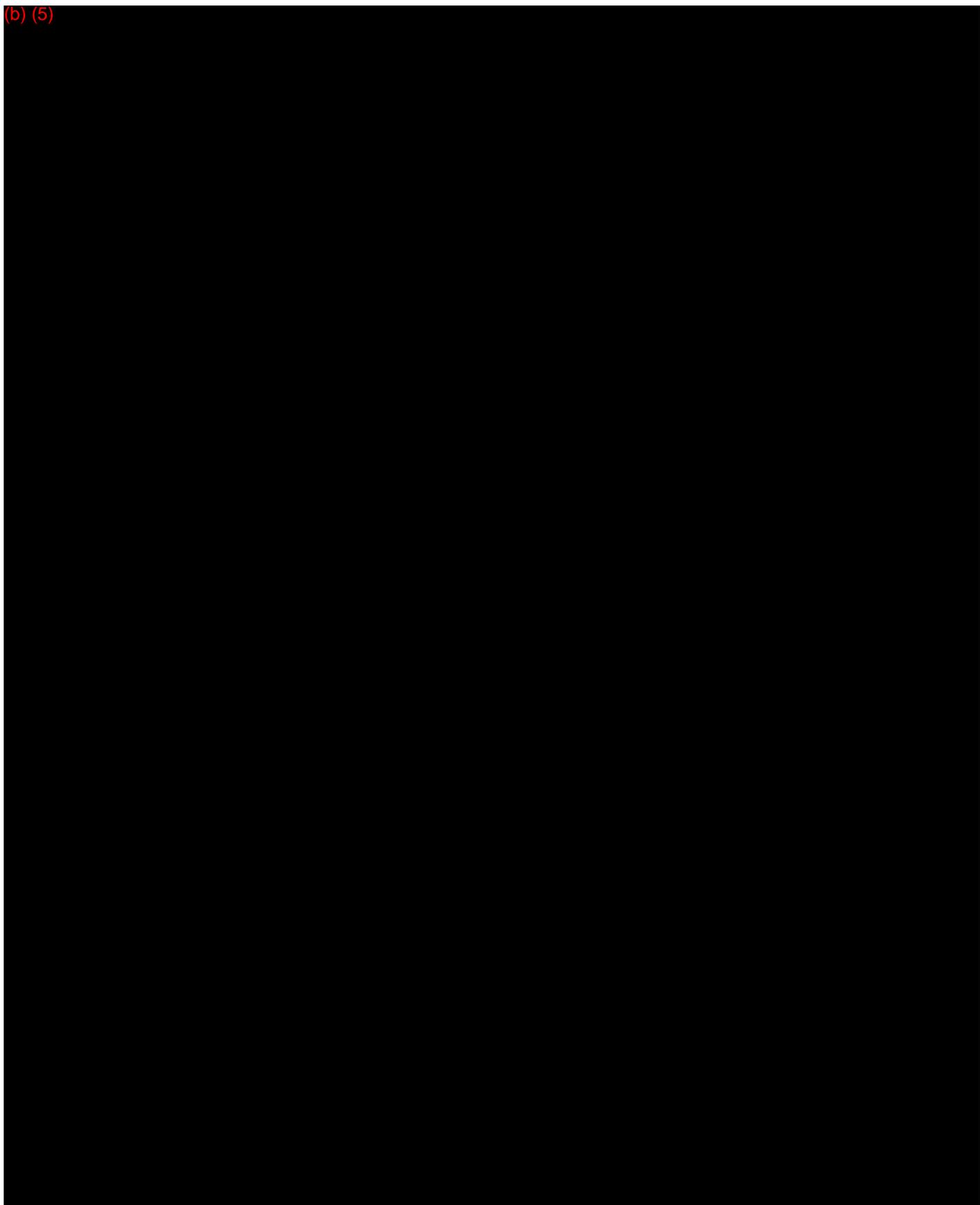
From: Borio, Luciana
Sent: Friday, October 17, 2014 10:08 PM
To: Hamburg, Margaret
Subject: HHS position

Hi Peggy – here is the position paper that Nicki asked me to pen. Ed Cox and NIH (Rick Davey and Cliff Lane) all drafted/edited.

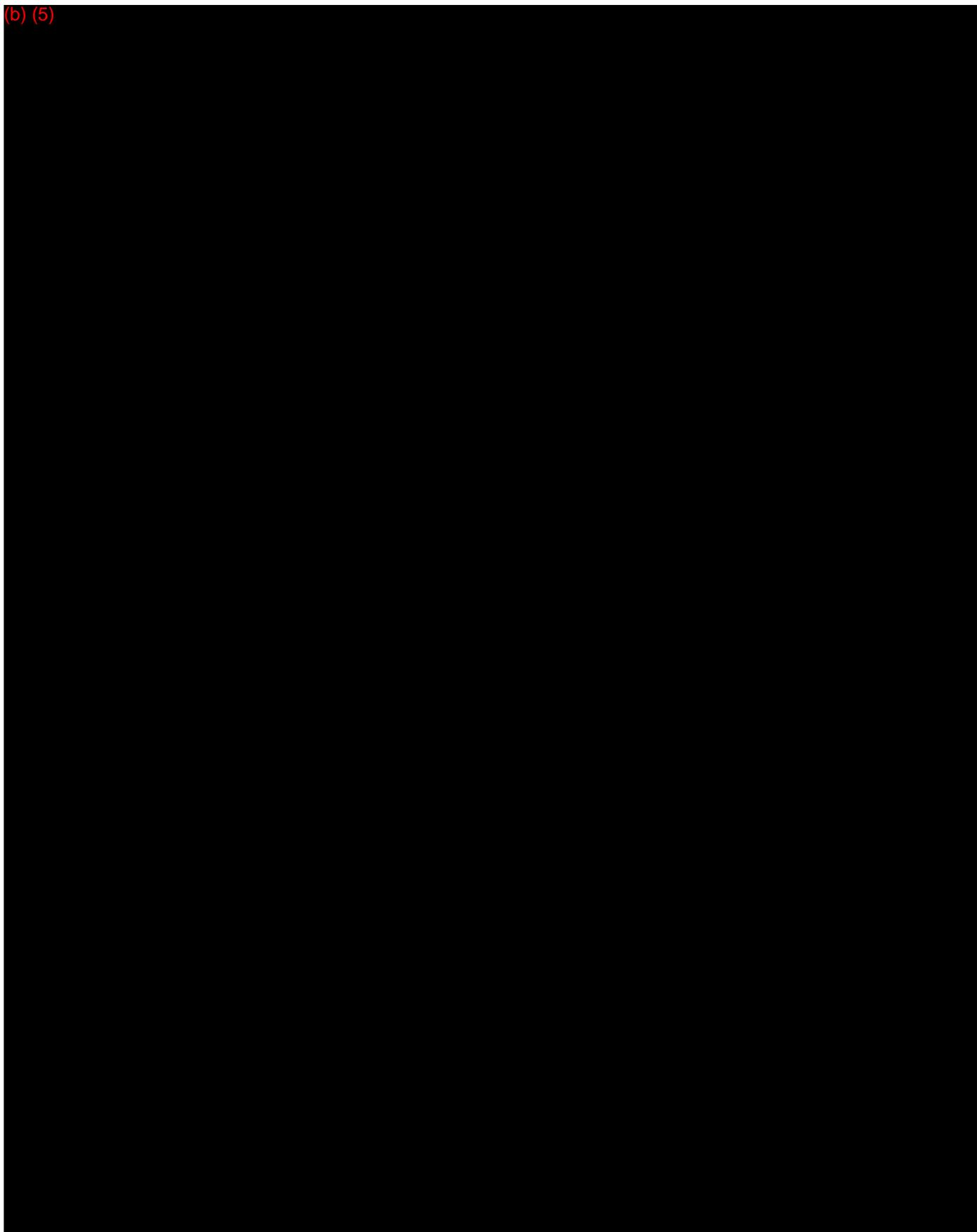
Looks good.

Hope you like it.

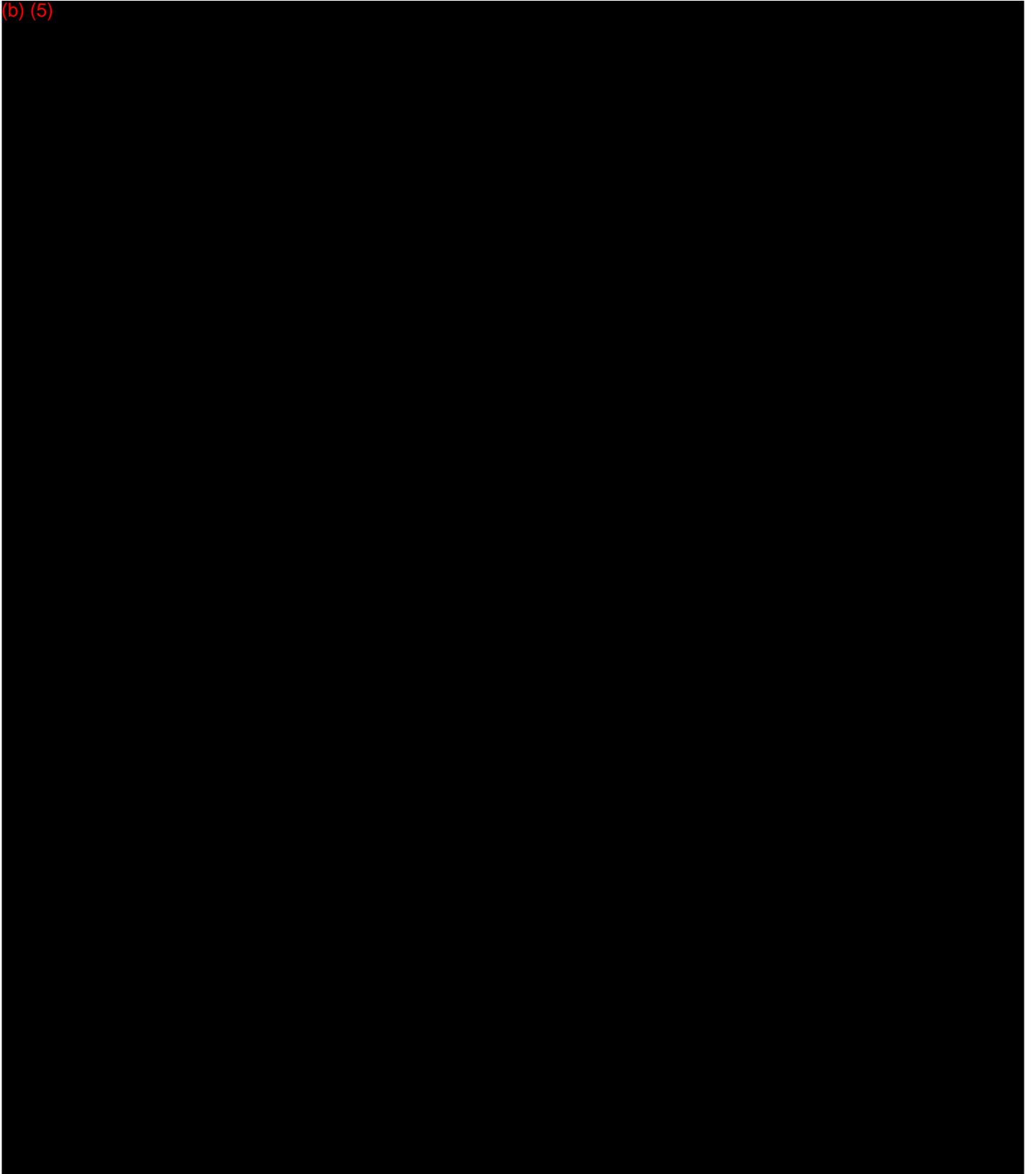
(b) (5)



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From: [Hamburg, Margaret](#)
To: [Pennington, Caitlin](#)
Subject: Fw: Useful information: WHO Consultation on potential Ebola therapies and vaccines, 4-5 September, Starling Hotel Geneva
Date: Tuesday, September 02, 2014 7:36:52 AM
Attachments: [Agenda Consultation potential Ebola therapies 4-5 September WHO web.docx](#)
[LOP Consultation potential Ebola therapies 4-5 September WHO web.docx](#)

Print

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

From: Borio, Luciana
Sent: Monday, September 01, 2014 08:44 PM
To: Hamburg, Margaret
Cc: Barclay, Lisa
Subject: FW: Useful information: WHO Consultation on potential Ebola therapies and vaccines, 4-5 September, Starling Hotel Geneva

FYI. Lot's of people...

From: SPARROW, Erin Grace [mailto:sparrowe@who.int]
Sent: Monday, September 01, 2014 4:11 PM
Cc: ebola2014archive
Subject: Useful information: WHO Consultation on potential Ebola therapies and vaccines, 4-5 September, Starling Hotel Geneva

Dear All,

Please find attached the latest agenda and list of participants for the upcoming meeting on 4-5 September 2014.

Please be reminded that the meeting will take place at the Starling Hotel in Geneva, Route François-Peyrot 34, 1218 le Grand-Saconnex, Geneva (<http://www.shgeneva.com/>). When traveling to and from the airport, the hotel offers a free complimentary limousine service every 15 minutes. For those of you coming from abroad, the hotel will offer you a free transport card for the duration of your stay which can be used on all public transport in the Geneva area.

Soon, we will be sharing some background documents with you in advance of the meeting (also available in hardcopy during registration). In addition, we will be sending you a short questionnaire to be completed and handed in at the meeting.

The meeting room at the Starling Hotel is called "Montana" and registration will start outside this room from 08:00 on Thursday morning, the meeting will begin promptly at 09:00.

Please do not hesitate to contact me should you require further information.

Many thanks,
Erin
[Ms Erin Sparrow](#)

Technical Officer
Technology Transfer Initiative (TTi)
Public Health Innovation and Intellectual Property (PHI)
Department of Essential Medicines and Health Products (EMP)
World Health Organization
Office 3032, Avenue Appia 20, 1211 Geneva, Switzerland
Email: sparrowe@who.int | Tel: +41 22 791 12 38 | Fax: +41 22 791 49 09
www.who.int/phi/programme_technology_transfer

**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel**

Background:

In response to the outbreak of Ebola in West Africa, on 11 August 2014, WHO convened a panel of medical ethicists, scientific experts, and lay people from the affected countries to consider and assess the ethical implications for clinical decision-making of the potential use of unapproved interventions. In the particular circumstances of this outbreak, and provided certain conditions are met, the panel reached consensus that it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention.

Purpose:

This meeting is being organized to discuss lead experimental treatments and vaccines for Ebola (including potential risks and benefits, availability in the short and long term, potential use and barriers for use) and key considerations for deployment in West Africa, clinical testing, use, ethics, regulation and data collection.

Objectives:

- To discuss needs in West Africa and other countries
- To discuss information on lead experimental products including:
 - Potential risks and benefits
 - Overview of product development (preclinical studies, clinical studies conducted or planned)
 - Product availability in the short and longer term
 - Considerations for use in different individuals/groups
- To discuss key issues to be taken into considerations for decision making:
 - Deployment issues
 - Regulatory issues
 - Ethical issues
 - Product availability issues
 - Liability issues
 - Financing issues (donation, procurement)
 - Data collection, product evaluation issues and clinical trials where appropriate
 - Communication issues
- To review strategies for deployment

Expected outcomes:

- Accurate information on experimental products disseminated
- Consensus on key issues to take into consideration for decision making
- Data gathering issues and sharing mechanisms identified
- NRAs informed of regulatory status of products and contacts made between countries and manufacturers



**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

Draft Agenda

Rapporteur: David Fitzsimons

Thursday 4 September

08:00-09:00 **Registration**

Session Chair: Anarfi Asamoah-Baah

09:00-09:15 Welcome, objectives of meeting, expected outcomes, Marie-Paule Kieny

09:15-09:45 General introduction/background to Ebola epidemic etc., Sylvie Briand

09:45-10:15 Presentation by Ebola expert, Amadou Sall

10:15-10:45 **Coffee**

10:45-12:30 Country perspectives

- Sierra Leone, (TBD)
- Nigeria, Abdulsalami Nasidi
- Canada, Theresa Tam
- Switzerland, Daniel Koch
- Other (TBD)

12:30-14:00 **Lunch**

14:00-15:30 Presentation on overview of lead experimental products and product specific considerations, Michael Kurilla

- Immunoglobulins
- Immune modulators
- Small molecule drugs
- Vaccines

15:30-16:00 **Coffee**

Session Chair: Marie-Paule Kieny

16:00-16:30 Presentations of key considerations for decision makers, Fred Hayden

16:30-17:30 Overview of ethical issues for consideration and presentation of ethical frameworks, Oyewale Tomori

17:30-18:00 Discussion

18:00-18:15 Wrap up of day 1

18:30 **Cocktail reception**



**World Health
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**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

Friday 5 September

Session Chair: Oyewale Tomori

09:00-09:30 Overview of regulatory issues for consideration, Helen Byomire Ndagije

09:30-10:00 Discussion

10:00-10:30 Overview of practical issues for consideration, Armand Sprecher

10:30-11:00 Discussion

11:00-11:30 *Coffee*

11:30-12:00 Overview of issues for risk mitigation and management, Ambrose Isah

12:00-12:30 Discussion

12:30-14:00 *Lunch*

Session Chair: Jeremy Farrar

14:00-15:30 Structured discussion

1. *What should be the overall OBJECTIVES of a plan for the evaluation and use of potential interventions (therapies and vaccines)?*
2. *What are the most important ACTIONS to ensure successful evaluation and use (if appropriate) of any of potential interventions (therapies and vaccines)?*
3. *What kind of SUPPORT is required to ensure proposed plans for the evaluation and use of potential interventions (therapies and vaccines) are successfully implemented?*

15:30-16:00 *Coffee*

16:00-16:30 Preparedness for prophylaxis and therapeutics for future epidemics

16:30-17:00 Wrap up, next steps, meeting closure

**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel**

List of participants:

1. Dr Marylyn Addo, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
2. Dr Clement Adebamowo, Chairman, National Health Research Ethics Committee of Nigeria, Federal Ministry of Health of Nigeria, Abuja, Nigeria
3. Dr Selidji Agnandji, Gabon
4. Dr Umberto d'Alessandro Director, MRC Laboratories, The Gambia
5. Dr Enrica Alteri, Head of Safety and Efficacy of Medicines, Human Medicines Development and Evaluation Unit, European Medicines Agency, United Kingdom
6. Dr Sylvain Baize, Biology of viral Emerging Infections, Institute Pasteur, France
7. Dr Younoussa Ballo, Secrétaire général du Ministère de la Santé, Guinea
8. Dr Ripley Ballou, GlaxoSmithKline Biologicals SA, Rixensart, Belgium
9. Ms. Helia Baradarani, Tekmira's Manager of Medical Countermeasure Business Development
10. Dr Jarbas Barbosa, Vice Minister, Ministry of Health Brazil
11. Dr Daniel Bausch, Associate Professor, Department of Tropical Medicine, Tulane University School of Public Health and Tropical Medicine, New Orleans, USA
12. Dr Sina Bavari, CIV USARMY MEDCOM USAMRIID, USA
13. Dr Stephan Becker, Direktor, Institut für Virologie, Marburg, Germany
14. Dr Fred Binka, Vice Chancellor of the University of Health and Allied Sciences, Ho, Ghana
15. Dr Fatorma Bolay, Director of the Liberia Institute for Biomedical Research, Liberia
16. Dr Luciana Borio, Director of the Office of Counterterrorism and Emerging Threats (OCET) in the Office of the Chief Scientist, U.S. Food and Drug Administration (FDA), USA
17. Dr Abdullah Brooks, Centre for Health and Population Research, Dhaka, Bangladesh
18. Dr Philippe Calain, Unité de Recherche sur les Enjeux et Pratiques Humanitaires (UREPH), Médecins Sans Frontières, Geneva, Switzerland

**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

19. Dr Michael Callahan, Command Physician, Rescue Medicine/Réseau Médical Patient Filovirus, Kinsasha, Harvard Medical School, Massachusetts General Hospital, Boston,, USA
20. Dr Benoit Callendret, Crucell, The Netherlands
21. Dr Iris Chang, Hong Kong Academy of Pharmacy, Hong Kong
22. Dr George Christopher, Chief Medical Officer, Joint Project Manager – Medical Countermeasure Systems, Department of Defense
23. Dr Supamit Chunsuttiwat, Ministry of Health, Thailand
24. Dr Jacob Cohn, Bavarian-Nordic, Denmark
25. Dr Christoph Conrad, Paul-Ehrlich-Institut, Germany
26. Mr Stephan Cook, Vice President, Vaccine Global Regulatory Affairs, Vaccine Value & Health Science, GlaxoSmithKline Biologicals SA, Rixensart, Belgium
27. Dr Marion Danis, Head, Sect. on Ethics & Health Policy (NIH), USA
28. Prof Jean-François Delfraissy,, Director of Agence nationale de recherche (ANRS), France
29. Dr Antal Tal Dia, NITAG Senegal chairman, Senegal
30. Dr Alpha Amadou Diallo, rapporteur du Comité national d’Ethique et de recherche en Santé, Guinea
31. Dr Mireille Dosso, Directrice de l'IP de Cote d'Ivoire
32. Pr Ousmane Doumbia, Secrétaire Général du Ministère de la Santé et del'Hygiène Publique, Mali
33. Dr Karifa Douno, Chef de la Division Etablissements Biopharmaceutiques, Ministère de la Santé, Guinea
34. Dr Mattias Egger, Professor of Epidemiology and Public Health, University of Bern, Switzerland
35. Dr Lindsay Elmgren, Director, Centre for Biologics Evaluation, Biologics and Genetic Therapies Directorate, Health Canada, Canada
36. Dr Carol Epstein, MediVector, Inc. Fujifilm Pharmaceuticals USA, Inc., Boston, USA
37. Dr Jeremy Farrar, Director, Wellcome Trust, UK
38. Dr Patricia Fast, International AIDS Vaccine Initiative, New York, USA



**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

39. Dr Eleanor Fish, University of Toronto, Canada
40. Mr David Fitzsimmons, Meeting Rapporteur
41. Prof. Fu Gao, Deputy Director General for sciences, China CDC, China
42. Jennifer Gibson, Director, Joint Centre for Bioethics, Director, World Health Organization Collaborating Centre for Bioethics, Associate Professor, Institute of Health Policy, Management & Evaluation, University of Toronto, Canada
43. Dr Jesse Goodman, George Town University, USA
44. Dr Dennis Giesing, MediVector, Inc. Fujifilm Pharmaceuticals USA, Inc., Boston, USA
45. Dr Barney Graham, Vaccine Research Centre, NIAID, NIH, USA
46. Dr Nyankoye Haba, National Blood Service, Guinea
47. Dr Fred Hayden, University of Virginia/WHO consultant, USA
48. Dr Lisa Hensley, NIH NIAID, USA
49. Dr Elizabeth Higgs, Global Health Science Advisor, Office of the Director, Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, USA
50. Dr David Hone, Chief, Vaccine Branch, Research and Development Directorate (J9), Defense Threat Reduction Agency DTRA, DoD, USA
51. Dr Johan van Hoof, Crucell, The Netherlands
52. Dr Peter Horby, University of Oxford, UK
53. Dr Ryuichi Ida, Member of the Expert Panel on Bioethics (National Bioethics Committee), Japan
54. Dr Giuseppe Ippolito, Scientific Director, National Institute for, Infectious Diseases Lazzaro Spallanzani, Rome, Italy
55. Dr Ambrose Isah, GACVS representative, Nigeria
56. Dr Aikichi Iwamoto, The Institute of Medical Sciences, Research Center for Asian Infectious Diseases, Japan
57. Dr Amandua Jacinto, Commissioner Clinical Services, Ministry of Health, Uganda
58. Mr Wiltshire Johnson, Registrar, Pharmacy Board, Sierra Leone



**World Health
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**Consultation on potential Ebola therapies and vaccines
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Geneva, Starling Hotel, Room Montana**

59. Dr Franca Jones, Medical Director, Chemical and Biological Defense Program Office of the Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs OASD(NCB/CB) Washington, DC, USA
60. Dr Markieu Jenneh-Kaira, Chief Pharmacist/ Registrar, National Pharmaceutical Services, Department of State for Health and Social Welfare, Ministry of Health and Social Welfare, Banjul, Gambia
61. Dr Robinah Kaitiritimba, Uganda National Health Consumers' Organisation (UNHCO), Kampala Uganda
62. Dr Francis N. Kateh, Medical Director / CEO, Jackson F. Doe Memorial Regional Referral Hospital, Tappita City, Lower Nimba County, Liberia
63. Dr Samuel Kargbo, Director, Reproductive and Child Health, Ministry of Health Sierra Leone
64. Dr Christopher Karp, Deputy Director, Discovery & Translational Sciences, Bill & Melinda Gates Foundation, Seattle, USA
65. Dr Steve Kern, Deputy Director, Integrated Development, Bill & Melinda Gates Foundation, Seattle, USA
66. Dr Nadia Khelef, Institut Pasteur, France
67. Dr Gary Kobinger, Public Health Agency of Canada
68. Dr Daniel Koch, Federal Office of Public Health, Bern, Switzerland
69. Dr Kader Kondé, Prèsident de la Commission Recherche Ébola, Guinée
70. Dr Bocar Kouyate, Office of the Minister of Health, Ministry of Health, Ouagadougou, Burkina Faso
71. Dr Sanjeev Krishna, London, UK
72. Dr Michael Kurilla, Director, Office of BioDefense, Research Resources, and Translational Research, Associate Director for BioDefense Product Development, DMID, NIAID, NIH, DHHS, Rockville, USA
73. Dr Randall Lanier, Executive Director of Biology, Chimerix Inc. Durham, USA
74. Dr James Lawler, Director, ACESO / clinical research partner in Uganda
75. Dr Robert Lenk, MediVector, Inc. Fujifilm Pharmaceuticals USA, Inc., Boston, USA

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76. Dr Bertand Lepine, FabEntech, Lyon, France
77. Dr Mike Levine, Director, Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, USA
78. Dr Nicole Lurie, Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS), USA
79. Dr Ian MacLachlan, Executive Vice President & Chief Technical Officer, Tekmira Pharmaceuticals Corp., Canada
80. Dr Alan Magill, Director, Malaria, Bill & Melinda Gates Foundation, Seattle, USA
81. Prof. Denis Malvy, Professor in Infectious Diseases, France
82. Dr Brian K. Martin, Director, Infectious Disease Division, BioProtection Systems, a wholly-owned subsidiary of NewLink Genetics, Ames, USA
83. Dr Jacques-François Martin, Fab Entech, Lyon, France
84. Dr Eric Mast, CDC Deputy Director Science and Research, USA
85. Dr Gisele Mbuyi, Department of Disease Control, Ministry of Health, DRC
86. Dr Jeffrey N. Meshulam, President, Profectus BioSciences, Inc., USA
87. Dr Philip Minor, NIBSC, UK
88. Ms Viviana Munoz, Manager of the Innovation and Access to Knowledge Programme at the South Centre, Geneva, Switzerland
89. Prof. Jean-Jacques Muyembe, National Institute for Biological Research, DRC
90. Dr Abdulsalami Nasidi, CDC Nigeria
91. Dr Helen Byomire Ndagije, Head of the Drug Information Department in the Ugandan National Drug Authority (NDA), Uganda
92. Dr Mariane Ngoulla, Special Adviser on Health to ECOWAS President, Nigeria
93. Dr Sérgio Nishioka, clinical expert, Brazil
94. Prof. Cheikh Niang, Anthropologist, Cheikh Anta Diop University, Senegal

**Consultation on potential Ebola therapies and vaccines
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95. Dr Dieudonné Nkoghe, Ministère de la Santé Publique, Centre International de Recherches Médicales de Franceville, Gabon
96. Dr Jeanne Novak, Principal, CBR International, Mapp Biopharmaceutical, Inc., USA
97. Dr Jean-Marc Olive, Scientific Researcher, French National Centre for Scientific Research, France
98. Dr Paul Orhii, Director General, NAFDAC, Nigeria
99. Dr Olga Popova, Crucell, The Netherlands
100. Prof. Peyramond , de l'hôpital de la Croix Rouse, Lyon, France
101. Dr W. Jay Ramsey, Clinical & Regulatory Compliance Officer, NewLink Genetics, Ames, USA
102. Dr Robin Robinson, Director of BARDA, US Department of Health and Human Services, USA
103. Dr Francois Roman, GSK
104. Dr Robin Ruepp, EMA
105. Dr Leonard Ruiz, International Medical Foundation
106. Dr Amadou Sall, Institut Pasteur, Dakar, Senegal
107. Dr Mohamed Samai, Deputy Director for Research, MOH, Sierra Leone
108. Dr Sangeeta Sashikant, Third World Network, Geneva, WHO
109. Dr Manuel Schilber, HUG, Geneva, Switzerland
110. Dr Michael Schmoyer, Director, Office of Pandemics and Emerging Threats, Office of Global Affairs–International Health Action for a Healthier US, U.S. Department of Health & Human Services, USA
111. Dr Jürg Seiler, toxicologist/assessor, Switzerland
112. Dr Michael Selgelid, Director of the Centre for Human Bioethics, Monash University, Australia
113. Ms Caroline Semaille, directeur des médicaments anti-infectieux, hépato-gastroentérologie, dermatologie, et maladies métaboliques rares from agence nationale de sécurité des médicaments, France
114. Dr Moussa Seydi, Professor and chief of SMIT, Senegal

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115. Dr William P. Sheridan, Senior Vice President and Chief Medical Officer, BioCryst Pharmaceuticals Inc. USA
116. Peter Smith, Professor of Tropical Epidemiology, London School of Tropical Medicine and Hygiene, UK
117. Dr Martin De Smet, Médecins sans Frontières, Brussels, Belgium
118. Dr Malamin Sonko, Chairman The Gambian ERC, The Gambia
119. Dr Kabiné Souaré, Directeur national de la pharmacie et des Laboratoires, Ministère de la Santé, Guinea
120. Dr Samba Sow, Director General, Center for Vaccine Development-Mali (CVD-Mali), CNAM, Bamako, Mali
121. Dr Christina Spiropolou, CDC, USA
122. Dr Armand Sprecher, Médecins sans Frontières, Brussels, Belgium
123. Dr Vernon Stringer, Health Canada, Canada
124. Dr Theresa Tam, Branch Head, Health Security Infrastructure Branch, Public Health Agency of Canada Public Health Agency of Canada
125. Dr Oyewale Tomori, Professor of Virology, Redemer's University, Nigeria
126. Dr Aissatou Toure, Head of Immunology Department, Pasteur Institute, Dakar, Senegal
127. Prof. Mamadou Souncalo Traore, Directeur Général de l'Institut national de recherche en santé publique, Mali
128. Dr Ross Upshur, Director, Joint Centre for Bioethics, University of Toronto, Canada
129. Ms Laurent Vacher, Responsable R&D et Business Development, Fab Entech, Lyon, France
130. Francisca Valdivieso, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Santiago, Chile
131. Dr Johan van Griensven, Clinical Sciences Department, Institute of Tropical Medicine, Antwerp, Belgium
132. Dr Ariane Volkman, Ebola vaccine program, Bavarian Nordic, Denmark
133. Dr Jay Wang, Program Manager, Emerging Infectious Diseases Therapeutics, Joint Project Manager – Medical Countermeasure Systems, Department of Defense, USA

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134. Dr Linghang Wang, Beijing Ditan Hospital, China
135. Dr John Whitehead, Lancaster, UK
136. Dr Christopher Whitty, Director Research & Evidence and Chief Scientific Adviser, DFID, UK
137. Dr Michael Wong, Sarepta, USA
138. Dr Tom Wong, Director, Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada, Ottawa, Canada
139. Kacey Wulff, Special Assistant to the Assistant Secretary of Preparedness and Response, US Department of Health and Human Services, USA
140. Dr Larry Zeitlin, President, Mapp Biopharmaceutical, Inc, USA

WHO Secretariat

141. Dr Dicky Akanmori, Technical Officer, AF/RIN - Routine Immunization and New Vaccines, WHO AFRO, Brazzaville, The Republic of Congo
142. Dr Bruce Aylward, Assistant Director General, Polio, Emergencies and Country Collaboration (PEC), Geneva, Switzerland
143. Dr Anarfi Asamoah-Baah, Deputy Director, Geneva, Switzerland
144. Mr Christopher Bailey, Coordinator, Online Communications, DCO, Geneva, Switzerland
145. Dr Marie Charlotte Bouesseau, Service Delivery and Safety, Geneva, Switzerland
146. Dr David Brett-Major, Global Preparedness, Surveillance and Response, Geneva, Switzerland
147. Dr Sylvie Briand, Director, Pandemic and Epidemic Diseases, Geneva, Switzerland
148. Dr Margaret Chan, Director General, Geneva, Switzerland
149. Mr Alejandro Costa, Scientist, Control of Epidemic Diseases, Geneva, Switzerland
150. Dr Caroline Marie Cross, Director, Staff Health & Wellbeing Services, Geneva, Switzerland
151. Dr Philippe Duclos, Immunization, Vaccines and Biologicals, Geneva, Switzerland
152. Dr Thomas Fletcher, Infection Control and Publications, Geneva, Switzerland

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153. Dr Pierre Formenty, Scientist, Control of Epidemic Diseases, HSE, Geneva, Switzerland
154. Dr Martin Friede, Scientist, Essential Medicines and Health Products, HIS, Geneva, Switzerland
155. Dr Keji Fukuda, Assistant Director General, Health Security and Environment (HSE), Geneva Switzerland
156. Dr Gaya Gamhewage, Coordinator, Communication Capacity Building, DCO, Geneva Switzerland
157. Mr Theo Grace, Technical Officer, Essential Medicines and Health Products, HIS, Geneva, Switzerland
158. Ms Marisol Guraiib, Technical Officer, Global Health Ethics, Geneva, Switzerland
159. Ms Celine Gurry, Global Preparedness, Surveillance and Response, Geneva, Switzerland
160. Dr Margaret Harris, DCO, Geneva, Switzerland
161. Dr Ana Maria Henao Restrepo, Technical Officer, Immunization, Vaccines and Biologicals, Geneva, Switzerland
162. Dr Marie-Paule Kieny, Assistant Director General, Health Systems and Innovation (HIS), Geneva Switzerland
163. Dr Rüdiger Krech, Director, Office of the Assistant Director-General, Health Systems and Innovation, Geneva, Switzerland
164. Mr Olivier Christian Lapujade, WHO Prequalification, Essential Medicines and Health Products, HIS, Geneva, Switzerland
165. Dr André Loua, Regional Adviser, Blood Safety, Laboratories and Health Technology, WHO AFRO, Brazzaville, Republic of the Congo
166. Dr Nicola Magrini, Scientist, Essential Medicines and Health Products, HIS, Geneva, Switzerland
167. Dr Dermot Maher, Coordinator, TDR, Geneva, Switzerland
168. Mr Issa Matta, Commercial and Contractual Matters, Geneva, Switzerland
169. Ms Anne Mazur, Principal Legal Officer, Commercial and Contractual Matters, Geneva, Switzerland
170. Dr Andrew Meek, WHO Prequalification, Essential Medicines and Health Products, HIS, Geneva, Switzerland
171. Ms Lisa Menning, Technical Officer, Immunization, Vaccines and Biologicals, Geneva, Switzerland

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172. Dr Vasee Moorthy, Technical Officer, Immunization, Vaccines and Biologicals, Geneva, Switzerland
173. Dr Jean-Marie Okwo-Bele, Direction, Immunization, Vaccines and Biologicals, Geneva, Switzerland
174. Dr Ana Maria Padilla, Essential Medicines and Health Products, HSE, Geneva, Switzerland
175. Dr Shanthi Pal, Group Lead, Medicines Safety, Safety & Vigilance, Geneva, Switzerland
176. Mr James Pfitzer, Technical Officer, Essential Medicines and Health Products, HSE, Geneva, Switzerland
177. Dr Analia Porras, Medicine Unit, PAHO/AMRO, Washington DC, USA
178. Dr Andreas Reis, Technical Officer, Global Health Ethics, Geneva, Switzerland
179. Dr Carmen Rodriguez-Hernandez, WHO Prequalification, Essential Medicines and Health Products, HIS, Geneva, Switzerland
180. Dr Cathy Roth, Advisor, HSE, Geneva, Switzerland
181. Dr Carla Saenz, Bioethics advisor, PAHO/AMRO, Washington DC, USA
182. Dr Abha Saxena, Coordinator, Global Health Ethics, HIS, Geneva, Switzerland
183. Dr Nahoko Shindo, Medical Officer, Health Security and Environment (HSE), Geneva Switzerland
184. Ms Erin Sparrow, Technical Officer, Essential Medicines and Health Products, HIS, Geneva, Switzerland
185. Mr Ludy Suryantoro, External Relations Officer, HSE, Geneva, Switzerland
186. Dr Kirsten Vannice, Technical Officer, Immunization, Vaccines and Biologicals, Geneva, Switzerland
187. Dr David Wood, Coordination, Technologies Standards and Norms, HIS, Geneva, Switzerland
188. Dr Wondiyfraw Worku, WHO Prequalification, Essential Medicines and Health Products, HIS, Geneva, Switzerland
189. Dr Patrick Zuber, Medical Officer, Safety and Vigilance, HIS, Geneva, Switzerland

From: [Califf, Robert](#)
To: [Auchincloss, Kalah](#)
Cc: [Kraus, Tom](#); [Conover, Katie](#)
Subject: RE: DMD update, NIH report, 510k mods guidance
Date: Thursday, May 26, 2016 10:40:00 AM

All ok. Please send guidance

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Auchincloss, Kalah
Sent: Thursday, May 26, 2016 10:37 AM
To: Califf, Robert
Cc: Kraus, Tom; Conover, Katie
Subject: DMD update, NIH report, 510k mods guidance

Rob –

As you know the PDUFA date for the DMD drug, eteplirsen, is today. CDER is missing the date while they are continuing to consider the info and discussion from the AC. The company knows we are missing the date and has told that to the press (e.g., <http://www.businesswire.com/news/home/20160525005442/en/Sarepta-Therapeutics-Announces-FDA-Complete-Review-Eteplirsen>). Katie and CDER OComm are aware, but we don't usually say much in these situations for confidentiality reasons. Expected decision is in the "next couple of weeks", per Janet.

Also, despite our best efforts, the internal NIH review report won't be coming your way today. The review team is still revising it, and I just saw it for the first time yesterday and had some questions about the structure and way we are presenting some of the content.

Lastly, the 510k modification guidance has been cleared through Policy, OCC, CDRH. I know you had questions after the briefing a few weeks ago – I suggested that CDRH send you the latest version of the guidance with a couple of bullets on how it has changed since the briefing. Does that work for you?

Enjoy Colorado!

Kalah

Kalah Auchincloss, JD, MPH
Deputy Chief of Staff, Office of the Commissioner
Food & Drug Administration
White Oak Bldg. 1, Rm. 2220
(301) 796-0659
kalah.auchincloss@fda.hhs.gov

From: [Moran, Kristy](#)
To: [Califf, Robert](#); [Kraus, Tom](#); [Auchincloss, Kalah](#); [Sharp, Jeremy](#); [Woodcock, Janet](#); [Brown, Heather](#); [Conover, Katie](#); [Roth, Deborah](#); [Edmonds, Amanda](#); [Moran, Kristy](#)
Cc: [Ligon, Sharnell \(CDER\)](#); [Pennington, Caitlin](#); [Watson, Sharron](#); [Morris, Larry](#)
Subject: Memorandum of Meeting: OC/CDER Monthly Leadership Meeting May 18 2016
Date: Friday, May 27, 2016 12:51:53 PM
Attachments: [OC CDER Leadership Meeting Memorandum 5 18 16 FINAL.doc.docx](#)

Attached is the Memorandum of Meeting for the OC/CDER Monthly Leadership meeting held on May 18, 2016.

The next meeting is scheduled for June 15, 2016 at 10:00 am.

Kindly,
Kristy Moran
OC/Office of the Executive Secretariat

MEMORANDUM OF MEETING
OC/CDER Leadership Meeting
May 18, 2016
10:00 am – 11:00 am

Subject: Action Items from the May 2016 OC/CDER Leadership Meeting

Participants: Robert Califf, Tom Kraus (by phone), Kalah Auchincloss, Jeremy Sharp, Janet Woodcock, Heather Brown, Katie Conover, Deborah Roth, Amanda Edmonds, and Kristy Moran

Decision/Action Items:

General Updates

- Update on actions related to Dr. Stanislaw Burzynski, Burzynski Institute for Cancer Research.
- Duchenne Muscular Dystrophy (DMD) Update – On April 25, FDA’s Peripheral and Central Nervous System Drugs Advisory Committee recommended against approval of eteplirsen, Sarepta Therapeutics’ experimental drug for the treatment of DMD. The recommendation against approval is nonbinding on the Agency. FDA must make a final decision on whether to approve eteplirsen by May 26. Dr. Woodcock has not received the write-up from the Office of New Drugs yet.
Action: CDER will be extend the user fee date.
- Cystic Fibrosis – CF is a serious genetic disorder affecting the lungs and other organs that ultimately leads to an early death. It is caused by mutations in a gene that encodes for a protein called CFTR that regulates ion and water transport in the body. Kalydeco, a prescription drug for treatment of CF has been approved for 9 mutations as a single agent. Company did a trial and submitted a supplement to FDA. CDER rejected it and told the sponsor that they would need to do a trial in all mutations. Dr. Woodcock disagrees with this approach and may have to intervene and work with CDER on the approach for this action.
Action: Dr. Woodcock will work with Jeremy Sharp on a strategy.
- In general, Dr. Woodcock asked for OC support as she makes difficult public health decisions.

Patient Medication Information (PMI) Rule Update

- Dr. Woodcock has signed off on the PMI and it has been submitted to the Office of Policy to be put on the unified agenda, but it will have to go up through the all the levels outside of CDER. This will be a proposed rule.

Opioids

- Dr. Woodcock’s proposal is to put out a Federal Register notice explaining the

different approaches to mandatory REMS training and accept comments on it.
Action: Dr. Woodcock, Jeremy Sharp, and Bruce Kuhlik will work together to work on the details of the strategy.

Drug Pricing

- Theresa and economist group will take over the lead for CDER and will do some studies to have an economic foundation. CDER was considering a small working meeting (with Dr. McClellan, academics, economists, and companies) and talk about the issues and then maybe a larger meeting and publish the minutes from that meeting.

Next meeting:

Wednesday, June 15, 2016, 10:00 am – 11:00 am

Executive Secretariat Contact: Kristy Moran, 301-796-4678

From: [Califf, Robert](#)
To: [Auchincloss, Kalah](#); [Moran, Kristy](#); [Sharp, Jeremy](#); [Kraus, Tom](#)
Cc: [Varnado, Martina](#); [O'Neill, Jeff](#)
Subject: RE: Proposed CDER/OC Monthly Leadership Agenda Items for June 15
Date: Tuesday, June 07, 2016 5:05:00 PM

On opioids I'd add:

1. Are there situations we haven't considered where non-ADF opioids will appear for approval (as in "turned down for ADF labeling but recommended for approval" by advisory committee)
2. Initial thoughts on broader societal risk as part of the approval decision
3. Update on cough syrup

And, of course, hiring.....

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Auchincloss, Kalah
Sent: Tuesday, June 07, 2016 10:57 AM
To: Moran, Kristy; Califf, Robert; Sharp, Jeremy; Kraus, Tom
Cc: Varnado, Martina; O'Neill, Jeff
Subject: RE: Proposed CDER/OC Monthly Leadership Agenda Items for June 15

Not clear to me what "approve the generics list Dr. Woodcock sent" is referring to? CDER has been approving generic opioids for weeks, and giving us appropriate heads up. I would also add Sarepta/DMD Update as an agenda item (will be quick).

Rob or others – anything else you would like to discuss?

From: Moran, Kristy
Sent: Friday, June 03, 2016 8:58 AM
To: Califf, Robert; Sharp, Jeremy; Kraus, Tom; Auchincloss, Kalah
Cc: Varnado, Martina; O'Neill, Jeff
Subject: Proposed CDER/OC Monthly Leadership Agenda Items for June 15

Good morning,

Below are the suggested topics that CDER/Dr. Woodcock would like to discuss at the CDER/OC Monthly Leadership meeting scheduled for June 15. Please let me know if there additional topics that you would also like to include on the agenda to discuss.

I've also attached the discussion/action items from CDER's meeting on May 18.

CDER Proposed topics:

1. Opioids –
 - a. How are we doing?
 - b. Can we approve the generics list Dr. Woodcock sent?
 - c. Update on prescriber education activities
 - d. Next steps?
2. Generics Program
 - a. Current productivity & FTE issues
 - b. GDUFA II negotiations
3. OTC
 - a. User Fee Negotiations
 - b. Policy
4. Kalydeco Update – follow-up from last conversation
5. B. cepacia Outbreak Update – if still ongoing

Kindly,
Kristy Moran
OC/Office of the Executive Secretariat

From: [Evans, Dana](#)
To: [Califf, Robert](#)
Subject: FW: First meeting of EMA/ FDA patient engagement Cluster held today on 22 June 2016
Date: Friday, June 24, 2016 9:56:00 AM
Attachments: [FINAL-EMA-FDA Patient Engagement Cluster - Kickoff Agenda - 22 Jun 2016.doc](#)

Dana Evans, M.P.H.

Program Support Specialist to the Commissioner
Office of the Commissioner Immediate Office
U.S. Food and Drug Administration
Phone: 301-796-2021
BB: 301-467-8987
Email: dana.evans@fda.hhs.gov

From: Haubenreisser Sabine [<mailto:Sabine.Haubenreisser@ema.europa.eu>]
Sent: Wednesday, June 22, 2016 5:29 PM
To: Ball, Leslie; Prater, Donald; Valdez, Mary Lou; Bell, Tammie Jo (CDER); Moscicki, Richard; Woodcock, Janet; Temple, Robert; Kweder Sandra; Dupont, Jarilyn; Jenkins, John K; Marks, Peter; Blair, Joan W. (CBER); Badoo, Judith
Cc: OC-OIP-Europe; Laine, Susan; Sklamberg, Howard; Commissioner FDA; Ostroff, Stephen; Haubenreisser, Sabine *; Quinn, Kathleen; lisa.turner@fda.hhs.gov; Conover, Katie; Marchand, Heidi; Furia-Helms, Andrea; Mullin, Theresa; Goldsmith, Jonathan; Dal Pan, Gerald
Subject: First meeting of EMA/ FDA patient engagement Cluster held today on 22 June 2016

Dear colleagues,

I would like to inform you that we held today the first meeting of the new EMA/ FDA 'cluster' on Patient Engagement. Please see the agenda attached.

The cluster will provide a forum to share experiences and best practices on the way the two agencies involve patients in development, evaluation and post-authorisation activities related to medicines. Patients bring real-life experience, as well as specific knowledge and expertise, to scientific discussions on medicines and on the impact of regulatory decisions. The increased interaction through the new cluster will allow us to exchange information on how we engage with and involve patients in our work and on priorities and goals to scale up future engagement with patients. Areas of discussion will include the processes for selecting and preparing patients to take part in the agencies' activities, how to ensure that patients are independent and representative, and how to report on the impact of patient involvement.

The new cluster is expected to meet three to four times per year via teleconference and will be chaired jointly by FDA and EMA.

Please see the link to the news item together with the terms of reference of the new cluster that we published today on the EMA website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/06/news_detail_002554.jsp&mid=WC0b01ac058004d5c1

Please do not hesitate to contact me if you would like any more information or have any questions.

Best wishes,
Sabine

Dr Sabine Haubenreisser
EMA Liaison Official at the FDA
+1 301 796 8748

This e-mail has been scanned for all known viruses by European Medicines Agency.



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DRAFT AGENDA

Patient Engagement Cluster – EMA/FDA

Wednesday 22nd June 2016

EMA Co-Chair: Isabelle Moulon,

FDA Co-Chair: Heidi Marchand

European Medicines Agency Participants

Co-Chair : Isabelle Moulon (Head of Patients and Healthcare Professionals Department, EMA)
 Participants : Nathalie Bere, Sabine Haubenreisser, Emer Cooke, and other colleagues as reported under each topic below.

US Food & Drug Administration Participants

Co-Chair : Heidi Marchand (Assistant Commissioner, Office of Health and Constituent Affairs, Office of the Commissioner)

OC Participants : Beth Fritsch, Andrea Furia-Helms, Richard Klein, Sandra Kweder, Salina Prasad, Matthew Scherer

CDER : Billy Dunn, Jonathan Goldsmith, Theresa Mullin, Elektra Papadopoulos, John Whyte
 CBER : Wilson Bryan

Call details

Date **Wednesday 22nd June 2016**
 Time (London) / Room **15:00 to 16:30 / 5C**
 Time (Washington) / Room **10:00 to 11:30 am / Building 32, Room 3344**
 UK call-in number (London) **08 08 145 3733 or 08 08 234 9421**
 USA call-in number **+1 855 828 1770 or +1 301 796 7777**
 Meeting ID # **(b) (4)**
 Attendee ID# **N/A**

Item	Topic	Speakers	Duration
EMA/CDER TOPICS			
EMA Co-Chair: Isabelle Moulon, FDA Co-Chair: Heidi Marchand			
1.	Introduction	Sabine Haubenreisser	5 min
2.	Adoption of Priority Topics - short, medium, and long term (see attachment)	All	15 min
	Actions:		

Item	Topic	Speakers	Duration
3.	 Microsoft PowerPoint Presentation Presentations <ul style="list-style-type: none"> EMA patient involvement overview 	Nathalie Bere (EMA)	20 min
	Actions:		
4.	Hot Topics, Disease/Condition or Product-Related Sharing <ul style="list-style-type: none"> Duchenne Muscular Dystrophy <p>Background: Sarepta is seeking FDA accelerated approval for eteplirsen for patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping ($\approx 13\%$ of patients with DMD). In such patients, skipping of exon 51 might restore the reading frame of dystrophin, increase the production of dystrophin, and lead to a clinical benefit for patients. The applicant undertook three studies: two small exploratory studies to assess eteplirsen's potential to increase dystrophin expression, and a 12-patient clinical study to further assess the extent to which eteplirsen increased expression of dystrophin protein, and to explore the potential clinical benefit.</p> <p>Reference: FDA Briefing Document, Peripheral and Central Nervous System Drugs Advisory Committee Meeting, April 25, 2016</p>	FDA Overview: Richard Klein Salina Prasad Billy Dunn John Whyte EMA Overview: Nathalie Bere Isabelle Moulon	25 min
	Actions:		
5.	Upcoming Meetings: DIA Meeting, 26-30 June, Philadelphia, PA <i>EMA/FDA Question Time</i> Thursday, 30 June • 9:00 am - 10:30am Workshop on new endpoints for diabetes - Diabetes Outcome Measures Beyond Hemoglobin A1c (HbA1c) , August 29, 2016 (see attachment)	Sabine Haubenreisser (EMA)	10 min
	Actions:		
6.	Communications about the Cluster <ul style="list-style-type: none"> - news item - internal news item - lines to take Open discussion	Sabine Haubenreisser (EMA)/All	10 min
	Actions:		
7.	Schedule for next teleconferences	All	5 min
	Actions:		

Organisers: Nathalie Bere (EMA), Andrea Furia-Helms (FDA), Sabine Haubenreisser (EMA), Heidi Marchand (FDA); Isabelle Moulon (EMA)

Next scheduled teleconferences:

TBD

From: [Califf, Robert](#)
To: [Woodcock, Janet](#)
Subject: RE: eteplirsen NDA
Date: Tuesday, July 05, 2016 8:54:00 PM

Janet,

I'm here all week. I have a lunch with John J tomorrow, but I think that should be preserved for broader discussion. Th and Fri are pretty flexible as it now stands.

I want to make sure I have what is written about appeals so that I don't make an inadvertent mistake.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Woodcock, Janet
Sent: Tuesday, July 05, 2016 5:16 PM
To: Califf, Robert
Subject: Fwd: eteplirsen NDA

Would be helpful if you met w them. ASAP. Ellis also thought that the original western blot data was not real so did not expect would be facing this issue. I have been upfront with them all along. Wish someone would show some leadership. Catastrophe-predictions have been made at frequent intervals. Jw.

From: Unger, Ellis <Ellis.Unger@fda.hhs.gov>
Date: July 5, 2016 at 3:36:37 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>, Temple, Robert <Robert.Temple@fda.hhs.gov>
Subject: eteplirsen NDA

Janet,

I don't have to tell you how difficult the eteplirsen decision has been for many of us in ODE-I. As you know, we have reached different scientific conclusions on the strength of the data, and in particular, the likelihood that the small increase observed in Becker-type dystrophin is reasonably likely to predict clinical benefit. This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed "reasonably likely to predict clinical benefit." Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated.

I know that Dr. Jenkins has mentioned the possibility of involving Dr. Califf in the eteplirsen decision on at least one occasion, and I would like to request a formal appeal to the Commissioner on this matter.

I'm aware that the Commissioner's official role is to consider the administrative aspects of review decisions and not the science. But given the potential for setting a precedent here, I think he should be aware of the various points of view and consider the potential ramifications of the matter at hand.

I'm also aware that you advised Sarepta that we would be prepared to grant accelerated approval of their NDA within 4 business days of receiving their new data, but there was a provision in the letter that the increase in dystrophin had to be meaningful, and we do not have agreement on this point. Thus, it is my hope that a Commissioner Briefing can be held before an action is taken.

I have discussed the above with Dr. Jenkins, and he supports this course of action.

I propose that we reserve a few minutes at the briefing tomorrow to discuss this matter.

Thank you for your consideration,

Ellis

From: [Evans, Dana](#)
To: [Califf, Robert](#)
Subject: FW: Opinion letter on Kyndrisa
Date: Wednesday, July 06, 2016 2:58:00 PM
Attachments: [Opinion letter on Kyndrisa, May 2, 2016.pdf](#)

Dana Evans, M.P.H.

Program Support Specialist to the Commissioner
Office of the Commissioner Immediate Office
U.S. Food and Drug Administration
Phone: 301-796-2021
BB: 301-467-8987
Email: dana.evans@fda.hhs.gov

From: Dave Martin [<mailto:dave@avidbiotics.com>]
Sent: Tuesday, July 05, 2016 6:01 PM
To: Commissioner FDA
Subject: FW: Opinion letter on Kyndrisa

Rob: The "missing" letter is now attached! Dave

From: Dave Martin
Sent: Tuesday, July 5, 2016 11:06 AM
To: 'robert.califf@fda.hhs.gov' <robert.califf@fda.hhs.gov>
Subject: Opinion letter on Kyndrisa

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David W. Martin, Jr., MD
AvidBiotics Corp.
100 Kimball Way

South SF, CA 94080
650-873-1115 office

From: CDER DRUG INFO <DRUGINFO@fda.hhs.gov>
Date: May 11, 2016 at 3:12:27 PM GMT+2
To: "(b) (6) (b) (6) (b) (6) (b) (6)"
Subject: RE: Opinion letter on Kyndrisa

Dear Dr. Heyneker,

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We appreciate your thoughts and comments regarding this issue, and have forwarded your email to the appropriate CDER Review Division. They will contact you if they have questions or need additional information.

Best regards,
RL
Drug Information Specialist
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration

This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

[<ATT89150 1.jpg>](#) [<ATT69106 2.jpg>](#) [<ATT85592 3.jpg>](#)
[<ATT56925 4.jpg>](#) [<ATT27175 5.jpg>](#) [<ATT40320 6.jpg>](#)

From: Herb Heijneker [[\(mailto:\(b\) \(6\) \(b\) \(6\)\)](mailto:(b) (6) (b) (6))]
Sent: Tuesday, May 10, 2016 9:20 AM
To: CDER DRUG INFO
Cc: Dave Martin; PCNS
Subject: Fwd: Opinion letter on Kyndrisa

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Begin forwarded message:

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Subject: Opinion letter on Kyndrisa
Date: May 5, 2016 at 8:15:02 PM GMT+2
To: pcns@fda.hhs.gov
Cc: Dave Martin <dave@avidbiotics.com>

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Sincerely,

Herbert L. Heyneker, PhD (b) (6)

<Opinion letter on Kyndrisa, May 2, 2016.pdf>

Opinion letter on the effectiveness of Kyndrisa for the treatment of DMD

The FDA's rejection of Kyndrisa on January 14, 2016, was clearly a very disappointing outcome and a profoundly emotional loss for the boys affected by Duchenne's Muscular Dystrophy (DMD) and their families. Last week, on April 25, 2016, when an advisory panel for the FDA rejected Eteplirsen, the outcome must have been simply devastating for the affected families. Kyndrisa and Eteplirsen have similar, novel molecular modes of action; each partially reverses the underlying genetic defect in DMD, for which there is no FDA-approved therapy or prophylaxis. In this opinion letter, I wish to opine on the effectiveness of only Kyndrisa because of my involvement with Prosensa as a board member and scientific advisor, well before the Company was acquired by BioMarin.

Seventeen FDA advisory committee panel members voted on BioMarin's Kyndrisa NDA package, and 15 were of the opinion that the lack of statistical significance of positive results in the phase III study weakened the persuasiveness of findings. This lack of statistical significance doesn't surprise me since both the phase II and III studies were short-term studies and short-term studies should not be expected to show effectiveness for an agent which is not expected to reverse the disease and certainly not quickly.

Apparently there is not a clear understanding of Kyndrisa's mode of action, so let me explain: **Kyndrisa does not restore muscle function; it slows down deterioration of muscle fibers and muscle function.** Dystrophin, the genetically absent protein in DMD, is essential for proper muscle function. In the absence of dystrophin, muscle cells slowly atrophy in an **irreversible** process. Kyndrisa is a modified exon-skipping oligonucleotide (nucleic acid), which partially restores RNA to code for the synthesis of a partially functional dystrophin protein in DMD patients with a mutation in exon 51. In younger patients who still have residual muscle function, Kyndrisa will delay the further deterioration of those muscle cells which are still functioning. So, the younger one begins to receive treatment with Kyndrisa, the better the chances are to delay the slow

progression of his disease and maintain sufficient residual muscle function to extend the limited period of ambulation and perhaps of even cardiac function.

In effect, **Kyndrisa is prophylactic and, thus, can only be proven efficacious in a long-term study.** Luckily, BioMarin has the results of such a long-term study, namely the phase I study, DMD114673, which was presented in a poster session at the 19th International Congress of the World Muscle Society, Oct 7 - 11, 2014 in Berlin, Germany. In summary, 12 boys were enrolled in DMD114673, which started in 2008. Two boys dropped out because of lost ambulation during the extension study. They were considered to have severely declined before the start of the study; of all ambulatory subjects, they had the lowest overall baseline 6 minutes walking distance test (6MWD) results (not surprising considering Kyndrisa's mode of action). When progression of the disease in this treated group was compared with extensive historical data from untreated affected boys, the remaining 10 boys were performing significantly better, and the results after 8 years are becoming only more impressive. All 10 boys are still enrolled, which tells me that side-effects of the drug are manageable and tolerable.

(b) (4) [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] (unpublished results).

I strongly encourage the FDA to carefully examine these data one more time in light of the full understanding of the drug's mechanism of action on muscle fibers: Kyndrisa, as a prophylactic agent, will not restore muscle function. Kyndrisa delays further the slow muscle deterioration characteristic of the disease., Accordingly, supporting efficacy data can only be obtained from a long-term study. My professional conclusion is that Kyndrisa (and probably Eteplirsen) are effective drugs in delaying the lethal progression of DMD in young, ambulatory boys.

Herbert L. Heyneker, PhD.

May 2, 2016

From: [Woodcock, Janet](#)
To: [Califf, Robert](#)
Subject: two documents you might want to read before the team briefs you tomorrow, they are short.
Date: Wednesday, July 06, 2016 6:36:31 PM
Attachments: [Reasoning underlying the finding that increased dystrophin is.docx](#)
[Sarepta dct.docx](#)

One is my first draft decisional memo—written before the latest bx data arrived. Now that there is agreement that there is substantial evidence, the argument has shifted to “reasonably likely to predict clinical benefit” . That is the second document. jw

Reasoning underlying the finding that increased dystrophin is “reasonably likely” to predict clinical benefit

1. There is substantial evidence that administration of the product results in increased levels of (shortened) dystrophin protein.
2. This protein localizes to the sarcolemma as does normal dystrophin and in samples tested by immunohistology also attaches to β -dystroglycan at the cell surface to form a complex, as does normal dystrophin.
3. The mean achieved levels of dystrophin are low, at or below 1% of a normal control sample. Mean values are useful for statistical comparisons, but do not provide complete information.
4. About 50% of patients in the 180 week cohort appeared to be non-responders (as defined by little increase from baseline in dystrophin) , and % in the 48 week cohort. Unlike many drugs, the proposed mechanism of action of this drug is very clear: it is intended to result in increased dystrophin production, and if this does not occur then the patient is not expected to get a benefit from the drug. (There may be sampling error involved in using biopsies for quantifying dystrophin, the variability introduced by this is not known). The patients tested include a mixture

of a number of different exon deletions that each lead to a DMD phenotype; these mutations were postulated to be amenable to exon skipping by this drug; however, it is quite possible that there is a drug-deletion interaction such that the pharmacodynamic activity is different in different deletions, i.e., some could be non-responders.

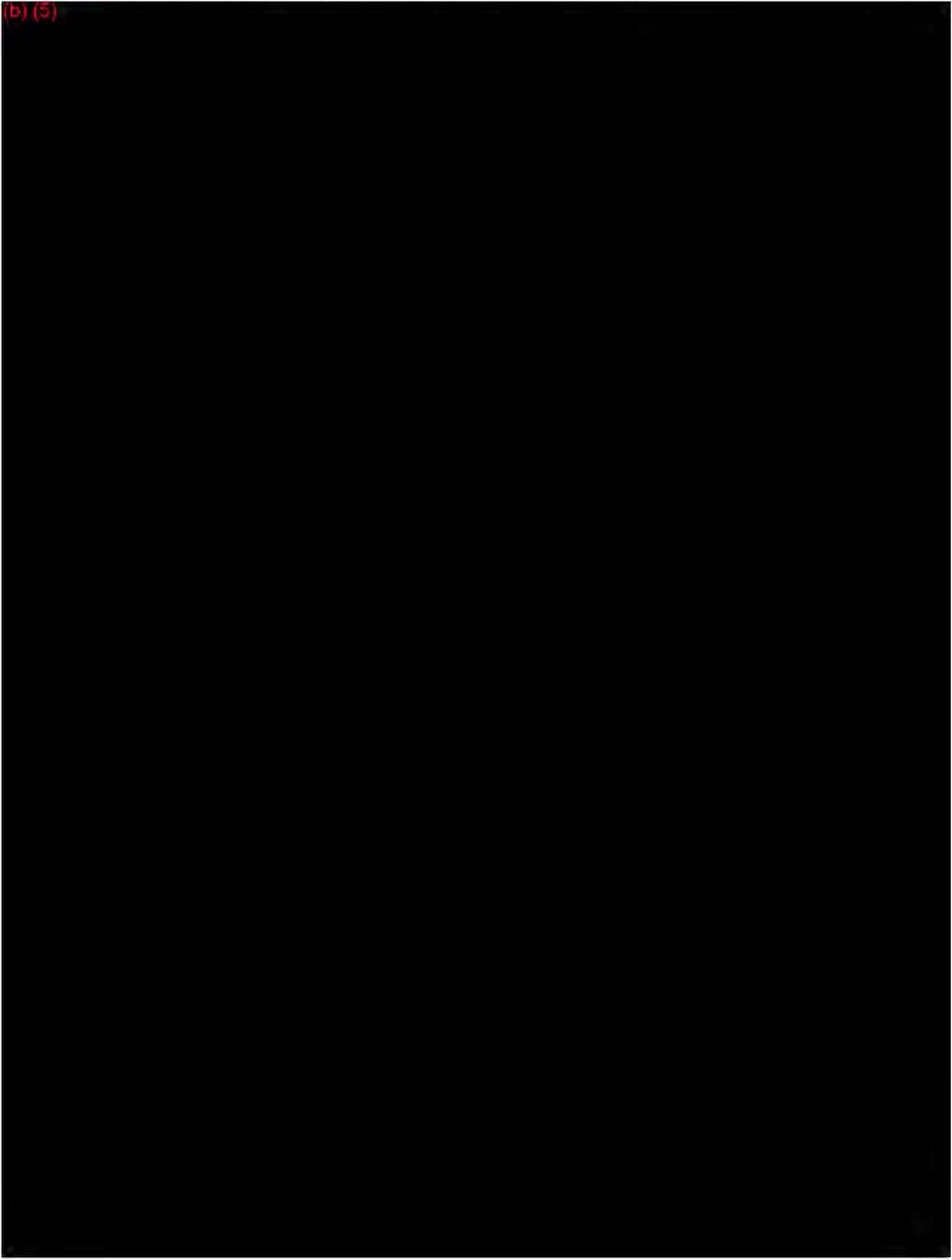
5. Responders to the drug achieved about 1-2.5% dystrophin.
6. “Becker” type muscular dystrophy (BMD), that often results from in-frame mutations, by definition has a significantly milder phenotype than DMD. Reported dystrophin levels (using different Western blot techniques from different muscle groups than the eteplirsen studies) in BMD range from 3-78% of normal levels (van den Bergen et al, J Neurol Neurosurg Psychiatry 2014; 85: 747-753). The impact of dystrophin levels on phenotype is clearly influenced by which segment of the protein is deleted, and also by other non-dystrophin-related factors. Van den Bergen et al also reported that the four patients in their study who were diagnosed as BMD but had less than 10% dystrophin clearly had a more severe disease course than the other Becker patients, implying a “grey zone” below 10% that might be milder than DMD but more severe than most BMD.

7. The protein expression-clinical response characteristics in DMD are not known. The eteplirsen drug development program initially aimed at creating a “Becker-type” level of protein, but the levels achieved by the drug are much lower than in typical BMD patients. The rigorous analytical techniques needed to confidently quantify low (DMD) levels of dystrophin and of induced dystrophin (1-2%) have only recently been deployed and so there is little information on the actual range of protein expression in untreated patients. It is not known if small differences in dystrophin levels in DMD patients result in different phenotypes, although it is clear that there is a range of severity and rate of progression within patients diagnosed as DMD. Therefore, the contention that small increases in dystrophin could not be clinically meaningful is a conjecture.
8. According to patients and family, any maintenance of muscle function in DMD is meaningful, including for example maintaining the ability to manipulate an electric wheelchair or to type.
9. The comparison to the external cohort can be criticized in many ways, due to the great underlying variability of the disease, and the fact that the data were collected for other reasons. However, I believe the data are consistent with a response in some of the treated patients.

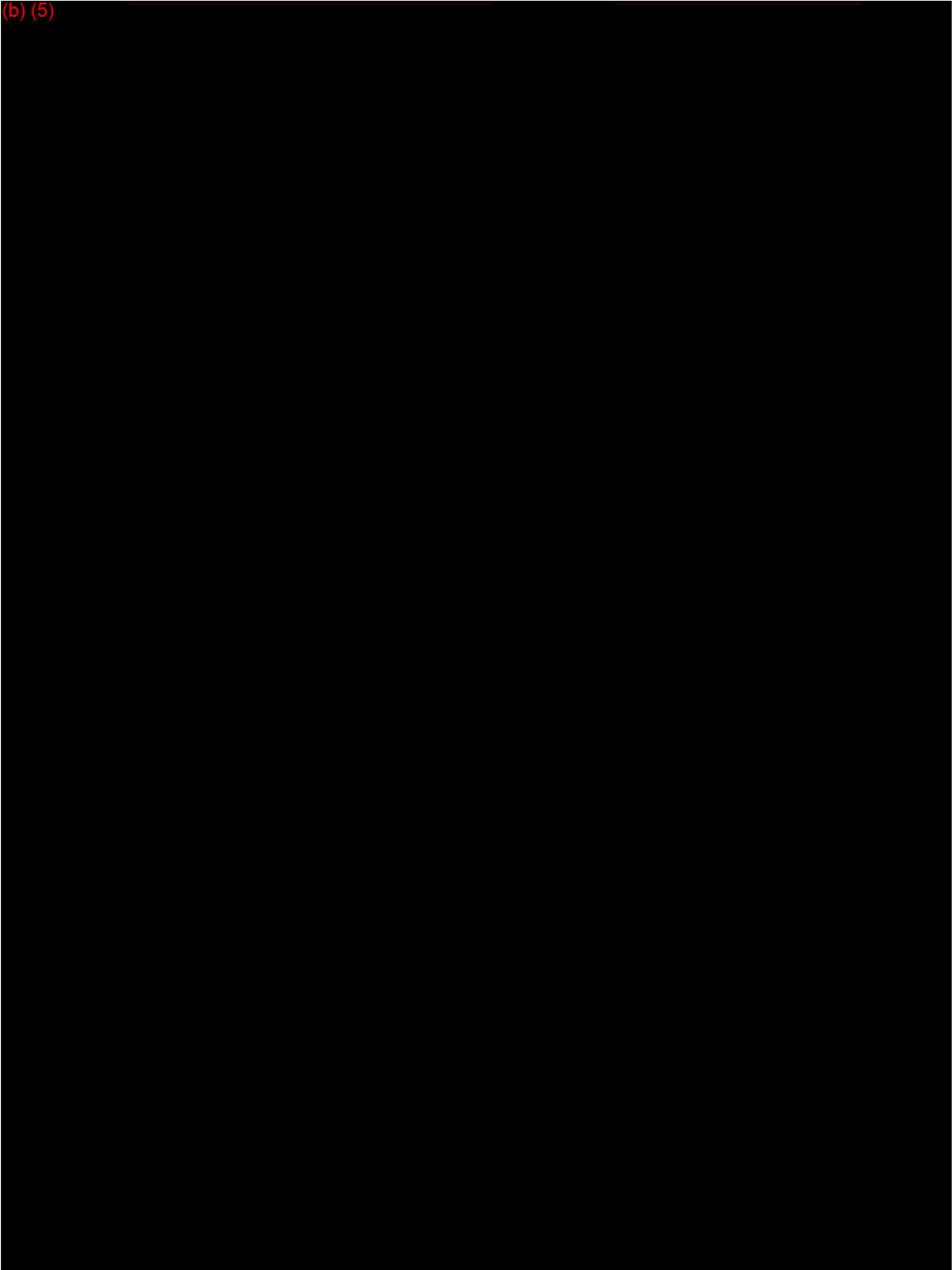
10. Figure 2 of my memo shows the inverse correlation ($r^2 = .8$) between achieved level of dystrophin at 180 weeks (baseline values not available) and rate of decline in the NSAA (a composite of muscle function tests).
11. In summary, the available data on localization of the protein (demonstrating its functionality within the cell), what is known about lower levels of dystrophin in BMD patients, the comparison of the four year patient cohort to concurrent controls, and the NSAA data, lead me to conclude that it is reasonably likely that increasing dystrophin production to the level of 1-2.5% of normal in DMD patients is reasonably likely to result in clinical benefit, although this may be small in magnitude.

Center Director Decisional Memo DRAFT

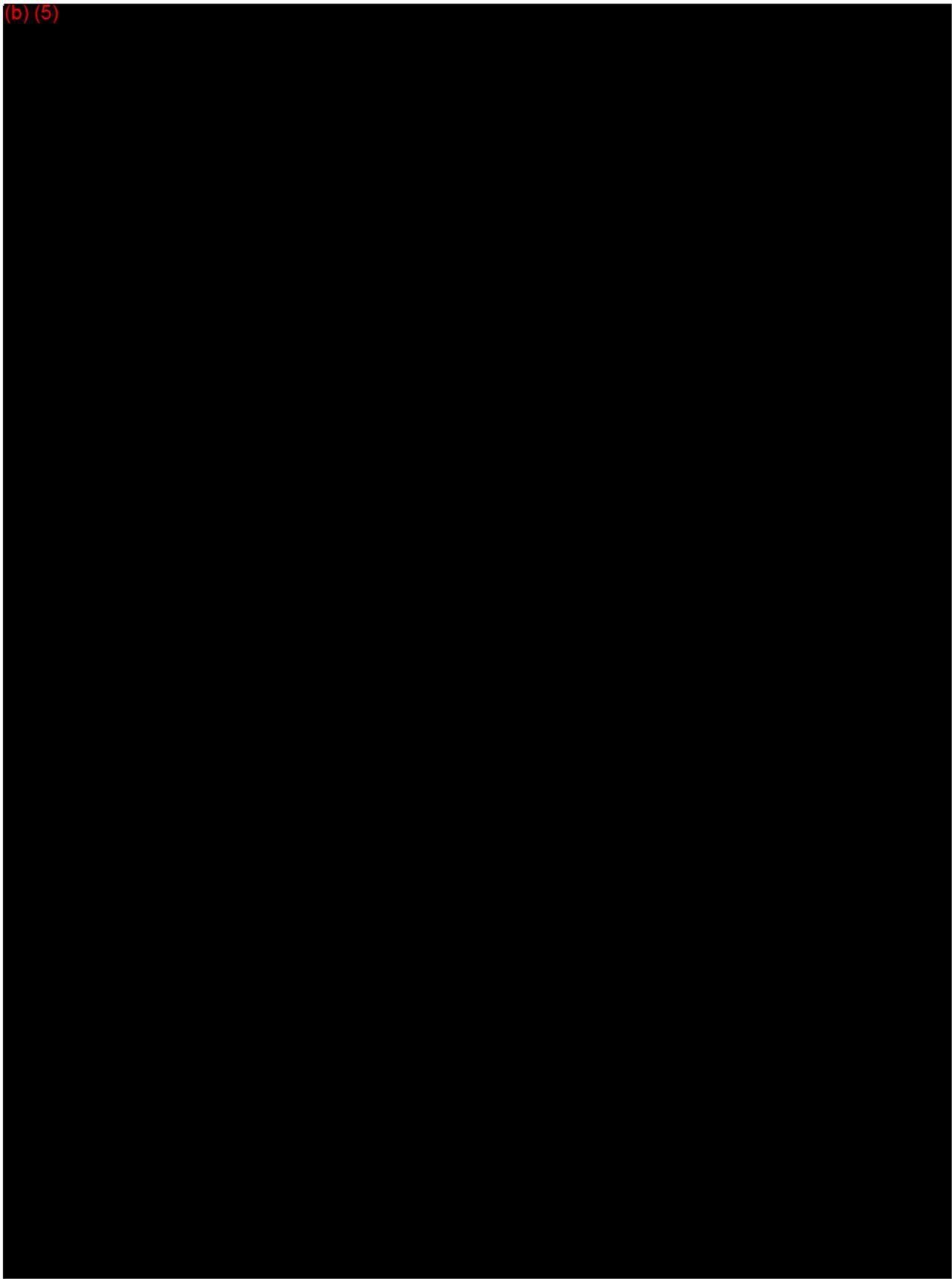
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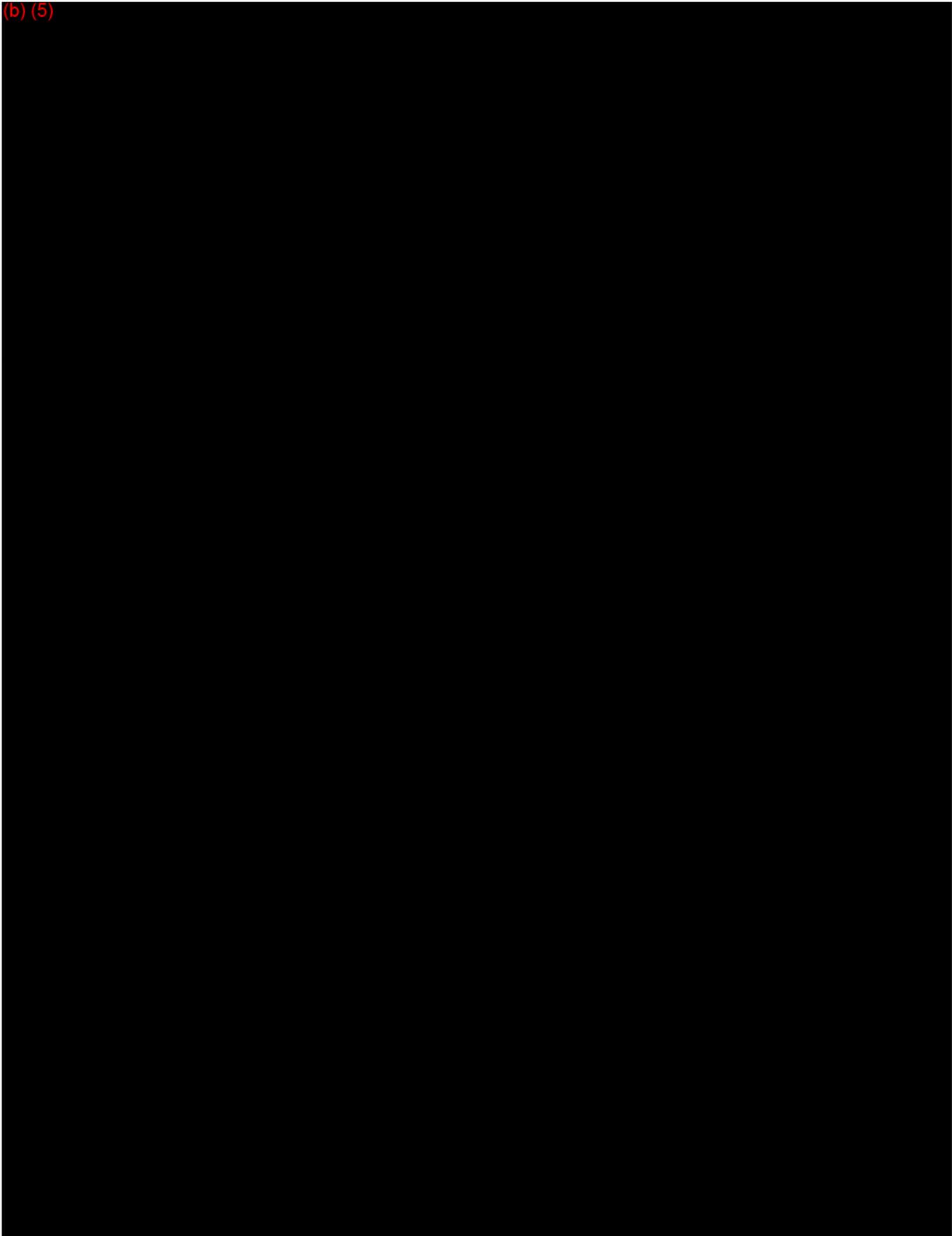
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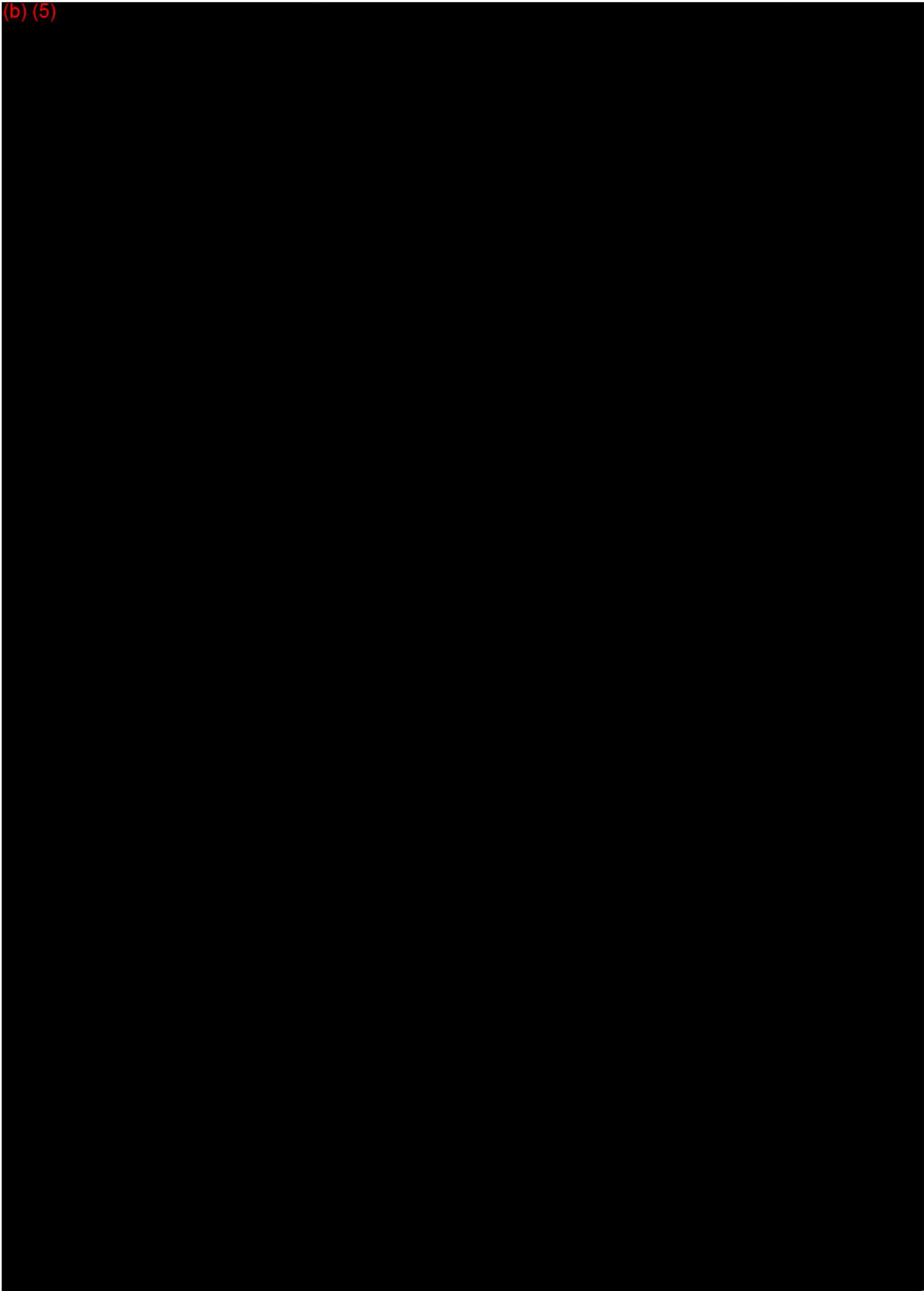
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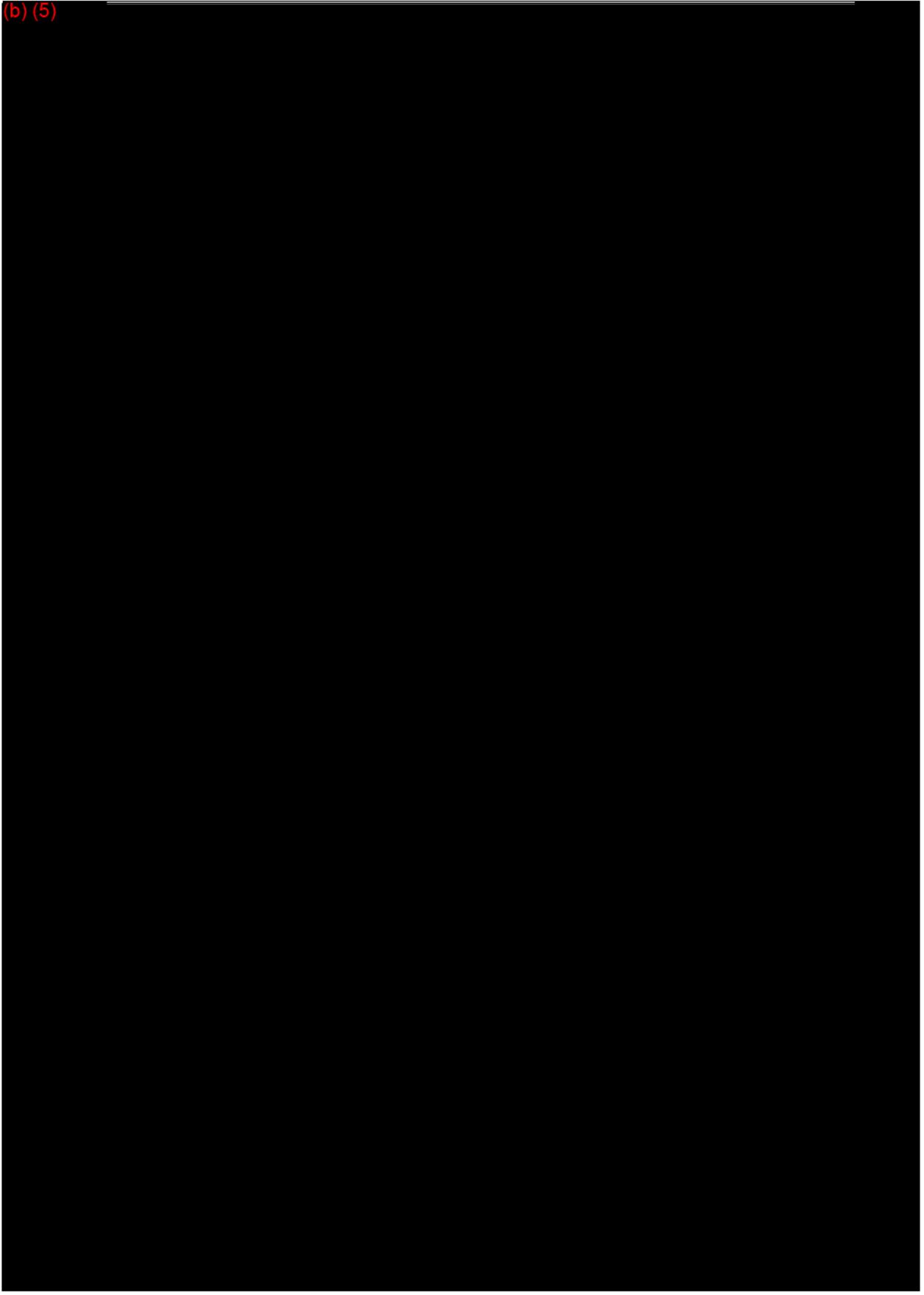
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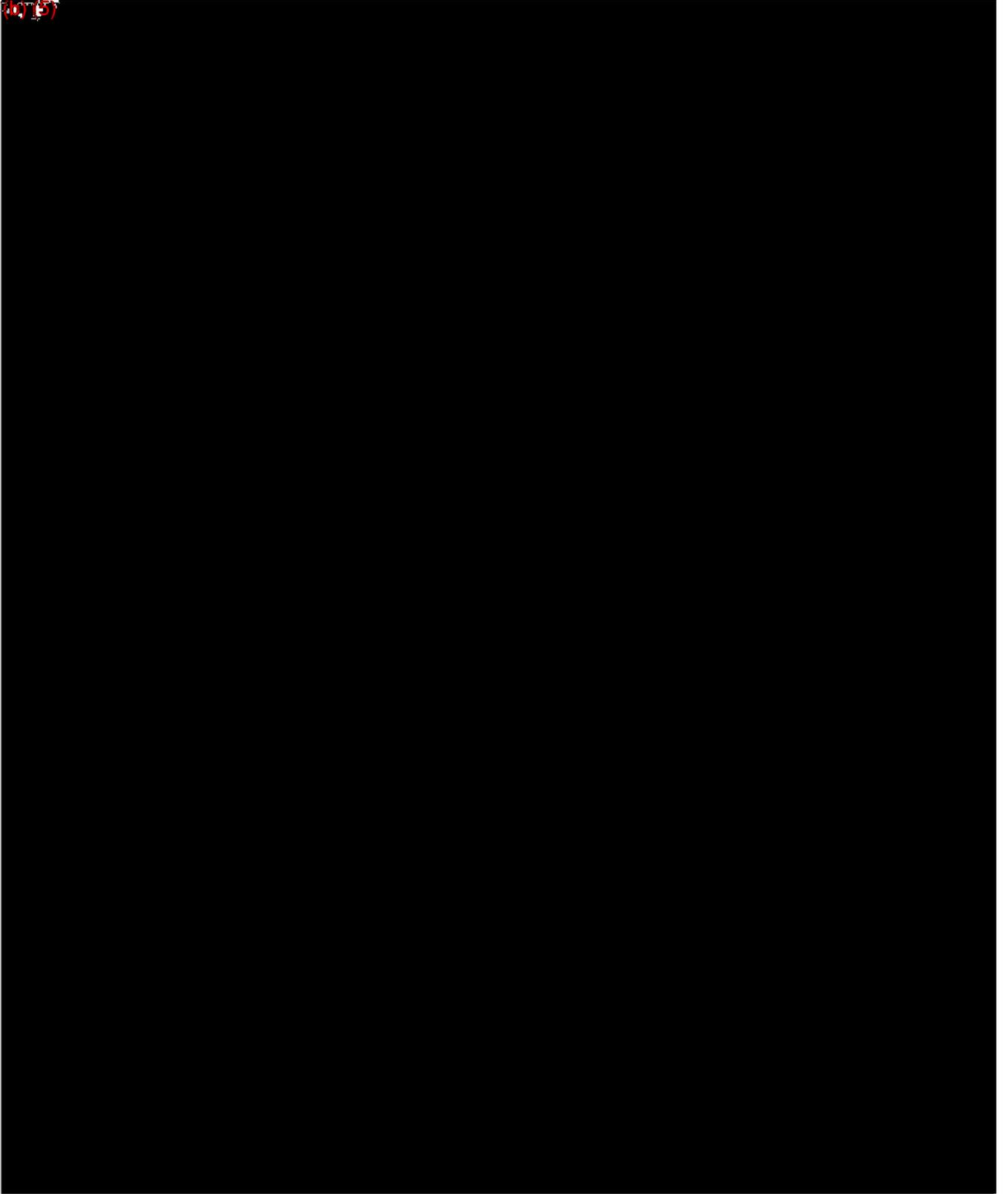
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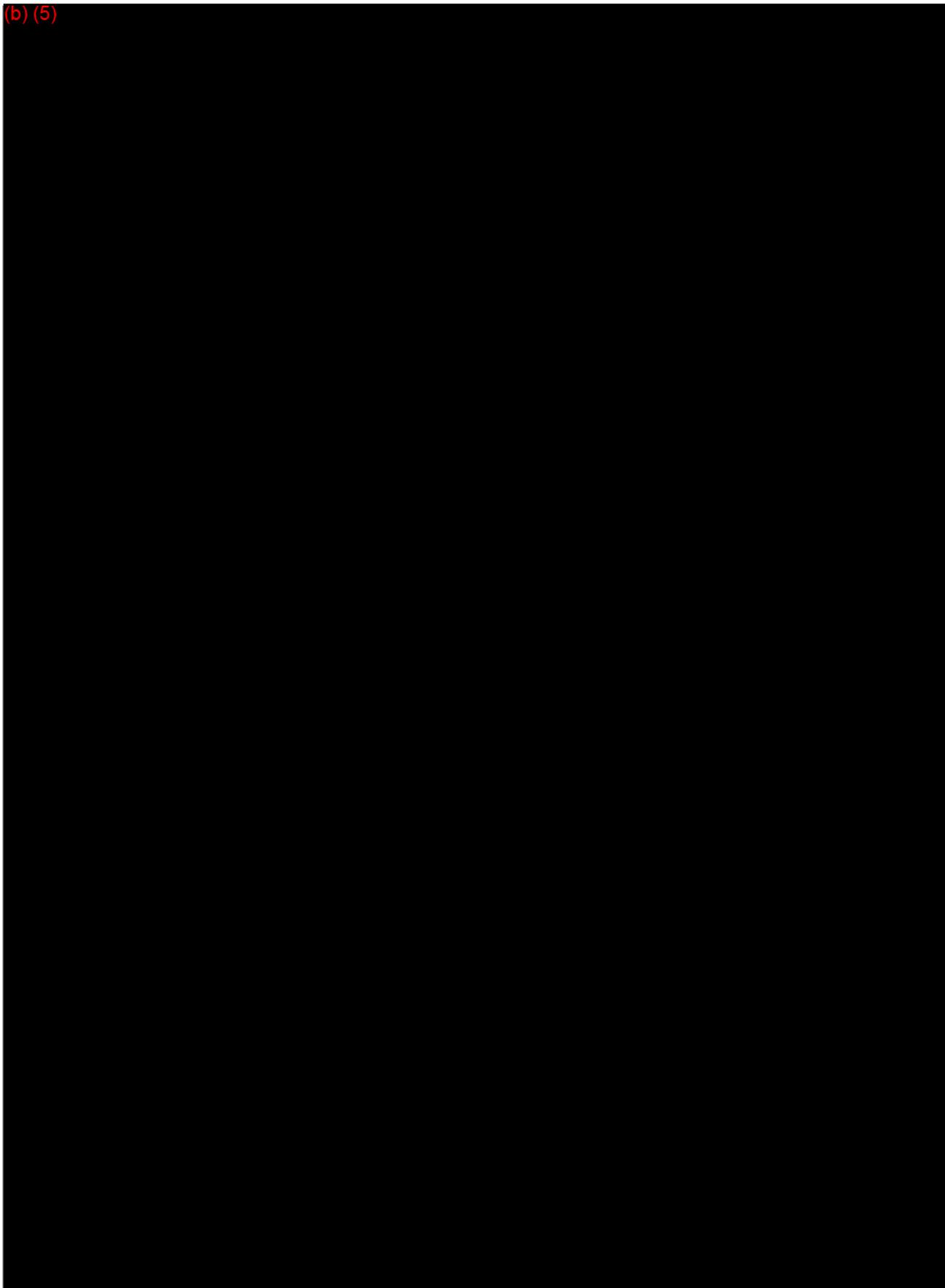
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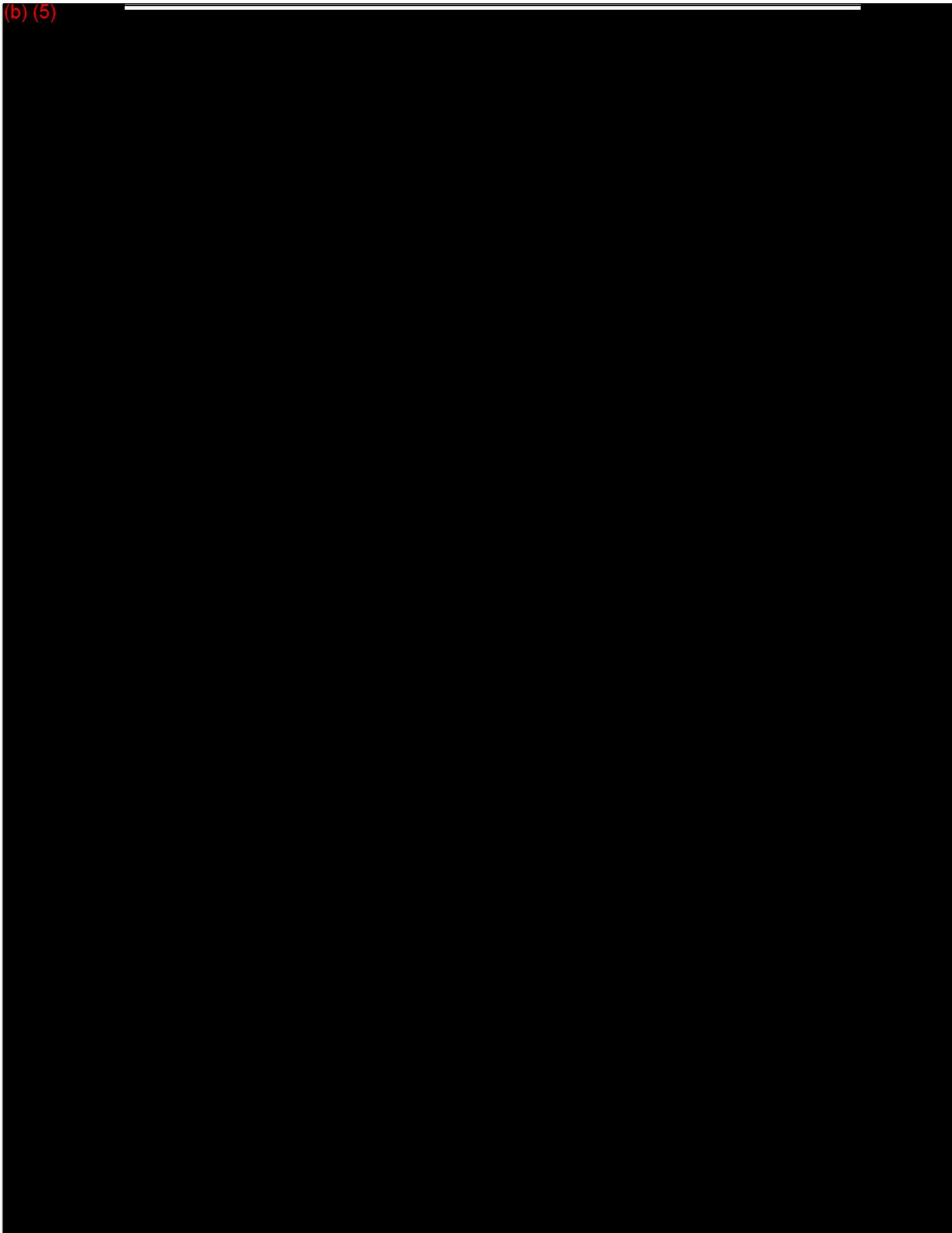
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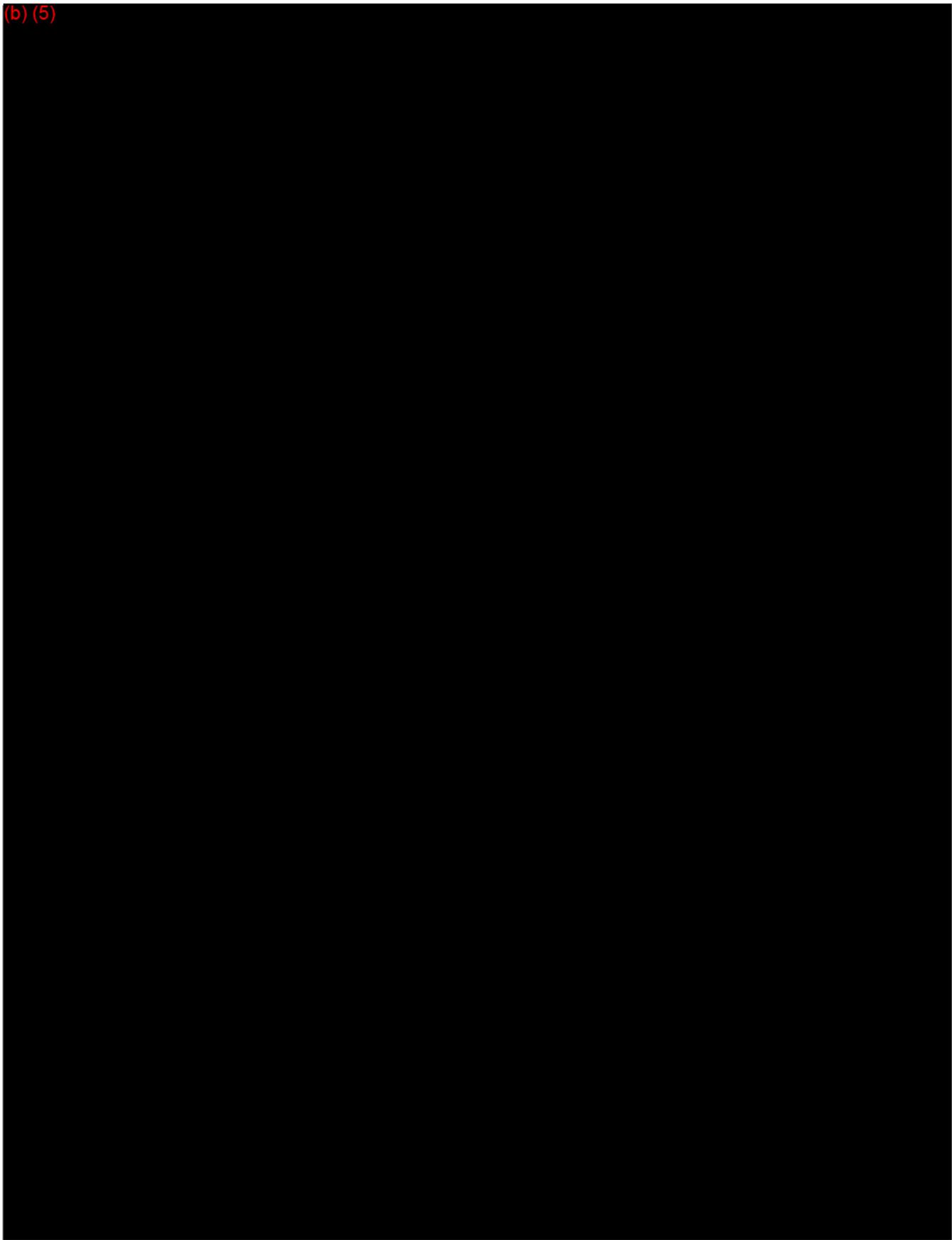
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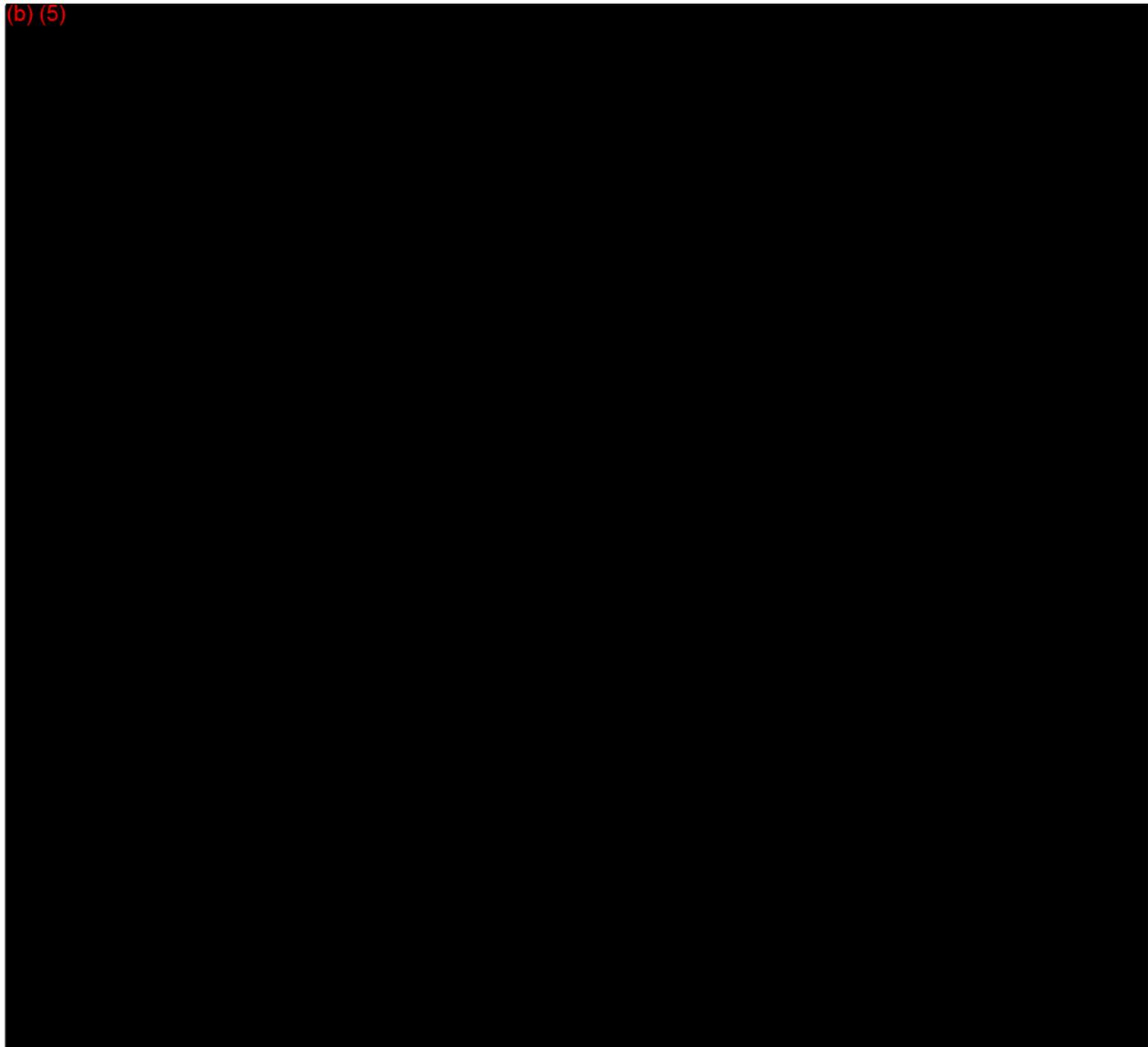
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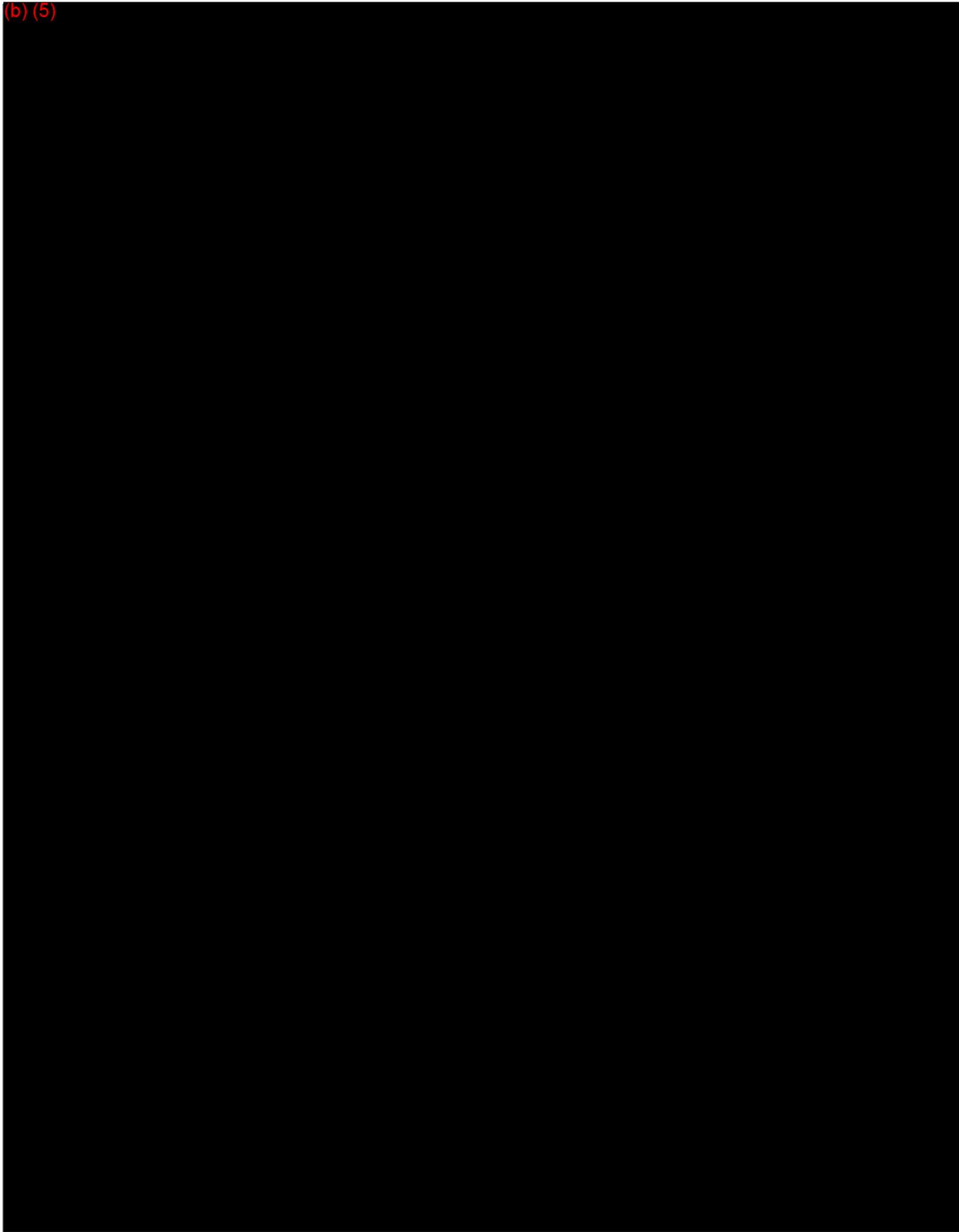
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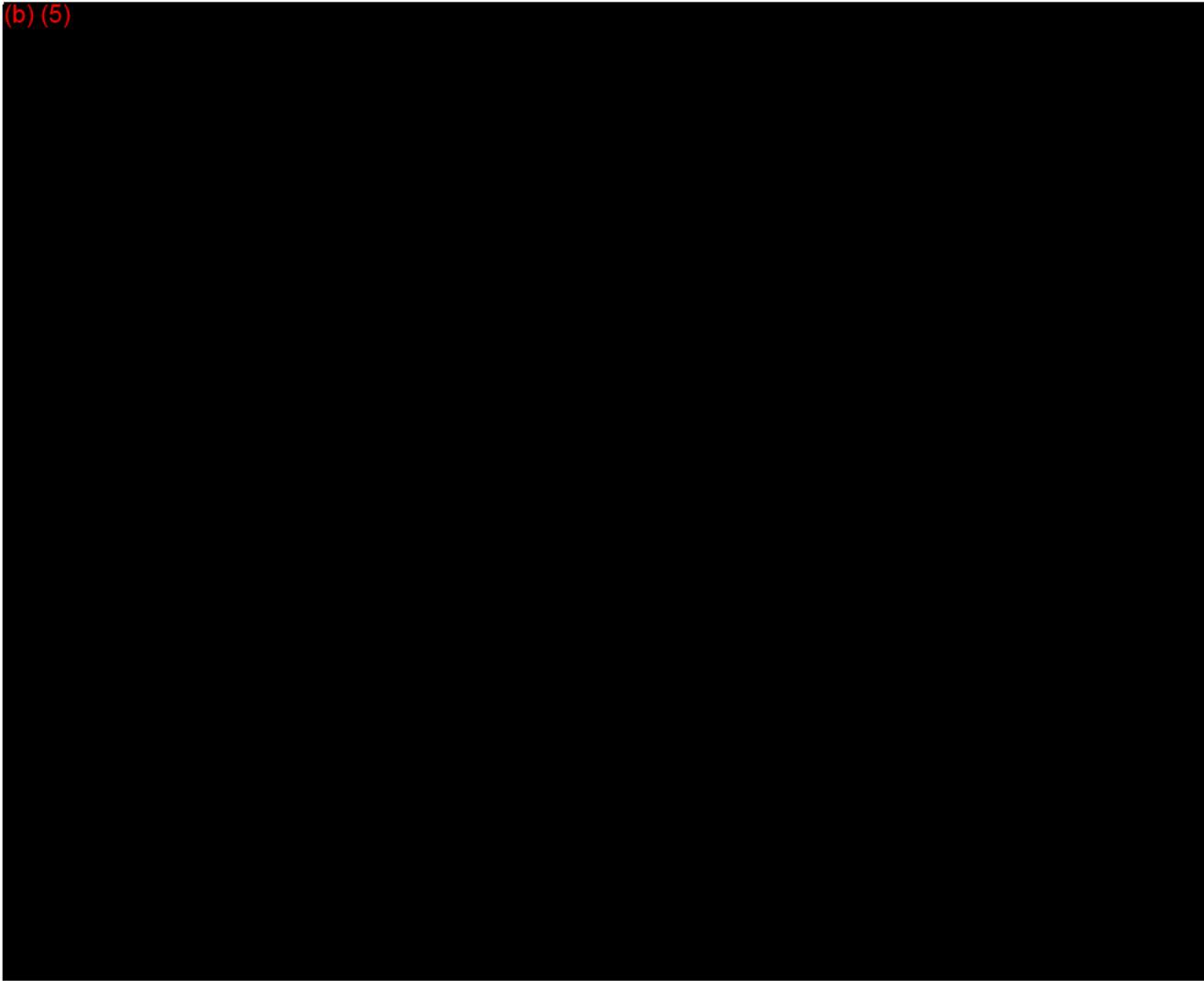
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From: [Califf, Robert](#)
To: [Kraus, Tom](#)
Subject: FW: Opinion letter on Kyndrisa
Date: Saturday, July 09, 2016 10:59:00 AM
Attachments: [Opinion letter on Kyndrisa, May 2, 2016.pdf](#)

Robert M Califf MD
Commissioner of Food and Drugs

From: Evans, Dana
Sent: Wednesday, July 06, 2016 2:58 PM
To: Califf, Robert
Subject: FW: Opinion letter on Kyndrisa

Dana Evans, M.P.H.

Program Support Specialist to the Commissioner
Office of the Commissioner Immediate Office
U.S. Food and Drug Administration
Phone: 301-796-2021
BB: 301-467-8987
Email: dana.evans@fda.hhs.gov

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Date: May 11, 2016 at 3:12:27 PM GMT+2
To: (b) (6) (b) (6) " (b) (6) (b) (6)
Subject: RE: Opinion letter on Kyndrisa

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Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration

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<Opinion letter on Kyndrisa, May 2, 2016.pdf>

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Seventeen FDA advisory committee panel members voted on BioMarin's Kyndrisa NDA package, and 15 were of the opinion that the lack of statistical significance of positive results in the phase III study weakened the persuasiveness of findings. This lack of statistical significance doesn't surprise me since both the phase II and III studies were short-term studies and short-term studies should not be expected to show effectiveness for an agent which is not expected to reverse the disease and certainly not quickly.

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progression of his disease and maintain sufficient residual muscle function to extend the limited period of ambulation and perhaps of even cardiac function.

In effect, **Kyndrisa is prophylactic and, thus, can only be proven efficacious in a long-term study.** Luckily, BioMarin has the results of such a long-term study, namely the phase I study, DMD114673, which was presented in a poster session at the 19th International Congress of the World Muscle Society, Oct 7 - 11, 2014 in Berlin, Germany. In summary, 12 boys were enrolled in DMD114673, which started in 2008. Two boys dropped out because of lost ambulation during the extension study. They were considered to have severely declined before the start of the study; of all ambulatory subjects, they had the lowest overall baseline 6 minutes walking distance test (6MWD) results (not surprising considering Kyndrisa's mode of action). When progression of the disease in this treated group was compared with extensive historical data from untreated affected boys, the remaining 10 boys were performing significantly better, and the results after 8 years are becoming only more impressive. All 10 boys are still enrolled, which tells me that side-effects of the drug are manageable and tolerable.

(b) (4) [REDACTED]
[REDACTED]
[REDACTED]
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I strongly encourage the FDA to carefully examine these data one more time in light of the full understanding of the drug's mechanism of action on muscle fibers: Kyndrisa, as a prophylactic agent, will not restore muscle function. Kyndrisa delays further the slow muscle deterioration characteristic of the disease., Accordingly, supporting efficacy data can only be obtained from a long-term study. My professional conclusion is that Kyndrisa (and probably Eteplirsen) are effective drugs in delaying the lethal progression of DMD in young, ambulatory boys.

Herbert L. Heyneker, PhD.

May 2, 2016

From: [Califf, Robert](#)
To: [Behr, Virginia L](#)
Subject: RE: eteplirsen NDA
Date: Saturday, July 09, 2016 7:49:00 AM

Virginia,

Thanks for your help with all of this.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Behr, Virginia L
Sent: Wednesday, July 06, 2016 12:23 PM
To: Califf, Robert
Subject: FW: eteplirsen NDA

Dr. Califf,

Janet Woodcock asked me to send you CDER's and FDA's formal processes for reviewing internal appeals. This morning, Ellis Unger, CDER ODE 1 Director, requested a Commissioner's Briefing to discuss the approvability of the eteplirsen NDA to treat Duchenne. I plan to attend the briefing that is currently in the planning stages, aiming for some day this week. Janet does not plan to attend, as she wants to give Dr. Unger and others the opportunity to discuss their concerns about her planned decision to overrule them. Following the Commissioner's Briefing, there is a chance that someone will initiate a formal appeal.

CDER's formal processes are pretty logical and straightforward, but it gets a little complicated once it gets to the Center Director level and the Commissioner's Office. Technically, if the Center Director's decision is appealed, it actually goes back to her for another decision, following her convening an expert ad hoc panel. After that decision, the disputants can appeal up to the Commissioner's level, which mandates an administrative process review to ensure that Center employees positions were taken into consideration for the decision and that we followed our own internal appeals process. For some historical context, when we were writing this SMG, Dr. von Eschenbach was Commissioner, and he and his staff changed direction a few times about whether the Commissioner's level review should be a substantive regulatory/scientific review or a process review. The current Staff Manual Guide 9010.1 is where we ended up when it finalized in 2009.

The following is an explanation of the formal processes (with SOP document links) that I sent to Drs. Woodcock, Unger, and Jenkins:

"Formal appeal options: If Janet makes a final decision about the eteplirsen approvability that anyone in CDER cannot align with, they may choose to formally appeal that decision. In this case, the disputant and others involved in the formal process would need to follow the procedures laid out in [MaPP 4151.2](#) (Center Director review with ad hoc panel). For this MaPP, the Center Director chairs a

panel of experts who would advise her on the final decision. Timelines for the review are in business days. If appellants want to appeal to the Commissioner, they must have exhausted the Center's dispute resolution SOPs. [Staff Manual Guide 9010.1](#) is the appropriate SOP to appeal to the Commissioner and it requires that the appeal be submitted within 10 calendar days of the decision being appealed. The SOP details how FDA's Chief Scientific Officer chairs a Board that makes a recommendation to the Commissioner about how successfully the Center followed its dispute resolution procedures. Technically, it's not another scientific review of the matter, though I suppose the Chief Scientific Officer and/or the Commissioner could certainly choose to conduct their own review. I'm happy to advise any individual or group about these options, either as a confidential or non-confidential discussion."

Please let me know if you need anything else. I think what it boils down to for the Commissioner's Briefing is that those who disagree with Janet want you to hear their thinking and their position. Ultimately, you may need to decide whether or not you'll keep the drug approval authority delegated to Janet or take on the responsibility of a review and decision in your Office. We don't typically delay a regulatory action because of a pending formal appeal, but you have the authority to do so.

Regards,

Virginia L. Behr
CDER Ombudsman

(301) 796-3436
WO51, Room 6158

<http://inside.fda.gov:9003/CDER/OfficeofExecutivePrograms/Ombudsman/default.htm>

From: Unger, Ellis <Ellis.Unger@fda.hhs.gov>
Date: July 5, 2016 at 3:36:37 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>, Temple, Robert <Robert.Temple@fda.hhs.gov>
Subject: eteplirsen NDA

Janet,

I don't have to tell you how difficult the eteplirsen decision has been for many of us in ODE-I. As you know, we have reached different scientific conclusions on the strength of the data, and in particular, the likelihood that the small increase observed in Becker-type dystrophin is reasonably likely to predict clinical benefit. This decision could be precedent

setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed “reasonably likely to predict clinical benefit.” Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated.

I know that Dr. Jenkins has mentioned the possibility of involving Dr. Califf in the eteplirsen decision on at least one occasion, and I would like to request a formal appeal to the Commissioner on this matter.

I’m aware that the Commissioner’s official role is to consider the administrative aspects of review decisions and not the science. But given the potential for setting a precedent here, I think he should be aware of the various points of view and consider the potential ramifications of the matter at hand.

I’m also aware that you advised Sarepta that we would be prepared to grant accelerated approval of their NDA within 4 business days of receiving their new data, but there was a provision in the letter that the increase in dystrophin had to be meaningful, and we do not have agreement on this point. Thus, it is my hope that a Commissioner Briefing can be held before an action is taken.

I have discussed the above with Dr. Jenkins, and he supports this course of action.

I propose that we reserve a few minutes at the briefing tomorrow to discuss this matter.

Thank you for your consideration,

Ellis

From: [Califf, Robert](#)
To: [Woodcock, Janet](#)
Subject: RE: Opinion letter on Kyndrisa
Date: Tuesday, July 12, 2016 8:06:00 AM

Dave Martin was one of my attendings at ucsf as an intern.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Woodcock, Janet
Sent: Tuesday, July 12, 2016 8:02 AM
To: Califf, Robert
Subject: RE: Opinion letter on Kyndrisa

Thanks. Germane to ongoing discussion. jw

From: Califf, Robert
Sent: Saturday, July 09, 2016 11:01 AM
To: Woodcock, Janet
Subject: FW: Opinion letter on Kyndrisa

Robert M Califf MD
Commissioner of Food and Drugs

From: Evans, Dana
Sent: Wednesday, July 06, 2016 2:58 PM
To: Califf, Robert
Subject: FW: Opinion letter on Kyndrisa

Dana Evans, M.P.H.

Program Support Specialist to the Commissioner
Office of the Commissioner Immediate Office
U.S. Food and Drug Administration
Phone: 301-796-2021
BB: 301-467-8987
Email: dana.evans@fda.hhs.gov

From: Dave Martin [<mailto:dave@avidbiotics.com>]
Sent: Tuesday, July 05, 2016 6:01 PM
To: Commissioner FDA
Subject: FW: Opinion letter on Kyndrisa

Rob: The "missing" letter is now attached! Dave

From: Dave Martin
Sent: Tuesday, July 5, 2016 11:06 AM
To: 'robert.califf@fda.hhs.gov' <robert.califf@fda.hhs.gov>
Subject: Opinion letter on Kyndrisa

Rob, a delight to see you in D.C. in February, and I also add my enthusiastic congratulations to you. Undoubtedly you're aware of the concern, noise, and controversy around the 2 submitted drug candidates for management of Duchenne muscular dystrophy that began before your current role. This is a quick note accompanying an opinion letter from a long-time scientific colleague and friend, Herb Heyneker. The letter has been passed through the proper channels at the Agency without substantive response, and in the context of the op-ed piece in the WSJ Saturday, I thought it appropriate to draw your attention to the content of Herb's letter. Herb was the first or second employee at Genentech, well before I was there, having completed his post-doc in Herb Boyer's lab at UCSF. I can strongly vouch for his scientific acumen and depth, and even though I have not seen the Phase I data to which he refers in his letter, I do understand the defect and mechanism of action of the exon skipping oligos. As a one-time medical geneticist, I have followed that field for years and have been impressed by the exon-skipping approaches. Herb's opinion makes very good sense to me. I recently talked to a senior person in BioMarin's regulatory affairs and learned of some adverse events; however, none were so adverse as the incessant deterioration and demise of these boys. Best regards, Dave

David W. Martin, Jr., MD
AvidBiotics Corp.
100 Kimball Way
South SF, CA 94080
650-873-1115 office

From: CDER DRUG INFO <DRUGINFO@fda.hhs.gov>
Date: May 11, 2016 at 3:12:27 PM GMT+2
To: (b) (6) (b) (6) (b) (6) (b) (6) > 7
Subject: RE: Opinion letter on Kyndrisa

Dear Dr. Heyneker,

Thank you for writing to the Division of Drug Information in the FDA's Center for Drug Evaluation and Research.

We appreciate your thoughts and comments regarding this issue, and have forwarded your email to the appropriate CDER Review Division. They will contact you if they have questions or need additional information.

Best regards,
RL
Drug Information Specialist
Division of Drug Information

Center for Drug Evaluation and Research
Food and Drug Administration

This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

[<ATT89150_1.jpg>](#) [<ATT69106_2.jpg>](#) [<ATT85592_3.jpg>](#)
[<ATT56925_4.jpg>](#) [<ATT27175_5.jpg>](#) [<ATT40320_6.jpg>](#)

From: Herb Heijneker [mailto:(b) (6)] (b) (6)
Sent: Tuesday, May 10, 2016 9:20 AM
To: CDER DRUG INFO
Cc: Dave Martin; PCNS
Subject: Fwd: Opinion letter on Kyndrisa

To whom this may concern, I am forwarding an opinion letter on Kyndrisa which I sent to Ms. Moon Hee V. Choi, who is the Designated Federal Officer, PCNS at the FDA. She was unable to accept my document/comments as the Advisory Committee meeting record is closed since the meeting was adjourned. She suggested that I submit my comments to the FDA Division of Drug Information at druginfo@fda.hhs.gov and that you will be able to direct my correspondence to enter the appropriate process for submitting my comments to the FDA/CDER Division of Neurology Products. Thank you for your help, Sincerely, Herbert Heyneker, PhD.

Begin forwarded message:

From: Herb Heijneker (b) (6) (b) (6)
Subject: Opinion letter on Kyndrisa
Date: May 5, 2016 at 8:15:02 PM GMT+2
To: pcns@fda.hhs.gov
Cc: Dave Martin <dave@avidbiotics.com>

Dear Ms. Choi, on November 24, 2015 the PCNS advisory committee concluded that Kyndrisa should not be approved for the treatment of Duchenne's Muscular Dystrophy due to lack of efficacy; especially the phase III data were unconvincing. On January 14, 2016 the FDA followed the recommendations of the advisory committee and rejected Kyndrisa for the treatment of DMD. Respectfully, I would like to ask the advisory committee to read my opinion letter (hereby attached) in which I explain why short-term clinical trials will not demonstrate clinical benefits. I would greatly appreciate if you could share this letter with the full advisory committee, that voted on the disapproval of Kyndrisa. My professional conclusion is that Kyndrisa (and probably Eteplirsen) are effective drugs in delaying the lethal progression of DMD in young, ambulatory boys. My motivation is purely altruistic: I like to help DMD patients live a

longer, more productive life, keeping in mind that there is no treatment currently available for this dreadful disease.

Sincerely,

Herbert L. Heyneker, PhD (b) (6)

<Opinion letter on Kyndrisa, May 2, 2016.pdf>

Subject: Jenkins Email

From: Jenkins, John K
Sent: Tuesday, July 12, 2016 5:25 PM
To: Woodcock, Janet; Unger, Ellis; Dunn, Billy; Bastings, Eric
Cc: Jenkins, John K
Subject: RE: MEMO

Janet

As we discussed in the hallway, I had some comments on your memo:

1. You said you did not consider data from the first three biopsies, but you do not say why. It was my understanding that the re-read of the first three biopsies for IHC was considered valid and the review team saw no change from baseline from the first biopsy to week 180. This is an important part of their perspective on the amount of dystrophin produced and its significance. They noted that the baseline ICH results from the patients in Study 201 were very different from the "new" baseline data that were conducted in parallel to the week 180 biopsy and that these differences were not explained. So, I think you need to explain why you are not considering the IHC data from the first three biopsies in your review, and instead focusing on the comparison of the "new" controls versus the week 180 IHC results.
2. I am not familiar with the references you added to the memo and cannot comment on your summary of the findings of each paper. Perhaps the review team know those references and can provide their take on the findings. Even taking your summaries at face value as accurate, I did not find the summary of the references to be particularly helpful in determining whether the dystrophin findings for eteplirsen are "reasonably likely" to predict clinical benefit. As you noted, there are issues related both to the quantity of dystrophin produced as well as its quality (functionality) that are hard to tease apart in the small sample of boys treated. It is possible that the "responders" are making functional protein, it is also possible they are making non-functional protein, and I don't think we have the data to sort this out. It still seems to be a judgment on the totality of evidence where reasonable people may disagree.
3. I find the correlation graphs at the end to be problematic since they graph a delta for a clinical endpoint on the y-axis against an absolute endpoint value for dystrophin on the x-axis. While one might assume the baseline dystrophin levels were low and therefore using the absolute endpoint value is a reasonable estimate of the effect of the drug on dystrophin (e.g., a surrogate for the delta); we don't know that and therefore it is hard to know whether the graphics are isolating a drug effect or capturing a prognostic difference that may have been present at baseline. So, I don't find them as convincing as you suggest, but again, that may be a judgment.
4. You focus on the "responders" in the population to support your argument, but we don't know how to identify the responders and therefore will have to approve based on the sponsor's grouping of mutations that are "amenable to exon 51 skipping," which likely include mutations that are not responsive to eteplirsen. This is a frustrating intersection of "targeted" therapies and approval based on a group mean based on characteristics chosen by the sponsor that we cannot validate. This is very analogous to the CF cases that we have been discussing and I think the review teams in both cases are struggling with these issues. It feels like we have to "unlearn" what we think we know from targeting and regress to approving an un-validated grouping of mutations. I know we do this all the time for non-targeted therapies, but it is still disconcerting to face this for targeted therapies. While the drug at the proposed dose has not been shown to be toxic, it will likely require a central line for chronic administration, which is not benign, and families/society will be burdened with a very

expensive drug that may only be working in a small subset of the indicated population. This is an issue we will have to grapple with for many "targeted" therapies for rare diseases.

As we discussed, I am asking the review team members to provide any feedback they have on your memo by COB tomorrow so you can finalize the memo. That step is necessary for the appeal process to be formally triggered and I think we all agree we need to move quickly to resolve this case on way or the other.

John

From: Woodcock, Janet

Sent: Monday, July 11, 2016 7:21 PM

To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric

Subject: MEMO

Here is a draft version of my decisional memo. I welcome comments on it. An appeal can't be done until I finalize this, I am told. Thanks. jw

Smith, Celeste

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 9:26 AM
To: Woodcock, Janet
Subject: RE: MEMO
Attachments: t-nstar-csv.txt; t-nstar-csv.xlsx; NSAA from Atul.csv

Here's a text file from the company (t-nstar-csv.txt) with the data through Week 216. Its full file description is:
[\\Cdsub1\evsprod\NDA206488\0025\m5\datasets\4658-us-202\listings\t-nstar-csv.txt](#)

It's a text file, and the data are separated by commas.

I've imported it into Excel and saved it as t-nstar-csv.xlsx (also attached).

Atul took these data and added the Week 240 data (attached – NSAA from Atul.csv). I'm not sure how/when the Week 240 data were transmitted by Sarepta, but I will find out from him. He's in India.

You'll note that at many of the major time points, the boys were tested on 2 consecutive days. The company used the best value from the two days, whereas Atul averaged the 2 values together. The values were always close, and so it doesn't matter much which way it is done. If you'd like to show the data using the company's method (best value of both days), I can send you another data set that is cleaned up. I suspect the values for the 2 consecutive days were close together because the evaluator had the prior day's data in front of them on Day 2.

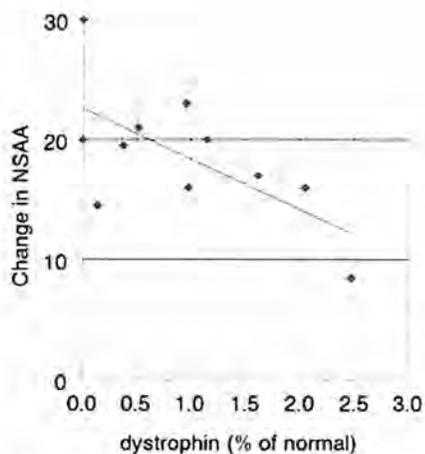
Let me know if you have any questions.

From: Woodcock, Janet
Sent: Wednesday, July 13, 2016 8:14 AM
To: Unger, Ellis
Subject: RE: MEMO

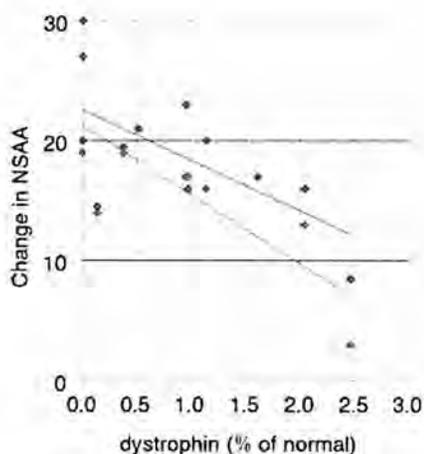
So can you tell me where you got the data for the table with the red lines below, and I will use that in my memo. Thanks for the correction. jw

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 12:57 AM
To: Woodcock, Janet
Cc: Jenkins, John K; Dunn, Billy; Bastings, Eric
Subject: RE: MEMO

I just noticed that the y-axis scales for the blue and red plots were different. This was not intentional. Here's the red plot on the same 0 to 30 scale as the blue plot:



And here they are together:



From: Unger, Ellis
Sent: Wednesday, July 13, 2016 12:52 AM
To: Woodcock, Janet
Cc: Jenkins, John K; Dunn, Billy; Bastings, Eric
Subject: RE: MEMO

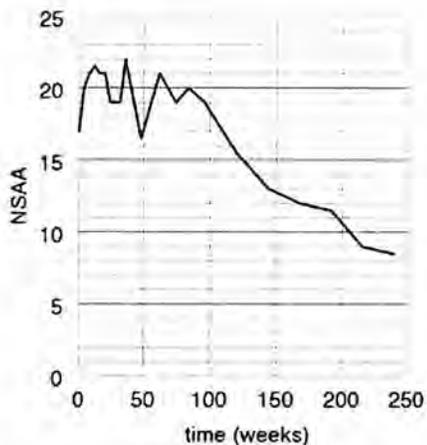
Janet,

I have some concerns with respect to Table 1 and Figure 2. You say that $R^2 = 0.8$. I've plotted the NSAA data in your Table 1, and I was able to reproduce your graph exactly. But I got $R=0.8$, which means that $R^2 = 0.64$. So I think that " $R^2 = 0.8$ " is a typo. If R^2 were actually 0.8, then R would have been 0.9 (0.9 squared = 0.81).

More importantly, I cannot tell how you got the deltas for the NSAA for each patient in Table 1. If you want to include the table and figure as they are now in your draft, I think you might consider citing your source for the table (presumably a Sarepta table or a reviewer's table). If it is your own work, then you might want to explain how you calculated the numbers, i.e., identify the name and location of the original data file you used and explain the methods you used to calculate the deltas.

Looking deeper at your table, I was curious about the data from patient 006. This patient had the highest dystrophin value (2.47%) and an NSAA change of just 3 units, as noted in the table.

Here are the NSAA data on this boy:



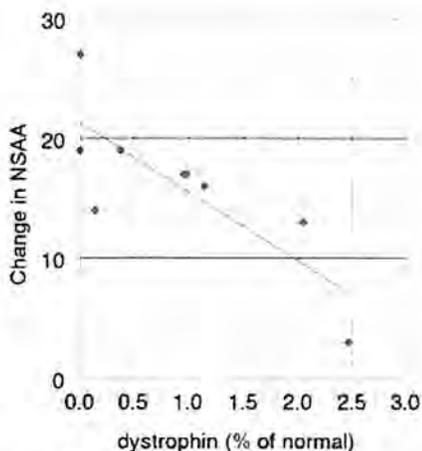
Looking at the data above, I have some difficulty characterizing his change as “3.”

Instead of picking an arbitrary time point as the “final” point, I thought that the most reasonable way of doing this would be to include all of the data that have been collected through Week 240. Because all patients have remained on weekly treatment for 240 weeks, I see no reason to truncate the data at the time the biopsy was obtained. Thus, for each patient I calculated their delta as their Week 240 score minus their baseline score. EXCEPT - for the 4 patients who started on placebo for 24 weeks, I considered Week 24 to be their baseline.

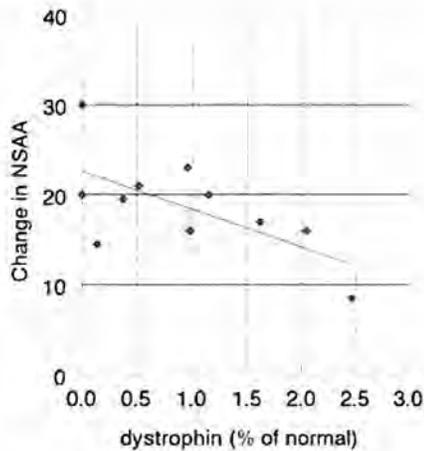
Also, I think we should use the data from all 11 patients with Week 180 biopsies, including the 2 who lost ambulation early, though I understand you might not agree.

Here is what I found...

First, below in blue is my version of your plot of 9 patients. My plot looks the same as yours, but I get $R=0.80$. (At the dystrophin value of 1%, there are two closely overlapping data points.)



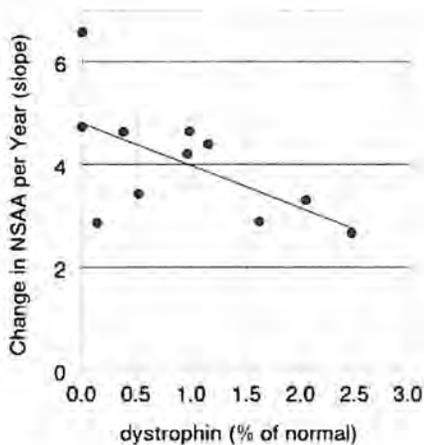
Second, below, my plot of all 11 patients, where I calculate delta as Week 240 minus baseline (for patients who started on placebo, it's Week 240 minus Week 24):



Using all of the data through Week 240, the slope is less steep and the correlation is worse. And knowing that you might not agree with inclusion of the 2 boys who became unable to ambulate, I will tell you that if I include all 11 boys, $R=0.65$. If I leave out the 2 non-ambulatory boys, $R=0.64$. So it makes no difference whether they are included or not. And the slope is essentially the same.

An alternate analysis I've been interested in is one that uses ALL of the aforementioned data for each patient. Rather than using just the first and last data points for each patient, we can calculate a slope for each patient using linear regression. For example, consider patient 006 graphed above. The red line is the linear regression. His slope is -0.051 units per week, or (multiply by 52) -2.7 units per year.

Below is a plot of the slope for each boy vs. dystrophin at Week 180 by Western blot. The slope for each boy is expressed as the change in NSAA per 52 weeks. For this plot, $R=0.60$, which is quite similar to the correlation of simple pre-treatment minus post-treatment (above).



In short, when you consider all of the NSAA data through Week 240, you get essentially the same plot whether you simply subtract pre- from post (red plot), or calculate a slope for each patient (black plot). And in either case, R is in the 0.6-range.

You can feel free to use some or all of these plots. Obviously, you can use your own table/plot, but if you do, I suggest you explain how you got your numbers, as I noted above.

Ellis

From: Jenkins, John K
Sent: Tuesday, July 12, 2016 5:25 PM
To: Woodcock, Janet; Unger, Ellis; Dunn, Billy; Bastings, Eric
Cc: Jenkins, John K
Subject: RE: MEMO

Janet

As we discussed in the hallway, I had some comments on your memo:

1. You said you did not consider data from the first three biopsies, but you do not say why. It was my understanding that the re-read of the first three biopsies for IHC was considered valid and the review team saw no change from baseline from the first biopsy to week 180. This is an important part of their perspective on the amount of dystrophin produced and its significance. They noted that the baseline ICH results from the patients in Study 201 were very different from the "new" baseline data that were conducted in parallel to the week 180 biopsy and that these differences were not explained. So, I think you need to explain why you are not considering the IHC data from the first three biopsies in your review, and instead focusing on the comparison of the "new" controls versus the week 180 IHC results.
2. I am not familiar with the references you added to the memo and cannot comment on your summary of the findings of each paper. Perhaps the review team know those references and can provide their take on the findings. Even taking your summaries at face value as accurate, I did not find the summary of the references to be particularly helpful in determining whether the dystrophin findings for eteplirsen are "reasonably likely" to predict clinical benefit. As you noted, there are issues related both to the quantity of dystrophin produced as well as its quality (functionality) that are hard to tease apart in the small sample of boys treated. It is possible that the "responders" are making functional protein, it is also possible they are making non-functional protein, and I don't think we have the data to sort this out. It still seems to be a judgment on the totality of evidence where reasonable people may disagree.
3. I find the correlation graphs at the end to be problematic since they graph a delta for a clinical endpoint on the y-axis against an absolute endpoint value for dystrophin on the x-axis. While one might assume the baseline dystrophin levels were low and therefore using the absolute endpoint value is a reasonable estimate of the effect of the drug on dystrophin (e.g., a surrogate for the delta); we don't know that and therefore it is hard to know whether the graphics are isolating a drug effect or capturing a prognostic difference that may have been present at baseline. So, I don't find them as convincing as you suggest, but again, that may be a judgment.
4. You focus on the "responders" in the population to support your argument, but we don't know how to identify the responders and therefore will have to approve based on the sponsor's grouping of mutations that are "amenable to exon 51 skipping," which likely include mutations that are not responsive to eteplirsen. This is a frustrating intersection of "targeted" therapies and approval based on a group mean based on characteristics chosen by the sponsor that we cannot validate. This is very analogous to the CF cases that we have been discussing and I think the review teams in both cases are struggling with these issues. It feels like we have to "unlearn" what we think we know from targeting and regress to approving an un-validated grouping of mutations. I know we do this all the time for non-targeted therapies, but it is still discomfoting to face this for targeted therapies. While the drug at the proposed dose has not been shown to be toxic, it will likely require a central line for chronic administration, which is not benign, and families/society will be burdened with a very expensive drug that may only be working in a small subset of the indicated population. This is an issue we will have to grapple with for many "targeted" therapies for rare diseases.

As we discussed, I am asking the review team members to provide any feedback they have on your memo by COB tomorrow so you can finalize the memo. That step is necessary for the appeal process to be formally triggered and I think we all agree we need to move quickly to resolve this case on way or the other.

John

From: Woodcock, Janet

Sent: Monday, July 11, 2016 7:21 PM

To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric

Subject: MEMO

Here is a draft version of my decisional memo. I welcome comments on it. An appeal can't be done until I finalize this, I am told. Thanks. jw

Smith, Celeste

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 11:19 AM
To: Woodcock, Janet
Subject: FW: NSAA numbers
Attachments: RE: Northstar for latest assessment of Study 202

Here are the Week 240 data (drill down). I don't see that it ever came in through the gateway.

From: Farkas, Ronald
Sent: Wednesday, July 13, 2016 11:04 AM
To: Bhattaram, Atul; Unger, Ellis; Bastings, Eric; Breder, Christopher D
Cc: Dunn, Billy
Subject: RE: NSAA numbers

Here it is
Thanks
Ron

From: Bhattaram, Atul
Sent: Wednesday, July 13, 2016 10:35 AM
To: Unger, Ellis; Bastings, Eric; Farkas, Ronald; Breder, Christopher D
Cc: Dunn, Billy
Subject: RE: NSAA numbers

Hi Ellis

I got the datasets via email from Ron and Eric.

Atul

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 10:28 AM
To: Bhattaram, Atul; Bastings, Eric; Farkas, Ronald; Breder, Christopher D
Cc: Dunn, Billy
Subject: RE: NSAA numbers

Greetings, Atul! One more question. Do you know where you got the Week 240 data? In other words, was this an email communication from Sarepta, or did it come in through the gateway? And if it came in through the gateway, I can probably find it if you know the approximate date.

Thanks for all,

Ellis

From: Bhattaram, Atul
Sent: Tuesday, July 12, 2016 12:19 AM
To: Unger, Ellis; Bastings, Eric; Farkas, Ronald; Breder, Christopher D

Cc: Dunn, Billy

Subject: RE: NSAA numbers

In the dataset that I sent before, there are blank cells in the column I (visit_number) after 168 weeks. The subsequent data points are for 192, 216 and 240 weeks. The reason behind is missing information at these visits for muscle strength measures which I integrated into this database. Let me know if it is not clear.

Atul

Smith, Celeste

From: Choy, Fannie (Yuet)
Sent: Wednesday, July 06, 2016 7:24 AM
To: Bastings, Eric; Farkas, Ronald
Subject: RE: Northstar for latest assessment of Study 202
Attachments: FW: Regulatory Contact: re: NDA 206488

Hi,

Please see attached email for Week 240 results. Formal submission pending.

Thanks
Fannie

From: Bastings, Eric
Sent: Wednesday, July 06, 2016 1:38 AM
To: Choy, Fannie (Yuet); Farkas, Ronald
Subject: Northstar for latest assessment of Study 202

Did Sarepta submit the latest northstar results for study 202? If not, please request them. Thanks.

Eric Bastings, MD
Deputy Director
Division of Neurology Products
CDER/OND

Smith, Celeste

From: Kelley, Laurie
Sent: Wednesday, June 08, 2016 7:50 AM
To: Breder, Christopher D; Farkas, Ronald; Bastings, Eric; Dunn, Billy
Cc: Choy, Fannie (Yuet); Ware, Jacqueline H; Kelley, Laurie
Subject: FW: Regulatory Contact: re: NDA 206488
Attachments: nsaa.csv

Morning All

The attached is the dataset from Sarepta containing the North Star Ambulatory Assessment total score, rise time, and rise ability data from study 4658-us-202 through the Week 240 time point.

Laurie

From: Matthew Rael [<mailto:MRael@Sarepta.com>]
Sent: Wednesday, June 08, 2016 7:47 AM
To: Kelley, Laurie
Cc: Ware, Jacqueline H; Shamim Ruff; Choy, Fannie (Yuet)
Subject: RE: Regulatory Contact: re: NDA 206488

Hi Laurie,

In response to the third bullet below, please find attached a dataset in CSV format containing the North Star Ambulatory Assessment total score, rise time, and rise ability data from study 4658-us-202 through the Week 240 time point.

Regards,

Matt

Matthew Rael, MS
Senior Manager, Regulatory Affairs
p 617.274.4029 (b) (6) 617.812.0509
e mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Friday, June 03, 2016 1:08 PM
To: Shamim Ruff <SRuff@Sarepta.com>

Cc: Matthew Rael <MRael@Sarepta.com>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: Regulatory Contact: re: NDA 206488

Dear Shamim,

This is to follow up on our phone call and other pending items on NDA 206488 for eteplirsen.

- I will be on leave starting June 6 through June 17, returning on June 20, 2016. My colleague, Laurie Kelley (Email: Laurie.Kelley@fda.hhs.gov), will be the contact during this period. In addition, please copy me and Jackie Ware (Email: Jacqueline.Ware@fda.hhs.gov) on all correspondence.
- As discussed yesterday, Sarepta will get back to us on the FDA's June 1st communication.
- The remaining Study Week 240 functional efficacy endpoint data (NSAA, Rise Time) are still pending. Do you have any update?
- Regarding FDA comments on the PI, Laurie will communicate updates on the progress as they become available.

Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
ODE I/OND/CDER
Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4215
Silver Spring, MD 20993-0002
301-796-2899 phone
fannie.choy@fda.hhs.gov

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Smith, Celeste

From: Kelley, Laurie
Sent: Wednesday, June 08, 2016 7:50 AM
To: Breder, Christopher D; Farkas, Ronald; Bastings, Eric; Dunn, Billy
Cc: Choy, Fannie (Yuet); Ware, Jacqueline H; Kelley, Laurie
Subject: FW: Regulatory Contact: re: NDA 206488
Attachments: nsaa.csv

Morning All

The attached is the dataset from Sarepta containing the North Star Ambulatory Assessment total score, rise time, and rise ability data from study 4658-us-202 through the Week 240 time point.

Laurie

From: Matthew Rael [<mailto:MRael@Sarepta.com>]
Sent: Wednesday, June 08, 2016 7:47 AM
To: Kelley, Laurie
Cc: Ware, Jacqueline H; Shamim Ruff; Choy, Fannie (Yuet)
Subject: RE: Regulatory Contact: re: NDA 206488

Hi Laurie,

In response to the third bullet below, please find attached a dataset in CSV format containing the North Star Ambulatory Assessment total score, rise time, and rise ability data from study 4658-us-202 through the Week 240 time point.

Regards,

Matt

Matthew Rael, MS
Senior Manager, Regulatory Affairs
P 617.274.4029 | (b) (6) | 617.812.0509
E mrael@sarepta.com



215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Friday, June 03, 2016 1:08 PM
To: Shamim Ruff <SRuff@Sarepta.com>

Cc: Matthew Rael <MRael@Sarepta.com>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>; Ware, Jacqueline H <Jacqueline.Ware@fda.hhs.gov>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: Regulatory Contact: re: NDA 206488

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301-796-2899 phone
fannie.choy@fda.hhs.gov

[Faint, illegible text, likely a placeholder or a very low-resolution scan of a signature block.]

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Smith, Celeste

From: Choy, Fannie (Yuet)
Sent: Wednesday, July 06, 2016 7:24 AM
To: Bastings, Eric; Farkas, Ronald
Subject: RE: Northstar for latest assessment of Study 202
Attachments: FW: Regulatory Contact: re: NDA 206488

Hi,

Please see attached email for Week 240 results. Formal submission pending.

Thanks
Fannie

From: Bastings, Eric
Sent: Wednesday, July 06, 2016 1:38 AM
To: Choy, Fannie (Yuet); Farkas, Ronald
Subject: Northstar for latest assessment of Study 202

Did Sarepta submit the latest northstar results for study 202? If not, please request them. Thanks.

Eric Bastings, MD
Deputy Director
Division of Neurology Products
CDER/OND

Smith, Celeste

From: Kelley, Laurie
Sent: Wednesday, June 08, 2016 7:50 AM
To: Breder, Christopher D; Farkas, Ronald; Bastings, Eric; Dunn, Billy
Cc: Choy, Fannie (Yuet); Ware, Jacqueline H; Kelley, Laurie
Subject: FW: Regulatory Contact: re: NDA 206488
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215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [<mailto:Fannie.Choy@fda.hhs.gov>]
Sent: Friday, June 03, 2016 1:08 PM
To: Shamim Ruff <SRuff@Sarepta.com>

From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#)
Subject: FW: Finalized - NDA 206488 Office Director Review (REV-SUMMARY-11)
Date: Tuesday, July 19, 2016 9:50:00 AM
Attachments: [Sareptafinal \(6\).pdf](#)

Robert M Califf MD
Commissioner of Food and Drugs

From: Woodcock, Janet
Sent: Friday, July 15, 2016 9:59 AM
To: Califf, Robert
Subject: FW: Finalized - NDA 206488 Office Director Review (REV-SUMMARY-11)

Here it is. The team got the IHC data wrong for some reason. I didn't want to put that in, but John J in his response pointed this out and then I had to include. You don't compare baseline of one experiment to the 180 week results from another experiment, when the baseline values in the two experiments were very different. jw

From: oasfda@fda.gov [<mailto:oasfda@fda.gov>]
Sent: Thursday, July 14, 2016 2:31 PM
To: Woodcock, Janet
Subject: Finalized - NDA 206488 Office Director Review (REV-SUMMARY-11)

[Proceed to DARRTS Welcome Screen](#)

Finalized - Office Director Review (REV-SUMMARY-11)

The following communication has been signed and finalized.

Functions

Communication	Communication Group	Communication Name
REV-SUMMARY-11	SUMMARY	Office Director Review

Linked Submissions

Application Type and Number	Sponsor	Preferred Product Name	Submission Type and Submission Number	Classification	Group ID
NDA-206488	SAREPTA THERAPEUTICS INC	Eteplirsen	ORIG-1	Type 1- New Molecular Entity	

Signers

Signer	Proxy Signer	Signed Status	Signed Date
WOODCOCK, JANET		signed	07/14/2016

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["Confidential Information"](#)

CENTER DIRECTOR DECISIONAL MEMO

NDA# 206488
Drug Name EXONDYS 51 (eteplirsen)
Indication Duchenne Muscular Dystrophy (DMD)
Sponsor Sarepta
Author Janet Woodcock, M.D.
**Director, Center for Drug Evaluation and Research (CDER),
Food and Drug Administration**

SUMMARY

This memorandum explains the CDER’s final decision on the above application. I have read the reviews and recommendations by Drs. Unger (Office level), Bastings (Division level), Farkas (Cross-Discipline Team Lead), Breder and Rao (Clinical Reviewers), Ling (Statistical Reviewer), and Bhattaram, Wu, and Rogers (Clinical Pharmacology Reviewers). In addition to the review memoranda, I have also reviewed the Advisory Committee briefing materials, pertinent portions of the sponsor’s submission, and multiple scientific statements submitted by the public, including a letter from a large number of DMD experts.

The review team has done an exemplary job in performing a detailed evaluation of the data submitted with the application. Nevertheless, I disagree with certain of their findings and come to a different conclusion, as discussed below.

I find that the data contained in NDA 206488 meet the standard for accelerated approval under 21 CFR 314.510 based on the surrogate endpoint of increased dystrophin protein production, a surrogate endpoint that I conclude is reasonably likely to predict clinical benefit.

DISCUSSION

Extensive analyses have been performed by the team on the clinical results of the long-term experience of 12 patients administered the drug, and I will not recapitulate these.

Approval under 314.510 is based, among other things, on adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Below, I discuss how both of parts of this standard are met.

A. Are the Data on Dystrophin Protein Production From One or More Adequate and Well-Controlled Studies?

The characteristics of adequate and well-controlled studies are laid out in 21 CFR 314.126. Three lines of evidence are pertinent to the conclusion that eteplirsen results in increased dystrophin production.

- Production of an appropriate mRNA transcript
- Quantitative assessment of dystrophin content in muscle biopsies by Western blot
- Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry (IHC) techniques

The sponsor provided data demonstrating an increase in mRNA expression following treatment with eteplirsen. The drug's proposed mechanism of action is to bridge a section of the pre-RNA to result in a shorter mRNA with an open reading frame, e.g., "exon skipping." In this case, the production of an appropriate mRNA transcript has been documented by PCR and Sanger sequencing. Although this establishes proof of mechanism, it does not mean that there is increased protein production.

In the following, I discuss the assessments related to dystrophin protein production (2. and 3.) in some detail. Much of the controversy over the adequacy of these assessments relates to the fact that rigorously validated assays were not used to evaluate the initial 3 muscle biopsies, apparently resulting in overestimation of the various readouts and some irreproducibility of IHC and Western blot dystrophin assays. For these reasons, I do not discuss or rely upon the results of these earlier assays, or on re-reads of them. With FDA's assistance, the sponsor improved the design and conduct of the assays and performed repeat biopsies on 11 of 12 patients at week 180. The control samples for these week 180 biopsies were stored baseline tissue (in 3 of 11 subjects) and baseline biopsies from subjects with exon 51 amenable mutations enrolled in another trial by the sponsor. FDA reviewers had the following concerns about these controls, leading them to conclude that the studies were not adequate and well controlled.

1. Most of the baseline biopsies were not from the same subjects as the week 180 biopsies (as the original tissue had been used up for the previous assays). Given this, the control subjects could differ in unknown ways from the test subjects.
2. The biopsies taken at week 180 were from different muscles in the upper extremity than the baseline biopsies, including subjects with baseline tissue as well as for control samples. It is hypothesized that there may be differences in dystrophin protein content among various muscles in DMD patients.
3. The existing baseline biopsies for the three subjects with 180 week data had been stored frozen for several years and may have changed (apparent decrease in dystrophin protein content) over time.

In my judgment, these issues increase the uncertainty around the results, but do not necessarily render them an inadequate basis on which to draw a conclusion. The non-treated control subjects were very similar in age and dystrophin mutation site to the treated subjects (sponsor Appendix 10, AC briefing package). The single deltoid muscle biopsy in the untreated control group (subject 7, sponsor Appendix 14, AC briefing package) had replicate dystrophin levels of 0.3% and below the limit of quantification, averaging out at below 0.3%, and not different than biceps biopsy results in other patients, suggesting

that variations in upper extremity biopsy site (concern b above) did not result in large differences in the findings. There was little difference in the dystrophin protein content found in the stored baseline samples and the frozen samples, as discussed below.

The data submitted with the original application, supporting the finding that eteplirsen increases the production of dystrophin protein, come from the quantitative assessment of (internally truncated) dystrophin in muscle tissue by Western blot using the controls described above. Much of the controversy around this method relates to the fact that the apparently achieved dystrophin levels are very much lower than originally hoped (and previously claimed by the sponsor and investigators).

In the 180 week assessment, the three subjects with baseline biopsies available had baseline dystrophin levels (reported as % of normal) below the level of quantification of the assay used (0.25%). These results were similar in magnitude to the baselines of the six additional control biopsies drawn from subjects in another study (highest level 0.37%). At week 180, two treated subjects had (an average of replicate) dystrophin levels above 2%, two had over 1%, and two additional had about 1%. Of these individuals, two subjects having both baseline and week 180 samples had clearly increased levels at week 180 compared to baseline. (The third subject with a baseline sample did not consent to a week 180 biopsy). Unsurprisingly, some subjects had week 180 dystrophin levels similar to the overall baseline control levels. Not all individuals are expected to respond to a drug intervention. The issue is whether the dystrophin levels found at 180 weeks were within the variability expected for this assay in such patients and, thus, could have arisen by chance, or whether they could have been caused by differences from the controls or from sample storage as outlined above, or whether they reflected a drug effect, and, thus, whether these data could be seen as adequate and well-controlled. The following data are relevant to this issue.

Because the original data on the presence of dystrophin by Western blot suffered some difficulties in interpretation because of lack of availability of baseline samples from most patients, the sponsor of this application submitted, subsequent to the Advisory Committee meeting on this drug, additional Western blot data from 12 patients with baseline and 48 week eteplirsen exposure, using baseline and post-treatment muscle biopsies from the same patients and muscle groups. This experiment clearly shows, using adequate controls, that the drug increases dystrophin protein production in some of the patients. The mean baseline dystrophin values in this study were very similar to the mean baseline values in the 180 week study. The achieved levels of dystrophin in these patients are lower than those seen in the Western blots from the week 180 patients. Only 2 of 12 patients achieved a level over 1% of normal control. It is not known if this result is due to a shorter duration of drug exposure or to other factors. Putting together the 180 week data and the additional 48 week data, I conclude that there is substantial evidence from Western blot experiments of increased dystrophin protein production, albeit at a low level.

A finding of increased dystrophin was also seen in several IHC assays performed by the sponsor. Both assays were originally performed with baseline and several pre-180 week assays by the sponsor as a part of the clinical trial. The validity of the results of these assays were questioned by FDA because of methodological problems in their conduct, as documented in the primary clinical review and in the inspection report. Therefore, I will not further consider the results of these original assays. As discussed for the Western blot above, the sponsor responded by performing an additional 180 week biopsy and repeating the assays. Baseline tissue was available, as for Western blot, from recut samples

in only three cases. In one of these, the subject did not consent to a biopsy at 180 weeks. To supplement the three baseline samples the sponsor included six other untreated patients from a different trial, as discussed above for the Western blot. In both assays, greater staining or intensity was observed after drug exposure at week 180 compared to controls. The results are described in more detail below.

A Percent Dystrophin Positive Fibers analysis was a semi-automated evaluation performed at 180 weeks and compared to the controls used for the 180 week study as discussed above. The percentage of positive fibers was assessed using a blinded read by Nationwide Children's Hospital and by three independent pathologists through Flagship Biosciences. The technique used to assess percent positive fibers was modified from the original assay in the following ways:

1. A computer algorithm (MuscleMap from Flagship) that performs non-linear mapping of all fibers was used for consistent and automated analysis of low intensity values, in contrast to a manual and non-standardized fiber counting technique in the prior assay.
2. The images were inverted and amplified to score the total fibers (the denominator for the percent positive fiber scoring).
3. An isotype matched secondary antibody staining step was incorporated to confirm lack of non-specific staining and reduce background noise. The background signal was subtracted from test sample values in calculation of percent intensity.
4. 8% of the images for re-analysis were blinded, renamed, randomized, and rotated 180 degrees.
5. A rejection factor for the inter-rater analysis score of <4 was established.
6. The images were acquired in a more systematic and random fashion to minimize bias, with predefined rules for random sampling of fields and avoiding artifacts.

These changes were likely to result in a more conservative reading of Percent Dystrophin Positive Fibers, and indeed the results, including the new untreated baseline controls, were read at 1.1% positive fibers (in contrast to a higher result in the prior baseline using the original technique). The 180 week cohort had a score, using this technique, of 17.4% positive fibers, showing a statistically significant difference. Now, these results are subject to the same caveats as discussed for the Western blot (1-3 above), in that there were only two baseline to 180 week pairs, that the baseline samples had been frozen for years, and that the external controls might differ in some way. So, these results cannot stand alone.

Other reviewers have pointed out that the (much higher) baseline values for Percent Positive Fibers from the original experiment are not very different from the 180 week values in this new experiment. However, I would point out that experimental conditions changed quite a bit, and very low values for all the external controls, statistically comparable to the frozen baseline results, were obtained in this recent experiment, suggesting that it returned a more conservative result. I do not believe that comparison of the original baseline data, obtained under one set of experimental conditions, can be compared to the later 180 week results, done under different, more optimized conditions and yielding very different results for new (external control) baseline samples.

The sponsor also performed a Mean Relative Fluorescence Intensity assay for dystrophin. This assay is commonly performed by laboratories evaluating DMD patients and is intended to be a semi-quantitative evaluation of dystrophin content. Using the six external baseline samples and the three stored study patient baseline samples, the mean intensity approximately doubled from baseline to 180 weeks. The technique for this assay did not change significantly from the technique used in the assay done as part of

the original protocol, and the baseline means for the patient samples were roughly comparable to the baseline means obtained in the new experiment.

Although the IHC assays provide only semi-quantitative assessments of dystrophin content, they do support an effect of eteplirsen on the proposed surrogate endpoint (an increase of dystrophin production as a result of drug exposure). The accompanying microscopy images also demonstrate correct localization of the molecule within the muscle fibers, a very important factor in any translation to clinical benefit.

In summary, I conclude that there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells.

B. Is the Effect on the Surrogate Endpoint “Reasonably Likely to Predict Clinical Benefit”?

In this case, the standard for clinical benefit does not require “cure” or “conversion to Becker MD (BMD) phenotype.” Clinical benefit encompasses improvements (including slowing of disease progression) in how an individual feels or functions, or an improvement in survival. There is no question that, for DMD patients and their families, small improvements in function or delays in loss of function are meaningful benefits. Therefore, the question is:

What amount of increase in dystrophin production is reasonably likely to predict clinical benefit (even small benefits)?

The usual way to address this question would be to rigorously evaluate what is known about the correlation between dystrophin levels in muscle and expression of disease. The following summarizes the existing scientific literature on this topic and the challenges in interpreting it.

1. The clinical classification of disease severity (i.e., phenotype) in the literature appears broad, variable, and somewhat subjective.

Experts usually classify patients clinically as DMD (severely affected at a young age); intermediate MD (also called DMD/BMD); or BMD, which can range from severe BMD to asymptomatic individuals with biochemical abnormalities, usually increased creatine phosphokinase (CPK). There is clearly a wide spectrum of disease wherein the ends of the spectrum are easily distinguishable, but the zone of real interest for this discussion, between DMD and intermediate presentations, is not rigorously categorized. In part, this is because “intermediate muscular dystrophy” (IMD) is less common, due to the consequences of having either in-frame mutations with a truncated protein expressed (leading to BMD) or out-of-frame mutations with little-to-zero protein expressed (leading to DMD), as discussed below.

2. Much of the prior data reporting the relationship of dystrophin protein levels to phenotype have been from IHC studies using a variety of techniques and antibodies.

Anthony, et al., (*Neurology*, 83, 2014) in a collaborative cross-laboratory study, investigated the variability of techniques used to quantify dystrophin in individuals with muscular dystrophy. Blinded tissue sections from three DMD and three BMD muscle biopsies were tested in five

different laboratories accustomed to performing dystrophin quantification. Estimates of dystrophin expression using a somewhat standardized IHC technique were about 20%, 11% and 10% of normal for the three DMD samples, on average among the laboratories. Corresponding estimates of dystrophin content by Western blot, using an actin antibody to normalize for loading, but not a serially diluted standard control, resulted in dystrophin estimates of about 11%, 0, and 0.4% respectively, with fairly high CV's. Therefore, in this small sample, repeated across five experienced laboratories, IHC estimates were about 10 percentage points higher than Western blot estimates.

Significantly higher estimates by IHC by fluorescence intensity (overall about 23% of normal) than by Western blot were also seen in the evaluation of week 180 muscle biopsies in the Sarepta trial. Because much of the historical data on protein content vs phenotype has been reported using IHC analysis, extrapolating these findings to the current trial data is challenging. Additionally, Anthony et al., found that the inter-laboratory variability was greatest for the low levels of dystrophin found in the DMD patients. Western blot data in the literature quantifying dystrophin and relating it to phenotype is often from experiments that were not designed to distinguish among dystrophin levels below 10% of normal. These may have been reported out as "less than 10%." From this sponsor's well-controlled studies, the analytically accurate dystrophin baseline for many DMD patients might be in the range of 0.02-0.35 % normal, hence previous estimates of 5-10% might be an over-estimation using non-standardized and semi-quantitative methods.

3. Both IHC analyses and WB results are influenced by the anti-dystrophin antibodies used, as well as other experimental conditions

Significantly, if the epitope recognized by the antibody is modified by the deletion, the dystrophin isoform may not be recognized and a result read out as zero. For this reason, recent studies use multiple antibodies against known regions. Additionally, muscle biopsies in patients with BMD and DMD may be quite variable in degree of fibrosis and fatty replacement; this may decrease the reproducibility and representativeness of muscle biopsy estimates of dystrophin content by Western blot. Additionally, imaging methods, choices for normalization, biopsy handling, background standing, and a multitude of other experimental conditions can influence results.

4. The phenotype is significantly influenced by *dystrophin isoform quality* as well as *dystrophin quantity*.

Dystrophin is a very large protein with multiple functional domains. Generally, DMD results from an out-of-frame mutation (often a deletion) that leads to an unstable or unreadable mRNA transcript. Thus, DMD patients usually have zero or very low levels of dystrophin, but the DMD phenotype can also result from in-frame mutations that result in a unstable transcript or dysfunctional dystrophin isoform. BMD usually results from an in-frame mutation (often an exon deletion) that affects the functional quality of the protein and also the quantity produced. It remains unclear what role protein function plays vs quantity in leading to the wide range of variability in BMD phenotypes. There are a vast number of mutations that can lead to each of these phenotypes (Tuffery-Giraud, et al., *Hum Mutat*, 30, 2009), all of which can have different effects on protein function as well as protein production. This micro-heterogeneity is common in genetic diseases and is highly germane to

evaluation of interventions targeting the gene, gene expression, or protein function. There are also non-dystrophin-related factors that can modulate phenotype.

5. The literature contains various findings on the relationship of dystrophin expression to clinical status, including the low levels of dystrophin protein of interest in this case.

I note that in the decades since 1988, much technical progress has been made in standardizing Western blot techniques, and the results from early studies may not be fully comparable to those from recent experiments.

- a. The seminal 1988 paper on this subject (Hoffman et al., *NEJM*, 318(21)) found that the majority of patients with DMD had undetectable levels of dystrophin using their Western blot technique and that 35 of 38 had levels below 3% in their assay. They also reported that one of seven “intermediate” patients had dystrophin levels below 3% of normal, as did one of the 18 patients with a BMD phenotype.
- b. Beggs et al., (*Am J Hum Genet*, 49, 1991) published one of the early studies on the correlation between the level of dystrophin on Western blot and clinical features of BMD. Western blot was performed using a polyclonal serum and had about a 20% variability between blots according to the authors. In this study a number of patients with BMD or intermediate phenotype (DMD/BMD) were found to have dystrophin contents that overlapped with those of the DMD patients. Of four patients included with DMD phenotype, two had less than 5% dystrophin, and two had 10%, by their assay. Of patients with BMD/DMD phenotypes, eight were found to have 10% of normal dystrophin, two had 15%, one had 50%, and one had 100%. Three BMD patients with dystrophin levels of 10% were found; two of these had relatively mild disease.
- c. Nicholson et al., (*J Med Genet*, 30, 1993) studied patients across a wide range of DMD and BMD phenotypes. They used loss of ambulation as a criterion to establish five functional groups, grouped from one (most severe, LOA before age 9) to five (LOA past age 40) (pre-steroid era). *They found a linear relationship overall between dystrophin levels (Western blot with Dy4/6D3 antibody, using myosin for a loading control) and their five categories, with more dystrophin protein translating to better function. They found no significant difference between any two adjacent groups however, which they interpreted as showing considerable overlap, as reflected in their patient level data (Appendix 1), which showed a number of less severe patients (e.g., Group 2 or 3) registering no or very low dystrophin abundance on their Western blot assay.* Of note, they reported a higher average level of dystrophin protein in severe DMD patients than other investigators, partly resulting from 5 of their 21 severe patients reported to have dystrophin protein levels above 20.
- d. Neri et al., (*Neuromuscular Disorder* 17, 2007) reported on families with X-linked Dilated Cardiomyopathy. In these families, mutations give rise to absent dystrophin in heart muscle, but only reduced levels of nearly normal dystrophin in muscle tissue. One patient in their series had a normal neurological exam at age 23, an elevated CPK, and 29% of normal dystrophin protein in skeletal muscle by Western blot. This example can contribute to understanding the role of abundance of dystrophin protein vs compromised function.

- e. Anthony et al., (*JAMA Neurology*, 71, 2014) evaluated the correlation between phenotype and mRNA and protein expression in patients with both in-frame and out-of-frame mutations amenable to exon 44 or 45 skipping. Studying a group of patients with closely related deletions could diminish variability due to differences in function of the truncated protein. Five samples from patients with clinical “mild” BMD and in-frame mutations underwent Western blot analysis using the Dys-2 antibody. Their mean protein expression was 17% (normalized to actin) with a standard deviation of 7.5%. Two of the “mild” patients had dystrophin levels in this assay of around 10%. Based on comparisons of IHC experiments with various antibodies, the authors found “*no clear correlation between the level of dystrophin transcript or protein expression with clinical severity*” in 13 patients with in-frame mutations leading to BMD. The finding of Neri et al., above, along with this report, reinforce the concept that protein function (i.e., quality) is an important determinant of clinical severity and undermine the concept that 10% dystrophin protein content is a threshold, since these patients had “mild” BMD.
- f. Van den Bergen et al., (*J Neurol Neurosurg Psychiatry*, 85, 2014) compared dystrophin levels by Western blot with clinical severity in 27 patients with a clinical diagnosis of BMD. Dystrophin expression ranged from 4-71% and 3-78%, depending on the antibody used. *The authors found no linear relationship between dystrophin expression by Western blot using newly acquired muscle biopsies and clinical severity, muscle strength, or fatty infiltration on MRI.* Although this was the case for the majority of the patients, who had dystrophin levels above 20% of normal, four patients had levels at or below 10%. These patients generally had a more severe phenotype: one patient with a dystrophin level of 10% was wheelchair dependent at 45 years; one patient with a level of 7% developed trouble with stair walking at age 21; one patient with a level of 4% had a DMD phenotype with wheelchair dependency at age 10, one patient with a level of 3% had wheelchair dependency at age 25.
- g. Anthony et al., (*Brain*, 134, 2011) studied 17 BMD patients with exon 51 or 53 skipping-amenable mutations by IHC methods. These patients primarily had very mild or asymptomatic disease; the one patient classified as severe was ambulatory at age 25 but unable to run. *There was a statistically significant difference in dystrophin expression by IHC when patients classified as mild disease were compared to asymptomatic patients.*
- h. Bello et al., (*Neurology* 87, 2016) published a detailed study of loss of ambulation in DMD patients with particular exon deletions, using the CINRG-DNHS, a prospective natural history study. They found patients with exon 44 amenable mutations to have a two-year delay in loss of ambulation compared to the overall comparison group. This finding had previously been reported by another group (van den Bergen, et al., *J Neuromuscul Dis*, 1, 2014). The mutations studied (primarily single-exon deletion of exon 45) are known to undergo spontaneous skipping with production of some dystrophin. According to the Bello report, of six patients previously tested by IHC, three showed traces of dystrophin production and 0/four (possibly other patients) had dystrophin detectable by Western blot. These authors suggest that the observed differences in loss of ambulation (LOA) could be due to small amounts of spontaneously induced dystrophin that slightly ameliorate the ordinary DMD phenotype.

- i. Cirak et al., (*Lancet*, 378, 2011) published a study (AVI-4658) using intravenously administered eteplirsen that showed a detectable increase in dystrophin protein levels using both Western blot and immunofluorescence in 3/19 patients. The authors reported that the functional properties of restored dystrophin were confirmed by assessing increased levels and co-localization of neuronal nitric oxide synthase (nNOS) and sarcoglycan with dystrophin. Such a protein assembly is suggested to be indicative of functional restoration of the dystrophin-associated glycoprotein complex in muscle fibers (Molza et al., *JBC*, 290, 2015; Wells KE et al., *Neuromuscul Disord*, 2003). Cirak et al., reported that the restoration was more so in patients with exon 49-50 deletions than in those with 45-50 deletions, which is consistent with a previous observation that nNOS binding domain is located in dystrophin exons 42-45 (Lai Y et al., *J Clin Invest*, 2009). These studies suggest that important functional domains are included in the dystrophin protein induced by eteplirsen.

To summarize what is known about the association between dystrophin levels and phenotype, dystrophin content above about 10% on Western blot is usually associated with a BMD phenotype, except in patients with higher levels of dystrophin (including above 50%) who potentially have functionally deficient protein leading to a DMD phenotype. Within the BMD phenotype, a proportional inverse relationship between disease severity and protein expression has not generally been demonstrated (i.e., between 10-100%), although there may be a broad association, as seen in the Anthony study (*Brain*, 134, 2011). This may be due to the fact that protein quality, rather than quantity, plays a key role in determining phenotype in BMD. Patients with DMD are usually found to have no detectable, or very low levels of, dystrophin. Dystrophin content in the 3-10% range has been associated with DMD, DMD/BMD, and BMD phenotypes. I find no evidence of a threshold value for protein content and expression of a DMD phenotype, although the majority of DMD patients reported in the literature have dystrophin that is undetectable by the Western blot assays used. Generally, the divide between DMD and BMD, in terms of protein, is the result of the consequences of an OOF or an in-frame mutation, respectively. I believe that the conventional threshold, at or below 10% protein, was derived from the IHC data that seem to estimate low-level protein content about 10% percentage points higher on IHC than on Western blot, so that the majority of DMD patients would read out at 10% of normal dystrophin on IHC. I believe that evidence from Western blot and other experiments discussed above show that protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation, all other things being equal, i.e., mutation status and non-dystrophin-related factors affecting phenotype.

These findings are germane to the determination of “reasonably likely to predict clinical benefit.” The broad phenotypic distinctions made in the clinic (e.g., DMD vs IMD vs BMD) are different from the prediction of benefit to an individual patient who has a specific baseline dystrophin level and whose mutation and external factors do not change pre- and post-drug. For example, extending ambulation by six months to a year would not normally move a patient from one to another of these categories, but could be very important to quality of life (e.g., as suggested in the Bello study). This is also true for other functional improvements.

For these reasons, incorporating the analysis of dystrophin content discussed above, I conclude that the biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit.

Additional support for “reasonably likely” comes from the long-term experience with the drug. The sponsor’s comparison of the experience of the treated cohort to natural history data does not reach the level of substantiation required for traditional approval based on the clinical data. However, it is highly suggestive of improvement in some parameters, in some patients, over natural history. My conclusion is informed by all the caveats expressed in the reviews about the pitfalls of non-randomized comparisons. Given that the two exon 52 deletion patients in the study had fairly good long-term results in terms of rate of disease progression, the question arises as to whether exon 52 is a prognostic factor that could have skewed the results.

Several facts militate against this conclusion. First, one of the exon 52 deletion trial subjects (subject 6) had a fairly low score on the 6MWT at entry and a very low score on the NSAA, compared to other subject around his age. He also was the only subject in the trial noted to be unable to rise without external support at baseline. Additionally, the Italian external cohort had exon 52 deletion representation.

Questions have been raised about the correlation of dystrophin levels from Western blot with clinical outcomes. The 6 Minute Walk Test does not show a strong correlation. I evaluated the NSAA in children who could still walk (because the NSAA primarily scores activities related to walking) and who also had a dystrophin result at 180 weeks (Table 1). I did this because the NSAA includes multiple measures and therefore might have some noise averaged out. I looked at the absolute decline in NSAA in patients since study initiation, and did not correct for the initial time some patients spent on placebo. I only evaluated patients who were ambulatory. There was a positive (inverse) correlation between dystrophin by Western blot and rate of decline in NSAA score, . (Figure 1) This adds additional support to the idea that dystrophin production is “reasonably likely to predict clinical benefit.” In totality, I find that the comparative disease course data provide additional support for the use of the surrogate endpoint of an increase in dystrophin expression as “reasonably likely to predict clinical benefit.”

Therefore, both the biochemical data and the clinical data lead me to conclude that an “increase in dystrophin production” is reasonably likely to predict clinical benefit in DMD.

CONFIRMATORY TRIALS

The sponsor is currently conducting a nonrandomized, concurrently controlled trial in patients with mutations amenable to exon 51 skipping compared to untreated DMD patients with other exon deletions. Because of the relatively low level of protein induced, additional doses should be aggressively pursued and, if successful, a dose-comparison trial could be confirmatory. The sponsor has also planned to initiate a randomized trial with a related compound in other exons. The clinical results from these trials can inform the predictive value of the surrogate endpoint.

EXPLORATION OF ADDITIONAL DOSES, REGIMENS, AND DRUG-MUTATION INTERACTION

The dystrophin levels achieved in this development program are well below those initially hoped for. I agree with Dr. Farkas and other reviewers that the sponsor should aggressively explore higher doses or more frequent administration of eteplirsen. It appears that this is possible given the toxicology data and the clinical safety profile observed to date.

Because patients in the Sarepta 180 week cohort had a range of deletions in the dystrophin gene, variability in the pharmacodynamic response among deletions is of great interest. The two patients with over 2% dystrophin in the 180 week Western blot both had exon 52 deletions. These patients also fared fairly well, clinically. This raises the question of whether patients with this exon deletion naturally produce more dystrophin. One of these subjects had a baseline sample available. It was found to be below the limit of quantitation. There was an exon 52 subject included in the added baseline controls. This subject's assay had replicate results of 0.3% and below the limit of quantification, respectively, as discussed above. This suggests that baseline dystrophin levels are not higher in exon 52 deletion subjects and that there may be a drug-deletion interaction, wherein subjects with this deletion may have a more robust pharmacodynamic response to the drug. There were a number of apparent non-responders to the drug. It will be important to find out if this is mutation specific. It is likely that more detailed knowledge about each patient's specific mutation will have to be generated to study this in detail.

COMMENTS ON THE DEVELOPMENT PROGRAM AND REVIEW

The development program for eteplirsen was seriously deficient in a number of respects that may have led to delay in broad access and certainly led to difficulties in regulatory review. In my assessment, the most egregious flaw was the lack of robust and high-quality assays early in the development program. Inaccurate conclusions from the assays used led to a flawed development program. Additionally, the entire drug development field must recognize that there is no such thing as an "exploratory study" for a serious, life-threatening illness without therapeutic options. Randomization should be performed very early in the development program, and open-label studies should be avoided. When possible, seamless adaptive dose-finding and early efficacy studies should be carried out with the goal of most efficiently generating the data needed to demonstrate safety and effectiveness.

The flaws in the eteplirsen development program led to severe challenges in regulatory review. 21 CFR 312.80, concerning drugs intended to treat life-threatening or severely-debilitating illness, states that FDA has determined "that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness...Physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses than they would accept from products that treat less serious illnesses." I note that the acceptable risks include greater uncertainty about the effects of the drug. The Peripheral and Central Nervous System Drugs Advisory Committee met on this application on April 25, 2016. There was a split vote (7 against, 6 for) on the question of accelerated approval for this drug, reflecting the greater than usual uncertainty about the application. This vote was taken before the additional data on protein expression were submitted.

To conclude, the studies used in this analysis to support the effect of eteplirsen on dystrophin were adequate and well-controlled as specified in 314.126. In addition, the surrogate of increased dystrophin production is reasonably likely to predict clinical benefit. Given the deficiencies that have been identified in the development program, my conclusion to rely on the surrogate endpoint described above represents the greatest flexibility possible for FDA while remaining within its statutory framework. In this case, the flexibility is warranted because of several specific factors, including: the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a fatal disease in children. Of note, the therapy has been relatively safe in the clinic, although intravenous administration always carries risk. In addition, adequate confirmatory studies are underway and planned and are capable of further refining our understanding of the biomarker and providing evidence about the nature of the clinical benefit. The approval does not create any risk of compromising the confirmatory trials because of their nature. Therefore, I find that the probable benefits outweigh the foreseeable risks and that this application should be approved under 21 CFR 314.510.

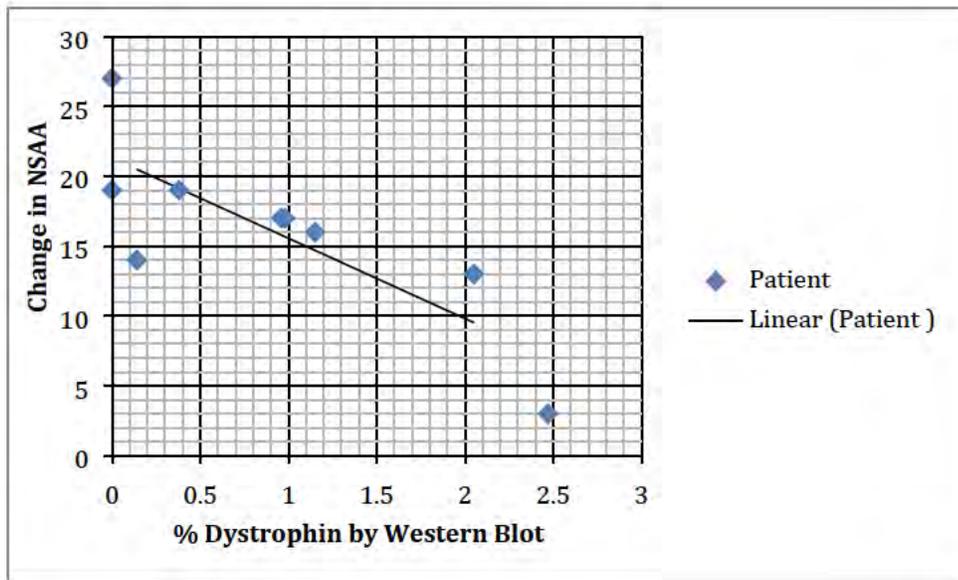
Table 1 Patient Data on Change from Baseline in 6MWT and NSAA

180 Weeks
Change from
Baseline

Subject	Baseline WB	180 Week WB	Fiber Intensity	PDPF	Δ 6MW	Δ NSAA
002	N/A	0.14	MD	4.54	-67	-14
003	N/A	0	7	1.42	-174	-27
004	N/A	0.96	28	29	-168	-17
005	0	N/A	N/A	N/A	-231	-19
006	N/A	2.47	29	21	-23	-3
007	N/A	0	12	7	-197	-19
008	N/A	0.98	26	12	-291	-17
009	N/A	0.52	23	22	0	0
010	N/A	1.62	21	24	0	0
012	N/A	0.38	26	33	-114	-19
013	0	1.15	32	19	-170	-16
015	0	2.05	30	18	-1	-13

Data from Sarepta
Therapeutics, Inc. PCNSD
Advisory Committee Briefing
Document, Appendix 5, p.
149 (6MW and NSAAO
Appendix 11, p. 155, (Percent
Positive Dystrophin Fibers
(PPDF), Appendix 12 p. 156
(fiber intensity) 14, p. 159.
(Western blot),

Figure 1. Decline in NSAA by % Dystrophin on Western blot



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET WOODCOCK
07/14/2016

Smith, Celeste

From: Woodcock, Janet
Sent: Monday, August 01, 2016 11:49 AM
To: Behr, Virginia L
Subject: FW: did you get my memo? jw
Attachments: Sarepta dct (2)_071216.docx

From: Rao, Ashutosh
Sent: Tuesday, July 12, 2016 10:30 AM
To: Woodcock, Janet
Subject: RE: did you get my memo? jw

Hi Janet,

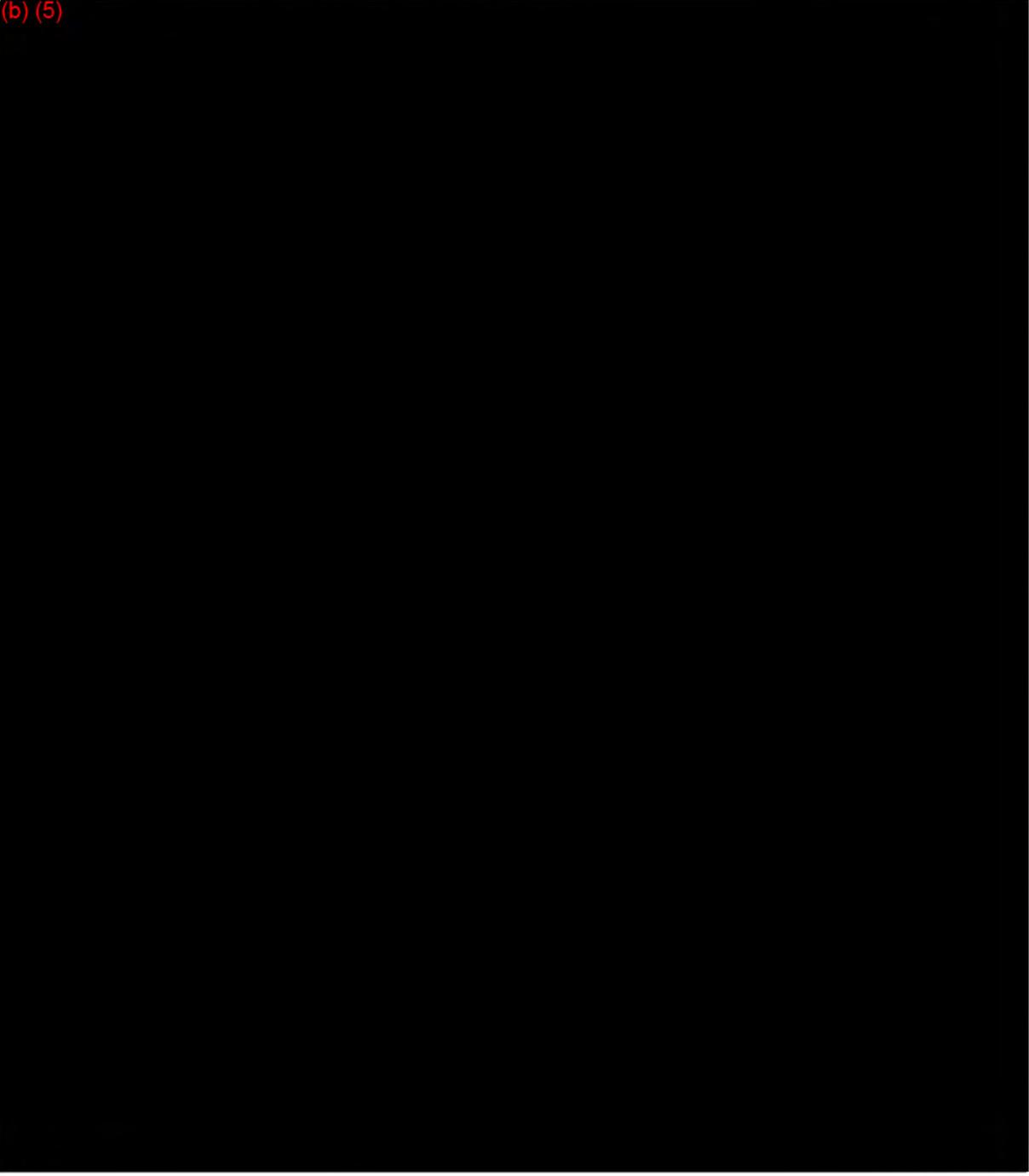
I thought the memo reads very well. Some comments and suggested edits are attached. Please let me know if there are questions.

Thanks
Ash

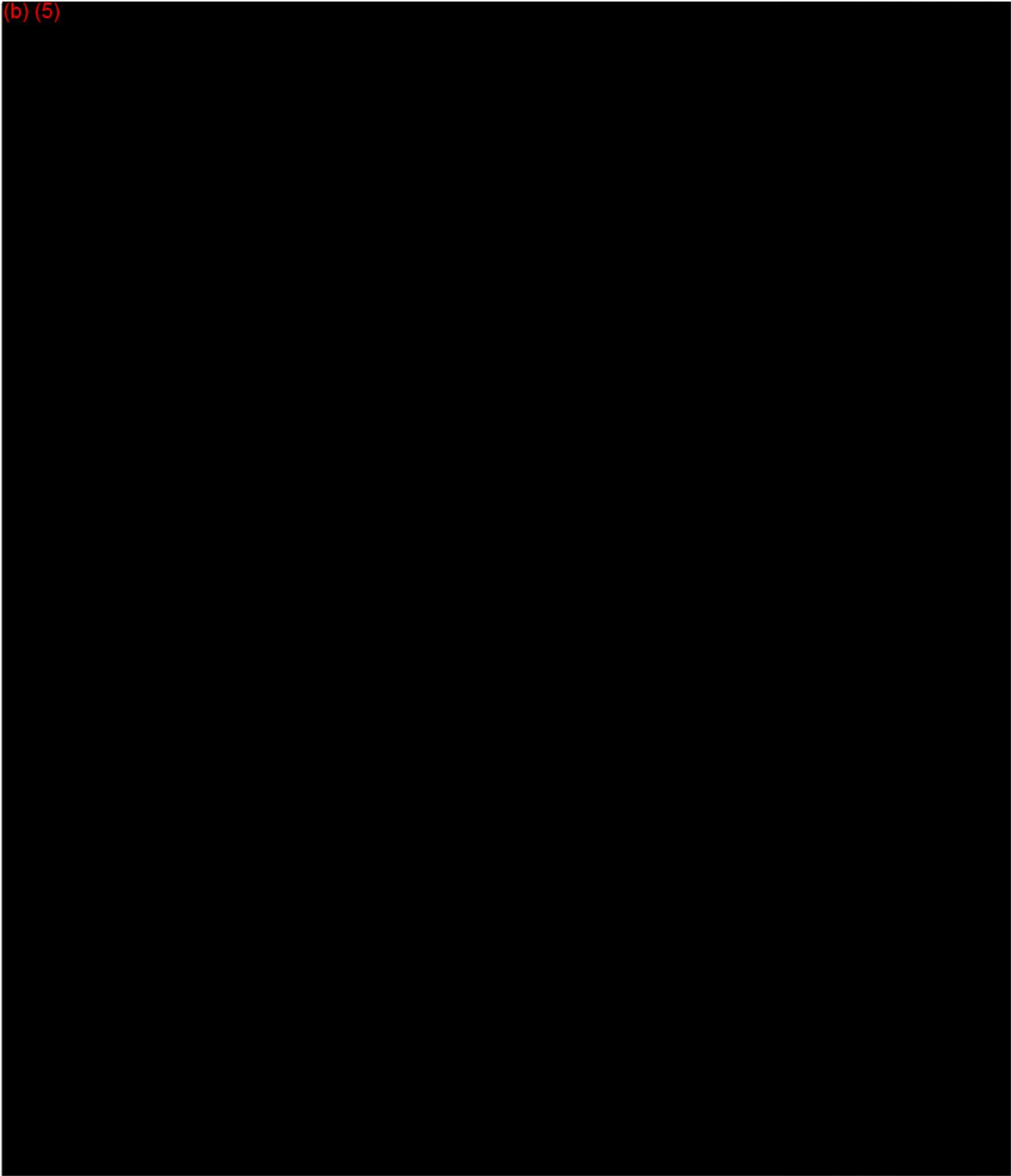
From: Woodcock, Janet
Sent: Tuesday, July 12, 2016 9:32 AM
To: Rao, Ashutosh
Subject: did you get my memo? jw

Center Director Decisional Memo DRAFT

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(b) (5)



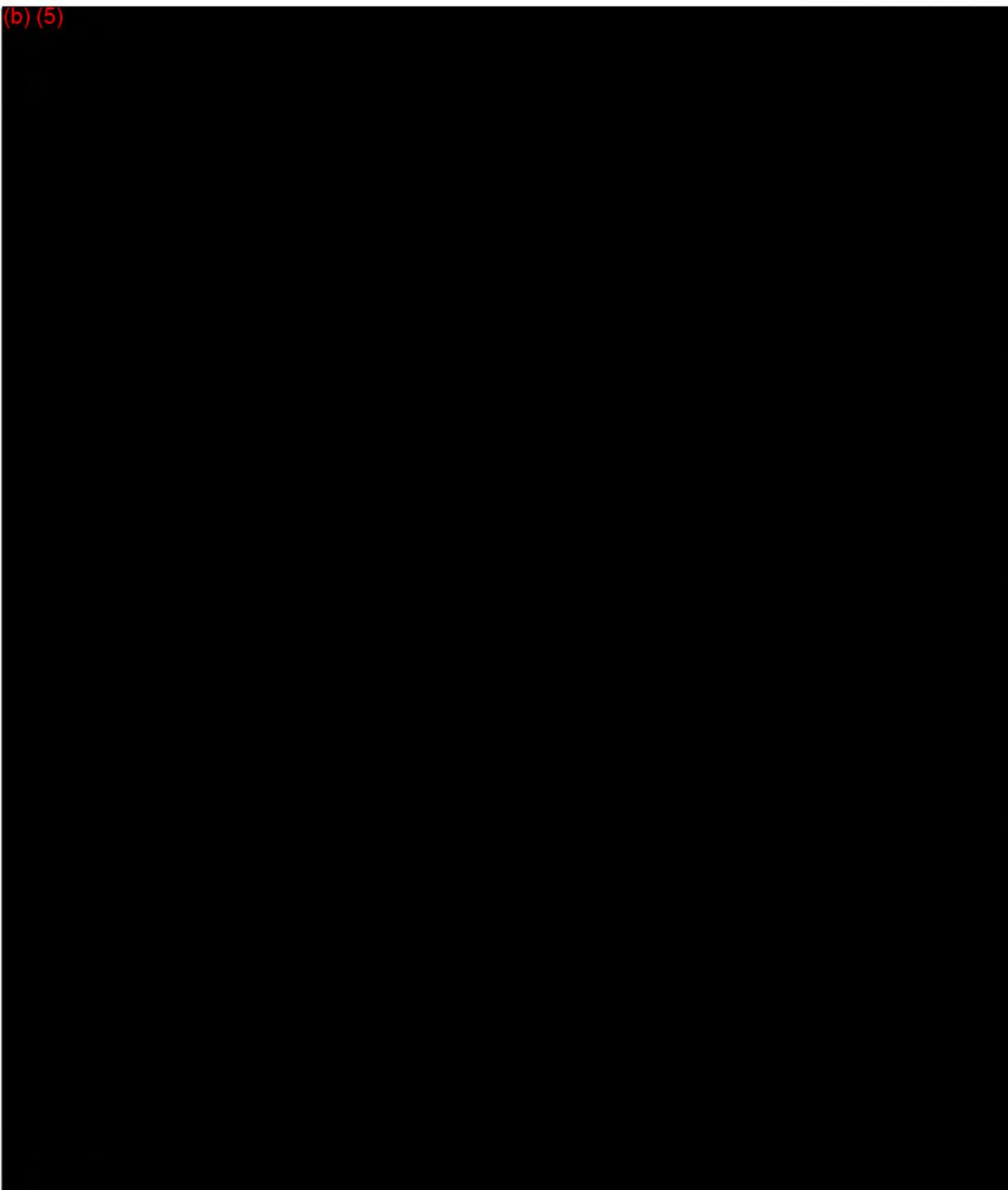
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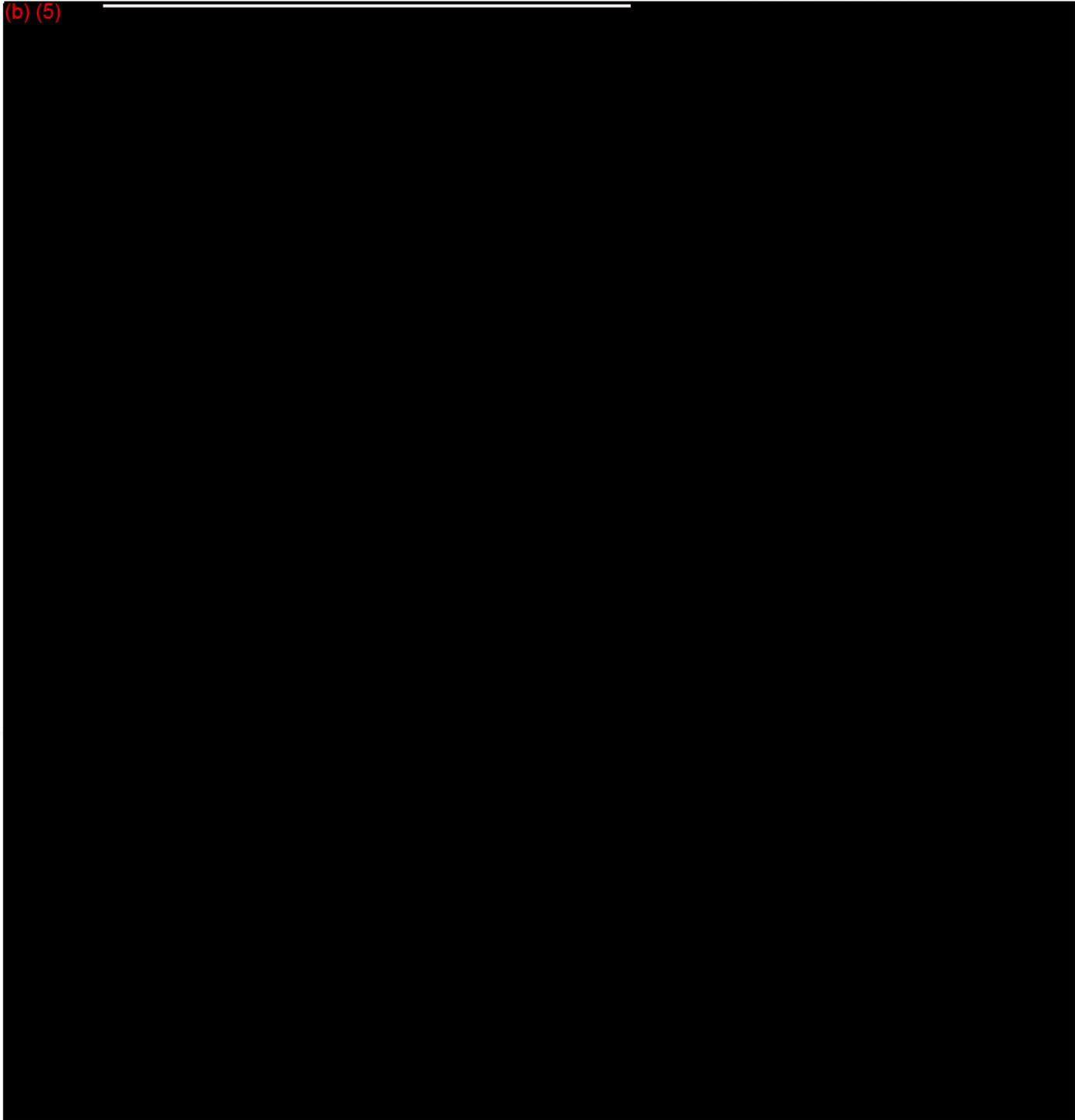
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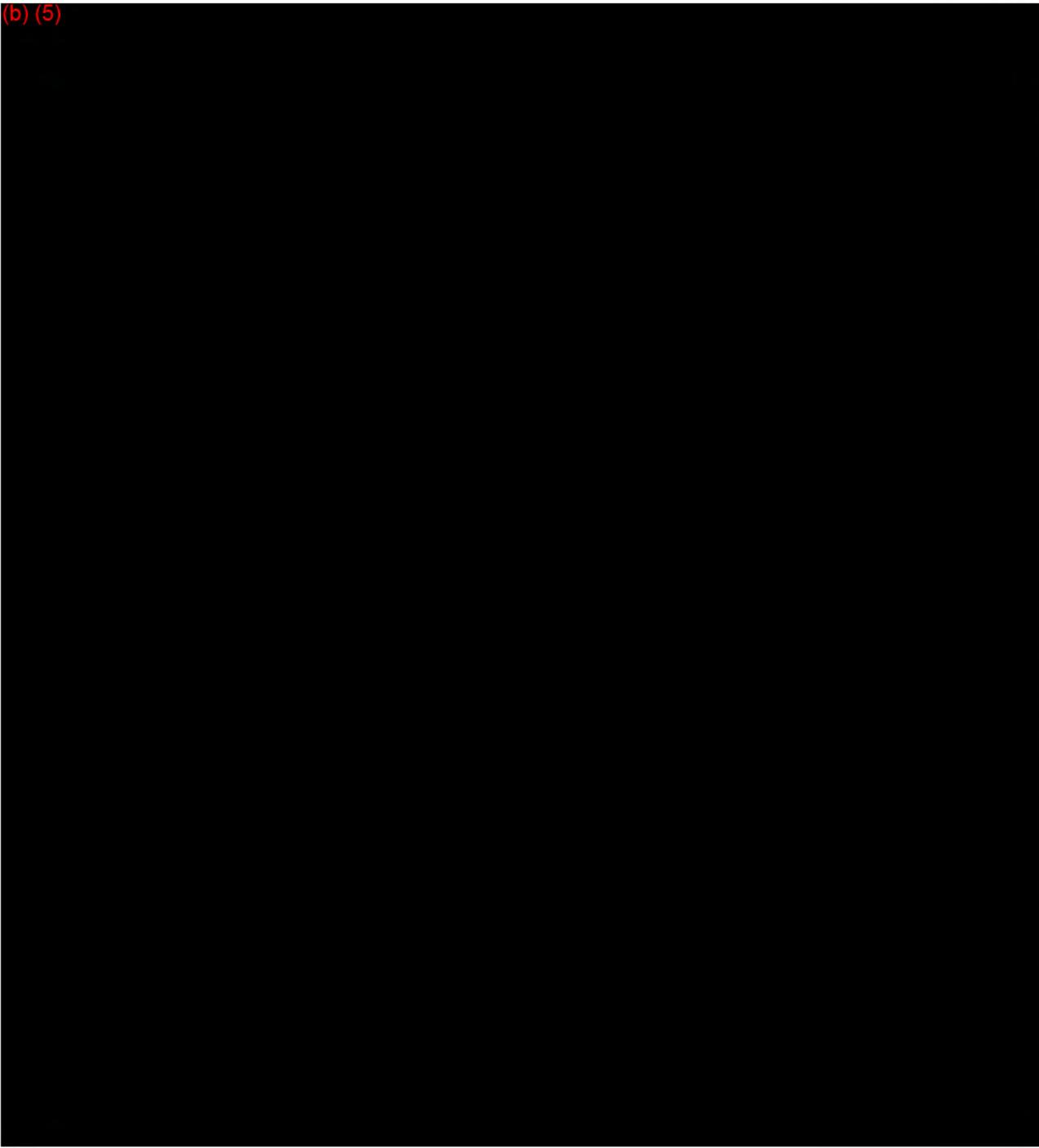
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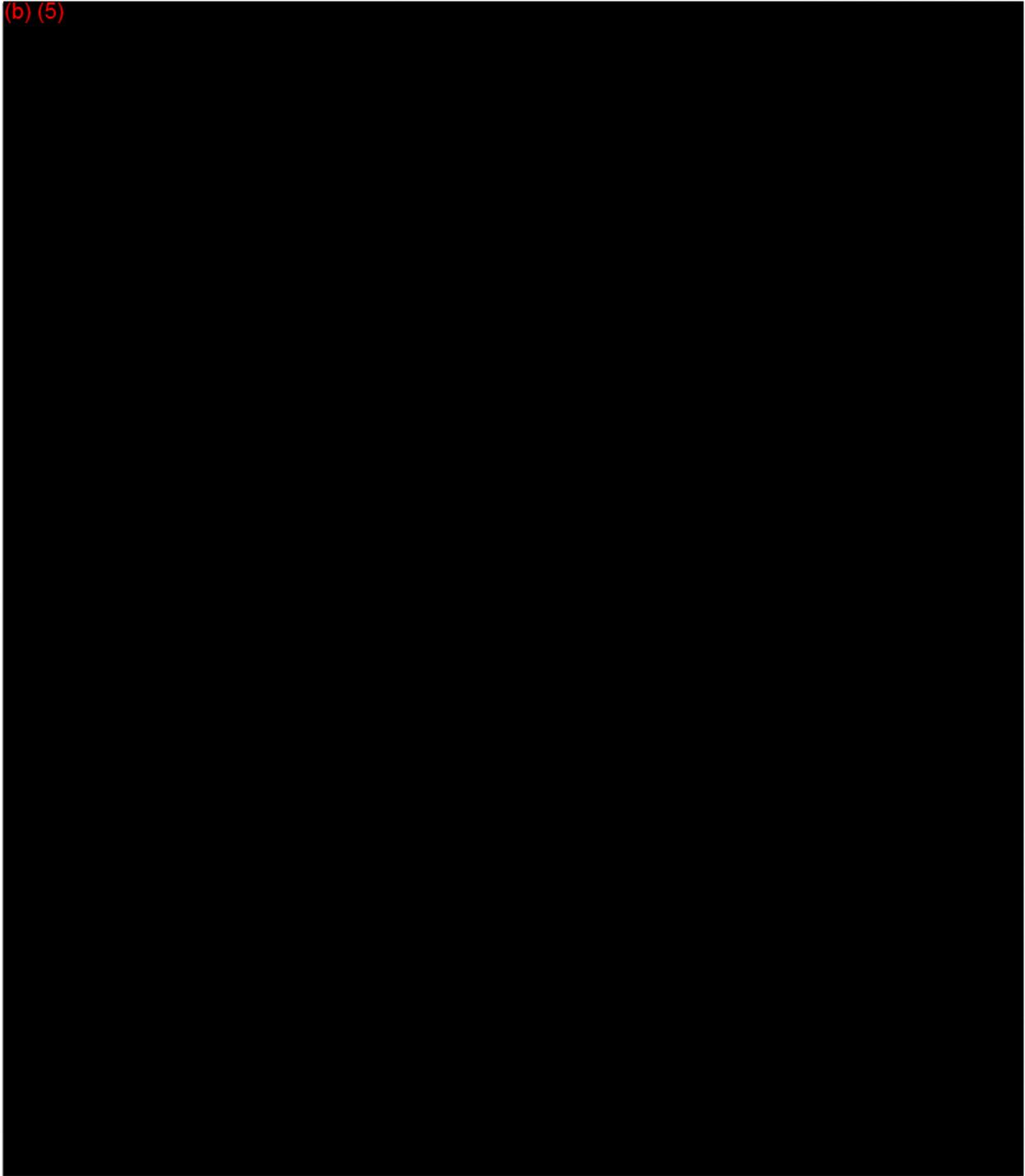
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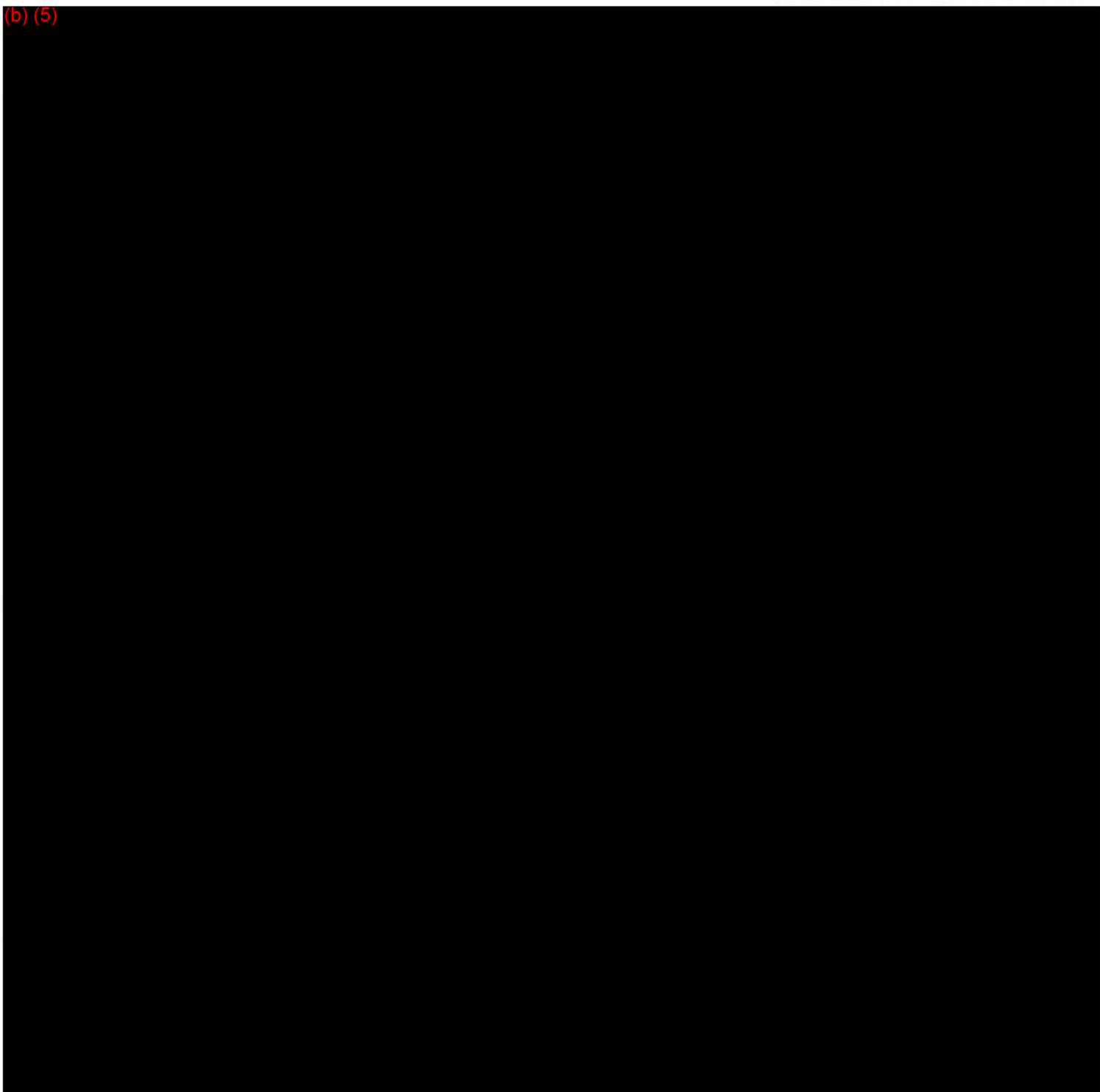
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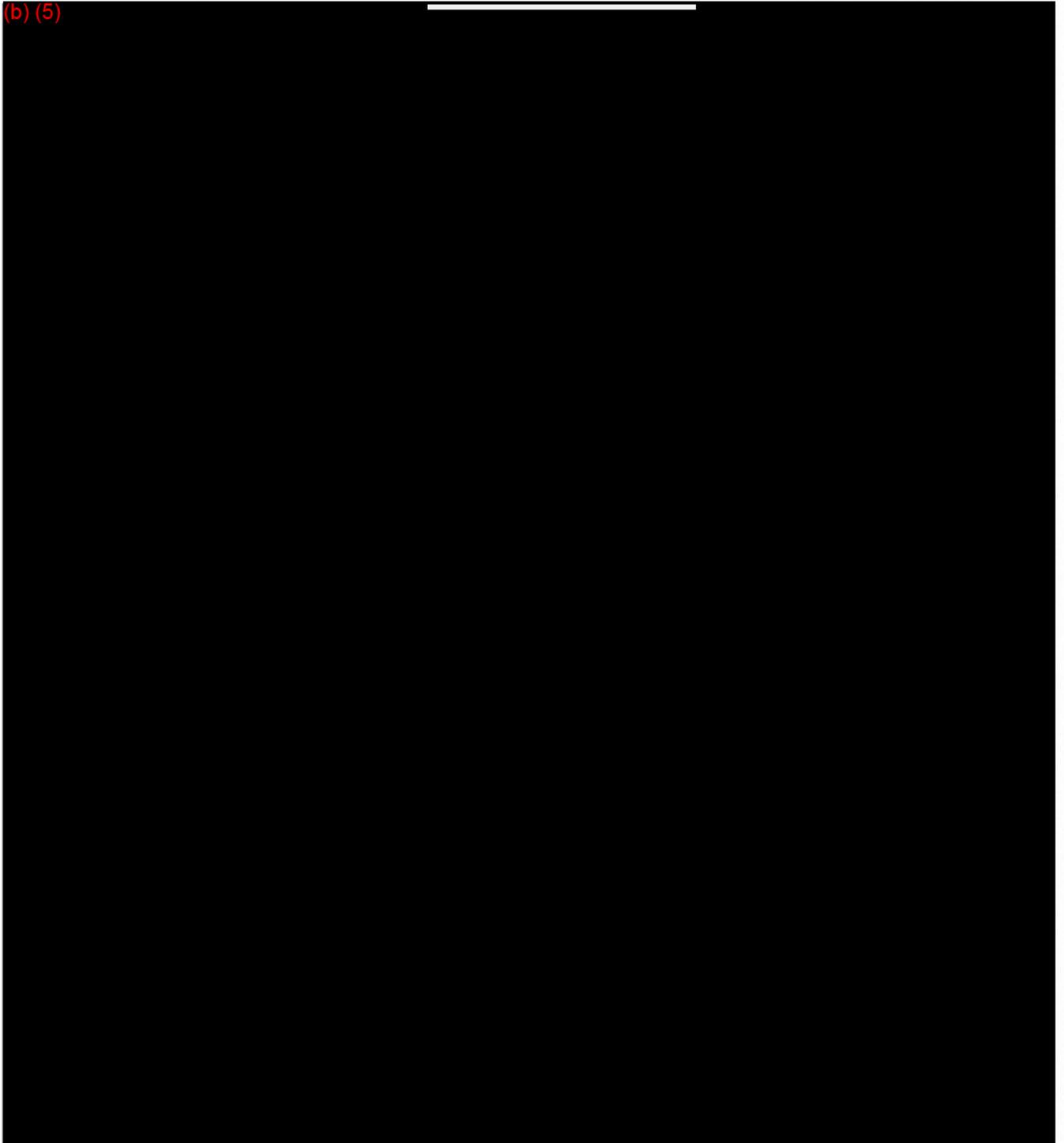
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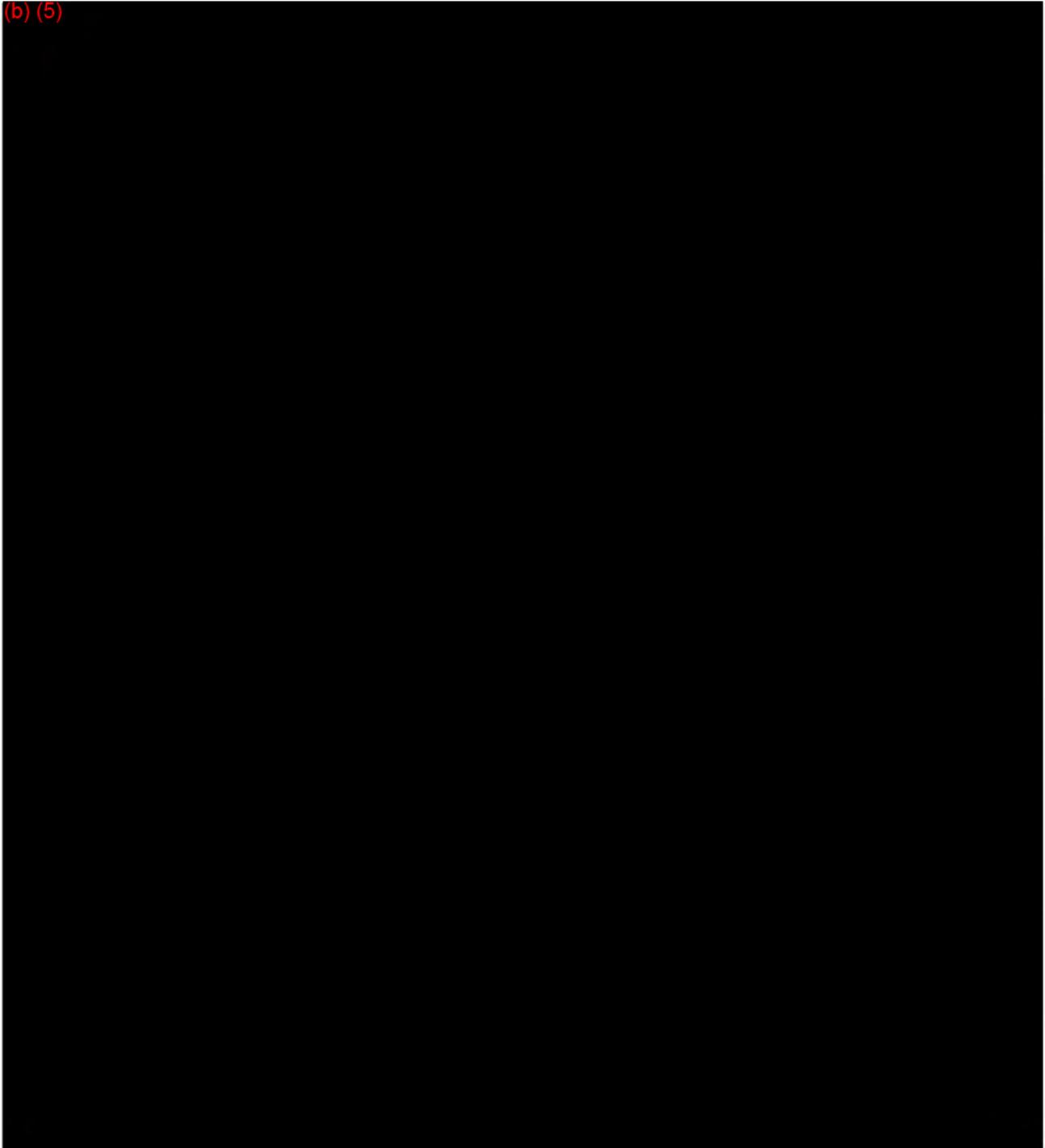
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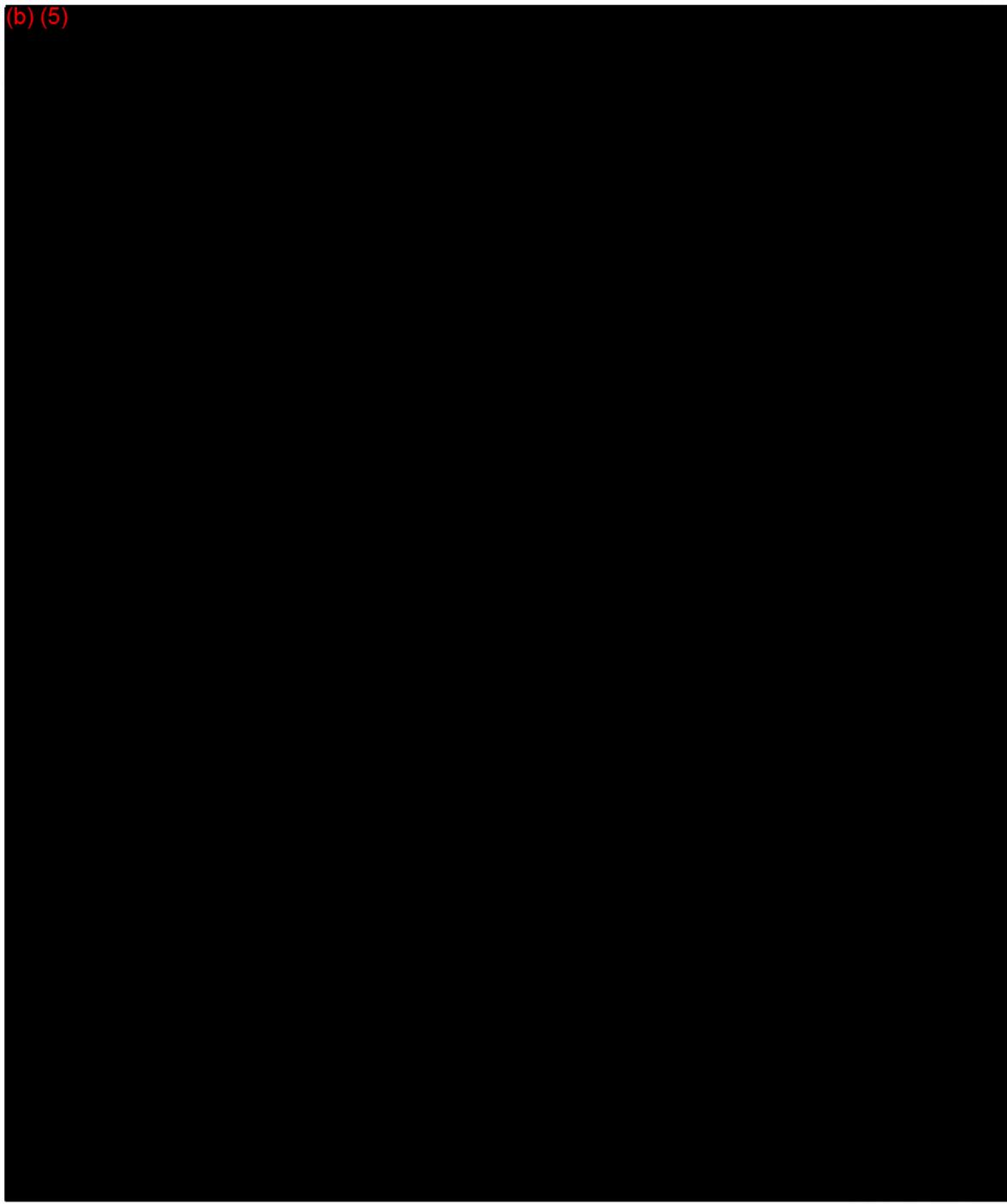
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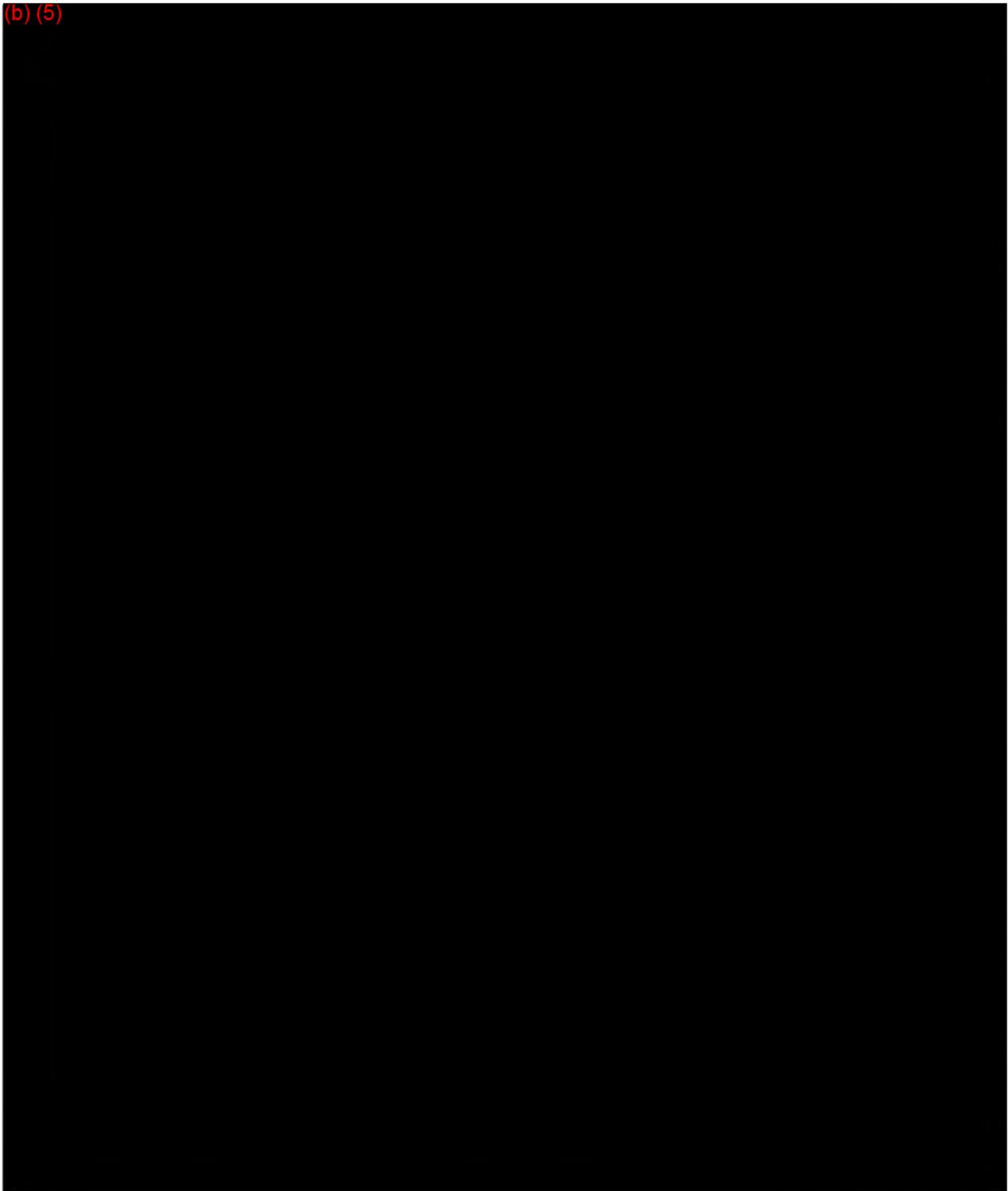
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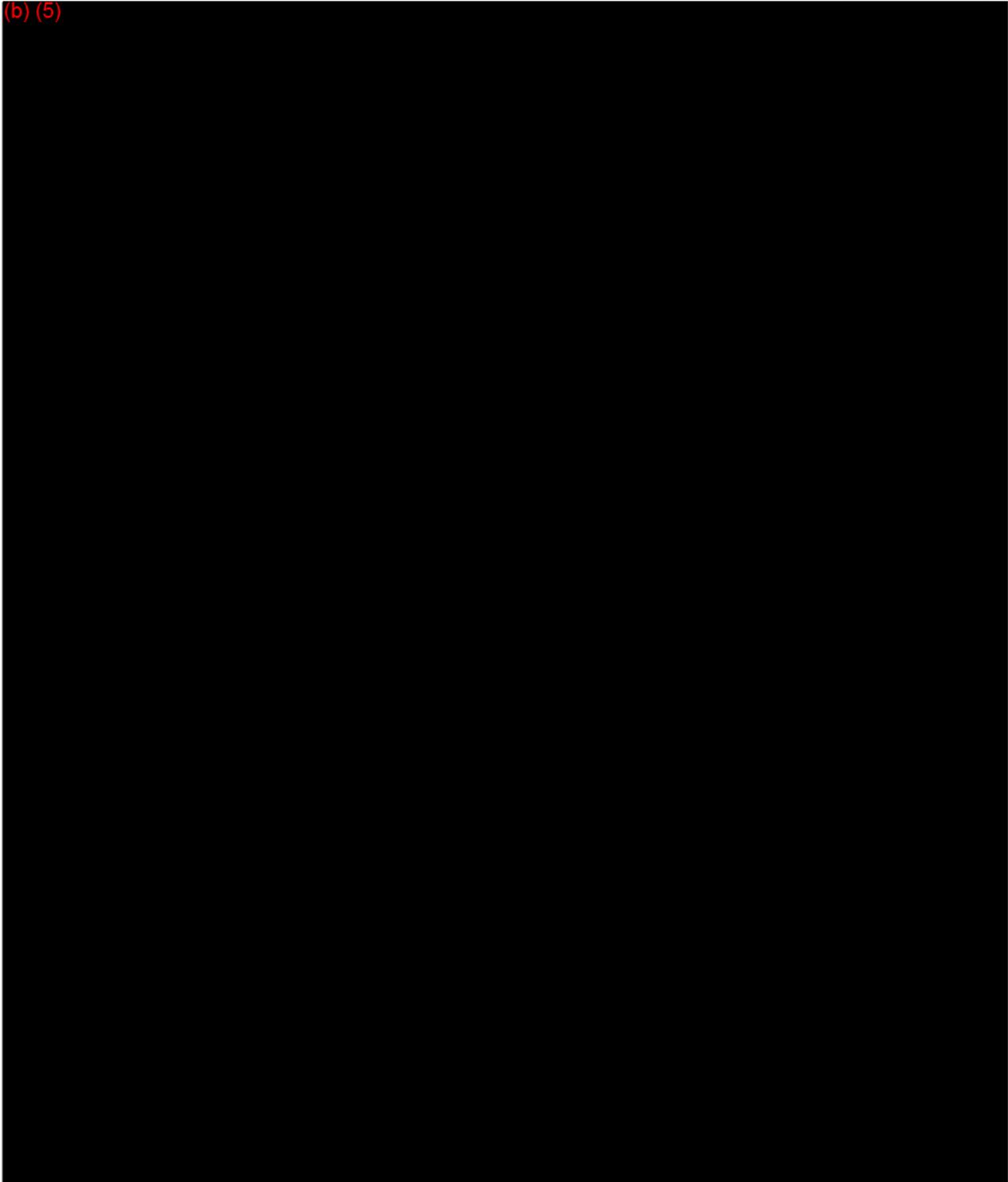
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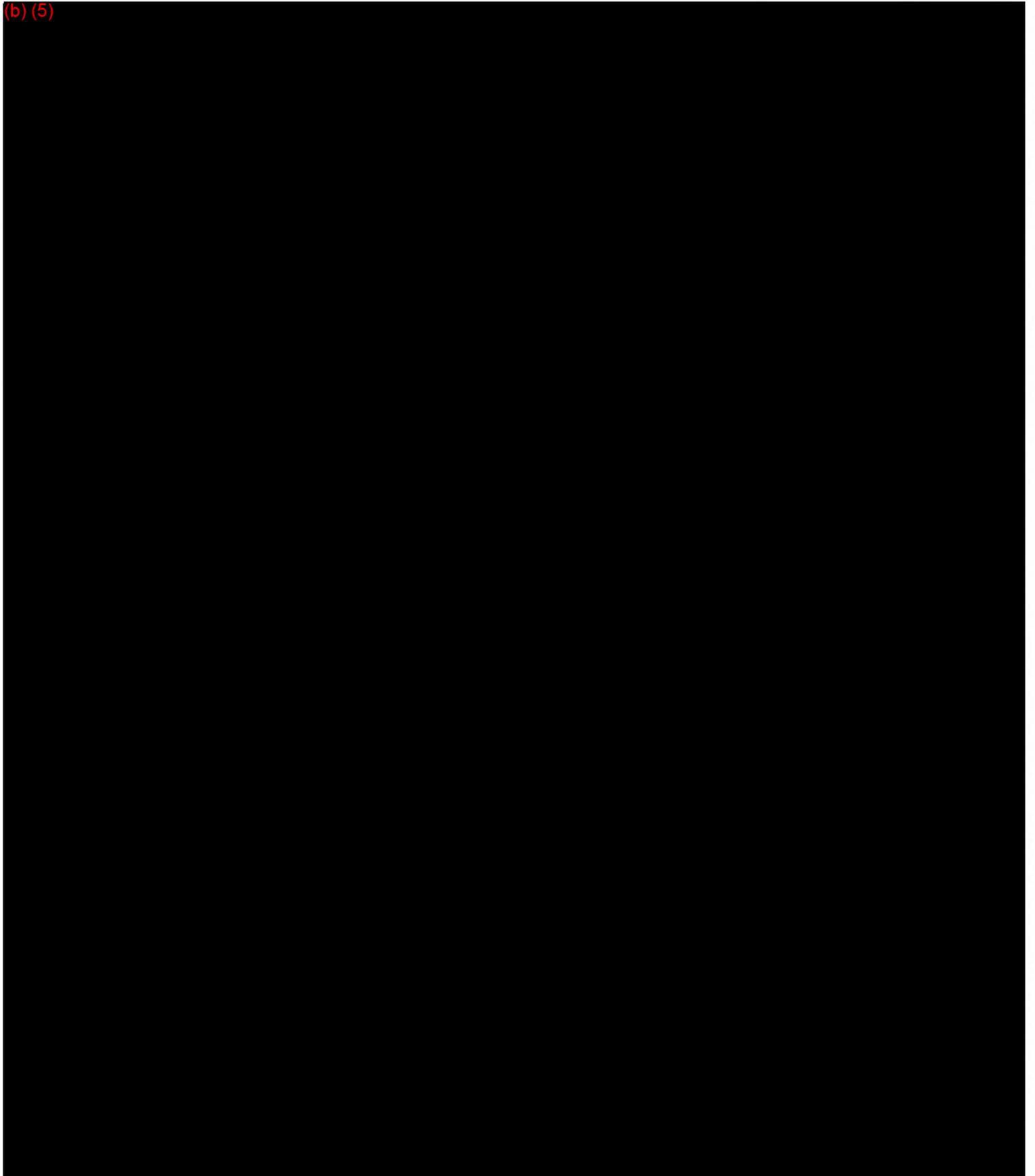
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(b) (5)



Smith, Celeste

From: Woodcock, Janet
Sent: Monday, August 01, 2016 11:48 AM
To: Behr, Virginia L
Subject: FW: so are my changes OK? tx jw
Attachments: Sarepta dct (4).docx

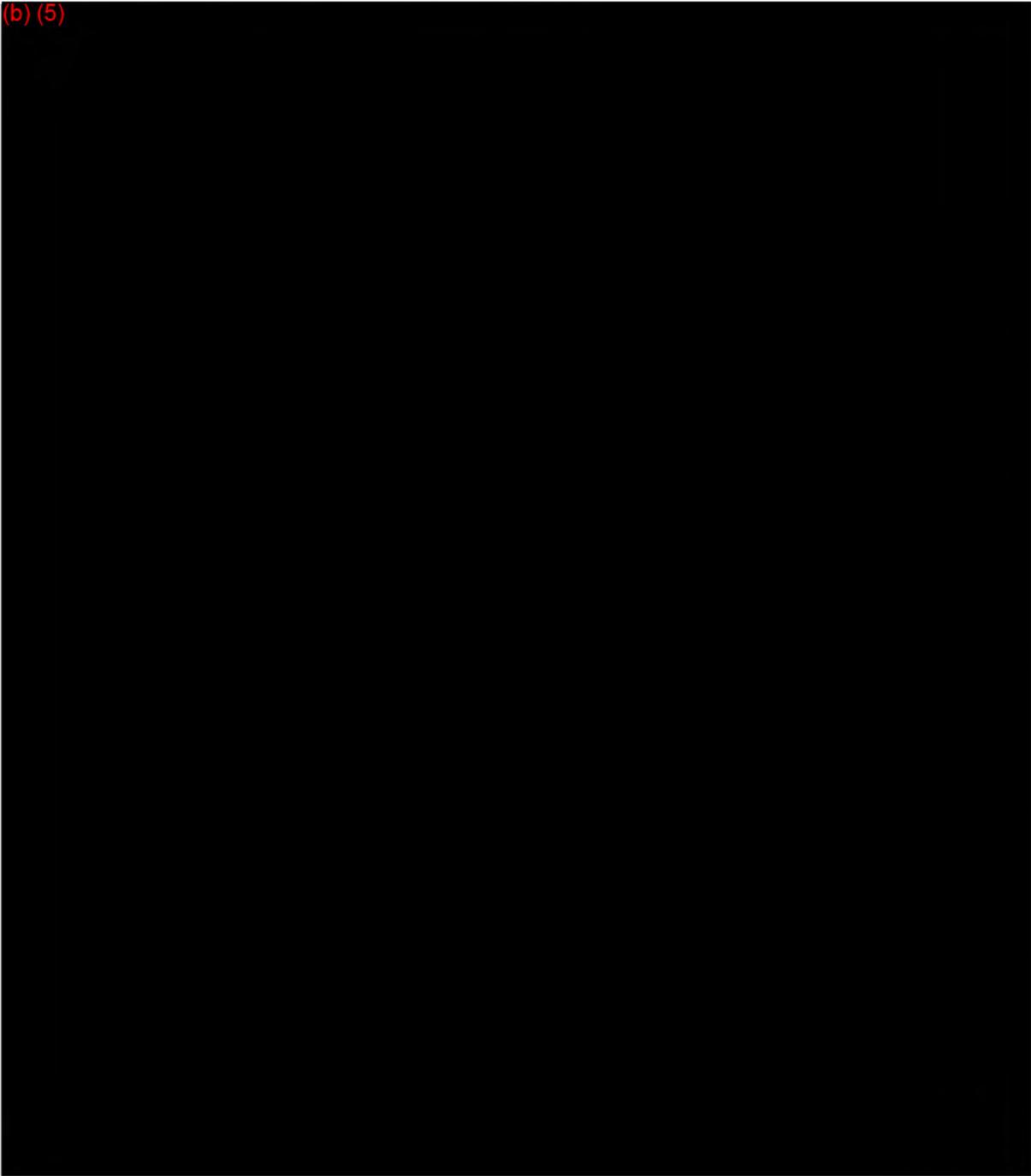
From: Rao, Ashutosh
Sent: Wednesday, July 13, 2016 6:03 PM
To: Woodcock, Janet
Subject: RE: so are my changes OK? tx jw

I made some suggested edits to the items through page 7 (only question# 1).

From: Woodcock, Janet
Sent: Wednesday, July 13, 2016 6:00 PM
To: Rao, Ashutosh
Subject: so are my changes OK? tx jw

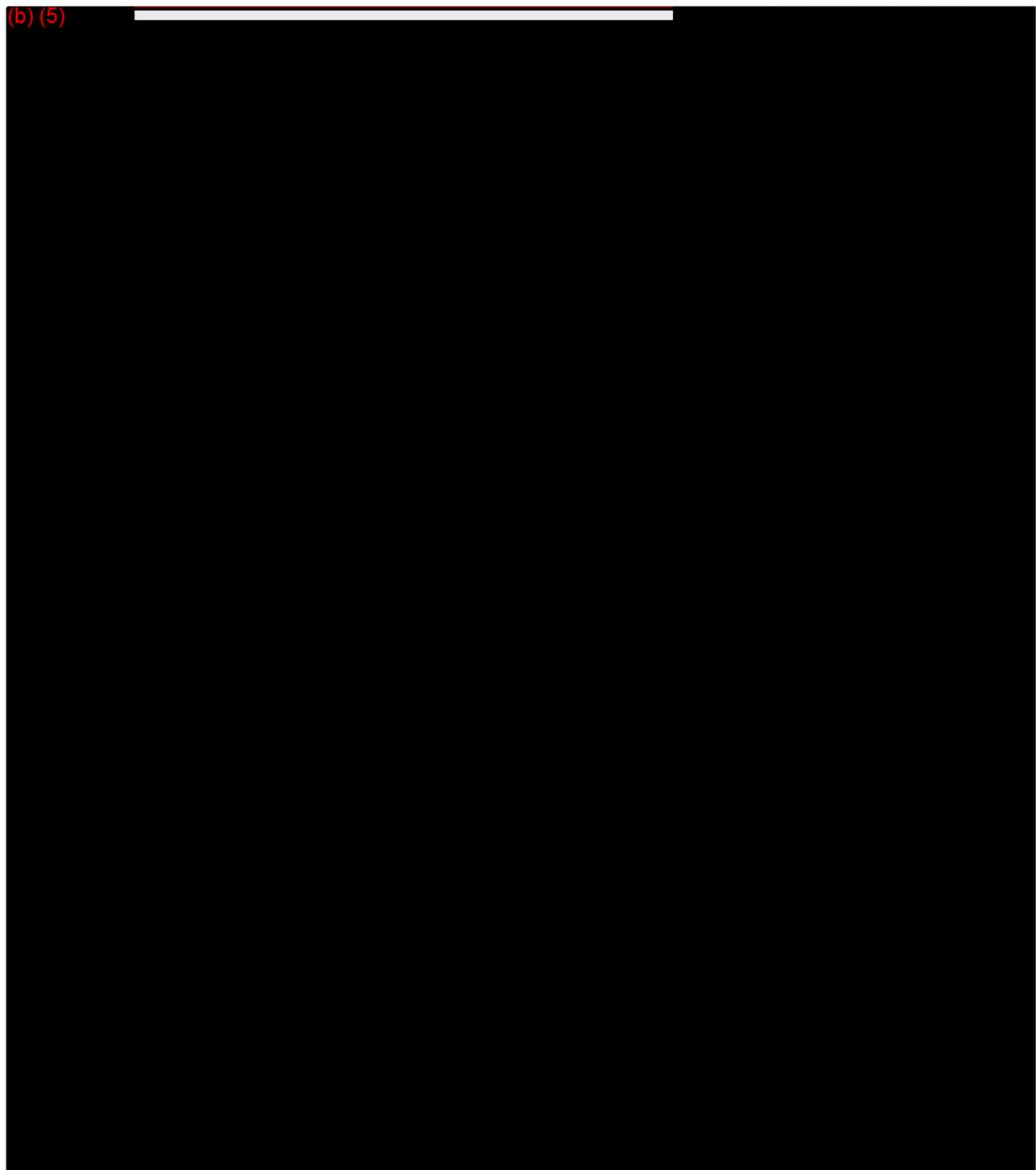
Center Director Decisional Memo DRAFT

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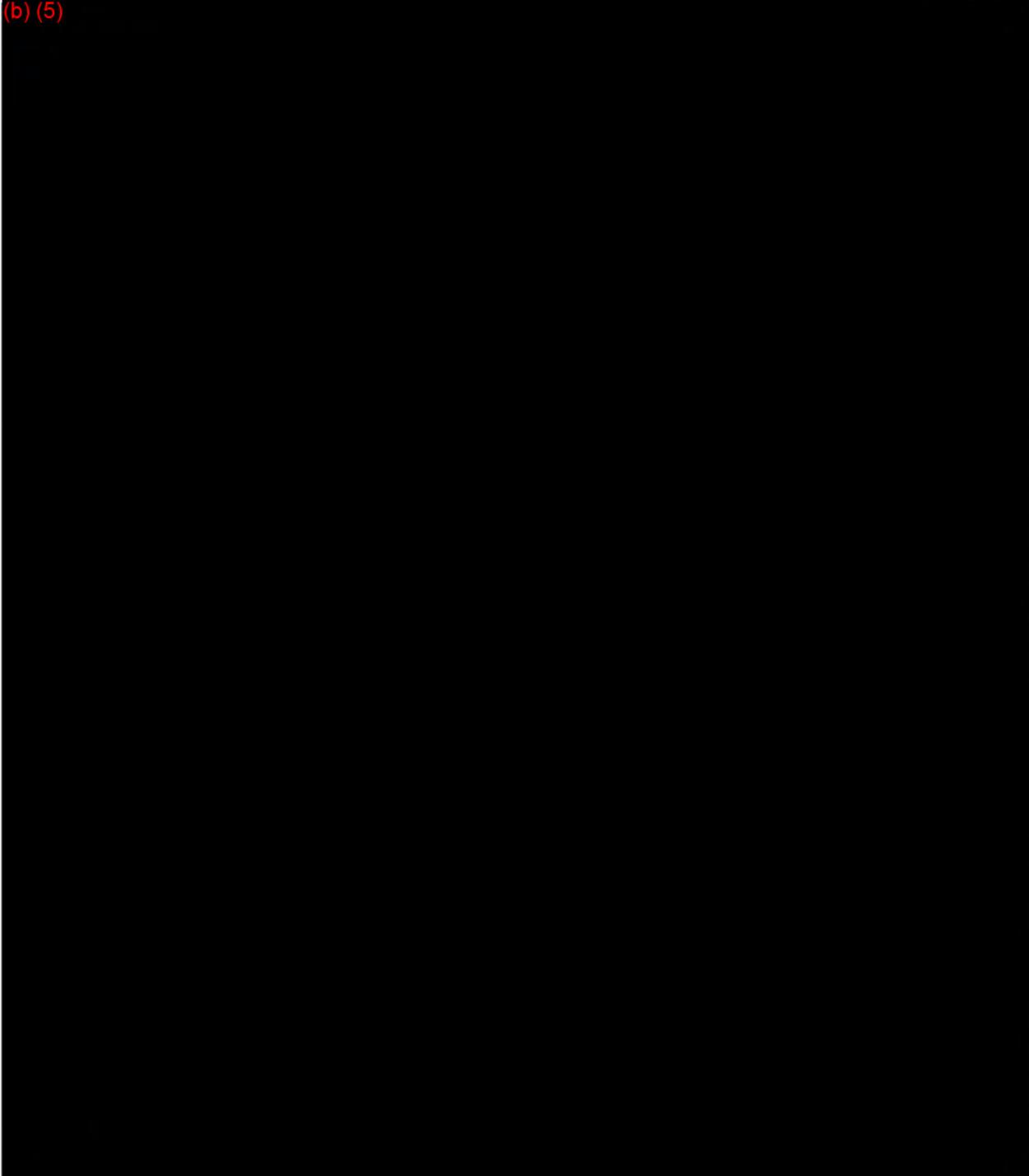


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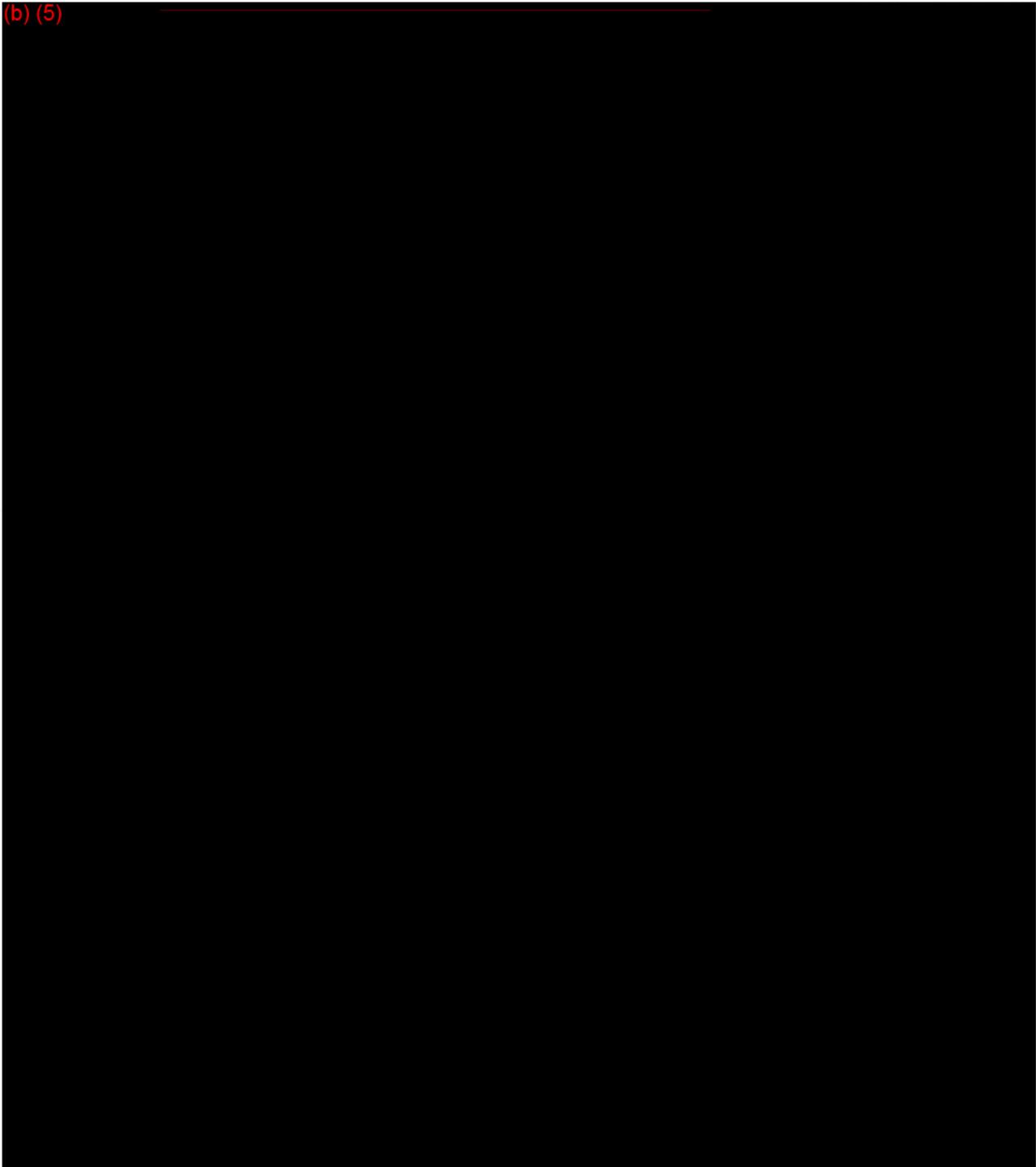
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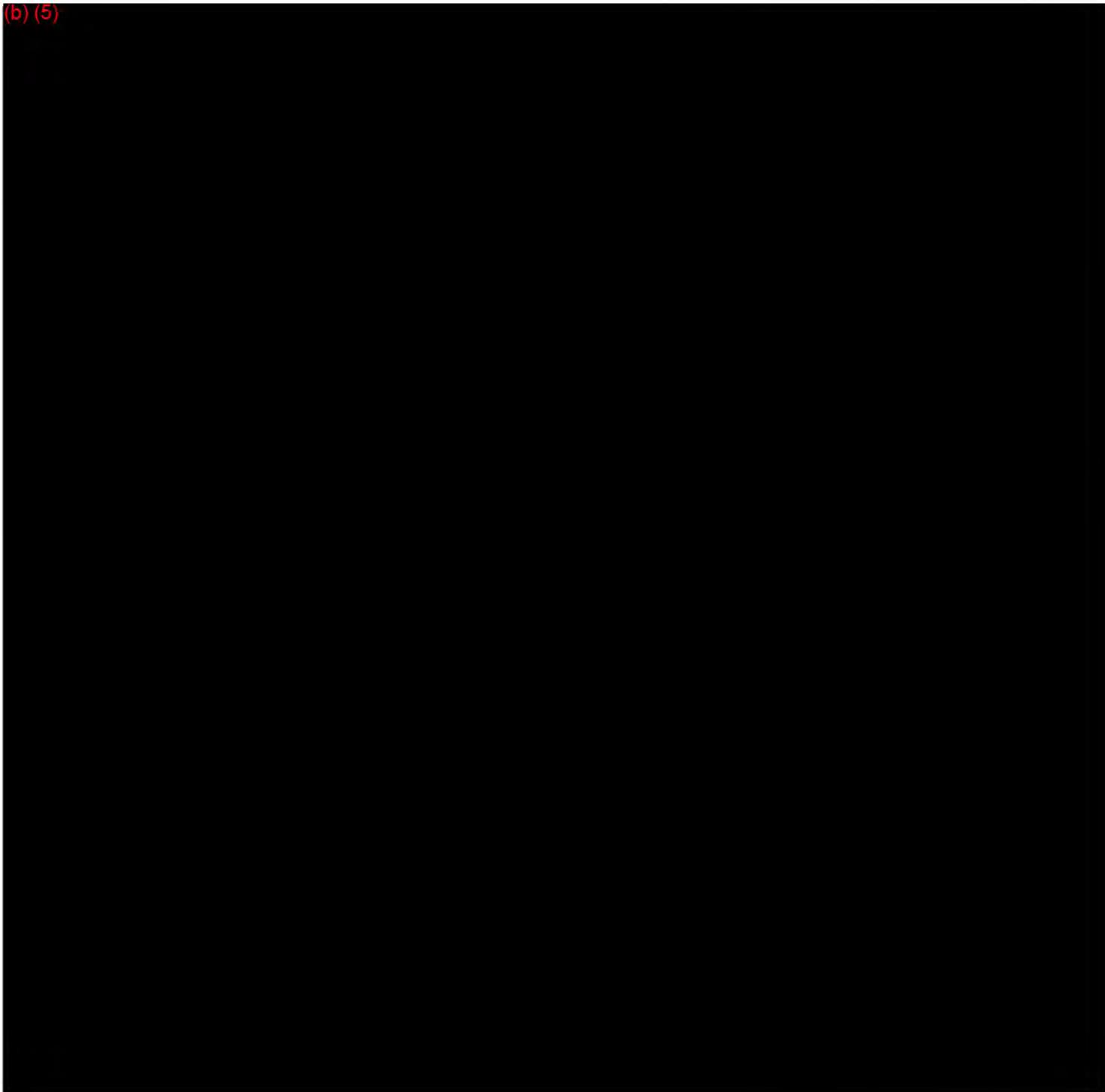
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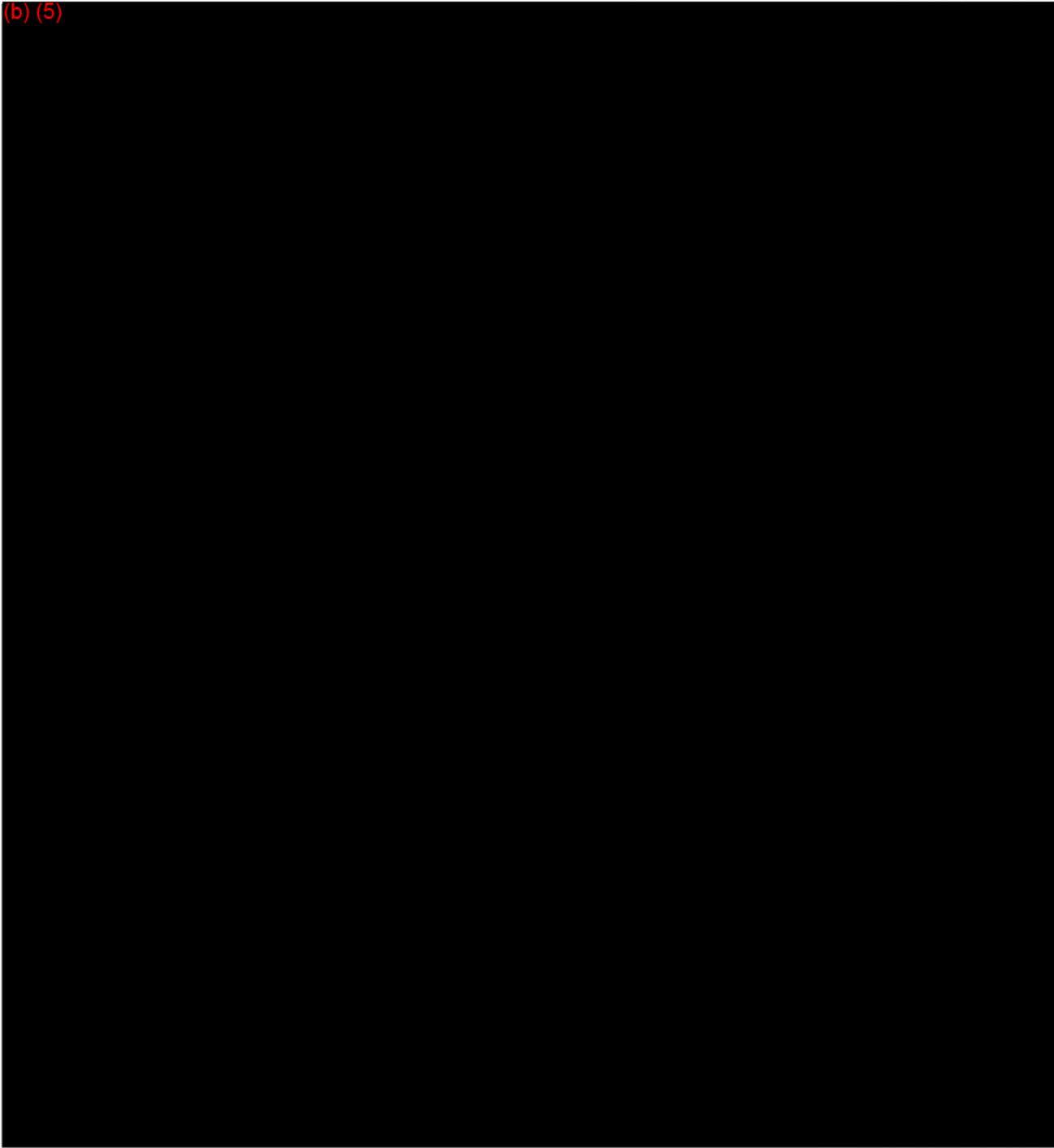
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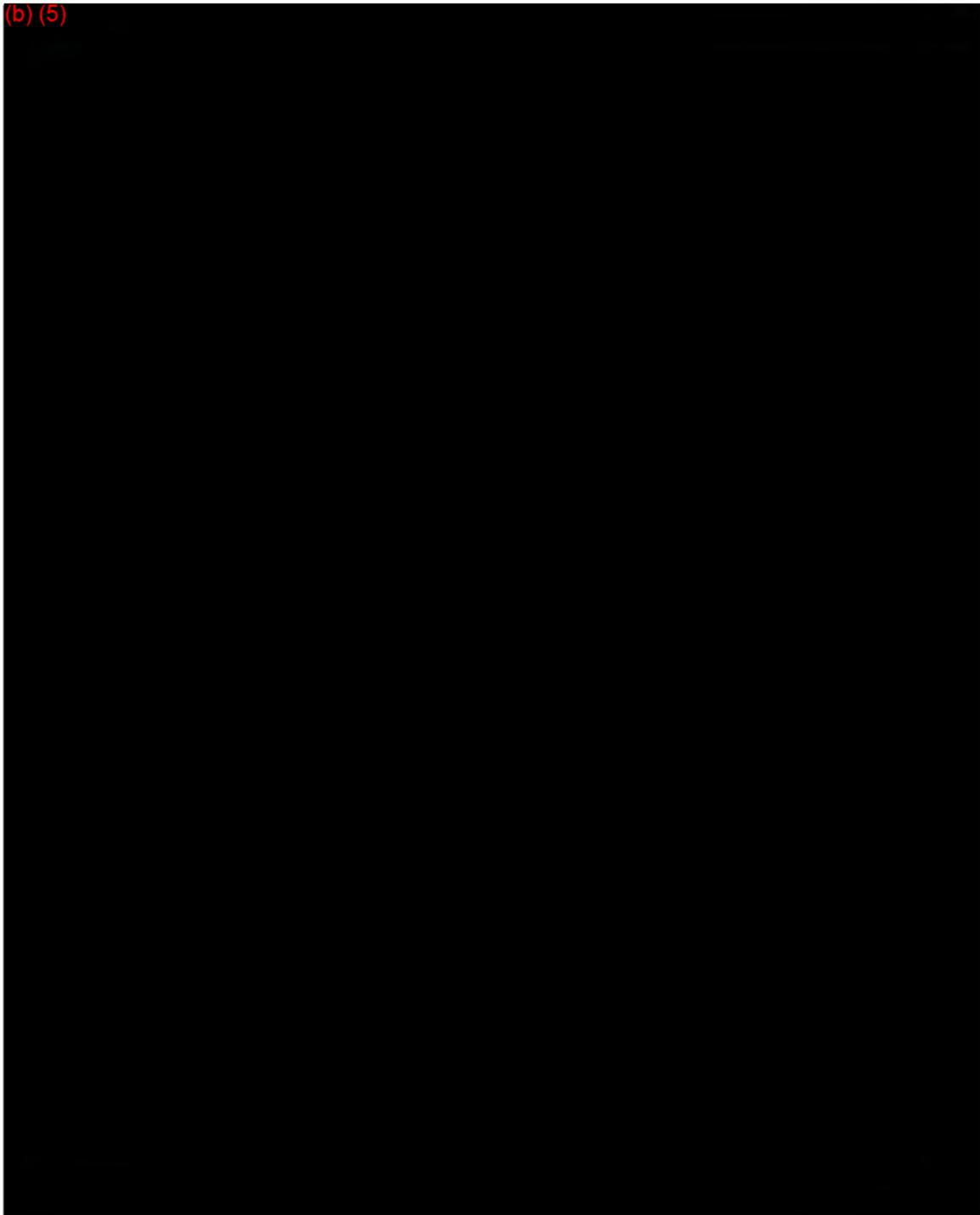
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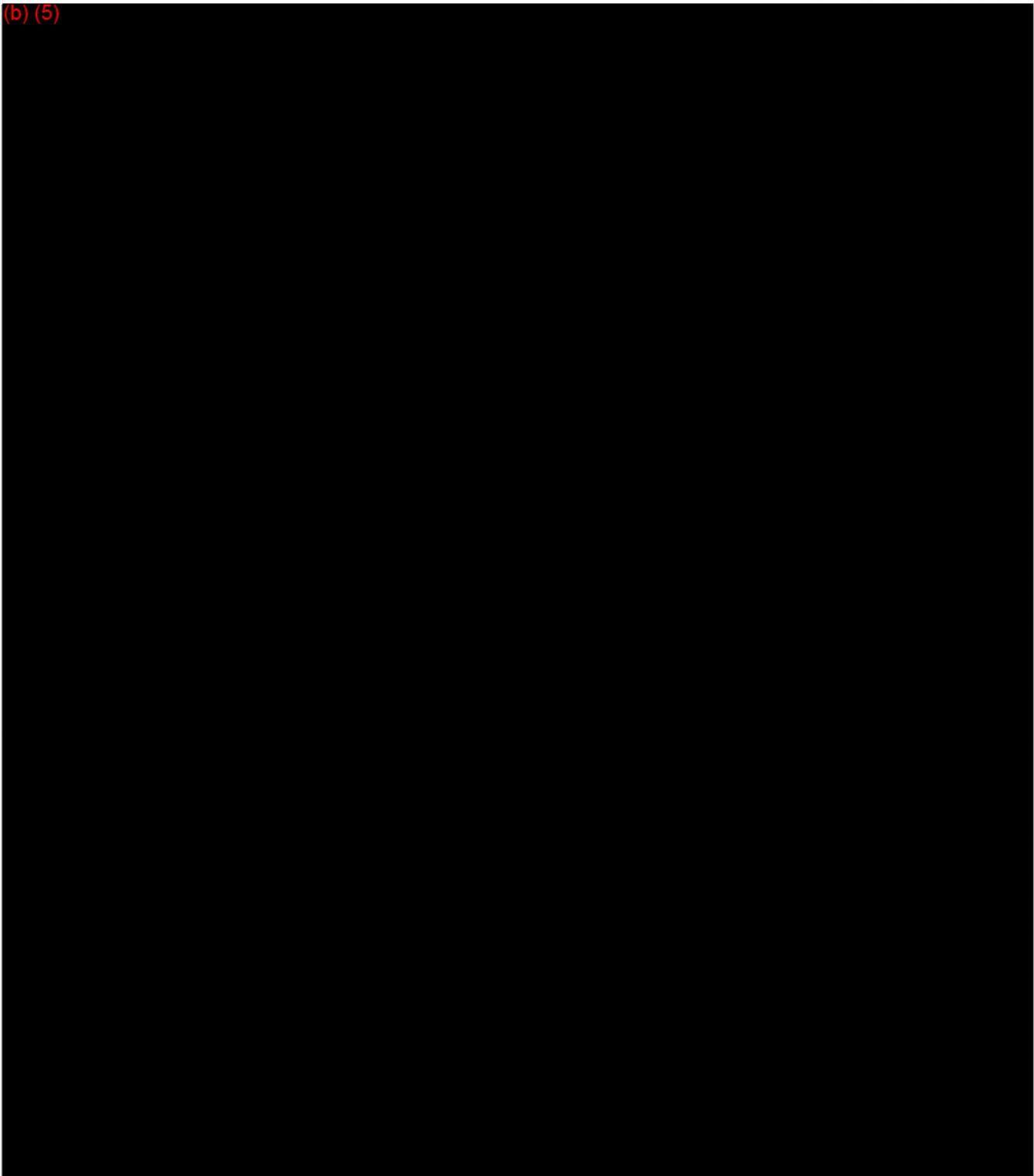
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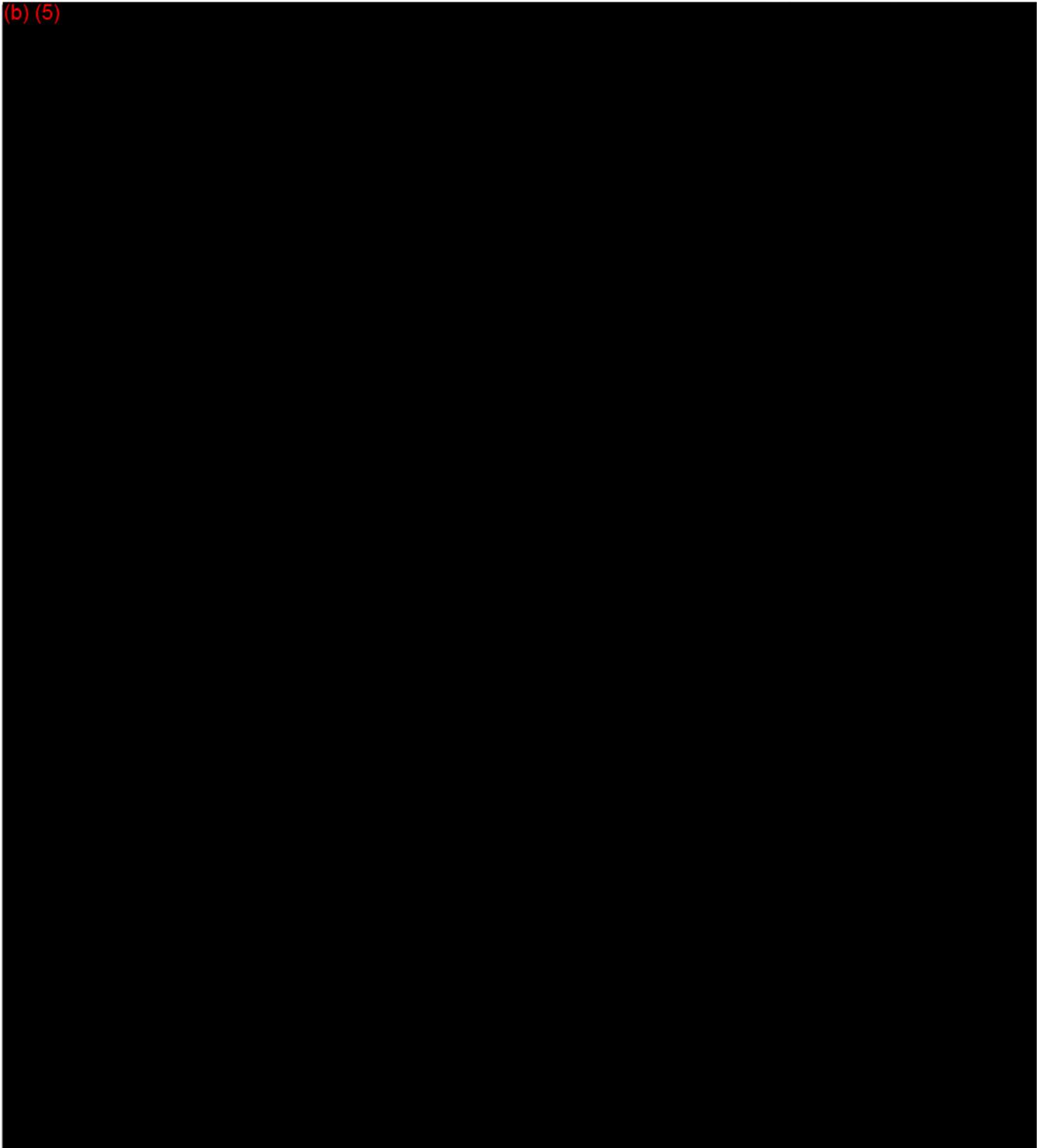
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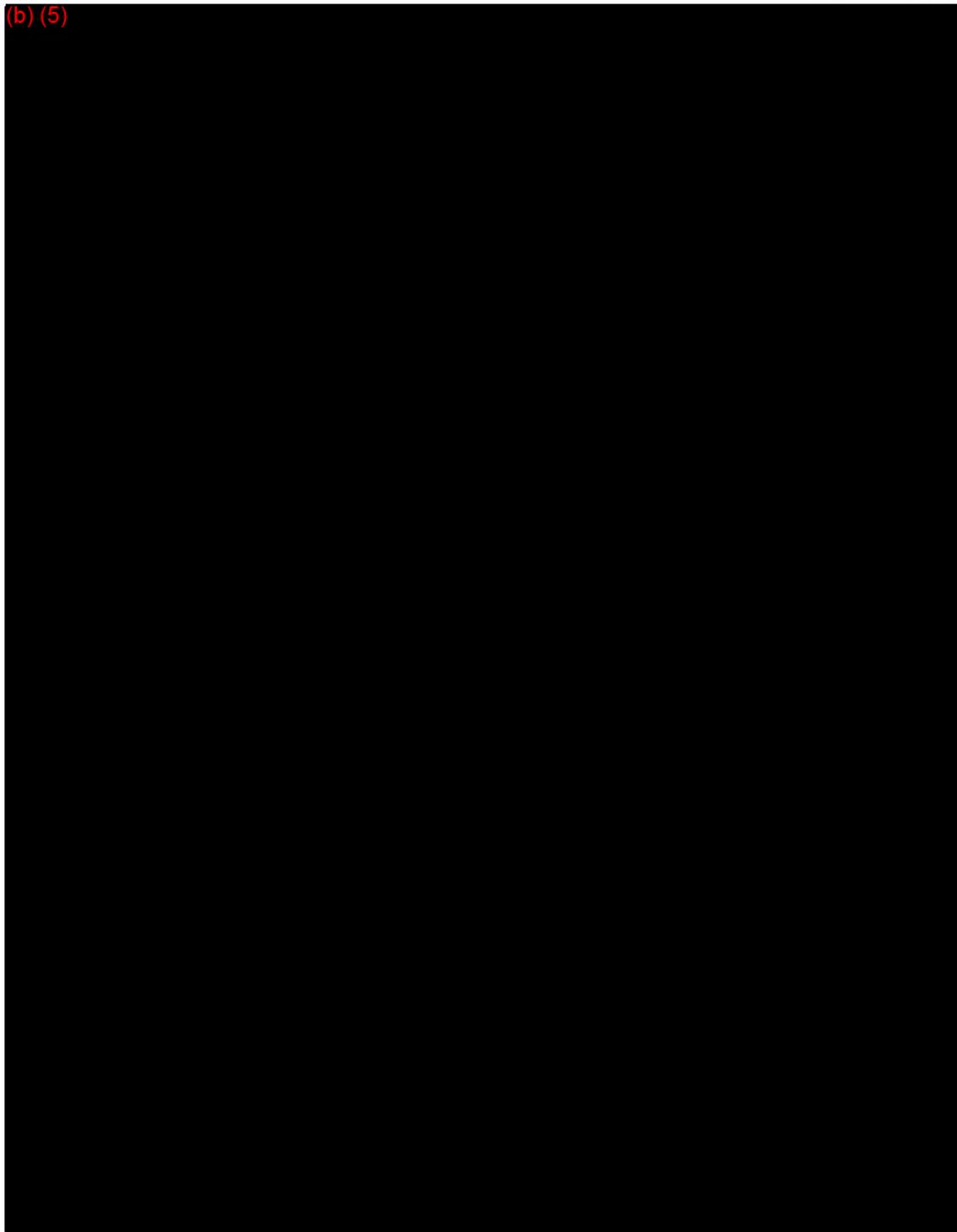
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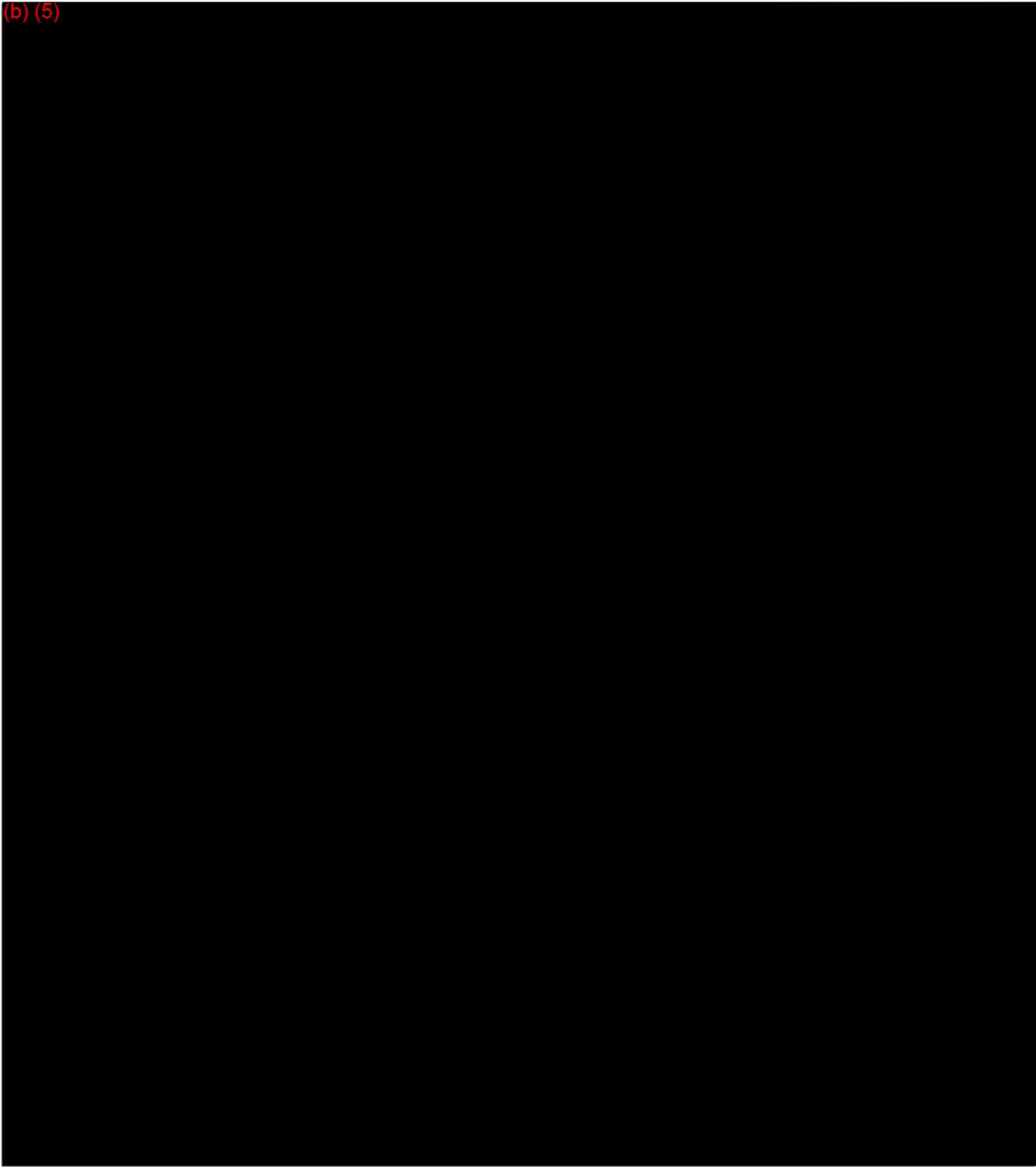
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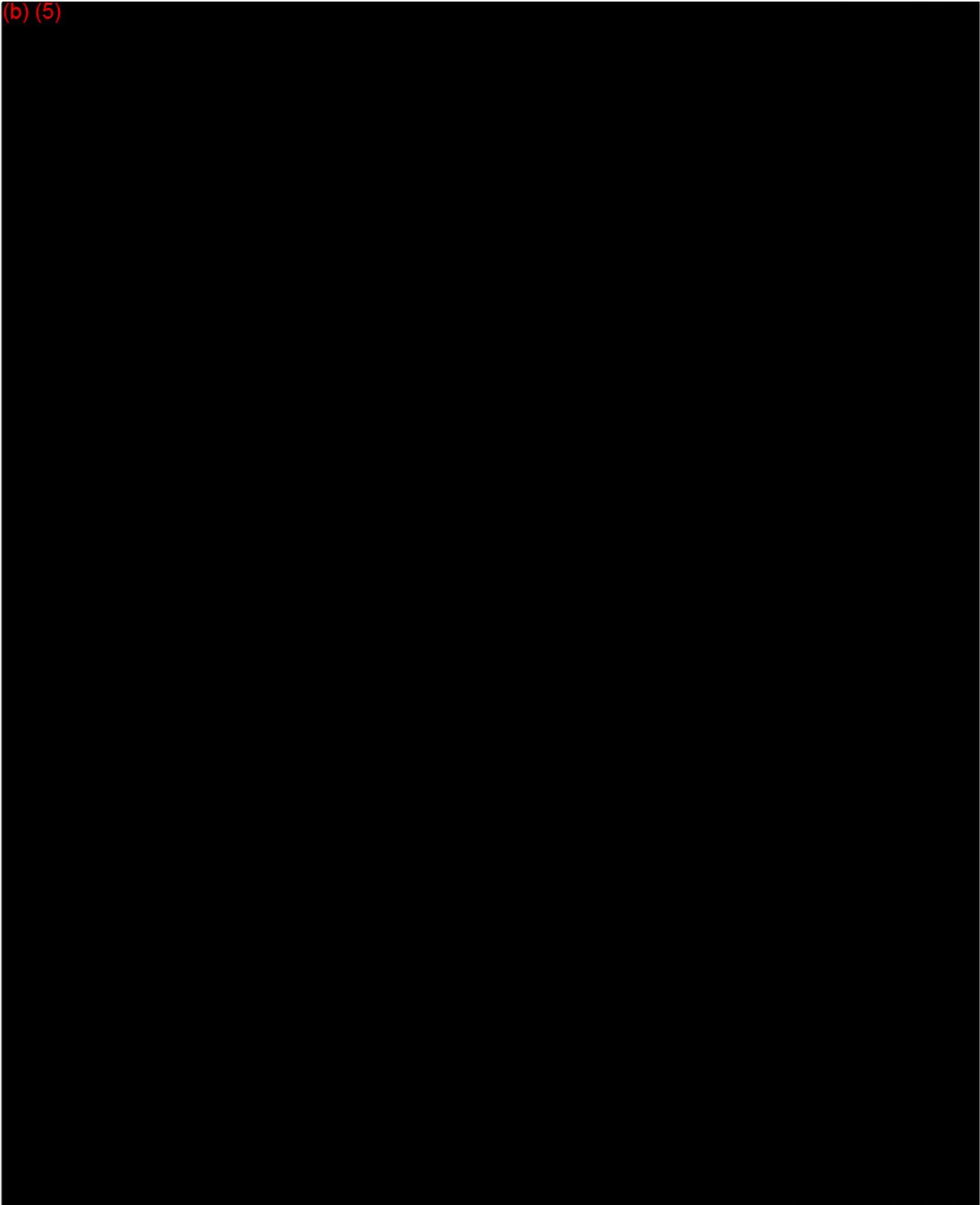
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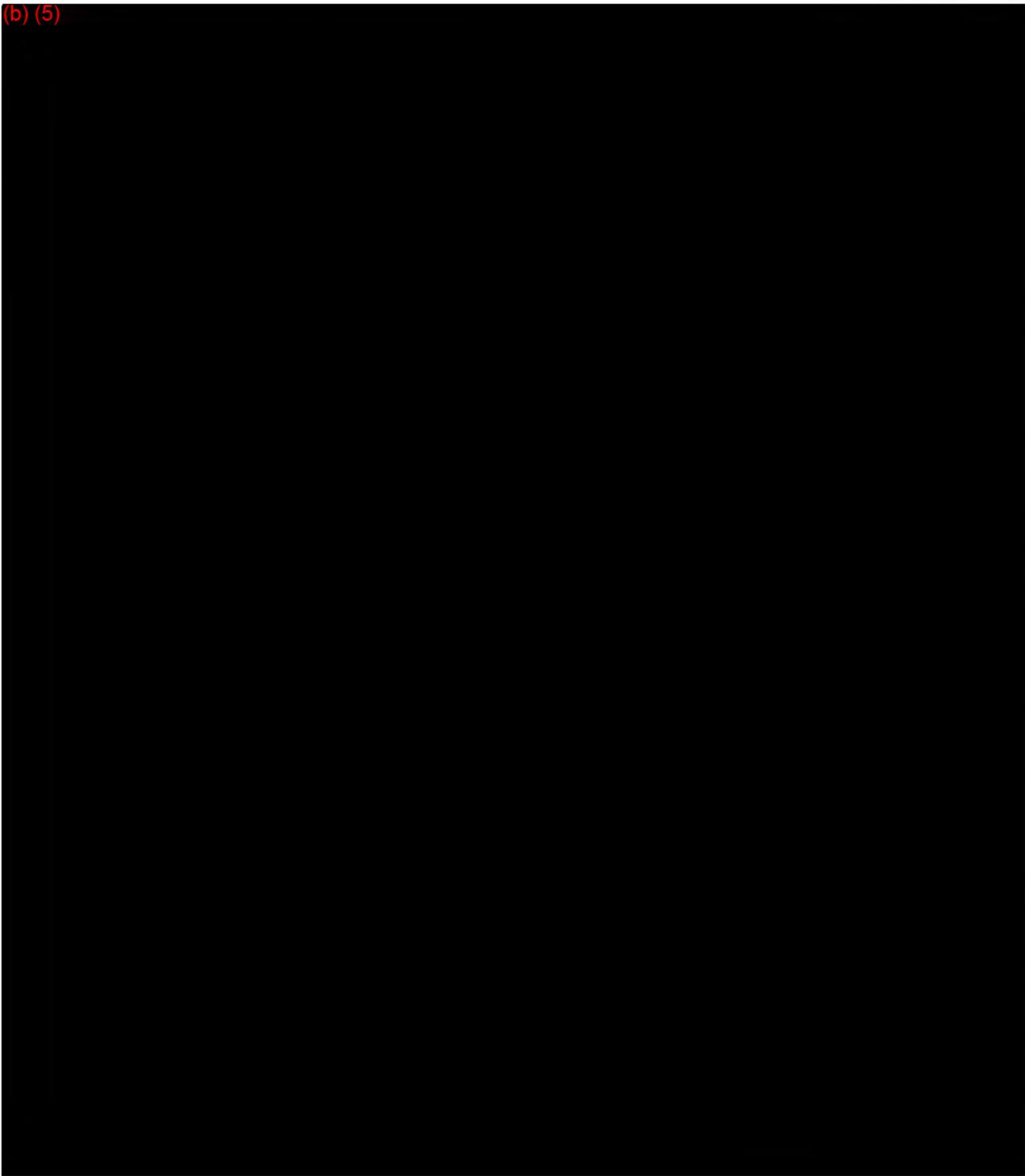
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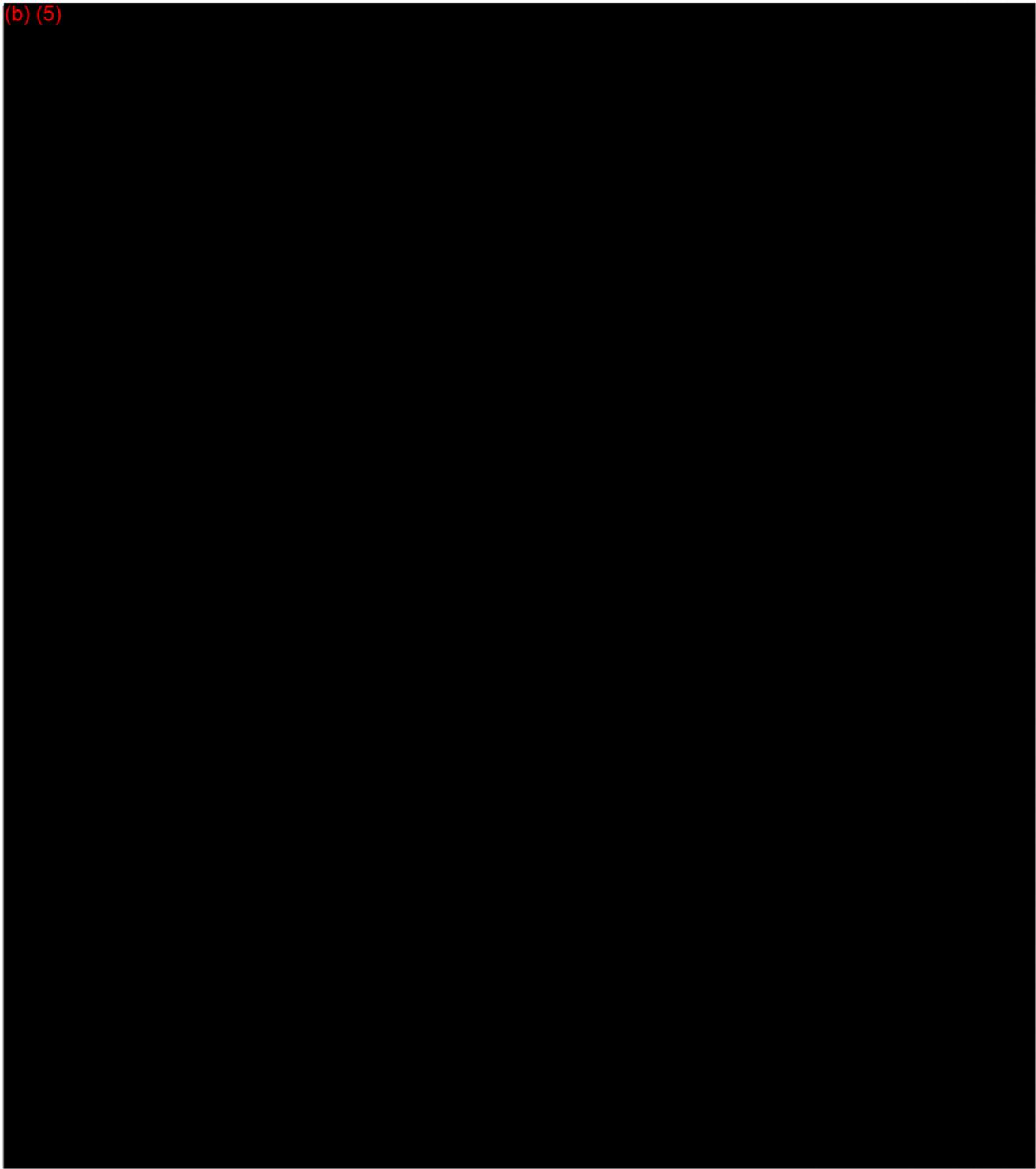
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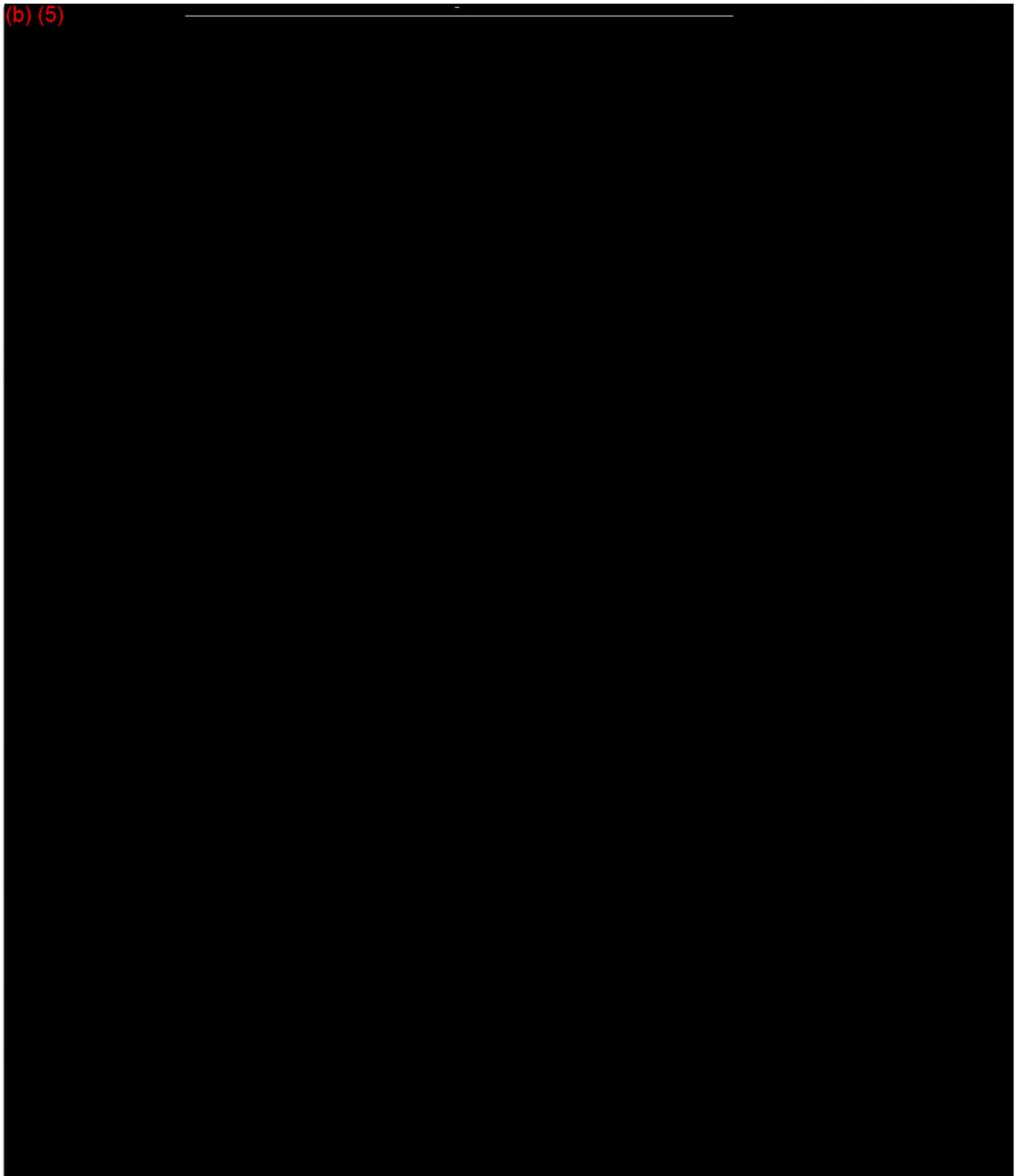
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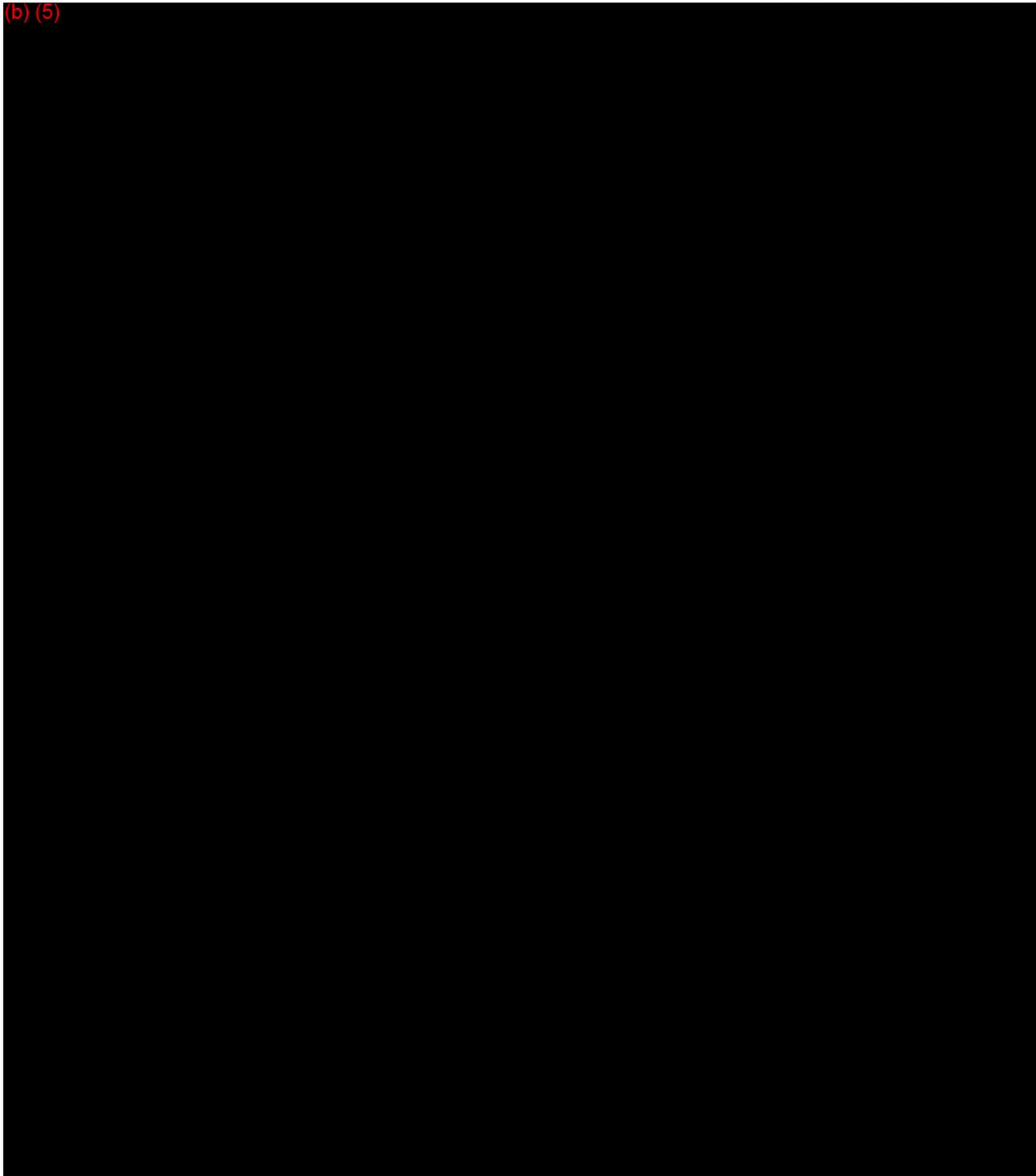
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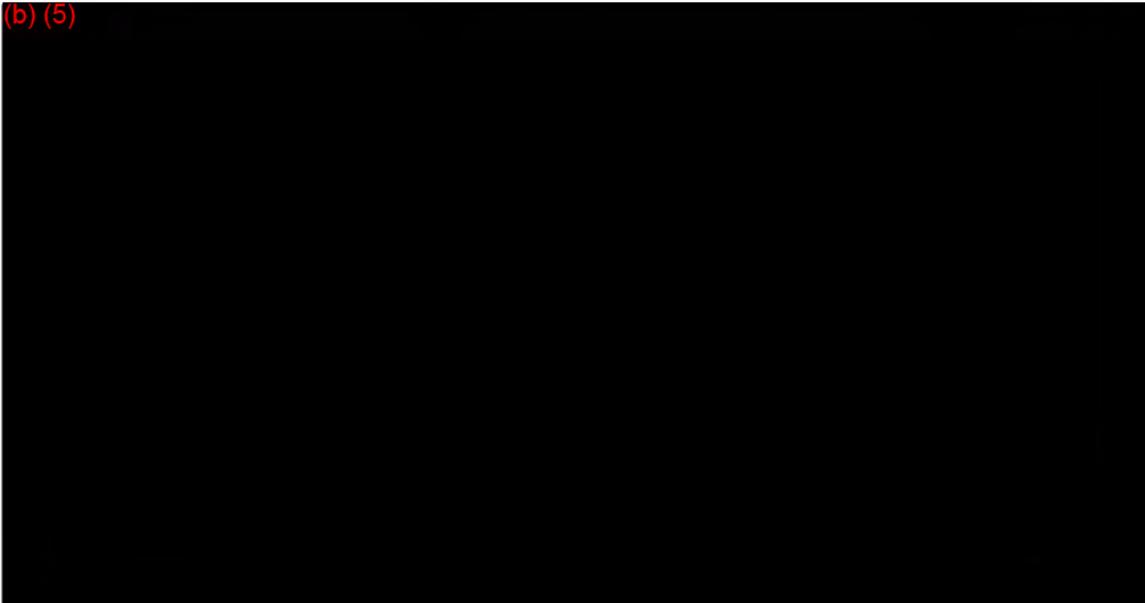
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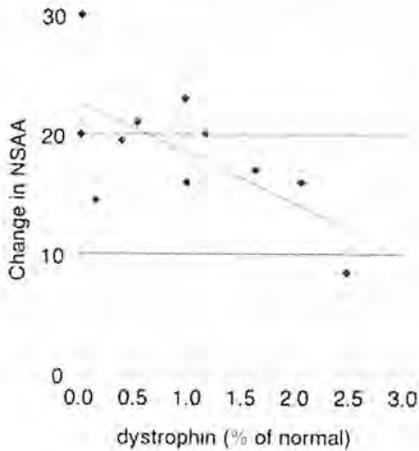


Smith, Celeste

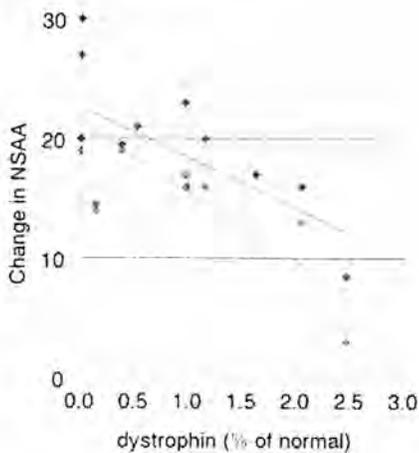
From: Woodcock, Janet
Sent: Monday, August 01, 2016 11:51 AM
To: Behr, Virginia L
Subject: FW: MEMO

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 12:57 AM
To: Woodcock, Janet
Cc: Jenkins, John K; Dunn, Billy; Bastings, Eric
Subject: RE: MEMO

I just noticed that the y-axis scales for the blue and red plots were different. This was not intentional. Here's the red plot on the same 0 to 30 scale as the blue plot:



And here they are together:



From: Unger, Ellis
Sent: Wednesday, July 13, 2016 12:52 AM
To: Woodcock, Janet

Cc: Jenkins, John K; Dunn, Billy; Bastings, Eric
Subject: RE: MEMO

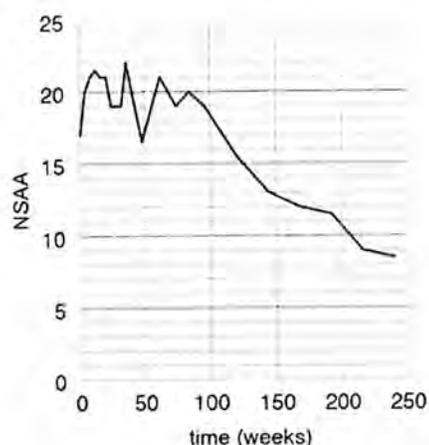
Janet,

I have some concerns with respect to Table 1 and Figure 2. You say that $R^2 = 0.8$. I've plotted the NSAA data in your Table 1, and I was able to reproduce your graph exactly. But I got $R=0.8$, which means that $R^2 = 0.64$. So I think that "R² = 0.8" is a typo. If R^2 were actually 0.8, then R would have been 0.9 (0.9 squared = 0.81).

More importantly, I cannot tell how you got the deltas for the NSAA for each patient in Table 1. If you want to include the table and figure as they are now in your draft, I think you might consider citing your source for the table (presumably a Sarepta table or a reviewer's table). If it is your own work, then you might want to explain how you calculated the numbers, i.e., identify the name and location of the original data file you used and explain the methods you used to calculate the deltas.

Looking deeper at your table, I was curious about the data from patient 006. This patient had the highest dystrophin value (2.47%) and an NSAA change of just 3 units, as noted in the table.

Here are the NSAA data on this boy:



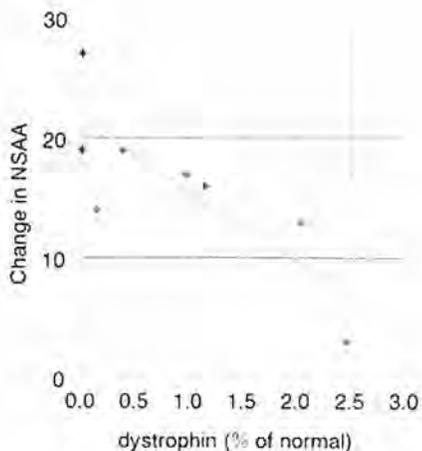
Looking at the data above, I have some difficulty characterizing his change as "3."

Instead of picking an arbitrary time point as the "final" point, I thought that the most reasonable way of doing this would be to include all of the data that have been collected through Week 240. Because all patients have remained on weekly treatment for 240 weeks, I see no reason to truncate the data at the time the biopsy was obtained. Thus, for each patient I calculated their delta as their Week 240 score minus their baseline score. EXCEPT - for the 4 patients who started on placebo for 24 weeks, I considered Week 24 to be their baseline.

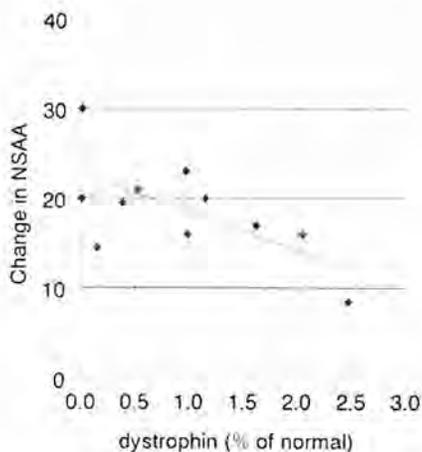
Also, I think we should use the data from all 11 patients with Week 180 biopsies, including the 2 who lost ambulation early, though I understand you might not agree.

Here is what I found...

First, below in blue is my version of your plot of 9 patients. My plot looks the same as yours, but I get $R=0.80$. (At the dystrophin value of 1%, there are two closely overlapping data points.)



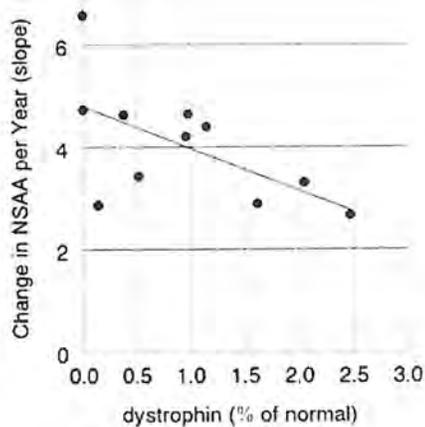
Second, below, my plot of all 11 patients, where I calculate delta as Week 240 minus baseline (for patients who started on placebo, it's Week 240 minus Week 24):



Using all of the data through Week 240, the slope is less steep and the correlation is worse. And knowing that you might not agree with inclusion of the 2 boys who became unable to ambulate, I will tell you that if I include all 11 boys, $R=0.65$. If I leave out the 2 non-ambulatory boys, $R=0.64$. So it makes no difference whether they are included or not. And the slope is essentially the same.

An alternate analysis I've been interested in is one that uses ALL of the aforementioned data for each patient. Rather than using just the first and last data points for each patient, we can calculate a slope for each patient using linear regression. For example, consider patient 006 graphed above. The red line is the linear regression. His slope is -0.051 units per week, or (multiply by 52) -2.7 units per year.

Below is a plot of the slope for each boy vs. dystrophin at Week 180 by Western blot. The slope for each boy is expressed as the change in NSAA per 52 weeks. For this plot, $R=0.60$, which is quite similar to the correlation of simple pre-treatment minus post-treatment (above).



In short, when you consider all of the NSAA data through Week 240, you get essentially the same plot whether you simply subtract pre- from post (red plot), or calculate a slope for each patient (black plot). And in either case, R is in the 0.6-range.

You can feel free to use some or all of these plots. Obviously, you can use your own table/plot, but if you do, I suggest you explain how you got your numbers, as I noted above.

Ellis

From: Jenkins, John K
Sent: Tuesday, July 12, 2016 5:25 PM
To: Woodcock, Janet; Unger, Ellis; Dunn, Billy; Bastings, Eric
Cc: Jenkins, John K
Subject: RE: MEMO

Janet

As we discussed in the hallway, I had some comments on your memo:

1. You said you did not consider data from the first three biopsies, but you do not say why. It was my understanding that the re-read of the first three biopsies for IHC was considered valid and the review team saw no change from baseline from the first biopsy to week 180. This is an important part of their perspective on the amount of dystrophin produced and its significance. They noted that the baseline ICH results from the patients in Study 201 were very different from the "new" baseline data that were conducted in parallel to the week 180 biopsy and that these differences were not explained. So, I think you need to explain why you are not considering the IHC data from the first three biopsies in your review, and instead focusing on the comparison of the "new" controls versus the week 180 IHC results.
2. I am not familiar with the references you added to the memo and cannot comment on your summary of the findings of each paper. Perhaps the review team know those references and can provide their take on the findings. Even taking your summaries at face value as accurate, I did not find the summary of the references to be particularly helpful in determining whether the dystrophin findings for eteplirsen are "reasonably likely" to predict clinical benefit. As you noted, there are issues related both to the quantity of dystrophin produced as well as its quality (functionality) that are hard to tease apart in the small sample of boys treated. It is possible that the "responders" are making functional protein, it is also possible they are making non-functional protein, and I don't think we have the data to sort this out. It still seems to be a judgment on the totality of evidence where reasonable people may disagree.

3. I find the correlation graphs at the end to be problematic since they graph a delta for a clinical endpoint on the y-axis against an absolute endpoint value for dystrophin on the x-axis. While one might assume the baseline dystrophin levels were low and therefore using the absolute endpoint value is a reasonable estimate of the effect of the drug on dystrophin (e.g., a surrogate for the delta); we don't know that and therefore it is hard to know whether the graphics are isolating a drug effect or capturing a prognostic difference that may have been present at baseline. So, I don't find them as convincing as you suggest, but again, that may be a judgment.
4. You focus on the "responders" in the population to support your argument, but we don't know how to identify the responders and therefore will have to approve based on the sponsor's grouping of mutations that are "amenable to exon 51 skipping," which likely include mutations that are not responsive to eteplirsen. This is a frustrating intersection of "targeted" therapies and approval based on a group mean based on characteristics chosen by the sponsor that we cannot validate. This is very analogous to the CF cases that we have been discussing and I think the review teams in both cases are struggling with these issues. It feels like we have to "unlearn" what we think we know from targeting and regress to approving an un-validated grouping of mutations. I know we do this all the time for non-targeted therapies, but it is still disconcerting to face this for targeted therapies. While the drug at the proposed dose has not been shown to be toxic, it will likely require a central line for chronic administration, which is not benign, and families/society will be burdened with a very expensive drug that may only be working in a small subset of the indicated population. This is an issue we will have to grapple with for many "targeted" therapies for rare diseases.

As we discussed, I am asking the review team members to provide any feedback they have on your memo by COB tomorrow so you can finalize the memo. That step is necessary for the appeal process to be formally triggered and I think we all agree we need to move quickly to resolve this case on way or the other.

John

From: Woodcock, Janet
Sent: Monday, July 11, 2016 7:21 PM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: MEMO

Here is a draft version of my decisional memo. I welcome comments on it. An appeal can't be done until I finalize this, I am told. Thanks. jw

From: [Moran, Kristy](#)
To: [Califf, Robert](#); [Sharp, Jeremy](#); [Kraus, Tom](#); [Auchincloss, Kalah](#)
Cc: [Varnado, Martina](#); [O'Neill, Jeff](#); [Saben, Alyson L](#)
Subject: Proposed CDER/OC Monthly Leadership Agenda Items for August 17
Date: Thursday, August 04, 2016 1:12:06 PM
Attachments: [CDER OC Leadership Monthly Meeting Memorandum of Meeting 7-20-16 FINAL.doc.docx](#)

Good morning,

Below are the suggested topics that CDER/Dr. Woodcock would like to discuss at the CDER/OC Monthly Leadership meeting scheduled for August 17 at 10:00 a.m. Please let me know if there additional topics that you would also like to include on the agenda to discuss.

I've also attached the discussion/action items from CDER's meeting on July 20.

CDER Proposed topics:

There may be additional items to add by CDER as the meeting approaches. Agenda items 1 & 2 are really standing topics Dr. Woodcock wants to make sure we keep on the agenda, but there isn't anything specific to cover as of now.

1. UFA updates
2. Opioids
3. Unfinished guidance update

Kindly,
Kristy Moran
OC/Office of the Executive Secretariat

MEMORANDUM OF MEETING
OC/CDER Leadership Meeting
July 20, 2016
4:30 pm – 5:30 pm

Subject: General Updates from the July 2016 OC/CDER Leadership Meeting

Participants: Robert Califf, Tom Kraus, Kalah Auchincloss (by phone), Jeremy Sharp (by phone), Luciana Borio (by phone), Janet Woodcock, Heather Brown, Deborah Roth, Liz Dickinson (by phone), Katie Conover, Deborah Roth, Rosemary Roberts, Brad Leissa, Andrei Nabakoski, Mark Russo, and Kristy Moran

Decision/Action Items:

General Updates

- B. cepacia Outbreak
 - Concern about who is in charge in center specific or multi-center product investigation.
 - Next Steps: Some key issues may need to be updated in the Emergency Operations Plan of 2014. Changes can be made on a page by page basis without updating the entire plan.
 - Tom Kraus will follow up on updating the procedures in the Emergency Operations Plan.
- Update on Opioids - CDER will be talking to the state boards next week about implementing the mandatory training on opioids. CDER will make decisions on next steps when they get intelligence on what the state's plan to do. A possible next step may be a public meeting.
- Cough Syrup – CDER is going to communicate with drug sponsors telling them that CDER is opening a drug safety issue to identify any new drug safety issues with these products; this will be followed up by sending drug safety letters to the sponsors. CDER will also call to urge them to remove the pediatric indication from the codeine cough syrups; CDER believes that sponsors will comply with the request. CDER's goal is to have a draft document in approximately 2 weeks that will identify findings as to why the benefits no longer outweigh the risks.
- Update Generics
 - No rescission.
 - CDER will be involving a 3rd party to take a look at the IT system to identify some inconsistencies in flagging data.

- OTC User Fee Negotiations
 - Started July 6, 2016.
 - CHPA issued a statement announcing their participation in the OTC program.
 - CDER will be talking to congressional staff on July 21 about the legislative revision of the monograph system.
 - CDER has issued one set of minutes on the user fee meeting. These minutes could be used for CDER's public talking points since there was agreement not to talk about user fees until further along in the process.

- Eteplirsen
 - An appeal has been filed.
 - Next steps: Lou Borio will follow up on the timeframe for action from the Commissioner's office.

- Committee for the Advancement of Clinical and Therapeutic Professional Education (CACTPE)
 - CDER and OSPD are proposing to realign the Committee for Advanced Scientific Education (CASE) with the Office of Scientific Professional Development, Office of the Chief Scientist.
 - The CASE is a multidisciplinary committee of members who represent major scientific disciplines from various offices within CDER. The Seminar and Curriculum courses provided by the CASE are of high interest to a broad Agency-wide regulatory and scientific target audience and are cross-cutting in nature.
 - The CASE will become the Committee for the Advancement of Clinical and Therapeutic Professional Education (CACTPE) with representation from OCS, CBER, CDER, CDRH, CTP and CFSAN.
 - CDER Scientific Rounds will remain with CDER given that the educational activity is CDER-specific and designed for the CDER target audience.

- Ethics - An OGE audit will be made public soon regarding confidential filers.
Next Steps: CDER is working with FDA Ethics on this issue.

- Unfinished Draft Guidances – the Commissioner urges the Center to complete unfinished draft guidances.

Next meeting:

Wednesday, August 17, 2016, 10:00 am – 11:00 am

Executive Secretariat Contact: Kristy Moran, 301-796-4678

From: [Califf, Robert](#)
To: [Pennington, Caitlin](#)
Subject: Re: Status of appeal
Date: Thursday, August 04, 2016 7:30:10 AM

Ok with me

Rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Caitlin Pennington <Caitlin.Pennington@fda.hhs.gov>
Date: Wednesday, August 3, 2016 at 5:26 PM
To: apple <rmc1@fda.hhs.gov>
Subject: FW: Status of appeal

Hi Dr. Califf,

Are you ok with taking this call from the car and do you want to include Rachel Sherman in this discussion?

Thanks!

Caitlin

From: Kraus, Tom
Sent: Wednesday, August 03, 2016 4:28 PM
To: Borio, Luciana; Pennington, Caitlin
Subject: RE: Status of appeal

OK. Thanks Lu.

He will be in West Virginia on Tuesday talking about opioids, but he will have plenty of time in the car.

Caitlin – Can we schedule 30 by phone on Tuesday morning? I'd suggest including Lu, me, Kalah, Rob, Liz, I think it would also be appropriate to include Rachel Sherman but please ask Rob if he agrees.

From: Borio, Luciana
Sent: Wednesday, August 03, 2016 1:47 PM
To: Kraus, Tom
Subject: RE: Status of appeal

Yes, I think it would be good to meet with him. The challenge is with timing. Matt Warren will be out of the office next week, and I will be out starting 8/9 (Tuesday). If it can be arranged with his schedule, I would be glad to brief him first thing Tuesday morning before I go on leave.

From: Kraus, Tom
Sent: Wednesday, August 03, 2016 1:40 PM
To: Borio, Luciana
Subject: RE: Status of appeal

After. I'm assuming your team will want to talk him through their recommendation.

From: Borio, Luciana <Luciana.Borio@fda.hhs.gov>
Date: August 3, 2016 at 1:34:08 PM EDT
To: Kraus, Tom <Tom.Kraus@fda.hhs.gov>
Cc: Auchincloss, Kalah <Kalah.Auchincloss@fda.hhs.gov>
Subject: RE: Status of appeal

Tom, just to be clear – before or after I submit the memo to him?

From: Kraus, Tom
Sent: Wednesday, August 03, 2016 1:30 PM
To: Borio, Luciana
Cc: Auchincloss, Kalah
Subject: RE: Status of appeal

Thank Lu. Can we reserve some time to brief Rob next week?

From: Borio, Luciana <Luciana.Borio@fda.hhs.gov>
Date: August 3, 2016 at 1:27:26 PM EDT
To: Kraus, Tom <Tom.Kraus@fda.hhs.gov>
Cc: Warren, Matthew <Matthew.Warren@fda.hhs.gov>, Auchincloss, Kalah <Kalah.Auchincloss@fda.hhs.gov>
Subject: RE: Status of appeal

Matt and I, as well as the board, are working expeditiously to finalize. We are still targeting next Monday.

From: Kraus, Tom

Sent: Wednesday, August 03, 2016 1:25 PM
To: Borio, Luciana
Cc: Auchincloss, Kalah
Subject: Status of appeal

Hi Lu,

Do you still think we're likely to get your team's recommendation regarding the Eteplirsen appeal before you go on leave? You're out next week, right?

From: [Borio, Luciana](#)
To: [Califf, Robert](#)
Cc: [Warren, Matthew](#); [Kraus, Tom](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: SDR Recommendation (and supporting documents)
Date: Monday, August 08, 2016 8:05:35 PM
Attachments: [Recommendation References.zip](#)
[SDR Recommendation Regarding Eteplirsen Final.pdf](#)

Dear Dr. Califf,

Please find attached: (1) the Scientific Dispute Resolution (SDR) Board's recommendation with respect to CDER's decision regarding eteplirsen and (2) a zip file containing copies of the other documents referenced in the recommendation. I note that, as this recommendation constitutes deliberative process for an unapproved NDA, it is protected from public disclosure. As you know, I am planning to brief you on the substance of the recommendation at 11:00 tomorrow (Tuesday, August 9), after you have had an opportunity to review the recommendation. I also plan to reach out to Drs. Woodcock and Unger to provide them with a summary of the conclusions reached by the SDR Board in making its recommendation.

Sincerely,

Luciana Borio, M.D.
Acting Chief Scientist
Food and Drug Administration
White Oak Building 1, Room 3317
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel. (301)796-4637

Smith, Celeste

From: Califf, Robert
Sent: Tuesday, August 30, 2016 1:46 PM
To: Woodcock, Janet; Unger, Ellis
Cc: Borio, Luciana; Dickinson, Elizabeth (FDA)
Subject: highly confidential
Attachments: Recommendation References.zip; SDR Recommendation Regarding Eteplirsen Final.pdf

Janet and Ellis,

Enclosed is a copy of the Board's recommendation and Lu's reflection in the form of an addendum. Please keep this in strict confidence, but I would like to hear from you by close of business Thursday if you have any major concerns or points of clarification. I have reviewed my reasoning with both of you, pending my conclusion which I will finalize over the weekend.

I do not want to launch a round of "lobbying" and know that you will keep this close and professional.

I appreciate your diligence and attention to procedure.

Regards

rmc



Date: August 8, 2016

To: Robert Califf, M.D.
Commissioner of Food and Drugs

From: Luciana Borio, M.D. Luciana Borio -
Acting Chief Scientist A

Digitally signed by Luciana Borio, DN: cn=Luciana Borio, o=FDA, ou=Office of the Commissioner, email=Luciana.Borio@FDA.HHS.gov, c=US

Subject: Scientific Dispute Resolution Appeal regarding Eteplirsen

This matter is before the Office of the Commissioner on an appeal submitted by Ellis Unger, M.D., Director of the Office of Drug Evaluation I (ODE-I) (the initiator), under Staff Manual Guide 9010.1, "Scientific Dispute Resolution at FDA" (the SDR-SMG). In his scientific dispute resolution (SDR) appeal, dated July 18, 2016, Dr. Unger challenges the basis for a decisional memorandum issued by Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research (CDER). Dr. Woodcock's decisional memorandum concludes that a new drug application (NDA) submitted by Sarepta Therapeutics Inc. (Sarepta) for eteplirsen, a drug intended to treat Duchenne muscular dystrophy (DMD), meets the standard for accelerated approval under 21 CFR § 314.510. Specifically, Dr. Woodcock's memorandum states that the data submitted in support of the NDA establishes "increased dystrophin protein production, a surrogate endpoint [for DMD] that [she] conclude[s] is reasonably likely to predict clinical benefit."¹ Dr. Unger states that he disagrees with Dr. Woodcock's decisional memorandum because he does not believe "the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit."²

Upon receipt of the appeal from Dr. Unger, in accordance with the SDR-SMG, the Office of the Chief Scientist convened the Agency Scientific Dispute Process Review Board (the SDR Board), a standing committee, which I chair, whose role in evaluating the appeal is to conduct a review of the processes used in the Center to render a decision on the scientific dispute at issue.³ Under the SDR-SMG, "The goal of this review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director."⁴ My role in the process, as Chair of the SDR Board, is to provide a recommendation to you, as Commissioner of Food and Drugs, with respect to "whether a Center failed to follow its processes and/or did not provide an adequate opportunity to the initiator to express his or concerns; [whether] all relevant evidence bearing on the scientific question at issue has been considered; and[] whether the dispute should be remanded to the Center Director."⁵ The written

¹ Woodcock Decisional Memorandum at 1.

² Appeal at 3.

³ SDR-SMG at 3. ("The Agency Scientific Dispute Process Review Board (hereafter Board) is a standing committee comprised of representatives of the Office of Accountability and Integrity, Ombudsmen from all Centers and the agency (or officials so designated) and representative(s) from the Office of the Chief Scientist. The Board is chaired by the Chief Scientist.")

⁴ *Id.* at 12.

⁵ *Id.* at 5.

recommendation must reflect the SDR Board's underlying rationale, along with minority views among the members, for those findings.⁶

In conducting its evaluation, the SDR Board reviewed pertinent aspects of the Center's administrative file for the eteplirsen NDA and interviewed Dr. Unger, Dr. Woodcock, one member of the review team for the NDA, who requested anonymity, and Virginia Behr, the Ombudsman for CDER. Based on its review, the SDR Board has determined that the processes followed by CDER provided Dr. Unger with an adequate opportunity to present his scientific views and that CDER considered all relevant evidence. As Chair of the SDR Board, I therefore recommend that you do not remand this matter to the Center Director for further action.⁷ However, there are additional considerations meriting your attention, which I describe below. Furthermore, the SDR Board encourages you to conduct a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as Commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit.

BACKGROUND

1. *Eteplirsen and DMD*

Dr. Unger provides an overview of eteplirsen and DMD in his appeal.⁸ In short, DMD is a genetic disorder with catastrophic effects on its sufferers:

[DMD] is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene[,] . . . [which] disrupt the messenger ribonucleic acid (mRNA) reading frame [and] lead[] to the absence or near-absence of dystrophin protein in muscle cells. . . . Absence of dystrophin leads to muscle damage, with replacement by fat and collagen. . . [and a concomitant] loss of physical function in childhood and adolescence, with premature death from respiratory and/or cardiac failure in the second to fourth decade.⁹

There are no FDA-approved therapies for DMD.¹⁰ Sarepta has designed eteplirsen to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded from the resulting mRNA:¹¹

[B]y restoring [] the mRNA reading frame, a 'truncated' but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, delaying disease progression. Similar truncated dystrophin is found in a less severe form of muscular dystrophy, Becker Muscular Dystrophy (BMD). In essence, the drug is hoped to induce production of sufficient Becker-type dystrophin to slow the progression of the disease. This drug is specific for exon 51 mutations, a subset of the mutations that cause DMD. If approved, the drug

⁶ *Id.* at 13.

⁷ *See id.* ("The Commissioner will review the [SDR Board's] recommendation and render a final decision on . . . whether the dispute should be remanded to the Center Director for corrective action" and "work with the Center Director to determine what corrective actions must be taken, if any.")

⁸ Unless otherwise indicated, Drs. Unger and Woodcock appear to agree as to the background provided in this section.

⁹ Appeal at 2.

¹⁰ *Id.*

¹¹ The charity, Muscular Dystrophy UK, has a nice description of the technology underpinning eteplirsen, which can be accessed at: <http://www.muscular dystrophyuk.org/progress-in-research/background-information/what-is-exon-skipping-and-how-does-it-work/>.

would be indicated for ~13% of the overall DMD patient population. Eteplirsen has not received marketing authorization from any regulatory authority, and no similar drugs are approved.¹²

In attempting to establish that eteplirsen is safe and effective for the treatment of DMD, and thus meets one of the standards for approval in the Federal Food, Drug, and Cosmetic Act (FD&C Act), Sarepta has submitted data from three clinical studies:

Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202. Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from 13 patients in this study.¹³

Dr. Unger further explains:

The endpoints for [the three] studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle – the surrogate endpoint. Dystrophin was quantified in this development program using two methods: Western blot and immunohistochemistry.¹⁴

Immunohistochemistry (IHC) analysis looks at thin slices of muscle biopsies to see if dystrophin is present or absent. Each muscle fiber that shows any amount of dystrophin is counted as positive, regardless of the actual quantity of dystrophin present. Western blot analysis assesses how much dystrophin is present.

For Study 201/202, Sarepta submitted Western blot and IHC analysis evaluating proteins in muscle samples obtained from the twelve patients before the study and then again at twelve, 24, and 48 weeks.¹⁵ “The Western blots submitted by the applicant for Study 201 were oversaturated, unreliable, and uninterpretable.”¹⁶ Because CDER also determined that the conditions under which the original IHC analysis was performed were inadequate, including that the reader was not masked to sequence and time, the Center requested a re-reading of the stored images by three masked pathologists under different conditions.¹⁷ The IHC results from the reread were not nearly as favorable, as compared to the initial IHC results reported by Sarepta.

¹² Appeal at 2.

¹³ *Id.*

¹⁴ *Id.*

¹⁵ *Id.* at 4, 8.

¹⁶ *Id.* at 4.

¹⁷ Unger Decisional Memorandum at 12-13.

The re-read showed a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group, but not the high dose group[] (. . . [T]he type-I error rate was not controlled for multiplicity.)¹⁸ Moreover, for the 4 patients who had received placebo through Week 24 and then switched to eteplirsen, there was no increase in dystrophin at Week 48.¹⁹

For Study 201/202, CDER also worked with Sarepta to improve the Western blot assays, and researchers performed repeat biopsies on eleven of twelve patients at Week 180.²⁰ Only three of the eleven patients had stored baseline samples that were adequate for evaluation, and so baseline samples were obtained from six additional patients external to Study 201/202.²¹ Dr. Unger also notes that all baseline samples were obtained from a different muscle group than the samples obtained at Week 180.²² Based on its own analysis of the IHC data, Sarepta claimed a remarkable increase of dystrophin immunostaining at Week 180: from 1.1% ± 1.3% positive muscle fibers at baseline to 17.4% ± 10.0% positive fibers at Week 180.²³ The Western blot analysis resulted in Week 180 dystrophin levels that were small, with a mean increase of only 0.93% of normal dystrophin levels in the muscle fibers.²⁴ Dr. Unger remarked that the lack of concordance between the IHC and the Western Blot results is “striking” and also noted that FDA did not verify the integrity of the IHC results.²⁵ As previously noted, each muscle fiber that shows any amount of dystrophin is counted as positive in IHC, regardless of the actual quantity of dystrophin present.

As noted above, Study 301 is an ongoing study. For purposes of its review of the NDA, CDER requested that Sarepta perform Western blot analysis on samples obtained from 13 patients enrolled in the study.²⁶ The analysis compared paired biceps samples: baseline samples and samples obtained at 48 weeks, after 48 weeks of treatment with 30 mg/kg of eteplirsen infusion.²⁷ Dr. Woodcock told the SDR Board that representatives from CDER were present in the laboratory for the Western blot analysis and oversaw the procedures and controls. The Western blot analysis showed a statistically significant increase in dystrophin, ranging in an increase from 0.22% to 0.32% of normal.²⁸ It should be noted, however, that a statistically significant increase in dystrophin, the surrogate endpoint, of an exceptionally small magnitude does not imply clinical benefit, which is the issue at the core of Drs. Unger and Woodcock’s scientific disagreement.

¹⁸ That is, with respect to time points of assessment and the 2 doses tested.

¹⁹ Appeal at 8-9. Of note, in her decisional memorandum, Dr. Woodcock rejected the findings in both the original and second evaluation of the images: “Much of the controversy over the adequacy of these assessments relates to the fact that rigorously validated assays were not used to evaluate the initial 3 muscle biopsies, apparently resulting in overestimation of the various readouts and some irreproducibility of IHC and Western blot dystrophin assays. For these reasons, I do not discuss or rely upon the results of these earlier assays, or on re-reads of them.” (Woodcock Decisional Memorandum at 2). She explained to the SDR Board that, after consultation with others in CDER, she does not view IHC results standing alone as a valid method to evaluate dystrophin levels.

²⁰ Appeal at 5.

²¹ *Id.* at 5, 9.

²² *Id.* at 5. Dr. Unger clarifies in his decisional memorandum that the baseline biopsies were from the biceps muscle, the Week 180 biopsies from the deltoid muscle. (Unger Decisional Memorandum at 17).

²³ Appeal at 9. As discussed below, however, Dr. Unger does not believe that those results are reliable.

²⁴ *Id.* at 5.

²⁵ *Id.* at 9-10.

²⁶ *Id.* at 6. Dr. Unger states that the biopsies were obtained from 13 patients but only reports the data as to 12 patients. “There was one patient for whom none of the values met the acceptance criteria [for the Western blot assay].” (Unger Decisional Memorandum at 21).

²⁷ Appeal at 6.

²⁸ *Id.*

2. *Legal Standard for Accelerated Approval and Patient Perspectives*

On December 11, 1992, on the basis of its broad statutory authority to approve drugs under the FD&C Act, FDA issued regulations providing for accelerated approval of drugs.²⁹ Under 21 CFR § 314.510, FDA may grant accelerated approval for a drug based on a surrogate endpoint under certain circumstances:

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a **surrogate endpoint that is reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, **to predict clinical benefit** or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.³⁰

The preamble to the proposed rule defines “surrogate endpoint” as follows:

A surrogate endpoint, or “marker,” is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy. For example, elevated cholesterol and hypertension, two surrogate endpoints, are important because they are risk factors for coronary and cerebral artery disease; but it is the impact of the diseases (e.g., angina, congestive heart failure after a heart attack, paralysis after a stroke, or sudden death) that is important to the patient.³¹

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA). Section 901 of FDASIA amended the FD&C Act to provide FDA with specific authority to grant accelerated approval to drugs for serious conditions.³² Section 506(c) of the FD&C Act now largely tracks language in the regulations issued by FDA in 1992. Section 901 of FDASIA also added current section 506(e) to the FD&C Act, which clarifies that the amendments were “intended to encourage [FDA] to utilize innovative and flexible approaches to the assessment of products under accelerated approval” but that “[n]othing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d) of [the FD&C Act].”³³

Section 901 of FDASIA also directed FDA to issue guidance to industry on the development of

²⁹ 57 Fed. Reg. 58942 (Dec. 11, 1992).

³⁰ Emphasis added.

³¹ 57 Fed. Reg. 13234, 13235 (Apr. 15, 1992).

³² FDASIA, PL 112-144, July 9, 2012, 126 Stat. 993.

³³ *Id.*

drugs for accelerated approval and required consideration of the following:

In developing the guidance . . . [FDA] shall consider how to incorporate novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence in such guidance, especially in instances where the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical.³⁴

Section 1137 of FDASIA further directs FDA to:

develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions, including by—(1) fostering participation of a patient representative who may serve as a special government employee in appropriate agency meetings with medical product sponsors and investigators; and (2) exploring means to provide for identification of patient representatives who do not have any, or have minimal, financial interests in the medical products industry.³⁵

In May 2014, FDA finalized a guidance on “Expedited Programs for Serious Conditions — Drugs and Biologics.” The Guidance provides general information on the evidence that the agency considers in determining whether to grant accelerated approval.³⁶ The Guidance clarifies that assessing a surrogate endpoint hinges on understanding both the disease process and the relationship between the drug’s effect and the disease process.³⁷ With respect to the latter, the Guidance states:

The extent to which a drug’s effect on the surrogate endpoint is known to predict an effect on the disease either because the effect is on the causal pathway or correlates with clinical outcomes is critical. Sometimes this relationship can be assessed epidemiologically[,] but it is most persuasively established by knowing that a drug that affects the surrogate endpoint also affects a clinical outcome.³⁸

The Guidance also provides some insight on how the agency exercises its judgment in evaluating surrogate endpoints when little is known about how an effect on a surrogate endpoint might affect clinical endpoints:

Particularly in rare diseases, there may be limited information in the literature, lack of in-depth epidemiological or historical data, and little or no experience with other drugs to inform the interpretation of surrogate endpoints or intermediate clinical endpoints. FDA may consult with external experts on surrogate endpoints and intermediate clinical endpoints where there is a lack of historical data for a given disease.³⁹

³⁴ *Id.*

³⁵ *Id.*

³⁶ Expedited Programs Guidance at 19-22.

³⁷ *Id.* at 20-22.

³⁸ *Id.* at 21.

³⁹ *Id.* at 21-22.

FDA obtains patient perspectives through a variety of avenues, “such as open public hearings on specific diseases or drug development issues, and as speakers at FDA-sponsored conferences and workshops.”⁴⁰

3. *SDR-SMG and CDER’s SDR-SOPs*

The Office of the Commissioner issued the SDR-SMG on January 13, 2009. Its stated purpose is “to improve the process of internal scientific dispute resolution[] and to encourage open communication throughout the agency.”⁴¹ The SMG “encourages the resolution of scientific disputes at the working level in the organization, starting with the frontline employees and their immediate supervisors or team leaders” and cautions that the “agency’s appeals process for scientific disputes is not a replacement for robust and fair Center-level processes.”⁴² As noted above, the SDR-SMG provides for submission of SDR appeals to the Office of the Commissioner and outlines the process and standards for evaluating such appeals. Under the SDR-SMG, the SDR Board evaluates whether “the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.”⁴³ As Chair of the SDR Board, the Chief Scientist then provides a written recommendation on those issues to the Commissioner, who renders a final decision on whether the scientific dispute should be remanded to the Center for further action.⁴⁴

In addition to outlining the process for elevating scientific disputes to the Office of the Commissioner, the SDR-SMG details the agency’s “requirements for the minimum standards for scientific dispute resolution processes in the Centers” and provides a collection of non-mandatory “best practice[s]” for such dispute resolution.⁴⁵ The SDR-SMG’s requirements for resolving scientific disputes at the Center-level begin with an obligation on the part of Center management to ensure open scientific debate on controversial issues:

Center management shall create an atmosphere in which consultation and open discussion on controversial issues are encouraged. When disagreements occur, it is necessary to follow appropriate procedures for resolving them. Informal methods, using good management practices for resolving conflict, should be employed prior to instituting the more formal procedures described here. Notwithstanding informal good management practices used to try to resolve the conflict, timely written reviews of the scientific matter in dispute should be completed by all members of a review group, including initiator and supervisors, to enable as open and complete a discussion of the issues as possible at the working level of the organization.⁴⁶

The SDR-SMG then goes on to require the Centers to have in place written standard operating procedures for formally resolving scientific disputes (SDR-SOPs) in the event that such informal attempts at resolution are unsuccessful.⁴⁷ In contrast to the procedural review contemplated by

⁴⁰ 79 Fed. Reg. 65410, 65411 (Nov. 4, 2014).

⁴¹ SDR-SMG at 1.

⁴² *Id.* at 2.

⁴³ *Id.* at 12.

⁴⁴ *Id.* at 12-13.

⁴⁵ *Id.* at 2-3.

⁴⁶ *Id.* at 6.

⁴⁷ *Id.*

the SDR-SMG, Center-level SDR-SOPs should provide for substantive review of the scientific disputes at issue within the Center.⁴⁸

At CDER, there are three interrelated chapters of the Center's Manual of Policies and Procedures (MAPPs) that serve to implement the SDR-SMG's requirements. The first, MAPP 4151.8, "Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions," sets forth CDER's principles for resolving scientific disputes informally and requires "a collaborative environment for decision-making."⁴⁹ According to the MAPP, "[s]uch an environment requires open communication and exchange of ideas in a mutually respectful professional environment[] and the full and open participation of all relevant disciplines and organizational components in the decision-making process."⁵⁰ MAPP 4151.8 states that "[e]ach individual who contributes to the decision-making process" must "be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that . . . organizational component" and that "[o]pinions of staff should be documented and supported by data in a matter commensurate with the magnitude of the decision being made."⁵¹

The second and third MAPPs at issue directly relate to CDER's formal SDR process. MAPP 4151.1, "Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain," provides for raising a scientific issue to the "Next Highest Management Official" (NHMO) if alignment on an issue cannot be reached by the staff on a team or through discussions with a team leader or first-level supervisor. The individual who disagrees with the decision (the disputant) ". . . may initiate a dispute resolution process by writing a statement (called a dispute statement) describing the position, concept, opinion, or recommendations with which the disputant disagrees . . . as well as the proposed changes and rationale for the changes in recommendations and/or conclusions."⁵²

The disputant submits the statement to the NHMO, i.e., "the management official one level above the management official who made the decision being disputed."⁵³ The NHMO then issues a written decision on the issue, and any disputant may then appeal the written decision up the chain of command all the way to the Center Director through use of the same process.⁵⁴ MAPP 4151.2, "Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director," provides for further formal review under certain circumstances if alignment cannot be reached under the process in MAPP 4151.1.⁵⁵ A CDER employee may initiate the process by submitting a written package, which must include "[a]n assessment of the possible significant negative consequences to the public health" at issue in the dispute, to the CDER Ombudsman.⁵⁶ The CDER Ombudsman and the Center Director then "determine whether the consequences of the decision in question are potentially serious enough to warrant" additional review.⁵⁷ If so, the Center Director appoints a chairperson to lead an *Ad Hoc* review panel for purposes of evaluating the scientific dispute and providing a recommendation to the Center

⁴⁸ See *id.*; see also footnote 136.

⁴⁹ MAPP 4151.8 at 2.

⁵⁰ *Id.*

⁵¹ *Id.* at 2-3.

⁵² MAPP 4151.1 at 3.

⁵³ *Id.*

⁵⁴ *Id.* at 4.

⁵⁵ *Id.* at 5; MAPP 4151.2 at 1-2.

⁵⁶ MAPP 4151.2 at 5.

⁵⁷ *Id.*; see also *id.* ("In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted")

Director, who renders the final decision.⁵⁸ The *Ad Hoc* panel typically includes one member with relevant technical expertise, one member chosen from a list provided by the person requesting review, and, if possible, one member with relevant expertise who is external to the agency.⁵⁹

4. Procedural History of the Dispute in CDER

Sarepta submitted its NDA for eteplirsen (#206488) on June 26, 2015.⁶⁰ CDER assigned it for review to the Division of Neurology Products (DNP) within ODE-I, the office for which Dr. Unger serves as Director.⁶¹ Even before submission of the NDA, however, representatives from the Office of New Drugs (OND), DNP and ODE-I (the review team) regularly briefed Dr. Woodcock on issues related to the ongoing study of eteplirsen pursuant to an investigational new drug application (IND) and the anticipated NDA.⁶² The discussions at these briefings included among their topics: the suitability of eteplirsen for accelerated approval, an overview and background for eteplirsen, study design, a clinical site inspection report for Sarepta, general brainstorming, and planned communications.⁶³ Dr. Unger told the SDR Board both that there were far more briefings of the Center Director than is typical and that the scope of those briefings included an unusual level of detailed discussion.

During the SDR Board's separate interviews of Dr. Unger and the review team member (RTM), the SDR Board learned that, at Dr. Woodcock's direction, the review team also joined her in meetings with patient advocacy groups for DMD on multiple occasions—anywhere from six to twelve times—from very early on in the review process. The RTM described the meetings with the patient advocacy groups, which frequently included boys with DMD and their parents, as “intense,” “personal,” and “intimidating.” Dr. Unger and the RTM both thought that Dr. Woodcock's early interest and involvement in DNP's approach to guiding the development of eteplirsen was based in part on the enthusiasm in the DMD community in relation to an article published about the initial findings for Study 201/202, which Drs. Unger and Woodcock now agree are misleading and unreliable. Indeed, Dr. Woodcock told the SDR Board that she became involved because of the broader public interest the article generated, along with encouragement from the Commissioner of Food and Drugs at the time and her long-held belief that OND has been very conservative in evaluating drugs for accelerated approval. In his decisional memorandum, Dr. Unger explains the excitement surrounding eteplirsen at the time as follows:

[The initial findings for Study 201/202] were substantially reported in a 2013 publication, which claimed that eteplirsen markedly increased functional dystrophin production: “...the percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients ($p \leq 0.002$). Even greater increases occurred at week 48 (52% and 43%

⁵⁸ *Id.* at 6-7.

⁵⁹ *Id.* at 6.

⁶⁰ Unger Decisional Memorandum at 1.

⁶¹ *Id.* at 2.

⁶² Appeal at 24-25; Chronology prepared by Virginia Behr and submitted to the SDR Board (Behr Chronology) at 1-2. In his appeal, Dr. Unger consistently refers to the representatives from OND, OND-I and DNP who were involved in the review of the eteplirsen NDA as the “review team” or as “the division,” even though he appears to be referring to senior management within OND on occasion. Dr. Woodcock has also used the same terminology on occasion, though not as consistently. For the sake of efficiency, this memorandum refers to everyone at CDER who was involved in the review of the eteplirsen NDA, besides Dr. Woodcock herself, as the review team. Nonetheless, the SDR Board notes that, within FDA, “review team” is often used to reflect the core team of individuals within a division who are directly engaged in the review of the science underlying a regulatory submission.

⁶³ Appeal at 24-25; Behr Chronology at 1-2.

in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma.” The publication also stated that dystrophin expression was confirmed by Western blot, with a figure showing what were termed “representative” results.

Publication of this paper was followed by a Sarepta press release, which also claimed a remarkable treatment effect from eteplirsen and raised wildly unrealistic expectations in the DMD community.⁶⁴

In their interviews with the SDR Board, Dr. Unger and Dr. Woodcock stated that FDA also received significant correspondence from the public and Congress, much of which urged approval of eteplirsen.⁶⁵ Some of the correspondence used vulgar language and was abusive to the review staff.⁶⁶

The briefings of Dr. Woodcock began again five to six months after submission of the NDA for eteplirsen.⁶⁷ The focus of these briefings was on preparation for a planned meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (AC meeting) to provide advice on the review of the eteplirsen NDA, which meeting was initially scheduled for January 2016 but then rescheduled for April 25, 2016.⁶⁸ The preparation involved discussions of the ongoing review of the data, including the “strengths, limitations, and uncertainties of the data, particularly with respect to the comparison between the open-label eteplirsen group and a contemporary untreated external control group.”⁶⁹ During their respective interviews with the SDR Board, both Dr. Unger and the RTM conveyed their belief that Dr. Woodcock was inclined to grant approval from very early on in the process. But the RTM stated that Dr. Woodcock’s views were not always clear during discussions throughout the review of the science—sometimes she seemed to agree with external constituents, sometimes not. The RTM told the SDR Board that, in his or her view, the review team was never sure whether they were discussing science, policies, or politics. According to both Dr. Unger and the RTM, Dr. Woodcock frequently conveyed that she thought the review team was being unreasonable and encouraged DNP to find a way to approve the eteplirsen NDA. Both Dr. Unger and the RTM told the SDR Board that Dr. Woodcock seemed focused on the external pressures, from both patient advocacy groups and Congress, and that she frequently talked about the effects of a decision regarding eteplirsen in terms of overarching policy (e.g., the need to be more flexible for ultra-rare diseases). The RTM highlighted to the SDR Board that at least two members of the review team were leaving FDA or had left the agency in the wake of both the decision-making process within CDER and the pressures exerted by outside forces.

Dr. Woodcock conceded to the SDR Board that she was leaning toward granting approval in light of the available data as early as 2014. She said that her goal throughout the discussions

⁶⁴ Unger Decisional Memorandum at 11 (emphasis in original), citing Mendell JR, *et al*: Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol* 2013;74:637-47 and Sarepta press release, dated 8/8/13 (<http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irolnewsArticle&ID=1846052>). Dr. Unger also notes, “It was these perceptions and expectations that led the applicant to declare that a placebo-controlled study was no longer feasible.” Unger Decisional Memorandum at 11.

⁶⁵ See also Appeal at 23.

⁶⁶ See, e.g., *id.* at 23-24.

⁶⁷ *Id.* at 25; Behr Chronology at 2-3.

⁶⁸ Appeal at 25; Behr Chronology at 2-3.

⁶⁹ Appeal at 25.

with the review team was to convince them to come around to her more flexible way of thinking about the data. According to Dr. Woodcock, she recognized that there were serious and significant flaws in the study design for Study 201/202 and the data it generated but that she did not “want to hold” those flaws “against the patients.” She conceded that the results produced by Studies 201/202 and 301 were always less than anyone in CDER had hoped.

In their respective interviews with the SDR Board, both Dr. Unger and the RTM focused to some extent on Dr. Woodcock’s involvement in the planning stages for the AC meeting. They expressed some surprise at the extent of her involvement. Dr. Unger indicated in his interview with the SDR Board that Dr. Woodcock even advocated, unsuccessfully, for changing the order of the questions to be posed to the committee and wanted the question on conventional approval to come before the one on accelerated approval.

The RTM told the SDR Board: (1) that Dr. Woodcock made it clear in one or more of the meetings leading up to the AC meeting that she intended to speak at the meeting but (2) that the substance and purpose of her participation were never communicated. Although the RTM affirmatively stated that the review team was free to develop its own presentation to the committee, uncertainty with respect to Dr. Woodcock’s role made doing so more difficult. The RTM also noted that Dr. Woodcock requested a longer than is typical Open Public Hearing portion of the AC meeting that, as a result, the review team thought there would insufficient time for them to make their presentations during a one-day meeting. The RTM stated that the review team asked to extend the advisory committee to two days but that they were overruled.

On April 25, 2016, CDER held the AC meeting. The meeting focused on the data from Study 201/202.⁷⁰ Dr. Woodcock spoke at the meeting several times. At the meeting she made a presentation that was intended to “provide a framework within which to consider [the] data [underlying the eteplirsen NDA] based on [her] 30 years of experience at FDA and really extensive experience in implementation of the legal standards for drug approval.”⁷¹ She highlighted many of the difficulties in interpreting the data.⁷²

At the AC meeting, Dr. Woodcock also described the standards for both conventional and accelerated approval of drugs but mentioned that the agency had not “articulated an evidentiary standard for determining if a surrogate endpoint is reasonably likely to predict clinical benefit.”⁷³ She concluded her presentation with the following remarks:

I would note that much of the effort in evaluating a drug development program goes into avoiding a specific mistake, that is erroneously approving a drug that is not effective.

There often is little consideration of another error, which is failing to approve a drug that actually works. In devastating diseases, the consequences of this mistake can be extreme, but most of these consequences are borne by patients who traditionally [] have little say in how the standards are implemented.

The accelerated approval program includes a requirement for confirmatory studies for efficacy, so as you've heard from the sponsor, you have to do further studies to explore and confirm effectiveness. An inherent

⁷⁰ Sarepta had not yet submitted the data from Study 301.

⁷¹ Advisory Committee Transcript at 151.

⁷² *Id.* at 151-155.

⁷³ *Id.* at 155-156.

presumption in this program of accelerated approval, which is written in the preamble to our regulation about it, is that more uncertainty is going to be tolerated initially and that in fact sometimes we will collectively get it wrong, otherwise accelerated approval would really have no different standards than regular approval.⁷⁴

During the questions to the committee members, Dr. Woodcock restated the standard for accelerated approval and emphasized that, with regard to the surrogate endpoint of dystrophin, there has never been a “threshold established [to show a reasonable likelihood of predicting clinical benefit] because there's never been a drug to do this.”⁷⁵ When later asked for clarification of the extent to which the committee members were to incorporate the testimony of the boys and their families into their evaluation of clinical outcomes for Study 201/202, Dr. Woodcock stated:

Well, we are instructed, as people said, to take the use of the patient community into account, more on the benefit and the risk. * * * So the statutory standard is more or less as described there, but there is flexibility, and that's where we should take the views of the community into account.⁷⁶

During his SDR Board interview, the RTM stated that, notwithstanding Dr. Woodcock's emphasis on accelerated approval and the standard of “reasonably likely to predict clinical benefit,” “[s]urrogacy was not discussed in any genuine scientific way” during the AC meeting because it had not been framed that way by Sarepta through its presentation to the committee. The RTM specifically stated that there was no discussion of “substantial evidence” in the context of accelerated approval, nor what might constitute “interpretable evidence.” The RTM believed that, by the end of an emotional AC meeting, the framework for evaluating the data under the appropriate regulatory standards, as provided by the review team toward the start of the meeting, had been forgotten by the committee members.

Dr. Woodcock explained to the SDR Board that she thought both that the review team did a poor job framing the issues during their presentations and that the questions were confusing and poorly worded. Indeed, during her interview with the SDR Board, Dr. Woodcock opined that the review team “did not put its best foot forward.” She speculated that the confounding factor was the number of interested persons attending both in person and by webcast. She stated that she did not interfere with either aspect of the AC meeting because she knew she disagreed with the review team and Dr. Unger had already signaled that he would file an SDR appeal if she decided to grant accelerated approval to eteplirsen. She thought that the review team's presentation of the IHC data, in particular, was confusing. She further opined that the review team's failure to highlight the clinical data made the questions on conventional approval and accelerated approval difficult for the committee members to understand. Dr. Woodcock also criticized the review team for how it downplayed and undercut the views of the patient advocates.

At the conclusion of the AC meeting, the committee voted against accelerated approval by a margin of 7-6.⁷⁷ Three of the members who voted in favor of accelerated approval were the consumer representative and the two patient representatives.⁷⁸

⁷⁴ *Id.* at 158-59.

⁷⁵ *Id.* at 484.

⁷⁶ *Id.* at 548-549.

⁷⁷ *Id.* at 486-95.

⁷⁸ *Id.* at 2-7, 486-88.

On May 4, 2016, Dr. Woodcock met with the review team to discuss the AC meeting and plan of actions for the NDA.⁷⁹ In his appeal, Dr. Unger contends that Dr. Woodcock “made clear her intent to approve the drug” at this meeting, even though she had not yet reviewed drafts of DNP’s final review memorandum or his review memorandum.⁸⁰ According to Dr. Unger, Dr. Woodcock explained that she had already “reached a different conclusion” than the review team.⁸¹ Dr. Woodcock explained to the SDR Board that the memoranda were discussed during the Center Director briefings and that she felt she understood the views of the review team and did not see the point of an “exchange of reviews.”

On May 24, 2016, Dr. Unger met privately with Dr. Woodcock to discuss the eteplirsén decision.⁸² On May 31, 2016, Dr. Woodcock met with representatives from the review team to discuss their reviews and her initial draft of a decisional memorandum based primarily on the data from Study 201/202.⁸³ Dr. Woodcock received comments back from the review team at the same meeting.⁸⁴ Dr. Unger told the SDR Board that he and members of the review team—including Dr. Robert Temple, Deputy Center Director for Clinical Science and Dr. John Jenkins, Director of OND—discouraged Dr. Woodcock from finalizing the decisional memorandum and granting accelerated approval for eteplirsén until the additional data from Study 301 could be obtained.

On June 3, 2016, in response to an email from Sarepta, a letter signed by Dr. Woodcock issued to the sponsor.⁸⁵ The letter requested the additional data from Study 301, which was to include comparisons of any biopsy samples obtained at Week 48 to the respective baseline samples for those patients.⁸⁶ The letter stated,

If you are successful in showing, to FDA’s satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable).⁸⁷

Dr. Woodcock explained that Dr. Unger and the review team essentially agreed to the timeframe of four business days, though they pushed instead for six. She felt that there was general agreement that data from only twelve patients could be reviewed quickly, especially given that representatives from CDER would be overseeing the Western blot analysis and ensuring that it was done properly.

On June 27, 2016, Sarepta submitted the requested data.⁸⁸ Dr. Woodcock explained that accelerated approval was not granted within four business days of that date precisely because the results of the analysis were disappointing in that they provided evidence of only a minimal increase in dystrophin at 48 weeks. Dr. Unger sent an email to Dr. Woodcock that read:

⁷⁹ Appeal at 25; Behr Chronology at 2.

⁸⁰ Appeal at 26.

⁸¹ *Id.*

⁸² Behr Chronology at 2.

⁸³ Appeal at 26; Behr Chronology at 2.

⁸⁴ Behr Chronology at 2.

⁸⁵ June 3, 2016, General Advice letter.

⁸⁶ *Id.* at 1.

⁸⁷ *Id.* at 1-2.

⁸⁸ Unger email to the SDR Board, dated July 22, 2016.

I don't have to tell you how difficult the eteplirsen decision has been for many of us in ODE-I. As you know, we have reached different scientific conclusions on the strength of the data, and in particular, the likelihood that the small increase observed in Becker-type dystrophin is reasonably likely to predict clinical benefit. This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed "reasonably likely to predict clinical benefit." Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated.

I know that Dr. Jenkins has mentioned the possibility of involving Dr. Califf in the eteplirsen decision on at least one occasion, and I would like to request a formal appeal to the Commissioner on this matter.

I'm aware that the Commissioner's official role is to consider the administrative aspects of review decisions and not the science. But given the potential for setting a precedent here, I think he should be aware of the various points of view and consider the potential ramifications of the matter at hand.

I'm also aware that you advised Sarepta that we would be prepared to grant accelerated approval of their NDA within 4 business days of receiving their new data, but there was a provision in the letter that the increase in dystrophin had to be meaningful, and we do not have agreement on this point. Thus, it is my hope that a Commissioner Briefing can be held before an action is taken.

I have discussed the above with Dr. Jenkins, and he supports this course of action.

I propose that we reserve a few minutes at the briefing tomorrow to discuss this matter.⁸⁹

On July 6, 2016, Dr. Woodcock met with the review team one final time.⁹⁰ During the meeting, Dr. Woodcock "indicated to the review team that [she] had read their memoranda that had been updated to reflect the new [Western blot] data, and that [she] maintained [her] position that the application should receive accelerated approval based on dystrophin production."⁹¹ She discussed her rationale, which—based on her notes—appears to have tracked the rationale in her final decisional memorandum.⁹²

On July 8, 2016, in light of Dr. Unger's stated intention of filing an appeal with the Office of the Commissioner, Virginia Behr, CDER Ombudsman, began working with him and Dr. Woodcock to determine whether the institution of any formal appeals under CDER's SDR-SOPs was warranted.⁹³ Ms. Behr had determined that the procedure outlined in MAPP 4151.1,

⁸⁹ Unger email dated July 5, 2016.

⁹⁰ Appeal at 26; Behr Chronology at 3.

⁹¹ Woodcock's handwritten notes, dated July 6, 2016, at 1.

⁹² *Id.* at 2. Also of note, on July 7, 2016, Dr. Unger briefed you on his rationale for disagreeing with Dr. Woodcock's underlying scientific reasoning for granting accelerated approval for eteplirsen (Behr Chronology at 3).

⁹³ See "Agreement to utilize FDA Staff Manual Guide 9010.1 for internal appeal related to NDA 206488, eteplirsen injection" (SDR-SOPs Agreement).

“Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain” did not apply because the disagreement was between the Center Director and a subordinate two levels below her.⁹⁴ She also questioned the utility of using MAPP 4151.2, “Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director.”⁹⁵ She reasoned that “the CDER Director ha[d] already fully evaluated the issues and [was] one of the parties involved in the dispute” and that “utilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days.”⁹⁶ She nonetheless consulted with both Drs. Unger and Woodcock, who both agreed to bypass the *Ad Hoc* panel process in favor of the process outlined in the SDR-SMG.⁹⁷ During his presentation to the SDR Board, Dr. Unger also indicated that he thinks referring the matter to an *Ad Hoc* panel would have been pointless because Dr. Woodcock had already made up her mind and a new process would not have changed the outcome.

On July 11, 2016, Dr. Woodcock provided a draft of her final decisional memorandum to the review team.⁹⁸ She received comments back from Dr. Unger; Dr. Jenkins, the Director of OND; and Dr. Ashutosh Rao, of the Office of Biotechnology Products, who was also on the review team.⁹⁹ The comments from Drs. Unger and Rao do not debate the action proposed in Dr. Woodcock’s draft decisional memorandum or its underlying scientific conclusions.¹⁰⁰ Instead, they focus on clarifying certain facts asserted in the memorandum, and Dr. Unger provided information regarding the clinical course of 11 patients enrolled in Study 201/202 to 240 weeks.¹⁰¹ Dr. Jenkins provided more detailed analysis on and critique of some of Dr. Woodcock’s findings and he expressed concern about her conclusions. However, he made no attempt in his written comments to dissuade her from her ultimate conclusion regarding accelerated approval.¹⁰² By email on the afternoon of July 13, Dr. Unger stated, “I’ve canvassed the Division, and we have no additional comments.”¹⁰³ Dr. Unger told the SDR Board that he and the review team understood that Dr. Woodcock had already made up her mind and that thus they did not see a point in criticizing Dr. Woodcock’s draft decisional memorandum.

Furthermore, the RTM told the SDR Board that some of the positions taken by Dr. Woodcock in the draft decisional memorandum were brand new to him but that he did not feel any feedback he could provide would receive due consideration by Dr. Woodcock. The RTM expressed concern that Dr. Woodcock’s analysis for “reasonably likely to predict clinical benefit” raised new issues and information that should have been presented at the beginning of the review and that had not been addressed by the review team or, perhaps more importantly, presented by the sponsor in support of the NDA. The RTM specifically discussed with the SDR Board the section of the finalized version of the memorandum addressing whether the data for eteplirsen is adequate to show a reasonable likelihood of predicting clinical benefit.¹⁰⁴ As an example of his concerns, the RTM pointed to section (B)(5) of the decisional memorandum, which details the findings in the

⁹⁴ *Id.* at 1. It is also clear from the record before the SDR Board that the supervisor between Drs. Unger and Woodcock, Dr. John Jenkins, agreed with Dr. Unger.

⁹⁵ *Id.*

⁹⁶ *Id.* at 2.

⁹⁷ *Id.*

⁹⁸ Behr Chronology at 3.

⁹⁹ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); Jenkins email dated July 12, 2016; and emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰⁰ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰¹ Unger emails dated July 13, 2016 and sent at 12:57 AM, 9:26 AM (including attachments), and 11:19 AM (including attachment); emails (including attachments) from Rao dated July 12 and 13, 2016.

¹⁰² Jenkins email dated July 12, 2016.

¹⁰³ Unger email dated July 13, 2016 and sent at 3:19 PM.

¹⁰⁴ Woodcock Decisional Memorandum at 5-10.

scientific literature regarding “the relationship of dystrophin expression to clinical status.”¹⁰⁵ The RTM indicated that he or she knows the scientific literature at issue very well and that he or she could have provided significant input into the evaluation of the literature and the underlying data and analysis. The RTM conveyed that he did not do so because he felt Dr. Woodcock had already made her decision.

On July 14, 2016, Dr. Woodcock finalized her decisional memorandum. She explained to the SDR Board that her conclusion regarding whether the increase in dystrophin production identified by Studies 202 and 301 was reasonably likely to predict clinical benefit was based on her own “medical/scientific judgment.” She emphasized that she has thirty years of experience at FDA and that she has far more experience in assessing this type of evidence for an “ultra-rare rare” disease than the review team. She thought that the review team was unreasonable in its position on a threshold for predicting clinical benefit in this case. Her stated goal for the decisional process was to move the review team toward what she viewed as a more reasonable approach. She acknowledged that there were clear weaknesses in the data but that accelerated approval should not be limited to “sure bet” drugs and that confirmatory trials are required for a reason. Dr. Woodcock emphasized her view that the agency needs to accept more uncertainty when granting accelerated approval. She also criticized OND for not issuing clear guidance on what constitutes a sufficient drug effect to be “reasonably likely to predict clinical benefit,” as she had suggested for an extended period of time. She also thought that the review team’s views on balancing the mean results of a clinical study with a targeted evaluation of responsive patients were misplaced, particularly in a DMD population, where additional genetic mutations or deficiencies could have a profound effect on the outcome.

In her presentation to the SDR Board, Dr. Woodcock suggested that, in making the decision, she was looking at the broader picture for the development of these types of drugs for very limited patient populations in the United States (between 600 and 1300) and that there needed to be some path forward for such innovative products. She opined that Sarepta in particular “needed to be capitalized.” She noted that the sponsor’s stock went down after the AC meeting and went up after FDA sent the June 3, 2016 letter. Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would “lapse into a position of” self-treatment.

On July 16, 2016, Dr. Unger finalized his own decisional memorandum. In her own decisional memorandum, dated July 14, 2016, Dr. Woodcock indicated that she had read Dr. Unger’s decisional memorandum,¹⁰⁶ although she could not have done so given the timing of the two memoranda. She explained to the SDR Board that she did not feel she needed to see a finalized version of Dr. Unger’s decisional memorandum because she was already familiar with his views on the data and the decision. She also stated that there was nothing in Dr. Unger’s appeal, which is based largely on his finalized decisional memorandum, that would have changed her mind on her decision or the underlying rationale. She stated, “He is entitled to his own opinion.”

5. Dr. Unger’s SDR Appeal

In his appeal, Dr. Unger focuses his arguments almost exclusively on the substance of his scientific disagreement with Dr. Woodcock. Indeed, Dr. Unger makes clear in his appeal that he

¹⁰⁵ *Id.* at 7-10.

¹⁰⁶ *Id.* at 1.

seeks “a scientific review on the matter of whether or not there is substantial evidence of a quantitative effect on dystrophin protein that is reasonably likely to predict clinical benefit.”¹⁰⁷ Insofar as he explicitly addresses potential procedural issues under the review process contemplated by the SDR-SMG, he does so in two paragraphs toward the end of the appeal.¹⁰⁸ He first states that Dr. Woodcock’s “direct involvement with this drug, compared to other development programs, has been unprecedented.”¹⁰⁹ He states further that “[s]he also attended the April meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, where she spoke and interjected a number of important comments.”¹¹⁰ After conceding that “[t]here is no question that there has been adequate time and place for the discussion of various views,” Dr. Unger notes that he found it unfortunate that “the Center Director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division’s final review memorandum or my review memorandum.”¹¹¹ As noted above, Dr. Unger indicates that Dr. Woodcock conveyed that she had “already . . . reached a different conclusion . . . than the review team.”¹¹²

In his presentation to the SDR Board, Dr. Unger highlighted that Dr. Woodcock had never seen the charts on page 10 of his appeal. Those charts show: (1) a comparison of the *original* IHC results for baseline samples in the three patients whose biopsies were available at 180 weeks to the IHC results for those same samples when they were re-evaluated after 180 weeks and (2) a comparison of the IHC and the Western blot results at 180 weeks.¹¹³ Dr. Unger stated, however, that those charts were consistent with his earlier positions and would likely not affect Dr. Woodcock’s analysis or decision. In a follow-up email to the SDR Board, Dr. Unger also contended that Dr. Woodcock diverted from protocol when she finalized her decisional memorandum on July 14, 2016, two days before his.

In his appeal, Dr. Unger frames his scientific disagreement with Dr. Woodcock as follows: “The disagreement is over the question of whether the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit.”¹¹⁴ Nonetheless, Dr. Unger explains his disagreement with Dr. Woodcock through multiple challenges to the reliability of the underlying data and specific issues he has with her rationale or the evidentiary basis for such rationale. Of note, he makes the following scientific arguments:

- As noted above, Study 201 showed only “a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group...”¹¹⁵
- Study 201/202 was fundamentally flawed in several respects:
 - “[T]he baseline biopsies were obtained from [external controls] . . . who could differ in unknown ways from the subjects in Study 201/202”;¹¹⁶
 - “[T]he Week 180 biopsies were obtained from different muscles than the baseline biopsies”;¹¹⁷ and

¹⁰⁷ Appeal at 26.

¹⁰⁸ *Id.*

¹⁰⁹ *Id.*

¹¹⁰ *Id.*

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ *Id.* at 10.

¹¹⁴ *Id.* at 3.

¹¹⁵ *Id.* at 9.

¹¹⁶ *Id.* at 5.

¹¹⁷ *Id.*

- “The baseline biopsies for the three subjects with Week 180 data had been stored for several years and the protein may have degraded, leading to a falsely low baseline value, and a greater apparent increase from baseline....”¹¹⁸
- Although the available data generated by Study 301 were the product of an adequate and well-controlled study and showed a statistically significant increase of dystrophin, the drug effect (i.e., an increase from 0.22% to 0.32% of normal) is not reasonably likely to predict clinical benefit.¹¹⁹
 - “The treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications”;¹²⁰
 - “Dr. Woodcock never provides a rational argument – based on reliable data – to support the concept that ‘...low-level increases in dystrophin production are reasonably likely to predict clinical benefit.’ She provides no rationale – no link between a mean increase in dystrophin of 3 parts per thousand and clinical benefit”;¹²¹ and
 - “No evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.”¹²²

He also makes several overarching policy and legal arguments that call into question the appropriateness of Dr. Woodcock’s decisional memorandum. His key arguments focus on the effects that Dr. Woodcock’s decision would have on the pathway for accelerated approval and the standard for “reasonably likely to predict clinical benefit.”¹²³ He also highlights the negative effects that accelerated approval would have on the patients themselves, including false hope, abandonment of other therapies, and a decline in drug development for DMD.¹²⁴ He further questions “the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic[] when the consequence of a sub-therapeutic dose is clinical deterioration and death.”¹²⁵ Finally he worries that approving eteplirsen based on the data submitted by the sponsor “would send the signal that political pressure and even intimidation—not science—guide[] FDA decisions.”¹²⁶

ANALYSIS

1. Whether CDER followed its own processes.

The first issue for the SDR Board to consider is whether CDER followed its own processes in addressing Dr. Unger’s scientific dispute. Dr. Unger does not contend that there were any issues with respect to how CDER chose to address and implement its own formal appeals process under the SDR-SOPs in this case. In his appeal, Dr. Unger points instead to four deviations from typical Center process: (1) Dr. Woodcock’s involvement in the early stages of review of the eteplirsen NDA; (2) her extensive involvement in planning the AC meeting and her participation

¹¹⁸ *Id.*

¹¹⁹ *Id.* at 7.

¹²⁰ *Id.* at 13.

¹²¹ *Id.* at 15.

¹²² *Id.*

¹²³ *Id.* at 21-22.

¹²⁴ *Id.*

¹²⁵ *Id.* at 23; *see also* Unger Review Memorandum at 4, 5.

¹²⁶ *Id.*

in the meeting; (3) her initial decision (on May 4, 2016) to approve the eteplirsen NDA before the review team had completed even their draft review memoranda; and (4) her issuance of her final decisional memorandum before Dr. Unger finalized his own decisional memorandum as Director of ODE-I. In its review of the administrative file and the surrounding circumstances, the SDR Board has also identified below other potential deviations from process at the Center level.

The agency-wide SDR-SMG directs the SDR Board to focus on the Center's SDR-SOPs in evaluating whether the Center followed its own processes in evaluating a scientific dispute. In this case, however, both Drs. Unger and Woodcock have agreed that the only applicable SDR-SOP, MAPP 4151.2, provides for a review by the Center Director in consultation with an *Ad Hoc* panel and that going through such a process at this stage would be futile. The SDR Board has determined that, absent the second aspect of that agreement regarding futility and the underlying unusual circumstance of this scientific dispute, there would be reason to refer the matter back to the Center for further review by an *Ad Hoc* panel.

The interplay between MAPP 4151.1 and 4151.2, the former of which provides for supervisory review of scientific disputes all the way to the Center Director, suggests that MAPP 4151.2 actually calls for additional review of a scientific dispute by the Center Director under certain circumstances even if she has already made a decision on the dispute. Although MAPP 4151.2 provides for bypassing review of the scientific dispute up the chain of command under MAPP 4151.1 if such exhaustion would impede the timely resolution of a serious public health issue, MAPP 4151.2 also emphasizes that it should not be used before other means of resolution have been attempted.¹²⁷ However, the key consideration for obtaining review by an *Ad Hoc* panel under MAPP 4151.2 is “whether the consequences of the decision in question are potentially serious enough to warrant [additional review],” not whether the resort to the process would be futile.¹²⁸ It appears that Dr. Woodcock has never made a determination regarding the seriousness of the decision in question, but it would be surprising if she determined that the dispute in this case did not meet the standard, as reflected in the statement she signed.¹²⁹

In this case, however, it is clear from the record before the SDR Board that Dr. Woodcock was so involved in the underlying scientific dispute—including direct and extensive personal review of the data and analyses offered in support of the NDA—that we agree with the conclusion in the agreements signed by Drs. Unger and Woodcock that “the CDER Director has already fully evaluated the issues.”¹³⁰ Indeed, she has already received advice from an advisory committee and had substantial conversations with her staff over an extended period of time with respect to the dispute in question. There is no reason to believe that receiving additional advice from an *Ad Hoc* panel would alter Dr. Woodcock's views of the scientific issues. As the agreement between her and Dr. Unger reflects, the process would be time-consuming and delay an important

¹²⁷ MAPP 4151.2 at 5. (“In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted before a [request for review under 4151.2] is filed. However, in some cases, an individual may believe that his or her professional opinion will not be considered by his or her supervisors or that there is not time to exhaust other options for dispute resolution without seriously endangering the public health. In this case, the submitter should include . . . a written request to bypass these other mechanisms. . . .”).

¹²⁸ *Id.*

¹²⁹ SDR-SOPs Agreement at 2 (“The difference of opinion between Drs. Unger and Woodcock could be considered to meet the criteria for filing an appeal under MAPP 4151.2 because the drug indication sought is one for a serious and life-threatening disease that has limited treatment options.”).

¹³⁰ *Id.*

regulatory decision unnecessarily.¹³¹ Dr. Unger also told the SDR Board that he thought going through the *Ad Hoc* panel process would have been pointless for the aforementioned reasons.

The difficulty for the SDR Board is that the agency-wide SDR-SMG is predicated on some level of formal scientific dispute resolution within the Center, particularly a decision by the Center Director regarding the formalized scientific dispute.¹³² For that reason, the focus of the SDR-SMG with respect to the process followed is on whether the Center followed its own SDR-SOPs in resolving the scientific dispute.¹³³ Yet, the SDR-SMG also directs the Centers to adopt “[i]nformal methods” for resolving scientific disputes, “to create an atmosphere in which consultation and open discussion on controversial issues are encouraged,” to use “good management practices for resolving conflict,” and “to enable as open and complete a discussion of the issues as possible at the working level of the organization.”¹³⁴ As a result, the SDR Board has determined that reviewing the processes used by a Center to resolve a scientific disagreement is appropriate under the SDR-SMG even when, as here, the initiator has not availed himself of the Center’s formal process for resolving scientific disputes and the Center Director has explicitly agreed to that approach.

Whether the Center followed its own processes for resolving a scientific disagreement cannot be viewed in a vacuum, however. Indeed, the SDR-SMG itself—at its most concise and in its clearest voice—states, “The goal of [the SDR Board’s] review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.”¹³⁵ Particularly in the context of a scientific dispute that did not go through a formal SDR process at the Center but nonetheless received extensive review by the Center Director, focusing on deviations from process without any regard to whether they affected the initiator’s opportunity to present his views of the science (and to some extent whether those views and the evidence were considered) would seem to miss the point of that review. Accordingly, the SDR Board finds that it is more appropriate to address Dr. Unger’s arguments regarding the Center’s deviations from appropriate process under the second prong of its analysis: whether the Center provided Dr. Unger an adequate opportunity present his scientific concerns.

The SDR Board’s one caveat is that, as noted above, the SDR-SMG does appear to assume that there has been both at least some use of the formal dispute resolution within the Center and, accordingly, a *formal* substantive review of the initiator’s scientific concerns before reaching the Office of the Commissioner.¹³⁶ The limited scope of the SDR Board’s review under the SDR-SMG—i.e., an evaluation of the Center’s decision-making process—means that Dr. Unger will also not receive a substantive review of his scientific concerns under the SDR-SMG. In fact, at the conclusion of the SDR Board’s review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level. Particularly in light of

¹³¹ *Id.* (“[U]tilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days.”).

¹³² See SDR-SMG at 6 (requiring as a mandatory process for formal scientific dispute resolution a written opinion by the Center Director and stating that such a written opinion as a step in the process is a “central criterion for advancement to the agency-level appeals process.”).

¹³³ See, e.g., *id.* at 12 (requiring the SDR Board to “obtain the full administrative record of the Center’s processes for the dispute and review the Center’s published SOP(s)” and to “review that information to determine whether written Center processes were followed.”).

¹³⁴ *Id.* at 6.

¹³⁵ *Id.* at 12.

¹³⁶ See *id.* at 6 (referring to SOPs for resolution of Center-level scientific disputes without limiting them to procedural reviews and contemplating the Center SOPs as a continuation of the informal SDR process).

Dr. Unger's explicit request for scientific review of the matter within the Office of the Commissioner, therefore, the SDR Board recommends additional substantive review at this level, as is discussed below.

2. Whether CDER provided an adequate opportunity to Dr. Unger to present his scientific concerns.

In his appeal, Dr. Unger admits, "There is no question that there has been adequate time and place for the discussion of various views."¹³⁷ In so doing, he appears to concede away most of his arguments with respect to whether he had an adequate opportunity to present his scientific concerns, notwithstanding the procedural deviations he identifies. The SDR Board, however, has not taken Dr. Unger's concession at face value and has instead looked beyond it to evaluate the administrative file and the surrounding circumstances to identify additional procedural issues. We conclude nonetheless that Dr. Unger had an adequate opportunity to present his scientific concerns to Dr. Woodcock before she issued her decisional memorandum.

As noted above, Dr. Unger identified four deviations from Center's typical decision-making process for the eteplirsen NDA: (1) Dr. Woodcock's involvement in the early stages of review of the eteplirsen NDA; (2) her extensive involvement in planning the AC meeting and her participation in the meeting; (3) her initial decision (on May 4, 2016) to approve the eteplirsen NDA before the review team had completed even their draft review memoranda; and (4) her issuance of her final decisional memorandum before Dr. Unger finalized his own decisional memorandum as Director of ODE-I. In reviewing this matter, the SDR Board—which includes among its members Ombudsmen from other Centers that oversee reviews of medical products—also considered other departures from the typical processes used by Centers in reviewing applications for pre-market approval or clearance.¹³⁸

The SDR Board agrees with Dr. Unger that it was unusual for a Center Director to be so involved in the early stages of reviewing an NDA, but the consensus on the SDR Board was that Dr. Woodcock went several steps further than mere involvement and thereby departed from typical practice among the Centers. By her own admission, Dr. Woodcock had a direct hand in reviewing the data submitted in support of the NDA, even before the review team had written their draft review memoranda, and actively encouraged the review team—including Dr. Unger—to come around to her way of thinking in their own reviews. Specifically, she wanted the review team to agree with her that the limited increase in dystrophin production established by the data in Studies 201/202 was sufficient to show a reasonable likelihood of predicting clinical benefit. At several points during the decision-making process for what is clearly a critical scientific issue for the agency, Dr. Woodcock also provided a very limited amount of time for Dr. Unger and the review team to provide feedback on additional data or her own scientific conclusions—most notably when Sarepta submitted the data from Study 301 and when she provided two separate draft versions of her decisional memorandum to the review team.

Notwithstanding the foregoing procedural shortcomings, the SDR Board finds that Dr. Unger had an adequate opportunity to present his scientific views. Not only does he admit in his appeal that he had an opportunity, but the record before the SDR Board demonstrates that he did. He and the rest of the review team met with Dr. Woodcock on multiple occasions both before and after the AC meeting. Drs. Unger and Woodcock both told the SDR Board that those meetings involved substantive and detailed discussions of the data and science and the appropriate

¹³⁷ Appeal at 26.

¹³⁸ See SDR-SMG at 3 (defining the SDR Board to include Ombudsmen from all of the Centers).

conclusions to be drawn from them. Although Dr. Unger complains that Dr. Woodcock was involved in aspects of the NDA that went far beyond the norm for a Center Director at CDER, including her role in the AC meeting, and that she reached or finalized decisions before reviewing review or decisional memoranda, he does not maintain that those procedural deficiencies compromised his ability to present his views. In fact, his own final decisional memorandum—which Dr. Woodcock apparently saw in draft form before she finalized her own—discloses that he felt empowered to push back on both Dr. Woodcock’s scientific conclusions and their basis, despite the fact that he believed his efforts would be futile. Indeed, he conceded to the SDR Board that nothing in his decisional memorandum or appeal submission would have affected Dr. Woodcock’s decision on the scientific issue in question (including the charts that he created for the first time in preparing his appeal submission under the agency-wide SDR-SMG). He further conceded as much when he agreed not to pursue further review through the *Ad Hoc* panel process under CDER’s SDR-SOPs. In short, through his own perseverance, confidence in his own scientific expertise, and perhaps dint of personality, Dr. Unger ensured that he himself had an adequate opportunity to present his scientific views despite the procedural irregularities in the decision-making process within CDER.

The SDR Board nonetheless remains concerned about Dr. Woodcock’s extensive involvement in the review of the eteplirsen NDA, including her degree of participation at the AC meeting, and the limited timeframe she provided for feedback on the data from Study 301 and her own scientific conclusions on that data. We fear that those actions could have chilled scientific debate within CDER and reduced the level of participation by the review team during the final stages of the decision-making process. By all accounts, Dr. Woodcock made clear her views that CDER should lean toward finding that eteplirsen met the standards underlying accelerated approval nearly from the outset of her involvement. By May 4, 2016, she had orally communicated her intention to grant accelerated approval for eteplirsen, even though she had not yet seen even the draft review memoranda from the review team or a decisional memorandum from Dr. Unger. Then, when she requested data from Study 301 from Sarepta, she communicated to the sponsor a compressed timeframe for CDER’s review. Although she later expanded the timeframe for review when the data proved to be disappointing, she apparently analyzed the data on her own, conducted her own additional search of the scientific literature, and took only six or seven business days to orally communicate to the review team her decision to grant approval.

To complicate matters further, Dr. Woodcock subsequently circulated a draft decisional memorandum but provided only a limited amount of time for comments, even though the draft decisional memorandum was the first time some on the review team had apparently seen key elements for the basis of her decision on “reasonably likely to predict clinical benefit.” The response from the review team is telling. As noted above, only Drs. Jenkins and Unger and another reviewer outside of DNP provided comments. Except for Dr. Jenkins, no one made any effort to make substantive comments beyond tips on how to make factual clarifications or to supplement her analysis with additional data. It appears that, because the review team knew Dr. Woodcock’s views by then, they saw no point in providing any additional substantive review or meaningful feedback on any new issues raised by Dr. Woodcock’s memorandum. Indeed, Dr. Unger and the RTM conveyed as much to the SDR Board.

There is no doubt that a Center Director should have wide latitude in leading the direction of the Center in a manner consistent with her priorities and vision. The SDR Board also believes that Center Directors have a role to play not only with respect to the resolution of scientific disputes at issue in individual applications for pre-market-authorization by FDA, as evidenced by both the SDR-SMG and CDER’s own SDR-SOPs, but also with respect to the ultimate decision on

scientific issues that are not the subject of a dispute. It is also clear from Dr. Woodcock's presentation to the SDR Board that she firmly believes in the correctness of her scientific decision in this case and that her involvement in the review of the eteplirsen NDA was always motivated by the best of intentions. However, the SDR Board finds Dr. Woodcock's extensive, early involvement in the review process troubling. Indeed, her involvement here appears to have upended the typical review and decision-making process.

Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Dr. Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages. As a consequence, the regulatory reviews did not start at the staff level with scientific reviews and then proceed through the chain of command for concurrence or non-concurrence at all appropriate levels within the management structure, as would be the typical course of decision-making for a regulatory decision grounded in science. Indeed, before the reviewers had even completed their draft scientific reviews, Dr. Woodcock had told them—on May 4, 2016—that she intended to grant accelerated approval. This sort of top-down review does not, in the SDR Board's view, "create an atmosphere in which consultation and open discussion on controversial issues are encouraged," as reflected in the SDR-SMG's requirements for resolution of scientific disagreements by the Center.¹³⁹ By the time Dr. Woodcock issued her draft decisional memorandum on what she herself acknowledged was a difficult scientific issue of incredible magnitude for the agency—i.e., whether the evidence regarding dystrophin production was reasonably likely to predict clinical benefit—the review team had decided it was pointless to challenge her ultimate conclusion or its basis.¹⁴⁰ Review teams should have the opportunity to conduct their reviews without preemption by the Center Director. As noted above, the SDR Board believes that Center Directors should have a role in shaping policy, expressing concerns, and resolving issues once they are ripe for their review, but we caution that care should be taken to avoid the appearance of interfering with the integrity of scientific reviews at the lower levels of a Center.

3. Whether the Center Director considered all relevant evidence bearing on the scientific question at issue.

The third issue for the SDR Board is whether CDER, including Dr. Woodcock, fully considered all relevant evidence in resolving the scientific dispute at issue, i.e., whether the evidence of eteplirsen's effect on dystrophin production is reasonably likely to predict clinical benefit. In this case, both Drs. Unger and Woodcock appear to agree that she *considered* all relevant evidence. As noted above, Dr. Unger does not believe that any additional data or evidence available to him could persuade Dr. Woodcock that she has reached the wrong scientific conclusion. For her part, Dr. Woodcock does not feel that she has disregarded any relevant evidence. Moreover, in her interview with the SDR Board, she demonstrated an awareness and command of all of the evidence weighing against the scientific decision she has made, including the arguments and analysis of the evidence presented in Dr. Unger's appeal.

Whether Dr. Woodcock has *addressed* all of the relevant evidence in her decisional memorandum is a more difficult question. In concluding that the minimal increase in dystrophin

¹³⁹ *Id.* at 6.

¹⁴⁰ In this regard, it is also worth noting again the language quoted above in the background section: "Each individual who contributes to the decision-making process" must "be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that . . . organizational component" and that "[o]pinions of staff should be documented and supported by data in a matter commensurate with the magnitude of the decision being made." (MAPP 4151.8 at 2-3).

production seen in the data is reasonably likely to predict clinical benefit, Dr. Woodcock has provided a very limited rationale.

At the risk of oversimplification, Dr. Woodcock found, in essence, that the studies attempting to correlate levels of dystrophin with clinical benefit, as have been reported in the scientific literature, are unreliable in this context for variety of reasons, including: (1) the subjectivity of the clinical evaluation, (2) the difficulty in correlating IHC results with Western blot results, (3) the influence of anti-dystrophin antibodies, (4) the lack of information on dystrophin quality (as opposed to quantity) in the different studies, (5) deficiencies in Western blot techniques from earlier studies, and (6) the wide range of findings with respect to the correlation of dystrophin levels with clinical benefit.¹⁴¹ She concluded, therefore, that “protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation, all other things being equal, i.e. mutation status and non-dystrophin-related factors affecting phenotype,” and that the “biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit.”¹⁴² She then attempted to bolster that conclusion with a theory regarding the effect of exon 52 deletion and her reanalysis of the intermediate clinical outcomes for a subset of subjects in Study 201/202.¹⁴³ She further explained to the SDR Board that she was exercising her “medical/scientific judgment” in reaching the scientific conclusion that she did.

It is easy for the SDR Board to understand why Dr. Unger’s appeal expressed such frustration with this explanation of Dr. Woodcock’s rationale. He states:

I believe the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her July 14, 2016 memo makes this case. I believe that the available evidence leaves open the possibility that some patients could benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit.¹⁴⁴

Of course, *considering* the relevant evidence and *addressing* the relevant evidence in a manner satisfactory to Dr. Unger or the SDR Board are two different propositions. The SDR Board finds, based on the record before us, that Dr. Woodcock has considered all relevant evidence in reaching her scientific conclusion. Based on her own medical judgment, she simply has a difference of opinion with Dr. Unger—both with respect to the scientific conclusion and the sufficiency of the underlying rationale.

4. Whether the dispute should be remanded to the Center Director.

Inasmuch as the SDR Board has concluded that Dr. Unger had an adequate opportunity to present his scientific concerns during the decision-making process at CDER and that Dr. Woodcock considered all relevant evidence in making her decision, the SDR Board does not recommend returning this matter to the Center Director for corrective action. We also believe that, for reasons discussed above, remanding this matter to the Center Director would be futile.

¹⁴¹ Woodcock Decisional Memorandum at 5-9.

¹⁴² *Id.* at 9.

¹⁴³ *Id.* at 10.

¹⁴⁴ Appeal at 20 (emphasis in original).

CONSIDERATIONS FROM THE ACTING CHIEF SCIENTIST

In my capacity as Acting Chief Scientist, I feel the responsibility to convey some comments regarding the underlying science for the decision being challenged by Dr. Unger in his appeal. I cannot begin to understand the depth of pain and suffering that patients with DMD and their families endure. As an experienced physician, I struggle to identify any other diseases associated with this degree of suffering, not only to patients but to their families. Nevertheless, my assessment is that the data presented by the sponsor to date are not adequate to support accelerated approval of eteplirsen

Studies in animals showing that eteplirsen leads to “exon 51 skipping” are an important first step in assessing whether eteplirsen might work for a subset of patients with DMD because skipping exon 51 is necessary for the production of dystrophin in these patients.¹⁴⁵ The next step is to assess whether eteplirsen actually leads to the production of dystrophin in patients with DMD and, if so, whether such an increase in dystrophin confers clinical benefit. Despite the promising animal studies demonstrating exon 51 skipping, both Drs. Woodcock and Unger, as well as the review team in CDER, agree that the amount of dystrophin produced in the clinical studies conducted at doses of up to 50mg/kg per week is very low. Animal data suggest that the doses studied in humans is too low; in animals, exon 51 skipping was detected in a nonlinear, dose-dependent manner (that is, higher doses led to significantly more exon 51 skipping). Specifically, with a 1-log increase in dose (from 5 to 40 mg/kg), there was little change in exon 51 skipping. With a second log increase in dose (from 40 to 320 mg/kg), however, there was more than a log increase in response. These dose-dependent responses are important because it is wholly conceivable that higher doses would lead to a much greater amount of dystrophin production, which could be important for clinical benefit. Because the drug appears to be safe, the review team recommended evaluation of much higher doses of eteplirsen, of at least 200mg/kg per week. Approving a drug at a dose that does not show a meaningful increase in dystrophin (when the drug could theoretically achieve one at higher doses) is concerning.

As for accelerated approval, the regulatory standard at issue requires a sponsor to show that the drug under review leads to an effect on the surrogate endpoint (in this case, the production of dystrophin) and that the effect is reasonably likely to predict clinical benefit (in this case, improving, or slowing down decline in, muscle function). The term “reasonably likely to predict” acknowledges the potential for doubt in the outcome of interest. Indeed, nobody knows the minimum level of dystrophin that is likely to confer clinical benefit in patients with DMD. The critical scientific and regulatory issue at stake in CDER’s decision here is whether such minute amounts of dystrophin are reasonably likely to predict clinical benefit at the dosage of the drug subject to approval. In this case, both Drs. Woodcock and Unger have attempted to provide a rationale, based on scientific and professional judgment, for whether or not such small levels of dystrophin are reasonably likely to predict the clinical effect of interest. By any meaningful objective standard, however, the overall evidence derived from eteplirsen’s limited clinical development program does not support that the levels of dystrophin produced by eteplirsen at the doses studied are reasonably likely to provide clinical benefit. As pointed out in Dr. Unger’s appeal, “Study 201 did not show a treatment effect on its 1^o clinical endpoint, change in 6-minute walk distance at Week 24. Study 202 failed on the same endpoint at 48 weeks. The course of these Study 201/202 patients, having received eteplirsen for some 3.5 years, was not distinguishable from external control patients.”¹⁴⁶

¹⁴⁵ Eteplirsen targets a subset of patients with DMD who are amenable to exon 51 skipping.

¹⁴⁶ Appeal at 16.

Some may argue that it would be reasonable to proceed with accelerated approval based on eteplirsen's safety profile, even where there are significant doubts about the drug's effectiveness. That argument does not take into account the risks of treatment with indwelling catheters to maintain vascular access in young patients, who would otherwise not need one and who often receive adjunct chronic corticosteroids, or, even more importantly, the detrimental impact on their quality of life.

I would be remiss if I did not note that the sponsor has exhibited serious irresponsibility by playing a role in publishing and promoting selective data during the development of this product. Not only was there a misleading published article with respect to the results of Study 201/202¹⁴⁷—which has never been retracted—but Sarepta also issued a press release relying on the misleading article and its findings. As determined by the review team, and as acknowledged by Dr. Woodcock, the article's scientific findings—with respect to the demonstrated effect of eteplirsen on both surrogate and clinical endpoints—do not withstand proper and objective analyses of the data. Sarepta's misleading communications led to unrealistic expectations and hope for DMD patients and their families. It is very disappointing that the findings did not hold up to careful review.

FDA must remain steadfast in its commitment to alleviating pain and suffering, approach the most challenging problems with absolute determination, and apply maximum flexibility to facilitate the development and availability of effective treatments. The agency's value centers on its ability to do all of the above while maintaining objectivity, even in the face of political pressure. FDA should never mislead patients by granting even accelerated approval to products that are not shown to offer the prospect of meaningful benefit to patients under the appropriate regulatory and scientific standard.

I acknowledge that there are currently no specific drugs available to treat patients with DMD and that issuance of a complete response letter would cast uncertainty on whether eteplirsen would continue to be developed, based on business and financial decisions that are external to FDA. However, approving products based on hope, on subjective clinical judgment, or on theoretical constructs that are not anchored in data leads to irreparable damage to patients. Approval at this time could deter others from pursuing the development of truly effective treatments, both for DMD and other serious, life-threatening conditions. Granting accelerated approval here on the basis of the data submitted could make matters worse for patients with no existing meaningful therapies—both by discouraging others from developing effective therapies for DMD and by encouraging other developers to seek approval for serious conditions before they have invested the time and research necessary to establish whether a product is likely to confer clinical benefit.

I remain deep in my conviction that, through science and a flexible, sound regulatory approach, good therapies will emerge to provide meaningful clinical benefit to patients with DMD and other rare serious diseases.

THE SDR BOARD'S ADDITIONAL RECOMMENDATION

Although the SDR Board acknowledges that the scope of our review, as prescribed by the SDR-SMG, is limited to procedural questions, we nonetheless feel duty-bound to make one additional recommendation. As noted above, Dr. Unger seeks from the Office of the Commissioner a substantive, scientific review of Dr. Woodcock's decision to grant accelerated approval to

¹⁴⁷ See Mendell JR, et al. *Ann Neurol* 2013;74:637-47.

eteplirsen. The SDR-SMG presumes that an initiator such as Dr. Unger has received some substantive review of the scientific dispute at issue as part of a formal appeals process in the Center. Dr. Unger has never received any such formal review of his scientific arguments or the underlying evidence. To the extent he has ever received any substantive review of his scientific disagreement with Dr. Woodcock, Dr. Woodcock herself was the one who conducted that review and resolved the conflict in her own favor. Neither the SDR-SMG nor CDER's SDR-SOPs contemplate a scientific disagreement that arises between a Center Director and another manager in that same Center—partly because no one has ever anticipated the unique circumstance of this case. Especially given the SDR Board's concerns regarding the decision-making process at CDER, we think additional review within the Office of the Commissioner is appropriate.

The SDR Board encourages you to conduct a thorough substantive review of the scientific dispute in this matter or, in the alternative, to convene a panel of relevant experts to conduct such a review and provide advice to the agency and you, as Commissioner, on whether the evidence of the effect of eteplirsen on the surrogate endpoint is reasonably likely to predict clinical benefit. If you choose the latter, in light of the public and political pressure evident during the entire review process at CDER, as detailed in this recommendation, we believe that delegating this critical evaluation to a panel of experts would help ensure that the agency makes the most appropriate decision from the perspective of protecting patients and the public health, especially for DMD patients. Knowing as we do that you value cross-Center collaboration with respect to medical product development, we recommend that you include on the panel experts from other Centers devoted to the regulation of medical products. Doing so would not only help ensure diverse expertise on the panel but also provide insights on the effects that any proposed regulatory decision on eteplirsen might have on products regulated by those other Centers. We further recommend that you consider whether to include experts from other components within the Department of Health and Human Services and whether, consistent with applicable laws and the appropriate timeframe for a decision, you should also include outside experts on the panel.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206488

GENERAL ADVICE

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exondys 51 (eteplirsen) injection, 50 mg per mL.

This letter is in response to your email of June 2, 2016, to Janet Woodcock, M.D., in which you agreed to perform Western blots on baseline and Week 48 biopsies from eteplirsen-treated patients to assess dystrophin content. We will work with you on the protocol and analysis plan, and on the dates for FDA observers to be present during the procedures.

We agree to have an FDA observer present at the Iowa site to monitor tissue sampling and blinding procedures, and to have an observer present at the Corvallis site during performance of the Western blot procedure. We also understand that Corvallis is not a GLP facility.

We understand that a new normal control will need to be established to generate the standard curve of a serially-diluted normal comparator as part of these procedures. Please confirm the healthy dystrophin genotype and phenotype of this new control and compare side-by-side with the limited previous healthy control you have available. Confirm that the validation parameters and acceptance criteria for the new healthy control are comparable to those for the previous healthy control used with the Week 180 samples (e.g., linearity of the serially diluted sample, %RSD).

You should provide each of the relevant protocols for our review that describe the methods you propose to use for testing dystrophin, including those related to tissue acquisition at the clinical site(s), processing, blinding, and shipping procedures at the University of Iowa or elsewhere, tissue quality control before analysis, validation of the new normal control, and Western blotting at the Corvallis location.

You should implement appropriate quality control measures including strict blinding procedures to ensure that the integrity of the other primary and secondary assessments is not compromised as a result of this specific dystrophin investigation.

If you are successful in showing, to FDA's satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to

grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable).

To allow for prompt approval, should your dystrophin analysis prove successful, we will work with you over the next several weeks on completing labeling negotiations to the degree possible and on necessary postmarketing requirements and commitments.

We request that you not publicly communicate the specific details of this plan until after completion in order to allow maximum procedural efficiency.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

(See appended electronic signature page)

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET WOODCOCK
06/03/2016

Guidance for Industry

Expedited Programs for Serious Conditions – Drugs and Biologics

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**May 2014
Procedural**

OMB Control No. 0910-0765
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See additional PRA statement in section X of this guidance.

Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics

Additional copies are available from:

Office of Communications

Division of Drug Information, WO51, Room 2201

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Ave., Silver Spring, MD 20993

Phone: 301-796-3400; Fax: 301-847-8714

druginfo@fda.hhs.gov

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

and/or

Office of Communication, Outreach and Development

Center for Biologics Evaluation and Research

Food and Drug Administration

10903 New Hampshire Ave., WO71, Room 3128

Silver Spring, MD 20993

Phone: 800-835-4709 or 240-402-7800

ocod@fda.hhs.gov

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**May 2014
Procedural**

Contains Nonbinding Recommendations

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Guidance for Industry¹ Expedited Programs for Serious Conditions – Drugs and Biologics

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The following four FDA programs are intended to facilitate and expedite development and review of new drugs² to address unmet medical need in the treatment of a serious or life-threatening³ condition: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation (see [section IV](#) for an overview of the programs). The purpose of this guidance for industry is to provide a single resource for information on FDA's policies and procedures for these four programs as well as threshold criteria generally applicable to concluding that a drug is a candidate for these expedited development and review programs.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The programs described in this guidance are intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks. The Agency first formally articulated its thinking on expediting the availability of promising new therapies in regulations codified at part 312, subpart E (21 CFR part 312).⁴ The subpart E regulations are intended to speed the availability of new therapies to patients with serious conditions, especially when there are no satisfactory alternative therapies, while preserving appropriate standards for safety and effectiveness. The regulations call for earlier attention to drugs that have promise in treating such conditions, including early

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² For the purposes of this guidance, all references to *drugs* or *drug products* include both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

³ Section III.A.1. explains that all references to serious conditions include life-threatening conditions.

⁴ Food and Drug Administration, Interim Rule, Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses (53 FR 41516, October 21, 1988).

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consultation with FDA for sponsors of such products and efficient trial design, potentially relying on well-controlled phase 2 studies for evidence of effectiveness. The subpart E regulations specifically recognize that patients and physicians are generally willing to accept greater risks and side effects from treatment of life-threatening and severely debilitating diseases than they would for other diseases. The four principal programs that support these principles are fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation (referred to in this guidance as the Agency's *expedited programs*).

FDA has a history of applying the philosophy underlying subpart E to drugs for rare diseases through use of the Agency's expedited programs. FDA recognizes that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of the disease. FDA will continue to apply flexibility in these situations to address particular challenges posed by each disease.

III. CONCEPTS FOR EXPEDITED PROGRAMS

The programs that are the subject of this guidance, fast track designation, breakthrough therapy designation, accelerated approval, and priority review, are summarized in [section IV](#) and described individually in detail in [sections V, VI, VII, and VIII](#). All four expedited programs represent efforts to address an unmet medical need in the treatment of a serious condition, which is discussed in the following paragraphs.

A. Serious Condition

1. Whether a Condition Is Serious

FDA intends to interpret the term *serious* as it has done in the past for the purposes of accelerated approval⁵ and expanded access to investigational drugs for treatment use.⁶ A serious disease or condition is defined in the expanded access regulations as follows:

. . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.⁷

⁵ Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992) and Food and Drug Administration, Proposed Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 13234, April 15, 1992).

⁶ Part 312, subpart I.

⁷ 21 CFR 312.300(b)(1).

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Note: For the purposes of this guidance, the terms *condition*, *disease*, and *illness* are used interchangeably. All conditions meeting the definition of life-threatening as set forth at § 312.81(a) would also be serious conditions.

2. *Whether the Drug Is Intended to Treat a Serious Condition*

As referenced in [section IV](#), the statutory and regulatory eligibility criteria for expedited programs require that a drug be intended to treat a serious condition. To satisfy this criterion, a drug must be intended to have an effect on a serious condition or a serious aspect of a condition, such as a direct effect on a serious manifestation or symptom of a condition or other intended effects, including the following:

- A diagnostic product intended to improve diagnosis or detection of a serious condition in a way that would lead to improved outcomes
- A product intended to mitigate or prevent a serious treatment-related side effect (e.g., serious infections in patients receiving immunosuppressive therapy)
- A product intended to avoid or diminish a serious adverse event associated with available therapy for a serious condition (e.g., product that is less cardiotoxic than available cancer therapy)⁸
- A product intended to prevent a serious condition or reduce the likelihood that the condition will progress to a more serious condition or a more advanced stage of disease

B. Available Therapy

For purposes of this guidance, FDA generally considers *available therapy* (and the terms *existing treatment* and *existing therapy*) as a therapy that:

- Is approved or licensed in the United States for the same indication being considered for the new drug⁹ and
- Is relevant to current U.S. standard of care (SOC) for the indication

⁸ Sponsors considering an expedited drug development designation or program for a drug intended to avoid a serious adverse event associated with available therapy or diminish its severity should be aware that they will need to provide data that directly support the effect corresponding to the level of evidence needed to meet the qualifying criteria for the relevant designation or program (e.g., phase 3 data demonstrating lower incidence or severity of the serious adverse reaction compared to available therapy for priority review). The requisite data may be very difficult to obtain in early development, particularly for purposes of breakthrough therapy designation.

⁹ There may be a substantial number of approved therapies with varying relevance to how a serious disease is currently treated in the United States, including therapies that are no longer used or are used rarely. Only in exceptional cases will a treatment that is not approved for the indicated use or is not FDA-regulated (e.g., surgery) be considered available therapy. In those cases, FDA may consider an unapproved or unlicensed therapy to constitute available therapy if the safety and effectiveness of the use is supported by compelling evidence, including extensive evidence in the published literature (e.g., certain well-established oncologic treatments).

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FDA's available therapy determination generally focuses on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive Cancer Network, American Academy of Neurology) based on clinical evidence and other reliable information that reflects current clinical practice. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic mutation), the SOC for the broader population, if there is one, generally is considered available therapy for the subset, unless there is evidence that the SOC is less effective in the subset.

Over the course of new drug development, it is foreseeable that the SOC for a given condition may evolve (e.g., because of approval of a new therapy or new information about available therapies). FDA will determine what constitutes available therapy at the time of the relevant regulatory decision for each expedited program a sponsor intends to use (e.g., generally early in development for fast track and breakthrough therapy designations, at time of biologics license application (BLA) or new drug application (NDA) submissions for priority review designation, during BLA or NDA review for accelerated approval). FDA encourages sponsors to discuss available therapy considerations with the Agency during interactions with FDA.

As appropriate, FDA may consult with special Government employees or other experts when making an available therapy determination.

When determining whether a drug granted accelerated approval or approved with a risk evaluation and mitigation strategy (REMS) that includes elements to assure safe use (ETASU) under section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1), is considered available therapy, the following principles will be applied:

- A drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by postapproval studies. (See [section III.C.3.](#))
- A drug would be considered available therapy if the drug is granted accelerated approval because of restricted distribution and the study population for the new drug under development is eligible to receive the approved drug under the restricted distribution program. Similarly, a drug would be considered available therapy if the study population for the new drug under development is eligible to receive the approved drug under the ETASU REMS.

C. Unmet Medical Need

An unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs).

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1. Where There Is No Available Therapy

If there is no available therapy for a serious condition, there is clearly an unmet medical need.

2. Where There Is Available Therapy

When available therapy exists for a condition, a new treatment generally would be considered to address an unmet medical need if the treatment:

- Has an effect on a serious outcome of the condition that is not known to be influenced by available therapy (e.g., progressive disability or disease progression when the available therapy has shown an effect on symptoms, but has not shown an effect on progressive disability or disease progression)
- Has an improved effect on a serious outcome(s) of the condition compared with available therapy (e.g., superiority of the new drug to available therapy when either used alone or in combination with available therapy (i.e., as demonstrated in an add-on study))
- Has an effect on a serious outcome of the condition in patients who are unable to tolerate or failed to respond to available therapy
- Can be used effectively with other critical agents that cannot be combined with available therapy
- Provides efficacy comparable to those of available therapy, while (1) avoiding serious toxicity that occurs with available therapy, (2) avoiding less serious toxicity that is common and causes discontinuation of treatment of a serious condition, or (3) reducing the potential for harmful drug interactions
- Provides safety and efficacy comparable to those of available therapy but has a documented benefit, such as improved compliance, that is expected to lead to an improvement in serious outcomes
- Addresses an emerging or anticipated public health need, such as a drug shortage

In some disease settings, a drug that is not shown to provide a direct efficacy or safety advantage over available therapy may nonetheless provide an advantage that would be of sufficient public health benefit to qualify as meeting an unmet medical need. For example, in a condition for which there are approved therapies that have a modest response rate or significant heterogeneity in response, a drug with a novel mechanism of action (but comparable safety and effectiveness) could have the potential to provide an advantage over available therapy in some patients. In such a case, the novel mechanism of action should have a well-understood relationship to the disease pathophysiology. In addition, there should be a reasonable basis for concluding that a significant number of patients may respond differently to the new drug compared with available therapy. Thus, mechanistic diversity, even without a documented efficacy or safety advantage, could be advantageous in disease settings in which drugs become less effective or ineffective over time.

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For example, infectious disease drugs or targeted cancer therapies with novel mechanisms of action, although appearing to have efficacy similar to available therapy across the disease population, could benefit patients who no longer respond to available therapy. Accordingly, FDA intends to consider a range of potential advantages over available therapy beyond those shown in head-to-head comparisons.

3. *Where the Only Available Therapy Was Approved Under the Accelerated Approval Program Based on a Surrogate Endpoint or an Intermediate Clinical Endpoint and Clinical Benefit Has Not Yet Been Verified*

As discussed in sections VII and III.B., FDA recognizes, as a general matter, that it is preferable to have more than one treatment approved under the accelerated approval provisions because of the possibility that clinical benefit may not be verified in postapproval confirmatory trials. FDA will therefore consider products as addressing an unmet medical need if the only approved treatments were granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by postapproval studies.

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IV. OVERVIEW OF EXPEDITED PROGRAMS

The table provides an overview of the four expedited programs. Additional details on the specific programs are found in the sections that follow. Note that a drug development program may qualify for more than one expedited program.

Comparison of FDA’s Expedited Programs for Serious Conditions

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Nature of program	Designation	Designation	Approval Pathway	Designation
Reference	<ul style="list-style-type: none"> Section 506(b) of the FD&C Act, as added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) 	<ul style="list-style-type: none"> Section 506(a) of the FD&C Act, as added by section 902 of FDASIA 	<ul style="list-style-type: none"> 21 CFR part 314, subpart H 21 CFR part 601, subpart E Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA 	<ul style="list-style-type: none"> Prescription Drug User Fee Act of 1992
Qualifying criteria	<ul style="list-style-type: none"> A drug that is intended to treat a <u>serious condition</u> AND nonclinical or clinical data <u>demonstrate the potential to address unmet medical need</u> OR A drug that has been designated as a qualified infectious disease product^a 	<ul style="list-style-type: none"> A drug that is intended to treat a <u>serious condition</u> AND <u>preliminary clinical evidence</u> indicates that the drug may demonstrate <u>substantial improvement on a clinically significant endpoint(s)</u> over available therapies 	<ul style="list-style-type: none"> A drug that treats a <u>serious condition</u> AND generally provides a <u>meaningful advantage over available therapies</u> AND demonstrates an effect on a <u>surrogate endpoint</u> that is <u>reasonably likely to predict clinical benefit</u> or on a <u>clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM)</u> that is <u>reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)</u> 	<ul style="list-style-type: none"> An application (original or efficacy supplement) for a drug that treats a <u>serious condition</u> AND, if approved, would provide a <u>significant improvement in safety or effectiveness</u> OR Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A^b OR An application for a drug that has been designated as a qualified infectious disease product^c OR Any application or supplement for a drug submitted with a priority review voucher^d

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Comparison of FDA's Expedited Programs for Serious Conditions

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Nature of program	Designation	Designation	Approval Pathway	Designation
When to submit request	<ul style="list-style-type: none"> • <u>With IND or after</u> • <u>Ideally, no later than the pre-BLA or pre-NDA meeting</u> 	<ul style="list-style-type: none"> • <u>With IND or after</u> • <u>Ideally, no later than the end-of-phase 2 meeting</u> 	<ul style="list-style-type: none"> • The sponsor should ordinarily discuss the possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned endpoint as a basis for approval and discussing the confirmatory trials, which should usually be already underway at the time of approval 	<ul style="list-style-type: none"> • <u>With original BLA, NDA, or efficacy supplement</u>
Timelines for FDA response	<ul style="list-style-type: none"> • <u>Within 60 calendar days of receipt of the request</u> 	<ul style="list-style-type: none"> • <u>Within 60 calendar days of receipt of the request</u> 	<ul style="list-style-type: none"> • Not specified 	<ul style="list-style-type: none"> • <u>Within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement</u>
Features	<ul style="list-style-type: none"> • <u>Actions to expedite development and review</u> • <u>Rolling review</u> 	<ul style="list-style-type: none"> • <u>Intensive guidance on efficient drug development</u> • <u>Organizational commitment</u> • <u>Rolling review</u> • <u>Other actions to expedite review</u> 	<ul style="list-style-type: none"> • Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit 	<ul style="list-style-type: none"> • <u>Shorter clock for review of marketing application (6 months compared with the 10-month standard review)^e</u>
Additional considerations	<ul style="list-style-type: none"> • <u>Designation may be rescinded if it no longer meets the qualifying criteria for fast track^f</u> 	<ul style="list-style-type: none"> • <u>Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy^g</u> 	<ul style="list-style-type: none"> • <u>Promotional materials</u> • <u>Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit</u> • <u>Subject to expedited withdrawal</u> 	<ul style="list-style-type: none"> • Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

^a Title VIII of FDASIA, *Generating Antibiotic Incentives Now (GAIN)*, provides incentives for the development of antibacterial and antifungal drugs for human use intended to treat serious and life threatening infections. Under GAIN, a drug may be designated as a *qualified infectious disease product (QIDP)* if it meets the criteria outlined in the statute. A drug that receives QIDP designation is eligible under the statute for fast track designation and priority review. However, QIDP designation is beyond the scope of this guidance.

^b Any supplement to an application under section 505 of the FD&C Act that proposes a labeling change pursuant to a report on a pediatric study under this section shall be considered a priority review supplement per section 505A of the FD&C Act as amended by section 5(b) of the Best Pharmaceuticals for Children Act.

^c See footnote a above.

^d Any application or supplement that is submitted with a priority review voucher will be assigned a priority review. Priority review vouchers will be granted to applicants of applications for drugs for the treatment or prevention of certain tropical diseases, as defined in section 524(a)(3) and (a)(4) of the FD&C Act and for treatment of rare pediatric diseases as defined in section 529(a)(3) of the FD&C Act.

^e As part of its commitments in PDUFA V, FDA has established a review model, *the Program*. The Program applies to all new molecular entity NDAs and original BLAs, including applications that are resubmitted following a Refuse-to-File action, received from October 1, 2012, through September 30, 2017. For applications filed by FDA under the Program, the PDUFA review clock will begin at the conclusion of the 60 calendar day filing review period that begins on the date of FDA receipt of the original submission.

^f A sponsor may also withdraw fast track designation if the designation is no longer supported by emerging data or the drug development program is no longer being pursued (see section A.5. of Appendix 1).

^g A sponsor may also withdraw breakthrough therapy designation if the designation is no longer supported by emerging data or the drug development program is no longer being pursued (see section B.5. of Appendix 1).

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V. FAST TRACK DESIGNATION

Section 506(b) of the FD&C Act provides for the designation of a drug as a fast track product “. . . if it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition.” This provision is intended to facilitate development and expedite review of drugs to treat serious and life-threatening conditions so that an approved product can reach the market expeditiously. This section describes the qualifying criteria and the features of fast track designation. [Appendix I](#) describes the process for fast track designation.

A. Qualifying Criteria for Fast Track Designation

Fast track designation applies to the drug (either alone or in combination with other drugs) and the specific use for which it is being studied. The term *drug* refers to the combination of two or more drugs if the combination is the subject of the fast track designation or request. Where appropriate, FDA may grant designation to the development of a new use of an approved drug.

1. Serious Condition

See [section III.A](#).

2. Demonstrating the Potential to Address Unmet Medical Need

The type of information needed to demonstrate the potential of a drug to address an unmet medical need will depend on the stage of drug development at which fast track designation is requested. Early in development, evidence of activity in a nonclinical model, a mechanistic rationale, or pharmacologic data could be used to demonstrate such potential. Later in development, available clinical data should demonstrate the potential to address an unmet medical need. See [section III.C](#).

B. Features of Fast Track Designation

1. Actions to Expedite Development and Review

There are opportunities for frequent interactions with the review team for a fast track product. These include meetings with FDA, including pre-IND meetings, end-of-phase 1 meetings, and end-of-phase 2 meetings to discuss study design, extent of safety data required to support approval, dose-response concerns, and use of biomarkers. Other meetings may be scheduled as appropriate (e.g., to discuss accelerated approval, the structure and content of an NDA, and other critical issues).

In addition, such a product could be eligible for priority review if supported by clinical data at the time of BLA, NDA, or efficacy supplement submission (see [section VIII](#)).

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2. *Submission of Portions of an Application (Rolling Review)*

If FDA determines, after preliminary evaluation of clinical data submitted by a sponsor, that a fast track product may be effective, the Agency may consider reviewing portions of a marketing application before the sponsor submits the complete application (see [Appendix 2](#)).¹⁰

VI. BREAKTHROUGH THERAPY DESIGNATION

Section 506(a) of the FD&C Act provides for designation of a drug as a breakthrough therapy “. . . if the drug is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.” It is important to recognize that the standard for breakthrough therapy designation is not the same as the standard for drug approval. The clinical evidence needed to support breakthrough designation is preliminary. In contrast, as is the case for all drugs, FDA will review the full data submitted to support approval of drugs designated as breakthrough therapies to determine whether the drugs are safe and effective for their intended use before they are approved for marketing. This section describes the qualifying criteria and the features of breakthrough therapy designation. [Appendix I](#) describes the process for breakthrough therapy designation.

Not all products designated as breakthrough therapies ultimately will be shown to have the substantial improvement over available therapies suggested by the preliminary clinical evidence at the time of designation. If the designation is no longer supported by subsequent data, FDA may rescind the designation.¹¹ Because FDA commits significant resources to work particularly closely with sponsors of breakthrough therapy products, the Agency needs to focus its resources on breakthrough therapy drug development programs that continue to meet the program’s qualifying criteria (see [section B.5. in Appendix I](#)).

A. Qualifying Criteria for Breakthrough Therapy Designation

Breakthrough therapy designation applies to the drug (either alone or in combination with other drugs) and the specific use for which it is being studied. The term *drug* refers to the combination of two or more drugs if the combination is the subject of the breakthrough therapy designation or request. Where appropriate, FDA may grant designation to the development of a new use of an approved drug.

I. Serious Condition

See [section III.A](#).

¹⁰ Section 506(d)(1) of the FD&C Act.

¹¹ After the sponsor completes the development program, the product may still have sufficient evidence to support marketing approval.

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2. *Existing (or Available) Therapies*

See section III.B.

3. *Preliminary Clinical Evidence*

Unlike the information that could support fast track designation, which could include theoretical rationale, mechanistic rationale (based on nonclinical data), or evidence of nonclinical activity, breakthrough therapy designation requires preliminary clinical evidence of a treatment effect that may represent substantial improvement over available therapies for the treatment of a serious condition. For purposes of breakthrough therapy designation, *preliminary clinical evidence* means evidence that is sufficient to indicate that the drug may demonstrate substantial improvement in effectiveness or safety over available therapies, but in most cases is not sufficient to establish safety and effectiveness for purposes of approval. FDA expects that such evidence generally would be derived from phase 1 or 2 trials. Nonclinical information could support the clinical evidence of drug activity. In all cases, preliminary clinical evidence demonstrating that the drug may represent a substantial improvement over available therapy should involve a sufficient number of patients to be considered credible. However, FDA recognizes that the data cannot be expected to be definitive at the time of designation.

Ideally, preliminary clinical evidence indicating a substantial improvement over available therapies would be derived from a study that compares the investigational drug to an available therapy (or placebo, if there is no available therapy) in clinical testing or from a study that compares the new treatment plus SOC to the SOC alone. FDA encourages sponsors to obtain some preliminary comparative data of this type early in development. Other types of clinical data that also could be persuasive include single-arm studies comparing the new treatment with well-documented historical experience. Generally, FDA expects that such historically controlled data would be persuasive only if there is a large difference between the new treatment and historical experience. For example, where lung function decline is a major manifestation of a disease, single-arm study data showing that a new drug significantly increases lung function could be persuasive if there is no available therapy that increases lung function. Data demonstrating that a cancer drug substantially increases overall response rate compared with historical controls (e.g., historical response rate with available therapy), with consideration of duration of the response, also could be persuasive. Sponsors contemplating the use of historical controls should consult FDA's ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* for more-detailed discussions.¹²

4. *May Demonstrate Substantial Improvement on Clinically Significant Endpoint(s)*

¹² We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> and the Biologics guidance Web page at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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To support a breakthrough therapy designation, the preliminary clinical evidence must show that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints.

Substantial Improvement: The determination of whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the drug's effect on a clinically significant endpoint (which could include duration of the effect) and the importance of the observed effect to the treatment of the serious condition or serious aspect of the condition. In general, the preliminary clinical evidence should show a clear advantage over available therapy.

Approaches to demonstrating substantial improvement include the following:

- Direct comparison of the new drug to available therapy shows a much greater or more important response (e.g., complete responses where the control treatment generally results only in partial responses). Such a trial could be conducted in treatment-naïve patients or in those whose disease failed to respond to available therapies, either as a comparison with the failed therapy (if ethically acceptable) or as a no-treatment controlled study.
- If there is no available therapy, the new drug shows a substantial and clinically meaningful effect on an important outcome when compared with a placebo or a well-documented historical control.
- The new drug added to available therapy results in a much greater or more important response compared to available therapy in a controlled study or to a well-documented historical control. This trial also could be conducted in treatment-naïve patients or in those whose disease failed to respond to available therapies.
- The new drug has a substantial and clinically meaningful effect on the underlying cause of the disease, in contrast to available therapies that treat only symptoms of the disease, and preliminary clinical evidence indicates that the drug is likely to have a disease-modifying effect in the long term (e.g., a sustained clinical benefit compared with a temporary clinical benefit provided by available therapies).
- The new drug reverses or inhibits disease progression, in contrast to available therapies that only provide symptomatic improvement.
- The new drug has an important safety advantage that relates to serious adverse reactions (e.g., those that may result in treatment interruption) compared with available therapies and has similar efficacy.

Clinically Significant Endpoint: For purposes of breakthrough therapy designation, FDA considers *clinically significant endpoint* generally to refer to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. It can also refer to findings that suggest an effect on IMM or serious symptoms, including:

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- An effect on an established surrogate endpoint that typically would be used to support traditional approval
- An effect on a surrogate endpoint or intermediate clinical endpoint (see [section VII.B.2.](#)) considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- A significantly improved safety profile compared with available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy

In a breakthrough therapy designation request, a sponsor should provide justification for why the endpoint or other findings should be considered clinically significant.

In rare cases, a pharmacodynamic (PD) biomarker may be considered a clinically significant endpoint if it strongly suggests the potential for a clinically meaningful effect on the underlying disease. In such cases, a sponsor should provide evidence supporting the use of the PD biomarker. Such evidence should include, for example, (1) the extent of understanding of the disease pathophysiology, (2) whether the biomarker is on a causal pathway of the disease process, and (3) the time course of the drug's effect on the biomarker (e.g., the biomarker can be measured earlier than a surrogate endpoint used for accelerated approval). In addition, strong evidence of the drug's effect on the PD biomarker generally is expected. FDA is more likely to rely on a PD biomarker for breakthrough therapy designation in a disease setting in which there is no available therapy, if the evidence supports such use.

B. Features of Breakthrough Therapy Designation

1. Intensive Guidance on an Efficient Drug Development Program, Beginning as Early as Phase I

As discussed previously, breakthrough therapy designation will usually mean that the effect of the drug will be large compared with available therapies. In such cases, the development program for the breakthrough therapy could be considerably shorter than for other drugs intended to treat the disease being studied. However, FDA notes that a compressed drug development program still must generate adequate data to demonstrate that the drug is safe and effective to meet the statutory standard for approval.¹³ Omitting components of the drug development program that are necessary for such a determination can significantly delay, or even preclude, marketing approval.

Sponsors can design efficient clinical trials in a number of ways. FDA will seek to ensure that a sponsor of a product designated as a breakthrough therapy receives timely advice and interactive communications to help the sponsor design and conduct a drug development program as efficiently as possible.¹⁴ During these interactions, the Agency may suggest, or a sponsor may

¹³ Section 505(d) of the FD&C Act and section 351(a) of the Public Health Service Act.

¹⁴ As noted in section IX., it is important that sponsors respond promptly to FDA inquiries, which may include, for example, requests for information on various aspects of the drug development program.

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propose, alternative clinical trial designs (e.g., adaptive designs, an enrichment strategy, crossover or N-of-1 design, use of historical controls) or use of an interim analysis by a data monitoring committee.¹⁵ These trial designs may result in smaller trials or more efficient trials that require less time to complete and may help minimize the number of patients exposed to a potentially less efficacious treatment (i.e., the control group treated with available therapy). Such approaches may be especially useful in studies in rare diseases. For example, single-arm trials may be an important option in rare diseases with well-understood pathophysiology and a well-defined disease course.

FDA anticipates that the review team and the sponsor will meet and interact throughout drug development to address these and other important issues at different phases of development. In addition, a sponsor should be prepared for a more rapid pace for other aspects of the drug development (e.g., manufacturing (see [section IX.A.](#)), development of a necessary companion diagnostic (see [section IX.D.](#))).

2. Organizational Commitment Involving Senior Managers

FDA intends to expedite the development and review of a breakthrough therapy by intensively involving senior managers and experienced review and regulatory health project management staff in a proactive, collaborative, cross-disciplinary review. Where appropriate, FDA also intends to assign a cross-disciplinary project lead for the review team to facilitate an efficient review of the drug development program. The cross-disciplinary project lead will serve as a scientific liaison between members of the review team (e.g., medical; clinical pharmacology; pharmacology-toxicology; chemistry, manufacturing, and controls (CMC); compliance; biostatistics), facilitating coordinated internal interactions and communications with a sponsor through the review division's regulatory health project manager.

3. Submission of Portions of an Application (Rolling Review)

FDA has determined that it is appropriate for a drug designated as a breakthrough therapy to be able to obtain rolling review. Therefore, if FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a breakthrough therapy product may be effective, the Agency may consider reviewing portions of a marketing application before the sponsor submits the complete application (see [Appendix 2](#)).

4. Other Actions to Expedite Review

In addition, such a product could be eligible for priority review if supported by clinical data at the time of BLA, NDA, or efficacy supplement submission.

¹⁵ For more discussion of alternative clinical trial designs, see the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* and the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. When final, these guidances will represent FDA's current thinking on these topics. See also the ICH E10 and the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

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VII. ACCELERATED APPROVAL

The accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to:

. . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

For drugs granted accelerated approval, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on IMM or other clinical benefit (see sections VII.D.2. and VII.D.3.)¹⁶

This section describes the qualifying criteria, relevant terms, and the conditions of accelerated approval. The provisions of FDASIA facilitate somewhat broader use of accelerated approval to expedite patients' access to important treatments for serious conditions. FDA believes the new provisions provide additional flexibility concerning the implications of available therapy on eligibility for accelerated approval (see section VII.A.2.). They also provide clarification concerning the use of clinical endpoints (herein referred to as intermediate clinical endpoints) as a basis for accelerated approval (see section VII.B.2.). In addition, the new provisions make clear that FDA has the authority to consider pharmacologic or other evidence developed using biomarkers or other scientific methods or tools, in conjunction with other data, in determining whether an endpoint is reasonably likely to predict clinical benefit (see section VII.C.)¹⁷ By indicating that FDA should take into account, ". . . the severity, rarity, or prevalence of the condition . . ." in considering whether to grant accelerated approval, FDASIA reinforces the Agency's longstanding commitment to regulatory flexibility regarding the evidence required to support product approval for the treatment of serious or life-threatening diseases with limited therapeutic options.

The accelerated approval pathway has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug. For example, accelerated approval has been used extensively in the approval of drugs to treat a variety of cancers and human immunodeficiency virus (HIV) disease where an effect on tumor growth or viral load can be assessed rapidly, but demonstrating an effect on survival or morbidity generally requires lengthy and sometimes large trials because of the duration of the typical disease course. Accelerated approval is also potentially useful in acute disease settings

¹⁶ Section 506(c)(2)(A) of the FD&C Act.

¹⁷ Section 506(c)(1)(B) of the FD&C Act. 21 CFR 314.510 and 601.41 provide that the Agency may consider ". . . epidemiologic, therapeutic, pathophysiological, or other evidence . . ." in determining whether an endpoint is reasonably likely to predict clinical benefit. FDASIA provides that FDA may consider ". . . epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

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where the intended clinical benefit can be demonstrated only in a very large study because the clinical event that would need to be evaluated to demonstrate clinical benefit occurs rarely. For example, accelerated approval could be used for an acute condition where an effect on a surrogate endpoint could be shown in a small number of patients, but a much larger study would be needed to show the effect on a clinical outcome, such as survival.

FDA encourages sponsors to communicate with the Agency early in development concerning the potential eligibility of a drug for accelerated approval, proposed surrogate endpoints or intermediate clinical endpoints, clinical trial designs, and planning and conduct of confirmatory trials. A sponsor seeking accelerated approval may also need to prepare for a more rapid pace for other aspects of the drug development (e.g., manufacturing (see [section IX.A.](#)), development of a necessary companion diagnostic (see [section IX.D.](#))).

A. Qualifying Criteria for Accelerated Approval

At the time a product is granted accelerated approval, FDA has determined that an effect on the endpoint used to support approval—a surrogate endpoint or an intermediate clinical endpoint—is reasonably likely to predict clinical benefit. The principal risk of this approach is the possibility that patients will be exposed to a drug that ultimately will not be shown to provide an actual clinical benefit. In addition, there generally will be fewer, smaller, or shorter clinical trials than is typical for a drug receiving traditional approval, which may generally mean there is less information about the occurrence of rare or delayed adverse events. Uncertainty about whether clinical benefit will be verified and the possibility of undiscovered risks are the primary reasons that accelerated approval is reserved for drugs intended to treat a serious condition and that appear to provide a meaningful advantage over available therapy.

1. Serious Condition

See [section III.A.](#)

2. Meaningful Advantage Over Available Therapy

The accelerated approval regulations state that accelerated approval is available only for drugs that provide a meaningful therapeutic benefit over existing treatments.¹⁸ The accelerated approval provisions of section 901 of FDASIA (amending section 506 of the FD&C Act) require FDA to “. . .tak[e] into account . . . the availability or lack of alternative treatments.”

Amended section 506(c) clarifies the Agency’s flexibility in administering the accelerated approval program. For example, an alternative therapy with efficacy comparable to available therapy, but with a different mechanism of action, could be of added clinical value in a disease setting in which a significant number of patients may respond differently to the new therapy. The discussion of unmet medical need in [section III.C.2.](#) provides examples of situations in which a drug could be shown to provide a meaningful advantage over available therapy, including some in which there may not be a demonstrated direct efficacy or safety advantage.

¹⁸ 21 CFR 314.500 and 601.40.

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Section III.B. describes what constitutes available therapy when determining whether a drug provides a meaningful advantage.

3. Demonstrates an Effect on an Endpoint That Is Reasonably Likely to Predict Clinical Benefit

These endpoints are discussed in section VII.B. The basis for determining whether an endpoint is reasonably likely to predict clinical benefit is discussed in section VII.C.

B. Accelerated Approval Endpoints

The two types of endpoints that can be used as a basis for accelerated approval are: (1) a surrogate endpoint that is considered reasonably likely to predict clinical benefit and (2) a clinical endpoint that can be measured earlier than IMM that is reasonably likely to predict an effect on IMM or other clinical benefit (also see section VII.D.2.). For purposes of this guidance, these categories of endpoints are referred to as surrogate endpoints and intermediate clinical endpoints, respectively.

A clinical endpoint is a characteristic or variable that directly measures a therapeutic effect of a drug—an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives.

A clinical benefit is a positive therapeutic effect that is clinically meaningful in the context of a given disease. The clinical benefit must be weighed against a treatment's risks to determine whether there is an overall benefit for patients (i.e., a positive benefit-risk profile).

1. Surrogate Endpoints

For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Depending on the strength of the evidence supporting the ability of a marker to predict clinical benefit, the marker may be a surrogate endpoint that is known to predict clinical benefit (a validated surrogate endpoint that could be used for traditional approval), a surrogate endpoint that is reasonably likely to predict a drug's intended clinical benefit (and that could therefore be used as a basis for accelerated approval), or a marker for which there is insufficient evidence to support reliance on the marker as either kind of surrogate endpoint (and that therefore cannot be used to support traditional or accelerated approval of a marketing application).

Examples of surrogate endpoints that FDA has used to support accelerated approval include the following:

- Prolonged suppression of HIV viral load in plasma has been shown to reduce the morbidity and mortality associated with HIV disease and has been the basis for traditional approval. Shorter-term suppression of viral load has been used in the past as a surrogate to support accelerated approval because it was considered reasonably likely to

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predict an effect on morbidity or mortality. Data now demonstrate that short-term suppression of viral load may support full approval, in some circumstances.¹⁹

- Clearance of bacteria from the blood stream as evidenced by a laboratory measurement of bacteria in the blood has been considered reasonably likely to predict the clinical resolution of infection.
- Outcomes of 6-month follow-up treatment (i.e., sputum culture status and infection relapse rate) have been considered reasonably likely to predict the resolution of pulmonary tuberculosis.
- Decrease in iron stores for patients with iron overload caused by thalassemia has been considered reasonably likely to predict a decrease in transfusion-related adverse events caused by iron overload in the body.
- Radiographic evidence of tumor shrinkage (response rate) in certain cancer types has been considered reasonably likely to predict an improvement in overall survival.

2. Intermediate Clinical Endpoints

For purposes of accelerated approval, an intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on IMM and is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit. An important question is whether the demonstrated therapeutic effect alone would be a basis for traditional approval. Approvals for products for serious conditions based on clinical endpoints other than IMM will usually be considered under traditional approval procedures. Approvals based on such clinical endpoints will be considered under the accelerated approval pathway only when it is essential to determine effects on IMM or other clinical benefit in order to confirm the predicted clinical benefit that led to approval. Although FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, FDA believes intermediate clinical endpoints generally could be used to support accelerated approval in situations such as:

- A study demonstrates a relatively short-term clinical benefit in a chronic disease setting in which assessing durability of the clinical benefit is essential for traditional approval, but the short-term benefit is considered reasonably likely to predict long-term benefit.
- A clinical endpoint demonstrates a clinical benefit that is reasonably likely to predict an effect on IMM in a disease setting in which it is essential to confirm the effect on IMM (e.g., because available therapy has established effects on IMM).

Examples of cases in which FDA has used an intermediate clinical endpoint to support accelerated approval include the following:

¹⁹ See the draft guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment*. When final, this guidance will represent FDA's current thinking on this topic.

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- A treatment for multiple sclerosis was approved based on a large therapeutic effect on relapse rate through approximately 13 months of treatment, but where there was uncertainty about the durability of the observed effect. Under accelerated approval, the sponsor was required to continue the existing trials into the postmarketing period to confirm durability of the observed effect at 2 years.
- A treatment for preterm labor was approved based on a demonstration of delay in delivery. Under accelerated approval, the sponsor was required to conduct postmarketing studies to demonstrate improved long-term postnatal outcomes.

FDA will not grant accelerated approval to products that meet standards for traditional approval. Sponsors considering a development program for accelerated approval based on an intermediate clinical endpoint should discuss their development program with the appropriate review division early in drug development.

C. Evidentiary Criteria for Accelerated Approval

Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.²⁰ For effectiveness, the standard is substantial evidence based on adequate and well-controlled clinical investigations.²¹ For safety, the standard is having sufficient information to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling.²² Under accelerated approval, FDA can rely on a particular kind of evidence, such as a drug's effect on a surrogate endpoint, as a basis for approval. FDA carefully evaluates such evidence to ensure that any remaining doubts about the relationship of the effect on the surrogate to clinical benefit are resolved by additional postapproval studies or trials.²³ An application for accelerated approval should also include evidence that a proposed surrogate endpoint or an intermediate clinical endpoint is reasonably likely to predict the intended clinical benefit of a drug.

Determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect and the empirical evidence to support that relationship. The empirical evidence may include "... epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."²⁴ Evidence of pharmacologic activity alone is not sufficient, however.²⁵ Clinical data should be provided to support a conclusion that a relationship of an effect on the surrogate endpoint or intermediate clinical endpoint to an effect on the clinical outcome is reasonably likely.

²⁰ Section 505(d) of the FD&C Act.

²¹ Section 505(d)(5) of the FD&C Act.

²² Section 505(d)(1) of the FD&C Act.

²³ 57 FR 58942 at 58948.

²⁴ Section 506(c)(1)(B) of the FD&C Act.

²⁵ 57 FR 58942.

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In making the judgment as to whether a drug's effect on a given endpoint is reasonably likely to predict clinical benefit, FDA considers all relevant evidence and may consult external experts, as needed. This guidance provides an overview of some of the important factors to consider in identifying and assessing the predictive potential of surrogate endpoints or intermediate clinical endpoints. This guidance does not, however, address the specific clinical evidence needed to support a conclusion that a particular surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict clinical benefit or IMM because such evidence is case-specific and is not readily generalizable.

1. Understanding of the Disease Process

Surrogate endpoints are often thought to be a measure of the following, for example:

- The underlying cause of the disease (e.g., elevated uric acid and gout, elevated blood pressure and hypertensive cardiovascular disease, low thyroxine levels and hypothyroidism, high ammonia levels and urea cycle disorders)
- An effect that predicts the ultimate outcome (e.g., tumor shrinkage could be expected to delay symptomatic progression and improve survival, diuresis could be expected to improve symptoms of heart failure, effects on serum creatinine or glomerular filtration rate (if not transient or reversible) are accepted surrogates for predicting effects on chronic renal disease and delaying the occurrence of end-stage renal disease)
- The state of the pathophysiologic pathway leading to the clinical outcome (e.g., low levels of the biomarker that increase with replacement of a missing enzyme or clotting factor)

In such cases, the extent to which the pathophysiology of a disease is understood is an important factor in determining whether an endpoint is reasonably likely to predict clinical benefit. If the disease process is complex, has multiple pathophysiologic or causal pathways, and is poorly understood, it may be difficult to determine whether an effect on a surrogate endpoint represents a meaningful effect on the causal pathway. For example, for some reasonably well-understood enzyme deficiencies, replacement of the deficient enzyme reliably predicts clinical benefit. In contrast, other enzyme deficiencies may involve a defect for which the pathophysiologic or causal pathways are not well understood and where enzyme replacement as measured by blood levels, but not tissue levels, will not reasonably predict the disease course or treatment results.

Some effects on well-established, disease-related biomarkers²⁶ may have little or no ability to predict clinical benefit or their ability to predict benefit may vary depending on the disease or the intervention. For example, in a patient with a fever caused by an infectious disease, a fall in a

²⁶ FDA's CDER has established the Biomarker Qualification Program to support work with external scientists and clinicians in developing biomarkers. The Biomarker Qualification Program offers a formal process to guide submitters as they develop biomarkers and rigorously evaluate them for use in the regulatory process. Details on the program are available at <http://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm284076.htm>.

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patient's body temperature in response to a non-steroidal anti-inflammatory drug does not predict the drug's effect on the disease. However, a fall in a patient's body temperature in response to an antibiotic may be an indication of an effect on the disease. Similarly, in prostate cancer, increased levels of prostate-specific antigen (PSA) may be the result of advancing tumor burden. Therefore, PSA may be correlated with the progression of prostate cancer and the risks of mortality. However, the relationship between increasing PSA and disease progression and morbidity is not uniform. Thus the ability of a drug to lower PSA levels cannot necessarily be relied upon to predict the drug's clinical benefit.

2. Understanding of the Relationship Between the Drug's Effect and the Disease Process

The extent to which a drug's effect on the surrogate endpoint is known to predict an effect on the disease either because the effect is on the causal pathway or correlates with clinical outcomes is critical. Sometimes this relationship can be assessed epidemiologically but it is most persuasively established by knowing that a drug that affects the surrogate endpoint also affects a clinical outcome. Thus, lowering blood pressure has been shown repeatedly, with a wide variety of drugs, to reduce the incidence of stroke and cardiovascular disease in people with hypertension. Similarly, killing infecting bacteria or viruses leads to curing infectious disease and shrinking a tumor for a sustained period can lead to improved survival in patients with some cancers. These surrogate endpoint responses are thus understood to have positive effects on the disease process.

Examples of factors to consider in identifying and assessing a surrogate endpoint thus include the following:

- Whether there is reliable and consistent epidemiologic evidence supporting the relationship between the endpoint and the intended clinical benefit.²⁷
- How precisely the epidemiologic relationship between the endpoint and clinical outcome is defined. For example, the extent to which an abnormal endpoint corresponds to a worse clinical outcome, as is the case for blood pressure and low-density lipoprotein (LDL) cholesterol. (The stronger the correlation between the abnormality and clinical outcome, the stronger the basis for concluding that an effect on the endpoint would have a reasonably well-defined effect on the clinical outcome.)
- Whether the effect on the surrogate endpoint has been shown to predict a clinical benefit with another drug or drugs. This factor would generally be more persuasive if the drug is in the same or a closely related pharmacological class.

Particularly in rare diseases, there may be limited information in the literature, lack of in-depth epidemiological or historical data, and little or no experience with other drugs to inform the interpretation of surrogate endpoints or intermediate clinical endpoints. FDA may consult with

²⁷ Note, however, that such a relationship does not always predict a favorable effect, as illustrated by failure of drugs that effectively lower premature ventricular beat rates or raise high-density lipoprotein (HDL) cholesterol to have the expected cardiovascular benefits.

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external experts on surrogate endpoints and intermediate clinical endpoints where there is a lack of historical data for a given disease.²⁸

D. Conditions of Accelerated Approval

1. Promotional Materials

Unless otherwise informed by the Agency, an applicant must submit to the Agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval.²⁹ After 120 days following marketing approval, unless otherwise informed by the Agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.³⁰

2. Confirmatory Trials

For drugs granted accelerated approval, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on IMM or other clinical benefit. These trials must be completed with due diligence.³¹

FDA has interpreted the due diligence requirement to mean that the postmarketing trial(s) intended to verify the clinical benefit must be conducted promptly to facilitate determination, as soon as possible, of whether clinical benefit has been verified. The protocol for a postmarketing trial should be developed as early as possible, and timelines for the trial should be specified; for example, timelines for enrollment and trial completion should be stipulated. There should be agreement between FDA and the sponsor on the design and conduct of the confirmatory trial(s).

If it is clear during development that a product is intended to be approved under accelerated approval on the basis of a surrogate endpoint or an intermediate clinical endpoint, confirmatory trial(s) should be underway at the time the marketing application is submitted. If it is not clear until shortly before or after submission of a marketing application that a surrogate endpoint or an intermediate clinical endpoint will be the proposed basis for accelerated approval, there should be agreement on the design and conduct of such trial(s) before approval.

Generally, the confirmatory trial would evaluate a clinical endpoint that directly measures clinical benefit. For example, the confirmatory trial population would ordinarily be the same disease population that was studied to support accelerated approval. In some cases, however, the commercial availability of a drug following accelerated approval may make it difficult to enroll patients in the same disease population. In these cases, a confirmatory trial may be conducted in

²⁸ See, for example, section 569(a)(2), (b), and (c) of the FD&C Act, *Consultation With External Experts on Rare Diseases, Targeted Therapies and Genetic Targeting of Treatments*, which describes general consideration for consultation with external experts, topics for consultation, and classification as special Government employees.

²⁹ 21 CFR 314.550 and 601.45.

³⁰ 21 CFR 314.550 and 601.45.

³¹ Section 506(c)(3)(A) of the FD&C Act and §§ 314.510 and 601.41. Where confirmatory trials verify clinical benefit, FDA generally will terminate the requirement (21 CFR 312.560 and 601.46).

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a different but related population that is capable of verifying the predicted clinical benefit. This is often the case in oncology, where after accelerated approval of a drug for late-stage disease is granted, the confirmatory trial is conducted in an earlier stage of the same cancer.

There are also cases in which additional evaluation (longer duration) of the same surrogate endpoint that was used to support accelerated approval (rather than a clinical endpoint) in the same population could be persuasive evidence of clinical benefit. For example, in the case of HIV treatment, an effect on viral load of relatively short duration (24 weeks) was considered reasonably likely to predict clinical benefit supporting accelerated approval. An effect of longer (1 year) viral load suppression was more convincingly related to durable clinical benefit in the setting of lifelong therapy and thus was used to verify clinical benefit for traditional approval.³²

When it is possible to use a later effect in a trial to verify the effect seen earlier in the same trial that supported accelerated approval, the same clinical trial(s) can be used to support accelerated approval and verify and describe the clinical benefit. In this case, the protocol and the statistical analysis plan should clearly account for an analysis of the surrogate endpoint data to provide support for accelerated approval, with continuation of the randomized trial(s) to obtain data on the clinical endpoint that will be the basis for verifying the clinical benefit. When the same trial is used to support accelerated approval and verify clinical benefit, the data to verify the clinical benefit may be, in some cases, nearly complete by the time of accelerated approval.

3. Withdrawal of Accelerated Approval

FDA may withdraw approval of a drug or indication approved under the accelerated approval pathway if,³³ for example:

- A trial required to verify the predicted clinical benefit of the product fails to verify such benefit.
- Other evidence demonstrates that the product is not shown to be safe or effective under the conditions of use.
- The applicant fails to conduct any required postapproval trial of the drug with due diligence.
- The applicant disseminates false or misleading promotional materials relating to the product.

Approval of a drug may be withdrawn if trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug (e.g., show a significantly

³² Although an effect on viral load changes of short duration had been used in the past as a surrogate endpoint to support accelerated approval, FDA now considers this endpoint acceptable, in some circumstances, to grant traditional approval based on years of experience with this endpoint.

³³ See section 506(c)(3) of the FD&C Act and §§ 314.530(a) and 601.43(a). Part 314, subpart E and part 601, subpart H describe additional grounds for withdrawal.

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smaller magnitude or duration of benefit than was anticipated based on the observed effect on the surrogate).

If FDA determines there are grounds for withdrawal, the Agency may ask the applicant to request withdrawal of approval under § 314.150(d) or notify the applicant of FDA's proposal to withdraw approval in a notice of opportunity for hearing (NOOH). The NOOH generally will state the proposed grounds for withdrawal of approval.³⁴ Upon receipt of an NOOH, an applicant has 15 days to file a written request for a hearing. If an applicant does not request a hearing within 15 days, the applicant waives its opportunity for hearing.³⁵ An applicant may also request the Agency to withdraw approval of an application approved under accelerated approval.³⁶

VIII. PRIORITY REVIEW DESIGNATION

An application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions provide for priority review for various types of applications, described in [section IV](#). A priority designation is intended to direct overall attention and resources to the evaluation of such applications. This section describes the qualifying criteria and the features of priority review designation. [Appendix 1](#) describes the process for priority review designation.

A. Qualifying Criteria for Priority Review Designation

1. Serious Condition

See [section III.A](#).

2. Demonstrating the Potential To Be a Significant Improvement in Safety or Effectiveness

On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition. Significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes

³⁴ 21 CFR 314.530(b) and 601.43(b).

³⁵ 21 CFR 314.530(c)(1) and 601.43(c)(1).

³⁶ 21 CFR 314.150(c) and 601.5(a).

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- Evidence of safety and effectiveness in a new subpopulation

Although such evidence can come from clinical trials comparing a marketed product with the investigational drug, a priority review designation can be based on other scientifically valid information. Generally, if there is an available therapy (see [section III.B.](#)), sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority relating to either safety or effectiveness. Alternatively, sponsors could show the drug's ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy. Although such showings would usually be based on randomized trials, other types of controls could also be persuasive, for example, historical controls.³⁷

B. Features of Priority Review Designation

A priority review designation means FDA's goal is to take action on the marketing application within 6 months of receipt (compared with 10 months under standard review). The PDUFA review clock for applications filed by FDA under the Program is described in [section IV.](#)

IX. GENERAL CONSIDERATIONS

Communication with the Agency is a critical aspect of expedited programs. FDA will strive to provide a timely response to a sponsor's inquiry regarding an expedited development program. It is equally critical that a sponsor respond promptly to FDA's inquiries.³⁸ This applies to formal meetings and related inquiries, written correspondence, and other interactions. In addition to the many types of formal meetings³⁹ and correspondence the Agency offers to sponsors, additional considerations for sponsors of expedited programs are highlighted in this section.

A. Manufacturing and Product Quality Considerations

The sponsor of a product that receives an expedited drug development designation may need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program. The sponsor's product quality and CMC teams should initiate early communication with FDA to ensure that the manufacturing development programs and timing of submissions meet the Agency's expectations for licensure or marketing approval.⁴⁰

When sponsors receive an expedited drug development designation, they should be prepared to propose a commercial manufacturing program that will ensure availability of quality product at the time of approval. The proposal should consider estimated market demand and the

³⁷ Sponsors contemplating the use of historical controls should consult ICH E10 for more-detailed discussions.

³⁸ For example, FDA may request updates on a breakthrough therapy designation program in order to provide the sponsor with guidance on drug development.

³⁹ See the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants*.

Also see the *CDER 21st Century Review Process Desk Reference Guide* accessible at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm>.

⁴⁰ See the guidance for industry *IND Meetings for Human Drugs and Biologics Chemistry, Manufacturing, and Controls Information*.

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commercial manufacturing development plan. The proposal should also consider manufacturing facilities and a lifecycle approach to process validation. Additionally, the proposal should include a timeline for development of the manufacturing capabilities with goals aligned with the clinical development program. After the initial discussion following designation, frequent communication during development will generally facilitate meeting manufacturing development goals and product quality goals.

Sponsors of such products should allow for an earlier submission of the CMC section (including product quality information) for timely review, and, critically, for inspection activities.⁴¹ Coordination with the sponsor and contract manufacturers may be necessary to ensure that manufacturing facilities and equipment are ready for inspection during review of the clinical section of the application. A comprehensive meeting with FDA's product quality review groups in advance of submission may facilitate the quality assessment of products designated for expedited programs.

Although sponsors must ensure the availability of quality product at the time of approval, FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components (e.g., stability updates, validation strategies, inspection planning, manufacturing scale-up). The level of flexibility will be determined on a case-by-case basis after consideration of factors such as the following: (1) product characteristics, (2) seriousness of the condition and medical need, (3) manufacturing processes, (4) the robustness of the sponsor's quality system, and (5) the strength of the sponsor's risk-based quality assessment. FDA's consideration of the sponsor's proposal for an integrated postmarketing plan will also take into account whether elements of the plan may be appropriately executed as a postmarketing commitment or requirement. For example, FDA will consider impacts on clinical performance, such as safety and immunogenicity. Sponsors should meet with the Agency to discuss their proposed plan as soon as possible and no later than the pre-NDA or pre-BLA meeting.

B. Nonclinical Considerations

To ensure timely submission and review of nonclinical data, sponsors should initiate early communication with FDA for their nonclinical study programs. Considerations such as study protocol modifications, sequence and scheduling of studies, and the need for specific studies (e.g., long-term toxicity) may be important in the context of expedited drug development. FDA will provide guidance to sponsors on the development of appropriate and timely nonclinical data needed to support an application for marketing approval or licensure.

C. Clinical Inspection Considerations

⁴¹ For products designated as fast track or breakthrough therapy, this can be accomplished through rolling review (see section V.B.2., section VI.B.3., and Appendix 2). For products submitted under an NDA without such a designation, flexibility is permitted in § 314.50(d)(1)(iv). For BLAs without such a designation, there is flexibility also to allow an early submission of the CMC section when resources permit.

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Sponsors should anticipate the Agency's need to inspect clinical trials, including, if applicable, the analytical component of bioavailability or bioequivalence studies. Sponsors should be prepared for inspections to be scheduled by the Agency early in the application review process so inspection results are available to inform the review division and to allow time for the sponsor to address significant inspection findings. To select sites for clinical inspections, it is important for reviewers to have timely access to adequate and accurate data in BLA, NDA, or supplement submissions. Sponsors should initiate early communication with FDA about information required for inspection planning and conduct.

D. Companion Diagnostics

Development programs utilizing one or more of the expedited programs described in this guidance may involve an in vitro companion diagnostic device. Sponsors using one of the expedited programs for a product that involves an in vitro companion diagnostic device should consult FDA's guidance on the topic.⁴²

X. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The time required to complete this information collection is estimated to average 30 hours per response to prepare a priority review designation request, 70 hours per response to prepare a breakthrough therapy designation request, and 120 hours per request to prepare promotional materials for accelerated approval under § 314.550, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy
10903 New Hampshire Avenue, Bldg. 51, rm. 6360
Silver Spring, MD 20993-0002

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR 202.1, certain parts of part 314, part 601, and sections 506(b)(1), 735, and 736 of the FD&C Act have been approved under OMB control numbers 0910-0686, 0910-0001, 0910-0338, 0910-0389, and 0910-0297. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0765 (expires 03/31/2017).

⁴² See the draft guidance for industry and Food and Drug Administration staff *In Vitro Companion Diagnostic Devices*. When final, this guidance will represent the FDA's current thinking on this topic.

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APPENDIX 1: PROCESSES FOR FAST TRACK, BREAKTHROUGH THERAPY, AND PRIORITY REVIEW DESIGNATIONS

This appendix describes general processes applicable to the submission and review of fast track, breakthrough therapy, and priority review designations.

A. Process for Fast Track Designation

1. When to Send a Designation Submission

Sponsors may request fast track designation when the IND is first submitted or at any time thereafter before receiving marketing approval of their BLA or NDA. The IND and potential fast track designation may be discussed before an IND submission in a pre-IND meeting, but a decision on designation would await submission of the IND. As a practical matter, FDA should ordinarily receive a fast track designation request no later than the sponsor's pre-BLA or pre-NDA meeting with the Agency because many of the features of fast track designation will not apply after that time. If a sponsor's drug development program is granted fast track designation for one indication and has subsequently obtained data to support fast track designation for another indication, the sponsor should submit a separate request.

2. Where to Send a Designation Submission

The IND or amendment should be sent to the IND administrative file to the attention of the appropriate review division or office in CDER or CBER.

3. Content of a Designation Submission

Fast track designation requests should contain the following information (in most cases, this information could be captured in approximately 10 to 20 pages):

- If the fast track designation request is submitted to the sponsor's IND as an amendment, identification of the submission in the cover letter as a **REQUEST FOR FAST TRACK DESIGNATION** in bold, uppercase letters. If the request is submitted with an initial IND, identification of the submission in the cover letter as both an **INITIAL INVESTIGATIONAL NEW DRUG SUBMISSION** and **REQUEST FOR FAST TRACK DESIGNATION** in bold, uppercase letters.
- In the cover letter of the submission, the name of the sponsor's contact person and the contact person's address, email address, telephone number, and fax number.
- If applicable, the IND application number.
- If available, for drug products, the proprietary name and active ingredient and for biological products, the proper name and proprietary name.
- The division or office to which the IND is being submitted or in which it is active.

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- The proposed indication(s).
- A concise summary of information that supports the fast track designation request for the indication being studied, including the following:
 - The basis for considering the drug to be one intended to treat a serious condition
 - The basis for considering the drug to have the potential to address an unmet medical need and an explanation of how this potential is being evaluated in the planned drug development program (e.g., a description of the trials intended to evaluate this potential)
- If applicable, a list of documents previously submitted to the IND that is considered relevant to the designation request, with reference to submission dates. Paper submissions can be resubmitted to FDA as appendices to the designation request.

4. FDA Response

FDA will respond to fast track designation requests within 60 calendar days of receipt of the request.

a. Designation letter

If the Agency determines that the criteria for designation as a fast track drug development program have been met, the designation letter will:

- State that fast track designation is granted for development of the product for use in treating the specific serious condition
- Point out that the sponsor should design and perform studies that can show whether the product meets an unmet medical need
- Alert the sponsor to the need for the drug development program to continue to meet the criteria for fast track designation

b. Nondesignation letter

If the Agency determines that a fast track designation request was incomplete or that the drug development program failed to meet the criteria for fast track designation, the Agency will send a nondesignation letter to the sponsor. The nondesignation letter will state that fast track designation is not granted and explain the reasons for the Agency's decision.

5. Continued Designation as a Fast Track Development Program

Over the course of drug development, it can be expected that some products granted fast track designation will not continue to meet the criteria for fast track designation. A drug product in a

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fast track development program may not continue to meet the criteria if the drug: (1) no longer demonstrates a potential to address unmet medical need or (2) is not being studied in a manner that shows the drug product can treat a serious condition and meets an unmet medical need. The drug product may no longer demonstrate a potential to address unmet medical need, for example, if a new product was approved under a traditional approval that addressed the same need or if emerging clinical data failed to show that the product in a fast track development program had the anticipated advantage over available therapy. For products in fast track drug development programs, the Agency expects that the appropriateness of considering particular drug development plans as part of the fast track program will be discussed and evaluated during the drug development process, including at the end-of-phase 2 meeting and the pre-BLA or pre-NDA meeting. If the sponsor recognizes that the fast track drug development program will no longer be pursued, the sponsor should inform the Agency of this change.

When fast track designation is no longer supported by emerging data or the designated drug development program is no longer being pursued, the Agency may choose to send a letter notifying the sponsor that the program is no longer designated as a fast track drug development program.

B. Process for Breakthrough Therapy Designation

1. When to Send a Designation Submission

Although sponsors may request breakthrough therapy designation when the IND is first submitted or at any time thereafter, they should not send breakthrough therapy designation requests until they have preliminary clinical evidence indicating that “. . . the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints.”⁴³ FDA therefore expects that in most cases breakthrough therapy designation requests would be submitted as an amendment to the IND. Ideally, FDA should receive a breakthrough therapy designation request before initiation of the clinical trial(s) intended to serve as the primary basis for demonstration of efficacy if most of the benefits of designation are to be obtained. Because the primary intent of breakthrough therapy designation is to develop evidence needed to support approval as efficiently as possible, FDA anticipates that breakthrough therapy designation requests will rarely be made after the submission of an original BLA or NDA or a supplement. If a sponsor’s drug development program is granted breakthrough therapy designation for one indication and has subsequently obtained preliminary clinical evidence to support breakthrough therapy designation for another indication, the sponsor should submit a separate request.

If a sponsor has not requested breakthrough therapy designation, FDA may suggest that the sponsor consider submitting a request if: (1) after reviewing available data and information, the Agency thinks the drug development program may meet the criteria for breakthrough therapy designation and (2) the remaining drug development program and review can benefit from the designation. However, the Agency still needs to review the submitted request (including preliminary clinical evidence) to determine if it meets the criteria for breakthrough therapy designation. A suggestion by the Agency that a sponsor consider submitting a request for

⁴³ Section 506(a)(1) of the FD&C Act.

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breakthrough therapy designation is advisory and should not be interpreted as guaranteeing breakthrough therapy designation once a request is submitted and reviewed.

2. Where to Send a Designation Submission

The IND or amendment should be submitted to the IND administrative file to the attention of the appropriate review division or office in CDER or CBER.

3. Content of a Designation Submission

Breakthrough therapy designation requests should contain the following information (in most cases, this information could be captured in approximately 10 to 20 pages):

- If the breakthrough therapy designation request is submitted to the sponsor's IND as an amendment, identification of the submission in the cover letter as a **REQUEST FOR BREAKTHROUGH THERAPY DESIGNATION** in bold, uppercase letters. If the request is submitted with an initial IND, identification of the submission in the cover letter as both an **INITIAL INVESTIGATIONAL NEW DRUG SUBMISSION** and **REQUEST FOR BREAKTHROUGH THERAPY DESIGNATION** in bold, uppercase letters.
- In the cover letter of the submission, the name of the sponsor's contact person and the contact person's address, email address, telephone number, and fax number.
- If applicable, the IND application number.
- If available, for drug products, the proprietary name and active ingredient and for biological products, the proper name and proprietary name.
- The division or office to which the IND is being submitted or in which it is active.
- The proposed indication(s).
- A concise summary of information that supports the breakthrough therapy designation request for the indication being studied, including the following:
 - The basis for considering the drug to be one intended to treat a serious condition
 - The preliminary clinical evidence that the drug may demonstrate substantial improvement over available therapies.⁴⁴ FDA does not expect the sponsor to submit primary data (data sets); but, the sponsor should describe the preliminary clinical evidence, including, for example, a brief description of available therapies (if there are any) and their effectiveness; justification for the comparator selected

⁴⁴ If the designation is being submitted with the IND, examples of information that could be submitted to support a designation request include data from foreign clinical trials not conducted under IND, a different formulation or route of administration, a use in an unrelated indication, or the published literature.

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for the clinical studies, the study design, the population studied, and the endpoint used; and a brief description of the study results and statistical analyses (including, for example, subgroup analysis).

- If applicable, a list of documents previously submitted to the IND that is considered relevant to the designation request, with reference to submission dates. Paper submissions can be resubmitted to FDA as appendices to the designation request.

4. FDA Response

FDA will respond to breakthrough therapy designation requests within 60 calendar days of receipt of the request.

a. Designation letter

If the Agency determines that the criteria for designation as a breakthrough therapy development program have been met, the designation letter will:

- State that breakthrough therapy designation is granted for development of the product for use in treating the specific serious condition
- Explain that FDA will work closely with the sponsor to provide guidance on subsequent development, including providing advice on generating evidence needed to support the drug approval in an efficient manner
- Alert the sponsor to the need for the drug development program to continue to meet the criteria for breakthrough therapy designation

b. Nondesignation letter

If the Agency determines that a breakthrough therapy designation request was incomplete or that the drug development program failed to meet the criteria for breakthrough therapy designation, the Agency will send a nondesignation letter to the sponsor. The nondesignation letter will state that a breakthrough therapy designation is not granted and explain the reasons for the Agency's decision. Where appropriate, the letter may also include advice to the sponsor regarding subsequent development, including what would be needed in a new breakthrough therapy designation request.

5. Continued Designation as a Breakthrough Therapy Development Program

Over the course of drug development, it can be expected that some products granted breakthrough therapy designation will no longer be considered a breakthrough therapy. For example, a drug development program may be granted breakthrough therapy designation using early clinical testing that shows a much higher response rate than available therapies. However, subsequent interim data derived from a larger study may show a response that is substantially smaller than the response seen in early clinical testing. Another example is where breakthrough

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therapy designation is granted to two drugs that are being developed for the same use. If one of the two drugs gains traditional approval, the other would not retain its designation unless its sponsor provided evidence that the drug may demonstrate substantial improvement over the recently approved drug. Additionally, if the sponsor recognizes that the development program designated as breakthrough therapy will no longer be pursued, the sponsor should inform the Agency of this change.

When breakthrough therapy designation is no longer supported by emerging data or the designated drug development program is no longer being pursued, the Agency may choose to send a letter notifying the sponsor that the program is no longer designated as a breakthrough therapy development program. Consistent with FDA's commitment to communicate frequently, and in an interactive manner, with sponsors of drugs designated as breakthrough therapies, FDA will notify the sponsor of its intent to rescind and will offer the sponsor an opportunity to justify its product's continued designation. FDA recognizes that sponsors of products that have had their breakthrough therapy designation rescinded because available data no longer support the designation may still have sufficient evidence after completion of the drug development program to support marketing approval.

C. Process for Priority Review Designation

FDA determines whether an application qualifies for priority review (versus standard review) for every application, not just when priority review is requested by the applicant. However, an applicant may expressly request priority review as described in the following sections.

1. When to Send a Designation Submission

Sponsors may request priority review designation when they submit an original BLA, NDA, or efficacy supplement. The Agency does not anticipate that priority review designation requests will be made after the filing of a BLA, NDA, or efficacy supplement.

2. Where to Send a Designation Submission

Priority review designation requests may be submitted with the original BLA, NDA, or efficacy supplement to the attention of the appropriate review division or office in CDER or CBER.

3. Content of a Designation Submission

Priority review designation requests should contain the following information:

- Identification of the submission in the cover letter as a **REQUEST FOR PRIORITY REVIEW DESIGNATION** in bold, uppercase letters.
- In the cover letter of the submission, the name of the sponsor's contact person and the contact person's address, email address, telephone number, and fax number.

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- If available, for drug products, the proprietary name and active ingredient and for biological products, the proper name and proprietary name.
- The proposed indication(s).
- A concise summary of information that supports the priority review designation request, including the following:
 - The basis for considering the drug to be intended to treat a serious condition
 - The basis for the assertion that the drug would be a significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition

4. FDA Response

FDA will inform the applicant in writing of a priority review designation by day 60 of the review. The division will inform the applicant in writing of a standard review designation by day 74 of the review. Applications that are not filed do not receive a review designation.

5. Continued Priority Review Designation

After priority review designation is assigned, the timeline will not change during the first review cycle, even if a redetermination of review status is made because of approval of other drugs, availability of new data, or submission of a request for formal dispute resolution by the applicant. In addition, applications filed over protest are assigned a standard review. If the application is resubmitted after FDA's refuse-to-file decision or if the application is withdrawn before FDA's action and resubmitted, FDA will make its determination of review designation based on the resubmitted application.

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APPENDIX 2: PROCESSES FOR ROLLING REVIEW

This appendix describes general processes applicable to the submission and review of portions of an application, a feature of fast track designation (see [section V.B.2.](#)) and breakthrough therapy designation (see [section VI.B.3.](#)).

A. Agreement on Proposal

Sponsors obtain preliminary Agency agreement on the proposal at the pre-BLA or pre-NDA meeting or earlier for products with breakthrough therapy designation (e.g., end-of-phase 2 meeting). At the meeting, the sponsor and the review division should discuss: (1) the data that will be used to support effectiveness, (2) the schedule for submission of each portion of the BLA or NDA, and (3) a description of portions of the application to be submitted separately.

A request to submit portions of an application ordinarily should be included in the information package for the pre-BLA or pre-NDA meeting. If a sponsor seeks to submit portions of an application to the IND after the pre-BLA or pre-NDA meeting, the sponsor should make such a request and provide a proposed schedule for submission of portions of an application to the IND as soon as possible.

A request for submission of portions of an application should be sent as an amendment to the IND; attach Form FDA 1571. The amendment should be clearly identified as a **REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION** in bold, uppercase letters. FDA responds to sponsors' requests for submission of portions of an application by letter. FDA also responds to changes to an agreement to accept portions of an application by letter.

B. Portions of an Application Eligible for Early Submission

Generally, the Agency accepts for submission a complete section of a BLA or NDA only, such as the entire CMC section, toxicology section, or clinical section.⁴⁵ A section of a BLA or NDA should be submitted for review in a form adequate to have been included in a complete BLA or NDA submission. Drafts should not be included in a submission; if final reports need to be updated, the applicant should submit a formal amendment to the BLA or NDA with the revised information. Occasionally, the Agency may, in its discretion, accept less than a complete section if the Agency determines that such a subsection would constitute a reviewable unit and be useful in making the review process more efficient (e.g., less than a complete section could be a CMC section lacking final consistency lot data and long-term stability data, a toxicology section lacking chronic toxicology data, final study reports for some or all of the principal controlled trials without integrated summaries). The sponsor should confirm these subsections are final reports.

At the pre-BLA or pre-NDA meeting, the Agency and the sponsor should work together to clearly define the parameters of accepting an incomplete section and to determine whether

⁴⁵ Form FDA 356h may be a useful guide to items in a BLA or NDA.

Contains Nonbinding Recommendations

FDA could conduct a meaningful review of the submission before receiving the missing information.

C. Submission of User Fees

A sponsor is required to pay applicable fees as stated in section 736 of the FD&C Act before FDA may commence review of any portion of an application. The applicant should submit Form FDA 3397 with applicable user fees and follow the same procedures as those followed when a complete application is submitted.

D. Commencement of Review

If FDA accepts a portion of an application, this does not necessarily mean that review will commence or proceed before the complete application is submitted. Actual commencement and scheduling of review depends on many factors, including staffing, workload, competing priorities, timeline for completing the application, and the perceived efficiency of commencing review before receipt of the complete submission.

E. Calculation of Review Time

The review clock will not begin until the applicant informs the Agency that a complete BLA or NDA was submitted.⁴⁶ After the Agency is notified of the complete application, we will make a filing determination within the usual time.⁴⁷

⁴⁶ Section 506(d)(2) of the FD&C Act provides that any time period for review of human drug applications shall not apply until the date on which the application is complete.

⁴⁷ See § 314.101, CDER MAPP 6025.4, *Good Review Practice: Refuse to File*, available on the Internet at <http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm370948.htm> and CBER SOPP 8404, *Refusal to File Procedures for Biologic License Applications* (August 27, 2007), available on the Internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073474.htm>.

Office of Drug Evaluation-I: Decisional Memo

Date	July 15, 2016
From	Ellis F. Unger, MD, Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
New Drug Application (NDA) #	206488
Applicant Name	Sarepta Therapeutics
Date of Submission	June 26, 2015
PDUFA Goal Date	May 26, 2016 (post-3-month extension for major amendment)
Proprietary Name/ Established (USAN) Name	EXONDYS 51™ eteplirsen injection
Dosage Forms/ Strengths	2 mL single-use vials containing 100 mg (50 mg/mL) eteplirsen 10 mL single-use vials containing 500 mg (50 mg/mL) eteplirsen
Indication originally sought by applicant (see page 29 for final)	"EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved on an intermediate endpoint demonstrating delayed disease progression as measured by the 6 minute walk test [see Clinical Studies (14)]. Continued benefit will be evaluated through confirmatory trials."
Action:	<i>Complete response</i>

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Yuet (Fannie) Choy, Laurie Kelley
Medical Officer/Clinical	Christopher Breder
Clinical Pharmacology/Pharmacometrics	Atul Bhattaram, Ta-Chen Wu, Hobart Rogers, Kevin Krudys, Angela Men, Christian Grimstein, Mehul Mehta
Statistical Review	Xiang Ling, Kun Jin, Hsien Ming (Jim) Hung
Pharmacology Toxicology	David Hawver, Lois Freed, Paul Brown
Office of Biotechnology Products	Ashutosh Rao, Amy Rosenberg
Office of New Drug Quality Assessment	Joseph Leginus, Mari Chelliah, Sung Kim, Denise Miller, Zhong Li, Dahlia Woody, Martha Heimann, James Laurenson, Donna Christner, Neal Sweeney, Edwin Jao, Zhihao Peter Qiu, Wendy Wilson-Lee, M. Scott Furness
Office of Scientific Investigations	Antoine El Hage, Cara Alfaro, Susan Thompson, Kassa Ayalew, Ni Aye Khin
Method Validation	Michael Hadwiger, Michael Trehy
Statistical Review – Stability data	Zhuang Miao, Xiaoyu Dong, Meiyu Shen, Yi Tsong
Office of Prescription Drug Promotion	Aline Moukhtara
Division of Medication Error Prevention and Analysis	Deborah Meyers, Justine Harris, Danielle Harris, Todd Bridges
Division of Risk Management	Robert Pratt, Jamie Parker, Kellie Taylor, Cynthia LaCivita
Associate Director for Labeling	Tracy Peters
Cross-Discipline Team Leader	Ronald Farkas
Deputy Director, Division of Neurology Products	Eric Bastings

1. Introduction

Sarepta Therapeutics is seeking accelerated approval for eteplirsen for the proposed indication:

"EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved on an intermediate endpoint demonstrating delayed disease progression as measured by the 6 minute walk test [see Clinical Studies (14)]. Continued benefit will be evaluated through confirmatory trials."

I agree with the views of the Division of Neurology Products (DNP), the Office of Biometrics, and the Office of Clinical Pharmacology that the applicant has not provided substantial evidence of effectiveness from adequate and well controlled trials to support conventional approval. I also agree that the applicant has not provided support for accelerated approval, i.e., evidence from adequate and well controlled trials of an effect on a biomarker that is reasonably likely to predict effectiveness. Thus, I agree with the DNP recommendation to issue a *Complete Response* for this application.

2. Background

Description:

Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. Theoretically, restoration of the mRNA reading frame would permit translation of an internally truncated, but nevertheless functional form of the dystrophin protein. The drug is targeted specifically for patients with DMD "who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping." It is not clear which of the specific mutations are amenable to exon 51 skipping.

PMOs are a class of synthetic molecules based upon a redesign of the natural nucleic acid structure. They are distinguished from native DNA and RNA because of a 6-membered morpholino ring that replaces the 5-membered ring found in native DNA and RNA. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in native DNA and RNA. Each morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits. The molecular formula of eteplirsen is $C_{364}H_{569}N_{177}O_{122}P_{30}$ and the molecular weight is 10.3 kilodaltons.

Disease Background:

Duchenne muscular dystrophy is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene located on the short arm of the X chromosome. These mutations disrupt the mRNA reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells. The disorder affects 1 in ~3,600 boys (~1 in 10,000 to 14,000 males). Patients who are amenable to skipping exon 51 constitute ~13% of the DMD patient population.

Dystrophin is thought to maintain the structural integrity of the muscle cell membrane by connecting the cytoskeleton to the underlying extracellular matrix, and acting as a scaffold for several molecules that also contribute to normal muscle physiology. Absence of dystrophin leads to mitochondrial dysfunction and damage, with inflammatory processes also appearing to contribute to muscle pathology. Muscle fibers ultimately undergo necrosis with replacement by adipose and connective tissue. Principal disease manifestations include progressive degeneration of skeletal and cardiac muscle, leading to loss of physical function in childhood and adolescence with premature death from respiratory and/or cardiac failure in the second to fourth decade.

No specific therapies are approved for DMD. Currently, glucocorticoid therapy is the cornerstone of clinical management, and is widely believed to delay loss of ambulation and respiratory decline by several years. Ventilatory assistance and physiotherapy are also thought to improve survival for DMD patients.

3. Product Quality

From a product quality perspective, NDA 206488 is recommended for approval. Eteplirsen would be marketed as a sterile, aqueous, preservative-free, concentrated solution for dilution prior to IV administration, to be supplied in single-use glass vials containing 100 mg or 500 mg eteplirsen (50 mg/mL).

OPQ recommends the following post-marketing commitments (PMCs), to be fulfilled no later than one year following NDA approval:

1. Investigate the root cause of the increasing assay trend observed in the drug product stability study.
2. Revalidate the accuracy of the in-process (b) (4) method used during drug product manufacture.
3. Revalidate the robustness of the in-process (b) (4) method in terms of (b) (4) (b) (4).
4. Investigate the consistent bias in the in-process (b) (4) results and the release (b) (4) (b) (4) results.

4. Nonclinical Pharmacology/Toxicology:

From a nonclinical perspective, NDA 206488 is recommended for approval. Pivotal toxicology studies were conducted in male monkeys (39-week study) and juvenile male rats (10-week study). A 26-week study was conducted in male transgenic mdx mice using a mouse-specific surrogate (AVI-4225). In all 3 species, the kidney was identified as the 1^o target organ, with dose-dependent renal tubular cytoplasmic basophilia and/or vacuolation and tubular degeneration and necrosis, primarily at the highest doses tested.

Dilatation of the lateral ventricles of the brain was observed at mid and high doses in the *mdx* mouse study. The mechanism of this effect and its relevance to humans are unknown. In juvenile rats, slight reductions in bone length, width, area, mineral content, and mineral density were observed at the high dose. These concerns could lead to recommendations for long-term monitoring in patients.

Mean eteplirsen plasma exposures (AUC) at the no observed adverse effect levels (NOAELs) for monkeys and juvenile rats were 20- and 6-fold, respectively, higher than that of patients who received the to-be-marketed dose of 30 mg/kg/week by the intravenous route.

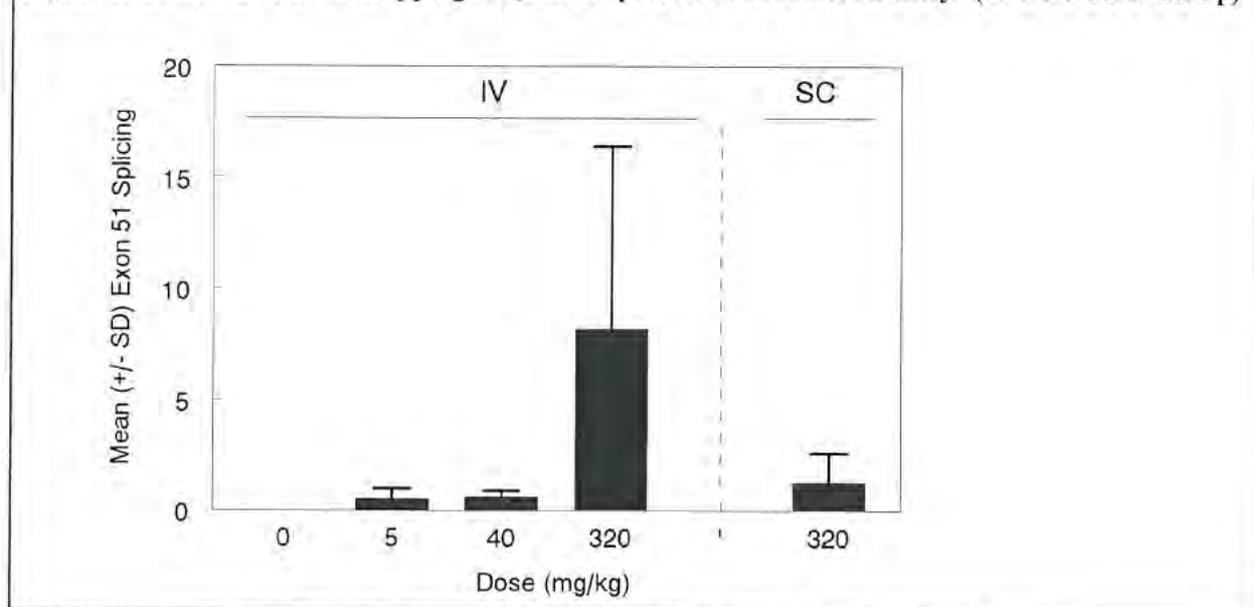
The applicant presented data on the exon skipping activity of eteplirsen in cynomolgus monkeys ("Exon skipping activity of AVI-4658 in cynomolgus monkey tissue samples from (b) (4) study (b) (4)" applicant study 4658-ssa-005). Samples of quadriceps muscle, heart, and diaphragm tissues were collected on Day 79 from cynomolgus monkeys after 12 weekly doses of eteplirsen at 0, 5, 40, or 320 mg/kg IV, or 320 mg/kg SC. Muscle samples were analyzed for exon 51 skipping of the dystrophin gene using polymerase chain reaction (PCR).

Exon skipping was detected in a nonlinear, dose-dependent manner (Table 1, Figure 1). With a 1-log increase in dose (from 5 to 40 mg/kg), there was little change in exon 51 skipping. With a second log increase in dose (from 40 to 320 mg/kg), however, there was more than a log increase in response. As noted below, the applicant studied doses of 30 and 50 mg/kg/week in the clinic (6 patients at each dose), and there is significant question as to whether the plateau of the dose-response curve was reached. It is possible that much higher doses could lead to substantially greater effects on dystrophin production – effects that could be important for efficacy.

Table 1: Average Percentage of Exon 51 Skipping in Intact Monkeys (N=8 for Each Group)

Tissue	Average % Exon 51 Splicing ± SD				
	0 mg/kg IV	5 mg/kg IV	40 mg/kg IV	320 mg/kg IV	320 mg/kg SC
Quadriceps muscle	0.0 ± 0.0	0.5 ± 0.5	0.6 ± 0.3	8.2 ± 7.4	1.3 ± 0.5
Heart	0.0 ± 0.0	0.1 ± 0.1	0.2 ± 0.2	4.5 ± 2.9	1.4 ± 0.5
Diaphragm	0.0 ± 0.0	0.2 ± 0.2	0.9 ± 0.7	6.1 ± 3.5	2.2 ± 0.9

Figure 1: Evidence of Exon Skipping in Quadriceps Muscle in Intact Monkeys (N=8 for Each Group)



With respect to the advisability of evaluating higher doses in humans, this subject is well summarized by Dr. Bastings in his Division Memo: "Considering the seriousness of DMD, the unmet medical need, and the nature of the toxicities observed in animals, I believe that the nonclinical data would support, with proper monitoring, dosing in DMD patients at least up to 200 mg/kg, a dose expected to provide exposure similar to the most sensitive species NOAEL for the toxicities seen in animals. If the human safety experience at these doses is acceptable, further dose escalation is possible in DMD patients."

Finally, the nonclinical review team provided insight that is relevant for the interpretation of clinical data with respect to production of dystrophin protein: "The most robust finding among the studies provided and referenced in this submission was the wide variability in the extent of PMO-induced dystrophin expression within a single muscle and among different muscles, suggesting that caution is warranted in generalizing from the results of biopsies taken from only one or a few sites, muscle types, or patients."

Carcinogenicity:

Carcinogenicity studies have not been conducted with eteplirsen. The nonclinical review team opined that carcinogenicity studies in 2 species should be conducted as a post-marketing requirement. Dr. Bastings agrees, and I agree, that for this serious indication with unmet need, carcinogenicity studies can be deferred until after marketing.

5. Clinical Pharmacology

The Clinical Pharmacology team does not recommend approval; they recommend generation of robust evidence of effectiveness prior to approval. Specifically, the team is recommending a double-blind, placebo-controlled study in patients with mutations amenable to exon-51 skipping who are likely to be ambulant for 1 year, with use of appropriate endpoints based on upper or lower body strength in patients between 4 and 12 years of age. They also suggest study of doses greater than 50 mg/kg administered weekly, or alternate regimens that would include loading and maintenance doses, for example, twice-weekly administration for 6 months followed by weekly administration for 6 months. Their recommendations are based on the 3- to 4-hour half-life of the drug, urinary excretion of 60-70% of the drug within 24 hours, and the absence of known toxicity at doses of 50 mg/kg. The immunogenicity of eteplirsen can be further assessed in future clinical trial(s) as well.

Summary of Pharmacokinetics:

- Pharmacokinetics was approximately dose-proportional and linear from 0.5 to 50 mg/kg/week, with insignificant accumulation in this dose range.
- Following single or multiple intravenous infusions, peak plasma concentrations (C_{max}) occurred near the end of infusion.
- Plasma concentration-time profiles showed multi-phasic decline, with virtually all drug eliminated within 24 hours (24 hours after completion of infusion, eteplirsen concentrations were 0.02% of C_{max}).
- At doses of 30 and 50 mg/kg, the elimination half-life is ~3.5 hours, with ~65% of the drug excreted unchanged in the urine. The drug is not metabolized.
- Protein binding of eteplirsen in humans is relatively low, ~6% to 17%, and is independent of concentration.

- The volume of distribution data suggest distribution or cellular uptake into peripheral tissues.
- Inter-subject pharmacokinetic variability is moderate, generally in the range of 20 to 55% for exposure measures (C_{max} and AUCs) as well as other key pharmacokinetic parameters.
- Intrinsic factors were not studied (typically, in a larger development program, age, gender, body weight, geographic region, hepatic impairment, renal impairment, and other potentially significant covariates would be studied).
- *In vitro* investigations on major CYP isozymes and transporters did not reveal the need for additional investigation in humans.
- Eteplirsen was not a significant inhibitor or inducer of CYP.
- Eteplirsen was not a substrate or inhibitor for any of the key human transporters tested.
- Eteplirsen is expected to have a low potential for drug-drug interactions.

Finally, the clinical pharmacology team noted that if eteplirsen were found to be safe and effective, it would likely benefit all mutations amenable to exon-51 skipping and should be labeled accordingly.

QT Effects:

QT effects were not formally investigated in man.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical Efficacy

Sarepta is seeking accelerated approval for eteplirsen for the proposed indication:

"EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved on an intermediate endpoint demonstrating delayed disease progression as measured by the 6 minute walk test [*see Clinical Studies (14)*]. Continued benefit will be evaluated through confirmatory trials."

In this section, I provide an explanation of how accelerated approval might be used as a potential pathway to approval, based on production of dystrophin in skeletal muscle. I then discuss the evidence that eteplirsen produces dystrophin in skeletal muscle, based on immunohistochemistry and Western blot analyses. Finally, I discuss the clinical data that could serve as the basis for a conventional approval.

Accelerated Approval:

The applicant has requested accelerated approval based on an endpoint of 6-minute walk distance. The proposed indication states that 6-minute walk test is considered to be an intermediate endpoint demonstrating delayed disease progression.

There is little in the NDA to explain the applicant's thought process here. In Sarepta's briefing materials for the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, they stated (page 16):

"The accelerated approval pathway means that there will be an acceptable degree of uncertainty about whether the therapy will actually result in the anticipated clinical benefit. This uncertainty is addressed by the requirement that 'appropriate post-approval studies to verify and describe the predicted effect' would usually be underway at the time of approval."

The applicant appears to misconstrue the intent of the accelerated approval pathway. They purport to show that, after 36 months of treatment, eteplirsen improves physical performance as assessed by the 6-minute walk test. We consider the 6-minute walk test to be a valid and meaningful measure of how well a patient functions – i.e., a clinical endpoint that would be a basis for full approval – not a surrogate endpoint or an intermediate endpoint. For slowly progressive diseases, an intermediate clinical endpoint, a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality and is considered reasonably likely to predict the drug's effect on irreversible morbidity or mortality or other clinical benefit, can be used to support accelerated approval. But all would agree that showing an improvement on a clinically meaningful endpoint at 36 months would be adequate to support a conventional approval in DMD, a position we have taken with other DMD drugs.

Thus, the applicant has provided study results that purport to show improvement in a meaningful clinical endpoint after a relatively long duration of treatment, but they appear to propose accelerated approval as a means to deal with uncertainty about whether the therapy has actually been shown to provide a clinical benefit in the trial.

Clearly, if the review team had reached the conclusion that the applicant had provided substantial evidence of an effect on 6-minute walk distance during some 3 to 3.5 years of treatment, they would recommend a conventional (full) approval, and not accelerated approval. As noted in the reviews, however, for a number of reasons the review team does not believe that the applicant has provided substantial evidence of an effect on 6-minute walk distance, or any measure of physical performance (see below). Importantly, accelerated approval is not intended to enable use of less than substantial evidence of a treatment effect as a basis for approval, to be bolstered by more compelling evidence to be developed in the post-marketing setting.

Despite the lack of substantial evidence of clinical efficacy from Study 201/202 (see below), it is important to consider whether accelerated approval, based on an effect on a surrogate endpoint, could provide a viable alternative pathway to approval. The relevant statutory and regulatory framework (section 506(c) of the FD&C Act and 21 CFR part 314, subpart H) states that a drug can receive accelerated approval if 3 factors are satisfied:

1. If the drug treats a serious or life-threatening disease or condition,
2. if FDA takes into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments, and
3. if the drug demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit OR demonstrates an effect on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. As noted in section 506(c)(1)(B) of the FD&C Act, the evidence to support the concept "...that an endpoint is reasonably likely to predict clinical benefit may include epidemiological,

pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

In terms of the prospect for accelerated approval for eteplirsen, DMD is clearly a serious, severe, and rare condition with no approved treatments; therefore, factors 1 and 2, above, are satisfied.

The critical issue is whether factor 3 is satisfied, and factor 3 can be subdivided into three parts: 1) whether the surrogate endpoint is appropriate for the disease; 2) whether there is substantial evidence of an effect on the surrogate endpoint; and 3) whether the effect demonstrated meets the test of being "reasonably likely" to predict clinical benefit.

As noted in 506(f)(1), the amendments made by the Food and Drug Administration Safety and Innovation Act (FDASIA) "...are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs."

Some have interpreted this "flexibility" as a lower standard for the demonstration of effectiveness, but this is not correct. Section 506(f)(2) of the FD&C Act specifically notes that drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval, notably the substantial evidence standard of section 505(d) with respect to the drug's claimed effect on a surrogate or intermediate endpoint. These requirements have not been altered by FDASIA.

To be clear, 506(f)(2) states: "Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act or under section 351(a) of the Public Health Service Act. Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective. Nothing in this section alters the ability of the Secretary to rely on evidence that does not come from adequate and well controlled investigations for the purpose of determining whether an endpoint is reasonably likely to predict clinical benefit as described in subsection (b)(1)(B)."

Again, the critical issue here is whether factor 3 (above) is met, in light of these considerations.

For the first part of factor 3, whether the surrogate endpoint is appropriate for the disease, the review team has agreed that the near-lack of dystrophin is the proximal cause of DMD, and that the level of dystrophin in skeletal muscle is an appropriate surrogate endpoint that could predict efficacy. (Of note, the best-case scenario for eteplirsen is the production of an abnormal Becker-type dystrophin, not normal dystrophin, but that will be discussed later.)

The second part of factor 3 is whether an effect has been demonstrated, and the standard remains 'substantial evidence' based on adequate and well-controlled clinical investigations. Typically, such evidence would be two studies, both achieving a p -value < 0.05 .¹

¹ In some situations, FDA has the flexibility to interpret data from a single trial, or a single trial with supporting evidence, as substantial evidence of effectiveness. See: "Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products;" May, 1998.

The third part of factor 3, the determination that the demonstrated effect is "reasonably likely" to predict clinical benefit, is a matter of judgment. Thus, once there is substantial evidence of a treatment effect, the determination of whether the effect size is "reasonably likely" to predict clinical benefit is an area where flexibility can be applied. Presumably there is some threshold effect that would have to be achieved in order to satisfy this criterion, but this is not described in the regulations.

Is There a Basis for Accelerated Approval: Production of Dystrophin Protein in Skeletal Muscle?

The applicant assessed skipping of the messenger RNA exon using reverse transcriptase polymerase chain reaction (RT-PCR), a standard laboratory technique to detect RNA expression. Exon 51 skipping was confirmed by RT-PCR analysis in all patients treated with eteplirsen, establishing proof of concept that eteplirsen can cause at least some degree of exon 51 skipping, as intended. Because PCR is a highly sensitive technique that can detect even a few copies of messenger RNA, the findings do not support efficacy.

Dystrophin production was assessed by two widely-used and complementary methods: immunofluorescence (immunohistochemistry) and Western blot. Immunofluorescence is generally used to assess the presence or absence of proteins in tissue sections, and is particularly useful for cellular localization of protein (by light microscopy). Western blot provides quantitative analysis of protein, but no information on cellular localization.

Originally, the applicant evaluated the effect of eteplirsen on dystrophin expression in Studies 28, 33, and 201/202.

Of note however, as the May 26, 2016 goal date was approaching, the Office of New Drugs (OND) and the Center for Drug Evaluation and Research (CDER) could not reach agreement on the regulatory action for this NDA: the Office of New Drugs favored issuance of a complete response whereas CDER favored approval.

Thus, in order to obtain definitive data on dystrophin production to support accelerated approval, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in the ongoing Study 301 (PROMOVI). The applicant was told by CDER that if they were "...successful in showing, to FDA's satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval...." Thus, data from Study 301 were included in this NDA and discussed below.

A. Immunohistochemistry

The applicant used immunohistochemistry in cross-sections of skeletal muscle biopsies to distinguish and count "dystrophin-positive" and "dystrophin-negative" muscle fibers. The methods are described in detail in Dr. Breder's review. Briefly, following immunostaining of tissue sections for dystrophin, 4 fields were manually selected from the 4 quadrants of each slide, and images were captured (digitized) at 20X magnification. The contrast of each image was manipulated to enhance background staining so that most of the muscle fibers became visible, making it possible for the reader to perform a manual count of the total number of fibers. Image contrast was returned to normal, and positive fibers – fibers with at least some degree of

positive staining – were manually counted. For each field, the number of positive fibers was divided by the total number of fibers to calculate the percentage of positive fibers. Various rules were prospectively established to define "positive" fibers; in essence, a fiber could be classified as "positive" if its staining intensity was only slightly perceptible over background. Importantly therefore, a reading of 50% "positive" fibers in a tissue field is not tantamount to 50% (normal) dystrophin. A 50% figure means only that half the fibers exhibited staining that was at least barely perceptible over background.

Immunofluorescence data were also analyzed using Bioquant software. For these analyses, the user determined a brightness threshold for each digitized image, in essence selecting all pixels where staining intensity exceeded a particular user-selected value. Once selected, the software calculated the mean intensity of the selected pixels. Given that the region of interest for these analyses was limited to the pixels that exceeded a threshold rather than the total image, I do not consider the Bioquant analyses to be readily interpretable.

Study 33 was a 7-patient, exploratory, phase 1 study, initiated in 2007 at the Hammersmith and Saint Mary's Hospitals, London, UK. Two subjects received a single 0.09-mg dose of eteplirsen in the extensor digitorum brevis (EDB) muscle of one foot and placebo in the contralateral foot. Five subjects received a single 0.9-mg dose of eteplirsen in the EDB muscle of one foot and placebo in the contralateral foot. After 14 to 28 days, dystrophin was detected adjacent to the needle tracks by immunohistochemistry and Western blot. Western blot analyses were not carried out for control muscles injected with placebo.

Study 28 was a 19-patient, exploratory, phase 1 study, initiated in 2009 at 2 sites in the UK. Patients had DMD amenable to exon 51 skipping. Eteplirsen was administered weekly by the intravenous route for 12 weeks at doses ranging from 0.5 to 20 mg/kg. There were up to 4 patients per dose level. After FDA expressed concerns about the reliability of the procedures and methods, the applicant responded that "Study 28 was an exploratory phase 1b study which was only intended to generate proof of concept data to guide future studies. For this reason, quality controls for the dystrophin data in Study 28 were not properly optimized." Some data were missing, and after considering all of this information, the review team did not deem the results to be interpretable.

Study 201 was a single-center, double-blind, placebo-controlled, parallel-dose study in 12 patients with DMD. The study was initiated in 2011. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (n=4 per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. The extension trial is well described in other reviews.

The 1^o endpoint of Study 201 was the percentage of dystrophin-positive fibers in muscle biopsies as assessed using immunohistochemistry. The main comparison was planned to be the 50 mg/kg/week group at Week 12 and the 30 mg/kg/week group at Week 24 to the combined placebo group. The applicant's original results are shown in Table 2, adapted from their clinical study report. As will be noted below, these results are not deemed to be reliable.

Table 2: Adapted From Table 11-1 of Applicant's Clinical Study Report: Effect of Eteplirsen on Dystrophin-Positive Fibers Detected by Immunohistochemistry with MANDYS106

Time point		Placebo N = 4	30 mg/kg/wk Eteplirsen N = 4	50 mg/kg/wk Eteplirs en N = 4
Baseline	Mean	15.64	18.19	11.00
	SD (SE)	10.742 (5.371)	5.501 (2.751)	4.668 (2.334)
	Min, Max	3.2, 28.2	11.9, 25.3	5.4, 15.6
On-Treatment^b	Mean	11.59	41.14	11.79
	SD (SE)	7.130 (3.565)	10.097 (5.049)	4.456 (2.228)
	Min, Max	5.7, 21.7	32.7, 54.3	6.4, 17.2
Change from Baseline	Mean	-4.05	22.95 ^c	0.79
	SD (SE)	5.834 (2.917)	5.792 (2.896)	7.099 (3.549)
	Min, Max	-8.5, 4.5	15.9, 29.0	-9.3, 7.4

It should be stressed again that the figures in the table represent the percentage of dystrophin-positive fibers, but in no way correspond to the percentage or quantity of dystrophin relative to a normal individual. Muscle fibers displaying virtually any staining intensity above background were considered "positive." As noted above, therefore, a reading of 50% positive fibers means only that 50% of fibers exhibited staining that was perceptively above background.

These results were substantially reported in a 2013 publication,² which claimed that eteplirsen markedly increased functional dystrophin production: "... *the percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients (p<0.002). Even greater increases occurred at week 48 (52% and 43% in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma.*" The publication also stated that dystrophin expression was confirmed by Western blot, with a figure showing what were termed "representative" results.

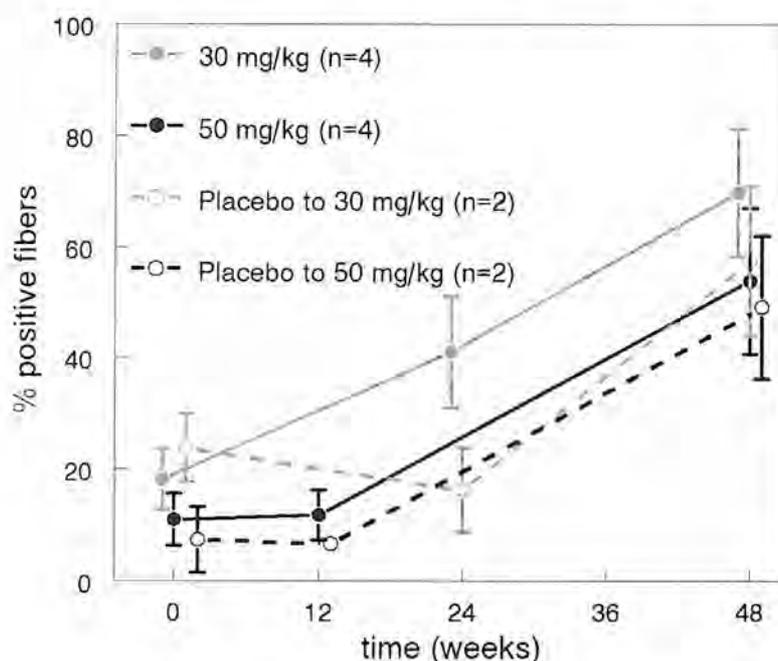
Publication of this paper was followed by a Sarepta press release,³ which also claimed a remarkable treatment effect from eteplirsen and raised wildly unrealistic expectations in the DMD community. It was these perceptions and expectations that led the applicant to declare that a placebo-controlled study was no longer feasible (see below).

² Mendell JR, et al: Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol* 2013;74:637-47

³ Sarepta press release, 8/8/13, at <http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=1846052> [downloaded 5/10/16]

The original data from Nationwide Children's Hospital submitted to FDA are plotted in Figure 2. Immunostaining for dystrophin appears to increase markedly in all 4 groups with time, with some 50 to 60% of fibers staining positive for dystrophin at 48 weeks. For reasons explained below, the review team disagrees with the veracity of these data.

Figure 2: Original Results of Dystrophin Immunostaining Using MANDYS106 Antibody: Percent Positive Fibers as a Function of Time – Results Not Verified on Re-read



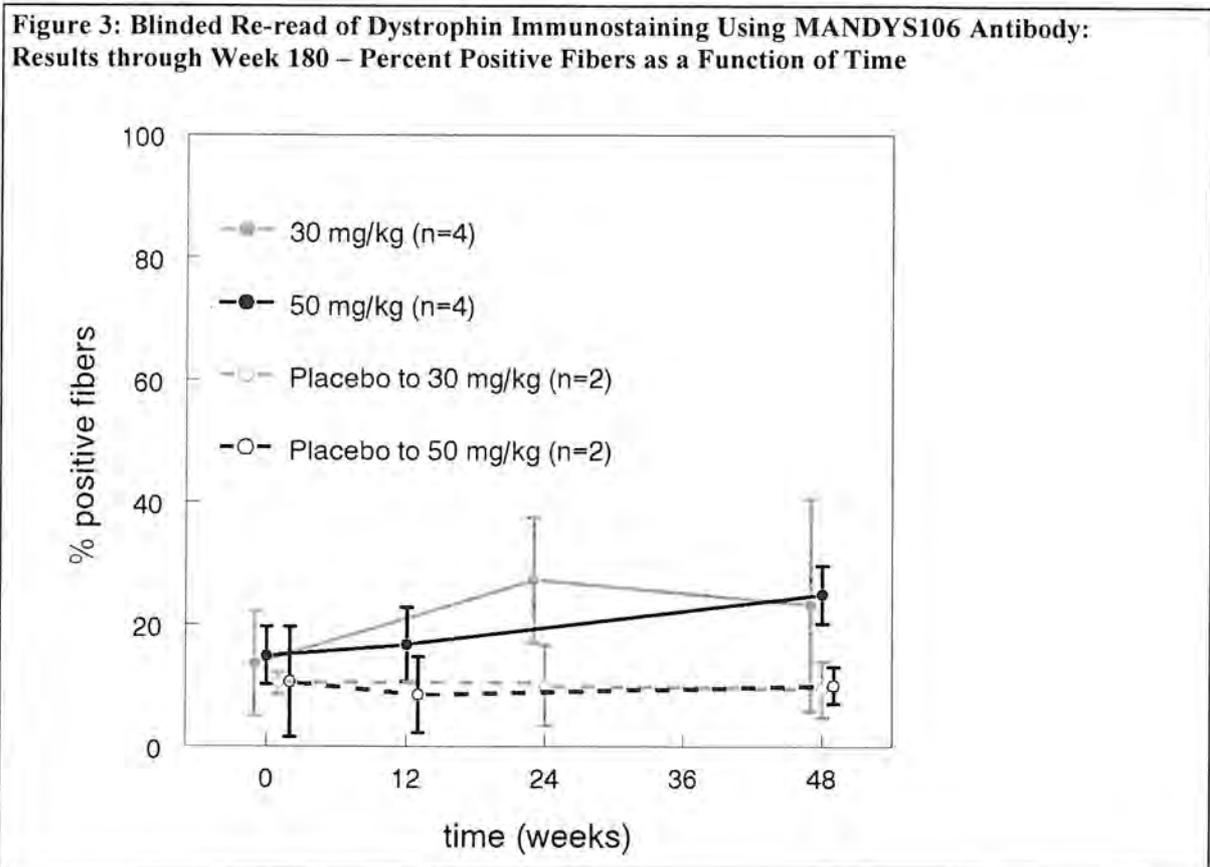
I was part of an inspection team that conducted (May 29 and 30, 2014) a site visit to Nationwide Children's Hospital in Columbus, OH, where Study 201 was conducted. We found the analytical procedures to be typical of an academic research center, seemingly appropriate for what was simply an exploratory phase 1/2 study, but not suitable for an adequate and well controlled study aimed to serve as the basis for a regulatory action. The procedures and controls that one would expect to see in support of a phase 3 registrational trial were not in evidence.

Although the technician had been blinded to treatment group, access to the treatment code was not protected with the kinds of safeguards and firewalls that one would ordinarily put in place for an adequate and well controlled trial. The immunohistochemistry images were only faintly stained, and had been read by a single technician using an older liquid crystal display (LCD) computer monitor in a windowed room where lighting was not controlled. (The technician had to suspend reading around mid-day, when brighter light began to fill the room and reading became impossible.) These issues are well described in a summary of inspectional findings in Dr. Breder's clinical review (page 27). There was also concern that the reader, although masked to treatment assignment, was not masked to sequence/time (see below). Importantly, in a trial where all patients eventually received the active drug, knowledge of sequence could lead to the false appearance of a treatment effect, i.e., the appearance of increasing dystrophin expression

with time, simply by having a lower threshold for calling fibers "positive" at later time points in the study.

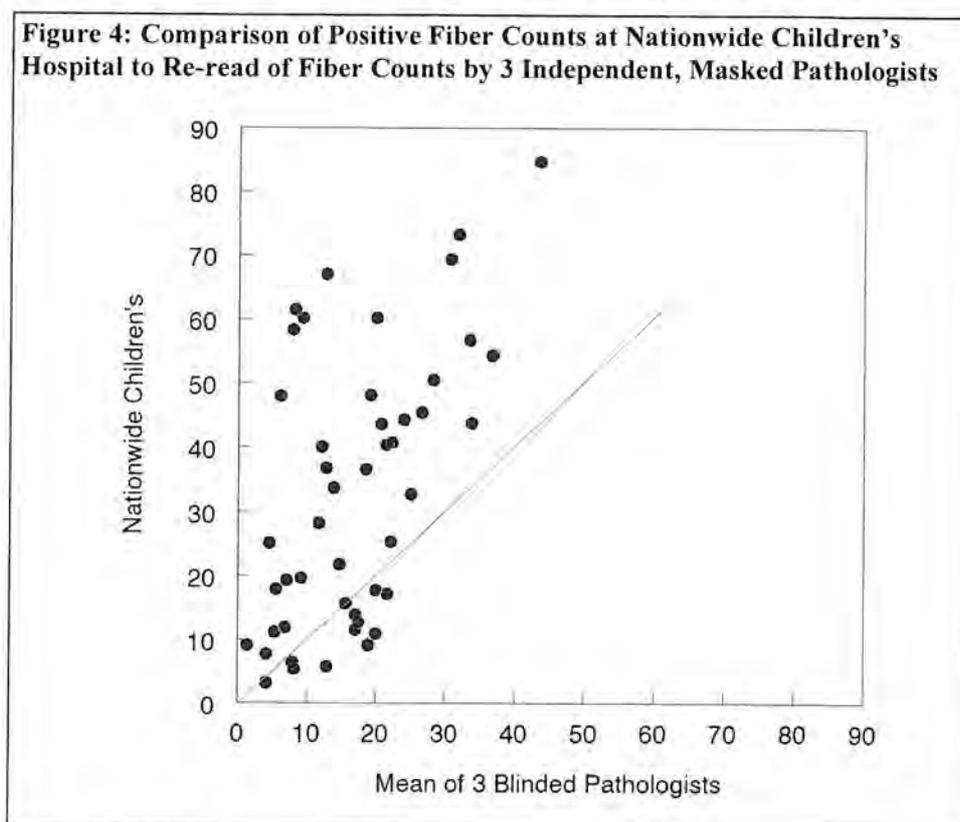
Having uncovered numerous technical and operational shortcomings in Columbus, our team worked collaboratively with the applicant to develop improved methods for a reassessment of the stored images. We suggested a re-read of all images by 3 independent masked readers, such that blinding could be assured and inter- and intra-observer variability could be characterized. We also suggested the use of better equipment, specifically, high-quality light-emitting diode (LED) computer monitors, in darkened rooms.

The applicant undertook a blinded re-analysis of the images on the server as FDA suggested. Unfortunately, the re-analyses failed to show a significant increase in dystrophin-positive fiber counts in eteplirsen treated patients (Figure 3). Note also that for patients who switched from placebo to eteplirsen at Week 24 (dashed red and black lines), there was no response between Weeks 24 and 48.



This re-analysis, along with the study published in 2013,² provides an instructive example of an investigation with extraordinary results that could not be verified. The publication, now known to be misleading, should probably be retracted by its authors.

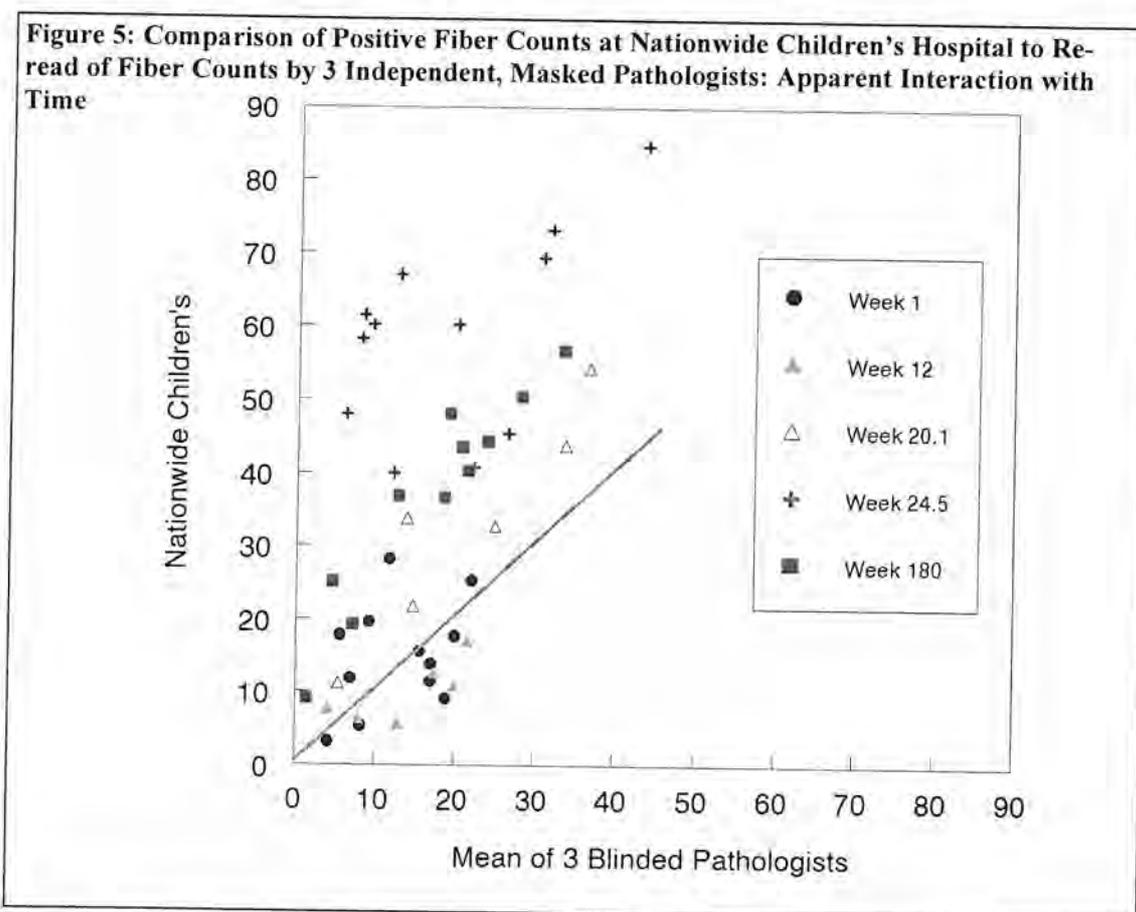
Figure 4 shows the correlation between the dystrophin immunohistochemistry data as read by the technician at Nationwide Children's Hospital and the 3 blinded pathologists. Each point represents data from a single patient at a single time point (an analysis of 24 images), as read by Nationwide Children's Hospital (y-axis) and the group of 3 blinded pathologists (x-axis). Readings from the 3 pathologists are averaged. Perfectly correlated readings would lie along the blue line of unity. In most cases, the reading from Nationwide exceeds the reading from the pathologists, i.e., above and to the left. Thus, despite less-than-optimal lighting conditions that should have favored reduced reading of positive fiber counts at Nationwide Children's Hospital, there was a striking tendency for the reporting of higher counts at that institution.



One might reasonably ask why the original readings were not reproduced by a blinded re-read. Figure 5 shows the same scatterplot between readings by Nationwide Children's Hospital and the 3 blinded pathologists. In this display, however, readings from samples obtained at the disparate time points are shown with unique markers.

It is striking that the deviations between the readings of Nationwide and the re-read by the blinded pathologists differ substantially by study time point. Thus, at Week 1 (●) and Week 12 (▲), time points before increased dystrophin production would be expected, there is reasonable agreement between Nationwide and the pathologists, i.e., the points lie close to the blue line. In contrast, for the Week 24.5 time point (+), readings from Nationwide Children's Hospital are much higher than those of the 3 pathologists, suggesting that blinding to sequence (i.e., time

point) was not achieved. At the time the Week 180 samples were read at Nationwide Children's Hospital, the technician was aware that the images would be re-read by 3 pathologists, which could explain why there is less exaggeration (i.e., the Week 180 readings are closer to the blue line of unity than the Week 24.5 readings).



Week 180 Data

As noted by the review team, the extension phase of the study (Study 202) has continued through the present. Eleven (11) of the 12 patients consented to undergo a fourth skeletal muscle biopsy at Week 180 (3.5 years), and these samples were analyzed using immunohistochemistry.

Prior to the analysis of the Week 180 samples, however, the applicant made changes to the immunohistochemistry protocol with the intent of decreasing non-specific staining. Their aim was to compare the Week 180 dystrophin level to baseline for each patient. Frozen archived baseline tissue was available for only 3 of the patients, however, and so the applicant supplemented these with samples from 6 untreated external DMD patients, all to be compared to the Study 201/202 patients at Week 180. Images were read by the same 3 pathologists, masked to treatment group.

For this analyses, the applicant claims a remarkable increase in dystrophin staining: the 9 baseline samples (including samples from 3 patients in Study 201/202 and 6 external controls) showed a mean percent positive fiber count of $1.1 \pm 1.3\%$ (mean \pm SD), whereas the Week 180 samples showed a mean percent positive fiber count of $17.4 \pm 10.0\%$. I will note that FDA made no attempt to inspect or oversee the new immunohistochemistry methods.

Given that the original baseline percent positive fiber count for patients from Study 201/202 was $13.0 \pm 6.2\%$, it would be important to understand why the results from a new immunohistochemistry protocol provided results more than an order of magnitude lower ($1.1 \pm 1.3\%$).

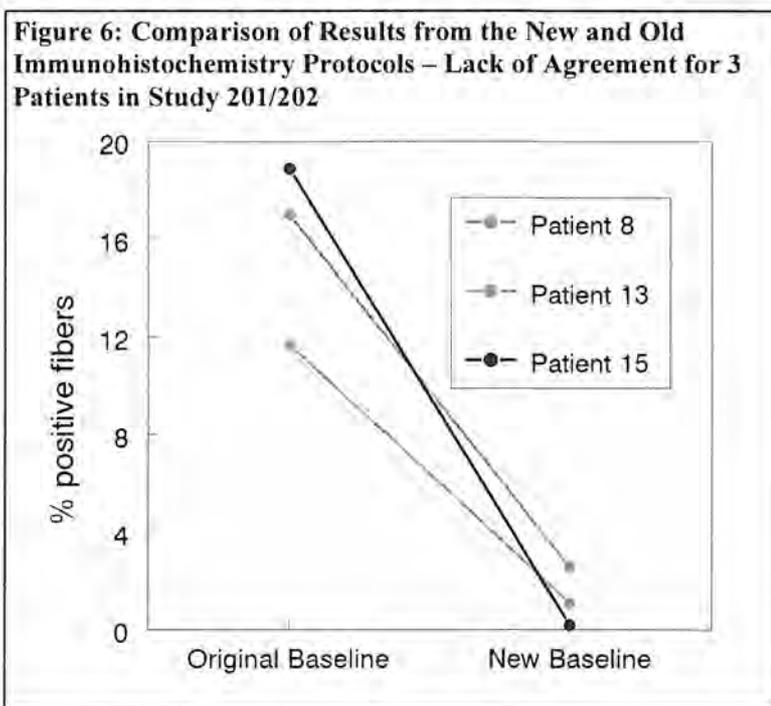
As noted above, there were 3 patients in Study 201/202 with adequate archived tissue for separate immunohistochemistry analyses using both the old and new methods. Figure 6 shows how the two methods compare. These are essentially replicate analyses of a single tissue sample using the two methods.

There is an inexplicable difference of more than an order of magnitude between results using the new and old immunohistochemistry protocols. These marked differences raise concerns with respect to the validity of the applicant's methods, and make interpretation impossible.

The disparity also underscores the difficulty of comparing results of immunohistochemical analyses for dystrophin across laboratories, or, for that matter, within the same laboratory.

Commentary:

The review team provided much thoughtful discussion regarding the relative merit of immunohistochemistry for the quantitative assessment of dystrophin in skeletal muscle. My view is that such analyses, if properly blinded and controlled, can yield semi-quantitative information that could show differences in dystrophin production, e.g., 50% is more than 25%, although the method does not allow correlation of particular values of "percent positive" fiber counts with quantitative measures of muscle protein. Moreover, comparisons of fiber counts across centers, across experiments, or, for that matter, across staining or reading runs within a single laboratory, do not seem likely to be informative.



Recognizing that Study 201/202 was a small exploratory phase 1/2 study that was not powered to show a small change in dystrophin, the study provides no evidence of increased dystrophin production by immunohistochemistry.

It is unfortunate that the original readings from Nationwide Children's Hospital, purporting to show a marked effect of eteplirsen on dystrophin-positive fiber counts – counts now known to be unreliable – led to the perception that the drug produces large amounts of dystrophin. These results fueled the public perception that eteplirsen is highly effective as well as the DMD community's reluctance to participate in placebo-controlled trials. Only recently, an unauthored report in the Wall Street Journal stated: "The trial turned up evidence that eteplirsen makes good on pumping out dystrophin, a feat no treatment has managed."⁴ Presumably this misperception has been carried over from the initial 2013 reports.

B. Western blot

1) Data analyzed prior to the PDUFA goal date

A second, more important line of evidence regarding dystrophin production is Western blot, a standard, widely-used, analytical technique to assess levels of protein in biological tissues. Western blot was used to quantify dystrophin protein directly, and the methods are described by others.

For a variety of reasons discussed by Dr. Rao, the Western blot analyses originally conducted by the applicant were technically unsatisfactory. The Western blots from the first 3 time points had oversaturated bands, lacked appropriate controls, and were essentially uninterpretable. After conducting a site visit to the Columbus OH laboratory, FDA rendered advice to the applicant with the goal of improving technical aspects of the assay for future use.

The applicant amended the study protocol to allow for an additional skeletal muscle biopsy at Week 180 (3.5 years), potentially enabling pre- to post-treatment comparisons of Becker-type dystrophin after prolonged eteplirsen treatment. As noted above, 11 of the 12 patients in Study 201/202 consented to undergo a fourth skeletal muscle biopsy at Week 180. Of note, the baseline samples had been obtained from biceps muscle, whereas the Week 180 samples were obtained from deltoid muscle.

Two blocks were prepared from each patient sample. Sections from both blocks were pooled during homogenization for lysate preparation, and Western blots were run in duplicate.

The individual (anonymized) values for the Western blot analysis are shown in Table 3. As reported by the review team, the analysis for 11 of the 12 original patients showed a mean dystrophin value of $0.93\% \pm 0.84\%$ of normal (mean \pm standard deviation) after 3 to 3.5 years of eteplirsen treatment (3 years in patients initially randomized to placebo; 3.5 years in the other patients). Mean values were virtually the same for the lower (30 mg/kg/week) and higher (50 mg/kg/week) dose groups; there is no suggestion of a dose-response.

⁴ A Legal Test for the FDA: Black letter law dictates approval for a muscular dystrophy drug; Wall Street Journal, May 9, 2016.

Of note, the Western blot values are quite variable, both between patients and between duplicate runs *within* patients (i.e., repeatability; intra-assay precision), Table 3.

Mean values ranged from a maximum of 2.47% in Patient J, to near-zero in Patient H, and to zero in 2 patients (E and G). For some patients, there were considerable discrepancies between duplicate runs (the intra-assay difference was >0.5% in Patients B, C, D, and J). Aside from patients with zero or near-zero dystrophin, only 3 patients showed reasonable intra-assay agreement: Patients F, L, and K.

Given that these numbers represent duplicate runs from tissue homogenates, intra-assay differences suggest limited precision/reproducibility of the method, heterogeneity of the samples, or both.

Table 3: Individual Week 180 Western Blot Analyses – Study 201/202

Subject	Dose	Western blot				Group Mean ± SD
		gel 1	gel 2	Mean (arithmetic)	Mean (per protocol)	
L	30 mg/kg	0.58	0.46	0.52	0.52	
K	30 mg/kg	1.45	1.78	1.62	1.62	
J	30 mg/kg	2.83	2.11	2.47	2.47	
H	30 mg/kg	0.02*	0.28	0.15	0.14	
G	Placebo to 30 mg/kg	0.17*	0.15*	0.16	0	
F	Placebo to 30 mg/kg	0.93	1.02	0.98	0.98	0.96 ± 0.95
E	50 mg/kg	0.19*	0.16*	0.18	0	
D	50 mg/kg	0.75	0.24*	0.50	0.38	
C	50 mg/kg	1.22	0.69	0.96	0.96	
B	50 mg/kg	2.43	1.67	2.05	2.05	
A	Placebo to 50 mg/kg		1.15	1.15	1.15	0.91 ± 0.79

* below limit of quantitation

Change in Dystrophin with Treatment:

The critical question, of course, is whether the value of 0.93% is meaningfully greater than the value at baseline, or even meaningfully greater than zero. Assuming that one considers this value greater than zero, the baseline pre-treatment levels of dystrophin in these 11 patients are critical in determining whether eteplirsen was responsible for the dystrophin detected at Week 180.

Unfortunately, adequate pre-treatment tissue samples were available for only 3 of these 11 patients. Thus, the applicant supplemented these data with muscle biopsies from 6 untreated patients with DMD amenable to exon 51 skipping who were external to the study.

Whereas the Week 180 samples were obtained from deltoid muscle, 8 of 9 of the controls were obtained from biceps muscle (the other one was obtained from deltoid). As noted above, the non-clinical review team found "...wide variability in the extent of PMO-induced dystrophin expression within a single muscle and among different muscles, suggesting that caution is

warranted in generalizing from the results of biopsies taken from only one or a few sites, muscle types, or patients." Use of disparate muscle groups between patients in Study 201/202 and controls was, obviously, ill advised. The finding of a difference between patients in Study 201/202 and the external controls could simply represent a difference between muscles.

FDA's advice to the applicant (March 30, 2015) is still germane: "The control biopsy tissue that you propose to use is from a number of different muscle groups, such that differences that may exist in dystrophin expression among muscle groups may affect your results. However, in the context of other major sources of variability among biopsies (including both intra- and inter-individual differences even within the same muscle group), it appears reasonable for you to proceed with these controls, with the understanding that dystrophin changes would need to be robust to be interpretable as a drug effect."

Averaging Western blot data from pre-treatment biopsies of the 2 patients from Study 201/201 and the external treatment-naïve patients, the applicant reported a baseline dystrophin value of $0.08\% \pm 0.13\%$ (mean \pm standard deviation). Obviously, all but 2 of these controls are external, such that the comparison to the treated patients in Study 201/202 is non-randomized and indirect.

Table 4: Individual Untreated DMD Control Samples, Western Blot Analysis (% Normal Dystrophin)

Study; Subject	Dose	Western blot				Group Mean \pm SD	All Mean \pm SD
		gel 1	gel 2	Mean (arithmetic)	Mean (per protocol)		
201/202; X	0	0.05*	0.07*	0.06*	0	0 \pm 0	0.08 \pm 0.13
201/202; A	0	0.19*	0.08*	0.14*	0		
201/202; B	0	0.13*	0.07*	0.10*	0		
external; A	0	0.12*	0.14*	0.13*	0	0.12 \pm 0.15	
external; B	0	0.03*	0.12*	0.08*	0		
external; C	0	0.37	failed	0.37	0.37		
external; D	0	0.04*	0.30	0.17*	0.15		
external; E	0	0.20*	failed	0.20*	0		
external; F	0	0.40	0.09*	0.25*	0.20		

* below limit of quantitation

In determining whether there is substantial evidence that eteplirsen produced dystrophin in the patients in Study 201/202, the critical questions are whether these values, near the lower limit of quantification of the assay, are actually interpretable, and whether the comparison between these subjects and a predominantly external group of untreated patients is valid.

The review team has pointed out important limitations with respect to comparability of the Western blot results from the untreated controls, summarized below:

- Biopsies from controls were obtained from biceps, whereas Week 180 biopsies from eteplirsen-treated patients were obtained from deltoid. There is some evidence that dystrophin concentrations differ by muscle group, and the study does not account for this possibility. Because the study is not well controlled, the difference between these groups of patients cannot be attributed to a drug effect.
- Two-thirds (6 of 9) of the control patients were from Study 301, and were external to study 201/202. There is no way to know how these particular patients were selected for the purpose of this comparison.
- Degradation of dystrophin or loss of immunoreactivity might occur during prolonged storage of tissue samples. If so, it could have affected the baseline samples from the 3 patients in Study 201/202, which were frozen for over 3 years prior to analysis. Note that the data are consistent with loss in immunoreactivity over time (Table 4). The per-protocol values for all 3 patients from Study 201/202 whose samples were stored for 3 years are 0 (top), whereas 3 of 6 of the samples from the external controls (bottom) are greater than zero. Although the numbers of samples are small and the comparison is non-randomized, the data nevertheless support the concept that immunoreactive dystrophin decreases during storage.

For these reasons, the review team questioned the comparability of these two groups of patients, and I agree. Having compared samples from different muscle groups in independent groups of patients, the study was not adequate and well controlled; therefore, the validity of the comparison is uncertain. The data provide little confidence that the study was designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation” (§314.126).

Having heard arguments and opinions from both the applicant and the review team, the Advisory Committee, despite extraordinary public activism and pressure to vote favorably, voted 7 to 6 that the applicant had not provided substantial evidence from adequate and well controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit. Moreover, 2 of the Committee members who voted “yes” were patient representatives.

Correlation between the applicant’s two methods to assess dystrophin

The discussion of the Week 180 dystrophin analyses would not be complete without a comparison of the results of the two complementary methods used by the applicant. Of note, the improved immunohistochemistry analyses and Western blot analyses were performed on *the same blocks of tissue*, and one should expect a reasonable correlation between the two methods if in fact the data are reliable.

Of note, there is a striking lack of correlation between these two methods of dystrophin assessment (Figure 7). It is simply not possible to determine whether the immunohistochemistry methods are inaccurate, whether the Western blot methods are inaccurate, or whether both methods are inaccurate. My view is that it is not possible to render a positive regulatory decision on the basis of unreliable data from these 11 patients. Internal consistency is lacking.

2) Data analyzed after the PDUFA goal date

As noted above, as the May 26, 2016 goal date was approaching, OND and CDER could not reach agreement on the regulatory action for this NDA.

In order to gain additional information that might provide evidence of an effect on a surrogate marker that was reasonably likely to predict clinical benefit, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in an ongoing study (Study 301 [PROMOVI]). These samples were originally planned to be analyzed at the end of the study;

however, we requested an interim analyses of a subset of samples. As described by Drs. Rao, Farkas, and Bastings, Western blot analyses were performed on paired biceps samples from 13 of the patients. For each of these patients, samples had been obtained at baseline (prior to treatment) and at Week 48, after 48 weekly infusions of eteplirsen 30 mg/kg.

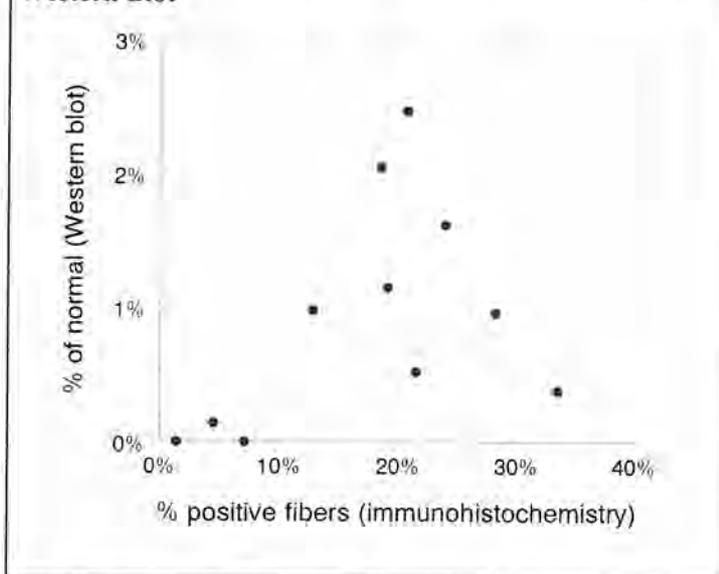
The age of these 13 patients ranged from 7 to 13 years. Paired pre- and post-treatment samples were run in side-by-side lanes on the gels, and each gel was run in duplicate. A muscle sample from a healthy 14 year-old boy with no pathologic diagnosis served as the reference sample; values from the DMD patients were reported as percent of normal.

Dr. Ashutosh Rao from the Office of Biotechnology Products reviewed the methodology and the technical reliability of the Western blot assay. Dr. Rao also conducted an inspection with Young Moon Choi, Ph.D. (Office of Study Integrity and Surveillance) and Mark Babbit (Office of Regulatory Affairs) as the analyses were being run. Xiang Ling, Ph.D., from the Office of Biostatistics, performed the statistical review on the data.

According to the protocol, acceptance of the result from each gel was contingent on two factors: 1) the R^2 value for the linearity of the standard curve of the normal control had to be > 0.9 ; and 2) the dystrophin band for the negative control DMD sample on the gel had to have a density lower than the lowest sample of the standard curve (0.25%). Samples that did not meet both criteria were deemed 'failed' and were not considered in the analyses. As it turned out, 22 of the 52 gels (42%) failed, such that many of the values represent single readings rather than the average of two. There was one patient for whom none of the values met acceptance criteria. Thus, the applicant reported pre- and post-treatment data for 12 of the 13 patients.

The applicant used 3 methods to consider values below the 0.25% lower limit of quantification: 1) consider such values to be zero; 2) analyze such values as actually reported; and 3) consider such values to be 0.24%.

Figure 7: Study 201/202 Week 180 Dystrophin Assessment – Lack of Agreement between Immunohistochemistry and Western Blot



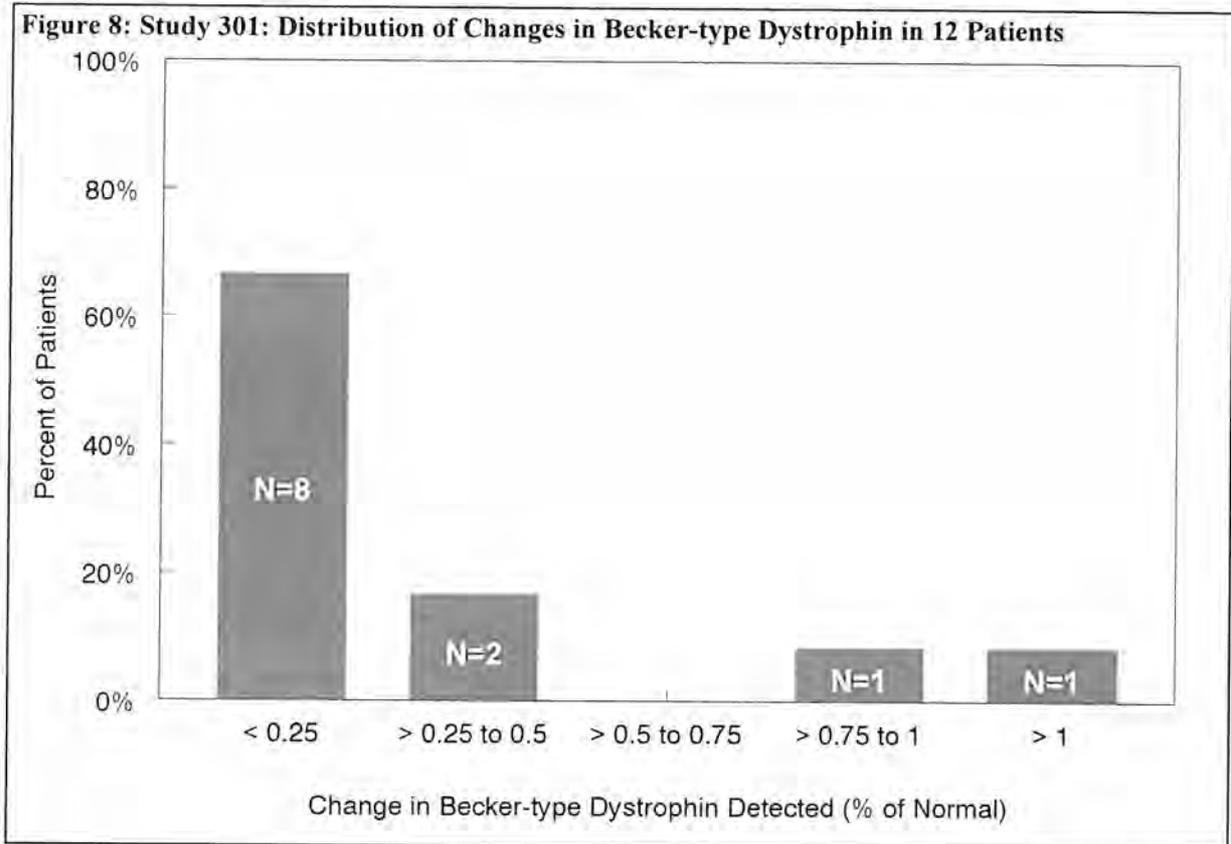
The review team believes the most appropriate analysis is the second: analysis of all values as reported, but the results were similar for all 3 methods.

Reporting values below the limit of quantification as 0, pre- and post-treatment values are 0.06% ± 0.14% and 0.38% ± 0.50%, respectively (mean ± standard deviation), $p < 0.05$. For the 'as reported' analysis, pre- and post-treatment values are 0.16% ± 0.12% and 0.44% ± 0.43%, respectively, $p < 0.05$. Reporting all values below the limit of quantification as 0.24%, pre- and post-treatment values are 0.26% ± 0.05% and 0.48% ± 0.41%, respectively, $p < 0.05$. Individual data for the 'as reported' analysis are shown in Table 5, adapted from listing 1.1 of the applicant's "Preliminary Report: Western Blot Interim Analysis of Novel Dystrophin Expression in Muscle Biopsy Samples from Week 48 of the Clinical Study 4658-301," submitted June 27, 2016.

Irrespective of the method used to express data below the limit of quantification, the mean change is similar, ranging from 0.22% to 0.32% of normal, a treatment effect of approximately 2 to 3 parts per thousand.

Patient	Time	status	value (%)	mean (%)	delta (%)	Patient	Time	status	value (%)	mean (%)	delta (%)
1	Baseline	pass	0.15	0.13	0.13	8	Baseline	fail	0.08		
		pass	0.11					fail	0.14		
	Week 48	pass	0.22	0.26			Week 48	fail	0.08		
		pass	0.29					fail	0.05		
2	Baseline	pass	0.35	0.35	0.01	9	Baseline	fail	0.14	0.24	1.33
		fail	0.26					pass	0.24		
	Week 48	pass	0.36	0.36			Week 48	fail	1.17	1.57	
		fail	0.12					pass	1.57		
3	Baseline	pass	0.06	0.06	0.31	10	Baseline	pass	0.11	0.11	0.01
		pass	0.06					fail	0.05		
	Week 48	pass	0.5	0.37			Week 48	pass	0.12	0.12	
		pass	0.24					fail	0.11		
4	Baseline	pass	0.04	0.04	0.06	11	Baseline	pass	0.01	0.05	0.43
		fail	0.06					pass	0.08		
	Week 48	pass	0.1	0.1			Week 48	pass	0.31	0.47	
		fail	0.19					pass	0.63		
5	Baseline	fail	0.1	0.17	0.85	12	Baseline	pass	0.02	0.02	0.07
		pass	0.17					fail	0		
	Week 48	fail	0.92	1.02			Week 48	pass	0.09	0.09	
		pass	1.02					fail	0.01		
6	Baseline	pass	0.37	0.37	-0.07	13	Baseline	fail	0.34	0.18	0.03
		fail	0.46					pass	0.18		
	Week 48	pass	0.3	0.3			Week 48	fail	0.34	0.21	
		fail	0.29					pass	0.21		
7	Baseline	fail	0.04	0.17	0.25						
		pass	0.17								
	Week 48	fail	0.22	0.42							
		pass	0.42								

The distribution of these changes is shown graphically in Figure 8. Of these 12 patients, 8 (two-thirds) had a change of 0.25% or less; only 1 patient (8%) had a treatment effect greater than 1%.



Commentary: Study 301 was a baseline-controlled study, where each patient served as his own control: pre- and post-treatment biopsies were obtained from the same muscle and Western blot analyses were run concurrently. An FDA inspection team observed the performance of the assays and considers the results to be reliable. Thus, unlike the data obtained from Study 201/202, the Study 301 data are considered by the review team to have been generated from an adequate and well controlled study. Study 301 provides substantial evidence of an effect of the surrogate endpoint – Becker-type dystrophin.

The critical question is whether the quantity of dystrophin produced here – a mean of 2 to 3 parts per thousand – is reasonably likely to predict clinical benefit.

With levels of Becker-type dystrophin higher in Study 201/202 (at Week 180) than in Study 301 (at Week 48), the applicant speculates that there is greater dystrophin accumulation with longer durations of treatment. These differences, however, could also be due to cross-laboratory methodological differences or play of chance; therefore, such an interpretation is highly speculative.

The Question of "Reasonably Likely to Predict Clinical Benefit"

As discussed above, the accelerated approval of eteplirsen hinges on: 1) whether Becker-type dystrophin is an appropriate surrogate endpoint for the disease; 2) whether there is substantial evidence that eteplirsen produces Becker-type dystrophin in skeletal muscle, and 3) whether such dystrophin produced is reasonably likely to predict clinical benefit, i.e., whether it is functional, and whether the quantity produced is adequate.

1. Is dystrophin an appropriate surrogate endpoint for Duchenne muscular dystrophy?

The review team believes that dystrophin is on the causal pathway of the disease, and there is no debate about the appropriateness of dystrophin as a surrogate endpoint for Duchenne muscular dystrophy.

2. Is there substantial evidence that eteplirsen produces dystrophin in skeletal muscle?

Prior to receiving the new Western blot data from Study 301 on June 27, 2016, the review team did not believe that substantial evidence from adequate and well controlled trials had been submitted to support an accelerated approval.

Study 201/202: Immunohistochemistry analyses were performed to assess and compare percent dystrophin-positive fibers at various time points before and during treatment. This is a standard technique that has been used by many laboratories for decades to assess dystrophin levels in DMD and Becker's patients. Importantly, the analysis showed no evidence of dystrophin production through 48 weeks of treatment with eteplirsen. This information is particularly germane, because, unlike the Western blot analyses from Study 201/202, the immunohistochemistry analyses are adequately controlled. The lack of a positive finding from the blinded re-read of the immunohistochemistry data with proper controls undercuts the evidence of dystrophin production from Western blot analyses.

The applicant supplemented these data with new analyses from Week 180 that purport to show a remarkable increase in dystrophin from pre-treatment levels. Unfortunately, an altered immunostaining protocol was used, and there was an inexplicable difference of more than a log between results from the new and old protocols, rendering interpretation impossible.

The Western blot data from Study 201/202 were largely externally controlled, and there were questions with respect to the proper selection of control patients, differences in the specific muscles analyzed, and concerns regarding the possible degradation of immunoreactive dystrophin in tissue samples that might occur during long-term storage and lead to a false-positive result. Importantly, ignoring the baseline data and focusing only on the Week 180 samples, there is a striking lack of correlation between the immunohistochemistry data and the Western blot data, i.e., there is no internal consistency. Thus, these data provide no basis to believe that the study was adequate and well controlled.

Study 301: The new data submitted on June 27, 2016 were obtained from an adequate and well controlled study. This baseline-controlled study shows a statistically significant increase in Becker-type dystrophin with treatment, the surrogate endpoint. Thus, there are now data showing Becker-type dystrophin production, albeit at a small level, from one adequate and well controlled trial (Study 301), with inconclusive data from Study 201/202.

The question of “reasonably likely” is, therefore, an issue of the quantity of protein produced. As noted above, Study 301 showed a treatment effect of 2 to 3 parts per thousand in Becker-type dystrophin after 48 weeks. Study 201/202, although not adequate and well controlled, nevertheless suggested a treatment effect of 8 to 9 parts per thousand after 3.5 years.

3. Is the dystrophin that was produced reasonably likely to predict clinical benefit, i.e., is it functional, and is the quantity adequate?

These two uncertainties, protein function and protein quantity, are separate issues that must be considered in series. The function of the Becker-type dystrophin detected in Study 301 cannot be assessed. Function is therefore a matter of judgment for which regulatory flexibility can be extended. The review team has been willing to assume that whatever Becker-type dystrophin is produced would function as well as in the Becker form of the disease. Although there can be no certainty on this point, the uncertainty is small relative to the uncertainty regarding the adequacy of the quantity, and so function is less germane to the question of “reasonably likely.” In short, it is the *quantity of Becker-type dystrophin produced that is central to the question of ‘reasonably likely,’ and central to the approvability of this NDA under accelerated approval.*

It must be stated that the minimum level of Becker-type dystrophin that is reasonably likely to predict clinical benefit in patients with DMD is unknown. The raw data are shown in Figure 9, but this is an area where we must consider what is known about the disease and apply medical judgment.

There are two ways to consider the quantity of Becker-type dystrophin produced: as a binary responder analysis, and as a mean response. The former has the advantage of considering the possibility that some patients may respond to the treatment whereas others do not; the latter does not allow for this type of consideration.

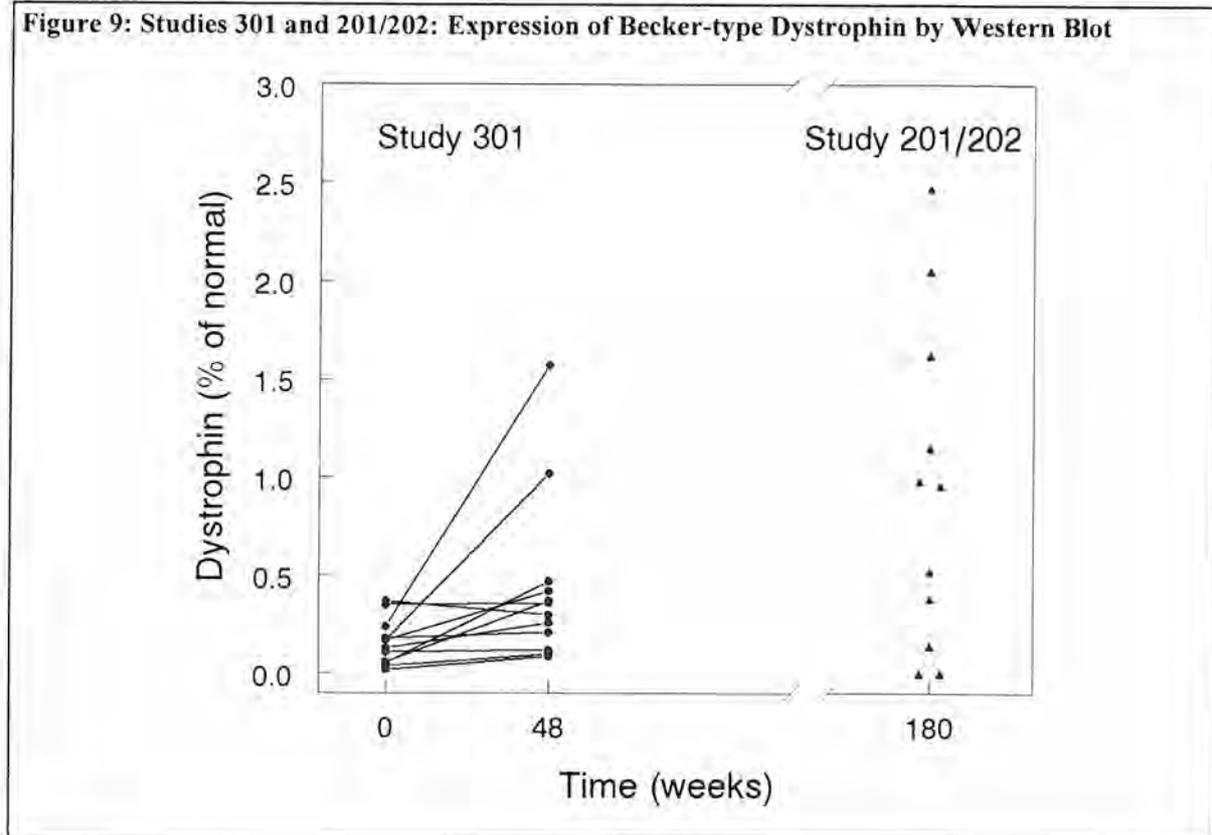
The problem with a responder analysis is that there is no rational basis upon which to define a threshold for a ‘response.’ Various cut-points could be selected, but their selection would be arbitrary, and the particular threshold chosen would have a major influence on the effect size.

Drs. Farkas and Bastings have tried to provide a framework to help put these small increases into perspective. The applicant’s data show that dystrophin levels in treatment-naïve DMD patients range from 0 to approximately 0.4% by Western blot; the applicant has not detected values > 0.4% in treatment-naïve patients.

DMD experts, including those involved with the development of eteplirsen, have stated that levels < 3% are generally associated with the typical DMD phenotype, and no patient has been found to have or produce a level of Becker-type dystrophin > 3% in response to treatment.

In order to place these small quantities of Becker-type dystrophin into a clinical perspective, many have focused on publications from a number of laboratories that attempt to relate particular levels of dystrophin protein to clinical course, e.g., maintenance of physical function, age at loss of ambulation. Some have also cited non-clinical data to relate dystrophin levels to maintenance of physical function. It is important to recognize, however, that many methodological factors affect the results of these assays, and comparison of values across various laboratories could lead to erroneous conclusions.

Figure 9: Studies 301 and 201/202: Expression of Becker-type Dystrophin by Western Blot



Van den Bergen *et al* studied the relation between dystrophin levels (quantified by Western blot) and clinical severity in 33 patients with Becker muscular dystrophy (van den Bergen JC, et al. *J Neurol Neurosurg Psychiatry* 2014;85:747). Although the authors did not find a linear relationship between dystrophin levels and disease severity, all 4 of their patients with dystrophin levels <10% showed low muscle strength and early symptom onset. As discussed by the review team, DMD experts have proposed that “induction of approximately 10% of normal dystrophin levels sets a minimum level to confer measurable clinical benefit.”

Chamberlain, who stated at the open public session at the advisory committee meeting that very low levels of dystrophin may be beneficial, discussed in a published paper (*Basic Appl Myol.* 7 [3&4]: 251, 1997) that “...a majority of fibers must accumulate approximately 20% of wild-type levels of dystrophin for a significant correction of the muscle pathology,” a view that seemingly contradicts the comments he made at the advisory committee meeting.

Anthony K *et al* (*Neurology* 2014;83:2062) compared results of Western blot analyses from 6 patients (3 with DMD; 3 with Becker Muscular Dystrophy) across 5 experienced laboratories, and found a high degree of variability. Only one of the 5 laboratories had a coefficient of variation (CV = SD/mean X 100) below 0.3%. Variability was particularly pronounced with low levels of dystrophin.

During their presentation at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Dr. Kaye, a pediatric neurologist and Interim Chief Executive Officer of Sarepta, stated:

"Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation. Furthermore, samples were randomized, blinded and run in duplicate on separate gels. In contrast, the Western blot methods in the majority of historical publications referenced by FDA were performed using older methodology that is semi-quantitative at best. Given these significant methodological differences, it is inappropriate to compare our data to literature approximations." (Source: official transcript of the meeting; underlining for emphasis.)

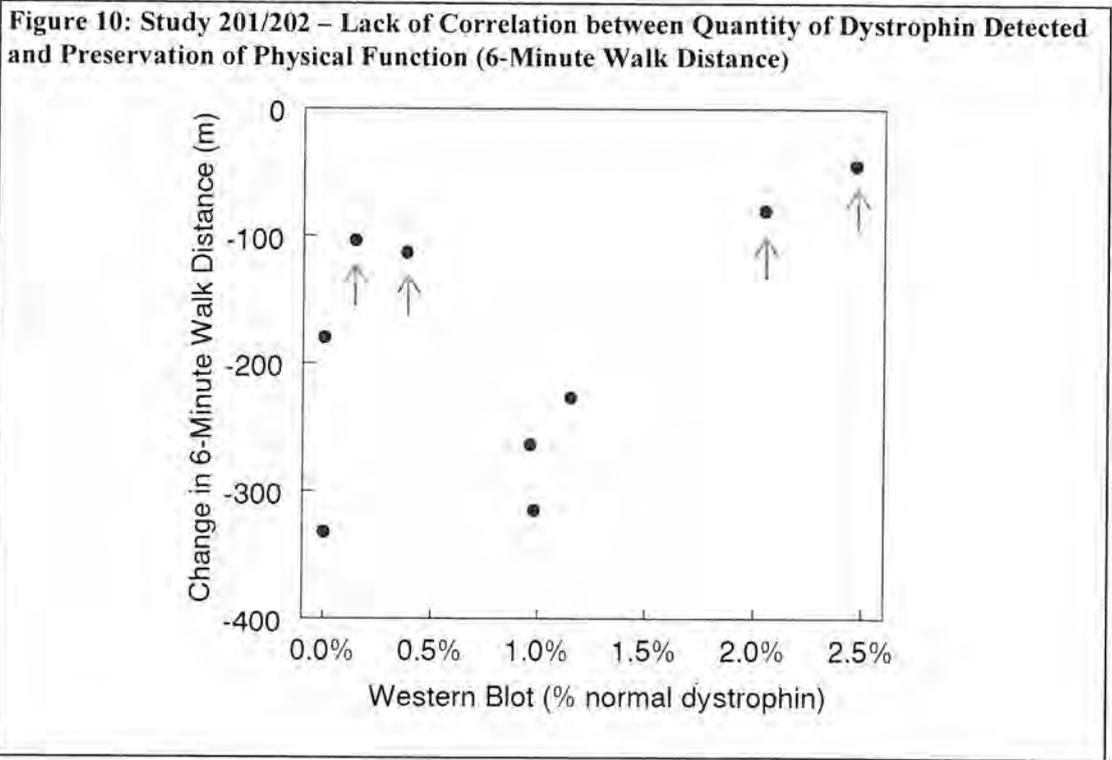
It appears, therefore, that reproducibility of assays among academic centers has not been established, such that it would not be feasible to compare an increase in Becker-type dystrophin of 0.2 to 0.3% (or even far greater increases) with dystrophin values cited in the literature for other mutations/patient populations, assessed by other laboratories.

Do the clinical data bolster the question of "reasonably likely?"

The applicant collected data on both dystrophin production and physical performance in Study 201/202. Such data have the potential to support the concept that the dystrophin level predicts clinical response, and would support the 'reasonably likely' premise. Despite detailed testimonials from patients in Study 201/202 claiming improvements in clinical performance, the Division concluded, on the basis of the data presented in the NDA, that no patient in Study 201/202 clearly deviated from the natural history of the disease. They reasoned, therefore, that whatever the quantity of Becker-type dystrophin detected, it did not predict clinical benefit. Dr. Bastings opines that the clinical data weaken, and do not strengthen, the "reasonably likely" argument.

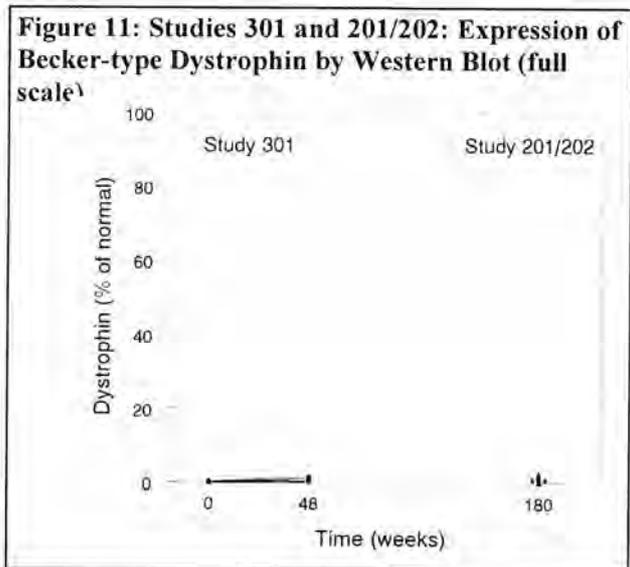
Within Study 201/202, it is also reasonable to consider the correlation between the quantity of dystrophin detected and maintenance of physical function in individual patients. The presence of a correlation would help support the "reasonably likely" question.

For the 9 patients who remained ambulatory at Week 180 and agreed to undergo a fourth muscle biopsy, Figure 10 shows little correlation between the quantity of dystrophin detected (x-axis) and preservation of physical function as assessed by the change in 6-minute walk distance from baseline (y-axis) after weekly infusions of eteplirsen for 3 to 3.5 years. For the 4 patients whose 6-minute walk performance was best preserved (red arrows), 2 had the highest dystrophin levels detected in the study, but 2 had levels that were close to zero. Importantly, therefore, these data do not show a quantitative correlation between the surrogate endpoint deemed reasonably likely to predict clinical benefit, i.e., Becker-type dystrophin levels, and the clinical benefit, i.e., maintenance of walking velocity. In Dr. Bastings' memorandum, he provides careful documentation of the trajectories of physical performance for each patient, comparing their changes in performance to the quantity of dystrophin detected. After careful consideration, he finds no correlation whatsoever.



Although it should be obvious that changes on the order of a percent or two are small, it is nevertheless worthwhile to view these data at full scale to gain perspective (Figure 11). The figure is identical to Figure 9, except for the scale on the y-axis.

If dystrophin were simply an enzyme responsible for biochemical activity in myocytes, one could posit that a very small quantity of the protein could exert a substantial treatment effect, especially because levels are so low in untreated patients. But given that dystrophin is a structural support protein that helps prevent myocyte injury from stress and strain, I find it difficult to conceive how a treatment effect of 3 parts per thousand could confer clinical benefit. If there were 10 inches of snow on a sidewalk that needed to be cleared, 3 parts per thousand would amount to 1/32nd of an inch. Finally, we must recognize receiving a treatment that increases dystrophin by 0.3% is not that same as being born with 0.3% more dystrophin.



3. Dose-response

Although the issue is somewhat peripheral to the “reasonably likely” question, the presence of a dose-response in Study 201/202 would have provided supportive evidence that the dystrophin that was detected was produced by eteplirsen. A dose-response was not evident, although one could reasonably argue that the trial was very small and that the difference between 30 and 50 mg/kg/week was unimportant.

In a monkey study conducted to assess the pharmacodynamic effects of eteplirsen, a 1-log increase in dose (from 4 to 40 mg/kg) caused minimal increase in exon 51 splicing as detected by PCR (Section 4, Table 1). However, with a 2-log increase in dose (from 4 to 320 mg/kg), there was a log increase in exon 51 splicing. As noted in Section 4 of this memorandum, it is possible that much higher doses of eteplirsen could have a substantially greater effect, which might translate to clinical benefit.

Advisory Committee

The Advisory Committee was asked to discuss: a) the strength of evidence that eteplirsen increased the amount of dystrophin in muscles of treated patients relative to their baseline, and b) the clinical meaning of the amount of dystrophin observed in the muscles of eteplirsen-treated patients, taking into consideration the range of amounts of dystrophin known to be typically present in patients with DMD and in patients with Becker muscular dystrophy. (Of note, the data from Study 301 were not known/available to the Advisory Committee.)

Although the Committee failed to reach consensus on these questions, the discussion, summarized below, is of interest.

With respect to production of dystrophin, about half of the committee members found evidence that eteplirsen increased the amount of dystrophin produced in skeletal muscles. Among those who were not convinced, two members cited issues with the controls (lack of pre- and post-treatment biopsies in the same patients; differences in muscle groups biopsied), two had concerns about inconsistencies between dystrophin levels and clinical response (Figure 10), and one cited concerns about the lack of a dose-response (Table 3).

Only four Committee members had explicit comments with respect to the clinical meaningfulness of the amount of dystrophin detected in treated patients, and their opinions were split. One member opined that the amount of dystrophin needed to impart clinical benefit is unknown, but could be very low, or very low in a subset of patients. One of the patient representatives felt strongly that dystrophin was produced, and that the amount was sufficient to produce clinical benefit. One committee member, having opined that some dystrophin was produced, stated that there is no basis to determine the quantity of dystrophin that would be clinically significant, or whether the dystrophin is functionally active. Another committee member, one who had not opined on whether dystrophin was produced, noted that whatever the amount of dystrophin produced in the study, the amount was not clinically meaningful, based on the lack of correlation between dystrophin levels and clinical results (Figure 10).

The Committee voted on whether the applicant had provided substantial evidence from adequate and well controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit.

Ultimately, 7 members voted “no” and 6 voted “yes,” after one member changed his vote from “no” to “yes.” In explaining their “no” votes, 5 committee members opined that the studies were not adequate and well controlled; they questioned the techniques used to measure dystrophin as well as the appropriateness of the controls. Four committee members expressed concern about the lack of correlation between the dystrophin levels and clinical measures. They agreed that even if some dystrophin was produced, there was no evidence that dystrophin production was at a level that would be reasonably likely to predict clinical benefit. The 6 “Yes” votes included the consumer representative and 2 patient representatives. These individuals believed that there was some difference in dystrophin production and some evidence of improvement in endpoints. One of the members who voted “Yes” stated that he was very troubled by not understanding what constitutes a clinically significant amount, but was impressed by the patients’ observations. Two members who voted “No” stated that their vote was justified by the way the question was phrased, but that the patient testimonies suggested the drug works.

Is There a Basis for a Conventional Approval Based on Clinical Data?

The clinical data have been well described by the review team. The development program consisted of one trial (Study 201/202) with a relatively short (24-week) placebo-controlled portion (Study 201) followed by a long-term extension study (Study 202). Although the applicant submitted biopsy data from the ongoing Study 301, no clinical data have been submitted from that study.

As noted above, for Study 201, patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (n=4 per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2) and followed for 4 additional weeks. The trial was extended to an open-label phase (Study 202), where all 12 patients continued to receive eteplirsen without interruption, although investigators and patients remained blinded to dose.

The 1^o endpoint of Study 201 was the percentage of dystrophin-positive fibers in muscle biopsies as assessed using immunohistochemistry, but there were numerous exploratory endpoints.

When the data from Study 201 were originally analyzed, the applicant found that eteplirsen caused a striking and unprecedented increase in dystrophin production, based on the reading of the immunohistochemistry data at Nationwide Children’s Hospital, with supportive data from Western blot analyses.

The clinical data, too, were interpreted as positive. As discussed by the review team, 2 patients in the 30 mg/kg/week treatment group became unable to ambulate soon after the trial began, and there were no significant differences in 6-minute walk distance among the groups. Despite clearly negative results, the applicant performed a *post hoc* analysis that omitted the 2 patients in the eteplirsen group who became unable to ambulate. They represented these results as positive, and publically promoted both the immunohistochemical dystrophin results and the 6-minute walk data as positive (see clinical review).

Although FDA would later determine that the analyses underlying these data were not valid, the publicity from the paper² and Sarepta’s press release³ raised unrealistic expectations of efficacy

in the DMD community. It was these perceptions that led the applicant to conclude that a second placebo-controlled study would not be feasible.

FDA strongly suggested a second, larger, adequately-powered, placebo-controlled trial, but the applicant was reluctant to run such a trial, in part because their supply of drug was limited, and in part because of their insistence that the DMD community would not agree to participate in a trial where there was a chance of receiving placebo. Faced with the applicant's unwillingness to conduct a second placebo-controlled trial, FDA agreed to an externally-controlled trial: a comparison between patients in the ongoing Study 202 and patients in an external control group. The Division expressed strong concern, however, with respect to the interpretability of such a trial with 6-minute walk distance as the endpoint, given that physical performance is not a "hard" endpoint, but can be influenced by motivation and other factors. Citing FDA Guidance,⁵ the Division noted that the treatment effect would have to be dramatic for the results from an externally-controlled study to be interpretable. Details of the interactions between FDA and Sarepta are well documented by the review team.

International guidelines, adopted by the FDA as guidance, stress caution with respect to the interpretation of data from externally-controlled trials. As noted in the International Conference on Harmonization (ICH) E10 Guideline,⁵ blinding and randomization, used to decrease bias in randomized controlled trials, are not utilized in externally-controlled trials; the inability to control bias is a critical limitation of externally controlled trials. Groups can be dissimilar with respect to a wide variety of factors that could influence outcome – factors that are both known and measurable as well as factors that are unknown. As explained by Dr. Robert Temple at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, it has been well documented that untreated historical-control groups tend to have worse outcomes than apparently similarly chosen control groups of randomized studies, possibly reflecting a selection bias.

The ICH E10 Guideline explains: "A consequence of the recognized inability to control bias is that the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than would be considered necessary in concurrently controlled trials. The inability to control bias restricts use of the external control design to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable. In addition, use of external controls should be limited to cases in which the endpoints are objective and the impact of baseline and treatment variables on the endpoint is well characterized." In essence, in order to be interpretable, the finding of a difference between groups should be large – so large that the difference is patently obvious without the need to rely on inferential statistics.

Having heard FDA's concerns regarding the potential difficulty in interpreting an externally-controlled trial, the applicant nevertheless obtained access to individual data from patients with DMD from Professor Eugenio Mercuri at the Catholic University in Rome on behalf of the Italian DMD Registry database (n=97) and from Professor Nathalie Goemans at the University Hospitals in Leuven (n=89). From these 186 patients, 50 had a genotype amenable to exon skipping therapy, were using corticosteroids at baseline, had 6-minute walk data available at baseline, and were ≥ 7 years old. Among these 50 patients, 13 had a genotype amenable to

⁵ Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials, May 2001

exon 51 skipping therapy. I will note that the review team has been unable to gain an understanding of how dates of inception were determined for registry patients, i.e., when patients were considered to have 'enrolled.'

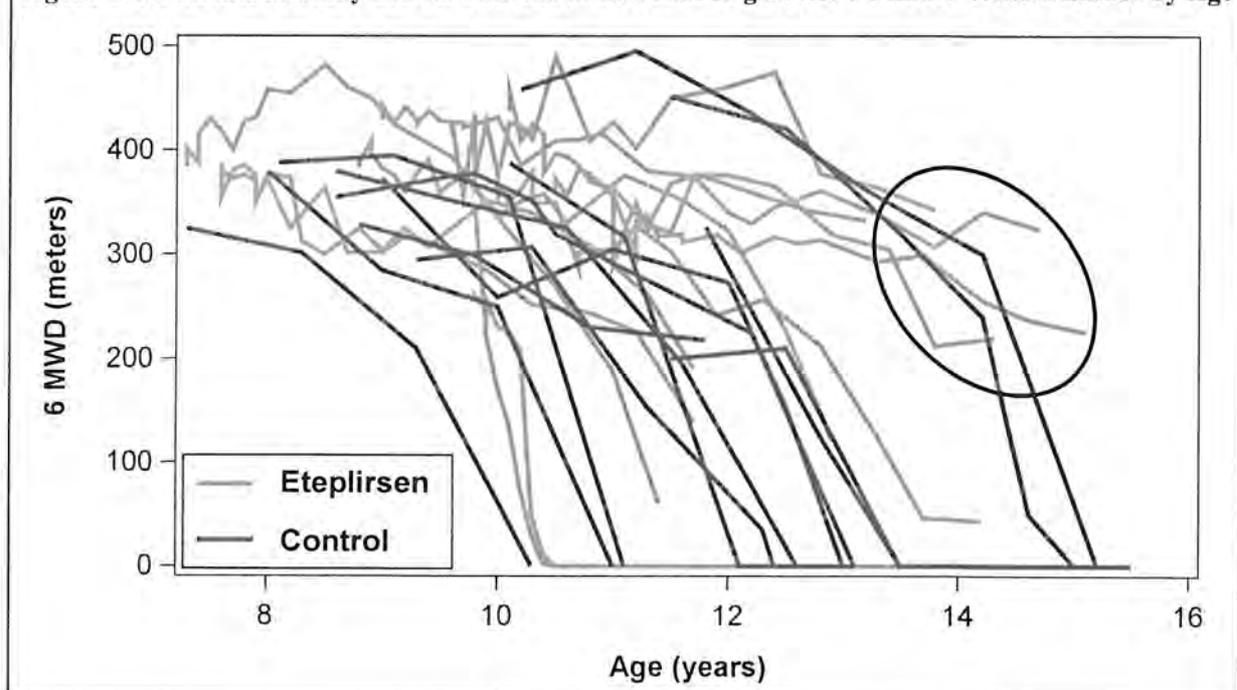
Study 202 was continued, therefore, with patients continuing to receive either 30 or 50 mg/kg/week eteplirsen. Numerous comparisons of physical function were planned between these 12 patients and the 13 patients in the external control group. Measures included 6-minute walk, rise time, timed 10-meter run, and North Star Ambulatory Assessment (NSAA).

With two small groups of patients, there was no way to match patient pairs. Fortunately, the mean ages and 6-minute walk distances were well matched at baseline, although the review team found that initial age of steroid use and baseline NSAA scores were dissimilar between groups – and both of these differences favored the eteplirsen group.

It is clear that some patients exited the registry to enroll in clinical trials. Thus, DMD patients who remained in the Italian and Belgian registries (the control group): 1) did not seek knowledge (or lacked knowledge) regarding applicable clinical trials into which they might have enrolled; 2) sought enrollment in trials but did not qualify; or 3) qualified for enrollment in a trial(s) but made a conscious decision not to participate. Obviously, such patients could differ substantially from patients in Study 201/202. The point is that there can be unknown factors beyond baseline age, weight, length of steroid use, and 6-minute walk distance that importantly affect outcomes.

The applicant presented the data by time-on-treatment, but because physical abilities change significantly with age in patients with DMD, the review team believes that the more meaningful way to display the longitudinal 6-minute walk data is by age (recognizing that both analyses have advantages and limitations, and that there is no ideal way to present these data). The 6-minute walk data are shown in Figure 12 as a function of age. The review team stresses that,

Figure 12: Patients in Study 202 vs. Patients in External Registries: 6-Minute Walk Distance by Age



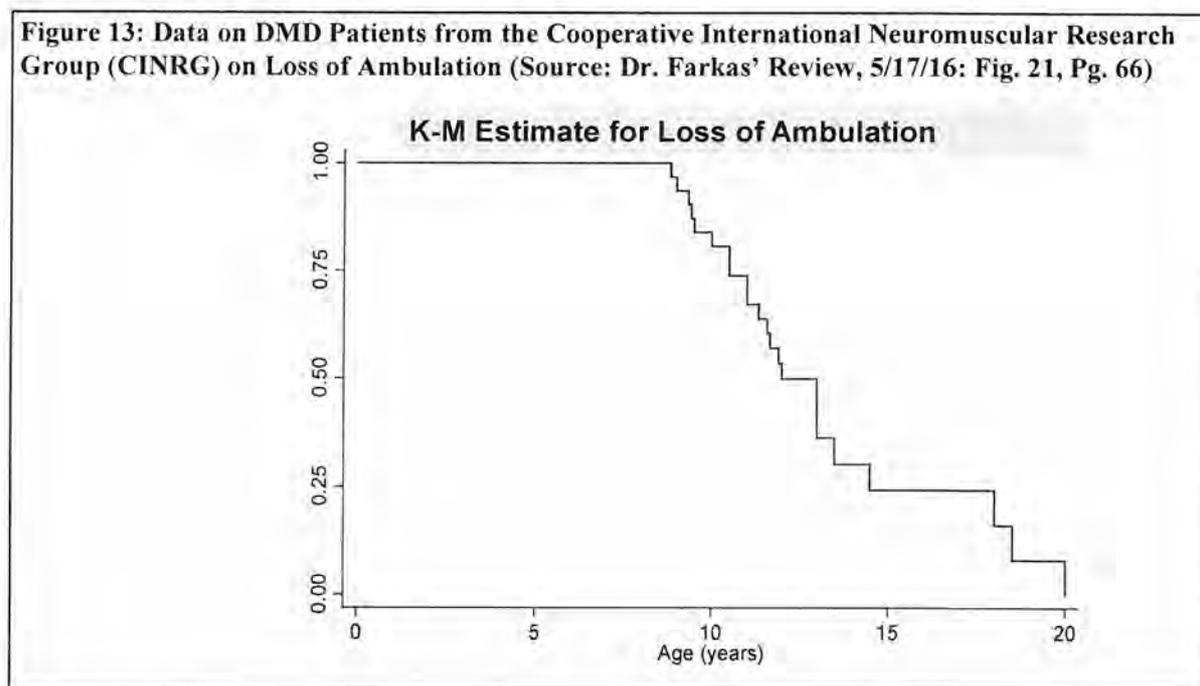
by simple visual inspection, the two groups show little difference in performance.

There are 4 patients in the eteplirsen group, ~14 to 15 years of age, who continue to retain good walking ability (inside the oval). There are 2 control patients in this age range who had been maintaining similar walking ability, but appear to have experienced a precipitous loss of ambulation between ages 14 and 15. As explained by the review team, there are concerns regarding the comparability of the assessments of these patients, and concerns about comparability of the groups in general.

The applicant's argument for accelerated approval is based on this comparison of 6-minute walk distance between the patients in Study 202 and the patients in the external control group from Italy and Belgium. The difference in 6-minute walk distance is certainly statistically significant. The problem is that the study was externally-controlled, and the statistical test was based on a non-randomized comparison.

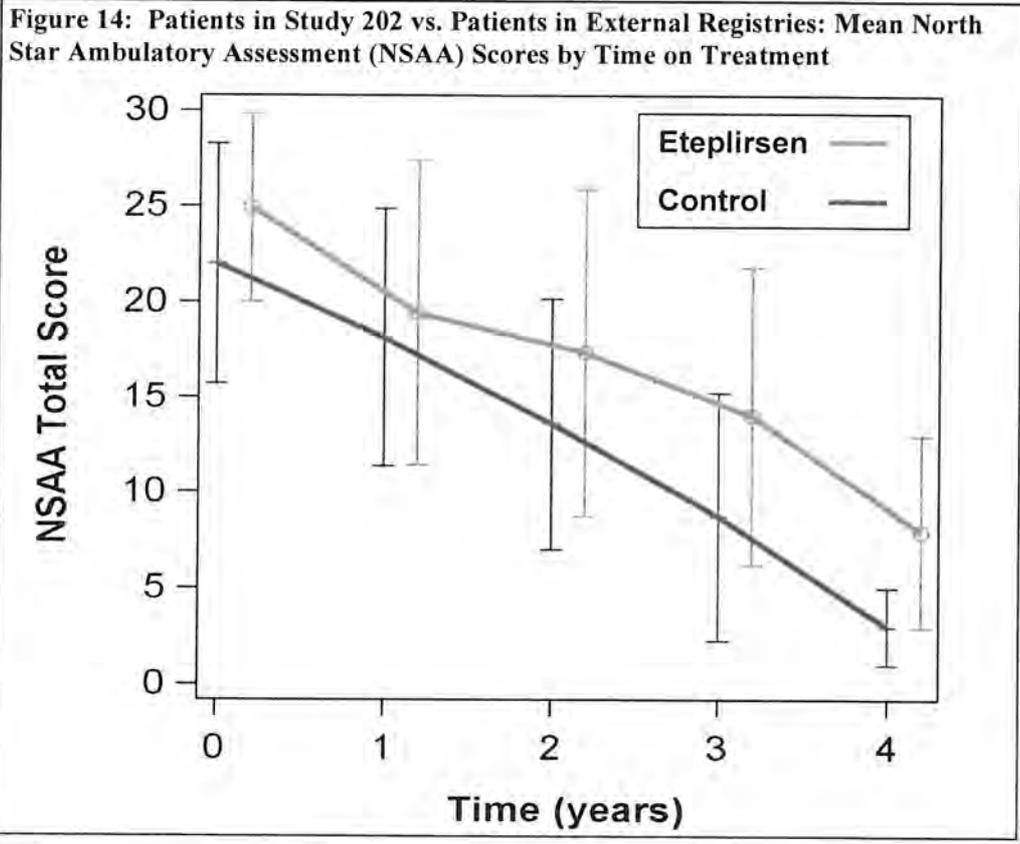
Data from the Cooperative International Neuromuscular Research Group (CINRG) provide an additional source of information on the natural history of patients with DMD. Figure 13 is a Kaplan-Meier (K-M) survival curve from CINRG showing time-to-loss of ambulation. Of note, 25% of patients remain ambulatory at age 17; their course seems quite consistent with that of patients from Study 201/202.

Figure 13: Data on DMD Patients from the Cooperative International Neuromuscular Research Group (CINRG) on Loss of Ambulation (Source: Dr. Farkas' Review, 5/17/16: Fig. 21, Pg. 66)



In summary, the review team strongly believes that patients on eteplirsen in Study 201/202 do not demonstrate a substantial treatment effect on walking velocity that clearly differentiates their course from the natural history of the disease. For a more complete description with comprehensive patient profiles, see the reviews of Drs. Breder and Farkas and the memo of Dr. Bastings.

Finally, as stressed by the review team, the data from other measures of physical function, i.e., rise time, timed 10-meter run, and North Star Ambulatory Assessment (NSAA), show steady decline in the eteplirsen-treated patients that does not differ substantially from the decline in the external control group. The NSAA data are shown in Figure 14 by time on treatment (eteplirsen patients) or time since inception (registry patients). The NSAA is thought to be a comprehensive outcome measure, well reflecting the functional abilities of DMD patients. Of note, the downward trajectories of the two groups are indistinguishable (the lines are virtually parallel with equal slopes).



Patient Testimony/Advisory Committee:

In addition to the presentations made by the applicant and the review team at the April 25, 2016, Advisory Committee Meeting, there were testimonies from over 50 individuals and families, including most of the patients who were participating in Study 202. (Per email communication from Frank Sasinowski, one of the applicant's consultants, 10 of the 12 patients testified and another patient had someone speak on his behalf.)

In addition, the applicant invited Christine McSherry, Executive Director of the Jett Foundation, to present "Patient and Caregiver Reported Outcomes of Patients in Clinical Trials of Eteplirsen for Treatment of Duchenne."

The testimonies of these patients were quite consistent and remarkably positive: all were convinced that eteplirsen had made a substantial positive impact on their physical performance, improving numerous aspects of their lives.

It was noteworthy that a number of individuals who were in Study 201/202 reported *improvement* in physical function with eteplirsen treatment. For example, one patient stated that he had required a wheelchair at a school he had attended in the past, whereas he no longer needed a wheelchair at his present school. A video showed a boy who, prior to treatment, had some difficulty climbing up into the seat of a minivan. After receiving eteplirsen for several months, he was shown jumping up easily into the seat. In another video, a boy in the study threw a football, a tight spiral, with ease and finesse.

Many of the Committee members seemed obviously moved and deeply affected by these testimonies and videos, seemingly convinced that there was a treatment effect.

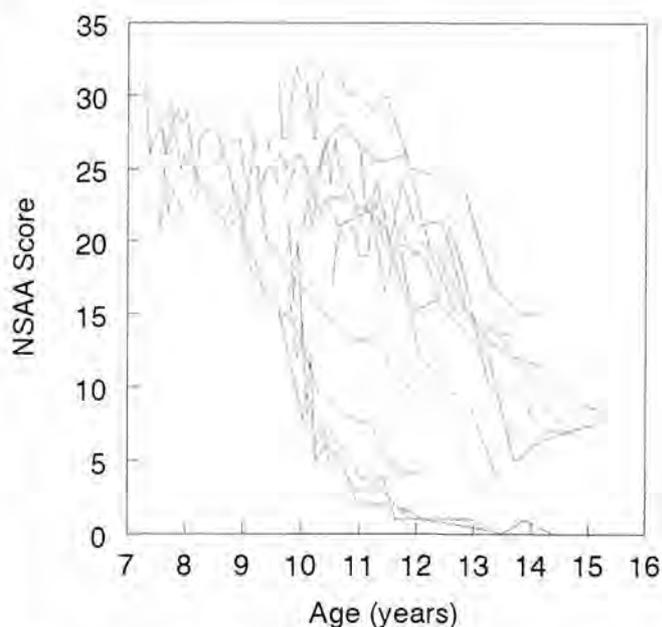
Importantly however, despite the claims of improvement made at the microphone at the Advisory Committee meeting, the review team did not find any patients in Study 201/202 with consistent improvement in physical performance as assessed by formal testing (6-minute walk, rise time, NSAA, 10-meter run). These tests have shown moderate to extreme declines in physical function for all patients (see NSAA data, Figure 15).

Thus, the review team and many on the Advisory Committee (including Benjamin Dupree, the patient representative with DMD), were unable to reconcile the patient testimonies with the data collected by the applicant: the testimonies spoke of *improvement*; the data showed *progressive worsening*.

The Advisory Committee voted (7 to 3 with 3 abstentions) that the clinical results of Study 201/202 did not provide substantial evidence that eteplirsen is effective for the treatment of DMD.

The 7-member majority of the committee who voted "no" agreed that Study 201/202 was not a well-controlled study. Most cited problems with the controls. One member explained that a historically-controlled study *could* provide evidence of effectiveness, but that Study 202 did not. Two committee members noted that the original placebo-controlled portion of the study was

Figure 15: Study 201/202 – Individual NSAA Performance by Age



negative. One member who cited issues with the controls also noted that a single trial would be insufficient to provide substantial evidence.

The 3 members who voted that there was substantial evidence of effectiveness explained that the study results correlated with the testimonies presented by the public.

Commentary:

I agree with the Division, the Office of Biometrics, the Office of Clinical Pharmacology, and the Advisory Committee with respect to the lack of substantial evidence of effectiveness for eteplirsen. The review team elaborates on many factors that differ, or could differ, between the treatment groups – factors that could lead to a difference in outcomes. Externally-controlled trials are best-suited for diseases where progression is highly predictable and treatment effects are extreme. Although there appeared to be a difference in ambulation between patients in Study 202 and patients in the external control group, the effect size was not sufficient to be persuasive, given the inability to control bias in an externally-controlled study. As explained in ICH E10, "...the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than would be considered necessary in concurrently controlled trials." With only 12 patients in the trial and a moderate difference in walking velocity, the study falls short.

Finally, it is critical to note that no dose-limiting side effects were observed at either dose tested in Study 201/202, and even the most optimistic interpretation of the data is that patients experienced gradual decline in function – not stabilization. Even if one were to reach the conclusion that the applicant showed substantial evidence of dystrophin production, deserving of accelerated approval, investigation of higher doses would be imperative.

8. Safety

As explained in the clinical review, the number of subjects exposed was too small to provide an adequate assessment of safety. On the other hand, I also agree with the review team that the deficiencies in safety assessments would not likely be an issue for approvability in their own right had the drug been demonstrated to be effective. In other words, for a therapy that is shown to be effective in a serious condition where there are no approved drugs, we would approve a marketing application even with substantial risks, as long as we could write adequate instructions for use. Moreover, we would not delay approval of a marketing application because of uncertainty of risks. Instead, we would work with the applicant to obtain more extensive safety data post-approval. Such would be the case for this application if there were substantial evidence of effectiveness.

Of note, many patients in these studies are now receiving infusions through chronic indwelling catheters. Although we are not aware of any serious adverse events cause by infections, with approval of this drug there would undoubtedly be serious infections and possibly rare deaths eventually. The risk of an indwelling IV line in patients on chronic corticosteroids should be mentioned in labeling if the drug is approved.

Although neither immunogenicity nor allergic reactions have been reported with eteplirsen, immunogenicity testing would be advisable in ongoing trials. Moreover, given that these

patients may be naïve to Becker-type dystrophin, the potential for anti-dystrophin antibodies should be studied as well.

9. Advisory Committee Meeting

There were many important discussions at the April 25, 2016 Advisory Committee Meeting, and they are summarized above, in context.

10. Pediatrics

Duchenne Muscular Dystrophy is an orphan indication, not subject to the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

Site Inspections:

The site at Nationwide Children's Hospital was inspected in 2014. See description and conclusions in Section 7, above, and, in particular, the summation and discussion in Dr. Breder's review.

Dr. Ashutosh Rao conducted an inspection with Young Moon Choi, Ph.D. (Office of Study Integrity and Surveillance) and Mark Babbit (Office of Regulatory Affairs) of the facilities at University of Iowa in Iowa City, IA and Sarepta Therapeutics Inc. in Corvallis, OR. The inspections confirmed that the blinding procedure, handling of the sample shipment, and the conduct of Western blot analyses of the samples from Study 301 (PROMOVI) were consistent as predefined in the protocol.

Name Review:

The Division of Medication Error Prevention and Analysis concluded that the proposed proprietary name, "EXONDYS 51," is acceptable from both a promotional and safety perspective.

12. Labeling

I do not recommend approval, but if the drug were to be approved, the label would need to state that no clinical benefit has been established, and explain the effect on the surrogate endpoint in clearly understandable language (i.e., 0.3% or 3 parts in a thousand). Section 6 would need to note that safety is not well characterized.

13. Decision/Action

DMD is a rare genetic disease characterized by the near absence of functional dystrophin protein, leading inexorably to myocyte degeneration, muscle dysfunction and inflammation, severe disability, and death, robbing patients of their dignity along the way. Although steroids are thought to slow the course of the disease and are typically considered standard of care, they are by no means curative, and they have their own side effects.

The cause of DMD is well established – the absence of structural dystrophin protein in myocytes. There is wide belief in the medical/scientific community that restoration of functional dystrophin protein has a strong potential to ameliorate the disease.

Eteplirsen is a novel PMO that is designed to lead to translation of an abnormal but functional dystrophin protein – a protein that is produced in Becker muscular dystrophy, a far less severe form of muscular dystrophy. The data from RT-PCR show that the drug produces the intended Becker-type messenger RNA; we have no data on the extent of messenger RNA production.

As noted by the review team, the clinical data generated from study 201/202 do not provide evidence of efficacy. The aim of Study 201, the only randomized placebo-controlled study conducted by the applicant, was to assess dystrophin production in response to lower and higher eteplirsen regimens (30 or 50 mg/kg/week) vs. placebo. Results of the original analyses of Study 201, published in a major journal, were remarkably positive, and their publication led to widespread enthusiasm for the drug. Unfortunately, an FDA inspection found a number of important technical factors that rendered the data unreliable and uninterpretable: the Western blot analyses were sub-standard; there were also critical problems with the reading of the immunohistochemistry images. FDA recommended a blinded re-read of the images, but upon re-read of the images by 3 blinded pathologists using FDA-recommended procedures, there was no increase in dystrophin production.

Likewise, Study 201 did not meet its 1^o clinical endpoint, 6MWT, at Week 24. Two patients in the low-dose eteplirsen group became unable to ambulate early in the study, such that a proper intent-to-treat analysis of the 6-minute walk data nearly showed a statistically significant difference in favor of *placebo*.

The applicant switched all patients to active drug in Study 202, and has continued to follow the patients for 6-minute walk distance, NSAA, and rise time.

Study 202 did not meet its 1^o clinical endpoint, 6MWT, at 48 weeks.

The alternative analyses of Study 202 proposed by the applicant are based on comparison to an external control group obtained from registry patients in Italy and Belgium. Questions about comparability notwithstanding, analyses have not shown a clear separation of the disease course between eteplirsen-treated patients and external controls. Moreover, there is not a clear separation between eteplirsen-treated patients and patients in the CINRG registry. Thus, neither external control group suggests there is a treatment effect.

The Western blot analyses from Week 180 of Study 201/202 showed a low quantity (0.9%) of dystrophin; however, the study was not adequate and well controlled (the baseline level of dystrophin was not known with certainty), and the lack of correlation between results of Western blot and immunohistochemistry demonstrates a troubling lack of internal consistency.

Study 301, on the other hand, was an adequate and well-controlled study that provided substantial evidence of Becker-type dystrophin production in response to eteplirsen. The mean change in Becker-type dystrophin with treatment was 0.22% to 0.32%, depending on the method used to impute values less than the lower limit of quantification. Although all members of the review team believe that Becker-type dystrophin is an appropriate surrogate endpoint, the mean quantity of dystrophin produced in Study 301 was minute by any standard. In considering

responders, even the largest responder in Study 301 produced only 1.33% of normal dystrophin, which is thought by many authorities to be insufficient. No other patient produced 1% dystrophin in response to treatment.

Recognizing that the threshold for the effect size needed to be 'reasonably likely' to predict clinical benefit is not known, the view provided in the literature suggests that at least 3% of normal dystrophin is inadequate, and levels perhaps much more, a minimum of 10%, would be necessary for detectable clinical benefit. The finding in Study 301, an increase in the range of 0.22 to 0.32% of normal, is an order of magnitude below this level.

The unprecedented finding of an increase in dystrophin protein in response to eteplirsen establishes proof-of-concept and provides great promise that this drug, or other therapies, will be capable of ameliorating the fundamental genetic defect of DMD, but the effect size seems insufficient at the tested doses.

Various individuals have opined that there appears to be some evidence that some patients are producing dystrophin in response to eteplirsen; however, such optimism fails to reach the legal threshold of 'reasonably likely to predict clinical benefit' required for accelerated approval.

Accelerated approval of this NDA based primarily on the change in Becker-type dystrophin in Study 301 would be problematic for these reasons:

1. The amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin. In other words, if a statistically significant change of 0.22% is considered adequate to support accelerated approval, then the question arises as to whether there is any statistically significant change that would be too small to support accelerated approval. Similarly, if a response had been defined as a treatment effect of 1%, there would have been only one (out of 12) responders in Study 301.

If we were to adopt the concept that, for rare diseases, accelerated approval can be supported by any statistically significant change in an appropriate surrogate (or by a response in a single patient), we would enable accelerated approval of numerous drugs for rare diseases. No doubt there are some who would applaud this as a regulatory advance, but these are typically the kinds of findings that support Breakthrough Designation, not approval. If accelerated approval based on any change in a surrogate endpoint is what is meant by regulatory flexibility and this is the new normal, a new approval pathway is clearly needed.

With lowering of the standard for accelerated approval, the result would be a world where traditional clinical trials are abandoned in favor of small proof-of-concept studies designed to show any level of production of a target protein – e.g., a statistically significant effect in a paired pre- vs. post-treatment analysis that is clinically meaningless. There would be no reason to pursue placebo-controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of failure would provide a substantial disincentive to the conduct of such trials. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.

2. Even if the 30 mg/kg/week dose were considered to have a meaningful effect on the surrogate endpoint, the dose is sub-therapeutic. Moreover, the short 3.5-hour half-life of eteplirsen by no means supports a weekly dosing regimen. I question the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic.

Imagine that 100 years ago a promising drug called penicillin is discovered – a potential cure for pneumococcal pneumonia – but the drug is difficult to produce and expensive. A dose of 5 mg weekly has been shown to have statistically significant bactericidal effects on *Streptococcus pneumoniae*. Would it be ethical to give the drug accelerated approval based on this finding and allow marketing of a dose of 5 mg, absent additional information? (The therapeutic dose is ~2 logs higher than 5 mg.) Patients who might receive a lifesaving therapy (i.e., a higher dose) would die because the dose is too low.

Despite considerable pressure from the DMD patient community and many well-intentioned members of the public who have lobbied on their behalf, I am unable to reach the conclusion that the applicant has provided substantial evidence to support either conventional or accelerated approval of eteplirsen for the treatment of DMD. This view is in agreement with the unanimous opinions of members of the review team from the Division of Neurology Products, the clinical pharmacology review team, and the biostatistics review team. The Advisory Committee was under intense and near-incessant pressure from a large public audience, urging them to believe that eteplirsen was effective, and life changing in some circumstances. Emotions in the room ran high. In spite of this pressure, that majority of the Advisory Committee voted against both conventional and accelerated approval.

In a June 3, 2016 letter from Dr. Janet Woodcock, the applicant was advised that “If you are successful in showing, to FDA’s satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval...” It is difficult to consider production of 2 to 3 parts per thousand as a “meaningful” change. To put this effect into perspective, if a normal amount of dystrophin were equivalent to a \$5 bill, this change would be equivalent to a penny.

With all of this information at hand, most sponsors would have concluded that exploration of higher doses was needed; however, this applicant chose instead to trumpet the preliminary findings from their 12-patient phase 1/2 study, convincing many in the DMD community that the drug was highly effective, and unleashing a public media campaign (with support of many politicians) to approve the drug. The reality is that FDA is a science-based organization. We do not – and should not – make approval decisions based on patient anecdotes or campaigns through social media.

I strongly agree with the decisions of Dr. Bastings, reviewer staff in the Division, the Office of Biometrics, and the Office of Clinical Pharmacology to issue a complete response for this NDA. I also agree that it would be desirable to provide access to this drug for DMD patients through expanded access programs, with cost recovery, while an adequate dose-finding study is conducted.

Path Forward:

Based on the quantity of Becker-type dystrophin produced in Study 301 and the clinical findings in Study 201/202, additional studies at this dose are unlikely to support any type of approval, i.e., the data obtained for eteplirsen at a dose of 30 and 50 mg/kg/week are adequate, but they do not support efficacy.

We remain comfortable with the concept that substantial evidence of dystrophin production from adequate and well controlled trials could support accelerated approval, but it is clear that higher doses are needed, and greater quantities of dystrophin would need to be produced. The path to a conventional approval would require a double-blind, placebo-controlled (or multi-dose) study, at least one year in duration, using some measure of physical performance as the 1° endpoint, again, testing higher doses.

The applicant is continuing to enroll the PROMOVI study, an open-label, multi-center, 48-week study in patients with DMD amenable to skipping exon 51. All patients are receiving eteplirsen, 30 mg/kg/week as an IV infusion.

The 1° endpoint is change in 6-minute walk test distance from baseline. A 2° endpoint is the percentage of dystrophin-positive fibers, as assessed by immunohistochemistry. Patients undergo muscle biopsies at baseline and various time points to assess dystrophin production.

My suggestion for a path to approval is to randomize patients in the ongoing PROMOVI study to:

- 1) remain on 30 mg/kg/week; or
- 2) have their dose significantly increased. This could be done through use of a higher dose, through more frequent dosing intervals (with dummy infusions), or both. Given that many patients receive eteplirsen through indwelling IV lines and no significant infusion reactions have occurred, perhaps these infusions could be performed at home. For example, the study could compare 30 mg/kg weekly to 30 mg/kg daily. Patients who do not tolerate more frequent dosing could have their doses decreased, as needed. Based on non-clinical findings, monitoring would need to be in place to assess renal toxicity.

Patients and investigators would be blind to treatment group. For accelerated approval, the 1° endpoint would be dystrophin production, comparing the higher and lower doses. For standard approval, the 1° endpoint would be a test(s) of physical performance such as rise time or the NSAA.

Such a trial would be methodologically sound and ethical. Virtually everyone, patients and physicians alike, want to know if higher eteplirsen doses would increase dystrophin production, and would have equipoise for participation. Although there is concern regarding performance of muscle biopsies in patients assigned to placebo, this concern would not exist in this study. And if the applicant were to forego immunohistochemistry studies, needle biopsies with local anesthesia (rather than open biopsies under more intensive anesthesia) would be sufficient.

This study design would simultaneously address another concern that I believe has been underappreciated by many. As noted above, it would be problematic in my view to approve a dose of 30 mg/kg/week, presumably leading to a dystrophin increase of ~0.3%, when it is

known that this dose fails to prevent the decline in physical function and yet produces no overt toxicity. The monkey data (Table 1) suggest that much higher doses might have a far greater effect on exon skipping, an impact that might prevent disease progression. Thus, it seems imperative to study higher exposures.

14. Final

Many of us would wish to approve this drug if we could. DMD is a horrible disease and there are no approved treatments. FDA takes seriously the patient perspective and our congressional mandate to be flexible. But patient-focused drug development is about listening to patient perspectives about what matters to them; it is not about basing drug approvals on anecdotal testimony that is not corroborated by data.

FDA is charged with the responsibility of ensuring that drugs are shown to be effective prior to marketing, based on substantial evidence. If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients, in essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope. If we were to turn the clock back to the days prior to the 1962 Kefauver Harris Amendments to the Federal Food, Drug, and Cosmetic Act, the damage to society and the field of evidentiary medicine would be enormous.

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/s/

ELLIS F UNGER
07/16/2016

**FDA STAFF MANUAL GUIDES, VOLUME IV - AGENCY PROGRAM
DIRECTIVES**

GENERAL OR MULTIDISCIPLINE

DISPUTE RESOLUTION

SCIENTIFIC DISPUTE RESOLUTION AT FDA

Effective Date: 01/13/2009

1. Purpose
2. Background
3. Scope and Policy
4. Definitions
5. Responsibilities
6. Procedures
7. Effective Date
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1. PURPOSE

As part of the ongoing effort to improve the process of internal scientific dispute resolution, and to encourage open communication throughout the agency, this document describes how issues of scientific dispute are managed throughout FDA.

This document sets forth mandatory elements to be included in all scientific dispute resolution processes at the Centers, Office of Regulatory Affairs (ORA) and Office of the Commissioner (OC). In addition, the document provides recommendations for "best practice" activities related to scientific dispute resolution that are either ongoing in Centers, ORA, OC, other agencies or other outside organizations, or that have been suggested by focus groups with FDA employees.

This document also establishes an agency-wide appeals process for internal scientific disputes. Scientific disputes should be resolved whenever possible at the working level within the organization, and after full and frank discussion involving interested parties. When that is not possible, the process contained in this document provides all FDA staff an avenue to further pursue significant scientific disputes that they feel has not been adequately addressed within their Center, ORA or OC.

2. BACKGROUND

The September 2007 Values and Vision all hands broadcast communicated the organizational values that are important to the agency and set the course for the future with a three-part plan to develop leadership, improve processes and enhance resources for a science-led agency, and empower employees through effective communication. In addition, six Agency core values were unveiled: integrity, excellence, accountability, equity, diversity and transparency. The Commissioner, Dr. Andrew von Eschenbach, highlighted the importance to a scientific agency of encouraging and valuing presentation and discussion of differences of opinion. In that spirit, the process of addressing internal differing scientific opinions at FDA is being strengthened.

3. SCOPE AND POLICY

This Staff Manual Guide (SMG) is issued under the following guiding principles:

- FDA encourages the resolution of scientific disputes at the working level in the organization, starting with frontline employees and their immediate supervisors or team leaders.
- The agency's appeals process for scientific disputes is not a replacement for robust and fair Center-level processes.

It is the Agency's policy that all staff should be aware of the paths available to them in case of issues of scientific dispute, that all staff, including initiators of disputes, are treated with openness and respect, and that the agency procedures should not be unnecessarily burdensome.

The FDA Scientific Dispute Resolution (SDR) program is intended to address serious scientific disputes concerning issues that could have a significant impact on public health. They are NOT intended to address issues related to personnel and work environment situations; these types of disputes already have processes in place for their resolution, as do other types of non-scientific disputes.

Every effort will be made to provide FDA staff with an opportunity to resolve scientific disputes internally. The agency-wide program for SDR has two components: agency requirements for the adoption of robust SDR processes at the Centers, ORA and OC (hereafter "Centers"), and an agency-wide process review. Through these processes, the agency will assure that all valid scientific disputes can and, if needed, will receive a full and fair hearing. (see Section Heading 5, sub heading E, for a description of the scope of the review that occurs at the Agency level).

Section 6.1 of this document details FDA's requirements for the minimum standards for scientific dispute resolution processes in the Centers. The Center SDR

requirements serve two purposes. First, robust Center processes foster the principle of resolution at the working levels within the organization. Second, the agency requires that a Center Director will provide a written decision on a case before the Commissioner will address it. These requirements ensure that disputes will be eligible for the agency's appeals process.

Section 6.2 of the document provides a collection of "best practice" SDR activities. The recommendations are not mandatory, but do reflect some of the best ideas for what thoughtful and effective Center SDR processes could include, and may be adopted by Centers as applicable to their own needs.

Section 6.3 of the document describes an appeals process for scientific disputes that are not resolved to the satisfaction of all involved at the Center level. The appeals process provides an avenue to internally resolve disputes by submitting a case for review to the Office of Accountability and Integrity and receiving a final decision from the Commissioner regarding the Centers' compliance with its procedures.

It is the responsibility of all those involved to ensure that all initiators of disputes are protected from any retaliation by their supervisors, peers, leadership and others, related to initiating or engaging in this process. This Staff Manual Guide does not supersede the fundamental protections pursuant to the Whistleblower Protection Act of 1989, the Federal Employee Anti-discrimination and Retaliation (No FEAR) Act of 2002 and all applicable federal laws, regulations and Executive Orders that afford protection under the law.

4. DEFINITIONS

- A. Agency Scientific Dispute Process Review Board:** The Agency Scientific Dispute Process Review Board (hereafter Board) is a standing committee comprised of representatives of the Office of Accountability and Integrity, Ombudsmen from all Centers and the agency (or officials so designated) and representative(s) from the Office of the Chief Scientist. The Board is chaired by the Chief Scientist. At the discretion of the Chair, additional members may be assigned to the Board on a case by case basis. The Board will assess whether Center processes were followed.
- B. Initiator:** In the Agency dispute process, the initiator is the party that believes that a significant scientific issue has not been adequately addressed by Center dispute resolution processes. The initiator may be an individual, group, or organizational unit (division, office, etc.). Because scientific disputes at the agency might span more than one Center, initiators need not come from the same Center where the decision was made.
- C. Scientific Dispute:** Disputes addressed through this process must be scientific in nature. Eligible disputes may, for example, involve the interpretation of science and decisions taken upon that interpretation. The following disputes are NOT

considered to be scientific disputes and would not be eligible for this process: personnel disputes such as EEO disputes, administrative disputes, labor and employment disputes, enforcement policy disputes and disputes related to the rule-making process.

5. RESPONSIBILITIES

- A. Initiator of SDR process:** The initiator is responsible for submitting the initial documents needed for entry into the SDR appeals process to the Office of Accountability and Integrity (see Section 6.3.C.1 for requirements for complete submission). As soon as it is apparent that Center-level dispute resolution procedures have not resolved the dispute, the initiator should consider the potential public health impact and promptly file a formal SDR request, if appropriate. In addition, the initiator is responsible for fully cooperating with the formal SDR process; this participation may include presenting his or her case to the agency SDR committee(s), providing other documentation as necessary to the case review, and being interviewed by the committees.
- B. Center and agency Ombudsman, or designated official from the Office of the Director:** Ombudsmen at the Centers and agency, or officials so designated, are responsible for being sufficiently familiar with the formal SDR process to effectively counsel potential initiators who approach their offices. At any point in the dispute process, these officials may be approached by the initiator, or any other persons involved in the dispute for consultation. Ombudsmen from the Centers and Agency will serve on the Agency Scientific Dispute Process Review Board. However, the Ombudsman of the involved Center will only participate in presenting the case and the Center's procedures to the Board, but will recuse him/her self from the Board's deliberations.
- C. Center leadership:** Leaders at each Center are responsible for designing a new, or modifying an existing, SDR process for their organization, such that it incorporates all aspects as required by this SMG. Center leaders are also responsible for instituting SDR processes that reflect the guiding principles of openness and resolution of scientific disputes at the lowest organizational level possible. Finally, Center leaders are responsible for communicating the SDR process and training all Center staff on the informal and formal procedures available to resolve scientific dispute internally.
- D. Center Directors:** For each scientific issue under dispute, Center Directors are responsible for ensuring that the SDR process in their organization is documented, communicated, implemented, and conforms to the standards required by the agency (see [21 CFR 10.70](#) and Section 6.1). This responsibility includes maintaining and providing a complete administrative record of the SDR process that was followed for each dispute. They are also responsible for rendering written decisions on disputes that have advanced to them through the scientific dispute resolution processes in their individual organizations. Center Directors are

also responsible for cooperating with the agency's appeals process through interviews, information requests, and presentations to the agency SDR committees, as necessary. Finally, the Center Director is responsible for working closely with the agency SDR committee, the Chief Scientist and the Commissioner throughout an appeal, and carrying out any corrective actions that the Commissioner requires.

- E. Agency Scientific Dispute Process Review Board:** Responsible for conducting full and fair evaluations of the disputes to assess whether the Center's processes were followed, whether the Center considered all relevant evidence bearing on the scientific question at issue, and whether the initiator was provided an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.

Specific responsibilities of the Board include the following:

- Collecting all information needed to fairly and objectively review a case
- Consulting all expert opinions that are relevant to the review of each case
- Documenting the findings and rationale behind any recommendations it makes
- Communicating the findings and recommendations to the Commissioner

The Board is also responsible for notifying the Center Director when a decision at their Center is being appealed. In every dispute, members of the Board from Center(s) where disputes arise will recuse themselves from the dispute review process.

- F. Chief Scientist (CS):** The Chief Scientist will chair the Agency Scientific Dispute Process Review Board. The CS will make recommendations to the Commissioner about whether a Center failed to follow its processes and/or did not provide an adequate opportunity to the initiator to express his or her concerns; that all relevant evidence bearing on the scientific question at issue has been considered; and, whether the dispute should be remanded to the Center Director.
- G. FDA Commissioner:** When Center decisions are appealed, the FDA Commissioner will be responsible for rendering a final decision on whether a Center followed its processes, whether the Center provided an adequate opportunity to the initiator to express his or her concerns; whether all relevant evidence bearing on the scientific question at issue has been considered; and whether the dispute should be remanded to the Center Director for corrective action. The Commissioner will work with the Center Director to determine what corrective actions must be taken, if any.

6. PROCEDURES

6.1 REQUIREMENTS FOR SDR PROCESSES AT THE CENTERS

Center management shall create an atmosphere in which consultation and open discussion on controversial issues are encouraged. When disagreements occur, it is necessary to follow appropriate procedures for resolving them. Informal methods, using good management practices for resolving conflict, should be employed prior to instituting the more formal procedures described here. Notwithstanding informal good management practices used to try to resolve the conflict, timely written reviews of the scientific matter in dispute should be completed by all members of a review group, including initiator and supervisors, to enable as open and complete a discussion of the issues as possible at the working level of the organization. If informal attempts fail, requirements for the formal procedures for resolving disagreements at each Center are described below.

A. Requirements for Inclusion in the Formal Scientific Dispute Resolution Process at Each Center

The following requirements should be considered mandatory process inclusions, and must be incorporated into Center activities within Fiscal Year 2008:

1. Required elements of each Center's Standard Operating Procedure (SOP)
 - a. Each Center is required to have an SDR SOP
 - b. If a dispute is not resolved before reaching a Center Director, the Director must render a written opinion on the matter, as this step is a central criterion for advancement to the agency-level appeals process.
 - c. While the scientific dispute resolution process is pending, work on the application and a final regulatory decision will continue unless the Center Director decides that:
 - (1) The appeal raises substantial questions involving a significant risk to the public health, and
 - (2) Postponing the decision would not result in a negative impact on the public health.

Further, center personnel are not expected to postpone regulatory decisions on INDs, IDEs, Food Contact Substance Notices, etc.

- d. Timeframe for rendering a written opinion must be included, and should be developed by each Center consistent with regulatory/statutory timeframes.
 - e. Each SOP must make reference to the agency-level process as the appeals process for a dispute, should the Center-level dispute resolution process be exhausted.
 - f. Timeframes for elevating a dispute to the agency scientific dispute appeals process must be included in the Center SOP.
 - g. Each SOP should include a process by which disputes of sufficient immediacy and scale of impact to public health are able to 'opt-up' to the Center Director in order that he or she can make a decision on the matter within a condensed timeframe.
 - h. SOPs must include certain key messages for SDR
 - (1) SOPs will encourage dispute resolution at the lowest organizational level possible.
 - (2) SOPs will encourage open communication throughout the organization.
 - (3) SOPs will clearly state that initiators will be protected from any repercussion or retaliation by supervisors, Center leadership, and peers.
 - i. Each SOP will make clear the roles and responsibilities of Center staff in the SDR process, including that of the Ombudsman, where one exists.
2. Required communication in each Center's SDR process
- a. Center leadership is responsible for developing and disseminating clear written procedures for internal scientific dispute processes, including the timeline for rendering a written opinion. Center leadership is also responsible for communicating SDR responsibilities to all levels of staff on an annual basis.
 - b. FDA's Administrative Practices and Procedures Regulations provides that all FDA employees responsible for handling a matter are also responsible for insuring the completeness of the administrative file (see 21 CFR 10.70).

- c. In addition to documentation required by 21 CFR 10.70, decisions related to the formal SDR process and their supporting rationale will be documented.
- d. At all Centers, decisions related to the formal SDR process and their supporting rationale will be communicated to appropriate parties.

6.2 RECOMMENDATIONS FOR SDR PROCESSES AT THE CENTERS

The following recommendations are offered as FDA's perspective on "best practice" SDR activities. While these recommendations are not considered mandatory, they do reflect some of the best ideas for what a thoughtful and effective Center SDR process could include, and can be adopted by Centers as applicable to their own needs.

A. Best Practices for Formal Scientific Dispute Resolution Processes at the Centers

1. Recommended communication in each Center's SDR process
 - a. Centers could employ various mechanisms to disseminate their SOPs
 - (1) Mechanisms for dissemination could include, but are not limited to, one or more of the following: e-mail, orientation for new staff, workshops, hard copy distribution, online training programs, and an interactive SDR website, interactive SDR slide presentation.
 - (2) Centers may decide to regularly reinforce the importance of SDR via Center retreats or other annualized training programs
 - b. Center SOPs should require that only written documentation of a dispute will trigger a formal dispute resolution process. This step would ensure that the necessary historical record of the dispute is available should it advance to the agency-level appeals process.
 - c. Centers may require each side of the scientific issue under dispute to present their case in writing to enable transparent review at successive steps of the process. It is also considered best practice to document all decisions made at successive levels in the dispute process.

Additionally, in-person meetings with the initiator of the dispute to communicate final decision(s) and rationale may be adopted by Centers as they see fit.
2. Recommended role of the Center Ombudsman, or designated official in the Office of the Director, in the Center's SDR process.

The Center Ombudsman could informally communicate with initiators throughout the SDR process to increase the initiators' comfort with it.

3. Training and mentorship as tools to encourage open communication and the resolution of scientific disputes
 - a. Because supervisors and scientists are often the first level where scientific disputes arise, they may be trained on good management practices, including how to resolve disputes.
 - (1) Centers may institute training programs for all staff on the SDR process and good dispute resolution practices in general.
 - (2) Centers may implement procedures to evaluate supervisors on their management skills and ability to resolve scientific disputes.
 - (3) Centers may enable a "feedback loop" through Center Ombudsmen to counsel individuals (e.g., supervisors or working-level staff) who are frequently involved in formal scientific disputes.
 - b. Mentorship and training programs to encourage open communication
 - (1) Scientists may be paired with non-supervisory mentors.
 - (2) Institute training to produce team norms, process of managing conflict in teams, team charters, etc. for review teams and other groups.
4. Monitoring use of the SDR process

Centers may include questions on annual staff surveys to gauge awareness of and satisfaction with SDR process.
5. Possible formal avenues for scientific dispute resolution apart from chain-of-command mechanisms
 - a. Utilize external experts to seek objective perspective, additional scientific expertise, and practical knowledge. Examples of these are experts from other Centers, ORA and OC, other agencies, and SGEs, who can be used for written consultation,
 - b. Make several avenues available to address scientific issues: regulatory briefings, advisory committees, internal discussions with Center Directors, standing subject matter committees, and multi-disciplinary teams.

B. Best Practices for Informal Scientific Dispute and Communication

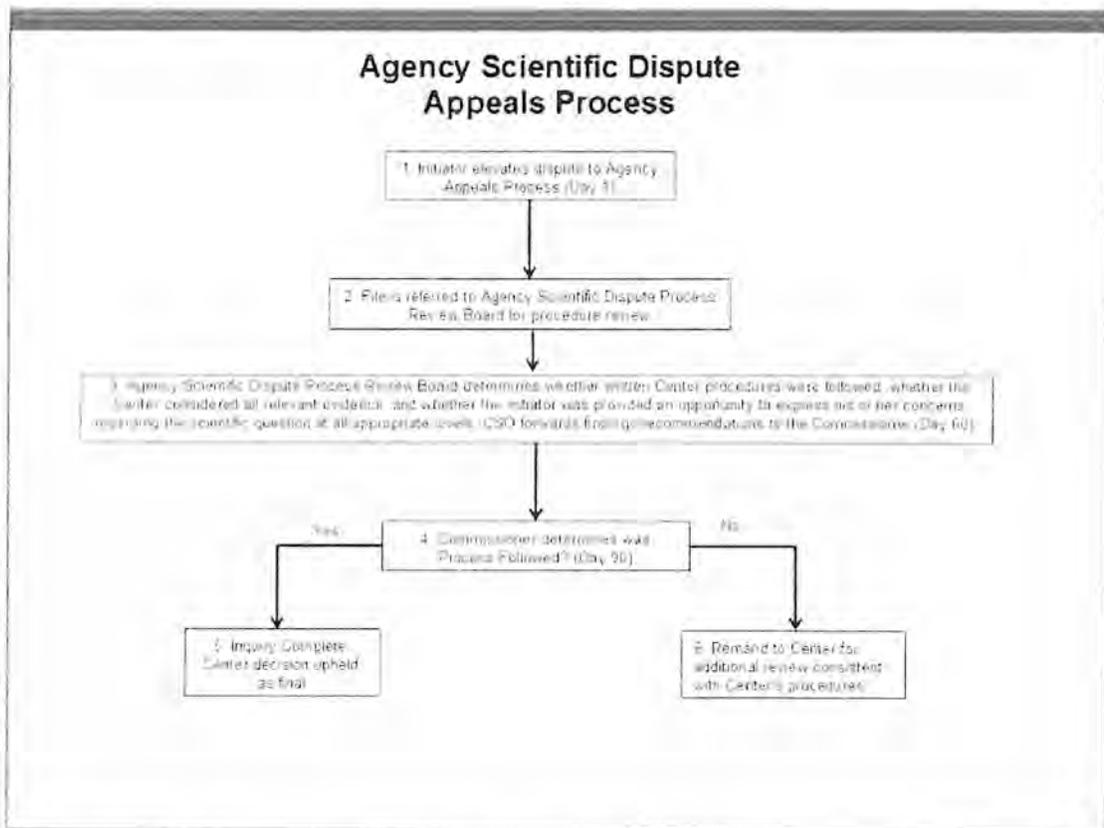
Every effort should be made to informally resolve differences in opinion on scientific matters. There are a variety of methods that Centers and other organizations already employ to foster informal dispute resolution, and still more that were suggested by internal focus groups.

A non-exhaustive list of informal resolution mechanisms includes the following:

1. Institute informal peer review and / or round table discussions. One method could be to institute formalized weekly meetings to informally discuss "hot topics," or issues of potential dispute.
2. Use Center Ombudsman (if applicable) for informal perspective and to help filter personnel-related issues.
3. Increase two-way communication within the review process. For example, Centers could choose to have employees meet regularly with their supervisors as a review team to discuss on-going reviews, substantive problems and their recommendations.

6.3 DESCRIPTION OF THE AGENCY'S APPEALS PROCESS FOR SCIENTIFIC DISPUTES

If an initiator is not satisfied after engaging in the scientific dispute resolution process at the Center, this appeals process provides an additional avenue to resolve disputes internally. All scientific disputes under appeal will be reviewed by the Agency Scientific Dispute Process Review Board, and the Commissioner will make a final decision about the issue under dispute.



A. Description of appeals process for scientific disputes

1. Elevation of disputes to the appeals process marks entry of internal scientific disputes into the formalized agency SDR appeals process. Disputes can advance from the individual Center-level SDR processes into the appeals process if the initiator feels that the dispute has not adequately been addressed / resolved at that level. The initiator must elevate the scientific dispute issue to the agency appeals process within 10 days of receiving the written opinion rendered by the Center.

At this step, the initiator must submit the case, in writing, to the Office of Accountability and Integrity (OAI). Receipt of case by OAI will be mark the first day of the agency scientific dispute appeals process. The submission will include:

- Description of how the initiator's position differs from Center's perspective
- Assessment of possible impact to public health should initiator's position not be adopted

- Detailed description of the history of the dispute, including initiator's description of the Center SDR procedures followed and/or not followed, dates of meetings, and decisions rendered throughout the process
 - Action, decision or remedy sought
2. The Agency Scientific Dispute Process Review Board will review the initiator's file, and obtain any other information necessary, to evaluate whether it meets the criteria for review. Other necessary information may include written documentation from the Center. They will assess the information and conclude whether the case meets the following criteria:
- At a minimum, the dispute must be scientific in nature. The Board will not evaluate disputes that are not based on science.
 - The Center Director must have rendered a decision on the scientific issue under dispute.

The Board will notify the Center Director that a scientific dispute has been submitted for appeal.

3. The Board will gather all necessary additional information that will enable a fully-informed recommendation on the case. The Board will obtain the full administrative record of the Center's processes for the dispute and review the Center's published SOP(s). As needed, the Board will conduct interviews with all relevant parties in the dispute, which may include the initiator, team leader, Center Director, and others. They will review the information to determine whether written Center processes were followed

The goal of this review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director. The Board will document findings and recommendations and the Chief Scientist will present his or her recommendations to the Commissioner. Representatives of the involved Center will not participate in this review.

The Board should complete its review by the sixtieth (60) calendar day in the agency SDR appeals process.

4. If the Agency Scientific Dispute Process Review Board determines that the Center's processes and procedures were followed appropriately, that the Center fully considered all relevant evidence and the initiator was provided an opportunity to express his or her concerns regarding the scientific question bearing on the dispute, the Center's decision will be

upheld as final and a written recommendation will be distributed to all internal parties involved in the dispute. The Board findings will be forwarded to the Commissioner and the agency SDR process will be concluded.

5. If the Agency Scientific Dispute Process Review Board finds that the Center's processes and procedures were not followed appropriately, that the Center did not fully consider all relevant evidence and/or the initiator was not provided an opportunity to express his or her concerns regarding the scientific question bearing on the dispute, the Chief Scientist will provide a written recommendation to the Commissioner that the case be returned to the Center for additional review consistent with the Center's procedures. This memo will consist of the Board's rationale for the recommendation, all minority opinions from panelists, and a proposed statement to be used to communicate the Commissioner's decision.
6. The Commissioner will review the Board's recommendation and render a final decision on whether a Center followed its processes, whether the Center provided an adequate opportunity to the initiator to express his or her concerns, and whether the dispute should be remanded to the Center Director for corrective action. The Commissioner will work with the Center Director to determine what corrective actions must be taken, if any.

The Commissioner will communicate this decision, and a short rationale for the decision, in writing to each side of the dispute.

The final decision will be rendered by the Commissioner, by the ninetieth (90) calendar day of the agency SDR appeals process.

B. Anticipated timing of the scientific dispute resolution appeals process

1. From the time that the initiator submits a dispute to the Office of Accountability and Integrity for review, the SDR appeals process will be completed within 90 calendar days.
2. At the discretion of the Commissioner, the process may be accelerated because of statutory or regulatory timelines or urgency of agency decision.

C. Documentation requirements throughout the SDR appeals process

1. Documentation required for entry to the process

The initiator's written case must include the following elements:

- (1) Description of how the initiator's position differs from Center's perspective

- (2) Assessment of possible impact to public health should initiator's position not be adopted
- (3) Detailed description of history of the dispute, including initiator's description of the Center SDR procedures followed and/or not followed, dates of meetings, and decisions rendered throughout the process
- (4) Action, decision or remedy sought

7. EFFECTIVE DATE

The effective date of this guide is January 13, 2009.

8. Document History -- SMG 9010.1, Scientific Dispute Resolution at FDA

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIAL
Initial	01/12/2009	N/a	OC/OP/OAI , HF-22	Susan C. Winckler, FDA Chief of Staff

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

(Docket No. 91N-0278)

New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing procedures under which the agency would accelerate approval of new drugs and biologicals for serious or life-threatening illnesses, with provisions for any necessary continued study of the drugs' clinical effects after approval or with restrictions on use, if necessary. These new procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic benefit over existing treatment. Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of any necessary studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under this proposal will have met the requisite standards for safety and effectiveness under the Federal Food, Drug, and Cosmetic Act (the act), or the Public Health Service Act (the PHS Act) and thus will have full approval for marketing. These drugs or biological products will, however, be subject to the necessary postmarketing requirements for study or limitations on distribution set forth in the regulations.

DATES: Written comments by June 15, 1992.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, Maryland 20857.

FOR FURTHER INFORMATION CONTACT: Marilyn L. Watson, Center for Drug Evaluation and Research (HFD-360), Food and Drug Administration, 5600

Fishers Lane, Rockville, MD 20857, 301-295-8038.

SUPPLEMENTARY INFORMATION: Because expediting the approval and increasing the availability of promising new drug therapies is important to the public health, in recent years FDA has developed a number of new procedures for regulating these drugs. For example, since 1983, FDA has given special emphasis to the development and review of potential new therapies for rare diseases, under its responsibility to implement the Orphan Drug Act.

In the Federal Register of February 22, 1985 (50 FR 7452), FDA comprehensively revised its new drug application (NDA) regulations (called the "NDA rewrite"). The regulations were designed to streamline the process for submitting and reviewing marketing applications. FDA supplemented these regulations with extensive guidelines to sponsors on how to prepare such applications so that they are complete and thus facilitate agency review.

In the Federal Register of March 19, 1987 (52 FR 8798), FDA revised its investigational new drug (IND) regulations (called the "IND rewrite"). These regulations were designed to clarify and simplify the rules governing clinical testing of new drugs.

In the Federal Register of May 22, 1987 (52 FR 19468), "treatment IND's" were specifically authorized by regulation to permit wide access to promising experimental drugs for serious or immediately life-threatening illnesses. Under this mechanism, more than 20 drugs have since been made available prior to marketing approval to patients for a wide variety of serious diseases: acquired immunodeficiency syndrome (AIDS), cancer, Parkinson's disease, obsessive-compulsive disorder, neonatal respiratory distress syndrome, and others.

In the Federal Register of October 21, 1988 (54 FR 41523), FDA announced new regulatory procedures (21 CFR part 312, subpart E). These procedures were designed to expedite the development, evaluation, and marketing of drugs for life-threatening and severely debilitating illnesses. Under these procedures the agency is committed to working closely with sponsors to decide as early as possible in the human testing of the drug what evidence will be necessary for marketing approval and to assist the sponsors in designing trials to evaluate the safety and effectiveness of the drug.

These actions, combined with management innovations made in recent years, have greatly increased patient access to promising experimental drugs and have also significantly shortened

the agency's time to review applications for important new drugs and approve the drugs for marketing. Additionally, in the Federal Register of May 21, 1990 (55 FR 20858), the Public Health Service (PHS) published a proposed policy to make promising new drugs more widely available to people with AIDS and HIV-related diseases through nonconcurrently controlled studies. These studies would be conducted in parallel with controlled clinical trials; thus the proposed policy became known as parallel track. Under the proposed policy, large numbers of AIDS and HIV-infected patients who are without alternative therapy would have access to investigational drugs as early in the drug evaluation process as possible.

Nevertheless, because, by their nature, life-threatening and other serious diseases represent particularly urgent needs, FDA believes that it should continue to modify its procedures to provide for the approval of new drugs for treatment of these diseases at the earliest time permitted under the law.

I. Introduction

FDA has determined that two additional steps should be taken in its current review process to facilitate the approval of significant new drugs, antibiotics, and biological products (generally referred to as "drugs" in this document) to treat serious or life-threatening illnesses. Accordingly, FDA is proposing regulations that would incorporate these steps into its review procedures for these products.

First, by providing for required postmarketing study to elaborate on the evidence of effectiveness, FDA is proposing to approve new drugs for serious or life-threatening illnesses at the earliest possible point at which safety and efficacy can reasonably be established under existing law.

Secondly, FDA is proposing procedures under which beneficial but highly toxic drugs can be approved for marketing. These drugs are one that the agency believes can be used safely only if distribution and use are restricted in certain ways.

Therefore, FDA is proposing to amend 21 CFR part 314 by adding subpart H, consisting of §§ 314.500 through 314.550, and to amend 21 CFR part 601 by adding subpart E, consisting of §§ 601.40 through 601.45.

II. Scope

The proposal would apply to new drug, antibiotic, and biological products used in the treatment of serious or life-threatening diseases, where the products provide meaningful therapeutic

benefits to patients over existing treatment.

A. Diseases Covered by the Proposal

The terms "serious" and "life-threatening" would be used as FDA has defined them in the past. The seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Thus, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes. For example, inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus, erythematosus, depression, psychoses, and many other diseases can be serious for certain populations or in some or all of their phases.

B. Meaningful Therapeutic Benefit Over Existing Therapy

As in past programs for expediting access to new drugs, FDA believes that procedures for doing so should be applied only where a serious medical need is not met by currently available therapies. If such a need does not exist, the agency believes that the usual procedures provide for the most appropriate and thorough approach to ensuring safety and effectiveness of drugs prior to marketing. Accordingly, FDA is proposing that the accelerated approval program should only apply to drugs that provide meaningful therapeutic benefit over existing treatment for patients with serious or life-threatening diseases. For example, if there is an approved treatment for a serious or life-threatening disease, individuals or a defined subset of patients may not respond well to that therapy or be intolerant of it. A treatment shown to be effective in those patients would be eligible for these procedures. Similarly, if a new therapy were a clear improvement over existing therapy in being more effective or better tolerated, that too would be eligible for accelerated approval.

At the same time, however, FDA is aware that drugs useful for one condition can often be useful in a range of other conditions. FDA's risk-benefit analysis in cases of serious or life-threatening diseases necessarily will

differ from cases where the majority of a drug's likely application in actual clinical practice will not meet these conditions. Accordingly, FDA reserves the right to apply FDA's traditional approval mechanisms rather than this accelerated process in cases where the agency believes in good faith that the new drug's foreseeable use is reasonably likely to be outside the scope of "life-threatening diseases without meaningful therapeutic benefit over existing therapy." Sponsors are encouraged to meet with FDA early in the drug development process to determine the nature of the regulatory review that FDA will apply.

III. Elements of the Program

For products covered under this program, FDA would grant accelerated marketing approval, with postmarketing requirements, in the following two situations:

A. Reliance on a "Surrogate" Endpoint or Other Appropriate Indicator of Effectiveness (e.g., Evidence of Efficacy Other Than an Effect on Survival or Irreversible Morbidity)

1. Criteria for Approval.

There may be information about the effect of a drug on a "surrogate" endpoint of disease before there is a demonstrated effect on patients' survival or overall well-being, particularly when the disease is one that progresses over a long period. A surrogate endpoint, or "marker," is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy. For example, elevated cholesterol and hypertension, two surrogate endpoints, are important because they are risk factors for coronary and cerebral artery disease; but it is the impact of the diseases (e.g., angina, congestive heart failure after a heart attack, paralysis after a stroke, or sudden death) that is important to the patient.

Surrogate endpoints can be established with different degrees of assurance. There is usually at least a theoretical possibility that the marker and the disease are not causally related, but are instead associated with a common underlying factor. For example, fever and respiratory impairment occur with pneumonia, but the fever does not cause the disease, and treating it will not improve the infection. Similarly, frequent premature ventricular beats after a heart attack signal an increased

risk of sudden death, but lowering the rate of these beats with antiarrhythmic agents has not been shown to decrease the risk of sudden death. In some cases, however, the evidence of a causal relationship is very persuasive, especially where treatment that changes the surrogate has been repeatedly shown to lead to improvement of clinical outcome. For example, substantially reducing elevated blood pressure has been repeatedly shown to reduce the likelihood of stroke and renal failure. Reliance on a surrogate endpoint is therefore a matter of scientific judgment, a judgment based on the available data, but still a judgment.

Approval of a drug on the basis of a well-documented effect on a surrogate endpoint can allow a drug to be marketed earlier, sometimes much earlier, than it could be if a demonstrated clinical benefit were required. FDA has in the past based approval of drugs on a demonstration of a favorable effect on a surrogate endpoint, where the agency has concluded that a favorable effect on the surrogate endpoint was very likely to predict a clinical benefit. In some cases, however, the judgment as to the likelihood of clinical benefit when the drug affects a surrogate endpoint is so close that it could be influenced by assurance that studies to evaluate actual clinical benefit would be conducted promptly.

Under this proposal, therefore, for drugs to treat serious or life-threatening diseases where there is meaningful benefit to patients over existing treatment, FDA would consider granting approval on the basis of adequate and well-controlled trials establishing that the drug has an effect on a surrogate endpoint that is reasonably likely (based on epidemiologic, therapeutic, or other evidence) to predict clinical benefit. Approval could be granted where there is some uncertainty as to the relation of that endpoint to clinical benefit, with the requirement that the sponsor conduct or complete studies after approval to establish and define the drug's clinical benefit.

It is also often possible to demonstrate a favorable clinical effect of therapy other than an effect on survival or the ultimate course of the disease that, for serious and life-threatening illnesses, would merit a decision to approve the therapy. For example, an anti-HIV drug might demonstrate that it could provide weight gain and reduce the frequency of opportunistic infections, even through evidence of an effect on long-term survival was not yet available. While

the favorable findings would be a basis for approval, in some instances additional study may be necessary to clearly determine long-term effects.

Finally, as in the past, FDA will continue to approve therapies for serious and life-threatening illnesses, for which there are no adequate therapies, as early in the development process as possible when the statutory standard of substantial evidence of safety and effectiveness is met through evidence on the clinical endpoints of survival or irreversible morbidity. The safety and efficacy determination would be made taking into account the risks to human life and health of the untreated disease. FDA made such a determination for AZT and would grant approval for other such drugs in the same expeditious manner. Approvals of drugs for which there is sufficient evidence of effectiveness on the clinical endpoints of survival or irreversible morbidity would not require postmarketing studies under this regulation.

2. Postmarketing Studies

For drugs approved on the basis of an effect on a surrogate endpoint, or other indicator of effectiveness the sponsor would be required to conduct any clinical studies necessary to ascertain the actual clinical benefit of the drug on such endpoints as survival, disease complications, or longer-term symptoms. It is important that the sponsor's postmarketing studies be adequate and well-controlled trials that are carried out in such a way that they are capable of obtaining the confirmatory data being sought. FDA will expect the sponsor to carry out such studies in a timely manner and in consultation with FDA. However, the requirements for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval, and new studies beyond those already in progress will not necessarily be needed. Indeed, it is anticipated that the requirement for postmarketing studies would usually be met by studies already underway at the time of approval. The plan for timely completion of the necessary studies would be included in the marketing application. FDA would interpret the requirement for conducting the studies with "due diligence" by assessing the sponsor's success in meeting normal developmental goals for a clinical trial. This assessment would include examining the pace of design of studies and the speed with which patients are enrolled.

3. Authority to Require Postmarketing Studies

FDA believes that sections 505 and 701 of the act (21 U.S.C. 355, 371) provide legal authority for the agency to promulgate regulations requiring postmarketing studies for new drugs. New drugs are approved for marketing if they meet the safety and effectiveness criteria set forth in section 505(d) of the act and the implementing regulations (21 CFR part 314). To demonstrate effectiveness, the law requires evidence from adequate and well-controlled clinical studies on the basis of which qualified experts could fairly and responsibly conclude that the drug has the effect it is purported to have. Under section 505(e) of the act, approval of a new drug application is to be withdrawn if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if new information shows that the drug's labeling is false or misleading.

Section 505(k) of the act authorizes the agency to promulgate regulations requiring applicants to make records and reports of data or other information that are necessary to enable the agency to determine whether there is reason to withdraw approval of an NDA. Section 701(a) of the act generally authorizes FDA to issue regulations for the "efficient enforcement" of the act.

For new drugs approved under proposed § 314.510 of these accelerated approval regulations, the judgment concerning likelihood of clinical benefit is based upon a demonstrated effect on a surrogate marker reasonably likely to predict clinical benefit. If, however, the surrogate marker turns out not to be such a predictor, then the drug would lack substantial evidence of effectiveness. The risk-benefit analysis of the drug may also be altered so that the drug can no longer be considered safe for use in treating the serious or life-threatening disease. In addition, in such cases the drug's approved labeling may be false or misleading.

When the correlation between surrogate endpoint or other indicator of effectiveness and clinical benefit is uncertain, the agency believes it would not be appropriate to approve drugs under section 505 of the act without the assurance of promptly conducted adequate and well-controlled studies evaluating actual clinical benefit. Evidence from such postmarketing studies evaluating actual clinical benefit (and thus confirming the predictive value of the surrogate marker or other indicator) is necessary for the agency to know whether the drug should remain

on the market or whether the NDA should be withdrawn.

Section 351 of the PHS Act (42 U.S.C. 262) provides legal authority for the agency to require postmarketing studies for biological products. Licenses for biological products are to be issued only upon a showing that they meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations (42 U.S.C. 262(d)(1)). The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)). When the correlation between surrogate endpoint and clinical benefit is uncertain for a biological product approved under proposed § 601.41, postmarketing studies are necessary to ensure that product's "continued" safety and effectiveness.

B. Restrictions on Use After Marketing

1. Criteria for Approval

Virtually all drug can be toxic to humans, and no drug is completely free of risk. In approving a new drug for marketing, FDA analyzes benefits and risks, and approves a drug if the benefit outweighs the risks. In general, the more serious the illness and the greater the effect of the drug on that illness, the greater the acceptable risk from the drug. If products provide meaningful therapeutic benefit over existing treatment for a serious or life-threatening disease, a greater risk may also be acceptable. FDA alerts health professionals and their patients to adverse effects that may result from drug use through labeling and other warning mechanisms and, where possible, provides advice on measures that can be taken to reduce the risks.

Some drugs, however, are so inherently toxic or otherwise potentially harmful that it is difficult to justify their unrestricted use. In 1990, for example, FDA approved the drug clozapine for schizophrenia when the manufacturer decided to restrict distribution to patients taking part in a monitoring program to guard against a potentially fatal side effect.

FDA has concluded that some clinically beneficial drugs can be used safely only if distribution and use are modified and restricted. In some cases, it is reasonable to expect that careful labeling will accomplish the needed limitations as, for example, is the case for most oncologic drugs, where the toxicity of the drugs is widely appreciated and monitoring for toxic effects is a routine part of patient care. In some cases, however, other kinds of restrictions may be necessary. FDA is

prepared to approve such high risk drugs for early marketing if the agency can be assured that postmarketing restrictions will be in place to counterbalance the known safety concerns.

2. Postmarketing Restrictions

The restrictions FDA may consider when approving drugs under this proposal may include restrictions such as the following:

a. *Restricting distribution to certain facilities or to physicians with special training or experience.* For example, if the drug were known to cause life-threatening reactions, it might be necessary to restrict a drug's use to settings in which emergency capabilities and equipment are readily available.

b. *Conditioning distribution on the performance of specified medical procedures.* The approval of clozapine, for example, was accompanied by a commitment to have regular blood tests performed on patients receiving the drug to monitor its toxicity. FDA can envision the need for similar procedures should it approve a drug that can be used safely only if regular monitoring is assured.

The limitation would be tailored to the specific safety issue raised by the particular drug and agreed to by the manufacturer at the time of approval. It should be emphasized that these restrictions will be considered necessary only rarely and in extraordinary cases. FDA believes that the safe use of most prescription drugs will continue to be ensured through traditional patient management by health professionals and through necessary safety warnings on the drug's labeling.

3. Authority To Impose Restrictions on Distribution

Sections 501, 502, 503, 505, and 701 of the act (21 U.S.C. 351, 352, 353, 355, and 372) provide broad authority for FDA to issue regulations to help ensure the safety and effectiveness of new drugs. These provisions reflect the congressional objective of protecting the public health by requiring safety and effectiveness of new drugs under the conditions of actual use, through a variety of mechanisms.

For example, under section 503 of the act drugs may be limited to prescription use when, because of their toxicity or other potentiality for harmful effect, or the methods of use, or the collateral measures necessary to their use, the drugs are not safe for use except under the supervision of a licensed practitioner. Section 502(a) of the act prohibits false or misleading labeling of drugs, including (under section 201(n) of the act) failure to reveal material facts

relating to potential consequences under customary conditions of use. Section 502(f) of the act requires drugs to have adequate directions for use and adequate warnings against unsafe use, such as methods of administration, that may be necessary to protect users. In addition, section 502(j) of the act prohibits use of drugs that are dangerous to health when used in the manner suggested in their labeling. Section 501 of the act contains provisions regarding the methods and controls for processing or holding to ensure that the drug is safe and has the quality and other characteristics the drug is represented to possess. (See section 501(a)(1) of the act; see also section 501(c) of the act.)

Moreover, new drugs may be approved under section 505(d) of the act only if safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. As previously discussed, section 701(a) of the act authorizes FDA to issue regulations for the efficient enforcement of the act.

For drugs approved with restricted distribution or use under proposed § 314.520, FDA will have determined that the particular restriction is necessary for safe use. The appropriate restrictions may vary with the circumstances of each drug. Without the restriction specified in the approval, the drug would be adulterated under section 501 of the act, misbranded under section 502 of the act, or not shown to be safe under section 505 of the act.

For biological products, section 351 of the PHS Act (42 U.S.C. 262) authorizes the imposition of restrictions through regulations "designed to insure the continued safety, purity, and potency" of the products. As with drugs approved under the NDA procedures, biological products will be licensed with restrictions on distribution or use only if FDA determines that such restrictions are necessary for safe use.

C. Promotional Materials

FDA is also proposing to require submission of promotional materials, including promotional labeling as well as advertisements, that the applicant intends to disseminate for drugs approved under the accelerated approval regulations. Because drugs approved under the restricted use provision may be highly toxic or otherwise potentially harmful, FDA is concerned that certain promotional claims could cause inappropriate and, therefore, unsafe use. Similarly, the risk/benefit balance for drugs approved based on evidence of the drug's effect on a surrogate endpoint could readily be adversely affected by promotion that

does not appropriately reflect the proper use of the product.

FDA does not intend specifically to approve promotional materials under proposed § 314.550, but does intend to require advance submission of such materials. FDA may therefore consider during the drug approval process and subsequent to approval whether such materials could undercut or counteract the drug's approved labeling so as to affect adversely the risk/benefit assessment. Accordingly, the sponsor must submit promotional materials to FDA during the approval process and subsequent to approval. The agency will determine the extent of review and potential modification on a case-by-case basis. Under section 505(d)(4) of the act, in determining whether a drug is "safe for use" under the conditions proposed, the agency may consider not only information such as data from clinical studies, but also "any other information" before the agency relevant to the determination. In deciding whether the drug's proposed labeling would be "false or misleading" under section 505(d)(7) of the act, the agency is also to evaluate "all material facts." Section 505(k) of the act authorizes FDA to require reporting of information necessary to determine whether there are grounds for withdrawing approval. For biological products, section 351 of the PHS Act authorizes the promulgation of regulations designed to ensure the continued safety, purity, and potency of the products.

For prescription drug products, NDA applicants are ordinarily required to submit mailing pieces and any other labeling or advertising devised for promotion of the drug at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement (21 CFR 314.81(3)). The current prescription drug advertising regulations provide for prior approval of advertisements in specific situations related to potential fatalities or serious damage from drug use (21 CFR 202.1(j)). In rare circumstances in the past, specific FDA approval of promotional materials prior to dissemination has been required.

Because of the special circumstances under which drugs will be approved within these accelerated approval regulations and the likelihood that promotional materials could adversely affect the sensitive risk/benefit balance in this context, FDA will require submission of the promotional material prior to marketing approval. In addition, FDA will require submission of promotional materials developed by the applicant subsequent to marketing

approval at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. Because promotional claims may adversely affect the risk/benefit assessment or may result in false or misleading labeling, FDA may wish to protect the public health by withdrawing approval as rapidly as possible if inappropriate promotional materials are disseminated. FDA believes that submission of these materials is necessary to enable the agency to determine whether such withdrawal proceedings should be initiated.

If the agency determines after approval that submission of promotional materials is no longer needed, it will so notify the sponsor. For example, if a drug is approved based on a surrogate endpoint, after a postmarketing study has verified the clinical benefit, FDA expects that such advance submission of promotional materials will no longer be required.

D. Withdrawal of Approved Drugs

1. Streamlined Withdrawal Procedures

Because FDA is accelerating the marketing of new drugs under these proposed regulations, the agency also believes it appropriate to propose a streamlined withdrawal process. Under current FDA regulations, holders of approved NDA's or license applications may request a formal evidentiary hearing under 21 CFR part 12 if the agency intends to withdraw the approval of the application (21 CFR 10.50(c), 12.21, 314.200, and 601.7). Part 12 proceedings ordinarily include written and oral testimony before an administrative law judge, who issues an initial decision that may then be appealed to the Commissioner for final decision.

In the agency's experience, such proceedings often take long periods of time, with months to years elapsing before issuance of the final decision. In the past, when significant safety problems have been discovered for marketed drugs, FDA and the sponsors of such drugs have often reached mutual agreement on the need to remove them from the market rapidly. However, sponsors usually have been unwilling to enter into such agreement when doubts about effectiveness have arisen, such as following the review of effectiveness of pre-1992 approvals carried out under the Drug Efficacy Study Implementation (DESI) program.

For drugs approved under these proposed accelerated approval regulations, the risk/benefit assessment is dependent upon the likelihood that a surrogate endpoint will correlate with

clinical benefit or that postmarketing restrictions will enable safe use. Without the assurances regarding demonstration of actual clinical benefit or the demonstrated adequacy of distribution restrictions, the risk/benefit assessment for these drugs changes significantly. The agency is proposing a streamlined, expeditious procedure for withdrawing approvals if: (1) A postmarketing clinical study fails to verify clinical benefit; (2) the drug's sponsor fails to perform the required postmarketing study with due diligence; (3) experience with the drug after marketing demonstrates that restrictions on distribution or use are inadequate to ensure safe use; (4) the drug's sponsor fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use. FDA believes that if any of these circumstances exists, continued marketing of the drug to treat patients with a serious or life-threatening disease is inappropriate and marketing approval should be rapidly withdrawn.

Although FDA believes that rapid withdrawal of approval under such circumstances is important to the public health, the agency also believes that the drug's sponsor should have an adequate opportunity to present data and information if the sponsor disagrees with the agency's position regarding the facts of a particular drug. Under FDA's current regulations, persons may waive the opportunity for a part 12 hearing and request instead a hearing before a public board of inquiry under 21 CFR part 13, a hearing before a public advisory committee under 21 CFR part 14, or a hearing before the Commissioner under 21 CFR part 15 (21 CFR 12.32(a)). Each of these alternative approaches can lead to more expeditious resolution of disputed issues.

For resolution of disputes concerning withdrawal of drugs approved under proposed §§ 314.510, 314.520, 601.41, or 601.42, the agency believes that a hearing combining and modifying aspects of part 14 and part 15 procedures would be most appropriate and expeditious. Although not required to do so, in most instances the agency will have consulted with one of its standing advisory committees before approving an application under these accelerated approval regulations. Advisory committee members have relevant technical expertise (a committee will ordinarily have been consulted prior to approval of a drug under these accelerated approval

provisions) and are subject to conflict of interest laws and regulations (21 CFR 14.80(a)). Especially if they have reviewed the existing data prior to the drug's approval, the committee members should be well situated to provide advice and recommendations concerning withdrawal based on subsequent information in an efficient manner.

Under the agency's current procedures, the Commissioner decides whether to withdraw a drug's approval after appeal of the Administrative Law Judge's initial decision following a part 12 hearing or, if the applicant requests, after an alternative form of hearing. When part 15 procedures are followed, the Commissioner or a designee presides at a hearing where interested persons may present their views on the pending matter.

In order to provide fair opportunity for presentation of views, as well as expeditious resolution of the issues, the agency proposes that when the agency intends to withdraw an NDA or license application approved under §§ 314.510, 314.520, 601.41 or 601.42, the applicant will have an opportunity for a hearing before the Commissioner (or designee) and an advisory committee. The withdrawal process would begin with a letter from the Director of the Center for Drug Evaluation and Research or the Director of the Center for Biologics Evaluation and Research notifying the applicant that the Center proposes to withdraw marketing approval and stating in general the reasons for the proposed action. This letter would also inform the applicant that unless the applicant requests a hearing within 15 days of receiving the notification, the applicant has waived the opportunity for a hearing.

If the applicant submits a timely request for hearing, the agency will publish a notice of hearing in accordance with § 15.20. Separation of functions (as in § 10.55) would not apply to these proceedings at any point in the withdrawal process. At a hearing under § 314.530 or § 601.43, an advisory committee would be present and would be asked to review information and make a recommendation on withdrawal of the NDA or license. Subsequent to the hearing, the Commissioner would render a final decision concerning the proposed withdrawal.

The Commissioner or designee would preside at such a hearing, which would essentially follow the procedures set forth in 21 CFR part 15, with some modifications. Under ordinary part 14 or part 15 procedures, only the committee members or the presiding officer (or

designated panelists) may question a person concerning that person's presentation at the hearing (§§ 14.29(f) and 15.30(e)). Under the proposed withdrawal procedures, the presiding officer, the committee members, a representative of the applicant, and a representative of the Center that initiates the withdrawal proceedings may also question participants. As with ordinary part 15 hearings, the rules of evidence would not apply to this hearing. No motions or objections relating to the admissibility of information or views could be made, but participants could comment on or rebut information and views presented by others (§ 15.30(f)).

The Commissioner's final decision would constitute final agency action from which the applicant may petition for judicial review under applicable statutes. Before requesting an order from a court for stay of action pending review, the applicant must first submit a petition for stay of action under § 10.35.

2. Authority for Withdrawal Procedures

Section 505(e) of the act authorizes the agency to withdraw approval of an NDA if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if the applicant has failed to maintain required records or to make required reports. In addition, approval may be withdrawn if new information, along with the evidence considered when the application was approved, shows the labeling to be false or misleading. Withdrawal for any of the specified reasons under section 505(e) of the act is to follow "due notice and opportunity for hearing to the applicant." As previously discussed, section 701(a) of the act authorizes FDA to issue regulations for the efficient enforcement of the act.

In issuing its general procedural regulations, FDA decided to afford NDA holders an opportunity for a formal evidentiary hearing even though the courts had not decided that such a hearing was necessarily legally required (see 40 FR 40891, September 3, 1975). The agency's procedural regulations permit denial of an applicant's hearing request if inadequately justified (21 CFR 12.28, 314.200(g)). As previously noted, the regulations also allow applicants to request, and the Commissioner to suggest, an alternative form of hearing (21 CFR 12.32).

For drugs approved under proposed § 314.510 the agency will have determined that reports of postmarketing studies are critical to the risk/benefit balance needed for approval. For drugs approved under

proposed § 314.520, FDA will have determined that the distribution or use restriction is critical to this risk/benefit balance needed for approval. For drugs approved under proposed § 314.520, FDA will have determined that the distribution or use restriction is critical to this risk/benefit balance. In addition, the agency has determined that the ability to withdraw approval expeditiously for such drugs is critical. If the agency is not able to withdraw approval rapidly in the event it loses the assurances regarding demonstration of actual clinical benefit or the demonstrated adequacy of distribution restrictions are removed, then the agency believes that, under authority of section 505(d) of the act, the drug cannot on an ongoing basis meet the standards of safety and efficacy required for marketing under the act. Otherwise, the risk of continued exposure of patients with serious or life-threatening diseases to ineffective or unsafe drugs outweighs the potential benefits.

For biological products, section 351(d)(1) of the PHS Act authorizes approval of license applications under standards designed to ensure continued safety, purity, and potency. The PHS Act does not specify license revocation procedures, except to state that licenses would be suspended and revoked "as prescribed by regulations" (42 U.S.C. 282(d)(1)). In promulgating its procedural regulations, FDA has determined that a formal evidentiary hearing is not required before withdrawing approval of biological products, but that it would be appropriate to apply the same procedures to biological products as to drug removal (see 40 FR 40891, September 3, 1975). Similarly, FDA is now proposing to revoke licenses for biological products approved under §§ 601.41 and 601.42 following the same procedures proposed for withdrawing NDA's.

The agency believes that the withdrawal procedures under proposed §§ 314.530 and 601.43 satisfy any applicable due process requirements for holders of NDA's and license applications. Through the proposed hearing process, applicants will be afforded the opportunity to present any data and information they believe to be relevant to the continued marketing of the drug. Moreover, as part of the approval process, applicants will have agreed that these withdrawal procedures apply to the drug for which they seek approval; applicants objecting to these procedures may forego approval under these proposed regulations and seek approval under the currently codified regulations. Under such circumstances, applicants would not

have the benefit of accelerated approval; however, if the drug were subsequently approved under current regulations, before withdrawal of the approval the applicant would have an opportunity for a part 12 hearing.

E. Additional Safeguards for Patient Safety

The accelerated drug approval program is intended to make significant new drugs available to patients earlier than under existing approval procedures, yet ensure that they are safe and effective for marketing. As with all new drugs, FDA has in place regulations that provide additional safeguards to ensure patient safety. Those regulations will apply to drugs approved under this program as well. Specifically, applicants will be expected to adhere to FDA's longstanding requirements for postmarketing recordkeeping and safety reporting. Those regulations also provide for additional "special reporting," at FDA's request, of other relevant information such as adverse drug experiences. FDA believes these safeguards are sufficient as currently promulgated in regulation and does not intend to develop new regulations imposing additional adverse reaction reporting requirements upon sponsors gaining approval under the accelerated approval procedures.

In addition, FDA's practices and procedures provide further safeguards to ensure the quality and integrity of the drug development and review process. These include conducting on-site audits of key studies and/or clinical investigators to ensure authenticity of data submitted to FDA, and inspections of manufacturing facilities before marketing approval is granted to ensure that manufacturers are able to produce properly formulated compounds.

IV. Economic Impact

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this proposal and has determined that the final rule, if promulgated, will not be a major rule as defined by the Order. Furthermore, the final rule, if promulgated, is not expected to impose significant economic impact on a substantial number of small entities so as to require a regulatory flexibility analysis under the requirements of the Regulatory Flexibility Act of 1980.

However, FDA is seeking public comment on the extent to which the contemplated postmarketing requirements would impose an economic impact upon affected drug manufacturers.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1980

This rule would not contain new collection of information requirements. Section 314.540 does refer to regulations that contain collection of information requirements that were previously submitted for review to the Director of the Office of Management and Budget (OMB) under section 3504 of the Paperwork Reduction Act of 1980 (Adverse Drug Experience Reporting, OMB No. 0190-0230).

VII. Request for Comments

Interested persons may, on or before June 15, 1992, submit to the Dockets Management Branch (address above), written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m. Monday through Friday.

List of Subjects in 21 CFR

Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

Part 601

Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 314 and 601 be amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 376).

2. Subpart H consisting of §§ 314.500 through 314.550 is added to read as follows:

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

Sec.

314.500 Scope.

314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

314.520 Approval with restrictions to ensure safe use.

314.530 Withdrawal procedures.

314.540 Postmarketing safety reporting.

314.550 Promotional materials.

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

§ 314.500 Scope.

This section applies to new drug and antibiotic products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Such approval will be subject to the requirement that the applicant study the drug further, when determined necessary by FDA, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would not necessarily be required and would usually be studies already underway. The applicant shall carry out any such studies with due diligence.

§ 314.520 Approval with restrictions to ensure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is

restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

§ 314.530 Withdrawal procedures.

(a) For circumstances of withdrawal for new drugs and antibiotics approved under §§ 314.510 and 314.520, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 314.510 or § 314.520. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the *Federal Register* in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at

any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, a representative of the applicant, and a representative of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 314.540 Postmarketing safety reporting.

Drug products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

§ 314.550 Promotional materials.

For drug products being considered for approval under this subpart, applicants must submit to the agency for consideration during the approval process copies all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication upon marketing approval. Subsequent to marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

PART 601—LICENSING

3. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 510, 513–518, 518–520, 701, 704, 706, 801 of the Federal

Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 376, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

4. Subpart E consisting of §§ 601.40 through 601.45 is added to read as follows:

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

Sec.

601.40 Scope.

601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

601.42 Approval with restrictions to ensure safe use.

601.43 Withdrawal procedures.

601.44 Postmarketing safety reporting.

601.45 Promotional materials.

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

§ 601.40 Scope.

This section applies to biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Such approval will be subject to the requirement that the applicant study the biological product further, when determined necessary by FDA, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would not necessarily be required and would usually be studies already underway. The applicant shall carry out any such studies with due diligence.

§ 601.42 Approval with restrictions to ensure safe use.

(a) If FDA concludes that a biological product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the biological product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the biological product.

§ 601.43 Withdrawal procedures.

(a) For circumstances of withdrawal for biological products approved under §§ 601.40 and 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Biologics Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 601.40 or § 601.41. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the *Federal Register* in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within

30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) Separation of functions.

Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) Procedures for hearings. Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, a representative of the applicant, and a representative of the Center may question any person during or at the conclusion of the

person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) Judicial review. The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 601.44 Postmarketing safety reporting.

Biological products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

§ 601.45 Promotional materials.

For biological products being considered for approval under this subpart, applicants must submit to the agency for consideration during the approval process copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication upon marketing approval.

Subsequent to marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

David A. Keseler,

Commissioner of Food and Drugs.

Dated: April 9, 1992.

Louis W. Sullivan,

Secretary for Health and Human Services.

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Office of the Center Director

**Equal Voice: Discipline and Organizational Component
Collaboration in Scientific and/or Regulatory Decisions**

CONTENTS

**BACKGROUND
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BACKGROUND

This MAPP provides the framework and principles for the implementation of Equal Voice (EV) in the Center for Drug Evaluation and Research (CDER). It provides general guidance for incorporating the philosophy and practices of EV into CDER decision-making processes. This MAPP should be referenced in all CDER MAPPs relevant to decision-making, and the principles and practices should be incorporated into those MAPPs directly, when appropriate.

CDER staff are involved in making a wide variety of decisions every day. These decisions may be scientific and/or regulatory in nature, or they may relate to the administration and management of the Center. The decision-making process is complex and may involve multiple staff members (primary reviewers, team leaders, supervisors, and managers) within one or more organizational components. After all appropriate input is obtained, CDER must reach an institutional decision and may need to do so efficiently within legislative, regulatory and/or practical time limits.

For each of the many regulatory decisions that CDER makes, someone must be designated as the decision-maker, i.e., the individual with the delegated responsibility and authority to make the decision. In many cases, this is the signatory authority. The EV initiative was developed to ensure that, regardless of where the signatory authority resides, decisions are made only after all appropriate expertise is brought to bear.

CDER has instituted a number of policies and procedures to foster quality and timely decision-making. Examples include numerous MAPPs defining drug review and

approval processes, MAPPs regarding dispute resolution (including the Differing Professional Opinion process), and a Memorandum of Agreement between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) that describes the roles and responsibilities of these Offices in the management of significant safety issues associated with pending drug applications and approved drug products.

EV expands on existing policies and procedures and requires a collaborative environment for decision-making. Such an environment requires open communication and exchange of ideas in a mutually respectful professional environment, and the full and open participation of all relevant disciplines and organizational components in the decision-making process. It is expected that the EV process will increase engagement and transparency and allow early identification of concerns that could disrupt the decision-making process. EV provides a foundation to achieve the "5 Cs" (Communication, Collaboration, Community, Conflict management, and Consumer focus) in the way CDER conducts its business. EV is designed to help the Center make high-quality decisions.

EV is intended to apply to pending decisions with potential outcomes that could have a substantive impact on the overall integrity, function, responsibilities, or mission of CDER, or on the public health. EV is not intended to include administrative disputes.

POLICY

- All appropriate expertise should be brought to bear for decisions made in CDER. Disciplines with expertise relevant to the decisions being made should be represented in the decision-making process. The designated decision-maker is expected to carefully consider the input of all relevant disciplines before reaching what he or she considers to be the best decision based on law, regulations, science, precedents, and public health concerns.
- CDER operates in a collaborative team-based environment that encourages the full and open participation of all relevant staff and disciplines, seeks and engages the professional input of all parties during the decision-making process, and strives to create alignment among the disciplines and organizational components involved in decision-making through discussion and scientific exchange.
- Each individual who contributes to the decision-making process is also responsible for fully representing the views of his or her discipline. To do this effectively, it is critical that each individual works within his or her management chain to be sure the position represented is consistent with the scientific, regulatory, and/or administrative policies of that discipline and organizational

component. If an individual disagrees with the position of his or her management chain, he or she should refer to guidelines set out in CDER MAPP 4151.1, Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain.

- While the decision-maker may not have considered each discipline's perspective to carry equal importance when reaching a conclusion, EV gives all disciplines and organizational components the opportunity to voice their concerns. Discipline and office representatives should provide an understanding of their discipline's role in the decision being made to all participants in the Equal Voice process, after considering how central their discipline expertise and policy is to the specific decision to be made. For example, if a decision to be made is central to regulation of pharmaceutical quality, then quality staff have a key role in the decision-making process and may plan to raise the matter to higher level staff if the decision is in conflict with existing policy. On the other hand, if there is a quality issue that toxicology and clinical staff need to be made aware of, but that is not crucial to policy in the quality area, then quality discipline representatives simply need to ensure that their analysis has been considered in making the decision. The delegated decision-maker should document how the differing opinions were taken into consideration and fully discuss with the team how the input of each discipline and organizational component was considered in making the final decision.
- Opinions of staff should be documented and supported by data in a manner commensurate with the magnitude of the decision being made. Each staff member in CDER is expected to produce high-quality reviews or other documents that provide the rationale for his or her position. These documents should reflect good scientific practices as well as be consistent with applicable laws, regulations, and policies.
- If an individual representing the views of his or her discipline cannot align with a decision to be made, the decision should be promptly escalated and resolved through the management chain (see MAPP 4151.1).
- Once all relevant disciplines and organizational components have had a chance to provide input, in most cases, the group will achieve alignment around the decision to be made. It is essential that the views of all persons involved in the review process be respected and that individual reviewers should not be pressured to change their viewpoints if alignment cannot be achieved. If alignment among disciplines and/or organizational components cannot be reached on a decision, those involved should meet to consider one another's positions, find areas of common agreement, identify specific areas of disagreement, and work to resolve them. When alignment cannot be achieved by the interdisciplinary team,

decisions should be elevated up through the management chain of the relevant disciplines.

- - Critical to the implementation of EV are 1) exercising good judgment in determining which issues are of sufficient magnitude to be elevated to increasingly senior management levels and 2) accountability and responsibility for raising such concerns and citing the data, policies, and regulatory authorities relevant to the concerns during the decision-making process in a timely manner. Concerns raised late in the EV process, and/or close to the deadline, by any party, are difficult to incorporate in timely decision-making. Therefore, all participants in the decision-making process are responsible for raising concerns as early as possible in the process to allow adequate time for resolution of differences of opinion. However, it is understood that some concerns may not emerge until later in the review process, or that emerging concerns may subsequently impact a participant's or participants' opinions about the decision-making process or the decision to be made.
 - All staff are expected to express their views and the rationale for them in a respectful manner.
-

RESPONSIBILITIES

Lead Office

- Invites the input of all relevant disciplines and/or organizational components.
- Solicits and fully considers the input of each discipline and organizational component represented in the decision-making process.
- Strives to create alignment, clearly identifies important areas of disagreement, and engages in constructive dialogue during the process as early as possible.
- Encourages individuals on the decision-making team to elevate areas of disagreement through their management team to clarify discipline-specific positions.
- Arranges to include more senior management in decision-making when it becomes clear that alignment cannot be reached among the disciplines involved.

- Provides feedback and documentation to all participants about the decision that is made, and the rationale for the decision, including how the input of participating disciplines and Offices was considered.

Individual Reviewer/Participant

- Fully participates in the decision-making process
- Represents the position of his or her specific discipline and ensures the position is understood and considered. If an individual reviewer or participant has views that differ from those of his or her specific discipline, the individual should feel free to discuss those views with the team, but must clearly specify when the views differ from those of his or her discipline. The individual should document his or her views, e.g., in a review, and discipline management should document the rationale for choosing an alternate position
- Evaluates the need for additional disciplines and organizational components to be included in the decision-making process. Informs the lead office when needed
- Discusses any contentious points with his or her supervisor and documents his or her point of view to include the rationale for his or her position
- Strives to achieve alignment and clearly identifies and communicates areas of disagreement throughout the process as early as possible

Office Director

- Each Office is responsible for developing and ensuring staff awareness of policies and processes for:
 - Early and continued involvement within the management chain regarding upcoming decisions to be sure each individual is representing the views of the discipline/Office
 - Escalating decisions within the management chain

PROCEDURES

- When a decision is to be made, the lead office/decision-maker should invite the input of relevant disciplines and organizational components to determine the appropriate action. This is described in other CDER processes, such as the *21st Century Review*

Desk Guide (Section 3 – Plan for the Review of the Application) and Interim MAPP 6700.8 *Establishing and Operating Safety Issue Teams in the Center for Drug Evaluation and Research*).

- All relevant disciplines identify individual(s) who are able to fully represent such disciplines to participate in the decision-making process.
- Each individual who contributes to the decision-making process works within his or her management chain to be sure the position he or she represents is consistent with the scientific, regulatory, and/or administrative policies of that discipline.
- If an individual cannot align with a decision, he or she may appeal through the management chain under CDER's existing dispute resolution process (see MAPP 4151.1).
- If, after following the dispute resolution process, an individual is not aligned with the decision-maker and believes a decision has the potential to result in an action (or inaction) with very serious negative public health consequence, that individual should invoke the Differing Professional Opinion (DPO) process (see MAPP 4151.2).
- Once all disciplines have had a chance to provide input, in most cases, the group will achieve alignment on a decision. Specific disciplines participating in the decision-making process are responsible for ensuring that their opinions and positions are understood.
- **If one of the disciplines or organizational components cannot align with a pending interdisciplinary decision because the proposed action is believed to be counter to law, regulation, interpretation of data, or existing precedent without adequate justification for deviation, or will result in a significant adverse impact on public health and safety, the decision should be escalated.** Escalation widens the circle of discussion and input to include more senior staff from each discipline or organizational component. Each Office and discipline should have clear policies and procedures for including more senior staff in decision-making when important differences cannot be resolved.
- Escalation should continue up the management chain, engaging more senior staff/representatives of each discipline until Office Directors or Super-Office Directors are involved.
- If alignment cannot be achieved at this level, the decision should be raised to the Center Director or his or her designee.

REFERENCES

- FDA Administrative Practices Regulations, 21 CFR 10.70 and 10.75 and the FDA-NTEU Collective Bargaining Agreement (CBA).
 - Memorandum of Agreement (MOA) Between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) in the Center for Drug Evaluation and Research, effective date June 16, 2008
 - CDER MAPP 4151.1 Revision 1, Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain, Effective 09/16/10
 - CDER MAPP 4151.2 Revision 1, Resolution of Differing Professional Opinions: Review by *Ad Hoc* Panel and CDER Director, Effective 09/16/10
 - CDER Interim MAPP 6700.8, Establishing and Operating Safety Issue Teams in the Center for Drug Evaluation and Research, Effective 05/08/09
 - 21st Century Review Desk Reference Guide for New Drug Application and Biologic License Application Reviews (NDA/BLA Review Process), version 12/3/09. <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf>
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DEFINITIONS

Alignment: A state of general support for a position to be taken or a decision to be made. Alignment does not necessarily mean full agreement by all disciplines and organizational components involved in a decision. Rather, alignment indicates that all involved individuals agree to support the action to be taken. This alignment should be based on the knowledge that all perspectives (including alternative opinions) and a range of potential options were considered and informed and justified the final action. Therefore, the action to be taken can be considered reasonable, even if the action differs from an individual's recommendation(s).

Discipline: An area of particular expertise that lends a relevant perspective to a decision to be made. For example, multidisciplinary review teams include a number of disciplines (e.g., medicine, biostatistics, clinical pharmacology). For the purpose of Equal Voice, some types of decisions, most notably those related to administrative or management issues, benefit from the perspectives of relevant organizational components, rather than disciplines. For example, a decision about how to manage advisory

committees would require input from different Offices, such as the Offices of Executive Programs, New Drugs, Surveillance and Epidemiology, Translational Science, and Pharmaceutical Science.

Lead Office: The office (or other CDER organizational component) that is coordinating and leading the process relating to the decision being made. Often this will be the office (or other CDER organizational component) that will be the signatory authority on documentation regarding the decision.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Office of the Center Director

Resolution of Differing Professional Opinions:
Review by Ad Hoc Panel and CDER Director

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PURPOSE

This MAPP provides the Center for Drug Evaluation and Research (CDER) staff a procedure to express Differing Professional Opinions (DPOs) concerning regulatory actions or policy decisions with significant public health impact in instances when the normal procedures for resolving internal disputes are not sufficient. The DPO procedure provides:

- Short time frames for hearing DPOs so they can be resolved expeditiously
- Review of the DPO by qualified staff not directly involved in the decision under consideration

BACKGROUND

When any scientific or regulatory decision is under consideration, CDER must reach an institutional position after all appropriate scientific and regulatory recommendations are obtained and considered. The decision-making process is complex and may involve multiple staff members (primary reviewers, team leaders, supervisors, and managers) within one or more organizational components.

In most cases, alignment on a decision is achieved through discussion as the reviews proceed. It is essential that the views of all persons involved in the review process be respected, that individual reviewers should not feel pressured to change their viewpoints if alignment cannot be achieved, and that the administrative file reflects differences of opinion if they exist. CDER MAPP 4151.1, Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain, describes how individual differences of opinion within a management chain are to be managed and documented. For CDER's policy on

the participation of various disciplines in the decision-making process and the resolution of disputes between disciplines, please refer to CDER MAPP 4151.8, Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions.

This MAPP should be used if, after exhausting the dispute resolution process outlined in CDER MAPP 4151.1, an employee believes that his or her opinion was not adequately considered. **This MAPP describes a formal process by which individuals in this situation can ensure that their views are heard; these individuals are given an opportunity to request a review of the dispute by the Center Director and an *Ad Hoc* panel.** This MAPP should be used only if an individual expects that an Agency action, or inaction, will have a significant negative impact on public health and: 1) the mechanisms detailed in CDER MAPP 4151.1 have been utilized to their full extent, i.e. up to the highest management official (see Definitions in CDER MAPP 4151.1) or 2) are unlikely to lead to a timely resolution.

POLICY

- It is the policy of CDER to maintain a working environment that encourages employees to make known their best professional judgments even when they may differ from a prevailing staff view, disagree with a management decision or policy position, or take issue with proposed or established practices.
- ***CDER is absolutely committed to the protection of employees from retaliation in any form for expressing differing viewpoints.*** Everyone in the supervisory and management chain is expected to support the DPO process outlined in this MAPP, protecting employees from even the appearance of retaliation for having a differing viewpoint and using the DPO process. The rights of employees should remain intact throughout the entire DPO process, the outcome, and in the resolution of subsequent issues.
- If there are disagreements about a regulatory action or policy decision, the decision-maker must take the differing opinions into consideration and make a final decision. In all cases, the views of all persons involved in the process must be taken into consideration. The administrative file should reflect any differences of opinion.
- When an employee believes a decision will be made, or the Agency is failing to act, and that decision or inaction will have a significant negative impact on public health (e.g., a major increase in the frequency, severity or both of a possible adverse effect or health outcome affecting a large subset of the population), it is CDER's policy to ensure that the employee has the opportunity to express a DPO and to have his or her views heard and carefully considered by CDER management.

- - The CDER Ombudsman is the focal point for receiving, managing, and facilitating the DPO process.
 - These DPO procedures are not intended for the resolution of routine disputes that can be addressed through the normal procedures for documenting and responding to different scientific and regulatory viewpoints (see CDER MAPP 4151.1). Rather, the DPO procedures should be reserved for the most serious differences of opinion when an action or inaction by CDER could have a significant negative impact on public health.
-

RESPONSIBILITIES

Reviewers/Participants in Decision Making

- File a DPO only when he or she feels an Agency action or inaction is likely to have a significantly negative public health impact and he or she has either exhausted existing mechanisms for resolving disputes, or feels the existing mechanisms are not likely to lead to a timely and satisfactory resolution of his or her concern
- Submit the DPO to the CDER Ombudsman
- If the DPO package is filed, prepare any material in a timely manner that will assist in dispute resolution or panel consideration of the DPO to allow the panel to finish the review in 35 business days
- If the DPO package is not filed, and he or she believes that the criteria for filing were met, he or she may appeal to the Agency level within 10 calendar days of the CDER Ombudsman's filing decision
- Appeal to the Agency level within 10 calendar days of the Center Director's issuance of his or her written decision if the DPO submitter believes there was not adequate opportunity to present concerns and/or believes that Center policies and procedures were not followed

***Ad Hoc* DPO Review Panel Chairperson**

- Appoint *Ad Hoc* DPO review panel members

***Ad Hoc* DPO Review Panel**

- Request technical assistance and additional documentation from appropriate resources, (and notify the CDER Ombudsman) and, review the necessary information. If consensus or alignment cannot be reached, the written recommendation to the Center Director must include documentation of differing panel member opinions
- Review all requested and submitted information in the DPO

- Make a written recommendation to the Center Director within 35 business days, including documentation of any differences of opinion if consensus or alignment cannot be reached

Center Director

- Consult with the CDER Ombudsman to determine whether the potential consequences of a regulatory/scientific action or inaction are serious enough to warrant initiating the DPO process
- Appoint the chairperson of the DPO Ad Hoc panel
- Determine whether or not the issues raised in the DPO warrant a change in review plan (e.g., missing a PDUFA goal date to consider a dispute about a planned action)
- Determine whether or not to shorten the review time allowed for the DPO Ad Hoc panel to conduct its review; if yes, notify the CDER Ombudsman
- Issue a written decision and rationale for that decision on the DPO within 5 business days of receipt of recommendation from the Ad Hoc panel

CDER Ombudsman

- Review the DPO package submitted and work with submitter to ensure that the package is complete
- In consultation with the Center Director, determine whether the potential consequences of a regulatory/scientific action or inaction are serious enough to warrant initiating the DPO process
- If the DPO is not filed, notify (in writing within 5 business days of receipt of the DPO) the DPO submitter, the CDER Director, all individuals within the submitter's supervisory chain, the submitter's team leader, and any Super-Office Directors directly involved in the decision, that the DPO will not be filed and the reasons why the DPO will not be filed; the Ombudsman will maintain a record of the DPO submission and the decision to not file
- If the DPO is filed, notify (in writing within 5 business days of receipt of the DPO) the person submitting the DPO, the CDER Director, all individuals within the submitter's supervisory chain, the submitter's team leader, and any Super-Office Directors directly involved in the decision that the DPO has been filed
- Notify the DPO submitter, the Ad Hoc DPO review panel, and all other parties involved in the review if the Center Director determines that the review time allowed for the *Ad Hoc* DPO review panel to conduct its review must be shortened in the interest of the public health
- Work closely with the Division/Office Project Manager to enter all relevant material into the administrative file if this process concerns a regulatory submission
- Retain all relevant material in a file if this process does not concern a regulatory submission
- Facilitate and coordinate the retrieval of additional documentation requested by the *Ad Hoc* DPO review panel
- Manage and facilitate the DPO process

- Ensure distribution of the written decision
-

PROCEDURES

1. Any CDER employee may initiate the formal DPO review process by preparing a written package that includes:
 - i. A summary statement of the position with which the person disagrees, whether it is a prevailing staff view, an existing management decision or stated policy position, or a proposed regulatory action or policy decision
 - ii. A description of the submitter's views and how they differ from the above
 - iii. A description of the nature of the disagreement (e.g., interpretation of data, methodology, judgment)
 - iv. An assessment of the possible significant negative consequences to the public health should the submitter's position not be adopted by CDER
 - v. A list of at least three potential candidates (FDA employees) with appropriate technical expertise for the *Ad Hoc panel* that will be convened (see below)
 - vi. Rationale for bypassing other possible venues for dispute resolution (if applicable)

Note: The package may be brief, but if it does not include the first five elements, it will not be processed as a DPO.
2. The package should be sent to the CDER Ombudsman
3. Within 5 business days of receipt of the DPO, the CDER Ombudsman, in consultation with the Center Director, will consider the merits of the DPO and determine whether the consequences of the decision in question are potentially sufficiently serious to warrant filing the DPO. In most cases, the Ombudsman will ensure that all other avenues for resolution (e.g., dispute resolution process, Advisory Committee discussion, CDER regulatory briefing) have been exhausted before a DPO is filed. However, in some cases, an individual may believe that his or her professional opinion will not be considered by his or her supervisors or that there is not time to exhaust other options for dispute resolution without seriously endangering the public health. In this case, the submitter should include in the DPO package a written request to bypass these other mechanisms and move directly to a DPO
4. If the CDER Ombudsman, in consultation with the Center Director, determines that the potential consequences of the contested decision are not sufficiently significant (i.e., do not have the potential to have a significant impact on public health), the Ombudsman will send notification of the decision in writing (within 5

business days of receipt of the DPO) to the person submitting the DPO, the CDER Director, all individuals within the submitter's supervisory chain, the submitter's team leader, and any Super-Office Directors directly involved in the decision. The notification will include a statement that the DPO will not be filed and the reasons why the DPO will not be filed. The CDER Ombudsman will retain the DPO in the files for the record. After considering the reasons why the DPO was not filed, the DPO submitter may appeal the filing decision using the Agency appeals process detailed in the Staff Manual Guide 9010.1 "Scientific Dispute Resolution at FDA" within 10 calendar days of the written filing decision

5. If the CDER Ombudsman, in consultation with the Center Director, determines that the DPO should be filed, the CDER Ombudsman will send notification of the decision in writing (within 5 business days of receipt of the DPO) to the person submitting the DPO, the CDER Director, all individuals within the submitter's supervisory chain, the submitter's team leader, and any Super-Office Directors directly involved in the decision that the DPO has been filed
6. The CDER Director will consider the impact of the DPO review on existing deadlines and will decide whether or not the issues raised in the DPO warrant a change in review plan (e.g., missing a PDUFA goal date to consider a dispute about a planned action)
7. The Center Director will appoint a chairperson to lead an *Ad Hoc* DPO review panel within two business days of the DPO filing
8. The chairperson will appoint an *Ad Hoc* DPO review panel within 5 business days of the DPO filing. The panel will be comprised of two to three additional members, including:
 - i. One member who has relevant technical expertise
 - ii. One member chosen from the list proposed by the employee submitting the DPO
 - iii. If time allows, one member with relevant technical expertise external to the Agency chosen by the *Ad Hoc* panel chairperson. Because of the short time frames involved, this member must be a special government employee (SGE). SGE panel members must be screened for conflict of interest (COI) and this can be a lengthy process; therefore, if an expert external to the Agency is needed for a robust review, the final appointment of the panel might be delayed to allow for COI screening
 - iv. To the extent possible, DPO panels should not include individuals who have directly participated in the decision-making process up to the time of the DPO and, when practicable, individuals who participated in the decision-making process should recuse themselves from the panel. However, the panel should include individuals with the *relevant technical expertise and experience* to understand the complex issues at hand

9. The Ombudsman will forward the DPO package to the *Ad Hoc* panel as soon as the panel has been appointed
10. Once the DPO package is received by the *Ad Hoc* panel, the panel should take no more than 35 business days to collect and review the necessary information and to make a written recommendation to the Center Director. The Center Director may decide to shorten the review time in the interest of public health. In this case, the Center Director will notify the Ombudsman, who will then immediately relay the revised timeframe to the DPO submitter, the *Ad Hoc* panel, and all other parties involved in the review
11. The DPO review panel will:
 - i. Determine whether sufficient documentation was provided by the DPO submitter to complete a detailed review and, if not, request additional information
 - ii. Request technical assistance and additional documentation (e.g., reviews, meeting minutes) from appropriate sources within or outside the Center, as necessary. The CDER ombudsman will coordinate these activities
 - iii. Review the DPO and all other relevant materials, and make a written recommendation to the Center Director regarding the appropriate course of action to be taken. If the panel is unable to reach consensus or alignment, the report should reflect the differing opinions of the panel
12. The Center Director must review the panel's recommendation and provide the employee who submitted the DPO and other Center staff included in review chains associated with the DPO with a written decision and rationale for that decision within 5 business days after receipt of the panel's recommendations
13. If the DPO submitter feels that there was not adequate opportunity to present his or her concerns and/or believes that Center policies and procedures were not followed, the DPO submitter may choose to appeal the decision. The DPO submitter must submit the appeal using the Agency appeals process detailed in the Staff Manual Guide 9010.1 "Scientific Dispute Resolution at FDA" within 10 calendar days of the Center Director's written decision
14. All records pertaining to DPOs will be maintained in the pertinent administrative file(s), if applicable. If the DPO is not related to a specific regulatory submission, records will be maintained by the CDER Ombudsman

REFERENCES

- FDA Administrative Practices Regulations, 21 CFR 10.70 and 10.75 and the FDA-NTEU Collective Bargaining Agreement (CBA)
 - CDER MAPP 4151.1 Revision 1. Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain, Effective 9/16/10.
 - CDER MAPP 4150.1, Role and Procedures of the CDER Ombudsman, Effective 10/10/02
 - CDER MAPP 4151.8 Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions, Effective 9/16/10.
 - FDA Staff Manual Guide 9010.1, Scientific Dispute Resolution at FDA, Effective 1/13/09.
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DEFINITIONS

Administrative File. Under 21 CFR Part 10, Administrative Practices and Procedures, 21 CFR 10.70 states “FDA employees responsible for handling a matter are responsible for insuring the completeness of the administrative file relating to it. The file must contain appropriate documentation of the basis for the decision, including relevant evaluations, reviews, memoranda, letters, opinions of consultants, minutes of meetings, and other pertinent written documents.” The file must also contain “recommendations and decisions of individual employees, including supervisory personnel, responsible for handling the matter” and “reveal significant controversies or differences of opinion and their resolution.” An employee who “has worked on a matter may record individual views on that matter in a written memorandum, which is to be placed in the file.” For a full description of the administrative file, see 21 CFR 10.75.

Alignment. A state of general support for a position to be taken or a decision to be made. Alignment does not necessarily mean full agreement by all disciplines and organizational components involved in a decision. Rather, alignment indicates that all involved individuals agree to support the action to be taken. This alignment should be based on the knowledge that all perspectives (including alternative opinions) and a range of potential options were considered and informed and justified the final action. Therefore, the action to be taken can be considered reasonable, even if the action differs from an individual's recommendation(s).

EFFECTIVE DATE

This MAPP is effective upon date of publication.

OFFICE OF THE CENTER DIRECTOR

Scientific / Regulatory Dispute Resolution for Individuals Within a Management Chain

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PURPOSE

This MAPP provides:

- Guidelines for documentation of scientific and regulatory review findings, perspectives, and opinions for individuals initiating or involved in the dispute resolution process.
 - A procedure for resolution of scientific or regulatory differences of opinion within a management chain.
-

BACKGROUND

When any scientific or regulatory decision is under consideration, the Center for Drug Evaluation and Research (CDER) must reach an institutional position after all appropriate scientific and regulatory recommendations are obtained and considered. The decision-making process is complex and may involve multiple staff members (primary reviewers, team leaders, supervisors, and managers) within one or more organizational components.

In most cases, alignment on a decision is achieved through discussion as reviews proceed. It is essential that the views of all persons involved in the review process be respected and that the official administrative file reflects differences of opinion if they exist. **This MAPP describes how individual differences of opinion within a management chain are to be managed and documented.**

For CDER's policy on the participation of various disciplines and organizational components in the decision-making process and the resolution of disputes, please refer to

CDER MAPP 4151.8, Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions.

REFERENCES

- FDA Administrative Practices Regulations: 21 CFR 10.70 and 10.75 and the FDA-NTEU Collective Bargaining Agreement (CBA).
 - CDER MAPP 4151.2, Revision 1, Resolution of Differing Professional Opinions: Review by *Ad Hoc* Panel and CDER Director, Effective 09/16/10.
 - CDER MAPP 4151.8, Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions, Effective 09/16/10.
 - 21st Century Review Desk Reference Guide for New Drug Application and Biologic License Application Reviews (NDA/BLA Review Process), version 12/03/09.
<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf>
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DEFINITIONS

Administrative File. Under 21 CFR Part 10, Administrative Practices and Procedures, 21 CFR 10.70 states “FDA employees responsible for handling a matter are responsible for insuring the completeness of the administrative file relating to it. The file must contain appropriate documentation of the basis for the decision, including relevant evaluations, reviews, memoranda, letters, opinions of consultants, minutes of meetings, and other pertinent written documents.” The file must also contain “recommendations and decisions of individual employees, including supervisory personnel, responsible for handling the matter” and “reveal significant controversies or differences of opinion and their resolution.” An employee who “has worked on a matter may record individual views on that matter in a written memorandum, which is to be placed in the file.” For a full description of the administrative file, see 21 CFR 10.75.

Alignment. A state of general support for a position to be taken or a decision to be made. Alignment does not necessarily mean full agreement by all disciplines and organizational components involved in a decision. Rather, alignment indicates that all involved individuals agree to support the action to be taken. This alignment should be based on the knowledge that all perspectives (including alternative opinions) and a range of potential options were considered and informed and justified the final action. Therefore, the action to be taken can be considered reasonable, even if the action differs from an individual's recommendation(s).

First Level Supervisor/Team Leader. A supervisor, team leader, or any other person who manages a reviewer's day to day work, directly oversees the work product of a reviewer, and sometimes writes secondary reviews. Cross-Discipline Team Leaders (CDTL) are not included in this definition; for an explanation of the CDTL, see the 21st Century Review Desk Reference Guide for New Drug Application and Biologic License Application Reviews (NDA/BLA Review Process).

Next Highest Management Official. The management official one level above the management official who made the decision being disputed. Ultimately, this could be the CDER Director.

POLICY AND PROCEDURES

1. It is the policy of CDER to maintain a working environment that encourages employees to make known their best professional judgments even when they may differ from a prevailing staff view, disagree with a management decision or policy position, or take issue with proposed or established practices.
2. If alignment is not achieved, unresolved scientific or regulatory issues may be brought to the Next Highest Management Official, as appropriate, for resolution. In all cases, the individual who disagrees with a decision (disputant) is responsible for presenting the dispute to the Next Highest Management Official, if they choose to do so. If the individual decides to initiate a dispute resolution process, prompt action is recommended so that the issues can be fully evaluated and resolved in a timely manner.
3. The disputant may initiate a dispute resolution process by writing a statement (called a dispute statement) describing the position, concept, opinion, or recommendations with which the disputant disagrees, the nature of and reasons for the difference in opinion, as well as the proposed changes and rationale for changes in recommendations and/or conclusions. This statement will be provided to the Next Highest Management Official for his or her consideration and resolution. This statement should also be distributed to the individual(s) with whom the disputant disagrees, to other relevant employees, and entered in the administrative file.
4. The dispute statement as well as all other supporting documents must:
 - i. Relate only and specifically to the factual, scientific issues under consideration
 - ii. Be dated and signed by the author

- iii. Be directed to the administrative file with copies directed to supervisory and all other relevant personnel
 - iv. Indicate to whom documents are sent (distribution)
 - v. Not be changed, altered, or removed by any party after completion, signing, and inclusion in the administrative file
 - vi. Avoid defamatory remarks, undocumented charges, or irrelevant matters (e.g., personnel issues)
5. A disputant, in developing and drafting an initial statement of disagreement, may develop successive drafts or alter a primary draft with the intent of clarification or improvement of the statement. Such early drafts are not considered part of the administrative file and can be discarded once a final draft of the statement has been submitted to the administrative file. Once a final draft of the statement of disagreement or any other supporting document is part of an administrative file, no changes can be made in those documents. Any subsequent revisions or amendments must be made as new documents.
6. After review, discussion, and consideration of all relevant points of view, the Next Highest Management Official will make a decision on the matter, write a memorandum stating and supporting his or her decision, provide a copy to the individuals involved in the dispute, and place the memorandum in the administrative file. The decision-maker must take differing opinions into consideration and the views of all persons involved in the process will be respected and included in documenting the disagreement.
7. If a disputant cannot align with the decision made, a disputant may choose to continue the dispute resolution process by presenting his or her disagreement with the decision up the management chain to the Next Highest Management Official, following the same dispute resolution process outlined above. This appeals process can be repeated until the dispute ultimately reaches the CDER Director for consideration and resolution.
8. If a dispute arises between two individuals within a discipline and neither one is the final decision-maker, the dispute should still be documented in the administrative file. For example, if a primary reviewer and his or her First Level Supervisor/Team Leader disagree, the First Level Supervisor/Team Leader should write a brief summary memorandum describing the precise nature of his or her disagreement with the primary review or recommended regulatory action. This memorandum should address and describe any differences in opinion or recommendations, should be shared with the primary reviewer, should be entered into the administrative file, and should serve as the initial tool to facilitate discussions with the decision-maker towards achieving alignment. This process is more fully described in the 21st Century Review Desk Reference Guide for New Drug Application and Biologic License Application Reviews (NDA/BLA Review

Process).

9. If a decision-maker reaches a decision that is inconsistent with the conclusions or recommendations made by any individual on his or her staff, that decision-maker must write a memorandum documenting his or her rationale for the decision, including a discussion of how differing opinions were taken into consideration, enter the memorandum into the administrative file, and provide the memorandum to relevant staff. This will apply even if an individual has not initiated the dispute resolution process.
10. If, after exhausting the dispute resolution process outlined in this MAPP, an employee believes that his or her opinion was not adequately considered, and, as a result, an Agency action or inaction will have a significantly negative public health impact, CDER MAPP 4151.2, Resolution of Differing Professional Opinions: Review by *Ad Hoc* Panel and CDER Director, can be used. CDER MAPP 4151.2 describes a formal process by which individuals in this situation can ensure that their views are heard; these individuals are given an opportunity to request a review of the dispute by the Center Director and an *Ad Hoc* panel. CDER MAPP 4151.2 should be used only if an individual expects that an Agency action, or inaction, will have a significantly negative public health impact and 1) the mechanisms detailed in CDER MAPP 4151.1 have been utilized to their full extent, i.e., up to the highest management official (see Definitions in this MAPP) or 2) are unlikely to lead to a timely resolution.
11. The CDER Ombudsman can respond to questions and concerns regarding this dispute resolution process.
12. CDER is committed to the protection of employees from retaliation in any form for expressing different professional viewpoints or opinions. Everyone in the supervisory and management chain is expected to respect the process of dispute resolution and to protect employees from retaliation or even the appearance of retaliation for expressing a difference of professional opinion.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE (PCNS)

Monday, April 25, 2016
8:00 a.m. to 7:37 p.m.

College Park Marriott Hotel and Conference Center
Chesapeake Ballroom
3501 University Boulevard East
Hyattsville, Maryland

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Moon Hee V. Choi, PharmD**

4 Division of Advisory Committee and Consultant
5 Management

6 Office of Executive Programs, CDER, FDA

7
8 **PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS**

9 **ADVISORY COMMITTEE MEMBERS (Voting)**

10 **G. Caleb Alexander, MD, MS**

11 *(Chairperson)*

12 Associate Professor of Epidemiology & Medicine

13 Johns Hopkins School of Public Health

14 Center for Drug Safety and Effectiveness

15 Baltimore, Maryland

16
17 **Nicole R. Gonzales, MD**

18 Associate Professor

19 University of Texas-Houston Medical School

20 Department of Neurology - Stroke Program

21 Houston, Texas

22

1 **Mark W. Green, MD, FAAN**

2 Professor of Neurology, Anesthesiology, and
3 Rehabilitation Medicine
4 Director of Headache and Pain Medicine
5 Icahn School of Medicine at Mt Sinai
6 New York, New York

7

8 **Richard P. Hoffmann, PharmD**

9 *(Consumer Representative)*
10 Drug Information Consultant/Medical Writer
11 Hernando, Florida

12

13 **Richard J. Kryscio, PhD**

14 Professor, Statistics
15 Chair, Biostatistics
16 University of Kentucky
17 Lexington, Kentucky

18

19

20

21

22

1 **Chiadi U. Onyike, MD**

2 Associate Professor of Psychiatry and Behavioral
3 Sciences

4 Division of Geriatric Psychiatry and
5 Neuropsychiatry

6 Department of Psychiatry and Behavioral Sciences
7 The Johns Hopkins University School of Medicine
8 Baltimore, Maryland

9
10 **Bruce I. Ovbiagele, MD, MSc, MAS**

11 Professor and Chairman of Neurology
12 Medical University of South Carolina
13 Charleston, South Carolina

14
15 **PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS**

16 **ADVISORY COMMITTEE MEMBER (Non-Voting)**

17 **Mark Gordon, MD**

18 *(Industry Representative)*

19 Director, Clinical Development and Medical Affairs

20 General Medicine/Central Nervous Systems

21 Boehringer Ingelheim Pharmaceuticals, Inc.

22 Ridgefield, Connecticut

1 **TEMPORARY MEMBERS (Voting)**

2 **Benjamin Dupree**

3 *(Patient Representative)*

4 Dallas, Texas

5

6 **A. Reghan Foley, MD**

7 Staff Clinician

8 Neuromuscular and Neurogenetic Disorders of

9 Childhood Section, Neurogenetics Branch

10 Division of Intramural Research

11 National Institute of Neurological Disorders of

12 Stroke (NINDS)

13 National Institutes of Health (NIH)

14 Bethesda, Maryland

15

16 **Cheri Gunvalson, RN, MS**

17 *(Patient Representative)*

18 Clinical Assistant Professor

19 University of North Dakota, College of Nursing

20 Grand Forks, North Dakota

21

22

1 Aaron S. Kesselheim, MD, JD, MPH

2 Associate Professor of Medicine

3 Harvard Medical School

4 Director, Program on Regulation, Therapeutics, and

5 Law (PORTAL)

6 Division of Pharmacoepidemiology and

7 Pharmacoeconomics

8 Brigham & Women's Hospital

9 Boston, Massachusetts

10

11 Glen Nuckolls, PhD

12 Program Director and Executive Secretary

13 Interagency Muscular Dystrophy Coordinating

14 Committee, Neurogenetics Cluster

15 Division of Extramural Research, NINDS, NIH

16 Bethesda, Maryland

17

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Paul Romitti, PhD

Professor
Department of Epidemiology and Interdisciplinary
Program in Toxicology
University of Iowa
Iowa City, Iowa

FDA PARTICIPANTS (Non-Voting)

Janet Woodcock, MD

Director
CDER, FDA

John Jenkins, MD

Director
Office of New Drugs (OND), CDER, FDA

Ellis Unger, MD

Director
Office of Drug Evaluation I (ODE-I)
OND, CDER, FDA

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Robert Temple, MD

Deputy Director
ODE-I, OND, CDER, FDA

Billy Dunn, MD

Director
Division of Neurology Products (DNP)
ODE-I, OND, CDER, FDA

Eric Bastings, MD

Deputy Director
DNP, ODE-I, OND, CDER, FDA

Ronald Farkas, MD, PhD

Clinical Team Leader
DNP, ODE-I, OND, CDER, FDA

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. ALEXANDER: Good morning, and thank you for joining us today. I'd like to first remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I'd also like to identify the FDA press contact, Sandy Walsh.

Sandy, if you are present, can you please stand and identify yourself? Thank you.

My name is Dr. Caleb Alexander. I'm the chairperson of the Peripheral and Central Nervous System Drugs Advisory Committee meeting, and I'll now call this meeting to order. We'll start by going around the table and introducing ourselves. Let's start down here on the right with Dr. Gordon, please.

DR. GORDON: Good morning, everyone. My name is Mark Gordon. I am the industry representative, and I work for Boehringer Ingelheim

1 Pharmaceuticals.

2 DR. HOFFMAN: Richard Hoffman. I'm a
3 pharmacist and medical writer, and I'm the consumer
4 representative for this meeting.

5 DR. GREEN: Mark Green. I'm a professor of
6 neurology, anesthesiology, and rehabilitation
7 medicine at Mount Sinai School of Medicine.

8 MR. DUPREE: I'm Benjamin Dupree, a
9 23-year-old with Duchenne muscular dystrophy, here
10 serving as a patient representative.

11 MS. GUNVALSON: I'm Cheri Gunvalson. I'm
12 the mother of a 24-year-old son with Duchenne. I'm
13 also a nurse and a clinical nursing professor at
14 the University of North Dakota.

15 DR. KRYSCIO: Good morning, I'm Richard
16 Kryscio. I'm from the University of Kentucky, and
17 I'm a biostatistician.

18 DR. ROMITTI: Good morning. I am Paul
19 Romitti, a professor of epidemiology and toxicology
20 at the University of Iowa.

21 DR. NUCKOLLS: Good morning. I'm Glen
22 Nuckolls. I'm program director for the muscular

1 dystrophies at NIH at the Neurology Institute, and
2 I'm the designated federal official for the
3 Interagency Muscular Dystrophy Coordinating
4 Committee.

5 DR. FOLEY: Good morning. I'm Reghan Foley.
6 I'm a pediatric neuromuscular specialist. I work
7 at the Neuromuscular and Neurogenetic Disorders of
8 Childhood Section of the Neurogenetics Branch of
9 the NINDS at NIH.

10 DR. KESSELHEIM: Good morning. I'm Aaron
11 Kesselheim, an associate professor of medicine at
12 Brigham & Women's Hospital in the Division of
13 Pharmacoepidemiology and Pharmacoeconomics at
14 Harvard Medical School.

15 DR. ALEXANDER: And once again, I'm Caleb
16 Alexander. I'm an associate professor of
17 epidemiology and medicine at Johns Hopkins
18 Bloomberg School of Public Health.

19 DR. CHOI: Moon Hee Choi, designated federal
20 officer.

21 DR. ONYIKE: Chiadi Onyike, associate
22 professor of psychiatry at Johns Hopkins.

1 DR. GONZALES: Nicole Gonzales, associate
2 professor of neurology at the McGovern Medical
3 School at the University of Texas in Houston.

4 DR. OVBIAGELE: Bruce Ovbiagele, professor
5 and chair of neurology at the Medical University of
6 South Carolina.

7 DR. FARKAS: Ronald Farkas, clinical team
8 leader at the Division of Neurology Products at
9 FDA.

10 DR. DUNN: I'm Billy Dunn. I'm the director
11 of the Division of Neurology Products at FDA.

12 DR. BASTINGS: Eric Bastings, deputy
13 director of the Division of Neurology Products at
14 the FDA.

15 DR. UNGER: Ellis Unger, director, Office of
16 Drug Evaluation I at the FDA.

17 DR. JENKINS: Good morning. I'm John
18 Jenkins. I'm the director of the Office of New
19 Drugs in CDER at FDA.

20 DR. TEMPLE: Good morning. Bob Temple,
21 deputy director of ODE-I.

22 DR. WOODCOCK: And I'm Janet Woodcock. I'm

1 head of the drug center at FDA.

2 DR. ALEXANDER: Thank you.

3 For topics such as those being discussed at
4 today's meeting, there are often a variety of
5 opinions, some of which are quite strongly held.
6 Our goal is that today's meeting will be a fair and
7 open forum for discussion of these issues and that
8 individuals can express their views without
9 interruption.

10 Thus, as a gentle reminder, individuals will
11 be allowed to speak into the record only if
12 recognized by the chairperson. We look forward to
13 a productive meeting.

14 In the spirit of the Federal Advisory
15 Committee Act and the Government in the Sunshine
16 Act, we ask that the advisory committee members
17 take care that their conversations about the topic
18 at hand take place in the open forum of the
19 meeting. We are aware that members of the media
20 are anxious to speak with the FDA about these
21 proceedings. However, FDA will refrain from
22 discussing the details of this meeting with the

1 media until its conclusion. Also, the committee is
2 reminded to please refrain from discussing the
3 meeting topic during breaks or lunch. Thank you.

4 Now I'll pass it to Moon Hee Choi, who will
5 read the conflict of interest statement.

6 **Conflict of Interest Statement**

7 DR. CHOI: The Food and Drug Administration
8 is convening today's meeting of the Peripheral and
9 Central Nervous System Drugs Advisory Committee
10 under the authority of the Federal Advisory
11 Committee Act of 1972.

12 With the exception of the industry
13 representative, all members and temporary voting
14 members of the committee are special government
15 employees or regular federal employees from other
16 agencies and are subject to federal conflict of
17 interest laws and regulations.

18 The following information on the status of
19 this committee's compliance with federal ethics and
20 conflict of interest laws, covered by but not
21 limited to those found at 18 U.S.C. Section 208, is
22 being provided to participants in today's meeting

1 and to the public. FDA has determined that members
2 and temporary voting members of this committee are
3 in compliance with Federal Ethics and Conflict of
4 Interest laws.

5 Under 18 U.S.C. Section 208, Congress has
6 authorized FDA to grant waivers to special
7 government employees and regular federal employees
8 who have potential financial conflicts when it is
9 determined that the agency's need for a particular
10 individual's services outweighs his or her
11 potential financial conflict of interest.

12 Related to the discussions at today's
13 meetings, members and temporary voting members of
14 this committee have been screened for potential
15 financial conflicts of their own as well as those
16 imputed to them, including those of their spouses
17 or minor children, and for purposes of 18 U.S.C.
18 Section 208, their employers. These interests may
19 include investments, consulting, expert witness
20 testimony, contracts, grants, CRADAs, teaching,
21 speaking, writing, patents and royalties, and
22 primary employment.

1 Today's agenda involves new drug application
2 206488, eteplirsen injection for intravenous
3 infusion sponsored by Sarepta Therapeutics for the
4 treatment of Duchenne muscular dystrophy in
5 patients who have a confirmed mutation of the DMD
6 gene that is amenable to exon 51 skipping. This is
7 a particular matters meeting during which specific
8 matters related to Sarepta Therapeutics NDA will be
9 discussed.

10 Based on the agenda for today's meeting and
11 all financial interests reported by the committee
12 members and temporary voting members, no conflict
13 of interest waivers have been issued in connection
14 with this meeting. To ensure transparency, we
15 encourage all standing committee members and
16 temporary voting members to disclose any public
17 statements that they have made concerning the
18 product at issue.

19 With respect to FDA's invited industry
20 representative, we would like to disclose that
21 Dr. Mark Gordon is participating in this meeting as
22 a non-voting industry representative acting on

1 behalf of regulated industry. Dr. Gordon's role at
2 this meeting is to represent industry in general
3 and not any particular company. Dr. Gordon is
4 employed by Boehringer Ingelheim.

5 We would like to remind members and
6 temporary voting members that if the discussions
7 involve any other products or firms not already on
8 the agenda for which an FDA participant has a
9 personal or imputed financial interest, the
10 participants need to exclude themselves from such
11 involvement, and their exclusion will be noted for
12 the record. FDA encourages all participants to
13 advise the committee of any financial relationships
14 that they may have with the firm at issue. Thank
15 you.

16 DR. ALEXANDER: Thank you very much. We'll
17 now proceed with the FDA's introductory remarks
18 from Dr. Billy Dunn, director of the Division of
19 Neurology Products.

20 **FDA Introductory Remarks - Billy Dunn**

21 DR. DUNN: Thank you, Dr. Alexander.

22 Good morning. Welcome to all our committee

1 members, guests who have traveled here, and all the
2 folks who are joining us by electronic means for
3 this important meeting.

4 I'm in a somewhat unusual situation of
5 delivering remarks that will, in part, be the same
6 as or similar to remarks I made to this committee
7 quite recently, when we gathered almost exactly
8 five months ago, to discuss drisapersen for the
9 treatment of Duchenne muscular dystrophy.

10 While perhaps familiar to some, I am certain
11 that we have quite a few people joining us today
12 who were not present in November of last year, and
13 many of my comments bear repetition.

14 I want to thank the committee for your
15 willingness to be here, your eagerness to consider
16 the important topics we will discuss today, and
17 your forthrightness in sharing with us your
18 perspectives on the application under
19 consideration. I want to especially thank the
20 public attendees, both in person and those joining
21 us by audio or video broadcast, for their
22 commitment to finding a treatment for Duchenne

1 muscular dystrophy.

2 I particularly want to note and thank the
3 patients with DMD who are joining us today. I am
4 extraordinarily impressed with the turnout for this
5 committee meeting as I look out over the audience
6 today, and I was particularly impressed as I walked
7 in through the public spaces of all the patients
8 with DMD who are here. Thank you for being here.
9 Your efforts to be here are invaluable and
10 tremendously appreciated.

11 On a broader note than just this committee
12 meeting today, I want to take a moment to mention
13 how much we here at FDA appreciate our interaction
14 with the DMD community. We have been very engaged
15 with the scientific and advocacy leaders in this
16 area, which I am confident has resulted in an
17 improved understanding for both the community and
18 ourselves.

19 The tireless efforts of the DMD community
20 resulted in a proposed draft guidance, as many here
21 know, from an advocacy group that was submitted to
22 us for our consideration. I am happy to be able to

1 say that building on that effort, we published our
2 own draft guidance in June of last year for DMD, a
3 major accomplishment and I think a source of great
4 collaborative progress for the field.

5 We are here today, after a delay due to
6 severe weather in January that has tried the
7 patience of many, to discuss eteplirsen for the
8 treatment of Duchenne muscular dystrophy in
9 patients with mutations amenable to exon 51
10 skipping.

11 There is without question a profound unmet
12 medical need in DMD. We have no approved
13 treatments for this disease. We are highly
14 sensitive to the urgency needed for the development
15 of an improved treatment for Duchenne. Before
16 briefly describing some of the issues we will ask
17 you to discuss today, I want to stress that we have
18 not made any final decisions on the approvability
19 of this application.

20 Many believe that we are here today to
21 render a final decision on approvability. We are
22 not. We are here to have a discussion and gain

1 input from you, the committee members.

2 The information in your background packages
3 are preliminary reviews only that do not yet take
4 into account today's proceedings. Though you may
5 encounter preliminary conclusions and
6 recommendations concerning approvability and, as
7 you have seen in your background materials, they
8 may often describe grave concerns about the data
9 put forth in support of the ostensible
10 effectiveness of eteplirsen.

11 Those conclusions and recommendations should
12 be viewed as just that, preliminary. They should
13 not be viewed as the opinion or conclusion of
14 anyone other than the author of the individual
15 review, and they should not be viewed as
16 necessarily indicative of our final decision.

17 The reason we are here today is to gain your
18 input into some of the challenging issues we have
19 confronted during our review process so that we may
20 incorporate it into our ultimate decision on
21 approvability.

22 As will be discussed in detail during the

1 presentations you will hear today, eteplirsen is
2 theorized to lead to clinical benefit by
3 potentially increasing the production of a
4 truncated form of dystrophin. The natural form of
5 dystrophin, a key muscle protein, is profoundly
6 deficient in DMD, and the gene defect giving rise
7 to this deficiency is thought to be the primary
8 underlying cause of the disease.

9 How much of this truncated dystrophin
10 eteplirsen is designed to produce could be helpful
11 is an open question. The committee will recall its
12 previous discussion in November during which the
13 committee expressed concern about the plausibility
14 of clinical benefit being derived from extremely
15 small increases in dystrophin on the order of
16 post-treatment absolute values of less than
17 1 percent of normal.

18 As you will hear today, we are again
19 confronted with post-treatment absolute values in
20 that range.

21 You will also hear of concerns concerning
22 limitations on the interpretation of these post-

1 treatment absolute values. Of possible relevance
2 to this question of how much dystrophin could
3 convey clinically meaningful benefit is the fact
4 that some patients with Duchenne have very small
5 amounts of the naturally occurring truncated
6 dystrophin that does not appear to be associated
7 with an appreciable slowing of muscle degeneration.

8 Some patients with a related form of
9 muscular dystrophy, Becker muscular dystrophy,
10 naturally produce such a truncated dystrophin and
11 have only mild disease. In these Becker patients,
12 the truncated dystrophin is present at levels often
13 50 to 100 percent of what normal dystrophin would
14 be.

15 The sponsor conducted three studies of
16 eteplirsen, two small exploratory studies, which
17 are referred to as study 28 and study 33, to assess
18 the potential of eteplirsen to increase dystrophin
19 expression, and a single small 12-patient clinical
20 study, which is referred to as study 201/202 but is
21 really a single study with two phases, to further
22 assess the extent to which eteplirsen might

1 increase expression of dystrophin and to explore
2 the potential clinical benefit.

3 As I said, though an initial phase of
4 study 201/202, the 201 portion, was placebo-
5 controlled, dividing the patients into 3 groups of
6 4 patients each, the second phase of the study was
7 an open-label extension.

8 Despite strong encouragement from FDA to
9 conduct an adequately powered, randomized, placebo-
10 controlled trial or trials to assess the clinical
11 effect of eteplirsen, the sponsor asserted that the
12 conduct of such a trial would be prohibitively
13 difficult.

14 Given the sponsor's assertions, FDA advised
15 the sponsor on the issues involved in an attempt to
16 compare the open-label extension data to data from
17 a natural history cohort identified post hoc that
18 might serve as an external control, emphasizing
19 that interpretation of such a comparison could be
20 difficult and that the acceptability of this
21 approach would be a matter for NDA review.

22 The sponsor identified two DMD patient

1 registries, one in Italy and one in Belgium, as a
2 source of external data, and conducted a post hoc
3 comparison of the data from the open-label
4 extension to data from these two registries.

5 The sponsor offers as primary support for
6 approval a comparison of ambulatory ability based
7 on 6-minute walk distance in these two groups. As
8 is clear from the background documents provided to
9 you, we have significant concerns about the
10 validity of this comparison.

11 It is these two primary issues, one, the
12 data concerning dystrophin, we will ask you to
13 discuss and vote on whether there is substantial
14 evidence from adequate and well-controlled studies
15 as required under the Food, Drug, and Cosmetic Act
16 that eteplirsen induces a production of dystrophin
17 to a level that is reasonably likely to predict
18 clinical benefit.

19 Two, the data concerning the historically
20 controlled comparison of ambulatory ability, we'll
21 ask you to discuss and vote on whether substantial
22 evidence of effectiveness has been provided as

1 required under the Food, Drug, and Cosmetic Act by
2 the clinical results of a single historically
3 controlled efficacy study. It is these two issues
4 that we primarily bring to the committee for your
5 discussion.

6 Why do we focus on these two issues in this
7 manner? We must, as required by law, determine
8 whether there is substantial evidence of
9 effectiveness of eteplirsen in order to consider
10 approval. Both of these issues have the potential
11 to provide such evidence if the data are
12 interpretable.

13 Substantial evidence of effectiveness is a
14 crucial concept and one worth spending a few
15 moments discussing. Prior to 1962, evidence of
16 effectiveness was not even required for drug
17 approval, it was only necessary to demonstrate
18 safety.

19 The 1962 Kefauver-Harris amendments to the
20 Food, Drug, and Cosmetic Act included a provision
21 requiring manufacturers of drug products to
22 establish a drug's effectiveness by substantial

1 evidence, an important advance that signaled the
2 beginning of the modern era of drug development and
3 regulation.

4 Senator Kefauver considered these amendments
5 requiring evidence of effectiveness his finest
6 achievement in consumer protection, and their
7 adoption laid the groundwork for FDA's development
8 of an evidence-based model for drug evaluation
9 decisions that stands as the global standard.
10 Their importance is impossible to overstate.

11 "Substantial evidence of effectiveness,"
12 these words are not vague words to be defined
13 according to whim or fashion. Substantial evidence
14 was defined in Section 505(d) of the Act as, quote,
15 "Evidence consisting of adequate and well-
16 controlled investigations, including clinical
17 investigations, by experts qualified by scientific
18 training and experience to evaluate the
19 effectiveness of the drug involved on the basis of
20 which it could be fairly and responsibly be
21 concluded by such experts that the drug will have
22 the effect it purports or is represented to have

1 under the conditions of use prescribed,
2 recommended, or suggested in the labeling or
3 proposed labeling thereof." It's a mouthful, but
4 that's what it is.

5 Adequate and well-controlled investigations
6 are further defined in FDA regulations as having
7 various characteristics, one of which is the use of
8 a design that permits a valid comparison with a
9 control to provide a quantitative assessment of
10 drug effect. Of the generally recognized controls
11 that are recognized in regulations, all are
12 concurrent except for the last one known as
13 historical control.

14 The regulations note that, quote, "Because
15 historical control populations usually cannot be as
16 well assessed with respect to pertinent variables,
17 as can concurrent control populations, historical
18 control designs are usually reserved for special
19 circumstances.

20 "Examples include studies of diseases with
21 high and predictable mortality, for example certain
22 malignancies, and studies in which the effect of

1 the drug is self-evident, for instance general
2 anesthetics or drug metabolism."

3 You will note that investigations are
4 referred to in the law, investigations being
5 plural. It has long been FDA's position that
6 Congress generally intended to require at least two
7 adequate and well-controlled studies, each
8 convincing on its own, to establish effectiveness.

9 The usual requirement for more than one
10 adequate and well-controlled investigation reflects
11 the need for independent substantiation of
12 experimental results. Independent substantiation
13 of a favorable result protects against the
14 possibility that a chance occurrence in a single
15 study will lead to an erroneous conclusion that a
16 treatment is effective.

17 Any clinical trial may be subject to
18 unanticipated, undetected systemic biases. These
19 biases may operate despite the best intentions of
20 sponsors and investigators and may lead to flawed
21 conclusions.

22 There are circumstances in which FDA may

1 rely on something less than at least two adequate
2 and well-controlled studies. In 1997, the FDA
3 Modernization Act, which we refer to as FDAMA,
4 amended Section 505(d) of the Act to make it clear
5 that FDA may consider data from one adequate and
6 well-controlled clinical investigation and
7 confirmatory evidence to constitute substantial
8 evidence if FDA determines that such data and
9 evidence are sufficient to establish effectiveness.

10 Reliance on only a single adequate and
11 well-controlled efficacy study to establish
12 substantial evidence of effectiveness is also a
13 possibility. Because reliance on two adequate and
14 well-controlled studies is generally more secure
15 than reliance on one similarly persuasive study,
16 FDA has generally relied on only a single adequate
17 and well-controlled efficacy study to support
18 approval only in cases in which a single
19 multicenter study of excellent design provided
20 highly reliable and statistically strong evidence
21 of an important clinical benefit, such as an effect
22 on survival, and a confirmatory study would have

1 been difficult to conduct on ethical grounds.

2 Examples of typical characteristics of a
3 single adequate and well-controlled study that
4 could make the study adequate to support an
5 effectiveness claim include those that you see
6 here. These are examples, they are not
7 requirements, but they have a common theme in that
8 such characteristics serve to increase the
9 reliability of the reported findings and might
10 allow the results of a single study to effectively
11 provide a similarly persuasive amount of
12 information as two independent adequate and
13 well-controlled studies.

14 Because of the inherent vulnerabilities
15 involved in reliance on a single study, it is
16 critical that the possibility of an incorrect
17 outcome be considered and that all the available
18 data be examined for their potential to either
19 support or undercut reliance on a single trial.

20 Generally, when discussing substantial
21 evidence of effectiveness, we are discussing
22 evidence based on primary assessment of clinically

1 meaningful effects, and such substantial evidence
2 may result in a conventional approval.

3 Accelerated approval is a particular type of
4 approval that FDA may grant to a product for a
5 serious or life-threatening disease or condition
6 upon a determination that the product has an effect
7 on a surrogate endpoint that is reasonably likely
8 to predict clinical benefit; or on a clinical
9 endpoint that can be measured earlier than
10 irreversible morbidity or mortality and is
11 reasonably likely to predict an effect on such; or
12 some other clinical benefit taking into account the
13 severity, rarity, or prevalence of the condition
14 and the availability or lack of alternative
15 treatments.

16 FDA has discussed accelerated approval in
17 the context of DMD specifically in our DMD guidance
18 that I mentioned earlier. We have indicated that
19 biomarkers that reliably reflect the health and
20 amount of skeletal muscle may, if supported by
21 sufficient scientific evidence and acceptable
22 analytical methods, be used as endpoints to support

1 accelerated approval of a new DMD drug. Such a
2 biomarker would have to be reasonably likely to
3 predict clinical benefit in order to be acceptable
4 as a basis for accelerated approval.

5 Concerning accelerated approval, it is
6 crucial to recognize that the evidentiary standards
7 for effectiveness are not lower for biomarker or
8 intermediate clinical endpoints used to support
9 accelerated approval. Substantial evidence of an
10 effect on those biomarker or intermediate clinical
11 endpoints must be demonstrated.

12 As we discussed, substantial evidence comes
13 from adequate and well-controlled investigations
14 and is evidence that the drug will have the effect
15 it purports or is represented to have. Accelerated
16 approval concerns the character of the endpoints,
17 not the strength of the results on those endpoints.

18 An effect on an endpoint supporting
19 accelerated approval must be an effect on an
20 endpoint that in its character is reasonably likely
21 to predict clinical benefit, and in its
22 persuasiveness provide substantial evidence of

1 effectiveness from adequate and well-controlled
2 trials just as substantial evidence of
3 effectiveness on a clinically meaningful endpoint
4 from adequate and well-controlled trials supports
5 conventional approval.

6 It is a common misconception that data not
7 sufficiently persuasive for conventional approval
8 can be shifted over to consideration for
9 accelerated approval. Accelerated approval is not
10 a rescue strategy for suggestive data that are
11 insufficient for conventional approval.

12 Although it is possible to consider
13 suggestive data, insufficient on their own for
14 conventional approval, in a supportive role to
15 complement substantial evidence of effectiveness
16 that has been provided for a biomarker, accelerated
17 approval cannot be used to compensate for weak or
18 inconsistent clinical findings.

19 It is more common to consider accelerated
20 approval when data on the biomarker are available
21 in advance of clinical results. If unconvincing
22 clinical results are reported in the face of what

1 are thought to be promising biomarker results, this
2 would tend to weaken confidence that the biomarker
3 results are reasonably likely to predict benefit.

4 As I mentioned previously, under the proper
5 circumstances, FDA regulations recognize that
6 historical control studies can be considered
7 adequate and well-controlled studies and used to
8 support approval. There are many issues to
9 consider with the interpretability of such studies
10 as discussed in an international guideline
11 concerning choice of control group in clinical
12 trials.

13 These issues are of critical importance when
14 considering any historical control trial, and so
15 Dr. Bob Temple will present a separate discussion
16 of this important topic that will help inform
17 issues specific to the eteplirsen application that
18 will be subsequently discussed by the review team.

19 Following my remarks, the applicant,
20 including consultants from the academic and
21 advocacy arenas, will make a series of
22 presentations supportive of eteplirsen's benefit,

1 and you will have a chance to ask clarifying
2 questions.

3 After a short break, we will reconvene for a
4 series of presentations from the FDA, beginning
5 with comments from Dr. Janet Woodcock, the director
6 of the Center for Drug Evaluation and Research.

7 Next, as I noted, Dr. Temple, the center's
8 deputy director for clinical science and the acting
9 deputy director of the Office of Drug Evaluation I,
10 will discuss issues to consider with external
11 control studies.

12 Following that, Dr. Ron Farkas, a team
13 leader in the neurology division, and Dr. Ash Rao,
14 the acting chief of the Laboratory of Applied
15 Biochemistry, will present a detailed discussion of
16 the multi-disciplinary team's concerns and findings
17 regarding the eteplirsen application.

18 Dr. Eric Bastings, the neurology division's
19 deputy director, will provide concluding remarks.
20 You will again have a chance to ask clarifying
21 questions.

22 After a break for lunch, we will have the

1 open public hearing followed by discussion and
2 questions to the committee. The FDA presentations
3 will highlight a number of issues that we'll ask
4 you to discuss and respond to, including the
5 strengths and weaknesses of findings regarding
6 dystrophin, the strength and weaknesses of the
7 clinical findings, the relative impacts of various
8 clinical outcome measures that were assessed, and
9 of fundamental importance, the comparability of the
10 eteplirsen and control groups. We have provided
11 discussion topics and questions to help frame your
12 discussion following the presentations.

13 As you consider the background materials, I
14 remind you that we have been made aware that some
15 of you have been approached by outside
16 organizations; some of you on the committee have
17 received materials that were ostensibly germane to
18 these proceedings.

19 I think you've been informed by the advisory
20 committee staff, and I've been asked to remind you,
21 that you are to consider only the background
22 documents that were provided to you by the

1 applicant and by the agency, not any other
2 materials that were provided to you by outside
3 agencies.

4 I urge the committee to keep several things
5 in mind as the remainder of the meeting gets
6 underway. It might fairly be asked, although you
7 say no final decision on approvability has been
8 made, isn't that disingenuous. Your background
9 materials are highly critical and you describe
10 fundamental concerns about the application. Why
11 was this even accepted for review?

12 It is important to note that when we were
13 involved in discussions with Sarepta about
14 application submission, it was our understanding
15 that dramatic increases of dystrophin were being
16 observed, as much as 50 percent of normal values,
17 and that this was accompanied by dramatic and
18 unprecedented clinical stabilization of patients.
19 Such reports, unless obviously dismissible on face,
20 clearly would warrant careful review.

21 An important, perhaps the important, issue
22 we bring to you for discussion, is comparability.

1 You will hear both scientific and emotional
2 commentary and testimony about how eteplirsen
3 treated patients are doing. We do not challenge
4 that. The concerns we raise about the application
5 are not trying to suggest that what these patients
6 are reporting, completing, achieving, living is not
7 real. It clearly is.

8 What we are concerned about is the accuracy
9 and acceptability of the comparison being made to a
10 group that could differ in important ways, both
11 known and unknown, from the eteplirsen treated
12 patients.

13 Please, as what will surely be an emotional
14 discussion might tend towards a suggestion that we,
15 the FDA, do not accept these reported improvements
16 as important, know that if these results were from
17 a well-designed, interpretable trial, there likely
18 wouldn't be much to talk about. We likely wouldn't
19 even be here.

20 We come to you with sincere concerns not
21 because we take some perverse delight in keeping
22 new medicines from those who urgently need them, as

1 has been somewhat bizarrely suggested by some, but
2 because it is our, we the FDA, and you our advisory
3 committee, collectively, it is our fundamental
4 responsibility to ensure, as required by law, that
5 the treatments we approve are effective.

6 Keep your focus on the comparability of
7 these groups and whether we can truly conclude that
8 what these few eteplirsen treatment patients are
9 experiencing is clearly outside the natural
10 variability of the disease.

11 There are many people here. It's
12 extraordinarily important that everybody that has
13 come is here, and it's extraordinarily important
14 that those who are watching from afar are doing so.
15 As Dr. Alexander noted, it's entirely possible that
16 emotions will run high. People are passionate and
17 invested, and we understand that.

18 Investment can influence perception. I have
19 no doubt that if I had DMD and I was receiving
20 eteplirsen, that I would attribute all of the
21 success of my activities to eteplirsen. I may be
22 right about that. The issue is whether or not we

1 have a group to which we can compare reliably.

2 I am truly glad everyone is here. The
3 outpouring of support for those with this disease
4 is nothing short of spectacular. It provides
5 needed context and awareness, but anecdote and
6 emotion do not change the data with which we are
7 confronted, no matter the attendance.

8 Whether we have 1,000 here or only 1, the
9 same data will be there to consider. And I know
10 that each of you will render the same
11 scientifically sound opinions and judgments to a
12 full room that you would to an empty one.

13 Speaking of a full room, even as I am deeply
14 moved by those here in attendance, it makes me
15 realize that I have a message for those, many who
16 are watching these proceedings, both with Duchenne
17 and even for illnesses other than Duchenne,
18 especially diseases that occur only in small
19 numbers, and those folks who have diseases that do
20 not have highly organized support systems and
21 advocacy machines capable of assembling such a
22 massive effort as that which we see today.

1 It must be frightening to think that there
2 is no way that you can be heard. I want to
3 reassure you, it is not the volume of the message,
4 but the content. We listen, and we listen closely.
5 To all those out there watching, your voice is
6 heard.

7 We have brought to you important issues for
8 which we seek your advice. These are complicated
9 issues, and we will be asking you to vote on
10 several questions, and we'll be listening very
11 carefully to your discussion of all these topics.
12 The content of your discussion and explanation of
13 your reasoning is of great importance to us.

14 Again, no final decision has been made on
15 approvability, and we very much look forward to the
16 insights you will provide. We have convened this
17 committee because we feel that a final decision
18 requires your input and advice.

19 Thank you for the substantial efforts you
20 have made in preparing for and attending this
21 meeting, and thank you for the important work you
22 will do today. It is vital.

1 Dr. Alexander, thank you for the time to
2 offer my comments, and I return the proceedings to
3 you.

4 DR. ALEXANDER: Thank you, Dr. Dunn.

5 Both the Food and Drug Administration and
6 the public believe in a transparent process for
7 information-gathering and decision-making. To
8 ensure such transparency at the advisory committee
9 meeting, FDA believes that it is important to
10 understand the context of an individual's
11 presentation.

12 For this reason, FDA encourages all
13 participants, including the sponsor's non-employee
14 presenters, to advise the committee of any
15 financial relationships that they may have with the
16 firm at issue, such as consulting fees, travel
17 expenses, honoraria, and interests in the sponsor,
18 including equity interest and those based upon the
19 outcome of the meeting.

20 Likewise, FDA encourages you at the
21 beginning of your presentation to advise the
22 committee if you do not have any such financial

1 relationships. If you choose not to address this
2 issue of financial relationships at the beginning
3 of your presentation, it will not preclude you from
4 speaking. We will now proceed with Sarepta
5 Therapeutics presentations.

6 **Applicant Presentation - Shamim Ruff**

7 MS. RUFF: Dr. Alexander, members of the
8 advisory committee, and FDA, good morning. My name
9 is Shamim Ruff. I'm the head of regulatory affairs
10 and quality at Sarepta. I am honored today to
11 begin our formal presentation on eteplirsen for the
12 treatment of Duchenne muscular dystrophy, or DMD.

13 Before we begin, however, permit me two
14 brief but important acknowledgements. First, those
15 who suffer from DMD, many of them here today, and
16 in particular the 12 boys who allowed us to follow
17 them for 4 years in our trials, this important
18 dialogue today is for you.

19 Second, to those so deeply committed to
20 combating this crippling disease, including
21 caregivers and investigators, we thank you for your
22 continued commitment.

1 We at Sarepta fully recognize that what we
2 are about to present to you is not a traditional
3 data set. It must be understood that DMD is an
4 enormously challenging disorder to study due to its
5 rarity, heterogeneity, and rapid progression.
6 Nevertheless, in that context, we believe we have
7 done both important and groundbreaking work.

8 Our colleagues at the FDA have
9 understandably challenged us on several fronts. We
10 both appreciate and welcome that challenge as it
11 has caused us to think more deeply about DMD and we
12 believe raises important questions for future
13 research.

14 Today, we will address the key issues head
15 on and offer you data that demonstrate three
16 important findings.

17 First, eteplirsen unequivocally produces de
18 novo dystrophin protein. Second, the external
19 control is valid, reliable, and reflective of the
20 natural history of DMD. And third, eteplirsen
21 treated boys behave differently to DMD natural
22 history with a large magnitude of benefit on the

1 6-minute walk test as well as loss in ambulation.

2 We look forward to a robust, scientific, and
3 candid discussion and thank the panel for your
4 participation in helping us advance the
5 understanding of this disease.

6 DMD is a pediatric X-linked recessive
7 neuromuscular disease caused by mutations in the
8 DMD gene that prevent the production of functional
9 dystrophin protein. Dystrophin plays a vital role
10 in the structure, function, and preservation of
11 muscle cells, and in its absence, patients follow a
12 predictable disease course.

13 Boys develop muscle weakness in their first
14 few years of life, then in early adolescence lose
15 the ability to walk. Complications from this loss
16 of ambulation have a major cascading effect,
17 including scoliosis, compromised respiratory
18 function, and premature death, usually in the
19 mid-to late-20s.

20 As you will hear in a moment from
21 Dr. Mercuri, despite welcome improvements in the
22 standard of care, including steroids and other

1 supportive measures, there is a profound unmet
2 medical need for DMD patients with no approved
3 therapies in the United States.

4 The proposed indication for eteplirsen is
5 for the treatment of DMD patients with mutations in
6 the dystrophin gene amenable to exon 51 skipping.
7 The proposed dose is 30 milligrams per kilogram,
8 administered as weekly IV infusions.

9 Here's a breakdown of the genetic mutations
10 for the 9 to 12,000 boys who suffer from DMD in the
11 United States. The dark blue section indicates a
12 subset of DMD boys who are amenable to skipping
13 exon 51 and can be treated with eteplirsen. This
14 represents 13 percent of the total DMD population
15 and shows how eteplirsen is one of the first
16 examples of precision genetic medicine.

17 In order to understand how eteplirsen works,
18 let's look at the underlying disease process and
19 how the drug addresses it. Here's a small section
20 of the dystrophin gene where we see a normal
21 reading of the mRNA by the ribosome, which in turn
22 produces a dystrophin protein of normal length.

1 But here's what happens in a DMD patient,
2 deletion mutations in the dystrophin gene disrupt
3 the reading frame; thus, the ribosome can't
4 correctly read the message after the deletion,
5 which results in little to no dystrophin, the
6 hallmark of the severe DMD phenotype.

7 Eteplirsen induces a skipping of exon 51,
8 restoring the reading frame and allowing the
9 production of a shorter, internally deleted,
10 functional dystrophin protein.

11 As I previously mentioned, Sarepta comes to
12 you today with a non-traditional data set, a small
13 study with a natural history comparator. Yet,
14 while the package may be unusual, it is not
15 unprecedented in the rare disease arena. Of note,
16 although the study size is not extensive, it is a
17 4-year clinical follow-up period that gives us both
18 robust insight into the benefit of eteplirsen.

19 So how did we arrive at this point? Over
20 the past couple of years, we've participated in
21 more than a dozen meetings with the FDA to agree on
22 an appropriate data package for an NDA submission.

1 Let me highlight a significant series of events
2 that transpired during that time.

3 First, due to the initial encouraging
4 results of our phase 2 study, the DMD community
5 expressed an unwillingness to participate in a
6 placebo-controlled study. This led FDA, in April
7 of 2014, to ask us to obtain natural history or
8 external control data for comparison. We did so,
9 and comparison to that untreated external group now
10 serves as the primary basis for establishing
11 clinical efficacy.

12 In December 2015, the agency made a request
13 for an additional 4-year data. The results were
14 striking with a 162-meter benefit in the 6-minute
15 walk test. In addition, Kaplan-Meier estimates
16 showed a 17 percent loss of ambulation for
17 eteplirsen compared to 85 percent for the untreated
18 external control.

19 Because of this new and important data, FDA
20 in February of 2016 extended the PDUFA date by
21 3 months. In recognition of this unique set of
22 circumstances, Sarepta is seeking accelerated

1 rather than full approval.

2 FDASIA, the Food and Drug Administration
3 Safety and Innovation Act, was signed into law in
4 July of 2012. It expands and encourages the
5 broader use of accelerated approvals beyond HIV and
6 oncology to rare diseases such as DMD.

7 Importantly, FDASIA also requires FDA to
8 seek patient input during drug development as well
9 as during the review of the application. Of note,
10 accelerated approval allows for an acceptable
11 degree of uncertainty regarding the anticipated
12 benefit.

13 Essentially, there are three specific
14 requirements of accelerated approval, and
15 eteplirsen meets them all. First, the disease has
16 to be serious and life-threatening and the drug has
17 to provide benefit over existing therapies. We
18 clearly meet this.

19 Second, approval must be based on either a
20 surrogate endpoint or an intermediate endpoint that
21 are reasonably likely to predict benefit. For
22 eteplirsen the FDA provided us two pathways, either

1 dystrophin as a surrogate endpoint or the 6-minute
2 walk test as an intermediate endpoint.

3 Lastly, post-marketing confirmatory studies
4 are required to verify the anticipated effect.
5 Sarepta in consultation with the FDA agreed to
6 conduct two post-marketing confirmatory studies.

7 We recognize that accelerated approval does
8 not change the statutory requirements, and today we
9 will demonstrate to you that the endpoints selected
10 are appropriate and we have established substantial
11 evidence of effectiveness.

12 So what constitutes substantial evidence of
13 effectiveness? It's important to note that the
14 intent of the statute was to reduce the chance of
15 an incorrect conclusion. Ideally, a randomized
16 placebo-controlled study would be used, but this is
17 not essential.

18 Historical controls can be considered
19 adequate and well controlled, particularly in the
20 rare disease arena, and there are multiple examples
21 of FDA approvals based on small studies and
22 historical controls.

1 Before we go through the rest of the
2 presentation, I'd like to address a few of the
3 concerns FDA raised and offer our position
4 beginning with dystrophin. First of all, in the
5 week 180 analyses, FDA only focused on the Western
6 blot results and discounted the immunohistochemical
7 results.

8 Experts suggest there is no single
9 definitive method for dystrophin quantification.
10 Multiple complementary methods are required to get
11 the full picture. Dr. Kaye will describe how
12 eteplirsen showed significant dystrophin production
13 using three distinct methods.

14 Second, eteplirsen Western blot results were
15 compared to published references going back to 1989
16 that were semi-quantitative at best. The more
17 appropriate comparison is to look at fold increases
18 over baseline within the same assay.

19 Finally, they concluded that the quantity of
20 dystrophin produced was not clinically relevant.
21 However, research in the field suggests that even
22 small amounts of dystrophin can have a clinical

1 effect. Of note, this is the first time that a
2 therapeutic has demonstrated an unequivocal
3 increase in dystrophin expression.

4 FDA also identified three main concerns with
5 our 6-minute walk test results. First, they
6 highlighted that study 201 failed to show an
7 advantage over eteplirsen versus placebo for the
8 6-minute walk test at week 24. I'd like to clarify
9 that percent dystrophin fibers was the primary
10 endpoint for that study, not the 6-minute walk
11 test.

12 They also outlined a concern about the use
13 of external control to determine efficacy. The key
14 issue here is the potential for bias due to
15 differences in the two patient populations. To be
16 clear, there were predefined selection criteria for
17 the external control, which were based on the
18 inclusion criteria for the eteplirsen 201 study.

19 Also, the key baseline characteristics were
20 highly comparable, as were the standards of
21 supportive care. They both had up to 4 years of
22 longitudinal data, and 6-minute walk test

1 measurement was according to the same standardized
2 protocol. The FDA guidelines also state that for
3 an external control comparison to be interpretable,
4 the effect size has to be large. We certainly saw
5 a compelling effect size.

6 Finally, we will provide longitudinal
7 comparisons to multiple databases that clearly show
8 eteplirsen-treated boys behaved differently from
9 natural history.

10 As you review the data we will present
11 today, we ask that you keep an open mind and
12 critically evaluate eteplirsen in context of
13 accelerated approval, the rarity of the disease,
14 and the profound unmet need. We know for certain
15 that DMD boys, if left untreated, will progress in
16 their disease with a known risk of serious and
17 fatal consequences.

18 Given this, along with the production of
19 de novo dystrophin protein and the benefits seen on
20 the 6-minute walk test and loss in ambulation is
21 the degree of uncertainty about whether the therapy
22 will result in the anticipated clinical benefit

1 acceptable for accelerated approval.

2 Turning now to the rest of the agenda, we
3 are extremely fortunate to have some of the world's
4 eminent experts in DMD available today. In a few
5 moments Dr. Mercuri, who provided much of the data
6 for the external control, will provide an overview
7 of the disease background and natural history.

8 Dr. Kaye, a pediatric neurologist and
9 interim CEO at Sarepta, will present the efficacy
10 data, followed by Dr. Eliopoulos, senior medical
11 director, who will review the safety data.

12 Dr. Mendell, the principal investigator for the
13 pivotal eteplirsen studies, will provide a clinical
14 perspective on the benefit-risk of eteplirsen. And
15 finally, Dr. Kaye will return to provide concluding
16 remarks.

17 In addition to answer questions, we also
18 have available Dr. Muntoni and Dr. Wilton, who are
19 two of the world's leading experts on dystrophin
20 methodologies; Dr. Muntoni was also the PI for our
21 phase 1 studies; Dr. Kinane, who is a pediatric DMD
22 pulmonary expert; Dr. McDonald, who is a leading

1 DMD natural history expert in the U.S. and study
2 chair of the Synergy Duchenne Natural History
3 study; and last but not least, Dr. Lu, who is our
4 consultant statistician.

5 Please note that after the concluding
6 remarks by Dr. Kaye, there will be a presentation
7 by the Jett Foundation, who requested that we
8 donate a portion of our allotted time for a
9 separate and independent presentation. We are
10 happy to do so.

11 Christine McSherry, executive director of
12 the Jett Foundation and the mother of a boy with
13 DMD, will provide a review of the patient and
14 caregiver reported outcomes collected from
15 eteplirsen trials. And with that, I'm happy to
16 invite Dr. Mercuri to come to the podium and
17 describe the natural history of DMD.

18 **Applicant Presentation - Eugenio Mercuri**

19 DR. MERCURI: Thank you.

20 Good morning. My name is Eugenio Mercuri.
21 I'm a pediatric neurologist working in Rome and
22 coordinator of the Italian Duchenne network. I'm a

1 paid consultant to Sarepta in preparation for this
2 meeting, and I have no direct financial interest in
3 the outcome of the meeting today.

4 As Ms. Ruff explained, Duchenne muscular
5 dystrophy is caused by mutation to the dystrophin
6 gene. In healthy boys, dystrophin is normally
7 expressed and contributes to the protection of
8 muscle fibers during contraction, acting as a
9 molecular shock absorber. In DMD, the absence of
10 dystrophin leads to progressive muscle degeneration
11 with progressive loss of muscle function.

12 Here we see a series of muscle biopsies
13 performed at different ages. The first picture on
14 the left shows a biopsy performed at birth. Even
15 though we know that dystrophin is already absent,
16 the muscle tissue appears normal.

17 As shown in the second picture, already in
18 the first years, there are aspects of inflammation
19 and necrosis with loss of functional muscle tissue
20 that increases over the years, and the major
21 tipping point in the disease progression occurs
22 around the age of 7.

1 At this age, you can see that muscle cells
2 are increasingly replaced by fibrotic tissue and
3 fat. Finally, in the fourth picture of a biopsy
4 performed in an older boy, we see a complete loss
5 of the normal muscle architecture.

6 Clinically, in the first month, there are no
7 obvious clinical signs, but a blood test will
8 reveal elevated CK levels, which is indicative of
9 muscle damage. DMD boys often show some delayed
10 milestones, but the diagnosis is on average after
11 the age of 3 years. At a time when they are
12 supposed to learn to hop, jump, and run, DMD boys
13 have difficulty running and hopping, standing from
14 supine, and in climbing stairs. After the age of
15 7, there is a more rapid decline leading to loss of
16 ambulation in early adolescence.

17 Historically, before the era of steroids,
18 DMD boys did not walk beyond the age of 12, with a
19 median age at loss of ambulation of 9.5 years.
20 Contemporary studies, however, have shown that the
21 median age with current standards of care is
22 between 11 and 13 years, and this is consistent

1 across countries.

2 Similar results were found in several U.S.
3 and EU countries as well as in Japan. Recently, a
4 new global data set from CINRG shows that the
5 median age for loss of ambulation for boys amenable
6 for skipping exon 51 is 12 years.

7 Loss of ambulation is an important endpoint,
8 but we hear from Duchenne boys and their families
9 that even after that, many other important physical
10 functions are progressively affected. At loss of
11 ambulation, boys are generally still able to
12 perform shoulder movements, but later there is a
13 progressive loss of upper limb function. And after
14 the age of 20, arm movements are generally limited
15 to distal movements of the fingers.

16 Respiratory impairment, which declines
17 steadily throughout the patient's life, usually
18 becomes significant enough to require nocturnal
19 ventilation in the patient's 20s, followed by
20 full-time ventilation. Heart muscle is also
21 affected, and despite advances in care, most
22 patients will die from cardiac disease in their

1 mid-20s. The mean survival is approximately
2 27 years.

3 Next, I'll talk about how disease
4 progression is most commonly measured in clinical
5 and research settings. The 6-minute walk test is
6 the most widely used measure in Duchenne
7 intervention or in natural history status. It's an
8 integrated global measure that is affected by
9 strength, endurance, and cardiorespiratory status.

10 As you can see in the video, the test is
11 performed by asking the patients to walk as fast as
12 possible for 6 minutes around a 25-meter course,
13 measuring the distance covered in 6 minutes.

14 The test has been slightly modified for
15 children with Duchenne from the original American
16 Thoracic Society version with introduction of a
17 second examiner that stays close to the patient for
18 safety reasons, as you can see on the video.

19 Another important modification is the use of
20 standardized encouragement to maintain the child's
21 attention and to limit bias. The examiner -- this
22 is very important. The examiner must follow very

1 strict instructions providing the wording and the
2 timing of when the encouragement should be given.

3 In clinical trials and in natural history
4 status, experienced and trained physiotherapists
5 follow very strictly these procedures. As a
6 result, the 6-minute walk test has been found to be
7 a sensitive, reliable, and reproducible outcome
8 measures in a multicenter setting.

9 It also has the highest test/retest
10 reliability of the commonly used measure for
11 Duchenne. And another advantage of the 6-minute
12 walk test is its high correlation with other
13 functional measures.

14 In particular, it shows a correlation with
15 the North Star Ambulatory Assessment. The scale
16 was originally developed as a clinical tool for
17 ambulant Duchenne and has only recently been
18 validated as an outcome measure. Although it's
19 less statistically robust than the 6-minute walk
20 test, it provides important additional clinical
21 information.

22 The scale includes 17 items. Each item is

1 scored from zero, if the boy is unable to perform
2 the task independently, to 2 if he's able to
3 complete the task. The order of the items follows
4 the progression of the disorder. Younger boys on
5 steroids are generally able to complete most
6 activities, but with increasing age, especially
7 after the age of 7, they gradually lose abilities
8 with the predictable disease course from bottom to
9 top.

10 Focus groups with families made a strong
11 point that each of the 17 activities are related to
12 important activities of daily living and losing
13 even one of them represents an irreversible loss
14 that is important and meaningful for their quality
15 of life.

16 Using these tools, we can measure sequential
17 loss of function in Duchenne. For example, rise
18 time is lost at early stage. It's actually the
19 first activity that is lost when boys are still
20 able to walk independently and perform the 6-minute
21 walk test.

22 The 6-minute walk test provides a major

1 functional ambulation, and once boys are unable to
2 complete the test, they are generally not able to
3 walk outdoors or at school anymore. In some cases,
4 the 10-meter test can be measured in these last
5 stages of ambulation and can have a positive value
6 at the time when they score zero on the 6-minute
7 walk test. When happening however, this usually
8 lasts only a few months. At this stage, they are
9 usually only able to perform minimal functional
10 walking at home, often holding on to furniture and
11 walls for safety as the risk of falls and bone
12 fracture is very high.

13 This has caused some confusion in the
14 definition of loss ambulation with different
15 definition in the literature. Moreover, this
16 definition is more challenging in retrospective
17 studies. For example, in the CINRG studies, which
18 allowed for retrospective outcomes, loss of
19 ambulation is defined as patient reported full-time
20 wheelchair use confirmed by the 10-meter test when
21 possible. In contrast, in many prospective
22 studies, including the Italian Telethon and Leuven

1 studies, the loss of ambulation is defined as zero
2 meters on the 6-minute walk test.

3 I will now review what we have learned from
4 recent natural history data. Using the 6-minute
5 walk test, we have been able to identify a number
6 of prognostic factors affecting disease
7 progression. The role of steroids is well-known,
8 but recently, we have been able to identify other
9 factors that affect the rate of decline, such as
10 age, type of mutations, or the values of the
11 6-minute walk test.

12 As I mentioned earlier, boys with Duchenne
13 initially gain in functional activity before
14 experiencing a progressive and irreversible
15 decline. In this study, 191 Duchenne patients were
16 assessed at different ages and followed for 1 year.
17 Patients who were younger than 7 when first
18 assessed improved their 6-minute walk performance
19 after 1 year by nearly 30 meters. In contrast,
20 those who were older than 7 had already started
21 declining by nearly 40 meters after 1 year.

22 This information has been extremely helpful

1 in identifying a more homogeneous declining patient
2 population in more recent studies.

3 Let's focus on the group of 68 patients who
4 were above the age of 7 when they were first
5 assessed. In a follow-on study assessing 6 minute
6 changes over 3 years, we not only confirmed that on
7 average there is a decline in the first year, but
8 also that there was progressive deterioration that
9 became more marked with each increasing year.

10 In addition to age, genetic mutation has
11 also been shown to impact performance on the 6-
12 minute walk test. In this study of 191 patients
13 with Duchenne, some differences in baseline
14 6-minute walk test were observed for different
15 mutation types. The vertical line in the middle of
16 the graph represents the mean values for the whole
17 cohort. When we subdivide the cohort according to
18 the type of mutation, all the different sub-groups
19 were relatively close to the mean, but some
20 differences could be observed. Patients with
21 duplications or point mutations had better
22 performance and on average walked more meters than

1 patients with deletions.

2 Some variations were also observed within
3 the boys with deletions depending on which exons
4 were deleted. Patients with exon deletions
5 amenable to skipping exons 45, 51, or 53 all walked
6 less far, indicating a more severe phenotype. In
7 contrast, patients with deletions amenable to
8 skipping exon 44 walked further at baseline.

9 This is consistent with other reports
10 indicating a milder phenotype for this patient
11 group, and it's probably related to the fact that
12 these patients, unlike other groups with deletions,
13 have low levels of naturally occurring dystrophin.
14 This is also corroborated by a recent CINRG study,
15 which reports that Duchenne patients with deletions
16 amenable to exon 44 have a delay in loss of
17 ambulation of up to 2 years.

18 As clinicians, we are often asked the
19 question, why is it important to maintain 6-minute
20 walk distance. And we have learned that
21 maintaining 6-minute walk test is important because
22 its distance can predict loss of ambulation.

1 This graph shows the results of a study
2 performed on 131 boys with Duchenne followed for
3 over 2 years. The study evaluated the risk of
4 losing ambulation in different sub-groups
5 subdivided according to the 6-minute walk test.

6 Looking from left to right, it's obvious
7 that the risk of losing ambulation increases as the
8 6-walk distance decreases. These results suggested
9 if we are able to maintain or even to slow down the
10 degradation of the 6-minute walk distance, we
11 therefore also decrease the risk of losing
12 ambulation.

13 Maintaining ambulation is of course
14 important per se, but it's also important as loss
15 of ambulation is related to the onset of further
16 progression of other aspects of disability. In a
17 recent French study, a cohort of boys with Duchenne
18 followed for over 20 years was subdivided into
19 3 groups based on age of loss of ambulation.

20 The study showed that boys who lost
21 ambulation at the later stage, after the age of 11,
22 also had a significant delay in the need for

1 ventilation and in the time when they lost the
2 ability to self-feed.

3 I would like to stress how important this
4 chain of events is. If we delay progression in the
5 6-minute walk test, we delay not only loss of
6 ambulation, but also the subsequent events of
7 disease progression, such as loss of self-feeding
8 or need for ventilation.

9 The natural history data I just showed are
10 the results of international efforts to harmonize
11 standards of care between U.S. and Europe that were
12 formally published in 2009. These include the use
13 of steroids, but also provides specific indication
14 on physical therapy and on the management of
15 orthopedic, respiratory, and cardiac risk.

16 In summary, the improvement in standard of
17 care has produced a clear shift in natural history,
18 delaying loss of ambulation and subsequent
19 functional decline, such as respiratory failure,
20 cardiac impairment, and ultimately death.

21 But this is not enough. Despite these
22 improvements, Duchenne is still a rapidly

1 progressive and ultimately fatal disorder. And as
2 a clinician, as part of the Duchenne community, we
3 strongly feel there is therefore an urgent unmet
4 need to find treatments that may further slow down
5 disease progression.

6 Now, I would like to turn the podium over to
7 Dr. Kaye to discuss efficacy of eteplirsen.

8 **Applicant Presentation - Edward Kaye**

9 DR. KAYE: Building on the scientific
10 foundation that Dr. Mercuri just presented, I would
11 like to describe the findings that confirm
12 eteplirsen benefit. We will look at the rationale
13 for development of eteplirsen, an overview of
14 Sarepta's clinical development program, a
15 description of the pharmacodynamic data, the
16 process for choosing the external control, the
17 clinical results, and finally an overview of our
18 confirmatory studies.

19 Let's begin by looking at the rationale for
20 why exon skipping could work in Duchenne muscular
21 dystrophy. As the previous speakers explained,
22 mutations that disrupt the RNA reading frame lead

1 to the production of little to no functional
2 dystrophin and result in the severe DMD phenotype.

3 The concept of exon skipping as a
4 therapeutic strategy is demonstrated through an
5 experiment in nature. In Becker muscular
6 dystrophy, deletion mutations, which maintain the
7 RNA reading frame, enable the production of an
8 internally deleted dystrophin. These in-frame
9 mutations result in a shortened dystrophin protein
10 generally associated with a milder phenotype. Exon
11 skipping aims to produce a protein similar to
12 Becker.

13 FDA has stated in their briefing document
14 that Becker muscular dystrophy patients have high
15 levels of dystrophin, however, after looking at the
16 literature we note a wide range of dystrophin
17 levels, ranging from 2 to 100 percent.

18 Given this wide range of dystrophin
19 expression, researchers over the past 25 years have
20 tried but failed to establish a definitive
21 dystrophin threshold that results in a clinical
22 benefit. What has been established is that the

1 presence of even small amounts of dystrophin may
2 have a clinical impact.

3 For example, Duchenne muscular dystrophy
4 patients amenable to exon 44 skipping express
5 slightly higher levels of dystrophin than the
6 general DMD population and experience a milder
7 phenotype. Ultimately, the most meaningful
8 assessment of dystrophin in a clinical trial is not
9 based on literature values but on increase from
10 baseline. The conclusion was emphasized at a March
11 2015 FDA NIH workshop on dystrophin quantification,
12 as well as in the FDA briefing guidance.

13 We are fortunate to have two academic
14 experts with us today, Dr. Francesco Muntoni and
15 Dr. Steve Wilton, who can answer questions and
16 provide insight on dystrophin quantification.

17 I would now like to take a moment to review
18 our complete DMD clinical program. Eteplirsen was
19 initially evaluated in two phase 1 studies. The
20 first established proof of concept through single
21 intramuscular injection, and the second study
22 tested weekly systemic IV administration at various

1 doses.

2 Having observed increased dystrophin in both
3 phase 1 studies, Sarepta initiated study 201/202.
4 This is the pivotal study, which will be the focus
5 of my presentation today. Enrollment included an
6 ambulatory population between the ages of 7 to
7 13 years.

8 To evaluate eteplirsen in a broader
9 population, Sarepta is completing two additional
10 phase 2 studies in both younger as well as more
11 advanced patients. To support accelerated
12 approval, the PROMOVI phase 3 confirmatory study is
13 already underway.

14 In addition to eteplirsen, Sarepta has
15 initiated two phase 1 studies with compounds that
16 use the same chemical backbone but are designed to
17 skip exons 45 and 53, respectively. The second
18 confirmatory study is ESSENCE, which tests these
19 follow-on compounds. I will further discuss these
20 confirmatory studies at the end of my presentation.

21 Study 201 was a 24-week study to evaluate
22 dystrophin expression as a pharmacodynamic

1 endpoint. The study tested eteplirsen at
2 2 systemic weekly IV doses, 30 milligrams per
3 kilogram shown in purple, and 50 milligrams per
4 kilogram shown in green, compared to placebo shown
5 in gray. Dosing was limited to 8 patients at study
6 initiation due to limited drug supply.

7 After week 24, the placebo group was rolled
8 over on to either 30 or 50 milligrams of
9 eteplirsen. Study 202 extended the trial to
10 further evaluate both continuing pharmacodynamic
11 and efficacy endpoints and is ongoing to date.
12 Data from all 12 of these patients were pooled to
13 enable comparison to an external control over
14 4 years.

15 In order to best observe a treatment effect,
16 the 201/202 enrollment criteria were chosen to
17 obtain a homogeneous group of patients that would
18 be predicted to decline. As Dr. Mercuri detailed
19 in his presentation, a number of prognostic factors
20 predict decline in DMD, including a mutation
21 amenable to exon 51 skipping, an age range of 7 to
22 13 years, a stable steroid regimen for at least

1 24 weeks prior to enrollment, and finally a
2 6-minute walk test distance between 180 and
3 440 meters. These same factors drove our
4 enrollment criteria.

5 The pivotal 201/202 studies included several
6 key endpoints. The primary endpoint for study 201
7 was increase in dystrophin protein expression. The
8 primary clinical endpoint for study 202 is the
9 6-minute walk test.

10 Supportive endpoints included mechanism of
11 action by RT-PCR, dystrophin protein production,
12 the NSAA, and the ability to rise from supine.
13 Importantly, we are here today to seek approval
14 based on clinical differences in walking ability in
15 addition to dystrophin production.

16 As I will now show, eteplirsen has a precise
17 mechanism of action as demonstrated by dystrophin
18 production. The most direct measure of
19 eteplirsen's mechanism of action is exon skipping,
20 which was evaluated by RT-PCR and sequencing. The
21 shortened PCR product was identified and sequenced
22 to confirm that the correct newly formed exon

1 junction was present. All biopsied eteplirsen
2 patients produced the expected product,
3 demonstrating that the drug is working as intended.

4 The March 2015 FDA NIH workshop on
5 dystrophin measurement concluded that complementary
6 methods are necessary to provide a complete protein
7 assessment. Western blot was used to quantify
8 dystrophin following extraction of protein from
9 muscle tissue. However, for dystrophin to be
10 functional, it must be localized to the sarcolemmal
11 membrane and only immunohistochemistry can provide
12 this information.

13 Immunohistochemical images were used to
14 assess the percent dystrophin positive fibers
15 providing information on sarcolemmal localization
16 and distribution of dystrophin in muscle tissue.

17 Finally, the immunohistochemical images were
18 assessed by a computer algorithm to measure
19 fluorescence intensity to quantify dystrophin at
20 the membrane. Taken together, these assays provide
21 a comprehensive view of dystrophin expression.

22 Study 201 was designed to test whether dose

1 or duration was most important in the production of
2 dystrophin positive fibers. No significant
3 increase was observed at 12 weeks for the
4 50 milligrams per kilogram cohort, but the endpoint
5 was met at 24 weeks for the 30 milligram per
6 kilogram cohort with an absolute change from
7 baseline and present dystrophin positive fibers of
8 13.7 percent with no increase seen in the placebo
9 group at week 24.

10 The FDA suggested that this lack of positive
11 effect at an earlier time point with higher dose
12 sheds doubt on the later time point. Our data
13 indicate, however, that duration rather than dose
14 appears to be the critical factor for
15 dystrophin production.

16 Although in an earlier study increased
17 dystrophin was observed in some patients by
18 week 12, the response was not consistent across all
19 patients. Study 201/202 showed increased
20 dystrophin in all biopsied patients at week 24 that
21 was sustained at later time points.

22 The week 180 biopsy is considered the most

1 important because samples were evaluated using
2 methods, blinding, and controls developed in
3 consultation with FDA. However, FDA noted concerns
4 regarding the selection of the untreated controls,
5 anatomical location of controls, and blinding
6 procedures.

7 Baseline tissue was only available for
8 3 patients from study 201, therefore we obtained
9 additional samples from a highly comparable group,
10 untreated patients who were the first 6 patients
11 with available tissue from the PROMOVI confirmatory
12 study.

13 Of note, they had similar enrollment
14 criteria to study 201 and were not previously
15 analyzed for dystrophin. Collectively, this
16 provided 9 untreated controls, which represent a
17 robust internal comparator for measurement of
18 dystrophin.

19 As the FDA noted, we compare biopsies from
20 deltoid to biceps. There is no evidence to suggest
21 that dystrophin levels would differ in these
22 muscles since both are proximal upper extremity

1 muscles equally affected in DMD patients. This was
2 confirmed by our own analysis of the baseline
3 samples.

4 Finally, these assays were performed by
5 independent technicians who were blinded to sample
6 treatment status with a different sample
7 randomization used for each assay.

8 We have learned a lot about dystrophin
9 measurement in the course of the eteplirsen
10 development, and our methods have evolved
11 accordingly. Our validated Western blot method,
12 optimized to detect low levels of dystrophin, is
13 arguably the first dystrophin Western blot to be
14 truly quantitative.

15 This was achieved by use of a 5 point
16 calibration curve on each gel and prespecified
17 loading and exposure limits to avoid signal
18 saturation. Furthermore, samples were randomized,
19 blinded and run in duplicate on separate gels. In
20 contrast, the Western blot methods in the majority
21 of historical publications referenced by FDA were
22 performed using older methodology that is

1 semi-quantitative at best.

2 Given these significant methodological
3 differences, it is inappropriate to compare our
4 data to literature approximations. Instead,
5 treatment effect should be assessed by comparing
6 untreated baseline tissue to post-treatment samples
7 using the same validated assay. This enables
8 accurate determination of a fold increase in
9 dystrophin level.

10 Western blot analysis of week 180 biopsies
11 show that 9 out of 11 biopsied eteplirsen patients
12 in the 201/202 study had an obvious and
13 quantifiable dystrophin band resulting in a mean of
14 0.9 percent. The untreated samples had a mean of
15 0.08 percent.

16 Importantly, this baseline calculation is
17 based on a predefined protocol that was developed
18 in collaboration with the FDA. This represents an
19 11.6-fold increase and includes the available
20 baseline samples obtained from study 201.

21 The FDA questioned whether this robust
22 increase in dystrophin level was significant based

1 on historical approximations in the range of
2 3 percent of normal. As detailed earlier, direct
3 comparison cannot be made to literature values.
4 The only scientifically valid comparison is to
5 these untreated DMD controls.

6 Turning to our analysis of percent
7 dystrophin positive fibers, FDA questioned certain
8 important details, which I would like to clarify.
9 First, only unenhanced images were used to score
10 positive fibers. Second, an unbiased systematic
11 sampling method was used to select the fields for
12 image capture.

13 Third, a prespecified protocol was carefully
14 developed to avoid overestimation of dystrophin
15 positive fibers, with viewing conditions controlled
16 to allow optimal viewing of the original unaltered
17 images, positive fibers defined as having intensity
18 above untreated DMD fibers in at least 30 percent
19 of the membrane circumference, and a requirement
20 that each pathologist be trained and pass
21 prespecified qualifications prior to scoring.

22 The rigor of the protocol and training is

1 supported by the higher inter-rater reliability
2 that was observed for analysis of the week 180
3 images.

4 Three pathologists observed a significantly
5 higher mean percent dystrophin positive fiber count
6 and a 15.5-fold increase for eteplirsen patients in
7 comparison to untreated controls. The
8 immunohistochemistry images were also assessed for
9 fluorescence intensity by a computer algorithm.

10 As shown in this graph, a significant higher
11 mean relative fluorescence intensity and a 2.4-fold
12 increase was observed for eteplirsen patients in
13 comparison to the untreated controls.

14 As both Dr. Mercuri and I mentioned earlier,
15 DMD patients amenable to exon 44 skipping
16 experience a milder phenotype. The mean intensity
17 for eteplirsen is 22.6 percent, which is comparable
18 to the approximately 20 percent seen for exon 44
19 amenable patients.

20 In contrast to Western blot data, which
21 cannot be compared to published reports,
22 immunohistochemical intensity comparison is valid

1 when contemporary standardized methods are used.

2 Evaluating the relationship between Western
3 blot and immunohistochemical intensity shows that,
4 as expected, the normal controls are in the highest
5 values. Untreated DMD samples are the lowest and
6 week 180 treated DMD and Becker samples fall in
7 between. It is important to note that one of the
8 low expressing Becker patients overlaps with our
9 week 180 treated samples.

10 A strong correlation between these two
11 quantitative measures has been reported in several
12 independent publications. As noted by the FDA, the
13 correlation between Western blot and PDPF is not
14 strong. This is not unexpected given that PDF is a
15 semi-quantitative measure.

16 To summarize, we have clearly demonstrated
17 that sustained production of de novo dystrophin by
18 all measures employed. Biochemical evidence of
19 functionality includes correct localization of
20 dystrophin and key associated proteins to the
21 sarcolemmal membrane. Taken together, these data
22 clearly demonstrate that eteplirsen is working as

1 intended.

2 Next, I will present the clinical data that
3 demonstrate that the observed increase in
4 dystrophin results in a clinically meaningful
5 benefit. Before I do that, I would first like to
6 describe our early 48 week data and explain why it
7 suggested the need for a longer study.

8 In an exploratory analysis, we looked at the
9 first 48 weeks of study 201/202. We saw that
10 2 patients, shown in light blue, experienced rapid
11 decline before the 24-week time point and lost
12 ambulation shortly thereafter.

13 Based on what we know now, consistent
14 increase in dystrophin is not observed until
15 24 weeks suggesting that these patients declined
16 prior to dystrophin production. An analysis was
17 conducted of continuously treated patients who
18 remained ambulant, shown in dark blue, as well as
19 the placebo delayed patients who rolled onto
20 treatment at week 25, shown in gray. Both groups
21 experienced relative stability.

22 Based on these limited but encouraging

1 results, study 202 was extended. To be clear, the
2 two boys who lost ambulation remained on treatment
3 and are included in all subsequent analyses
4 presented.

5 In order to evaluate the long-term data from
6 study 201/202, FDA suggested comparison to an
7 external control group. This was accomplished by
8 pooling eteplirsen data into a single group with
9 the original placebo patients reset to time zero at
10 the initiation of the eteplirsen treatment. This
11 provides data from 12 patients for a 4-year time
12 period.

13 A key aspect to the data comparison of
14 course is the appropriateness of the external
15 control. We recognize that a key issue for
16 external controls is the potential for bias. We
17 looked carefully at the regulations and guidance,
18 and I would like to begin by addressing the key
19 issues.

20 First, bias can be due to both known and
21 unknown prognostic factors. We controlled for the
22 key prognostic factors that are known.

1 Second, the selection of the control group
2 should be made prior to the comparative analysis.
3 We used prespecified selection criteria that were
4 based on the 201 enrollment criteria.

5 Third, the disease course has to be
6 predictable. We selected a homogeneous patient
7 population with a predictable disease course.

8 Fourth, the endpoints need to be objective.
9 We used a highly standardized 6-minute walk test
10 measure.

11 Fifth, patient level data are required for
12 comparison. We had 4-year longitudinal patient
13 level data that was highly comparable on baseline
14 characteristics, including steroid use and other
15 standards of care.

16 Sixth, external controls are often perceived
17 to have worse outcomes. I will show that the
18 external control group was reflective of other
19 natural history databases.

20 And finally, and most importantly, the
21 treatment effect needs to be dramatic. You will
22 see that this was certainly the case with

1 eteplirsen.

2 In partnership with leading DMD experts,
3 Sarepta actively searched for a natural history
4 data. Twelve databases were identified having
5 extensive clinical data, however only two had
6 6-minute walk test data beyond baseline available
7 for analysis. Of note, the CINRG database did not
8 have long-term 6-minute walk test data at that
9 time.

10 The two databases identified were the
11 Italian DMD Telethon and the Leuven Neuromuscular
12 Research Center in Belgium. The studies began
13 enrolling patients in 2007/2008 and have continued
14 in a time period that is contemporary with study
15 201/202. Both databases had longitudinal 6-minute
16 walk test data available, but only the Italian
17 registry had the NSAA data available as well.

18 Importantly, all patients attending a
19 participating clinic who met eligibility criteria
20 were enrolled in the studies. Results from these
21 investigator initiated studies have been published
22 in peer review journals.

1 All centers in the studies were treating
2 patients according to the international standards
3 of care for DMD that were discussed by Dr. Mercuri.
4 FDA raised concerns about lower adherence to
5 standards of care for children in Italy, however,
6 this is of limited relevance to the actual care
7 received by our external control patients who were
8 seen at neuromuscular specialty clinics. As I will
9 later demonstrate, our external control had
10 extremely high compliance to the standards of care.

11 As is common in rare diseases, treating
12 clinicians represent a small but highly
13 collaborative international community.
14 Importantly, the 6-minute walk test was assessed by
15 the same method for eteplirsen patients and for
16 external controls.

17 Both databases as well as the eteplirsen
18 study used the modified 6-minute walk test protocol
19 adapted for use in DMD. As was described by
20 Dr. Mercuri, this included use of the same scripted
21 encouragement. In addition, the lead physical
22 therapist for the Italian registry and study

1 201/202 previously worked together on an
2 international effort to standardize the protocol
3 and training for the 6-minute walk test in DMD.
4 This ensured comparable clinical evaluations
5 between the various sites.

6 Having obtained the patient level data, we
7 next set out to find the most appropriate patients
8 for comparison. The enrollment criteria for
9 study 201/202 were used to select patients from the
10 external control group. These included steroid
11 use, age greater than or equal to 7 years, and a
12 mutation amenable to exon 51 skipping.

13 Importantly, these filters were defined before data
14 analysis began.

15 I would like to remind you that these
16 criteria were specifically designed to select for
17 boys in the decline phase of the disease.

18 Pooling the data that Sarepta received from
19 the two databases rendered a raw data set of 186
20 patients. The Italian Telethon only provided
21 patients who had been evaluated for at least 3
22 years, while the Leuven Neuromuscular Research

1 Center provided patients who had been evaluated for
2 varying lengths of time. The selection criteria
3 from 201/202, just described, were applied to these
4 patients.

5 An initial filter was applied requiring
6 steroid use at baseline as well as a minimum of
7 both a baseline and one post-baseline 6-minute walk
8 test result. A second filter was applied to
9 exclude patients younger than 7 who were likely to
10 be improving in the 6-minute walk test due to
11 growth and maturation.

12 Since mutation type impacts disease
13 severity, filters were applied to find patients
14 amenable to skipping any exon, and finally amenable
15 only to exon 51 skipping. Efficacy results will
16 compare eteplirsen patients to this primary
17 analysis group.

18 In addition, a secondary more conservative
19 comparison to a larger population of 50 patients
20 amenable to any exon skipping included milder
21 exon 44 patients was presented in our briefing
22 document.

1 A critical question is how comparable this
2 external control group is to the eteplirsen group.
3 We see here that the eteplirsen cohort on the left
4 is highly comparable on key prognostic factors to
5 the primary external control group on the right.
6 Looking first at the mean baseline age, we see that
7 the groups are very similar.

8 Mean baseline 6-minute walk test values are
9 also highly comparable with the groups differing by
10 less than 10 meters. Of note, all deletion
11 mutations observed among the 12 eteplirsen boys are
12 also represented in the external control.

13 As Dr. Mercuri detailed, steroid use has
14 been shown to impact disease progression.
15 Importantly, the eteplirsen patients as well as all
16 external controls were on a stable dose of steroids
17 at least 6 months prior to enrollment and remained
18 on steroids throughout the study.

19 The two most commonly described steroids in
20 DMD, deflazacort and prednisone, were used in equal
21 proportion by both groups. Of note, the majority
22 of patients in the external control actually

1 maintained a higher dose than the eteplirsen
2 patients.

3 As FDA noted, there are two minor
4 differences in steroid treatment between the
5 external control and eteplirsen, neither of which
6 significantly impacted the 6-minute walk endpoint.

7 First, the mean age of steroid initiation
8 for external control is approximately 1 year older
9 than eteplirsen. This difference is partly
10 attributed to a single external control patient who
11 began steroid use at age 10.7 years. Of note, he
12 had a better prognosis and maintained ambulation
13 until he was over 15.

14 Second, a lower percentage of eteplirsen
15 boys received an intermittent steroid regimen in
16 comparison to external control. Sensitivity
17 analyses for both of these variables demonstrate
18 minimal impact on the primary endpoint.

19 In addition, we plotted the change in
20 6-minute walk test by steroid regimen for the
21 external control. The intermittent patients shown
22 in orange experienced similar declines as the

1 continuous patients shown in green. Taken
2 together, with a sensitivity analysis, this
3 suggests that steroid dosing frequency did not
4 affect the results of the 6-minute walk test in our
5 analysis.

6 Physical therapy and use of orthoses can
7 also impact ambulation. As shown here, the
8 external control patients received a higher level
9 of physical therapy intervention with all 13
10 meeting with a physical therapist at least twice a
11 week.

12 Additionally, there was a high compliance
13 with the use of night splints. This demonstrates
14 that the external control patients had high
15 adherence to standards of care. This is not
16 surprising since they were treated in leading
17 neuromuscular centers.

18 In addition to looking at comparability of
19 baseline characteristic, it is important to address
20 concerns regarding the potential for motivational
21 bias in the external control. FDA had performed an
22 alternative comparison for eteplirsen based on the

1 drisapersen placebo data.

2 To test for the potential motivation bias,
3 we did an analysis comparing the 6-minute walk test
4 results for our external control group to this
5 data. Patients in the drisapersen study were also
6 amenable to exon skipping and on steroids.
7 However, they included patients younger than 7 who,
8 as Dr. Mercuri noted, would be expected to improve
9 over time.

10 These drisapersen patients were initially on
11 placebo, shown in dashed black, and then rolled
12 over onto treatment, shown in solid black.
13 Motivation does not appear to be a factor given
14 that our external control, shown in yellow,
15 experienced similar declines to patients in the
16 drisapersen trial.

17 I would now like to clarify a few
18 misunderstandings regarding our key data and then
19 review the clinical results. As it relates to the
20 external control, FDA raised three key issues.

21 First, there was a concern that revisions
22 occurred to the external control data regarding

1 continuous versus intermittent steroid use. To
2 clarify, 3 patients with unknown regimens at the
3 time of NDA submission were later reported by the
4 investigator as receiving a continuous regimen.

5 Second, the FDA stated that 2 patients left
6 to enter interventional trials, leading to
7 potential difference between eteplirsen and
8 external control patients. In fact, we acquired
9 the missing 6-minute walk test data for these two
10 patients after they participated in the placebo arm
11 of an interventional study and have included their
12 6-minute walk test results in the analyses.

13 Third, as Dr. Mercuri noted, it is common
14 for patients to have a 6-minute walk test of zero
15 while still being able to perform the 10-meter walk
16 run.

17 In addition, FDA raised two key concerns in
18 the approach to Sarepta's analysis of the 6-minute
19 walk test and the North Star ambulatory assessment.
20 First, they noted that eteplirsen patients had two
21 opportunities to perform a functional test whereas
22 natural history patients had only one. To be

1 clear, day 1 values for the 6-minute walk test and
2 all other measures were compared to single external
3 control measurement.

4 Finally, we would like to clarify that while
5 FDA identified 2 external control patients as
6 having missing North Star ambulatory assessment
7 values, we correctly incorporated these values into
8 our analysis and did not assign them values of
9 zero. You can see that we have carefully reviewed
10 the data, and we will be happy to address any other
11 questions.

12 Comparison to the external control to
13 eteplirsen was conducted over 3 to 4 years. Four
14 years of data were analyzed for 6-minute walk test
15 and loss of ambulation, while 3 years of data were
16 analyzed for the North Star ambulatory assessment
17 and ability to rise. These time periods were based
18 on the availability of external control data.

19 As I review the results, keep in mind that
20 the treatment expectation for eteplirsen is to
21 delay but not necessarily to stop disease
22 progression. Any preservation of ambulation, even

1 by a couple of years, would significantly impact
2 the lives of patients and their families.

3 Our primary analysis is comparison of the
4 external control group to eteplirsen patients on
5 change in the 6-minute walk test. In this
6 analysis, any patient who lost ambulation
7 contributed a score of zero to the mean.

8 As you can see the two groups had highly
9 comparable 6-minute walk test values at baseline
10 and year 1, confirming their similarity. We did
11 not expect an immediate separation between treated
12 and untreated patients because, first, an increase
13 in dystrophin expression is not observed until
14 24 weeks. And second, time is required for the
15 untreated control group to decline.

16 After year 1, the groups diverge, and by
17 years 3 and 4, we see a nominally significant
18 difference of 148 and 162 meters, demonstrating
19 that eteplirsen slowed disease progression. This
20 large magnitude of effect is equal to the length of
21 nearly two football fields.

22 In this graph, individual 6-minute walk test

1 results are shown in yellow for the exon 51
2 external controls. These patients experienced
3 declines in 6-minute walk test over 4 years, and 10
4 lost ambulation by year 4, as indicated by a
5 6-minute walk test score of zero.

6 In comparison, the eteplirsen group, shown
7 in blue, declined more slowly after year 1. No
8 additional patients lost ambulation after year 1.
9 As you can see, the difference is not driven by a
10 few patients who performed particularly well or a
11 few external control patients who performed
12 particularly poorly.

13 For our analysis, loss of functional
14 ambulation is defined as the inability to execute
15 the 6-minute walk test. This bar graph shows the
16 estimated loss of ambulation at annual time points
17 based on Kaplan-Meier analysis. Two external
18 control patients had missing data, and Kaplan-Meier
19 analysis properly accounts for this.

20 The cumulative loss of ambulation over the
21 first 4 years remain constant at 17 percent for
22 eteplirsen patients. In contrast, a continual

1 increase in loss of ambulation is observed in the
2 external control patients culminating in an
3 85 percent probability of losing ambulation by
4 year 4.

5 FDA presented the loss of ambulation by age.
6 The analysis shown here is from the CINRG database,
7 a global, multicenter study of DMD. These are
8 steroid treated patients amenable to exon 51
9 skipping similar to eteplirsen and external control
10 patients, however, there are two important
11 differences when comparing the CINRG data to
12 eteplirsen.

13 First, the definition of loss of ambulation
14 for CINRG was full wheelchair use and was confirmed
15 by inability to perform the 10-meter walk/run when
16 possible. This is critically different from our
17 definition, which was zero on the 6-minute walk
18 test.

19 As mentioned earlier, it is not unusual to
20 see a zero on the 6-minute walk test and still have
21 a positive value on the 10-meter walk/run. Because
22 of these different definitions, the CINRG database

1 is more likely to report a later loss of ambulation
2 in some patients. Despite this, our external
3 control, shown in dashed yellow, performed somewhat
4 better than these CINRG patients.

5 The eteplirsen patients shown in blue appear
6 to behave differently than either the CINRG or the
7 external control groups. Of note, the eligibility
8 criteria used for eteplirsen has an upper limit of
9 440 meters on baseline 6-minute walk test, which
10 precludes milder patients who are likely to walk
11 longer. However, these milder patients were not
12 excluded from the CINRG database.

13 FDA focuses on the outliers from the CINRG
14 database to suggest DMD patients maintain
15 ambulation into their late teens, concluding that
16 eteplirsen boys do not differ from the natural
17 history. Of note in the CINRG database, there are
18 only 3 boys who are walking past the age of 15.

19 The more appropriate comparison is the
20 median loss of ambulation between these three
21 groups. The median ages of loss of ambulation are
22 12 for CINRG, 12.9 for the external control, and

1 the median loss of ambulation has not yet been
2 reached for eteplirsen boys. Most importantly,
3 eteplirsen preserves ambulation longer than either
4 the CINRG database or the external control.

5 We are fortunate to have Dr. Craig McDonald,
6 the chair of the CINRG study, available today to
7 answer questions regarding the database and loss of
8 ambulation in DMD.

9 In addition to ambulatory ability, a number
10 of supportive endpoints were also evaluated.
11 Comparison to external control for these endpoints
12 is shown through year 3. Similar to the 6-minute
13 walk test results, the North Star ambulatory
14 assessment shows a slower decline in the treated
15 group at 2 and 3 years following the same trend as
16 the 6-minute walk test. While the observed
17 difference of 2.4 points on the North Star
18 ambulatory assessment is not significant, it
19 represents the critical preservation of one or more
20 activities of daily living.

21 Here we show the ability to independently
22 rise from supine for external controls compared to

1 eteplirsen patients. Ability to rise is a more
2 standardized definition since in contrast to rise
3 time, it does not allow for external support.
4 Consistent with the 6-minute walk test results, the
5 two groups are initially comparable and then
6 diverge.

7 By year 3, more than half of the eteplirsen
8 patients could still rise from the floor
9 independently compared to only 8 percent of
10 external control, a difference that is nominally
11 significant.

12 In summary, it is our position that the data
13 you have seen confirm eteplirsen's mechanism of
14 action and demonstrate that eteplirsen slows
15 disease progression. Eteplirsen is the first
16 therapeutic to unequivocally demonstrate an
17 increase in dystrophin following treatment.

18 The external control is a highly comparable
19 and appropriate comparator to evaluate eteplirsen's
20 clinical effect. Analysis of drisapersen placebo
21 and CINRG data confirm that our external control is
22 representative of natural history.

1 Eteplirsen slowed disease progression,
2 demonstrating a clinically meaningful effect on the
3 6-minute walk test and a dramatic difference in
4 loss of ambulation. Eteplirsen benefit is further
5 supported by the North Star ambulatory assessment
6 and ability to rise from supine.

7 While we demonstrated clinical benefit in
8 our initial studies, because we are seeking
9 accelerated approval, confirmatory studies are
10 required for full approval. When we had to make
11 the critical decision of how to further evaluate
12 eteplirsen, we determined that a placebo-controlled
13 trial would not be feasible because there were not
14 enough eligible exon 51 amenable patients due to
15 other ongoing trials. In addition, the patient
16 community expressed opposition to a long-term
17 placebo-controlled eteplirsen study.

18 Therefore, in consultation with FDA, a
19 flexible approach was adopted using non-exon 51
20 amenable patients to a comparator arm. This
21 approach incorporated what we learned, including
22 the need for a longer study duration and updated

1 enrollment criteria to exclude rapidly progressing
2 boys such as the two who lost ambulation in
3 study 201.

4 The first confirmatory study is an
5 open-label comparison of exon 51 patients treated
6 with eteplirsen to untreated DMD patients who are
7 amenable to skipping other exons but who would not
8 benefit from eteplirsen.

9 The second study is a double blind,
10 placebo-controlled trial of two follow-on drugs.
11 Both have the same PMO backbone as eteplirsen and
12 utilize the same mechanism of action, but rather
13 than skipping exon 51 these drugs skip exons 45 and
14 53, respectively.

15 To provide further detail, the first
16 confirmatory study, PROMOVI, is a 96-week
17 open-label, multicenter study comparing 60
18 eteplirsen patients to 60 untreated, non-exon 51
19 amenable boys having the same entry criteria.

20 These criteria are similar to study 201/202
21 but with updated 6-minute walk test cutoffs to
22 exclude patients likely to decline before

1 dystrophin can be produced. This study is already
2 underway, but a data readout is not expected for at
3 least another 2 to 3 years.

4 The second study, ESSENCE, is a 96-week
5 randomized, double-blind, placebo-controlled
6 multicenter study of our next two drugs, which
7 treat patients amenable to skipping exon 45 and 53,
8 respectively.

9 Recall from Dr. Mercuri's presentation that
10 patients amenable to skipping exon 45 or 53
11 experienced a similar rate of decline on the
12 6-minute walk test as patients amenable to skipping
13 exon 51. This will be a 99-patient study with a
14 2 to 1 randomization of drug to placebo with entry
15 criteria matching PROMOVI. Enrollment is expected
16 soon.

17 I would now like to introduce Dr. Eliopoulos
18 who will review the safety data.

19 **Applicant Presentation - Helen Eliopoulos**

20 DR. ELIOPOULOS: Thank you, Dr. Kaye.

21 Good morning. Following a brief description
22 of non-clinical data, I will present the integrated

1 analysis of safety, including adverse events that
2 were common, serious or severe, resulted in
3 discontinuation, or were of special interest.

4 Eteplirsen is a PMO structurally and
5 biologically distinct from other RNA analogues. In
6 non-clinical studies of eteplirsen, the kidney was
7 identified as the organ of toxicity. In contrast
8 to other RNA analogues, including one recently
9 reviewed by this committee, toxicities such as
10 immune activation, thrombocytopenia, coagulopathy,
11 or vasculitis were not seen with eteplirsen.

12 The integrated safety analysis includes 114
13 DMD patients from 7 studies, all patients with
14 mutations specifically amenable to exon 51
15 skipping. Twenty-six patients received lower
16 eteplirsen doses and were from study 33, which
17 administered a single IM dose or study 28,
18 dose ranging for IV eteplirsen.

19 Eighty-eight boys received the proposed dose
20 of 30 milligrams per kilogram or higher, including
21 12 boys from pivotal studies 201/202, who have
22 received eteplirsen for about 4 years. Younger

1 patients, age 4 to 6 from study 203, as well as
2 patients with more advanced DMD from study 204,
3 have contributed to the integrated set.

4 This table lists common adverse events
5 occurring in 10 percent or more of the 114
6 patients. The majority of events were mild and
7 transient, resolving with continued eteplirsen.
8 And as you could see, many of these could be
9 anticipated in a pediatric population with
10 Duchenne.

11 Only 2 of 114 patients had serious adverse
12 events, but neither of these appear drug related.
13 One patient, an 11-year-old boy, had a femur
14 fracture after falling out of his wheelchair. He
15 had previous events of severe but non-serious
16 balance disorder and bone pain. And the second, a
17 9-year-old boy, had post-operative vomiting after
18 general anesthesia. Of note, there have been no
19 fatal or life-threatening events with eteplirsen.

20 Out of 114 patients, there was only 1 who
21 discontinued eteplirsen due to adverse events, and
22 this was a 10-year-old boy who was reported to have

1 cardiomyopathy after 7 weeks of a low dose of
2 eteplirsen at 4 milligrams per kilogram. This was
3 based on an observed decrease of left ventricular
4 fractional shortening on echo. The investigator
5 considered this as severe and possibly related to
6 drug.

7 To further evaluate, Sarepta undertook an
8 independent cardiology review, which interpreted
9 the echo findings as normal and considered that
10 changes in fractional shortening were possibly due
11 to technical factors.

12 There was one additional case of
13 cardiomyopathy in the integrated set, not leading
14 to study drug discontinuation, in a patient with
15 preexisting history. Overall, these two reports
16 represent a rate of about 2 percent consistent with
17 the known prevalence of cardiomyopathy in DMD.

18 Severe events were experienced by three
19 additional patients. A 7-year-old boy experienced
20 bleeding from a Portacath incision site after
21 swimming. Coagulation parameters were normal at
22 the time of the event.

1 In two other patients, events of nasal
2 congestion, hemorrhoids, and back pain due to a
3 fall were reported, and again, these appeared
4 consistent with events that may occur in a
5 pediatric DMD population.

6 Adverse events of special interest were
7 based on the non-clinical findings for eteplirsen
8 as well as events of interest from the clinical
9 experience with other RNA analogues.

10 As non-clinical studies identified the
11 potential for kidney toxicity, a broad review of
12 renal events was conducted. There were 11 patients
13 with proteinuria described as protein detected by
14 dipstick based on urinalysis. All events were mild
15 and transient. There was one patient with adverse
16 events of increased BUN and creatinine in the
17 setting of dehydration occurring at week 88 of
18 eteplirsen. These resolved by the time of retest
19 11 days later and have not recurred with continued
20 eteplirsen for a period of over 2 years.

21 As immunogenicity has been an issue for
22 other RNA analogues, potential infusion reactions

1 have been reviewed. A subset of 107 patients have
2 received IV eteplirsen, representing over 3900
3 infusions. Twenty-two percent of these patients
4 experienced an infusion site event, this table
5 listing those occurring in 2 or more patients.

6 Most events were described as catheter or
7 infusion site pain or hematoma consistent with
8 placement of a catheter device. Of note, there
9 were 4 events of mild pyrexia considered unrelated
10 to drug. An additional report of mild temperature
11 elevation occurred coincident with an eteplirsen
12 infusion and is therefore considered a potential
13 adverse drug reaction. There have been no serious
14 or severe infusion site reactions with eteplirsen.

15 In the all-eteplirsen group, 24 percent of
16 patients had events, which were assessed for
17 potential hyper-sensitivity. All events were
18 non-serious and resolved. The majority, including
19 rash and pruritus, were mild and considered
20 unrelated to study treatment by nature of the
21 temporal relationship or lack of recurrence with
22 ongoing treatment.

1 Two types of events, mild erythema, and
2 flushing, occurred during eteplirsen infusions.
3 They were considered related by the investigators
4 and represent potential mild adverse drug
5 reactions. There have been no serious or severe
6 events related to hypersensitivity with eteplirsen.

7 Review of the safety database and
8 longitudinal laboratory data identified no
9 clinically significant events for thrombocytopenia,
10 coagulopathy, vasculitis, immune-mediated
11 disorders, or hepatic toxicity, consistent with the
12 absence of such findings in non-clinical studies of
13 eteplirsen.

14 In summary, characterization of the
15 eteplirsen safety profile is early, however, no
16 significant safety risks have been identified. The
17 majority of reported adverse events have been mild
18 and resolved with continued therapy, suggesting
19 they were not drug related.

20 Favorable tolerability is demonstrated by
21 the low rate of discontinuations and serious
22 events. Sarepta continues to evaluate the safety

1 of eteplirsen through monitoring of ongoing trials,
2 as well as planned post-marketing surveillance and
3 a DMD registry.

4 I would now like to introduce Dr. Mendell,
5 the principle investigator for study 201/202, who
6 will provide the clinical perspective for
7 eteplirsen in the treatment of boys with DMD.

8 **Applicant Presentation - Jerry Mendell**

9 DR. MENDELL: My name is Dr. Jerry Mendell,
10 and I currently serve as director of the Center for
11 Gene Therapy at Nationwide Children's Hospital.

12 I'm uniquely positioned to provide a clinical
13 perspective as the PI for the eteplirsen 201 and
14 202 studies since 2011. I'm a paid consultant for
15 Sarepta in preparation for today, but I stand to
16 gain no financial benefit from FDA approval of
17 eteplirsen.

18 My experience in the management and care of
19 DMD boys extends back to my post-doctoral position
20 at NIH in 1969. When I started caring for DMD boys
21 at that time, there were no treatments, and I made
22 a personal commitment that over my lifetime, I

1 would make a difference for boys with this
2 devastating disease.

3 There are three elements that emphasize the
4 foundation for eteplirsen approval for the
5 treatment of DMD. I refer to these as the
6 treatment triad.

7 The first leg of the triad is prolonged
8 ambulation. To be clear, the FDA is suggesting
9 that boys with DMD are able to walk until the age
10 of 16. This is not my experience, nor is it
11 reflected in the data from CINRG, which shows loss
12 of ambulation at a median age of 12 in exon 51
13 amenable patients. In the eteplirsen study,
14 10 boys are still walking 4 years after starting
15 therapy. Their median age is 13.4, and the median
16 age of loss of ambulation has not been reached for
17 this cohort.

18 Why is this important? Simply put, the
19 complications of wheelchair dependency have a major
20 cascading effect that is both physical, including
21 scoliosis and osteoporosis, and emotional, a change
22 in body image leading to a loss of self-esteem. In

1 addition, many of the rapidly advancing
2 translational treatments are denied to
3 wheelchair-dependent patients.

4 The second leg of the triad is the safety
5 profile of eteplirsen. I have done many clinical
6 trials over the past 40 plus years, and I have
7 never seen tolerability like we have seen in this
8 trial. There has not been a single serious adverse
9 event related to treatment in over 3900 infusions
10 of eteplirsen.

11 The third leg is what I refer to as the
12 consistency profile of eteplirsen treatment. This
13 is best illustrated by the maintenance of
14 ambulation after 4 years of therapy.

15 Dr. Kaye presented an exploratory analysis
16 excluding the two boys who lost ambulation early in
17 the study. Here we see the mean change from
18 baseline through week 216. For clarity, we have
19 shown both treatment groups starting at the zero
20 point.

21 What interests me is what happens after
22 week 48. Here we see a long-term stabilization and

1 a consistent parallel course between both groups,
2 however the placebo delayed treatment group never
3 catches up, sending a clear message that there is a
4 treatment effect of eteplirsen. The consistency of
5 the data is remarkable giving the protocol mandates
6 that the distance measured for each patient be
7 recorded and transcribed in the case report forms
8 without looking back at the previous result.

9 I'd also like you to know that what we have
10 observed in the eteplirsen treated patients is very
11 different from what I have seen in the natural
12 history. I know this because every DMD boy who
13 comes to Nationwide Children's Hospital for ongoing
14 care undergoes a 6-minute walk test with the same
15 physical therapist, under the same condition as the
16 eteplirsen trial, and we simply don't see similar
17 results.

18 This graph also emphasizes that there are no
19 claims that eteplirsen is a cure for DMD.
20 Eteplirsen slows progression, which results in
21 maintained ambulation.

22 The next slide allows us to look again at

1 loss of ambulation over 4 years. In the exon 51
2 external control matched for age and mutation, the
3 risk of loss of ambulation is 85 percent for
4 external control patients compared to 17 percent
5 for eteplirsen.

6 As previously stated, a major goal of this
7 trial was to delay the loss of ambulation. Our
8 data suggests that the unequivocal increase in
9 dystrophin by eteplirsen cannot be ignored as an
10 explanation for prolonged ambulation. Preserving
11 walking is key to maintaining physical and
12 emotional wellbeing.

13 The numbers are one thing, but my personal
14 enthusiasm for these findings is best demonstrated
15 by the quality of walking in eteplirsen treated
16 patients, as we see on the next slide.

17 This is Billy in the red cap. He's now 15,
18 and he's one of my patients in the eteplirsen
19 trial. Here he's walking in the last mile of the
20 Pittsburgh marathon. First of all, boys at this
21 age with DMD usually don't walk, and they certainly
22 don't walk in the last leg of a marathon. But here

1 he is, and I want you to watch closely because not
2 only does he walk, but he has gained enough self-
3 esteem to attempt jogging as if to emulate other
4 participants in this highly competitive trial. Go
5 Billy.

6 (Applause.)

7 This quality of ambulation at 15 just
8 doesn't happen in DMD.

9 In summary, I see treatment of DMD as a race
10 against time. If you shadowed me in clinic, you
11 would find that most boys at age 14 are in a
12 wheelchair. Fifteen-year-old boys like Billy don't
13 maintain ambulation by accident. This is a very
14 gratifying result for a long-term clinician.

15 Eteplirsen offers a genuine opportunity to
16 change the natural history of this disease by
17 slowing progression and improving quality of life.
18 I can't see any grounds for withholding this drug
19 for DMD boys. The opportunity before the panel is
20 to give the DMD boys in my clinic, and in other
21 clinics, the same chance as we observed in the
22 eteplirsen trial.

1 I want to thank this panel of reviewers, the
2 team of researchers at Nationwide Children's
3 Hospital, and the collaborators at multiple sites
4 for helping to make this happen. Most of all, I
5 want to thank the 12 heroic boys and their families
6 who selflessly dedicated themselves to this
7 groundbreaking research. And finally, I want to
8 turn this podium back over to Dr. Kaye for
9 concluding remarks.

10 (Applause.)

11 **Applicant Presentation - Edward Kaye**

12 DR. KAYE: Today the FDA has presented to
13 you a number of important questions for your
14 consideration. To help you in your deliberations,
15 allow me to conclude by reviewing three of the most
16 critical and then offer Sarepta's position on each.

17 The first question focuses on the provision
18 of adequate evidence. The agency has asked if
19 eteplirsen produces dystrophin to a level that is
20 reasonably likely to predict clinical benefit.
21 Today we presented data that shows an unequivocal
22 increase in functional de novo dystrophin by three

1 complementary methods. Most important, we shared
2 with you the fact that even small amounts of
3 dystrophin are known to confer clinical benefit.

4 The second question focuses on the 6-minute
5 walk test. It asks if the test is sufficiently
6 objective and free of bias to allow for a valid
7 comparison. Sarepta's position is clear. The
8 6-minute walk test is both standardized and
9 considered highly reliable. Moreover, our external
10 control results are consistent with other natural
11 history databases.

12 The third and final question focuses on
13 whether our clinical studies have provided
14 substantial evidence that eteplirsen is effective
15 for the treatment of DMD. Once again, our answer
16 is yes. The data set we've presented to you shows
17 a dramatic positive effect on the 6-minute walk
18 test as well as on the loss of ambulation for over
19 4 years.

20 All of us here today agree that bringing new
21 and effective therapies to boys suffering from DMD
22 is both critical and urgent. But we also know that

1 in the field of rare diseases large
2 placebo-controlled studies present significant
3 challenges.

4 As Ms. Ruff said in her opening remarks,
5 given the limitations of our database, we both
6 understand and appreciate the difficulty of your
7 decision today, yet we believe it is both
8 reasonable and prudent to approve eteplirsen based
9 on the totality of the data we have presented
10 today.

11 Let me conclude our formal presentation with
12 this. Sarepta stands ready to work with the entire
13 DMD community, patients, caregivers, providers, and
14 our colleagues at the FDA to continue our
15 groundbreaking work and hasten the day when we can
16 say with certainty we have a cure.

17 I would now like to introduce Christine
18 McSherry from the Jett Foundation.

19 (Applause.)

20 **Applicant Guest Speaker Presentation**

21 **Christine McSherry**

22 MS. McSHERRY: Thank you, Dr. Kaye, and to

1 Sarepta for donating some of your time today for
2 our presentation. I am Christine McSherry, a
3 registered nurse, the executive director at Jett
4 Foundation, but most importantly a mom of a
5 20-year-old with Duchenne.

6 My son, Jett, is enrolled in study 204,
7 Sarepta's safety study for the advanced patient
8 population, and he's been receiving eteplirsen for
9 18 months. Jett took his last step when he was 13.

10 I started the Foundation in 2001 with a
11 mission to improve the lives of those affected by
12 Duchenne. The Foundation does not have any
13 financial interest in the outcome of this meeting,
14 and has not been compensated for this project.

15 As you heard from the sponsor's
16 presentation, FDASIA gives patients a voice in the
17 drug development process. With this law in mind,
18 we met with CDER officials many times over the last
19 4 years.

20 It was never our intent for the results of
21 the videos to be part of this outcome. It was
22 simply intended to bring context and perspective to

1 FDA on outcomes that are meaningful to patients.

2 In the spring of 2012, prior to the release
3 of public data, we heard stories about boys doing
4 well on eteplirsen. There were small but
5 meaningful things that they had never done prior to
6 taking the drug, like opening bottles of water and
7 bags of chips. Boys with Duchenne often struggle
8 with these types of activities.

9 In April 2013, we met with CDER to discuss
10 the patient experiences that we heard about and
11 they asked us for video evidence. In June, we
12 returned and presented videos of boys who were
13 jumping into pools, walking their dog, and
14 participating in sports.

15 CDER officials asked us to quantify outcomes
16 important to patients, so as requested, in July of
17 2015, we presented and submitted data on activities
18 of daily living, or ADLs, to FDA. At this meeting,
19 they indicated these results would be included in
20 the review of the eteplirsen NDA.

21 We collected this information through
22 semi-structured videotaped interviews that included

1 rating scales. Many themes emerged in this data,
2 but due to our limited time today, I'll only be
3 sharing 4 key findings: spontaneous falls, walking
4 after fractures, fatigue, and ADLs.

5 Through social media requests, 8 of the 12
6 participants in study 202 agreed to be interviewed.
7 All of these boys were over the age of 7 and in the
8 decline phase of ambulation. And importantly, we
9 interviewed the 3 largest decliners in the study,
10 including the 2 patients who lost ambulation early
11 and a boy who broke his tibia.

12 These interviews took place after the boys
13 had been receiving therapy for 3 years. We also
14 interviewed 3 boys from study 204. In total, 11
15 boys participated.

16 Our research led to several key findings,
17 all things that we would never expect to see in the
18 normal progression of Duchenne. The first finding
19 was a decrease in spontaneous falls. Now, let's
20 take a look at a video of what a typical fall looks
21 like for a child with Duchenne. This video was
22 taken during a 6-minute walk test.

1 Now, watch carefully. We've all tripped.
2 This boy doesn't trip. As you're watching, look at
3 his feet very carefully. He doesn't trip. His
4 quads just give out, giving him no time or warning
5 to brace his fall.

6 (Video played.)

7 MS. McSHERRY: That is a Duchenne fall. In
8 this instance, the physical therapist is there to
9 pick the boy up off the floor. By the age of 9,
10 the majority of boys with Duchenne are losing the
11 ability to get off the floor themselves. So if
12 this happens when no one is around, the only
13 alternative is to lie and wait until someone comes
14 to find him. Boys of this age are typically
15 gaining independence. In contrast, these boys can
16 no longer be left alone.

17 Now, let's listen to how one boy describes
18 his experience falling prior to taking eteplirsen
19 and then after he's been on therapy.

20 (Video played.)

21 MS. McSHERRY: "I don't even remember when I
22 collapsed the last time." Daily diary, spontaneous

1 falls. So the mother of this patient kept a daily
2 diary of his spontaneous falls. The Y-axis
3 represents the number of spontaneous falls per day,
4 while the X-axis represents time. This boy started
5 on drug in November of 2014, and he was falling
6 twice a day, and the falls decreased until March of
7 2015 when his falls stopped. And without the fear
8 of falling, he's able to play soccer, his favorite
9 activity, for an extended period of time.

10 We asked caregivers to report the number of
11 daily falls from the beginning of the trial to the
12 time of our interview. The bars on the X-axis
13 represent the patients from study 202 at baseline
14 and 3 years later. The Y-axis represents the
15 number of falls they experienced at those two time
16 points.

17 The gray bars in the red circle represent
18 the boys, 2 boys, who lost ambulation early in the
19 trial, and as you can see, they experienced over
20 4 spontaneous falls a day prior to losing
21 ambulation.

22 The red arrows highlight 4 boys who had been

1 falling anywhere between 5 times a day to twice a
2 week. The yellow bars reveal that over time, they
3 all essentially stopped collapsing. And
4 surprisingly, the red arrows signify that no
5 ambulatory boy is falling 3 years after starting
6 drug. This just doesn't happen with boys who have
7 Duchenne at this stage in their disease.

8 Walking after fracture, key finding
9 number 2. Spontaneous falls are also devastating
10 because they can lead to fractures, which typically
11 marks the end of our sons' walking. Families
12 affected by Duchenne have the same fear that you
13 would have of an elderly parent falling and
14 breaking a hip.

15 During our interviews, a highly experienced
16 physical therapist, who specializes in Duchenne,
17 told us, quote, "If you're 10, 11, or 12 and you
18 break a leg, I'm shocked if you would ever walk
19 again. I would say 9 times out of 10, that's the
20 end of your walking."

21 Boys with Duchenne are at high risk of a
22 fracture due to corticosteroid use. We learned

1 that 4 boys on eteplirsen had fractures, yet all 4
2 regained the ability to walk. For boys their age,
3 it's not what we would expect. We would expect
4 them to never walk again.

5 Key finding number 3, Duchenne related
6 fatigue. It's important to understand this
7 distinction. Because of Duchenne, these boys reach
8 the point of exhaustion much faster. As the
9 disease advances, they often can't make it through
10 a full day of school. They crash, sleeping for
11 hours.

12 However 5 of the 8 boys taking eteplirsen
13 either decreased or maintained their level of
14 fatigue. This is not what we would expect over
15 3 years. The other 3 boys were the ones who either
16 lost ambulation or experienced a fracture.

17 As I said before, I'm a mom of a 20-year-old
18 boy with Duchenne. And as the disease progresses,
19 these boys are completely exhausted and lose the
20 ability to do everyday things. The simple task,
21 such as lifting a spoon to their mouth, feels like
22 they're lifting heavy weights for them. And simple

1 tasks, like scratching your nose or turning over in
2 bed, become impossible.

3 Earlier in the disease when boys tire, it
4 leads them to use a wheelchair more often. Let's
5 listen to one boy's experience after being on
6 eteplirsen.

7 (Video played.)

8 MS. McSHERRY: Maintaining the ability to
9 walk, something we take for granted, but this boy
10 is able to walk with his friends. He can walk his
11 dog, and he can play like a normal kid.

12 The loss of ambulation changes every aspect
13 of normal daily living, from accessing a friend's
14 house, to taking family vacations, to home
15 modifications. It's just endless. Remember,
16 ambulation isn't just about walking. It also
17 benefits bone health, prevents scoliosis, and
18 supports breathing. It touches not just the boy,
19 but everyone else.

20 For the boy that we just heard from, the
21 6-minute walk test tells a story, but not the whole
22 story. For example, while this boy's 6-minute walk

1 test remains stable, it didn't capture the
2 improvements that we saw. He stopped falling, and
3 his fatigue was reduced. Just looking at the
4 6-minute walk test you wouldn't see the
5 improvements in these other important outcome
6 measures.

7 Key finding number 4, participating in life
8 for ADLs. Typically, when boys lose ambulation,
9 they quickly lose upper arm strength. And we fully
10 understand that eteplirsen is not a cure, and it
11 only slows the progression of the disease. So it
12 was important for us to see if the drug was having
13 a benefit in the non-ambulatory boys.

14 For this reason, we looked at the twin boys
15 who lost ambulation. We assessed 8 activities of
16 daily living that don't involve walking, such as
17 using a computer, feeding oneself, brushing teeth,
18 and using a cell phone. Despite coming off their
19 feet, both boys have maintained the ability to do
20 these activities over the 3-year time frame. This
21 would suggest a benefit in the non-ambulant
22 population.

1 The collective experience tells us that
2 eteplirsen is having a real and concrete impact on
3 the rate of disease progression. For the boys that
4 we interviewed, who were all between the ages of 10
5 and 13 and on drug for over 3 years, we saw a
6 decrease in spontaneous falls, the ability to walk
7 after a fracture, and the stabilization or
8 improvement in fatigue, and the maintenance of ADLs
9 in the non-ambulatory boys. In the time that it
10 will take to complete the confirmatory study, many
11 boys in our community will either lose the ability
12 to walk, to lift their arms, or to breathe.

13 Just two short weeks ago, Dr. Janet Woodcock
14 spoke at a breakthrough therapy briefing on Capitol
15 Hill by Friends of Cancer Research. She spoke
16 about type 1 errors, false positives, and type 2
17 errors, false negatives.

18 In the context of FDA, a type 1 error would
19 be risk of approving drugs that are unsafe or
20 ineffective, whereas a type 2 error is not
21 approving a drug that is safe and effective. She
22 said that type 2 errors are not talked about enough

1 and there needs to be a balance between the risk of
2 committing a type 1 versus a type 2 error.

3 This afternoon when you hear the human side
4 of this story, from those who have benefited from
5 this drug as well as others waiting for treatment,
6 I hope you keep in mind type 2 errors and recognize
7 that there is a very real human cost to making a
8 conclusion that a drug doesn't work when it really
9 does. Thank you.

10 (Applause.)

11 DR. ALEXANDER: Thank you. Thank you for
12 the presentation.

13 (Applause.)

14 **Clarifying Questions**

15 DR. ALEXANDER: Thank you very much. If
16 everyone could please take their seats.

17 Thank you. We'll now proceed with
18 clarifying questions to Sarepta Therapeutics. Are
19 there any clarifying questions? Please remember
20 that all participants from the panel, FDA, and
21 Sarepta should state their name for the record
22 before you speak. If you can, please direct

1 questions to a specific presenter.

2 Dr. Hoffman?

3 DR. HOFFMAN: Richard Hoffman. Eteplirsen
4 looks to be a very promising disease-modifying
5 agent, and I was wondering if the sponsor had any
6 plans to do a larger study in younger boys and at a
7 much higher dose. Thank you.

8 MS. RUFF: I'd like to ask Dr. Kaye to come
9 to the podium.

10 DR. KAYE: So the answer to your first
11 question is, yes, we have a large 60-treated
12 patient open-label study that is ongoing, and we
13 have another study in our -- which will be a
14 double-blind, placebo-controlled study, that will
15 be 99 patients in the 2 to 1 randomization for the
16 next two drugs. So that was the way of being able
17 to do a double-blind, placebo-controlled.

18 Our dose that we had determined is
19 30 milligrams per kilogram, and this was based on
20 the pharmacodynamic effect. We didn't see any
21 difference. However, we do plan to continue to
22 look. We're looking at -- we have a study right

1 now in younger patient populations, and we have a
2 study in older populations. And we have plans to
3 go down to the newborn level, and we will be
4 looking at a number of different ways of dosing,
5 even at younger ages.

6 DR. ALEXANDER: Thank you. Dr. Onyike?

7 DR. ONYIKE: So I'm not exactly sure who I'm
8 directing this to, so please, Dr. Kaye or someone
9 else with the technical qualifications should take
10 the question. What I really want to understand is
11 about the mean relative fluorescence intensity.
12 I'm having difficulty understanding how it's a
13 quantitative measure because you're
14 essentially -- it seems to me you have pathologists
15 looking at slides and trying to make decisions
16 about the intensity of a dye relative to what scale
17 is very unclear.

18 But I can imagine that with the naked eye,
19 it's very hard to achieve very graded
20 quantification of staining unless you have some
21 sort of spectrum that you make a reference to,
22 which I don't think you have.

1 So explain how exactly we should take the
2 mean relative fluorescence intensity as seriously
3 as say, the Western blot, in terms of
4 quantification?

5 MS. RUFF: So to address your question about
6 quantification using intensity, I'd like Dr. Frank
7 to come to the podium.

8 DR. FRANK: Thank you. My name is Diane
9 Frank. I'm the senior director of translational
10 research at Sarepta. The intensity measures were
11 made using a computer algorithm, because as you
12 correctly stated, the human eye is not very good at
13 measuring intensity levels with the resolution that
14 the computer program's able to do. Because a
15 computer program has a definition to look at the
16 pixel intensities in the region of the membrane, it
17 can calculate the average intensity pixel by pixel
18 across the image.

19 DR. ONYIKE: If I may follow on, how do you
20 translate then these intensities into actual tissue
21 concentrations at the sarcolemma?

22 DR. FRANK: So one of the challenges in the

1 field is there is no absolute standard for
2 dystrophin, therefore, we have no ability to do an
3 absolute dystrophin concentration, such as a
4 microgram per square centimeter.

5 As a result, we make our comparisons to one
6 consistent normal control, and that's why you're
7 seeing percent normal. And then the change of our
8 therapeutic effect is a relative change due to the
9 lack of an absolute standard, so that we're looking
10 at the change from baseline.

11 DR. ALEXANDER: Thank you. Dr. Green?

12 DR. GREEN: Yes, I wanted to know whether
13 there was any specific language that was included
14 or excluded before the 6-minute walking test in
15 both subjects and the controls.

16 MS. RUFF: If I can just clarify. Are you
17 talking about the script for the 6-minute walk
18 test?

19 DR. GREEN: Well, I'm talking about -- no,
20 I'm actually talking more about in advance in
21 preparation for the 6-minute walking test, and not
22 only in those who had it administered as part of

1 the trial but in the control group.

2 MS. RUFF: So I'd like Dr. Mendell to talk
3 about the eteplirsen boys, and then Dr. Mercuri to
4 talk about the external control boys.

5 DR. MENDELL: Well, the 6-minute walk test
6 is done in a standard fashion. The boys are
7 explained the test prior to it being done. And
8 then during the trial, they, one, are told that
9 they must walk and not run, and they should try as
10 hard as they can. And there is encouragement for
11 them to continue the walk as long as they can.

12 If they fall, there is someone behind them
13 to, as you saw in the video, help them get up and
14 then continue to walk. For those boys who can't
15 continue because they have been injured or in pain
16 or whatever, then they will stop, and that will be
17 the end of the walk test.

18 But it's done in a standardized fashion.
19 The same therapist does the same test on every
20 single patient, and it's the same thing for our
21 clinic when the boys come, even outside of the
22 study.

1 DR. ALEXANDER: Can you speak into the
2 microphone please, Dr. Green?

3 DR. GREEN: And there are no family members
4 present during this?

5 DR. MENDELL: There are absolutely no family
6 members present when the boys are tested.

7 DR. MERCURI: The same applies for the
8 external controls. There is a manual. There are
9 strict instructions on how to perform it. It's the
10 same way we perform it in clinical routine and in
11 the clinical trials. And the instructions are very
12 strict also on the time of the encouragement and so
13 on.

14 So these children know the test very well
15 because it's part of our clinical routine. But
16 again, I want to stress that the training is very
17 specific on giving strict instructions according to
18 what is specified in the manual.

19 DR. GREEN: Thank you.

20 DR. ALEXANDER: Thank you. Dr. Nuckolls?

21 DR. NUCKOLLS: Yes, I have a question for
22 Dr. Mendell regarding --

1 DR. ALEXANDER: Could you please just state
2 your name on the record again?

3 DR. NUCKOLLS: I'm Glen Nuckolls. So a
4 question for Dr. Mendell regarding genotypes that
5 modify disease progression, such as osteopontin and
6 LTBP4. So you were an author on a publication in
7 2013 that demonstrated that the major protective
8 haplotype of LBTP4 is associated with prolonged
9 ambulation, up to 2 years, a level comparable to
10 the effects of corticosteroid treatment.

11 So what is known about the modified
12 genotypes of the treated and control groups and how
13 might that information aid in interpreting the
14 data?

15 MS. RUFF: One thing I'd like to point out
16 is the prevalence of these modifiers are very, very
17 low. But anyway, I will ask Dr. Mendell.

18 DR. MENDELL: Well, Glen, thanks for the
19 question. I think what you have to appreciate is
20 that back in 2010 when we designed this study,
21 there were no modifiers, and so it was not part of
22 the original protocol. And then, as the study

1 evolved and we saw the results, and then compared
2 it to the Italian group and the Leuven group, we
3 had comparable number of patients, comparable age,
4 and as Ed Kaye showed, they were matched
5 demographically in every way.

6 We appreciate that the modifiers would be
7 equally distributed between the groups. There's 12
8 in our group, 13 in the comparable control group.
9 And we felt that there would be the same
10 statistical possibility for the modifying mutation
11 to appear in both groups.

12 So it has not been done, but it could easily
13 be done at any point in time. It's unlikely to
14 have an effect given that the groups are the same
15 size. And in the Italian group, there is no
16 difference in terms of the 6-minute walk and so
17 forth, as you saw.

18 DR. ALEXANDER: So this is Caleb Alexander.
19 Just to clarify, you don't have information, it's
20 never been studied, for either the control or
21 treated patients, the presence of this genetic
22 phenotype?

1 DR. MENDELL: At this point, yes.

2 DR. ALEXANDER: Thank you. Dr. Ovbiagele?

3 DR. OVBIAGELE: Bruce Ovbiagele. My
4 questions pertain to the nature and the timing of
5 dystrophin, and so perhaps this question might be
6 for Dr. Kaye.

7 First, I recognize of course that it's the
8 increase from baseline that's the most meaningful
9 determination of treatment effect. But from the
10 literature, do we know what the magnitude of
11 increase from baseline that's most meaningful?

12 That's the first thing.

13 Secondly, have exon 51 patients actually
14 been studied with regard to that, and what exactly
15 is the clinical relevance?

16 The last question pertaining to that is
17 about dose and duration. Are there any other
18 supportive data at 24 weeks showing that there's an
19 increase in dystrophin at that time point?

20 MS. RUFF: So I'd just like to clarify your
21 question. So I believe you had three questions.
22 One was about increase from baseline, are there any

1 details in the literature.

2 DR. OVBIAGELE: Right. So on one particular
3 slide, it was pointed out that the increase from
4 baseline is the most meaningful determination of
5 treatment effect, and certain references were
6 cited. So I was trying to figure out what the
7 magnitude of that increase actually is and whether
8 exon 51 patients were actually studied, and what
9 was the actual clinical impact.

10 MS. RUFF: Okay. So I'll ask Dr. Kaye to
11 come first to discuss the magnitude of effect from
12 baseline, and then Dr. Muntoni to discuss the
13 clinical relevance.

14 DR. KAYE: One of the challenges of course
15 that we had with this study is there is no
16 information before this therapy was initiated. The
17 reason being is that no other drug has produced
18 dystrophin as a comparator, so we don't have a good
19 comparator to know how much is enough. The only
20 way we can compare is to know what's available in
21 the exon 51 boys and other boys who have certain
22 amounts of dystrophin.

1 What we do appreciate from the field is that
2 if you have a small amount of dystrophin, what's
3 been recorded in the exon 44 population, that does
4 seem to make a difference. You can prolong
5 ambulation by at least 2 years. So we have to make
6 that comparison by stretching to the literature,
7 but there is no baseline that has been established
8 because no one's really been able to make
9 dystrophin before to compare.

10 DR. MUNTONI: My name is Francesco Muntoni.
11 I'm a pediatric neurologist. I work at UCL in
12 London. I was a principle investigator the first
13 two clinical trials where this drug was given for
14 the first time to boys with Duchenne. I have
15 received compensation from Sarepta for being here
16 at this meeting, and I have no financial interest
17 in the outcome of the meeting today.

18 I will address two points from your
19 question. The first is, what is the significance
20 of this increase in this treated boy, and the
21 second is, has other patients with exon 51 been
22 studied.

1 So regarding the first point, as a person
2 who looks at the biopsy of these children as well,
3 one thing that is unusual in the biopsy of these
4 children that convinced me that there is a
5 functional significance of this level of dystrophin
6 is that not only there is dystrophin at the
7 sarcolemma but there is restoration of protein of
8 the dystrophin associated complex.

9 So dystrophin is a member of a protein
10 complex, and its deficiency leads to a
11 destabilization of a number of protein associated
12 with the sarcolemma. And in the fibers that have
13 dystrophin, you can see and also quantify using the
14 immunocytochemistry if the protein of the complex
15 have been restored.

16 I will ask in a second a slide to come up
17 where you will see that there will be black when
18 there is no dystrophin, there will be white at the
19 sarcolemma where there is dystrophin. And you will
20 see that whenever there is dystrophin, the protein
21 of dystrophin, as a safety complex had been
22 restored.

1 If I can have this slide up, please. So if
2 you concentrate on the left side of the screen, you
3 will see that every single circle on the top with
4 white is dystrophin. The same fibers in the
5 intermediate and lower panel also have other
6 dystrophin associated protein that are not present
7 in the fibers that do not have dystrophin. So that
8 I think is a very powerful argument that that
9 dystrophin is doing something functional.

10 In terms of the second part of your
11 question, if I understood it correctly -- will you
12 please correct me if I didn't -- so we did look at
13 a patient who have exon 51. They are the
14 equivalent of what we want to do by skipping exon
15 51. They are Beckers who have the equivalent
16 deletions. And I co-authored the paper that was
17 also cited in the briefing document for FDA.

18 So when we look in these patients, what we
19 found were two things that are important. The
20 first is that the level of dystrophin in this group
21 of patients was very high in general. The lowest
22 patient was in the range of 40 percent.

1 However, one important point to make, the
2 great majority of these patients were either
3 symptomatic or had minimal symptoms, and therefore
4 what we concluded is that if you were able to put
5 40 percent dystrophin, this patient potential could
6 be asymptomatic. So that of course is an
7 extrapolation regarding the treatment now.

8 Does that answer your question?

9 DR. OVBIAGELE: No, that's very helpful.
10 And just a last question, please, about the timing
11 of the increase in dystrophin, which was at
12 24 weeks, which was somewhat contradictory to one
13 of your earlier studies. And I wondered if there
14 any literature supporting that increase at
15 24 weeks.

16 MS. RUFF: Dr. Kaye?

17 DR. KAYE: So again, one of the limitations
18 is that there hasn't been any other drug that has
19 been able to really measure dystrophin. We know
20 that dystrophin lasts a very long time and has
21 about a 2-month turnover, so we know in order for
22 the protein to turn over and to make new one, it's

1 going to take a fairly long period of time.

2 What Dr. Muntoni had shown in his
3 laboratory, within the first 12 weeks, you could
4 see some dystrophin. He had a very sensitive
5 assay, but it wasn't as, let's say, reproducible
6 and validated as the second assay that we
7 performed.

8 But what we saw at 24 weeks is a consistent
9 increase in all of the patients, and this is
10 probably consistent with the half-life. So this
11 was really the first time that this has been
12 appreciated, and, again, because eteplirsen was
13 really the first drug to show dystrophin.

14 DR. ALEXANDER: Does that answer your
15 question? Okay.

16 So we'll take a question from Dr.
17 Kesselheim, and then after that, we'll convene for
18 a break.

19 DR. KESSELHEIM: I just wanted to follow up
20 on the dose question just to clarify how it was
21 that you determined the 30 and 50 milligram dose on
22 the basis of the prior studies that didn't test

1 that, and then how you determined to choose the
2 30-milligram dose as the one that you are
3 approaching. And then my other question is whether
4 you had a physiologic basis for the 24-week
5 hypothesis, but I think you addressed that in the
6 previous discussion.

7 MS. RUFF: Okay, so Dr. Kaye.

8 DR. KAYE: So as you can imagine in rare
9 diseases, dose ranging can be challenging because
10 you don't have large numbers of patients. So we
11 had determined early to do a dose ranging based on
12 the percent dystrophin positive fibers. And what
13 I'd like to show you is at our week 48 biopsy, we
14 had a comparison of the percent dystrophin positive
15 fibers and also the dystrophin intensity.

16 Slide up, please. In looking at this slide,
17 in the purple, we see the 30 milligrams and the
18 50 milligrams. And we see that they were very
19 similar for percent dystrophin positive fibers and
20 for intensity.

21 But obviously this is not a perfect dose
22 finding, and what we did do is an additional study

1 to look at 30 and 50 in addition to clinical.
2 Slide up, please. And when we compare to the
3 clinical 6-minute walk test distance, if we look at
4 the 30 and 50, they're very similar.

5 So based on these data, we decided that we
6 didn't know if there was any potential long-term
7 toxicity. We know this would be a lifelong
8 therapy. We chose the lower dose because we
9 couldn't see a difference. But I think as we go
10 forward, we will look at other dose regimens, and
11 potentially at higher doses, and just to make sure
12 that we understand how to properly use this drug.

13 DR. ALEXANDER: Thank you very much. We'll
14 now take a 15-minute break, so we'll return here at
15 10:55, promptly. Panel members, please remember
16 that there should be no discussion of the meeting
17 topic during the break amongst yourselves or with
18 any member of the audience. Once again, we'll
19 resume at 10:55 a.m.

20 (Whereupon, at 10:40 a.m., a recess was
21 taken.)

22 DR. ALEXANDER: We're going to get started.

1 If everyone can please take their seats, we'll
2 begin with the meeting.

3 Thank you. We'll now begin with the FDA
4 presentations, and first, we'll hear from Janet
5 Woodcock, director at the Center for Drug
6 Evaluation Research.

7 **FDA Remarks - Janet Woodcock**

8 DR. WOODCOCK: Thank you, Mr. Chairman, and
9 good morning. The purpose of today's meeting is
10 for FDA to get expert advice from the committee on
11 a marketing application for the drug eteplirsén.
12 And what I'd like to do is provide a framework
13 within which to consider these data based on my
14 30 years of experience at FDA and really extensive
15 experience in implementation of the legal standards
16 for drug approval.

17 The clinical development program for this
18 product has features that render the data
19 particularly difficult to interpret. It consists
20 primarily of long-term observation of a group of 12
21 treated individuals.

22 When a large treatment effect is observed,

1 for example significant improvement in a disease
2 characterized by overall progression, an
3 uncontrolled study can provide compelling data.
4 Where overall effects are smaller, and especially
5 if there's large inter-individual heterogeneity in
6 the disease course, interpretation of data like
7 this can be challenging.

8 The sponsor and FDA have attempted
9 interpretation by comparing the results in treated
10 children to the disease trajectory that is recorded
11 in a number of external cohorts. It's possible to
12 reach different conclusions about these comparisons
13 as is being discussed today.

14 Eteplirsen is intended to improve outcomes
15 in a targeted subset of DMD patients by enabling
16 muscle cells to produce a truncated version of the
17 protein dystrophin, which is missing or present at
18 very low levels in patients with DMD.

19 There is agreement that eteplirsen does
20 achieve its primary intended pharmacodynamic
21 effect, that is production of a truncated messenger
22 RNA, and this is based on PCR results from muscle

1 biopsies.

2 It was originally hoped that this effect
3 would result in a substantial increase in
4 expression of the truncated dystrophin molecule,
5 perhaps to the average level of individuals with
6 Becker muscular dystrophy. This has not turned out
7 to be the case. The increase in dystrophin so far
8 observed is a fold increase over baseline, well
9 below the average dystrophin content in individuals
10 with Becker muscular dystrophy.

11 Now, it hasn't been established for any
12 given person with Duchenne muscular dystrophy
13 whether a small fold increase in dystrophin will
14 provide clinical benefit, or whether there's a
15 threshold, for example an absolute percentage of
16 normal, that is required to deliver a benefit.
17 This is unknown, and of course the sponsor has just
18 argued based on observing other mutations that
19 perhaps small levels may be associated with
20 benefit.

21 It's unlikely an absolute threshold can be
22 established given the fact that within muscular

1 dystrophy, the phenotype, in other words the
2 disease expression, appears to be influenced by
3 factors beyond dystrophin expression, so there are
4 other factors at work.

5 Interpretation of dystrophin expression has
6 been complicated by many technical difficulties.
7 The FDA has put a huge effort into trying to render
8 the results interpretable, along with the sponsor.
9 To me, it is remarkable that the field of exon
10 skipping has advanced far into clinical development
11 generally without well-validated methods of
12 determining pharmacologic success, especially when
13 assessing this biomarker requires muscle biopsies
14 in children with compromised musculature, usually
15 under general anesthesia.

16 There are a lot of questions that still
17 remain, not just about quantitating the Western
18 blot, but also about specimen handling and intra-
19 and inter-muscle variability and results,
20 especially in later stages of disease. There are
21 also questions, and they've been raised today,
22 about the utility of the information supplied by

1 immunofluorescence techniques in comparison to
2 Western blot, and these questions are going to be
3 quite important today.

4 The translational science supporting these
5 development programs is inadequate, and this state
6 of affairs is not atypical in rare and not so rare
7 diseases, and it significantly hinders the tasks of
8 drug developers, as well as the FDA, in assessing
9 the results of these programs.

10 After the presentations by FDA, the sponsor,
11 and the public, the committee will be asked a
12 series of questions about the robustness of the
13 data support marketing approval, either regular
14 approval or approval under the accelerated pathway.

15 The determination that a drug's approvable
16 from a clinical standpoint is a two-step process.
17 First, a finding of substantial evidence of
18 effectiveness, usually based on clinical outcomes,
19 must be made, as Dr. Dunn said earlier. In the
20 case of accelerated approval, this finding can be
21 made based on substantial evidence using a
22 so-called unvalidated surrogated endpoint, believed

1 reasonably likely to predict clinical benefit.

2 Then, the second step after that is
3 determine whether the likely benefits of a drug
4 outweigh the foreseeable harms. And a final
5 approval decision from a clinical basis is whether
6 the benefits outweigh the foreseeable risks.

7 The issue of substantial evidence for
8 regular approval, in this case we're talking about
9 today, turns on how compelling you find the
10 comparisons to the external cohort data. I believe
11 the committee has experience with this question,
12 and so I'm not going to into it anymore.

13 Accelerated approval is a more nuanced
14 issue. In the FDA Safety and Innovation Act of
15 2012, Congress instantiated and statute our
16 accelerated approval regulations, and in doing so
17 urged FDA to apply accelerated approval more
18 broadly, particularly in rare diseases, while
19 maintaining our standards. FDA has never
20 articulated an evidentiary standard for determining
21 if a surrogate endpoint is reasonably likely to
22 predict clinical benefit.

1 In applications of accelerated approval
2 outside of cancer and HIV, FDA has used various
3 types of data, including natural history data,
4 pharmacologic, pathophysiologic, and clinical data
5 to assist with this determination in a wide variety
6 of settings, most of them rare disease settings.
7 The agency has exercised considerable flexibility
8 in applying these criteria of reasonably likely.

9 In the case before us today, the linkage
10 between the observed levels of dystrophin
11 expression and potential clinical benefit will be
12 explored. If the committee were to recommend that
13 the clinical data represent substantial evidence,
14 then the question of accelerated approval does not
15 need to be taken up by you.

16 If the committee does not make this finding,
17 then the clinical data generated in this
18 development program that you've heard about this
19 morning may be used as part of the assessment of
20 whether the surrogate of dystrophin expression at a
21 particular level is reasonably likely to predict
22 clinical benefit. And I'm happy to answer

1 questions later about that statement if you wish.

2 Finally, I would note that much of the
3 effort in evaluating a drug development program
4 goes into avoiding a specific mistake, that is
5 erroneously approving a drug that is not effective.

6 There often is little consideration of
7 another error, which is failing to approve a drug
8 that actually works. In devastating diseases, the
9 consequences of this mistake can be extreme, but
10 most of these consequences are borne by patients
11 who traditionally who have little say in how the
12 standards are implemented.

13 The accelerated approval program includes a
14 requirement for confirmatory studies for efficacy,
15 so as you've heard from the sponsor, you have to do
16 further studies to explore and confirm
17 effectiveness. An inherent presumption in this
18 program of accelerated approval, which is written
19 in the preamble to our regulation about it, is that
20 more uncertainty is going to be tolerated initially
21 and that in fact sometimes we will collectively get
22 it wrong, otherwise accelerated approval would

1 really have no different standards than regular
2 approval.

3 I hope these remarks have been helpful, and
4 I look forward to hearing the deliberations. Thank
5 you.

6 DR. ALEXANDER: Thank you. Next, we'll hear
7 from Dr. Robert Temple.

8 **FDA Presentation - Robert Temple**

9 DR. TEMPLE: Good morning. I'm going to
10 talk about historically controlled trials,
11 generally as a basis for what you would call full
12 approval. The point Dr. Woodcock made that there
13 are other ways to consider this is important.

14 So this will be a brief discussion of the
15 history of our use of historically controlled
16 studies and the concerns associated with the
17 design, which will I'm sure be quite familiar to
18 the committee. I want to emphasize, I am not in
19 any way addressing the eteplirsen data in study
20 201/202; that's going to come in subsequent
21 presentations.

22 Section 505(d) of the Food, Drug, and

1 Cosmetic Act defines the standards for drug
2 approval calling for substantial evidence of
3 effectiveness. I don't necessarily have to read
4 all this stuff, but it means evidence consisting of
5 adequate, well-controlled studies that allow you to
6 reach a good conclusion.

7 Adequate and well-controlled studies were
8 actually first defined in regulations in 1970, a
9 long time ago, and they are now in 21 CFR 314.126
10 in the current regulations. And from the
11 beginning, they've always included as one kind of
12 adequate and well-controlled study, the historical
13 control, which is interesting because a lot of
14 people would have considered those not quite
15 controlled studies. But it's always been part of
16 it, absolutely part of it.

17 This is what the regulation says. Sorry to
18 have to read so much. "The results of treatment
19 with the test drug are compared with experience
20 historically derived from the adequately documented
21 natural history of the disease or condition, or
22 from the results of active treatment in comparable

1 patients or populations.

2 "Because historical control populations
3 usually cannot be as well assessed with respect to
4 pertinent variables as can concurrently controlled
5 populations, historical control designs are usually
6 reserved for special circumstances, and the
7 examples include studies of disease with high and
8 predictable mortality, like certain malignancies,
9 and studies in which the effect of the drug is
10 self-evident, general anesthetics, drug
11 metabolism."

12 Note, although this isn't specifically
13 discussed, that a baseline control trial where a
14 single arm treatment is compared with what would
15 have been expected in the absence of an
16 intervention is a kind of historical control,
17 although it's not generally mentioned.

18 ICH E-10 went into a number of different
19 kinds of controls, non-inferiority studies and
20 others, but it also spent some time on the
21 historical control and renamed it as a kind of
22 quote, "external control."

1 It notes several different kinds. One is a
2 population treated earlier. That's really a
3 historical control. A population treated
4 contemporaneously at another institution. That's
5 not exactly historical but it is external. It
6 could be a group outside the study within the same
7 institution. And it identified specifically the
8 baseline control where the patient's course is
9 compared with the expected course, always a
10 difficult thing. And it again notes the design is
11 most clearly usable when the effect is dramatic and
12 rapid.

13 ICH E-10 goes at some length into what the
14 difficulties are with these trials, and the major
15 one, of course, is the inability to control bias,
16 which is a major and well-recognized limitation of
17 externally controlled trials and in many cases
18 makes the design unsuitable.

19 It's worth noting the really two distinct
20 aspects of bias. One is bias before the trial,
21 that is, in who you put into the study, and then
22 the other is bias during and after the trial, sort

1 of bias in the observations.

2 Bias before the trial refers to patient
3 selection. Who have you put into the trial? But
4 even that is really two issues. One, since you
5 don't really know, you're not randomizing, the
6 groups can be non-comparable in ways that you don't
7 really understand because you haven't randomized.
8 Randomization doesn't always lead to comparability
9 either, but in something like this it's more of a
10 problem.

11 The other part of this is selection bias;
12 that is, the control patients could be chosen in a
13 way that means they're sicker. That's
14 non-comparability, but it's got a bias in it. So
15 those are two slightly different aspects of it.

16 As I said, non-comparability of a random
17 nature can go in either direction. It might not
18 favor the treatment. But the guidance, the E-10
19 particularly, notes that it is well-documented that
20 untreated historically controlled groups tend to
21 have worse outcomes than an apparently similar
22 chosen control group in a randomized study,

1 possibly reflecting a selection bias.

2 There are some examples of this of a classic
3 nature. One of my favorite papers was one by
4 Sacks, Chalmers, Smith and coworkers in 1982 that
5 compared randomized trials and historically
6 controlled trials for the same disease, finding
7 results regularly more favorable for the
8 historically controlled trials.

9 The following figure was created by
10 Dr. Unger from a table in this paper, and it's
11 clear that the results of randomized trials are
12 regularly less positive than historically
13 controlled trials. In the examples given in the
14 paper, there were 10 out of 50 that were favorable
15 for the randomized trials and 44 out of 56
16 favorable for the historical controlled trials, and
17 that's what it looks like.

18 The historically controlled trials are on
19 the left, the randomized are on the right.
20 Effective means red. And you can see that in
21 randomized trials in the cirrhosis, surgical
22 treatment to prevent variceal bleeding, in coronary

1 artery surgery, and so on, the historically
2 controlled trials almost always do better.

3 One particular example was a pooled analysis
4 of shunt surgery for preventing bleeding in
5 cirrhotics, and you can see that the bottom line
6 there, which is the historical control, they do
7 much worse than the randomized treatments. My
8 explanation of this has always been that surgeons
9 don't like to lose, so they put healthier people
10 into their control group when they're in control of
11 the assignment.

12 So it seems very likely that in general in
13 Chalmers' studies, the historical control untreated
14 patients were sicker than the surgical candidates
15 in the randomized trials. Selection bias in this
16 case, with patients being different at baseline, is
17 the only real source of potential bias here.
18 Mortality is objective. We don't think that could
19 have been done in a biased way. But the baseline
20 differences could have been very important.

21 So ICH E-10 specifically notes that
22 selection of the control retrospectively with the

1 results known and in hand poses a particular
2 problem.

3 There could also be biases during and after
4 the trial, and you'll hear discussions of some of
5 these things. But the lack of blinding and the
6 investigator's knowledge of treatment in patients
7 getting the test treatment can also allow bias to
8 affect endpoints if they have subjectivity in them.
9 And many endpoints, even ones you might think are
10 highly objective, have a subjective element,
11 including whether a person's had a heart attack or
12 not, cause of hospitalization, and most of the
13 other endpoints we typically use. That is why we
14 blind the people who decide those things.

15 You'll hear later a discussion of the
16 possible subjectivity of ability to ambulate.
17 There will be a debate about that, of course. But
18 importantly, expectation bias and motivation can
19 very markedly affect symptoms and performance, and
20 there are some examples I'll show you where that
21 seems to have been the case.

22 There can also be other biases, I won't

1 dwell on this, but the choice of endpoints. You
2 know, in a controlled trial, you choose the
3 endpoints beforehand. When you're looking at data
4 after the fact, you can look around.

5 So in ICH E-10, the overall tone is
6 relatively skeptical about the use of external
7 controls for most situations, as is also our
8 adequate and well-controlled studies regulation,
9 but both accept them as credible in particular
10 situations.

11 What ICH E-10 urges is selection of a
12 control group for which there's detailed
13 information: demographics baseline state,
14 concomitant medications, and steady course, and
15 you've already heard from Dr. Kaye arguments that
16 that is in fact what they did; try to assure
17 similar treatment other than the test drug and
18 similar observations in the treatment and control
19 groups. It's not a bad idea to have multiple
20 external control groups if you can do it; and it
21 doesn't come up here, consideration of blinded
22 endpoint reassessment in the treatment and external

1 control groups, which can be done sometimes.

2 ICH E-10 also suggests that the main
3 credible use of external controls is when there's
4 ethical difficulty in doing the randomized trial.
5 They strongly urge early randomization, which
6 certainly we've urged in many other cases.

7 The concurrently controlled trial can detect
8 extreme effects very rapidly and can detect modest
9 but still valuable effects that would not be
10 credibly demonstrated by an externally controlled
11 trial. And ICH E-10 again notes that external
12 control trials are most likely be persuasive when
13 the effect is large.

14 Just a couple of more examples that have
15 always interested me. This first one was of
16 interest to me because the person who wrote the
17 letter I refer to there was my first attending at
18 Columbia, a guy named David Gocke, an infectious
19 disease guy.

20 So he wrote a letter to the New England
21 Journal in 1971 about fulminant hepatitis B treated
22 with serum containing antibody to what I used to

1 call the Australian antigen. They had 9
2 consecutive cases of acute fulminant hepatitis B.
3 All were fatal even though they did exchange
4 transfusions, gave steroids, and provided other
5 support. Then they treated eight coma patients
6 with the same treatment plus an anti-Australian
7 antigen, and 5 out of 8 survived.

8 And his letter to the New England Journal
9 says, you know, we thought maybe we were done, but
10 then we were worried that the treatment -- that
11 there's better care, earlier treatment, so we urged
12 a randomized trial, and they did one, in which he
13 participated.

14 This was published in 1977 in the Annals of
15 Internal Medicine. There were 53 patients at
16 30 centers. Survival was as follows. In the
17 placebo group it was 9 of 28, or 32 percent, in the
18 people who got the antigen it was 28 percent.
19 There was no effect at all; pretty sobering and
20 hard to understand given the early results.

21 More recent example, you've all probably
22 read about this, a widely publicized renal artery

1 denervation device was studied in three trials.
2 The first one was an open-label single-arm study
3 called SYMPPLICITY HYPERTENSION-1. It found an
4 average 3-year fall in blood pressure of 33/19.
5 Pretty impressive. This was in people who aren't
6 responsive to other stuff.

7 Then they did a randomized trial, device
8 versus no device, but no sham control, and they
9 found an almost identical effect. Finally, they
10 did a randomized trial with a sham control,
11 SYMPPLICITY 3, and they found at 6 months a change
12 of minus 14 in the denervation population versus
13 12 millimeters in the sham operation. Nothing. So
14 again, sobering on what seems like a very objective
15 endpoint.

16 Then Dr. Unger has provided me with help on
17 transmyocardial laser revascularization therapy.
18 That's where you make holes in the heart to allow
19 blood to flow, and this is what you do. You use a
20 laser to make holes in the heart and allow blood to
21 go in.

22 Initially, at least, it required open heart

1 surgery to use the laser to create channels through
2 the heart muscle, and no one thought you could do a
3 placebo-controlled -- sham-controlled trial -- if
4 you had to do open-heart surgery, so that was
5 pretty reasonable.

6 The results were very striking. This was
7 effects on exercise tolerance for angina, a typical
8 test for angina. So I'm showing two studies here.
9 One showed a gradual increase over time for
10 12 months, almost a doubling of the exercise
11 ability, and the second trial shows almost the same
12 thing. The effects were sustained over a year. It
13 really seemed beyond what anybody could imagine a
14 placebo response was.

15 Then it became possible to do these things
16 without open-heart surgery through catheters. So
17 they did a double-blind, placebo-controlled trial
18 in almost 300 patients comparing 2 doses as well as
19 no treatment, comparing to a sham procedure. And
20 as you can see, there was just no effect at all.
21 All of this is obviously very sobering.

22 So having said that, we do rely on

1 historically controlled trials, just as the
2 regulations contemplate. And the question always
3 is, when are they credible enough and when are they
4 not. There are some obvious cases where it's
5 reasonable.

6 When I was in training, leukemias were
7 always fatal within 3 months, and then there began
8 to be treatments where there were cures. Well,
9 that never happened. You didn't need a control
10 group to know that that couldn't happen.

11 The first three treatments for metastatic
12 testicular cancer, at least some of which I signed
13 off on, were cisplatin, ifosfamide, and etoposide.
14 They were all based on success rates in people with
15 metastatic disease, who would not have been alive
16 at one year, much less alive and tumor free. And
17 in the case of cisplatin, it was 90 percent
18 tumor-free survival at one year. You didn't need a
19 control group to know that that worked. So those
20 were very, very easy.

21 Less easy, but we did it anyway, when I was
22 directing the cardio-renal division a long time

1 ago, we used to approve drugs for stone disease
2 based on comparing the stone rate in the 6 months
3 before they got the drug with the stone rate in the
4 next 6 months or 3 months -- I don't remember
5 anymore -- and we approved the drugs because the
6 differences were large and persuasive. I don't
7 know if we'd still use that trial design today, but
8 we did then and we were perfectly happy with it.

9 Then, in many orphan diseases where the
10 course is clear and very well-known, we do use
11 these designs. Alglucosidase alpha for Pompe
12 disease in 2006, the endpoint was 1 year
13 ventilator-free survival in 18 treated patients
14 versus 62 historical controls. I didn't put the
15 response rates here, but 15 out of 18 in the
16 treated group survived and 1 out of the 62 in the
17 historical controls survived that time. Pretty
18 persuasive. It would be hard to argue.

19 There are others. Lomitapide was approved
20 for LDL cholesterol lowering in patients with
21 familial hypercholesterolemia. Huge change in LDL,
22 obviously not something that could happen

1 spontaneously. And then a treatment of Cushing's
2 disease markedly lowered urinary free cortisol.
3 Again, that doesn't happen in people with that
4 disease. And then deferiprone was approved in 2011
5 for treatment of iron overload, and again marked
6 changes showing reduced ferritin in something that
7 almost surely would not have changed. So those can
8 be persuasive.

9 There have been anti-infective approvals
10 where we didn't think you needed to compare the
11 drug to existing therapy. It wasn't a question of
12 relative effectiveness, but where getting rid of
13 the organism was self-evident evidence that the
14 drug worked. So those are all cases where we found
15 historical controls persuasive.

16 The ones I've cited are typically cases
17 where there were very well-defined diseases with
18 very predictable outcomes, where you really didn't
19 think that the benefits could have been the results
20 of treatments other than the test drug, and where
21 the course was thought to be very variable.

22 There are obviously, and you're going to

1 hear one, cases in which there could be a debate
2 about how predictable the course of the disease is
3 in the absence of treatment, and thus whether
4 historical controlled approaches can be considered
5 and would be well supported as stressed in
6 ICH E-10, and that's what the discussion is about.
7 Thanks.

8 DR. ALEXANDER: Great. Thank you very much.
9 Next, Dr. Ronald Farkas and Dr. Ashutosh Rao
10 for the FDA efficacy review.

11 **FDA Presentation - Ashutosh Rao**

12 DR. RAO: Good morning, everyone. Thank you
13 for being here. I'm Dr. Ashutosh Rao. I am a
14 reviewer and researcher in the Office of
15 Biotechnology Products at the FDA. I provided the
16 clinical review team with a consult review of the
17 dystrophin bioassays and the supporting assay
18 validation information, some of which that you've
19 seen before and more will be presented today.

20 The FDA efficacy review will be presented by
21 both myself and Dr. Ronald Farkas, a clinical team
22 leader in the Division of Neurology Products in

1 CDER, FDA.

2 I'm going to start by discussing the assay
3 methods used to gather data about biomarkers in the
4 eteplirsen drug development program. Dr. Farkas
5 will then follow up to discuss the biomarker data
6 in detail and the clinical findings that go with
7 them.

8 Eteplirsen is proposed to increase the
9 production of exon skipped and truncated
10 dystrophin. The goal of my slides is to describe
11 to the committee and the audience how this
12 important endpoint for a proposed exon skipping
13 therapeutic was tested by the applicant, Sarepta.

14 I will provide an overview of our
15 understanding of the applicant's methodologies, our
16 understanding of the caveats of each of them, our
17 current thinking on the extent to which they can or
18 cannot analytically provide you with reliable data
19 indicating whether exon skipped dystrophin was
20 produced by eteplirsen, and if so, how much.

21 We would like you to consider these
22 technical caveats as you consider and discuss the

1 merits of the clinical findings presented by the
2 applicant and by FDA.

3 As stated previously by Dr. Dunn and by
4 Dr. Woodcock, FDA understands that lack of
5 dystrophin causes DMD and is very interested in
6 dystrophin as a biomarker and potential surrogate
7 for accelerated approval for drugs for DMD. Such
8 an approval would be based on a conclusion that the
9 dystrophin produced by a drug is reasonably likely
10 to predict clinical benefit. Reasonably likely
11 seemingly must depend on the amount, location, and
12 function of the dystrophin produced by the drug.

13 It is important to stress the need for
14 reliable assays and consistent findings to support
15 potential accelerated approval based on dystrophin
16 expression. Hence, the first part of the FDA
17 presentation will focus on FDA's views on the
18 methods and the results of dystrophin measurement
19 for eteplirsen.

20 Our current knowledge of dystrophin
21 bioassays based on literature and input from
22 several experts around the world is that a

1 scientific understanding of dystrophin requires
2 that the method or methods, a combination of
3 methods perhaps, be capable of answering basic
4 questions about the relative levels of dystrophin
5 mRNA and protein, its location, whether the newly
6 expressed dystrophin is increased beyond the
7 baseline levels of trace or revertant dystrophin,
8 and if it is functional in muscle fibers.

9 This slide lists the three common methods
10 used to show production of skipped messenger RNA
11 and dystrophin protein, reverse transcriptase PCR
12 for mRNA, and protein measurements using either a
13 Western blot or immunofluorescence-based method.

14 Each is a variation of a standard
15 methodology that's used in most laboratories, but
16 adapted for this large and very complicated
17 427 kilo Dalton protein. As a reminder, revertant
18 dystrophin, which arises from rare spontaneous
19 restoration of dystrophin in Duchenne patient
20 samples, is also present in each of the samples
21 that's going to be shown today and was shown
22 previously by the applicant and cannot be

1 distinguished from non-revertant dystrophin using
2 the currently used methodologies being discussed
3 here.

4 For each method, I will briefly highlight
5 the type of data submitted by the applicant and
6 summarize our current thinking of whether the
7 approach is analytically capable of providing
8 meaningful results. A typical data set from the
9 applicant's qualitative RT-PCR consisted of a gel,
10 as shown here on the slide, showing the presence or
11 absence of the skipped band representing the
12 expression of an exon 51 skipped dystrophin mRNA,
13 which reflects the fundamental and proposed
14 mechanism of action for this drug, eteplirsen.

15 As you can see from the example data set
16 here and by the red arrows on the slide, the
17 applicant's method is capable of demonstrating
18 whether or not skipped mRNA was produced.

19 A positive RT-PCR supports eteplirsen's
20 putative mechanism of action, but keep in mind that
21 the method is not quantitative. It does not
22 measure the number of copies of mRNA or test the

1 stability of this very large and unstable mRNA. It
2 has the largest exon set of sequence in the genome
3 at 79, so it is a very unstable mRNA.

4 Moreover, the production of mRNA being one
5 step prior to protein synthesis provides no
6 information on the protein itself, no information
7 on whether even protein was made from that mRNA.
8 Or whether that protein was functional, in other
9 words, whether it was capable of functioning as
10 normal dystrophin would in muscle fibers.

11 In order to detect dystrophin protein, the
12 applicant used either immunofluorescence or Western
13 blotting methods. The next few slides address
14 immunofluorescence. There are two endpoints used
15 by the applicant to present immunofluorescence
16 data, first by measuring fluorescence signal
17 intensity of microscopy generated images using a
18 computer software. The second is by scoring fibers
19 that are either positive or negative for an
20 anti-dystrophin antibody based fluorescence signal.

21 The applicant's immunofluorescence method is
22 capable of showing the location of dystrophin

1 protein based on reactivity with an anti-dystrophin
2 antibody. However, it is not designed to be truly
3 quantitative and compared to Western blotting has
4 serious shortcomings when it comes to quantifying
5 the levels of protein. Specifically, the intensity
6 measured by microscopy does not use healthy samples
7 of serial dilution or a reference standard of say
8 recombinant dystrophin protein or a fragment of the
9 protein that one would need to reliably compare and
10 objectively quantify the immunofluorescence signal.

11 During our review, we noted that the
12 intensity measurements tend to overestimate the
13 dystrophin fluorescence, especially at low levels
14 that are present in untreated and in some treated
15 samples. For instance, immunofluorescence signal
16 may indicate 10 percent of signal compared to a
17 healthy tissue specimen, but it would be far less
18 when the same sample, the exact same sample would
19 be tested by Western blotting.

20 The second immunofluorescence method used by
21 the applicant reports a score of dystrophin
22 positive fibers or percent positive dystrophin

1 fibers. This is also a standard technique. It's a
2 standard technique adapted but primarily
3 well-suited to confirm the location of proteins in
4 tissue sections.

5 On the right-hand side on top here is a
6 processed image of muscle section stained to
7 identify dystrophin. In this case the colors on
8 this image were inverted and amplified by the
9 applicant to allow a pathologist to score the
10 fibers.

11 You can see that the staining for dystrophin
12 by the applicant localizes to the sarcolemma as
13 would be expected. Staining fibers such as the
14 ones in this image are used to then score them as
15 dystrophin positive or negative. However, the
16 scoring is based on staining intensity and is not
17 an all or nothing type of scoring, and hence the
18 reading is subjective. For instance, fibers can be
19 classified as positive if the staining is only
20 barely above the background, as is the case in some
21 of the fibers here.

22 The staining between patients, and even

1 within the same patient but different muscle groups
2 or a biopsy taken on different days, is not uniform
3 and contain a mix of staining intensities. Also,
4 it is simply not possible to differentiate fibers
5 with new drug-induced dystrophin from the
6 spontaneously occurring revertant fiber dystrophin
7 using this method.

8 In general, for any fluorescence analyses to
9 provide reliable findings, here are some critical
10 factors that need to be part of a predefined study
11 design. The investigators need to be blinded to
12 patient identity and treatment assignment. There
13 should be a systematic and random selection of
14 fields, even better if this is automated.

15 Control sections with positive,
16 intermediate, and negative samples can estimate the
17 range of the signal obtained by one's test sample.
18 So even though the method is not quantitative, if
19 you were to use appropriate controls, you could at
20 least determine a range of your signal.

21 Careful consideration needs to be given to
22 how the image is processed, displayed, and even the

1 consistency and ambient light can be an important
2 factor. Independent reassessment by more than one
3 pathologist and blinded sequence for reading can
4 also help control for inter- and intra-observer
5 variability.

6 We believe that the data generated from
7 studies 28 and the early biopsies from
8 study 201/202 were largely exploratory, not
9 validated, and not consistent with all these
10 principles highlighted here.

11 Appreciating the potential significance of
12 dystrophin measurement towards the development of
13 much needed therapies for DMD, we worked very
14 closely with this and other applicants to clarify
15 and improve the scientific credibility of their
16 dystrophin findings.

17 Following discussions with the applicant and
18 the investigators, we scheduled and visited the
19 laboratory testing site at Nationwide Children's
20 Hospital to assess methodology and raw data where a
21 number of issues were identified. Extensive
22 technical advice was provided to the investigators

1 during and following the visit.

2 As has been mentioned before, we also held a
3 NIH/FDA joint workshop bringing together experts in
4 the field to discuss the current state of
5 dystrophin methodologies. Also, with input from
6 external stakeholders, FDA released a draft
7 guidance for industry on developing therapies for
8 DMD that included some guidance on the potential
9 for dystrophin to validate the findings of other
10 endpoints.

11 Following several rounds of discussion with
12 the FDA, the applicant developed and implemented a
13 technically satisfactory set of methods for
14 immunofluorescence. Specifically, they implemented
15 a systematic and random field acquisition protocol
16 for image acquisition, improved blinding processes,
17 implemented quality assurance steps, and
18 independent reassessment by three pathologists
19 outside the primary testing lab was carried out.
20 The experimental analyses included positive,
21 negative, and intermediate control samples in the
22 form of healthy Duchenne and Becker tissue

1 sections.

2 This slide shows an example of data from the
3 applicant's fourth biopsy showing two images on top
4 that are stained for dystrophin and the two
5 corresponding inverted and amplified images on the
6 bottom that were used for the pathologist to
7 identify total fibers.

8 The images that are on top are stained red
9 where the antibody had reacted with an
10 anti-dystrophin antibody. Both images contain
11 fibers scored positive by the applicant. However,
12 as I stated earlier, it is not possible to
13 differentiate between dystrophin spontaneously
14 present in revertant fibers and drug-induced or
15 newly expressed and truncated dystrophin. For
16 instance, it may be tempting to believe that
17 particular fibers in both of these images represent
18 drug-induced dystrophin, but there is no way to
19 know whether they are revertant or not using this
20 particular method. Analytically,
21 immunofluorescence is unable to tell us whether
22 dystrophin is new or not.

1 Also, the method cannot provide data on the
2 absolute levels of new truncated protein that
3 correspond to a given fluorescence intensity. From
4 the applicant's data, we can however tell that the
5 dystrophin as present in these samples is localized
6 to the sarcolemma region of the cell or the fiber,
7 which is where you would expect it to be if it were
8 functional.

9 Overall, we believe that the applicant's
10 overall immunofluorescence methodologies, both of
11 them, are capable of confirming location and are
12 supportive but tend to overestimate the signal
13 compared to other methods and cannot differentiate
14 between drug induced and truncated dystrophin from
15 the other forms of spontaneously occurring
16 dystrophin.

17 The next few slides cover the Western
18 blotting. The applicant's Western blot measures
19 the relative amounts of this 425 kilo Dalton
20 protein that reacts with an anti-dystrophin
21 antibody. This is the most quantitative method
22 used by the applicant and the best to compare the

1 relative levels of signal in samples in Duchenne
2 either before and after treatment, and comparing it
3 to Becker dystrophy or healthy control samples.

4 Although this method is technically
5 challenging, the image shown on this slide from a
6 1989, as has been said before, is representative of
7 a significant body of literature that suggests that
8 Western blotting can be performed reliably using
9 human tissue.

10 During discussions with the applicant and
11 the collaborating investigators about study 28 and
12 early biopsy data from study 201/202, several
13 concerns were identified in the methods that
14 obscured interpretation of the dystrophin data.

15 The full length gel image shown on the
16 right-hand side is an example of Western blotting
17 data from the bicep muscle tissue of the early
18 three biopsies in 201/202. On the left is from
19 study 28. As you can appreciate, the gels were
20 overloaded and the bands consequently were
21 oversaturated.

22 Because this method critically depends on

1 the presence of clear, distinct bands used for
2 quantitation based on the density of those
3 individual bands, these blots cannot provide
4 reliable quantitation of dystrophin protein.
5 Overall, the methods of dystrophin protein
6 quantitation from the first three biopsies in
7 study 201/202 were not considered reliable, and the
8 results were not considered interpretable.

9 Here the left image again shows the results
10 obtained before technical advice provided by the
11 FDA. The right side is from a fourth biopsy sample
12 after discussions with the FDA and using deltoid
13 muscle. While this slide should really require no
14 explanation, you can see how the Western blot
15 images from the early biopsies were clearly not
16 discernable to allow meaningful quantitation.

17 The red arrow on the gel on the right-hand
18 side shows the proposed location of the 427 kilo
19 Dalton protein that was then used for quantitation.
20 We consider the quality of the fourth biopsy set of
21 data to be satisfactory to quantify relative
22 protein levels.

1 This slide is meant to illustrate why we
2 consider the fourth biopsy data to be reliable,
3 essentially because of the inclusion of a standard
4 curve of serially diluted healthy samples on each
5 gel that are shown on the legend on the top of that
6 gel.

7 The presence of these serially diluted
8 samples allows the generation of a standard curve.
9 The curve is shown on the right, and the samples
10 were quantitated in the validated range of 0.25 to
11 4 percent of healthy dystrophin. We also consider
12 the fourth biopsy method to be more reliable
13 because of the inclusion of either a Duchenne or a
14 Becker, and a healthy control in the same
15 experiment corresponding to negative, intermediate,
16 or positive controls to allow a credible side-by-
17 side comparison of relative differences.

18 The fourth biopsy was acceptable but
19 problems with controls make the change in
20 dystrophin challenging to interpret. Ideally, the
21 change in dystrophin would have been assessed by
22 comparing pre-treatment samples to post-treatment

1 samples from the same patient and the same muscle,
2 but this is not how the analysis was conducted.

3 Here are some specific issues that were
4 identified with the choice of controls prior to the
5 fourth biopsy experiments that you should consider.
6 These are important to consider because the
7 applicant is proposing changes in dystrophin levels
8 following eteplirsen treatment when the samples
9 were tested and compared to this set of control
10 samples and not to each patient's matched baseline.

11 As mentioned before, different muscle groups
12 from treated samples were used for the analysis,
13 including the fourth biopsy where deltoid samples
14 were used in contrast to biceps from the first
15 three biopsies.

16 As a reminder, there were no deltoid
17 baseline samples for the same patients for
18 comparison and matched baseline samples were used
19 for only 2 of the 11 patients, and those two were
20 from a different muscle group, biceps in those
21 cases.

22 The DMD negative control samples that were

1 used for comparison were also from different
2 muscles, essentially including biceps, quadriceps,
3 and deltoid. And the data from all of these
4 different muscle groups were combined for a
5 comparison to the fourth biopsy data that was from
6 deltoid muscle.

7 The controls were not sex matched because
8 one female sample was included in the set of
9 samples used to calculate the mean healthy value.
10 And even within the healthy control data set, there
11 is variability as was seen in the reported range of
12 51 to 95 percent.

13 In summary, at this time, we believe that
14 the applicant's fourth biopsy data methods for the
15 201/202 study were the most quantitative and were
16 reasonably adequate for determining the relative
17 dystrophin levels for the purpose of their drug
18 development program, with the caveat that there are
19 some issues with the control sample that make it
20 difficult to accurately calculate the change from
21 baseline that could be caused by eteplirsen
22 treatment.

1 We also believe that immunofluorescence can
2 provide supporting information. It cannot reliably
3 quantitate dystrophin protein levels. It is
4 capable of informing on the location of potentially
5 newly expressed protein.

6 Overall, a combination of the applicant's
7 methods, immunofluorescence and Western blotting,
8 was considered reasonably capable of demonstrating
9 an increase in dystrophin by eteplirsen.

10 I will now turn it over to Dr. Farkas to
11 present the clinical findings from the applicant's
12 studies and their relevance.

13 **FDA Presentation - Ronald Farkas**

14 DR. FARKAS: Good morning. I'm Ron Farkas,
15 a clinical team leader in the Division of Neurology
16 Products at FDA. And the first thing I'd like to
17 say is that I've had the opportunity to talk to
18 Duchenne patients and caregivers at meetings
19 before, and I'm really glad that I've been invited
20 to talk at a parent project muscular dystrophy
21 meeting. And one of the things that I raised at
22 that meeting is it's really important to take a

1 close look at what you're being told and the kind
2 of analyses that are being done.

3 That was about a year ago, and there really
4 wasn't really an opportunity to go into the data,
5 and I would have really liked to then. But now we
6 have an opportunity to go closely into the data and
7 the way the data is being analyzed.

8 I'd just like to perhaps take a slightly
9 unusual approach and go for some slides in the
10 middle of my presentation because I think that what
11 might be in people's mind is that there's a very
12 large clinical effect, that all the control boys
13 are no longer walking and almost all the treated
14 boys are still walking.

15 So there's going to be a lot of talking, and
16 I'm going to explain a lot of sources of difference
17 between patients in drug trials and natural history
18 trials. So as I go through all that detail, I just
19 wanted to, again, kind of show people right now
20 where I'm headed to and to get people to think
21 about what the observations are showing.

22 If I could just have slide 67 pulled up.

1 It's going to take me a while to get to through
2 slide, but I think that one of the key things I'm
3 going to try to explain is that the way to look at
4 this data is to take a look at age of loss of
5 ambulation and not time to loss of ambulation.

6 One of the things I'm going to be driving at
7 is that contrary to what is suggested by some of
8 the applicant's analyses, there does not appear to
9 be evidence of a difference in age or future age.
10 And that future age is important, future age of
11 loss of ambulation in the eteplirsen patients and
12 controls.

13 So this graph shows, going from left to
14 right, it shows 6-minute walk test on the Y-axis
15 and age on the X-axis. And it shows going from
16 left to right, basically an alteration between the
17 course of the blue control patients and the red
18 eteplirsen patients.

19 So kind of going over at 200 meters -- so
20 going over, there's a blue patient and then a red,
21 a red, a blue, a blue, a red, a red, a blue over at
22 200. And I think one of the -- so let me just step

1 over here for a second.

2 So what's going on is that we're comparing
3 two different kinds of Kaplan-Meier curves to each
4 other. I'll explain that in a second, too. But
5 the blue patients have all gone down to zero in
6 6-minute walk test, and so the red patients
7 haven't, but we have to be very careful about if
8 we're thinking of what their age is or what their
9 walking ability is. Anyway, I'll get back to that
10 in just a minute.

11 I think the other slide I'd like to show is
12 slide 75. I think the issue here, and I'm going to
13 come back to this later, is the age or the
14 percentage of the patients that maintain ambulation
15 to 16 years old. So what we need to do is try to
16 picture what percentage of the eteplirsen treated
17 patients are going to be walking at age 16. And
18 actually it's older than age 16, so there's been
19 discussion about what age exon 51 patients walk to.

20 The best numbers that we have are 25 percent
21 at age 16, but actually there's -- and I'll get to
22 these slides later when I go through in order -- is

1 that 15 percent of patients are walking until
2 age 18.

3 So I'm going to start going back now to all
4 the details of -- well, perhaps all the small
5 things and all the medium sized things that add up
6 to problems with interpretation. But I think just
7 to start out with perhaps trying to show the way
8 that we've seen the data, that there is not this
9 very large difference in the age of loss of
10 ambulation between the treated patients and the
11 natural history patients.

12 So I'll go back. Could I have slide 21?
13 Just to go back to the beginning. I'm not going to
14 spend a lot of time describing the studies that
15 were conducted by the applicant because they did
16 that, but I'd like to focus on the advice that FDA
17 gave to the applicant and on the study results.

18 Phase 1 and 2 studies are important in drug
19 development. Study 28 was designed to identify a
20 route of administration and dose of eteplirsen that
21 might be effective. For most new drugs, and
22 especially those for serious diseases, the dose

1 should be increased until limited by safety or
2 tolerability or until there's no further increase
3 of a biomarker such as dystrophin in this case.
4 The eteplirsen doses in study 28 ranged from 0.5 to
5 20 milligram per kilogram per week, with 4 or fewer
6 patients in each dose cohort.

7 The study 28 investigators reported
8 dystrophin levels from zero to 5 percent of normal
9 in untreated patients, and that's an amount that
10 fit expectations for the trace levels of dystrophin
11 that are present in untreated DMD patients. The
12 investigators also reported finding dystrophin
13 levels after 12 weeks of eteplirsen treatment of 10
14 to 20 percent of normal, and that's an important
15 number to keep in mind because the experts, when
16 they saw that 10 to 20 percent, they were
17 encouraged, and that fit the expectations of
18 experts about the amount of dystrophin that might
19 result in clinical benefit.

20 No safety issues were identified that would
21 limit higher dosing. The highest dose was
22 20 milligram per kilogram per week. This lack of

1 toxicity is of course good, but only good in some
2 ways because it also represents a shortcoming, a
3 missed opportunity to study higher doses.

4 The next study, 201/202, tested doses only
5 modestly higher than 20 milligram per kilogram per
6 week. That is not much higher than in study 28.
7 There were 4 patients at 30 milligram per kilogram
8 per week, 4 patients at 50 milligram per kilogram
9 per week, and 4 patients on placebo.

10 With only 4 patients per arm, there were too
11 few to learn much about dose response, and that was
12 a question that came up earlier. And in truth,
13 really there's too few to learn anything about dose
14 response. Dystrophin was measured at week 12, as
15 in study 28, and also at weeks 24 and 48. As
16 mentioned by Dr. Rao, these three time points are
17 referred to as the first three biopsies.

18 The study 201/202 investigators reported
19 that dystrophin increased at week 24 but not at
20 week 12. This was different than study 28, which
21 has been mentioned before, in which robust
22 dystrophin expression was reported at week 12.

1 Consistency of findings is something that we're
2 going to talk a lot about in these first few
3 slides, and that's a great concern in all areas of
4 science, including drug development.

5 I think the issue is that without
6 consistency of findings, it's really hard to know
7 if something's true, if just the basic numbers that
8 we're looking at are true. So one of the things
9 that drives the FDA standards is trying to find
10 something that's true, a number that's true, an
11 estimate of dystrophin expression that's true. And
12 the results need to be consistent to know if that's
13 really a true number that you're looking at.

14 In study 201/202, by week 48, dystrophin
15 levels of 25 to 50 percent or higher were reported
16 in all patients. These published findings seemed
17 highly encouraging, and helped lead the DMD
18 community to the conclusion that eteplirsen was
19 effective and to an understandable reluctance to
20 participate in future placebo-controlled studies.
21 This essentially marked the end of phase 1 and 2
22 studies for eteplirsen.

1 FDA learned more about the data in
2 discussions with the applicant about NDA filing and
3 became concerned about the reliability and
4 consistency of the data, communicating this clearly
5 to the applicant. FDA nevertheless agreed to file
6 the NDA based on assertions by the applicant and
7 many DMD experts, of both high levels of dystrophin
8 expression and clear clinical stabilization in the
9 12 eteplirsen treated patients.

10 FDA worked with the applicant on more
11 reliable dystrophin assays as described by Dr. Rao.
12 The applicant obtained a fourth muscle biopsy at
13 week 180 of eteplirsen treatment from 11 of the 12
14 original patients, and as the NDA was being
15 submitted, studied these biopsies with the more
16 reliable dystrophin assays.

17 In the meantime, detailed review of the
18 study 28 and first three biopsy of study 201/202
19 findings confirmed FDA's concern that the earlier
20 dystrophin assays were not reliable. For example,
21 as described by Dr. Rao, Western blot bands were
22 oversaturated. Also, regarding dystrophin positive

1 fibers, immunofluorescence images were captured and
2 read in a way that might have been overly
3 subjective with preferential selection of brighter
4 staining muscle regions.

5 Now, I'd like to shift though to the way
6 that these dystrophin staining images were
7 captured. Because dystrophin staining fades, only
8 one set of images could be captured from the
9 stained tissue. So there was an independent
10 blinded rereading of the images that were taken,
11 but the issue is how the original images were
12 taken.

13 So the independent blinded rereading can get
14 rid of bias from the reading, but it can't get rid
15 of bias in the way that the images were originally
16 selected. And that's one of the things that we're
17 concerned about because the original images were
18 not selected in a way that was more or less fully
19 automated that would allow for unbiased selection
20 of images.

21 One other point that came up was, Dr. Rao
22 had said, that it's not possible to tell the

1 difference between revertant fibers and
2 drug-induced dystrophin. And one of the issues
3 that came up in the question and answer with the
4 sponsor was talking about dystrophin associated
5 proteins. And it's true that if there's dystrophin
6 associated proteins in those fibers, that provides
7 reassurance that the dystrophin is functional. But
8 the issue is that if there's preferential selection
9 of revertant fibers, you'll also see the dystrophin
10 associated proteins.

11 So that can tell you something about the
12 exon skipped dystrophin working, but if you select,
13 preferentially select the revertant fibers, it
14 can't tell you if the drug is doing that or if
15 that's what was present at baseline.

16 So this is the fourth biopsy results, and
17 it's one of the most important slides that we're
18 going to be looking at today. Instead of the
19 expected 25 to 50 percent normal dystrophin, as was
20 mentioned before, there was only 0.93 plus or minus
21 0.84 percent of normal dystrophin in the treated
22 patients. This was measured by Western blot, the

1 most accurate method of quantification used by the
2 applicant.

3 It seems concerning that the fourth biopsy
4 result was so inconsistent with earlier results,
5 and this appears to raise additional important
6 questions and to highlight the need for independent
7 confirmation of findings. The fourth biopsy result
8 was based on one group of patients at one
9 investigative site. No matter how many times a
10 single set of data is reanalyzed, including by
11 independent readers, it does not constitute
12 independent confirmation of findings. It's still
13 just one experiment.

14 One of the critical questions today is
15 whether eteplirsen produced dystrophin. A
16 dystrophin level of about 0.1 percent was reported
17 in the controls for the fourth biopsy. It's
18 important to highlight, however, that because of
19 the lower limit of reliable detection of the assay
20 was 0.25 percent, it would be more accurate to view
21 the level in these controls as something like less
22 than 0.25 percent.

1 The reason that I'm spending some time on
2 this is that if one were to compute ratios about
3 how much dystrophin increased, you'd really want to
4 think about the lower level of detection of the
5 assay. So the levels in the control patients was
6 not accurately determined to be 0.08 percent. All
7 that we really know is that it's something -- if it
8 was zero, it might be anything between slightly
9 less than 0.25 percent and whatever number was
10 measured. We just don't know that information
11 because of the assay.

12 The dystrophin level in the controls was
13 still, even given what I said, lower than the
14 1 percent in the eteplirsen treated patients. But
15 as discussed by Dr. Rao, the controls were not
16 matched. The tissue came from different patients
17 and different muscle groups such that there is
18 concern that the comparison may be apples to
19 oranges.

20 It was mentioned before that there isn't
21 evidence that dystrophin levels are different in
22 the different muscle groups that were used, but I'm

1 not quite sure if that's the right question to ask.
2 When the applicant first identified using controls
3 from a different muscle group, we raised concern
4 about that. And normally when controls are used,
5 you try to match the controls.

6 So we advised the sponsor at that time that
7 unless there was a substantial change in
8 dystrophin, it would be confounded by using this
9 different muscle group. And as it happens,
10 different muscles do progress differently in
11 muscular dystrophy, so some muscles degenerate more
12 quickly and some more slowly. And the relative
13 amount of dystrophin in different muscle groups is
14 not well-characterized. So there's certainly
15 reason to be concerned that this was not an
16 appropriate control to pick.

17 But I think the thing that we need to focus
18 on, too, is how little the difference is between
19 the controls and the eteplirsen treated patients.
20 So we're talking about something in absolute terms
21 of less than a 1 percent difference, and that might
22 get lost when talking about the ratios.

1 How different were the controls in the
2 treated patients? Well, we know it's less than
3 1 percent in absolute terms, so that leaves, I
4 think, some question about how similar those
5 controls were.

6 So as a result, there appears to be
7 uncertainty about how much or perhaps even if any
8 of the 0.93 percent dystrophin in treated patients
9 at week 180 might have been from an effect of
10 eteplirsen versus how much might have been present
11 at baseline.

12 Again, it should be stressed that we don't
13 have Western blot data from 9 of these 11 patients
14 prior to treatment, so it's really not possible to
15 assess the change in dystrophin in these patients.

16 Now, let's shift to discussion of percent
17 dystrophin positive fibers, as determined by
18 immunofluorescence. This was the other principle
19 way that dystrophin was assessed by the applicant.

20 First, as discussed by Dr. Rao, percent
21 positive fibers is not a helpful measure of the
22 amount of dystrophin because a positive fiber does

1 not mean a normal amount of dystrophin, a
2 functional amount, or really any specific amount of
3 dystrophin. It only means an intensity judged by
4 eye to be above background of the image.

5 One of the numbers that came up before, too,
6 was greater than 30 percent of staining, but that's
7 not a measure of intensity. It's not greater than
8 30 percent of normal intensity. That's greater
9 than one-third of the circle of the muscle fiber
10 having some detectable amount of dystrophin. So
11 that's something that's just an intensity judged by
12 the eye to be above background of the image, but
13 only in a fraction of the muscle fiber. So
14 two-thirds of the muscle fiber might have no
15 detectable dystrophin staining.

16 In the fourth biopsy, the applicant reported
17 10 percent positive fibers in the eteplirsen
18 treated patients and 1 percent in the controls.
19 These were the same samples used for Western blot,
20 so similarly it's uncertain how much of this
21 difference might have been from an effect of the
22 drug versus other differences between the samples.

1 As you'll see, it also remains difficult to find
2 consistency in the percent positive fiber counts,
3 even with the improved method with three blinded
4 readers.

5 Here are the results showing percent
6 positive fibers from the muscle biopsies. The
7 results on the left were analyzed by a single
8 reader at Nationwide Children's Hospital. They
9 were read at baseline, week 12, week 24, and week
10 48. On the right are the rereads from 3 blinded
11 readers shown in blue, at the same time points,
12 week 12, 24 and 48, and then there's also a reading
13 at week 180 of eteplirsen treatment.

14 In the first three biopsies, the results
15 from the 3 blinded readers found far fewer positive
16 fibers than the original reading, shown in the gray
17 rectangle. So for example, 70 percent here,
18 23 percent here, and on down the line, 58 percent
19 versus 9 percent.

20 Percent positive fibers, there was
21 discussion about when dystrophin was produced by
22 eteplirsen, and we've been talking about maybe at

1 week 12, maybe not at week 12. But actually at
2 week 24, there weren't consistent findings either.
3 So percent positive fibers did not consistently
4 increase at week 24, even within study 201/202.

5 The numbers of patients here are small, but
6 whereas the results in the blue squares for the
7 patients started on 30 milligram per kilogram per
8 week, they do show an increase at 24 weeks of
9 treatment that wasn't seen in patients who were
10 started on placebo and switched to 30 milligram, or
11 who were started on placebo and switched to
12 50 milligram per kilogram per week.

13 So these patients were treated initially
14 with placebo for a 24-week period, but then they
15 were treated with eteplirsen for an additional
16 24 weeks. So if it was going to be a consistent
17 result, you should see the same kind of increase in
18 the second 24-week period that you saw in this
19 first 24-week period, but the dystrophin positive
20 fibers in fact for these other two groups of
21 patients don't increase at 24 weeks.

22 The fourth biopsy controls that were

1 selected by the applicant had 1 percent dystrophin
2 positive fibers. This is compared to 10 to
3 15 percent dystrophin positive fibers in the
4 original matched controls, as shown by the black
5 rectangle. So that seems like a big difference,
6 1 percent versus 15 percent, and this is in two
7 different sets of controls.

8 That seems to raise some questions, where
9 did that inconsistency come from? Was it
10 differences in the methods, or in the reading, or
11 one thing that we're worried about is it's a
12 difference between the controls, between the
13 original controls from those patients and the later
14 controls that weren't matched?

15 So there's the same kind of concern with
16 comparison of the week 180 samples and the
17 baseline. So, of course, you'd expect and hope to
18 see a substantial difference in the percent
19 positive fibers of the biopsies treated for
20 180 weeks versus those at baseline. But instead,
21 in the same baseline samples had levels -- or had
22 dystrophin positive fibers of roughly 10 to 15

1 percent, whereas the 180 week samples had
2 17 percent positive fibers. So that seems like no
3 difference or very little difference.

4 So let me just summarize the dystrophin
5 findings. There was 0.93 percent of normal
6 dystrophin as measured by Western blot after
7 long-term treatment with eteplirsen with 17 percent
8 of muscle fibers with at least some detectable
9 amount of dystrophin.

10 Because of poorly matched controls, the
11 proportion of the dystrophin produced by eteplirsen
12 as opposed to the dystrophin present at baseline
13 seems uncertain. Thus, it's not clear how much or
14 perhaps even whether these values represent an
15 increase over the dystrophin levels that were
16 present at baseline.

17 Consistency of findings is key in drug
18 development, but there is no independent
19 confirmation of these findings. The week 180
20 findings appear to be strikingly inconsistent with
21 earlier reports.

22 Ratios of dystrophin levels in treated

1 compared to control tissue that have been presented
2 by the applicant may be apples to oranges
3 comparison because of poorly matched controls. The
4 ratios also lack reliability because of small and
5 questionably calculate denominators.

6 As Dr. Rao explained, FDA is very interested
7 in drugs that might restore dystrophin, and
8 dystrophin could serve as a surrogate endpoint for
9 accelerated approval. I think as pointed out by
10 many speakers today, there's a lot of interest in
11 the relationship between dystrophin levels and
12 clinical course, and there are many publications in
13 this area, but it's important to understand that
14 when discussing very low levels of dystrophin,
15 literature reports are not always accurate.

16 The reports might state that a patient
17 expressed no dystrophin or only trace dystrophin,
18 but this may only mean that the patient had less
19 than some often poorly defined lower limit of
20 detection of the assay. In addition, reports may
21 not be precise in describing low levels of
22 dystrophin. Trace dystrophin levels are often

1 detected, but trace is not a defined or useful
2 measure of amount of dystrophin.

3 So the FDA has relied heavily on what
4 experts have written in the past about the
5 association between dystrophin and a decline in
6 progression in muscular dystrophy, and that's what
7 a lot of this information is taken from, what the
8 experts have said. So with the most reliable
9 Western blot methods, it appears that dystrophin
10 levels less than about 3 percent of normal would in
11 most patients be associated with the typical DMD
12 phenotype.

13 You may hear today, and have already heard
14 today, that DMD is milder at the high versus low
15 end of this range, and FDA can't stress enough that
16 we're open to evidence that shows this. But from
17 our review, and really from what the experts have
18 said in the past, there appears to be little
19 reliable evidence that DMD is milder at the high
20 versus low end of the range between zero and about
21 3 percent of normal.

22 There does appear to be some evidence that

1 levels need to be higher. DMD experts previously
2 suggested the need for perhaps 10 percent or higher
3 levels of dystrophin, with expression in most
4 muscle fibers, to predict a milder than average DMD
5 clinical course.

6 Let me just switch to one slide, to
7 slide 141. So it was brought up that -- so this
8 data is actually immunofluorescence data, and I
9 hadn't intended to show it at first. What we're
10 really looking for, what really allows comparison
11 of different patients to each other, and especially
12 across different studies, we're looking for Western
13 blot data, and that has an internal standard, a
14 dilution standard. It still might be cross-study
15 comparisons, but it allows some sort of more
16 reliable comparison.

17 So this data here is taken from Anthony.
18 This is the paper that the applicant cited with
19 exon 44. And I think what's striking here, and I
20 think this is the big question, the big question
21 when we're talking about the correlation between
22 dystrophin levels and the rate of decline in DMD.

1 And that is the correlation. It's taking a look at
2 which patients are doing well, which patients are
3 doing less well, and how much dystrophin is in each
4 of those 2 groups of patients.

5 So I'm not really sure how reliable this
6 data is, and it is immunofluorescence data, but one
7 of the things to take a look at is the amount of
8 dystrophin in patients that are doing well. This
9 is patient 3 from that paper. And by
10 immunofluorescence, the dystrophin level was
11 getting close to 50 percent, and then patient 4 and
12 5.

13 So patient 3 had a Becker phenotype.
14 Patient 4 and 5 were exon 44 skippable patients,
15 and they lost ambulation at 11 or 12 years old.
16 And then patient 1 and 2 had lower levels of
17 dystrophin and were still able to walk. So at
18 these low levels in patient 1, 2, 4 and 5, there
19 seems to be kind of an opposite relationship
20 between dystrophin levels and walking.

21 Then, what I really want to point to,
22 though, what I think really merits the attention,

1 is that there's really a concern that patients who
2 are doing substantially better, they have higher
3 dystrophin levels. And that's why it's important
4 to take a look at the details. That's why just
5 saying that exon 44 patients do better doesn't
6 really tell you how much dystrophin is needed for a
7 less severe phenotype.

8 I think also when we need to keep in mind
9 some of the things that were discussed more in the
10 memo, in the FDA memo, and that is that -- I mean,
11 certainly we don't want to be too pessimistic about
12 dystrophin that might lead to clinical benefit, but
13 we really do need --

14 (Laughter.)

15 DR. FARKAS: I appreciate that laughter and
16 I -- actually I want to interrupt myself to say
17 that, really, what I'm trying to do is -- what I
18 feel like I'm trying to do is set the record
19 straight, and try to explain to people the way that
20 we see the data and some of the things that we're
21 not real happy about, the way that the data is
22 often presented, and some of the things that we're

1 not really able to say to people.

2 So I think that there's also a risk in
3 comparing exon 44 patients to exon 51 patients.
4 There is a lengthy literature in Becker muscular
5 dystrophy about how the mutation really matters.
6 And the fact that exon 44 and exon 51 are close in
7 numbers, it doesn't really mean that there can't be
8 a difference in the dystrophin. And some of the
9 biggest differences are in numbers that are close
10 together. So that really doesn't tell you what's
11 going on.

12 So I wouldn't say that it makes it
13 impossible to use data from exon 44 to understand
14 how much dystrophin is necessary in exon 51
15 patients, but that needs to be considered.

16 Could we go back to slide 43? So then going
17 back to the percent dystrophin positive fibers,
18 dystrophin positive fibers, it's been mentioned
19 before, it's very sensitive to the subjective view
20 of the person reading it, and it's also sensitive
21 to the conditions of the assay.

22 So what we've seen is that in DMD, typical

1 DMD patients can have dystrophin staining anywhere
2 from zero to 100 percent of their fiber. So it's
3 not a very good method to differentiate patients
4 who are going to have a more severe course from
5 patients who are going to have a less severe
6 course.

7 But what we've seen with the 17 percent
8 number, 17 percent dystrophin positive fibers in
9 the eteplirsen treated patients, that's more
10 typical of untreated DMD. At least in the range of
11 zero to 100 percent, the 17 percent is more typical
12 of untreated DMD. And what is more typical in
13 patients with a milder course, in patients with
14 Becker muscular dystrophy, they have irregular, it
15 is irregular dystrophin staining, but that
16 irregular dystrophin staining is found in basically
17 100 percent of fibers.

18 Then there's this issue of the lowest amount
19 of dystrophin that might be associated with the
20 Becker phenotype, and that's really a problematic
21 question to answer. It's not a very helpful
22 question because the truth is that some patients do

1 well with zero dystrophin. It's that the
2 correlation between dystrophin and how patients do
3 is very real, but it's absolutely not absolute. So
4 there are rare patients with the milder Becker
5 muscular dystrophy phenotype that have dystrophin
6 levels near zero.

7 These unusual cases highlight that there is
8 often a lack of clear relationship between
9 dystrophin levels and severity. Mild disease in
10 these individuals is likely unrelated to -- not the
11 result of trace levels of dystrophin. So this is
12 an active area of research, a very important area
13 of research, but it's really unrelated to the
14 proposed mechanism of action for eteplirsen.

15 These half-brothers just demonstrate this
16 point. They have the same mutation, but their
17 disease course is very different. Both
18 half-brothers are dystrophin negative, except for
19 revertant fibers. So again, this idea of trying to
20 find the correlation between revertant fibers and
21 how well patients do, there's been a lot of
22 interest in that, but there hasn't really been much

1 ability to find that kind of correlation.

2 The younger half-brother become wheelchair
3 bound at age 9. The older half-brother remained
4 walking until age 15, walking well still at age 15.
5 Although these cases are rare, it illustrates the
6 complex relationship between dystrophin, other
7 genes, and clinical course.

8 Now, I'm going to switch to talking about
9 the clinical data, starting with the 24-week
10 placebo-controlled period of study 201/202. As
11 described earlier, study 201/202 was planned as a
12 24-week placebo-controlled trial in 12 patients,
13 randomized to either eteplirsen 50 milligram per
14 kilogram per week, eteplirsen 30 milligram per
15 kilogram per week, or placebo. Each group had 4
16 patients.

17 The primary endpoint was dystrophin
18 expression, but multiple clinical endpoints were
19 also measured, including 6-minute walk test, the
20 North Star Ambulatory Assessment.

21 The prespecified clinical endpoints of
22 study 201 at week 24 and study 202 at week 48 were

1 negative. The applicant performed a post hoc
2 analysis based on a number of major changes,
3 including removing two patients treated with
4 eteplirsen who deteriorated rapidly, and picking a
5 time point to analyze that was outside the control
6 trial period.

7 FDA explained that these types of changes
8 did not appear reasonable, even for hypothesis
9 generation, and that the post hoc analyses were not
10 interpretable. However, the applicant announced
11 the post hoc results generating considerable public
12 attention.

13 Now, let's consider the clinical data from
14 long-term open-label treatment with eteplirsen in
15 study 201/202. As others from FDA will also stress
16 today, it's important to make clear that FDA
17 consistently and strongly encouraged the applicant
18 to perform an adequately powered, randomized,
19 double-blind, controlled trial, and expressed
20 strong doubts regarding the interpretability of
21 comparisons of patients in study 201/202 to
22 external controls.

1 I should add that we gave that advice when
2 we already saw how patients were progressing, so we
3 were open. We are open to data that could be -- we
4 are open to an effect that could be large enough to
5 be interpretable in a historically controlled
6 trial. But what we saw that that didn't seem to be
7 occurring, we gave very strong and very consistent
8 advice to the applicant that we didn't think this
9 was going to lead to an interpretable comparison to
10 historical controls. So again, as I mentioned, FDA
11 is receptive to interpretable data from externally
12 controlled trials.

13 FDA also explained to the applicant that
14 data from externally controlled trials in DMD may
15 only be interpretable if a relevant objective
16 endpoint, obviously insulated from bias,
17 demonstrated compelling data that were clearly
18 outside the known variability range for DMD. And
19 I'm going to spend quite a lot of time talking
20 about the amount of effect that can be introduced
21 by endpoints that are partially subjective.

22 So FDA's advice has been entirely consistent

1 with what is known about externally controlled
2 trials, including in muscular dystrophies. DMD
3 experts, and we have been looking at the advice of
4 DMD experts, have noted that physical function may
5 be affected by simply being in an efficacy study.
6 Patients outside of efficacy studies can perform
7 worse for reasons that are not well understood.

8 This example is from studies of
9 facioscapulohumeral muscular dystrophy. The
10 investigators wrote, "Whereas natural history data
11 showed a decrease in strength over one year, there
12 was in the efficacy studies an apparent increase in
13 strength in both the placebo and treatment groups."

14 So this is the kind of difference, the
15 difference of an increase versus a decrease. It's
16 a binary difference, and even that can occur when
17 comparing patients who are in a drug trial to
18 patients who are in a natural history cohort.

19 The DMD experts went on to say, "Patients in
20 clinical trials in FSHD may have better outcomes
21 than those in natural history studies regardless of
22 treatment assignment, emphasizing the importance of

1 placebo groups."

2 The observations of DMD experts also guided
3 FDA advice to the applicant that ambulation was a
4 particularly problematic endpoint in externally
5 controlled trials in DMD. This is a near quote
6 from one of the publications and from talking to
7 experts. This is because near the age at which
8 patients lose ambulation, loss of walking is not a
9 sudden hard endpoint. Preservation of ambulation
10 and other skills is affected by subjective decision
11 making from families and caregivers about those
12 skills, with such factors as risk of falls and
13 injury from continued ambulation weighed against
14 the safety and speed of allowing patients to use a
15 wheelchair.

16 It was mentioned before that recovery of
17 walking after a fracture might be an indication of
18 efficacy. And we've taken a look at this, but
19 there are other ways to look at that same kind of
20 data. People or patients who experience fractures,
21 that might mark a reasonable time, based on
22 clinical judgment, for that patient not to walk

1 because they got a fracture.

2 So there are a lot of decisions that need to
3 be made, too. It's not just a fracture leads to
4 loss of ambulation. It's really a fracture leads
5 to a series of clinical decisions about what to do.
6 And concern about a fracture leads to a series of
7 clinical decisions about what to do.

8 I see some heads shaking out there. This is
9 the advice that we see, the information that we see
10 in publications, people trying very hard to try to
11 get kids walking again after they have a fracture,
12 and that seems to be something that's possible to
13 do in many cases, not all, if one's mind is set on
14 it.

15 In a randomized controlled study, the only
16 major difference between the treatment groups is
17 the presence or absence of the drug. In contrast,
18 for an externally controlled trial, there are
19 potentially many differences, both known and
20 unknown, between drug treated patients and
21 controls.

22 To understand if there's evidence of drug

1 efficacy in an externally controlled trial, it's
2 absolutely necessary to study the sources and
3 possible sizes of non-drug related differences
4 between groups. A few examples of non-drug related
5 differences between the study arms in study 201/202
6 follow, and others are described in the FDA memos.

7 I should just add that looking for these
8 differences, that's just absolutely critical to try
9 to understand if drugs work or not. It's not
10 something that the FDA could avoid doing. It's
11 something that we need to look into.

12 So first, interpretability of externally
13 controlled trials -- for an interpretable
14 externally controlled trial, it's necessary that
15 efficacy endpoints be assessed the same way in the
16 groups being compared. So that's fairly obvious,
17 the things that are being compared have to be
18 similar to each other. They have to be measured
19 similarly to each other for a fair comparison.

20 One reason that 6-minute walk test is
21 problematic is that the decision to ask a patient
22 to attempt to perform the test, to attempt to do

1 6-minute walk test, versus deeming the patient
2 unable, is based partially on judgments and
3 attitudes of the investigator, patients, and
4 caregivers. Moreover, the distance walked could
5 depend on motivation and cooperation.

6 The FDA's concerned that there may have been
7 important differences in how such decisions were
8 made for eteplirsen treated patients compared to
9 external controls. And this is something that came
10 up in the applicant's discussion earlier. I'd just
11 like to talk a little bit more in detail about it.

12 So I'm going to focus on two specific
13 patients, but it's important to understand that the
14 issue of endpoints being assessed differently is
15 not limited to these two patients. It's just that
16 there is more evidence of a difference for these
17 two patients.

18 Two of the 13 control patients selected by
19 the applicant were able to perform 10-meter
20 run/walk reasonably well but were deemed unable to
21 attempt 6-minute walk test. Data for one of these
22 patients is shown in the table.

1 So at age 10, this patient walked 10 meters
2 in 10 seconds, and walked 356 meters in 6 minutes.
3 But age 11, the patient walked 10 meters in
4 12 seconds, which is still a reasonable walking
5 ability, but was said to have lost ambulation as
6 measured by 6-minute walk test.

7 So there's been some discussion earlier
8 about how far patients might be able to walk, or if
9 patients could walk, or I think what the real
10 discussion was is that it wouldn't be unusual to
11 lose ability to do 6-minute walk test before one
12 lost the ability to do 10-meter walk/run. And I
13 think one thing to point out before I get to some
14 more of the numbers, there's not very much
15 difference between walking 10 meters in 10 seconds
16 and walking in 12 seconds.

17 So there's a 6-minute walk test. If you
18 calculate it out distance that somebody could walk
19 if they were given multiple 12-second intervals,
20 you'd think they should be able to walk something
21 more than none, if given the opportunity to attempt
22 to walk for 6 minutes, that there could be some

1 distance recorded.

2 This is also talked about a little bit more
3 in the memo, and I'd like to call up a slide that
4 was in the memo, slide 125. So this is also from
5 the Italian cohort, and there are some patients
6 here who walked 12 seconds, and then 6-minute walk
7 distance is down at the bottom.

8 So there's certainly a range of values here.
9 One patient who did 10-meter run/walk was walking
10 about 125 meters on 6-minute walk distance. But
11 there really is a whole range, so if you trace
12 12 seconds over, and then down, there's also
13 patients who did 10-meter run/walk in 12 seconds
14 who were walking more than 300 meters in 6-minute
15 walk test.

16 So that's one of the reasons that we're very
17 concerned about when patients are deemed unable to
18 do a test because when the test isn't measured, you
19 really don't have any way of knowing what distance
20 the patient would have walked.

21 Of course, too, the way that the applicant
22 is counting ambulatory versus non-ambulatory, these

1 Kaplan-Meier curves or other graphs, that's based
2 on the 6-minute walk test. So that's based on
3 deeming the patient unable to walk.

4 So that gets right back to the whole issue
5 of clinical judgment, that the patients aren't
6 expected to be able to walk, so 6-minute walk test
7 isn't attempted, so there's the conclusion that the
8 patient is no longer ambulatory.

9 Could I have slide 57? So I'd just like to
10 switch a little bit now to the impact, or possible
11 impact of differences in supportive treatment. So
12 supportive treatment, including steroids, can have
13 important effects on slowing disease decline in
14 DMD.

15 The issue that FDA would like to point out
16 is that there are some differences in the
17 supportive care received by patients in the
18 eteplirsen trial and patients from external natural
19 history studies. One example is that the
20 eteplirsen patients were treated with steroids for
21 about a year longer, and that could be important
22 for maintaining ambulation.

1 But that's not really the key point that the
2 FDA is trying to make. The key point is really
3 that small differences, seemingly small differences
4 in care that patients receive can seemingly lead to
5 larger than expected differences in the disease
6 course and in the age of loss of ambulation.

7 Can I have the next slide? So this slide
8 shows some recent observational data from the
9 Cooperative International Neuromuscular Research
10 Group, also known as CINRG. The investigators
11 compared the course of patients on different
12 steroid regimens to try to determine which might be
13 the most effective. What they concluded is that
14 seemingly small differences in patient care can
15 confound interpretation of observational data in
16 DMD.

17 This is data taken from a larger table, but
18 it shows two groups of patients who seemingly have
19 a very similar steroid treatment, deflazacort that
20 was given daily, or deflazacort that was sometimes
21 given daily or switched to every other day or some
22 other dosing regimen.

1 But the point is these patients, they're not
2 exon 51 patients, but groups of DMD patients with
3 seemingly similar care and not selected for any
4 particular mutation, that there was a two-year
5 difference in loss of ambulation between these
6 patients.

7 So based on this data, and similar data that
8 the DMD experts showed, they concluded that
9 differences in standards of care and dosing
10 complicate interpretation. This study emphasizes
11 the necessity of a randomized, blinded trial of
12 glucocorticoid regimens in DMD.

13 The eteplirsen data are similar in some
14 ways, including the small sample size. So that
15 there were just 8 patients in this group, that
16 might have led to an unstable estimate of age of
17 loss of ambulation, but there's that same kind of
18 concern in the small eteplirsen study. Thus, even
19 a two-year difference in age of loss of ambulation
20 between eteplirsen treated patients and external
21 controls may not be a drug effect.

22 There can be other perhaps less obvious

1 sources of differences between study arms that can
2 confound interpretation of externally controlled
3 studies. Patients who are not motivated, able, or
4 qualified to enroll in drug studies may remain in
5 natural history studies. So one of the things
6 that's important to consider is that drug studies
7 and natural history studies were being conducted at
8 the same time when data for these groups of
9 patients was being collected.

10 Patients who have progressed more rapidly
11 may be over-represented in natural history studies
12 if they no longer meet eligibility requirements for
13 drug studies. Again I'm going to talk about a
14 specific example, but it's important to stress that
15 this is not limited to these specific patients;
16 rather it's only that there is clearer evidence of
17 differences for some patients than for others.

18 One of the 13 eteplirsen controls lost
19 ambulation after 1 year and stayed in the
20 observational study for several years, long enough
21 to enable matching to eteplirsen patients. Two
22 other exon 51 patients had similar baseline age and

1 6-minute walk distance, but discontinued the
2 observational study to participate in drug studies,
3 and were therefore not under observation long
4 enough to potentially be controls for the
5 eteplirsen study.

6 It even goes beyond matching. They weren't
7 there for long enough to enable matching. You can
8 only do matching to patients that remained in the
9 observational study for the same amount of time
10 that patients were treated with eteplirsen. So the
11 concern is that the only patient out of these three
12 who was available to be matched to the eteplirsen
13 patients was the one who definitely had a rapid
14 decline in ambulation.

15 Here's an important point. Different
16 analysis approaches are needed for externally
17 controlled trials than for randomized,
18 double-blind, placebo-controlled trials. As just
19 discussed, in externally controlled trials, data
20 may be gathered differently from each group, and
21 groups are different in ways that are impossible to
22 fully understand or measure.

1 P-values, sensitivity analyses, the kinds of
2 evidence that we're used to looking at from
3 randomized placebo-controlled trials, they can only
4 tell you that there's a difference between the two
5 sets of numbers, but they can't tell you where that
6 difference came from.

7 So again, the important part of the
8 randomized placebo-controlled trial is it's a
9 really good way to get the two groups of patients
10 the same. You don't know all the differences, but
11 you've sorted one part of the patients to one arm,
12 one part of the patients to the other arm randomly,
13 and that takes care of most of the differences.

14 Then the p-value can be interpretable. It
15 can tell you something about the chance of seeing
16 the size difference that you might see. But when
17 you start out with patients that are different from
18 each other and where the endpoints have been
19 measured differently from each other, taking a look
20 at the p-values doesn't give you the kind of
21 information that you need.

22 The key question to ask, really, the only

1 question that can help in a situation like
2 this -- and we are open to historically controlled
3 trials at FDA. But the question that needs to be
4 asked is kind of what we're going through right
5 now, how big were the differences between the
6 patients at baseline? How many differences were
7 there during the course of the study? You have to
8 use your judgment about how big those differences
9 were. And then take a look at the difference in
10 the endpoints between the two groups of patients
11 and try to decide if it was from some of these
12 known or unknown sources of differences between the
13 patients or if you're convinced that it was from an
14 effect of the drug.

15 So now let's turn to the figure, some of the
16 figures that I showed earlier, that compare the
17 clinical data from the eteplirsen patients and
18 external controls.

19 The applicant has shown these 6-minute walk
20 test data as a function of time on study, but
21 showing by age is more meaningful because loss of
22 ambulation is correlated with age in DMD, and so

1 it's important to adjust for age.

2 The patients and controls in the study
3 varied widely by age at baseline from as young as 7
4 to as old as almost 12 years old. In the context
5 of DMD, these are very different ages. So when
6 we're talking about just the original baseline
7 matching that was done for the patients, the
8 patients were matched by quite a range, 7 to
9 12 years old, so that's not really very close
10 matching for the DMD.

11 So that's one of the problems with the way
12 the applicant's presenting the data, and what we
13 really need to do to understand the course of the
14 patients is compare patients who are of similar
15 age.

16 So in these slides, patient's age is shown
17 on the X-axis, and the 6-minute walk test is shown
18 on the Y-axis. The red lines show eteplirsen
19 patients and the blue show the applicant's external
20 controls. Each line begins at the patient's age at
21 enrollment and continues through 4 or 5 years,
22 depending on the available data.

1 As described earlier, there are many reasons
2 why there may be very real but not drug-related
3 differences between eteplirsen and control
4 patients. Differences in the way the endpoints
5 were assessed are highlighted here. Patients
6 marked with an X -- so this patient's marked with
7 an X, so those were the two patients who were
8 described on slide 56 who had 6-minute walk test
9 values of zero assigned when they could still walk
10 fairly well as measured by 10-meter run/walk.

11 The patients marked with question marks,
12 these three patients, those were patients in whom
13 6-minute walk test was assigned zero based on a
14 yes/no question, was this patient walking at year
15 4?

16 The problem is that that's comparing data
17 that was measured differently. It's simply not
18 possible to know if the value would have been the
19 same if 6-minute walk test had been measured under
20 the same careful testing procedures used for
21 eteplirsen patients, including, as brought up
22 before, that all eteplirsen patients were tested

1 twice at most visit.

2 Because of many types of non-drug related
3 differences, including the way endpoints were
4 assessed, these figures may really be apples to
5 oranges comparisons. So we're going to continue to
6 show the data that we have, but there's a great
7 deal of uncertainty in the similarity of how these
8 data were obtained, if they really represent
9 measurements of the same thing. This is important
10 to keep in mind.

11 The arrows in this figure are only there to
12 illustrate that some patients declined in 6-minute
13 walk test earlier than average, some about average,
14 and some older than average across a wide range of
15 ages.

16 Importantly for eteplirsen and control
17 patients, there appears to be a general similarity
18 in age and rate of decline. So again, if we take a
19 look at going all the way across here -- and again,
20 part of the issue of comparing these two groups of
21 patients is that the natural history patients, a
22 lot of those patients were from past history, so we

1 know the course of those patients. We know the age
2 at which they lost ambulation.

3 One of the things that we really need to
4 think about when we're making comparisons about the
5 patients who are currently walking and the patients
6 who are not currently walking is that the patients
7 who are not currently walking, they were measured
8 in some cases years ago, and the patients who are
9 still walking are at similar or younger ages, but
10 they're measured now.

11 So again, taking a look at the course of the
12 different patients, we have the age at which
13 patients are starting to decline and the general
14 course of that decline. And it really more or less
15 alternates with blue and red and blue and red
16 across most of this figure.

17 I showed this before. So it doesn't look
18 like there's this binary kind of difference in age
19 of loss of ambulation between eteplirsen treated
20 patients and historical controls.

21 There's no bigger apples to oranges
22 comparison than comparing walking in an 11-year-old

1 patient with DMD to walking in a 15-year-old with
2 DMD, but that's what is done with some of the
3 applicant's analyses. Instead we need to compare
4 eteplirsen patients to controls of similar age.

5 So the 11-year-old, marked by the arrow
6 here, appears to be progressing about the same as
7 the controls on either side. So there are blue
8 patients here, and then there's a red eteplirsen
9 patient, and blue controls here. It's simply not
10 correct to say that the 11-year-old is necessarily
11 doing better than these 15-year-olds because it's
12 confounded by age. The 11-year-old is still 11 and
13 it's hard to know what's going to happen when the
14 11-year-old becomes 15.

15 Then going along the patients, the same
16 comparison can be made for these two 12-year-old
17 patients marked by the arrows. They are
18 progressing at a rate similar to control patients,
19 and in fact for these patients the lines are
20 basically overlapping here.

21 More or less the same comparison can be made
22 for these 13 and 14-year-old patients. And it's

1 important to say again it doesn't have to be exact.
2 There's concern that the patients were measured
3 under conditions that were different. But the
4 general course of progression, even in these
5 patients, these 13 and 14-year-old patients marked
6 by the arrows, is similar to the natural history
7 patients.

8 So now for some patients, the ones in the
9 oval here, there may be differences in reported
10 6-minute walk test for eteplirsen and control
11 patients. Again, it needs to be remembered that
12 there were differences in the way that these values
13 were assessed.

14 So the FDA is certainly keen on looking at
15 the data in different ways to see if there's a
16 change in the average age of walking of patients,
17 treated patients, or to see if maybe only some
18 patients are responding in a way that could be
19 clearly attributed to drug.

20 So it's been suggested that the performance
21 of some eteplirsen patients is very different from
22 the natural history of DMD. So there are one or

1 two patients, eteplirsen treated patients, who are
2 currently walking at an age when none of the 13
3 natural history patients selected by the applicant
4 are walking.

5 But unfortunately, there's recent data that
6 suggests that this is still what can be expected
7 from natural history patients. What we have to do
8 is take a look at other groups of natural history
9 patients, and I think that's the same thing that
10 we're talking about with consistency. It's really
11 necessary when taking or trying to interpret
12 historically controlled trials, to take a look at
13 the variety of different kinds of natural history
14 experience to try to understand the variability
15 between groups.

16 DR. ALEXANDER: Dr. Farkas, I'd just like to
17 ask you to be mindful of the time as we proceed.

18 DR. FARKAS: Sure.

19 Okay, so this is the Kaplan-Meier curve that
20 we saw before. A key point is that the age of loss
21 of ambulation in exon 51 skippable patient appears
22 to be older than is sometimes realized. And that's

1 really a huge point to be made, and we've heard
2 experts talk here today, but I think the bottom
3 line, and perhaps to save time, is that we've been
4 looking at all the data that we can get about the
5 age of loss of ambulation in exon 51 skippable
6 patients. And from the CINRG data, 25 percent of
7 exon 51 boys are walking at 16 years of age, and
8 15 percent are walking at 18 years of age.

9 This I showed before, the kind of
10 interpretation that seems appropriate is to try to
11 figure out what percent of the eteplirsen patients
12 would be walking at 16 years of age.

13 Other historical data appear to be generally
14 consistent with the CINRG data. The exon 51
15 skippable patients in the placebo arms of recent
16 randomized placebo-controlled studies of
17 drisapersen that this committee talked about in
18 November, they seemed to also indicate that
19 patients can walk to 16 years of age. And then
20 that group is described more in the memo. They
21 were younger patients who still had well-preserved
22 rise times and 6-minute walk test that seemed

1 generally consistent with the Kaplan-Meier curve
2 for the CINRG patients.

3 There's also data being collected about the
4 natural history of muscular dystrophy from the MD
5 STARnet program of the Centers for Disease Control
6 and Prevention. And I'll skip over some of this
7 data, but we can refer to it later if we need to.

8 But the key thing from this data is that
9 there were 26 exon 51 patients identified, and out
10 of those 26 patients, 3 patients were walking at or
11 beyond 14 years, and 2 of these 3 patients were
12 walking at or beyond 16 years. And also out of
13 these 26 patients, there's still 15 who are still
14 ambulant. So the number of these patients who
15 might ultimately be found to be walking past age 14
16 or age 16 might be more than that.

17 So we were talking about correlation between
18 dystrophin levels and change in 6-minute walk test.
19 This is just an exploratory analysis done by the
20 FDA. There's change in 6-minute walk test found
21 versus dystrophin expression, and we didn't see a
22 correlation. And this is a very small data set,

1 but this is the kind of data that if you saw a
2 correlation, that's the kind of correlation you'd
3 like to see, to understand if there was a
4 difference in the small amounts of dystrophin that
5 we see, that we might see.

6 So other functional endpoints can be very
7 important. NSAA may be a particularly important
8 measure of disease progression in DMD because it
9 measures the number of underlying abilities related
10 to muscle strength and to safe and practical
11 walking. And in the eteplirsen study, it may be a
12 more reliable measure than 6-minute walk test
13 because it was more consistently measured, with
14 fewer, although some instances of zero being
15 assigned without the measurement being conducted.

16 So the arrow here indicates what appears to
17 be a generally similar slope of decline for both
18 treated and control patients. You'll notice that
19 more control patients are to the left of the
20 figure, but that's because of lower mean baseline
21 scores in the controls. So that itself is
22 something important to take a look at.

1 On this slide, we did take a look at the
2 NSAA score by years on treatment, and you can see
3 that there's a baseline imbalance between the two
4 groups of patients, with the control patients a
5 little bit lower on the NSAA score at baseline.
6 And this is one of the kinds of differences that
7 could also lead to the control patients not doing
8 as well over the course of the study.

9 So this slide is a little bit complicated,
10 but it takes a closer look at, again, the FDA also
11 trying to figure out are there some
12 patients -- patients who are the oldest that are
13 doing the best, are there some patients who might
14 suggest that the course of decline in the treated
15 patients is less than could be expected by natural
16 history.

17 I think that the main point of this is that
18 there's a similar decline in NSAA score and a
19 fairly dramatic decline in NSAA score even for the
20 patients who were walking relatively well. So the
21 NSAA score in these patients is down at 10 or 9 or
22 so, and that indicates a substantial loss of

1 walking ability.

2 So even though at this time, the 6-minute
3 walk test is relatively well preserved versus other
4 patients, there's really no clear indication that
5 these patients would continue walking beyond the
6 known natural history of exon 51 patients.

7 Ability to rise from the floor may be
8 another useful measure of disease progression in
9 DMD. Lower values indicate a better score and more
10 horizontal course indicates slower progression. So
11 it's notable that two of the patients with the most
12 preserved rise time at older ages were historical
13 controls.

14 This graph also shows how it looks like
15 there may be a difference in how endpoints were
16 assessed for eteplirsen patients versus external
17 controls. Six of the eteplirsen patients have rise
18 time values of more than 25 seconds, just these
19 patients here, whereas none of the controls have a
20 value larger than 25 seconds, and that's delineated
21 by the dotted line.

22 We can't know why there was this difference

1 in the maximum values measured. The protocols and
2 case report forms from the Italian and Belgium
3 studies were very brief and don't provide details
4 about that. But we do know that in a different
5 natural history study, in the CINRG study,
6 25 seconds is indicated in the protocol as a time
7 beyond which testing of some endpoints might not be
8 considered.

9 FDA recently received data, additional data
10 from the CINRG study for 10-meter run/walk, rise
11 time, and 4-step climb. FDA is still in the
12 process of analyzing this data but would like to
13 present some initial observations.

14 Prior to the receipt of the data, the FDA
15 made a prespecified plan for the matching, so that
16 it will be a fair matching not based on FDA looking
17 at the data. And that was based on exon 51
18 skippable, ambulatory at baseline, baseline age 6
19 to 12 years, and 10-meter run/walk time less than
20 10 seconds. 10-meter run/walk was considered the
21 primary comparison because there wasn't much
22 6-minute walk test data currently available in the

1 CINRG database.

2 So here, the 10-meter run/walk time is shown
3 on the Y-axis, and age is shown on the X-axis.
4 Lower values indicate better performance. The red
5 lines show the course of eteplirsen patients, and
6 the blue lines show the course of the CINRG
7 controls. The lines show the results for the
8 10-meter run/walk test that were actually
9 attempted, not deemed as unable. And the circles
10 at the ends of these lines, those indicate patients
11 in whom the next value was imputed as unable.

12 The course of 10-meter run/walk appears to
13 be similar for eteplirsen treated and CINRG
14 patients. You can see many CINRG patients tracking
15 with the eteplirsen patients, including the
16 patients who did best was a CINRG patient. But
17 there's a wide range of different courses, but
18 basically overlap of the red and blue lines.

19 Again, eteplirsen patients were measured the
20 higher values, but this may reflect a difference in
21 when patients who were deemed unable to attempt the
22 endpoint. And there are patients from the CINRG

1 study that had the best preserved function on
2 10-meter run/walk.

3 Now, we're looking at rise time, and the
4 course of rise time also appears to be similar for
5 eteplirsen treated and CINRG patients for values
6 that were measured. The CINRG patients looked much
7 like the external controls from Italy and Belgium
8 also that were shown in slides 88 and 89. Note
9 that none of the CINRG patients are attempting the
10 test once the rise time reaches 20 to 25 seconds.
11 And this is the course of 4-step climb, which also
12 appears to be similar for eteplirsen treated and
13 CINRG patients for values that were measured.

14 I'd like to move on to, again, conclusions.
15 And I know that I've tried to explain things
16 quickly and I think shown clearly that I think you
17 haven't heard the whole story, for many years that
18 you haven't heard the whole story.

19 But I really do want to reassure everybody
20 that I remain open to what we hear from the
21 community, and I remain open from what we hear from
22 the applicant. And I've made no final decision and

1 nobody else on the review team has made any final
2 decisions about what they think about the data.

3 From the placebo-controlled portion of
4 study 201/202, including from the applicant's
5 post hoc analyses, there does not appear to be any
6 evidence of efficacy for eteplirsen.

7 Interpretation of the externally controlled portion
8 of study 201/202 must keep in mind the limitations
9 of an externally controlled study, which are well
10 known and detailed in FDA guidance and
11 international guidelines, such as ICH E-10.

12 Based on an assessment of all the physical
13 performance measures, disease progression appeared
14 to be similar for eteplirsen treated patients and
15 external controls. All eteplirsen patients who
16 have maintained ambulation are still well within
17 the age range in which exon 51 skippable patients
18 appear commonly to walk.

19 It does not appear possible to conclude that
20 differences in physical performance between
21 eteplirsen treated patients and external controls
22 resulted from an effect of eteplirsen instead of

1 from other differences and influences, both known
2 and unknown, between the groups, both at baseline
3 and during conduct of the study.

4 Regarding general drug development
5 considerations, this is very important. It's
6 really one of the most important slides here
7 because what we have to remember is that we're
8 developing these drugs -- we need to develop these
9 drugs as thoroughly, as effectively, as efficiently
10 as possible. Dose limiting toxicity from
11 eteplirsen was not observed at the doses studied.
12 Higher doses and more frequent dosing could hold
13 promise for the future. Thank you.

14 So I'd like to introduce Dr. Bastings,
15 the --

16 DR. ALEXANDER: I think we'll wait actually
17 for that, but thank you very much for your
18 presentation.

19 DR. FARKAS: Thanks.

20 DR. ALEXANDER: So I'd like to suggest that
21 we break for lunch, and then when we resume after a
22 45-minute break, we'll hear from Dr. Bastings, as

1 well as have an opportunity for clarifying
2 questions for the FDA.

3 So we'll return at 12:45. I'm sorry. We'll
4 return at 1:45. Please take any personal
5 belongings you may want with you at this time. And
6 committee members, please remember that there
7 should be no discussion of the meeting during lunch
8 amongst yourselves, with the press, or with any
9 member of the audience. Thank you very much.

10 (Whereupon, at 12:57 p.m., a lunch recess
11 was taken.)

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A F T E R N O O N S E S S I O N

(1:48 p.m.)

DR. ALEXANDER: We're going to begin with the afternoon portion of the committee. Thank you very much, and welcome back.

So we'll continue where we left off with concluding remarks from the FDA. I'd like to ask Dr. Eric Bastings to come to the podium.

FDA Presentation - Eric Bastings

DR. BASTINGS: Good afternoon. My name is Dr. Eric Bastings. I am deputy director of the Division of Neurology Products. Duchenne muscular dystrophy is a serious and devastating disease with profound unmet medical need and no approved treatment.

Great hope was raised by early reports by the applicant that with eteplirsen treatment, dystrophin numbers were increased to levels as high as 50 percent of normal and that the course of the disease had stabilized, effects which would have been unprecedented for Duchenne muscular dystrophy.

FDA provided extensive discussions and

1 guidance during the eteplirsen development program.
2 Just between 2013 and 2015, FDA held 13 formal
3 meetings with the applicant about eteplirsen. As
4 was discussed earlier by Dr. Rao and Dr. Farkas,
5 FDA identified significant methodological concerns
6 about the biomarker assessment and provided
7 extensive guidance on methods for collection of
8 additional biomarker data. Eteplirsen's
9 development program also benefited from extensive
10 involvement and guidance from senior FDA
11 management.

12 Study 201/202 was also the object of
13 extensive discussions. After study 201 did not
14 meet its primary clinical endpoint, and as FDA did
15 not consider the post hoc analyses conducted by the
16 applicant to be scientifically valid, FDA advised
17 the applicant to conduct an adequately controlled,
18 adequately powered, randomized placebo-controlled
19 trial to assess the clinical benefit of eteplirsen.

20 At the time, the company heard the view that
21 a placebo-controlled trial would not be feasible,
22 that few, if any patients, would be willing to

1 participate in a second placebo-controlled trial
2 because they already felt so strongly that
3 eteplirsen was effective. This was an unfortunate
4 situation.

5 The publication of the results of study 201
6 may have led to this perception. It stated that
7 after 48 weeks of eteplirsen treatment, 52 percent
8 of muscle fibers seemed positive for dystrophin,
9 and that 6-minute walk distance was augmented by
10 67 meters.

11 Unfortunately, as explained by Dr. Rao and
12 Dr. Farkas this morning, there were problems with
13 these conclusions. In any case, the applicant
14 instead elected to continue open-label
15 administration of a eteplirsen in study 202, which
16 has now been ongoing for over four years and is
17 proposing approval primarily based on the post hoc
18 comparisons of patients in study 201/202 to an
19 external control.

20 Many of you may be wondering why the public
21 is only hearing now about such extensive FDA
22 concerns about eteplirsen and why only after the

1 NDA has been submitted. Because of laws governing
2 trade secret, FDA is generally unable to provide
3 any information to the public about its finding
4 regarding drugs under development and is unable to
5 comment about information provided by the drug
6 developer.

7 Because of those restrictions, some
8 decisions or positions taken by the FDA, or FDA's
9 silence, might be construed by the public and the
10 patient community as a lack of caring, a lack of
11 understanding, or a lack of expertise when they
12 simply reflect a legal restriction against sharing
13 commercial confidential information with the
14 public.

15 Advisory committee meetings, such as today,
16 provide a unique opportunity for FDA to discuss
17 with a panel of advisors developer data and FDA
18 views on these data, and we very much look forward
19 to hearing from the committee later this afternoon.

20 I would now like to briefly review with you
21 the evidence that was provided this morning and
22 discuss why we came to very different conclusions

1 than those of the applicant. So let's start with
2 the biomarker evidence.

3 We agree that there is evidence of
4 production of exon 51 skipped mRNA with eteplirsen
5 treatment, supporting its proposed mechanism of
6 action. The method, however, does not show how
7 much RNA was produced or whether this mRNA led to
8 production of dystrophin.

9 After 3 and a half years of treatment, the
10 proportion of muscle fibers with detectable
11 dystrophin, identified by immunofluorescence, was
12 17 percent of normal plus or minus 10 percent. As
13 was discussed by Dr. Farkas, it is not clear
14 whether 17 percent constitutes an increase from
15 baseline. Also, as discussed by Dr. Rao, this
16 method is most useful for showing location of
17 dystrophin in the muscle and has major shortcomings
18 for quantifying dystrophin.

19 Therefore, we believe that the most relevant
20 measure of dystrophin for you to consider is the
21 amount assessed by Western blot. That amount after
22 3 and a half years of treatment is 0.9 percent of

1 normal, plus or minus 0.8 percent. That number,
2 which became only known to FDA after the NDA had
3 been submitted, is very disappointing and far lower
4 than estimates presented earlier by the applicant.

5 The biomarker data are important for the
6 committee to consider. As you've heard, if we
7 believe that the biomarker data are reasonably
8 likely to predict clinical benefit, it would open
9 up the prospect of accelerated approval.

10 There are two parts to this question.
11 First, is there adequate evidence that eteplirsen
12 produced dystrophin? And second, was the amount
13 produced reasonably likely to predict clinical
14 benefit?

15 There are some aspects of the data that can
16 be considered that if positive would support the
17 reasonably likely question. If there were a
18 correlation between the amount of dystrophin
19 detected in the muscles of individual boys, and
20 preservation of their physical abilities, such a
21 link would help support the concept that the amount
22 of dystrophin detected was reasonably likely to

1 predict clinical benefit. So let's briefly discuss
2 an exploratory analysis FDA conducted.

3 In the figure, which was shown on
4 Dr. Farkas' slide 80, the amount of dystrophin as
5 measured by Western blot is shown on the X-axis,
6 and the change in 6-minute walk distance is shown
7 on the Y-axis. For the 4 patients with the best
8 preserved 6-minute walk distance, at the top of the
9 figure, 2 had among the lowest dystrophin levels,
10 and 2 the highest, as indicated by the arrows.

11 The data are sparse, but there doesn't seem
12 to be much of a correlation between dystrophin
13 levels and change in 6-minute walk test in this
14 particular group of patients.

15 You haven't seen this figure before, but as
16 you recall, patients in study 202 received either
17 30 or 50 milligram per kilogram of eteplirsen for
18 some 3-plus years, so it is worth considering the
19 dose response for the dystrophin detected at
20 week 180. If there were a correlation between the
21 dose of eteplirsen administered and the amount of
22 dystrophin detected, this would help support that

1 eteplirsen produced the dystrophin that was
2 detected.

3 Again, the data are sparse, but there is no
4 support for dose response here. Had a dose
5 response been present, it could have helped support
6 a concept the eteplirsen treatment was in fact
7 responsible for dystrophin detected by Western
8 blot.

9 Now, let's review the clinical evidence. As
10 was discussed by Dr. Farkas, study 201 did not show
11 a significant difference between boys treated with
12 eteplirsen and those treated with placebo for the
13 prespecified primary endpoint.

14 When you think of the 6-minute walk data,
15 it's worth considering just how small the sample
16 size is and about the fragility of the findings.
17 So let's consider the two patients in the low-dose
18 30 milligram per kilo group who quickly lost their
19 ability to ambulate.

20 If by chance they had been randomized to the
21 placebo group, it is likely the trial would have
22 shown a statistically significant difference in

1 favor of the drug, and the result would have been
2 interpreted as showing a large and clinically
3 important treatment effect based on these 12
4 patients.

5 Of course, the study did not turn out that
6 way, but it is important to consider how easily one
7 can be misled by a single study with a small sample
8 size. In addition, just as study 201, study 202
9 did not meet its prespecified clinical endpoint.

10 As you heard this morning, the applicant
11 describes highly statistically significant results
12 in the comparison between boys treated with
13 eteplirsen in study 201/202 and external controls,
14 presenting a difference of 162 meters between the
15 groups.

16 The applicant also describes that in a
17 comparison of eteplirsen to external control over
18 4 years, only 2 of the eteplirsen treated boys lost
19 ambulation compared to 10 of the 13 untreated
20 external controls.

21 The 160 meter difference in the 6-minute
22 walk distance, if demonstrated in an adequate and

1 well-controlled study, would provide evidence of
2 effectiveness, but study 202 was not a randomized
3 controlled trial. And several lines of evidence
4 raise concerns that the differences in ambulation
5 between eteplirsen treated boys and external
6 controls are not related to a treatment effect and
7 may be due to other factors.

8 As was described by Dr. Farkas, there appear
9 to be differences between important baseline
10 characteristics that could affect outcome in boys
11 enrolled in the eteplirsen study compared to those
12 of the registries.

13 For example, the age at initiation of
14 steroid treatment was on average over one year
15 earlier for eteplirsen treated patients. This
16 difference alone could have had a significant
17 impact on clinical outcomes.

18 Dr. Farkas also described evidence
19 suggesting a differential selection of patients for
20 the registry versus for drug studies, which leads
21 to questions about the comparability of the groups.
22 There may also be unrecognized and potentially very

1 important factors, which were not balanced by
2 randomization, between the study and the registry
3 cohorts.

4 There were apparent differences in the
5 administration and on the performance of functional
6 tests between eteplirsen treated boys and those of
7 the registry. You have seen this basic figure in
8 Dr. Farkas' presentation. Patient age is shown on
9 the X-axis and the rise time in the Y-axis.
10 Eteplirsen is shown in red and external control in
11 blue.

12 It is striking that no boy in the Belgium or
13 in the Italian registry had a recorded rise time
14 greater than 22 seconds, whereas some two-thirds of
15 eteplirsen treated boys did. Some rise times were
16 extremely long, in some cases even greater than
17 40 seconds.

18 To be very clear, it wasn't that patients in
19 the registries didn't experience this degree of
20 loss of function, the point is that there is a
21 difference, boys outside of the eteplirsen study do
22 not contribute data for rise time greater than

1 22 seconds. There is a difference, but we cannot
2 really know why there is a difference.

3 Perhaps the eteplirsen boys were more highly
4 motivated, or perhaps they continued to receive
5 encouragement from parents or staff, or perhaps the
6 physician or the physical therapist at the Italian
7 and Belgium sites elected not to perform testing,
8 or to abort testing, once physical function had
9 worsened.

10 Our concern is that there is an apparent
11 difference, and it is precisely these kinds of
12 differences, differences for known or unknown
13 reasons, that can confound comparisons between
14 patients in an open-label drug study and patients
15 in an external observational cohort. And this
16 observation is also supported by the comparison to
17 the CINRG data as presented this morning by
18 Dr. Farkas.

19 Similarly, extreme results were recorded for
20 the 4-step climb time in some eteplirsen treated
21 boys, but again not in registry patients. In
22 addition, as discussed by Dr. Farkas, some boys in

1 the registry had recorded 10-meter run/walk results
2 and at the same time were declared unable to
3 ambulate, which illustrate the subjectivity in the
4 decision to declare a boy as having lost
5 ambulation.

6 These observed differences indicate that the
7 functional test appeared to have subjective
8 elements and that their performance may have been
9 influenced by decisions made by the boys, the
10 caregivers, or by study investigators. These types
11 of differences may have a large impact on test
12 results, and there is no way to correct for that by
13 statistics.

14 Another line of evidence that calls into
15 question interpretation of the 6-minute walk test
16 findings comes from the inconsistencies between
17 6-minute walk test results and other clinical
18 endpoints.

19 As displayed earlier by Dr. Farkas, the left
20 figure shows no clear difference between eteplirsen
21 treated boys and external controls in patterns of
22 changes in rise time by age, with the exception of

1 some more extreme recorded values in eteplirsen
2 treated boys, as we discussed earlier. And the
3 North Star Ambulatory Assessments on the right
4 indicate a similar decline over time for eteplirsen
5 treated patients and external controls, with large
6 overlap in confidence intervals through 4 years of
7 observation.

8 Importantly, there is a substantial overlap
9 of ambulation results between eteplirsen treated
10 boys, external controls, and natural history. As
11 was discussed by Dr. Farkas, on the right, the
12 proportion of eteplirsen treated patients still
13 ambulating at age 14 is not clearly different from
14 what is expected for patients with mutation
15 amenable to exon 51 skipping, as shown by the
16 comparison to the Kaplan-Meier curve of loss of
17 ambulation from the CINRG database on the left.

18 As we heard earlier from Dr. Temple,
19 important issues to consider with external control
20 trials are the possibility of bias before the trial
21 and the possibility of bias during and after the
22 trial. In addition, external control trials are

1 more likely to be persuasive when the effect is
2 very large and when the natural history is highly
3 predictable.

4 We have seen from the CINRG database and the
5 MD STARnet database that the age of loss of
6 ambulation spans over a decade with 25 percent of
7 boys with mutation amenable to exon 51 skipping
8 ambulatory at age 16. That variability is
9 problematic for a historical control study using
10 loss of ambulation or a 6-minute walk test as an
11 endpoint.

12 Overall, the historical control comparison
13 conducted by the applicant raises serious concerns
14 about many factors that should be considered in
15 interpreting a historical control study.

16 As Duchenne muscular dystrophy is an orphan
17 disease, an important issue to consider is whether
18 it would have been possible for the applicant to
19 conduct an adequate and well-controlled study. The
20 answer clearly is yes. This committee discussed in
21 November 2015 an application for another drug
22 developed to treat boys with mutations amenable to

1 exon 51 skipping. As you remember, the application
2 included three placebo-controlled studies, two
3 phase 2 studies with a sample size of about
4 50 patients, and a phase 3 study with over
5 180 patients.

6 In the discussion at the November meeting,
7 the committee raised major concerns about the
8 impact of the sample size of the two phase 2
9 studies on their interpretability. These two phase
10 2 studies, which were randomized and
11 placebo-controlled, dwarf the single eteplirsen
12 study.

13 As we know, the entire eteplirsen efficacy
14 database consists of 12 patients from a single site
15 with a single investigator, with an open-label
16 design, and an external control. While there is no
17 specific minimum number of patients that should be
18 studied to establish effectiveness of a treatment
19 for any rare disease, the number of patients must
20 be sufficient to draw scientific conclusions,
21 taking into account the study design and the study
22 outcome measures.

1 This afternoon, you will discuss whether
2 evidence has been presented to you to support
3 approval based on a biomarker reasonably likely to
4 predict clinical benefit or based on a clinical
5 endpoint.

6 It is important to keep in mind that the
7 difference between accelerated and full approval is
8 the type of endpoint and not the strength of the
9 evidence. As was discussed by Dr. Dunn,
10 substantial evidence is required for both pathways,
11 and accelerated approval cannot be used to
12 compensate for weak or inconsistent clinical
13 findings.

14 Now, I would like to speak directly to the
15 study participants and their families. I want to
16 thank you for your extraordinary commitment and
17 efforts to the incredibly important endeavor to
18 make a new drug available for the treatment of
19 Duchenne muscular dystrophy. I do understand your
20 situation. You have a devastating disease, and you
21 have placed great hope that this experimental
22 treatment will change the course of your disease.

1 I understand your fight because it has been
2 my family's fight. I have a sister who is
3 profoundly disabled since birth, and who almost did
4 not make it through her first days of life. My
5 parents spent considerable time and resources to
6 get her access to experimental treatments.

7 My parents would have done anything,
8 anything to create a brighter future for my sister,
9 and I would do the same for my children. And a
10 number of my close collaborators, some in this
11 room, are facing similar situations.

12 But my role here today as a member of the
13 neurology review division is very different. My
14 role, regardless of the pressure that has been
15 placed on my division, and in particular on the
16 eteplirsen review team, is to present our
17 scientific review and conclusions about eteplirsen.

18 We are a science-based organization. That
19 review has been very careful. Really, it has been
20 exhaustive, and has involved a large
21 multidisciplinary team of reviewers. Even though
22 just a few of us are talking to you this morning, I

1 want to assure you that nothing that was presented
2 today represent the unique view of a single
3 reviewer. Instead, it is the product of a large
4 team effort with considerable oversight and
5 feedback by all levels of FDA management.

6 We are looking forward to your testimony
7 this afternoon, and I'm looking forward to a good
8 and productive discussion with the members of the
9 advisory committee. Thank you.

10 **Clarifying Questions**

11 DR. ALEXANDER: Thank you, Dr. Bastings.

12 We now have 15 minutes for questions,
13 clarifying questions for the FDA. Again, please
14 remember to state your name for the record before
15 you speak. And if you can, please direct your
16 questions to a specific presenter.

17 I'll take the prerogative as chair to ask a
18 first question, which is clarifying the selection
19 of the controls from the CINRG study. There was
20 some concern raised on the part of the sponsor, if
21 I understood correctly, regarding the way that the
22 controls were selected and that the individuals

1 that were selected may have represented outliers.

2 So I'm wondering, from the FDA, if someone
3 could speak to how these controls were selected.
4 And in particular, I'm interested in whether there
5 were sensitivity analyses performed using different
6 criteria to select different control groups from
7 the CINRG study, that is, is there an opportunity
8 to look at how the conclusions that one reaches
9 differ based on the control patients selected from
10 CINRG.

11 DR. FARKAS: It's Ron Farkas. Well, let me
12 start. One thing is actually in my mind, it's not
13 exactly clear to me what the issue -- or what the
14 concern was that was raised, but I can describe how
15 we picked the controls. And that was being very
16 careful to separate -- so the review division
17 didn't take a look at any of the data. We took a
18 look at some of the baseline characteristics of the
19 patients without knowing their course, and then
20 matched patients that were similar just on those
21 baseline characteristics, and then the
22 statisticians conducted these comparisons.

1 So there were no -- I mean, on purpose,
2 there were no multiple looks, no sensitivity
3 analyses. It was pick some patients that looked
4 similar. And again, it was not close matching. I
5 think that's something that's important to
6 understand, too. We tried close matching. We
7 actually wrote out a detailed protocol to do close
8 matching, but there weren't any matches, and so we
9 relaxed and relaxed and relaxed until it just
10 seemed like there was kind of some similar baseline
11 characteristics and had the statisticians then do
12 the calculations.

13 DR. ALEXANDER: Thank you. Dr. Ovbiagele?

14 DR. OVBIAGELE: Bruce Ovbiagele. My
15 question is for Dr. Farkas.

16 DR. ALEXANDER: Can you speak into the
17 microphone a little more, please?

18 DR. OVBIAGELE: Sure, sure. My question is
19 for Dr. Farkas. Of course, when you look at the
20 different prognosticators, the big differences you
21 see already with the steroid treatment. And as you
22 might remember from page 39 of the applicant's

1 presentation, the two issues were the age at
2 steroid start, and the other issue was continuous
3 treatment with steroids, which was much, much
4 higher in the eteplirsen group.

5 The applicant looked at the effect of
6 continuous treatment in the external control group
7 and found there was no significant difference. Did
8 you look to see if there was a difference in terms
9 of age at steroid start, in terms of its effect on
10 the outcome?

11 DR. FARKAS: Right. I think that there was
12 a difference in the age at steroid start. But
13 getting back to the daily versus every other day
14 treatment, I think one of the concerns that we have
15 is that it didn't seem like the data was reliable
16 for the daily versus every other day.

17 The NDA came in. We took a look at the
18 counts for daily versus every other day. We raised
19 some concern about that. And then we heard later
20 from the applicant that the data was incorrect as
21 submitted, in that there were more patients on
22 every other day treatment in the historical

1 controls than had been originally reported, which
2 raised some definite concerns in our mind when the
3 data seems to change or wasn't really certain.

4 With regard to seeing if there's a
5 correlation between the treatment given and the
6 clinical course, I think at some point -- I think
7 we tried to be careful to point out that, you know,
8 lack of a correlation between low levels of
9 dystrophin and how patients did on clinical course,
10 it's so very underpowered. And then for some of
11 these other comparisons, we're dividing the
12 patients in half again.

13 So it's true. There wasn't a correlation
14 shown there, but if it's comparing four patients to
15 four other patients, I'm not sure what we can
16 really see.

17 But again, I think that the main point that
18 I tried to make in the original version of the memo
19 that I wrote, and even later on, is that it isn't
20 necessarily large differences that might account
21 for differences in clinical course. I mean, the
22 whole issue that's been identified by experts in

1 DMD is that things that seem small can confound
2 differences between groups.

3 DR. OVBIAGELE: No, I recognize that, but I
4 think the issue of course is that since that of
5 course is one of the issues that has been raised as
6 potentially problematic, at the very least, it
7 might be somewhat reassuring if there was no impact
8 of age of steroid start on the actual clinical
9 outcome in the external control group, if you see
10 what I mean.

11 DR. FARKAS: Yes. I'm just not sure that
12 you can -- so on one particular factor, you can see
13 that very small groups of patients don't divide
14 from each other. But I'm not really sure how much
15 reassurance that gives that the differences
16 couldn't have resulted in a changing clinical
17 course.

18 Of course, but backing up, I mean, in some
19 sense I regret that almost that I brought this
20 up --

21 (Laughter.)

22 DR. FARKAS: -- because the sources of

1 difference between the patients is so large in so
2 many other respects. It was a true point the
3 differences in care can lead to differences in
4 clinical outcome, but it's overshadowed by I think
5 other issues.

6 DR. ALEXANDER: Thank you. Dr. Bastings and
7 then Dr. Hoffman.

8 DR. BASTINGS: Yes, listen. What we know is
9 that patients in the registries started the
10 steroids over one year earlier. The cohort size is
11 just too small to look for any correlation with
12 outcomes, but it's a fact that steroid treatment is
13 effective and widely used in Duchenne muscular
14 dystrophy, and the effect of initiating earlier
15 cannot be overstated.

16 Yes, yes. I'm sorry, I said it backwards.
17 The eteplirsen patients started earlier. Okay.

18 DR. ALEXANDER: Thank you. So the
19 eteplirsen patients started on average one year
20 earlier, started steroids.

21 DR. BASTINGS: Over one year earlier.

22 DR. ALEXANDER: Thank you. Dr. Hoffman?

1 DR. HOFFMAN: Richard Hoffman. I just have
2 a general question. It appears that the FDA is
3 suggesting that another placebo-controlled trial
4 will be needed. And I was wondering if eteplirsen
5 is granted accelerated approval, would a future
6 placebo-controlled trial ever be possible?

7 DR. ALEXANDER: Who is that a question for?

8 DR. HOFFMAN: Anybody in the FDA.

9 DR. ALEXANDER: And when you say possible,
10 are you speaking --

11 DR. HOFFMAN: Well, once it receives
12 accelerated approval, it would be available to all
13 patients, and what patients would want to be a
14 placebo patient at that point?

15 DR. BASTINGS: I think this is a very good
16 question. It seems unlikely that if the drug
17 becomes accessible to patients, that anybody would
18 enroll in a future study that is
19 placebo-controlled.

20 DR. ALEXANDER: Dr. Jenkins?

21 DR. JENKINS: Yes, this is John Jenkins. To
22 help address that question, if you recall the

1 applicant stated their trials are ongoing or
2 planned that they consider to be confirmatory.
3 They had some externally controlled trials for
4 eteplirsen in exon 51 amenable patients. They also
5 had a couple of trials in two other exons that are
6 placebo-controlled hoping that if they can show a
7 significant difference in those placebo-controlled
8 trials in other exons, it would help to validate
9 the findings for eteplirsen.

10 So their confirmatory trials are externally
11 controlled for eteplirsen, placebo-controlled for
12 two other exon-skipping patient populations. But I
13 think you raise a good point about -- anytime a
14 product is approved under accelerated approval, or
15 any type of approval, the question of whether you
16 can then do a trial that's placebo-controlled
17 becomes very challenging, particularly in serious
18 and life-threatening diseases where patients may
19 not be willing to be on placebo.

20 DR. ALEXANDER: Thank you. Dr. Onyike and
21 then Dr. Gordon.

22 DR. ONYIKE: Thank you. Chiadi Onyike.

1 Now, I'd just like to take attention to slide 72,
2 if we could pull that up please. Slide 72. And,
3 yes, acknowledging -- this is for Dr. Farkas.
4 Acknowledging that you've looked at converting
5 multiple levels of evidence and converging
6 outcomes, especially on the clinical side, I just
7 wanted to explore for a minute the subset of
8 subjects in the treatment group who seem to have
9 function -- I mean preserved walking, so the ones
10 that are encircled.

11 I just wondered if you had a way -- I know
12 that most of the comparisons that are done with
13 respect to the two groups are based on a visual
14 analysis, at least the way you presented it, on a
15 visual analysis of the trajectories of the slopes.

16 I just wondered if you had some way to
17 quantitatively analyze the trajectories of those
18 slopes and to compare them. And the reason I say
19 that is because your analysis of any extrapolation
20 as to what might be the future of these subjects
21 was based on other sources of data as opposed to
22 direct comparisons. So I just wondered if you were

1 able to do that.

2 DR. FARKAS: Yes, well I guess the first
3 thing, or to pick up on the last part of what you
4 said, is that everything is external, all the
5 comparisons are external. So this was one group of
6 patients that were selected by the applicant, and
7 other sources of information were basically
8 available at the same time.

9 Part of the issue is -- I mean, the FDA had
10 asked for comparison to multiple sets of data, all
11 the data that might be available. So there is no
12 primary comparison to one historical group versus
13 another historical group.

14 But as to your question of numerical
15 comparisons, I think that's an important point, but
16 that's not the way we can analyze studies like
17 this. This is just the truth about historically
18 controlled trials. There's not really going to be
19 an answer in the numbers because we have to account
20 for these other sources of differences between the
21 groups.

22 So one of the key pieces of advice that we

1 give to people is that if there's the opportunity
2 for doing a historically controlled trial for
3 sponsors, but that unless there's a clear
4 difference, kind of an obvious difference, is the
5 answer in the end between the treated patients and
6 the controls, it wouldn't be possible normally to
7 conclude that it was an effect of the drug and not
8 other differences between the patients and the way
9 the study was conducted.

10 DR. ALEXANDER: I'd like to wait one minute,
11 please, for Dr. Gordon and just go to Dr. Romitti
12 if we can, and then we'll come to Dr. Gordon at the
13 close of this section.

14 DR. ROMITTI: Okay. Paul Romitti. So there
15 has been discussion by both the applicant and the
16 FDA about dialogue that's gone back and forth. And
17 in going through the materials and trying to
18 construct my own timeline of all these dialogues,
19 it's just unclear to me when this recommendation
20 from slide 50 of Dr. Farkas' slides was first
21 given.

22 So that slide, as you see there, says the

1 FDA consistently and strongly encouraged the
2 applicant to perform a randomized double-blind
3 control trial. Can you give us the month and the
4 year that recommendation was first made?

5 DR. FARKAS: Well, I mean I have the month
6 and the year somewhere. It's not right in my head.
7 But I would be able to say that -- so the applicant
8 conducted an analysis at about week 48 in the
9 original study 201 and presented those analyses to
10 us in late 2012 or 2013.

11 We were very much concerned that their
12 analysis was not supportable, not scientifically
13 supportable, and were giving them very strong
14 feedback from that point that we thought that would
15 not be convincing data.

16 DR. ALEXANDER: Dr. Bastings?

17 DR. BASTINGS: I think Dr. Dunn has the
18 exact date. Maybe he does. This has been stated
19 on multiple occasions, not just one time, on
20 multiple occasions. Dr. Dunn?

21 DR. DUNN: I have one exact date for you.
22 Keeping in mind that 1, 2, 3, 4, 5, at least 6

1 people in a row here have said, more times than I
2 can count individually to the sponsor, you need to
3 do that. The date that's in front of me right here
4 from Dr. Breder, the primary reviewer of this
5 application, mentions the importance of conducting
6 a placebo-controlled design using multiple fixed
7 doses in phase 3 development, on June 14th of 2011.

8 DR. ROMITTI: Thank you.

9 DR. ALEXANDER: Thank you.

10 Dr. Cohen [sic], final question for this
11 section? I'm sorry, Dr. Gordon.

12 DR. GORDON: This is Mark Gordon, industry
13 representative. So to follow up on the comments
14 from Dr. Farkas and Dr. Bastings, both of you
15 mentioned that the inability to perform the
16 6-minute walk test was an important determinant in
17 the loss of ambulation.

18 You also mentioned that there was some level
19 or element of a subjective component that possibly
20 influenced the function. So my question is both in
21 the sponsor's study and in CINRG, was there any
22 protocol defined definition of the inability to

1 perform the 6-minute walk test?

2 DR. FARKAS: That's an important point. And
3 the protocols from the natural history study were
4 extremely brief, and they didn't specify anything;
5 extremely brief, just several pages.

6 The protocol for the CINRG study is very
7 detailed. It does make mention of a 25-second
8 cutoff for the 10-meter run/walk, but it doesn't
9 specify very clearly actually how or when endpoints
10 will be measured. And I mean we have, you know
11 Dr. McDonald here, and he's been extremely helpful
12 to the FDA, and we've discussed on the phone with
13 his collaborators.

14 To our understanding, it is a subjective
15 discussion the patients and the parents and the
16 investigators do decide at the study visits what
17 test the patient will attempt and which they won't.

18 DR. ALEXANDER: Thank you. I'd like to give
19 the sponsor a chance to respond either or both to
20 that question and any other very brief responses to
21 questions that have been raised, and then we'll
22 move to the open public hearing.

1 MS. RUFF: Thank you very much. We have
2 Dr. McDonald here, who will answer a question about
3 the choice or the decision about 6-minute walk test
4 and loss in ambulation. And then Dr. Kaye would
5 like to just address a comment about when FDA told
6 us about placebo-controlled studies.

7 DR. MCDONALD: My name is Dr. Craig
8 McDonald. I'm director of neuromuscular disease
9 clinics at University of California Davis. And I'm
10 the study chair of the CINRG Duchenne Natural
11 History study. I've been compensated by Sarepta
12 Therapeutics for my time, and I have no direct
13 financial interest in the outcome of today's
14 meeting.

15 I would like to make some a few very
16 important clarifying points here with regard to the
17 definition of loss of ambulation. If I could have
18 the first slide up.

19 The CINRG has a very specific definition of
20 loss of ambulation. We've published multiple
21 studies in peer reviewed journals based on this
22 definition. It's based on a physician assessment,

1 patient and parent report a full-time wheelchair
2 use on a standard CRF, so there's no independent
3 household ambulation or minimal ambulation.

4 This is, when available, corroborated by the
5 loss of the ability to perform the 10-meter
6 walk/run test. That's a very different definition
7 and standard than what I think the sponsor
8 appropriately used in this trial. If I could have
9 the next slide up.

10 The sponsor defines the loss of ambulation
11 as the acquisition of a 6-minute walk distance of
12 zero. And what you see on the left is actually the
13 worldwide available literature on 6-minute walk
14 distance that has been obtained both in placebo
15 arms as well as registries.

16 The data on the right is actually published
17 registry information from Goemans. What's really
18 quite dramatic here is you see that the data is
19 almost superimposable in terms of that obtained by
20 natural history studies and that obtained in
21 placebo-controlled arms of studies.

22 So this really I think addresses the concern

1 about motivational aspects or biases, where we're
2 seeing very similar data. The most important point
3 here is if you look at this definition of loss of
4 ambulation, virtually only about 2 to 3 percent of
5 patients, based on a 6-minute walk distance
6 definition, continue ambulating past the age of 15.

7 If I could have the next slide. This was
8 the CINRG data that was discussed by the sponsor as
9 well as by Dr. Farkas. And what we see here is the
10 patients from the CINRG cohort exon 51 mutations,
11 the 25 percent of patients that Dr. Farkas alluded
12 to there, that's based on a CINRG definition of
13 inability to perform the 6-minute walk test as well
14 as physician and patient determination of full-time
15 wheelchair use.

16 I should point out that this is rather
17 limited data set. It only represents 3 patients,
18 that when you talk about 25 percent, that only
19 represents 3 patients. And what we see in the blue
20 line there is something very different I think with
21 the eteplirsen treated patients. We're seeing,
22 first of all, those patients haven't reached the

1 age of 16 yet. But what we see is 10 of
2 12 patients still walking based on rigorous
3 definition of 6-minute walk distance as the
4 definition.

5 If I could just finish by focusing on rise
6 time, as this has been something that has been an
7 important point made by the FDA. If I could have
8 the next slide up.

9 So rise time and rise ability is really an
10 important prognostic endpoint. If I could have the
11 next slide up. And I think it's important to point
12 out here, there's a matter of definitions. The FDA
13 focuses on the absolute time taken to perform the
14 test. The sponsor, on the other hand, really
15 focuses on the critical importance of the loss of
16 this endpoint in terms of independent ability to
17 perform the test.

18 So the loss of this endpoint as we know it
19 is really what's prognostic. And this is CINRG
20 data here. If we could pull up the slide actually
21 on this screen. Slide up, please.

22 This is actually CINRG data on rise ability

1 and loss of rise ability and its prognostic
2 importance for loss of ability to ambulate. And
3 what you see here actually in the CINRG data is
4 it's not the absolute value of rise time that's of
5 prognostic value, it's the loss of the rise
6 ability.

7 So what you see there in the red are those
8 patients who have completely lost the ability to
9 rise independently. And virtually 50 percent of
10 those patients have lost the ability to ambulate
11 within 12 months. And in fact, 70 percent of those
12 patients lose the ability to ambulate at 24 months.

13 If you look at purple and blue lines at the
14 top, that shows the survival curves when rise time
15 is less than 5 seconds, 5 to 10 seconds, or greater
16 than 10 seconds. The actual rise time is not a
17 prognostic value. The importance is the loss of
18 rise ability independently.

19 If we could just show the next slide, this
20 shows how the sponsor has actually focused on loss
21 of rise ability independently. And what you see
22 there is 3 years out a high percentage of

1 eteplirsen treated patients have maintained the
2 rise ability, a very small percentage of the
3 external controls. But I think what's even more
4 striking is when you look at years 1, 2 and 3, the
5 patients that have lost rise ability have still
6 maintained the ability to ambulate over a prolonged
7 period of time. Thank you.

8 DR. ALEXANDER: Thank you very much. I do
9 want to move on to the portion of the open public
10 hearing.

11 (Applause.)

12 DR. ALEXANDER: Thank you very much.

13 Dr. Bastings, and then we'll move on to the
14 open public hearing.

15 DR. BASTINGS: I would like the applicant to
16 bring back the slide comparing the Kaplan-Meier
17 curve from the eteplirsen patients to the CINRG
18 database that they just showed.

19 DR. ALEXANDER: Can the sponsor please
20 project that slide?

21 DR. BASTINGS: Yes. I would like to point
22 out that that slide is totally misleading, because

1 most of the eteplirsen patients shown in blue here
2 have not reached the age 15. So there is just no
3 way to make that sort of comparison because they
4 simply have not reached that age yet.

5 **Open Public Hearing**

6 DR. ALEXANDER: Thank you. We will have
7 more time for discussion during the question period
8 after the open public hearing.

9 Both the Food and Drug Administration and
10 the public believe in a transparent process for
11 information-gathering and decision-making. To
12 ensure such transparency at the open public hearing
13 session of the advisory committee meeting, FDA
14 believes that it is important to understand the
15 context of an individual's presentation.

16 For this reason, FDA encourages you, the
17 open public hearing speaker, at the beginning of
18 your written or oral statement, to advise the
19 committee of any financial relationship that you
20 have with the sponsor, its product, and if known,
21 its direct competitors.

22 For example, this financial information may

1 include the sponsor's payment of your travel,
2 lodging, or other expenses in connection with your
3 attendance at the meeting. Likewise, FDA
4 encourages you at the beginning of your statement
5 to advise the committee if you do not have such
6 financial relationships.

7 If you choose not to address this issue of
8 financial relationships at the beginning of your
9 statement, it will not preclude you from speaking.

10 The FDA and this committee place great
11 importance on the open public hearing process. The
12 insights and comment provided can help the agency
13 and this committee in their consideration of the
14 issues before them.

15 That said, in many instances and for many
16 topics, there will be a variety of opinions. One
17 of our goals today is for this open public hearing
18 to be concluded in a fair and open way where every
19 participant is listened to carefully and treated
20 with dignity, courtesy, and respect. Therefore,
21 please speak only when recognized by the
22 chairperson. Thank you for your cooperation.

1 Will speaker number 1 please come to the
2 podium and introduce yourself? Please state your
3 name and any organization you are representing for
4 the record.

5 MR. FITZPATRICK: Good afternoon, and thank
6 you for allowing me --

7 DR. ALEXANDER: Can you please speak a
8 little more directly into the microphone?
9 Microphone on, please. We need audio at the
10 podium.

11 MR. FITZPATRICK: Good afternoon, and thank
12 you for the opportunity to address the advisory
13 panel this afternoon. My name is Mike Fitzpatrick.
14 I represent the 8th Congressional District of
15 Pennsylvania.

16 I want to begin by thanking you for holding
17 this hearing, as well as for the agency's ongoing
18 commitment to use its full range of tools and
19 authorities to expeditiously review candidate
20 therapies for rare but devastating diseases, like
21 Duchenne muscular dystrophy.

22 I'm a member of the Congressional Rare

1 Disease Caucus, and I've discussed and advocated
2 for funding and research opportunities for a number
3 of medical conditions, many of which have
4 connections to my district in Bucks County,
5 Pennsylvania.

6 That connection for Duchenne muscular
7 dystrophy is 15-year-old Jake Wesley, who suffers
8 from this terrible disease. Sadly, like so many in
9 Jake's position, the decline of his health has been
10 precipitous. The risk of doing nothing for someone
11 like Jake is unacceptable. I've seen his disease
12 progress year after year, robbing him along the way
13 of any sense of his own independence, and Jake
14 deserves better.

15 There is a path forward, one which could
16 alter the lives of all Duchenne patients in a very
17 positive way, giving them a chance to live a
18 longer, better life. As you know, in recent years
19 the Congress along with the FDA have made
20 tremendous progress toward, through the Food and
21 Drug Administration Safety and Innovation Act,
22 providing new therapies intended to treat persons

1 with life-threatening and severely debilitating
2 illnesses, especially where no satisfactory
3 alternative therapy exists, in this case Duchenne.

4 The accelerated approval pathway outlined in
5 Section 901 of the Act, allows demonstrably safe
6 therapies that treat an unmet medical need, and
7 appear to be efficacious, even with some
8 uncertainty, to avoid the years of regulatory
9 barriers and become accessible earlier to patients
10 who otherwise have no other option.

11 FDA has been most successful at applying
12 flexibility in oncology and HIV/AIDS to speed
13 patient access to apparently safe treatments, but
14 the need and the opportunity to adopt innovative
15 and flexible approaches to the review of rare
16 disease drugs has never been greater than it is
17 today. Children like Jake are waiting.

18 That is why today my urgent call is echoed
19 by 108 other bipartisan members of Congress who
20 have joined me in writing to Dr. Janet Woodcock,
21 and I would ask, with the panel's permission, that
22 this letter, signed by 108 of my colleagues, be

1 entered as a part of this record today.

2 I remain committed to ensuring --

3 (Applause.)

4 MR. FITZPATRICK: -- and it's difficult to
5 get 108 of my colleagues to agree -- [mic off].

6 DR. ALEXANDER: Thank you very much.

7 (Applause.)

8 Will speaker number 2 please come to the
9 podium and introduce yourself. Please state your
10 name and any organization you are representing for
11 the record.

12 MS. JURACK: Yes. Good afternoon,
13 committee. My name is Karen Jurack, and I have not
14 been financially compensated by anyone to be here
15 today. I am the mother of a soon to be
16 15-year-old. His name is Joshua. He has been
17 battling Duchenne muscular dystrophy for 10 years
18 now. He was diagnosed at 4 and a half with a
19 deletion mutation in genes 49 and 50, making him a
20 perfect candidate for exon 51 skipping therapies.

21 Joshua lost his ability to walk at age 9,
22 had spinal fusion surgery at age 13, and since the

1 surgery Joshua has lost a great deal of his arm
2 mobility. He can no longer feed himself, which is
3 a distressing loss of independence.

4 As a parent, it's very difficult to watch
5 your child continue to get weaker every day. You
6 feel absolutely helpless, and you never believe
7 you're doing enough to help your child get better.
8 Because steroids alone are not sufficient, I
9 constantly check the availability of clinical
10 trials for Joshua. And unfortunately, in the
11 majority of cases, he did not qualify for those
12 studies because he has not been ambulatory for
13 several years.

14 When I found the Sarepta eteplirsen study, I
15 was delighted because the study parameters were
16 such that we could potentially qualify. In March
17 2015, Joshua and I went to Johns Hopkins and tried
18 to take part in this trial, however he was excluded
19 because he could not lift a glass of water to his
20 mouth. We were devastated by this news.

21 In the fall of 2015, as part of their
22 medical training, Joshua was interviewed by some

1 medical students. One of the questions he was
2 asked was what he worries most about for the
3 future. I fully expected him to say college, but
4 very calmly and soberly said he was worried most
5 about his lungs and heart failing him. This shows
6 the reality in which he lives, the thoughts of his
7 mortality that totally consume his every being.

8 Joshua has a brilliant mind, however he is
9 trapped in a body that doesn't work. He's always
10 been an exceptional child. He's an overachiever in
11 academics, scouting life, and unfortunately with
12 Duchenne. Joshua's muscular dystrophy seems to be
13 progressing at a faster rate than most of his
14 peers. Now more than ever time is of the essence
15 for our family.

16 Despite his physical decline, Joshua remains
17 optimistic and determined to meet his goals in
18 life. For example, he'll be completing his Eagle
19 Scout service project this coming Saturday.

20 Although Joshua was not included in the
21 trial for eteplirsen, we would welcome the
22 opportunity to have access to this drug therapy.

1 For Joshua, success would include gaining some
2 strength in his arms where he could once again feed
3 himself and not be secluded from others during
4 school lunch. If there's the slightest chance exon
5 skipping could improve and prolong his quality of
6 life, we would be thrilled with the prospect.

7 Exon skipping therapies offer our family and
8 many like ours a tangible hope that a viable option
9 for slowing the progression of Duchenne is at hand.
10 With exon 51 skipping therapies, Joshua's future
11 may become more of a reality. Thank you for your
12 time.

13 (Applause.)

14 DR. ALEXANDER: Thank you very much. Will
15 speaker number 3 please come to the podium and
16 introduce yourself. Please state your name and any
17 organization you are representing for the record.

18 MR. BASILE: My name is Carlo Basile, and
19 Make Duchenne History Coalition paid for my trip
20 today to be here. I thank you for the opportunity
21 to speak today. Again, my name is Carlo Basile.
22 I'm chief secretary to Massachusetts Governor

1 Baker. He wants everyone in the Duchenne family to
2 know he stands behind us.

3 As one public servant to another, I want to
4 remind you that your job's here to serve the
5 people. But before that, before I go on -- and
6 everything I say is as a parent and not as the
7 governor's chief secretary -- I find it insulting
8 that someone would tell me or these people behind
9 me that you understand. Unless you have a child
10 that has muscular dystrophy, you don't understand.

11 Today, your job is to serve all Americans
12 who are living with Duchenne, have lost one to
13 Duchenne, or yet to be diagnosed or born with
14 Duchenne. To help inform your deliberations, I
15 would like to make two important points lacking in
16 the FDA's framing of the vote questions. These
17 points are important to ensuring you should uphold
18 the integrity of the vote process.

19 First, the FDA states in framing the vote
20 questions that, quote, "The intent of the statutory
21 requirements is to reduce the chance of incorrect
22 conclusion that a drug is effective when in fact it

1 is not effective."

2 Earlier today, Christine McSherry mentioned
3 this is type 1 error. I'm disappointed that there
4 is no similar mention in FDA's briefing materials
5 about type 2 errors, where the FDA fails or delays
6 approval of a drug that is in fact effective. I
7 would like the FDA to address after the open public
8 hearing how they are accounting for type 2 errors
9 today.

10 Every day with my son, I witness the human
11 costs would be making type 2 error Duchenne in the
12 Duchenne population. In the past year alone,
13 Carlo Jr. has followed the natural history of
14 Duchenne and lost the ability to carry his
15 backpack, run with his brother at a natural speed,
16 bouncing a basketball, amongst other things. And
17 the next three years, I don't even want to imagine
18 what he'll be facing.

19 My second point is, the FDA emphasizes
20 upholding statutory standards of approval. Yes, a
21 drug must demonstrate effectiveness to be approved.
22 But according to the regulations, the FDA also must

1 apply the broadest flexibility in applying the
2 statutory standards for the drugs that treat
3 life-threatening, severely debilitating diseases,
4 especially where no alternative therapy exists.

5 Just the context, the Congress passed the
6 FDASIA 2 -- [mic off].

7 DR. ALEXANDER: Thank you very much for your
8 comments.

9 (Applause.)

10 DR. ALEXANDER: And I'd like to ask if
11 everyone would mind holding their applause until
12 the end. We have about 52 speakers that we'll be
13 hearing from and would just request that you hold
14 your applause until the final speaker. The next
15 speaker is speaker number 4. If you could please
16 come to the podium and state your name and any
17 organization that you're representing for the
18 record.

19 MS. MINER: My name is Malanie Miner. My
20 travel was paid for by Make Duchenne History
21 Coalition. My 17-year-old son, Cobi, has Duchenne.
22 By the time Cobi was 3 years old, we had a feeling

1 something just wasn't quite right. By the time he
2 was 5, we got a diagnosis of Duchenne.

3 During a visit to Cincinnati Children's
4 Hospital in 2011, we were told that Cobi could be a
5 candidate for a new drug trial, the same trial that
6 is under review today. An initial pre-screening
7 showed that he met all of the strict requirements
8 for this trial. At this time, Cobi was ambulatory
9 and relatively healthy for an 11-year-old with
10 Duchenne.

11 Unfortunately, there was a delay in the
12 start of the trial, and by the time Cobi was
13 screened in July of 2011, at age 11, his baseline
14 walk test had declined so much that he no longer
15 met the study's strict trial criteria. We were
16 devastated by the decline at only 11 years old.

17 Cobi broke his leg soon after and never
18 walked again. It is very bittersweet for me to be
19 here and see the boys who have been on eteplirsen
20 since 2011 and compare them to my son. Five years
21 ago, Cobi was just like them, but now the
22 difference is stark and painful.

1 A few weeks ago, Cobi contracted pneumonia.
2 He suffered from septic shock. During a prolonged
3 stay in the ICU, we heard more devastating news.
4 Cobi is now in heart failure.

5 In their briefing documents, FDA states that
6 the loss of ambulation ranges from 8 to 18 years
7 old. This is not what I see in the hundreds of
8 people I know in the Duchenne community. There are
9 a lot of 9 and 10-year-olds with Duchenne dying,
10 yet there was no mention of that in the briefing
11 documents.

12 There are a lot more boys like Cobi who have
13 Duchenne dying in their late teens than there are
14 ones walking until their late teens, as described
15 in the FDA's briefing documents. My son is the
16 true placebo and a true natural history of
17 Duchenne, the eteplirsen boys are not.

18 In summary, Cobi would be with us today, but
19 because of his heart failure he could not attend.
20 And if eteplirsen is approved, I believe that it
21 could still help Cobi. If he had access to it, it
22 could still potentially improve and prolong his

1 life.

2 (Applause.)

3 DR. ALEXANDER: Thank you for sharing your
4 experience. Will speaker number 5 please come to
5 the podium and introduce yourself? Please state
6 your name and any organization you are representing
7 for the record.

8 MS. McSHERRY: Thank you, Malanie.

9 This is Christine McSherry. Jett Foundation
10 and Make Duchenne History Coalition provided the
11 funds for my travel this morning. Just to get to
12 Dr. Bastings point, I just want to remind FDA and
13 the panel that one of the reasons why the parents
14 came to you before the data was presented is
15 because we saw those signs that the drug was
16 working, and therefore a placebo-controlled trial
17 would be not feasible. I just wanted to make the
18 comment.

19 But I'd like to talk to you today as mother
20 and advocate. You did hear from me this morning in
21 the Patient Reported Outcome project. My son Jett
22 was diagnosed when he was 5, today he's 20. Jett

1 took his last steps at the age of 13 despite being
2 on 40 milligrams of daily deflazacort. It's a high
3 dose. Last year, Jett enrolled in a limited
4 ambulation safety study for eteplirsen, and in my
5 view, he has stabilized and some things have gotten
6 better, and you've heard about those things.

7 But that's not what I'm here to talk to you
8 about today. I want to make sure that the panel
9 understands what all of us are advocating for.

10 We're asking the FDA to approve a drug that's
11 demonstrated consistently efficacy on multiple
12 measures.

13 We're asking that the agency utilize
14 flexibility in the tools it has to approve a
15 remarkably safe drug while pursuing confirmatory
16 trials. If as a result of those trials, it becomes
17 clear that eteplirsen is not working, we will stand
18 behind the agency should it decide to remove it
19 from the market. You see, we only want drugs that
20 work.

21 We're not asking the FDA to lower its
22 standards or grant wishes to a desperate community.

1 We are a community that is well-informed, a
2 community that funds and drives research, a
3 community that writes draft guidance for drug
4 development. We are here in large numbers because
5 eteplirsen has met the safety and effectiveness
6 standards for accelerated approval.

7 As a mother and an advocate, I'm surprised
8 and disappointed by the briefing documents released
9 in January, even more so by those released last
10 week. What's clear from those documents is that
11 the Division of Neurology is seeking to send a
12 message to Sarepta, industry, and the rare disease
13 community; a message that we will only accept a
14 large randomized, double-blind, placebo-controlled
15 trial, no matter what the severity or the disease.

16 We were very encouraged when FDA issued the
17 DMD draft guidance, which included historically
18 controlled data as a potential pathway for
19 approval. Now to see the FDA distancing itself so
20 aggressively from that guidance is extremely
21 disheartening.

22 If FDA really wanted a large placebo-

1 controlled trial, why did the neurology division
2 guide the company to start a single-arm study in
3 the 4 to 6-year-olds who would age into that study?
4 There's virtually no one left who is drug naïve to
5 enter into such a trial. We expect the FDA to
6 provide clear, viable regulatory pathways towards
7 approval. The goal post cannot be changed.

8 Twenty-five years ago, FDA utilized
9 accelerated approval to save a generation of young
10 men dying of AIDS. Today the agency has another
11 generation of young men that they could also save
12 from Duchenne. It's time for the neurology
13 division to join oncology and the anti-viral
14 divisions, among others, follow [mic off].

15 (Applause.)

16 DR. ALEXANDER: Thank you. Will speaker
17 number 6 please come to the podium and introduce
18 yourself? Please state your name and any
19 organization you are representing for the record.

20 MR. WILLIAMS: My name is Brady Williams.
21 My friend, Bryson Foster, a former NBA goodwill
22 ambassador, said if we can find a cure, we can save

1 people's lives. We have not found a cure, but we
2 are saving lives with this drug. The average boy
3 stops walking with DMD around 10 years old, but I
4 am still going strong, nearly 15 years old.

5 MS. WILLIAMS: My name is Martha Williams,
6 and the Make Duchenne History Coalition arranged
7 for our travel. This is my son Brady standing here
8 with me today. He walked in at 14 years and
9 11 months old. He's still able to walk
10 independently, other than long distances, and
11 that's quite an accomplishment for any boy Brady's
12 age with Duchenne muscular dystrophy.

13 Brady's steroid usage has only changed once
14 in the 9 and a half years that he's been on it.
15 The change was simply due to the recommended dosage
16 for his weight, and he's still under-dosed for his
17 weight. He's been off and on physical therapy with
18 many extended breaks.

19 The therapy consists of 1 to 2 times a week,
20 in the pool and on land, and there's been times
21 that we've had a break or more from therapy. At
22 home we do some stretches, and he wears night

1 splints a few nights a week, but this is the
2 typical regimen for a boy with DMD, and this is by
3 no means to be considered an intense treatment.

4 Although Brady still falls on occasion,
5 these falls have gone from almost a daily
6 occurrence to 1 to 2 times a month. It's a relief
7 to know that we don't have to fear a fall every
8 time he's out of our sight. At MDA camp, Brady is
9 one of the only boys in his age range with Duchenne
10 muscular dystrophy still able to walk.

11 He can get out of the pool and jump in from
12 the side independently. He can keep his head above
13 water for 10 minutes at a time, and before he was
14 on the medication, he would sink immediately below
15 the water because he didn't have enough strength in
16 his neck to hold himself up.

17 Brady's lung function continues to be good,
18 and his heart is functioning normally, which was
19 confirmed with his recent cardiac MRI. Although
20 Brady's ability to walk is reassuring us that this
21 treatment is working as intended, him having good
22 lung and heart function is more than we could hope

1 for at his age with this disease.

2 Brady has been infused weekly for 5 and a
3 half years without missing one single dose. Other
4 than the occasional bruise, which would be expected
5 with any needle, he has had zero side effects from
6 this medication.

7 We have no doubt without the treatment,
8 Brady would have been confined to a wheelchair full
9 time, and we would not see the heart and lung
10 function he has from being in this trial. This
11 medication is safe, it's effective, it's working.

12 Brady along with these other boys have
13 endured more than most do in a lifetime. The
14 approval of this medicine is essential to ensure
15 his continued stabilization for his heart and lungs
16 and reduce the overall decline for him and the
17 others afflicted with Duchenne muscular dystrophy.
18 Thank you.

19 (Applause.)

20 DR. ALEXANDER: Thank you very much. Once
21 again, please hold your applause until the final
22 speaker has spoken.

1 Will speakers number 7 please come to the
2 podium and introduce yourselves? Please state your
3 names and any organization you're representing for
4 the record.

5 MR. DUNNE: My name is Chris Dunne. My wife
6 and I are the parents of Ryan, a 12-year-old boy
7 who was born with Duchenne muscular dystrophy.
8 Being a parent of a child with DMD means that there
9 are a lot of milestones ahead. In the not too
10 distant future, Ryan will lose the ability to walk
11 and will be forced to rely on a wheelchair.

12 After that, Ryan will lose the ability to go
13 to the bathroom on his own, and then he will not be
14 able to feed himself. Finally, he will lose the
15 ability to breathe on his own, and he will die
16 before he has a chance to truly live.

17 Those are just a few challenges that Ryan
18 has to look forward to. He already has to live
19 with the fact that he cannot play with his peers,
20 that he has to struggle in school, that as a fifth
21 grader he is smaller than most second graders
22 because he has to take steroids all of his life.

1 In 2014, Ryan had the opportunity to become
2 part of the eteplirsen trial. We jumped at the
3 chance. Ryan did not jump because he had lost the
4 ability when he was 9. Ryan's been receiving
5 eteplirsen for 72 weeks without any adverse events
6 or side effects. Time has always been the worst
7 enemy of children with DMD. Eteplirsen has however
8 given us a reason to hope.

9 The people who see Ryan daily, teachers,
10 therapists, friends and family, notice that things
11 are better, less falls, more stamina, greater
12 strength, and even a regained ability to jump. All
13 this on a steroid dosage that is less than half of
14 the standard 0.9 milligrams per kilogram.

15 Not a single person here believes that
16 eteplirsen is the cure for DMD, but no one can deny
17 that it is a valuable treatment. Eteplirsen is as
18 important to boys with DMD as insulin is for
19 diabetics. We know what will happen if our
20 children are denied this life-saving medicine, a
21 steady downward progression ending in an untimely
22 death. You can change that today.

1 (Applause.)

2 MR. PASCHAL: Hello. My name is Kris
3 Paschal, and I am a father of a 13-year-old boy,
4 Samuel, with Duchenne muscular dystrophy. Our son
5 Sam and our family moved to England in 2011 because
6 we didn't have much faith in the FDA's ability to
7 take up orphan drugs, and thought the best
8 opportunity would be in Europe where Sam
9 participated in the drisapersen trial. We have
10 since repatriated and become a part of the
11 eteplirsen trial.

12 The difference between the two have and
13 night and day in efficacy. Sam had no less than
14 6 times when the protein in his urine on the other
15 drug was elevated. He has never had that since
16 we've been on eteplirsen, so the efficacy is night
17 and day.

18 I'd like to remark that this morning, we
19 spoke of the law behind this, and I think Estes
20 Kefauver and Oren Harris would be appalled at the
21 process we are going through. It was meant to
22 protect the consumer who was uneducated from the

1 unscrupulous drug companies. I think today we have
2 clear evidence that we have an educated consumer
3 here who is asking that you seriously consider this
4 given the merits of the drug.

5 (Applause.)

6 DR. ALEXANDER: Thank you very much. Will
7 speaker number 8 please come to the podium and
8 introduce yourself? Please state your name and any
9 organization you are representing for the record.

10 DR. FLETCHER: My name is Sue Fletcher. I'm
11 a researcher with Murdoch University in Australia.
12 We pioneered PMOs for exon skipping and developed
13 the eteplirsen sequence license to Sarepta, I
14 therefore have a financial interest in the outcomes
15 of today. I am also a consultant to Sarepta.

16 In this presentation, I comment on three
17 issues: the validity of Western blot to assess
18 dystrophin expression, how much dystrophin is
19 normal, and lessons learned from the mdx mouse.
20 Western blotting is a useful technique for
21 assessing protein quantity and quality and
22 comparing between samples within a study.

1 At this time, no universal dystrophin
2 reference standard is available, and therefore,
3 each study must stand alone and be accompanied by
4 valid reference standards. This means that we
5 cannot equate dystrophin expression in one study
6 with data from another that uses a difference
7 reference and different protocols.

8 Dystrophin levels cited in Duchenne and
9 Becker are mostly from early reports relying on
10 technologies not consistent with accurate
11 quantitation. If signals from the test and
12 reference samples do not all lie within the linear
13 range, quantitation is not possible.

14 A black image band from a blot means pixels
15 are saturated, and therefore using current
16 technology are interpreted as infinity. I present
17 a blot showing muscle protein expression in
18 non-dystrophin subjects; dystrophin in samples D
19 and E differ by approximately 9-fold. It is
20 obvious that such a broad range in dystrophin
21 levels would have implications for the analysis of
22 de novo dystrophin expression in samples.

1 The dystrophin Western blot data presented
2 by Sarepta demonstrates greater scientific rigor
3 than is evident in any other published reports I
4 have studied. Dystrophin expression in untreated
5 DMD muscle is reported as average 0.08 percent
6 relative to the reference sample used, and that in
7 muscle from treated patients 11-fold higher.

8 Use of a different reference sample and/or
9 protocol would deliver different numbers, but it is
10 the increase in dystrophin expression after
11 eteplirsen treatment that is the important outcome.
12 If the 180-week dystrophin analysis of 0.9 was
13 relative to the higher dystrophin on our
14 immunoblot, that is sample E, then comparison to
15 sample E would yield a figure of 8.1 percent. I
16 use this data to illustrate it is not the actual
17 number that is important, it is the increase in
18 dystrophin after treatment.

19 My extensive experience as a scientist
20 working on mdx mice has yielded key findings
21 relevant to the discussion today. Systemic PMO 23
22 treatment in mdx mouse induces de novo dystrophin

1 in all muscles, which correlates with improved
2 function. PMO M23 [ph] treatment initiated in
3 newborn mice prevents the onset of dystrophin
4 pathology.

5 In closing, based on all our research and
6 the data presented by Sarepta, it is evident that
7 eteplirsen induces de novo dystrophin expression.
8 I believe that it is reasonable to conclude that
9 the increase in dystrophin is responsible for the
10 clinical benefit reported in the patients. Thank
11 you.

12 (Applause.)

13 DR. ALEXANDER: Thank you very much. Will
14 speaker number 9 please come to the podium and
15 introduce yourself? Please state your name and any
16 organization you are representing for the record.

17 DR. BYRNE: Mr. Chairman and the committee,
18 my name is Barry Byrne. I'm a clinician scientist
19 with experience caring for boys with Duchenne
20 muscular dystrophy as a pediatric cardiologist.

21 I'm a member of the FDA committee on
22 cellular tissue and gene therapies advising CBER,

1 and I have no financial interest in the outcome of
2 this meeting. I've served as a scientific advisor
3 to Sarepta, and our center is a hub site for the
4 PROMOVI phase 3 study. Most importantly for the
5 discussion today, I am privileged to care for one
6 of the patients in the 201/202 study who is here to
7 share their experience as a participant of the
8 pivotal eteplirsen study under review.

9 My objective in these brief comments is to
10 draw a parallel between the study of eteplirsen and
11 a related pivotal study leading to the marketing
12 approval of Myozyme for Pompe disease. Our center
13 was the lead enrolling site of the Myozyme studies,
14 and I think a comparison to this small study using
15 historical cohort is relevant to the discussion
16 today.

17 The primary endpoint of the Myozyme study
18 was ventilator-free survival. The secondary
19 endpoint of overall survival was compared to an
20 only 2 percent survival rate in the historical
21 cohort. Based on the comparison to this historical
22 cohort, Myozyme was approved for commercial use

1 when the initial findings showed overall improved
2 survival. After 4 years of treatment, 44 percent,
3 or 7 of the 16 subjects were alive without assisted
4 inhalation.

5 In comparison, the clinical endpoint of
6 functional ambulation is an equally critical
7 important endpoint in Duchenne. The importance of
8 this type of binary endpoint is often emphasized by
9 the agency and experts in the field. I think that
10 the finding of 83 percent of eteplirsen study
11 participants who are ambulant after 4 years to
12 therapy compared to the finding of 44 percent
13 survival in the Myozyme study should not be
14 overlooked.

15 Movement and freedom of ambulation is really
16 life sustaining for a boy with Duchenne, and the
17 open-label Pompe studies relied on historical
18 cohorts since we accept that pediatric studies
19 require a prospect for direct benefit, therefore
20 prohibiting a contemporary placebo control.

21 So I think Sarepta has designed and
22 conducted the 201/202 studies with these important

1 principles in mind, and they've been diligent as a
2 sponsor of the studies under consideration today.
3 Although this is a small study, the effect is in
4 fact well controlled given the constraints of
5 pediatric rare disease research. And based on
6 these observations of my patient in the study and
7 in the light of the findings today, I strongly
8 believe eteplirsen meets the standard for
9 substantial evidence of effectiveness and warrants
10 approval in boys with Duchenne muscular dystrophy.
11 Thank you.

12 (Applause.)

13 DR. ALEXANDER: Thank you very much. Will
14 speaker number 10 please come to the podium and
15 introduce yourself? Please state your name and any
16 organization you are representing for the record.

17 DR. GOTTSCHALK: Hi, I'm Dr. Laura
18 Gottschalk speaking on behalf of the National
19 Center for Health Research. I received my PhD from
20 Johns Hopkins School of Medicine. Our center
21 scrutinizes medical data and provides objective
22 health information to patients and providers. We

1 do not accept funding from pharmaceutical
2 companies, and I have no conflicts of interest.

3 We agree that FDA should get safe and
4 effective new treatments to patients as quickly as
5 possible, especially for devastating disease such
6 as Duchenne. We were hoping for persuasive data on
7 eteplirsen, but with only 12 patients, inadequate
8 control groups, and variation in disease
9 progression, approval would only be appropriate if
10 there is very clear benefit. Sarepta was warned
11 about this in advance.

12 Unfortunately, the data do not meet a
13 scientific standard of evidence of effectiveness.
14 While there was an increase in dystrophin, the
15 Western blot shows a total amount of protein below
16 what is estimated to be clinically significant, and
17 a 6-minute walk test was fraught with problems.
18 After less than half a year, Sarepta eliminated
19 placebo controls for a drug intended for lifelong
20 use. It became an open-label study, which could
21 influence the walk test results.

22 There are problems with the historical

1 controls used such as evidence that boys in the
2 control group had little incentive to comply with
3 the walk test, and so some were mislabeled as
4 non-ambulatory. Two of the patients did very
5 poorly on the drug. Sarepta assumes that their
6 early loss of ambulation was related to treatment,
7 but this hasn't been proven. Any one of these
8 problems undermines the study results, but to have
9 all these problems and others is simply
10 unacceptable.

11 U.S. law requires evidence of safety and
12 effectiveness. The burden of proof lies with
13 Sarepta. If this drug actually works, then Sarepta
14 has failed itself, the patient, and their families
15 by not conducting a better study that could provide
16 convincing evidence showing it works.

17 Since 2014, Sarepta has been enrolling
18 patients into a larger study, more than 100 boys,
19 but none of those results were provided to the FDA
20 for this meeting. Why not? Even 40 more patients
21 would provide better evidence and the results show
22 clear benefits.

1 Sarepta should have provided the additional
2 data to FDA to examine and provide to this advisory
3 committee. That's how the process works. This
4 committee should not make a decision based on
5 evidence that has not been vetted by the FDA.

6 You're hearing from many patients and family
7 members today who believe in this drug. Your role
8 on the advisory committee is to pressure the
9 company to provide scientific evidence before
10 approval, not to pressure the FDA to ignore the
11 lack of scientific evidence.

12 Your decision today will send a message
13 about whether scientific standards should matter to
14 the FDA. I am very sorry to say that approval of
15 eteplirsen based on today's data would set a
16 dangerously low bar for drugs in the future.

17 We all want an effective drug for Duchenne.
18 I strongly urge the FDA and Sarepta to work
19 together as quickly as possible to prove whether or
20 not eteplirsen is that drug.

21 Treatments for rare diseases can be proven
22 on small samples but not based on 12 patients in a

1 poorly designed study with ambiguous results.

2 Thanks.

3 DR. ALEXANDER: Thank you. Will speaker
4 number 11 please come to the podium and introduce
5 yourself? Please state your name and any
6 organization you are representing for the record.

7 DR. LOWES: I would like to disclose that my
8 trip was paid for by the Make Duchenne History
9 consortium, and I am involved in the ongoing
10 Sarepta trials. My name is Linda Lowes, and I am
11 the lead therapist on the eteplirsen trial, which
12 means that along with Lindsay Alfano, I collected
13 all of the trial outcome measures.

14 I have been a physical therapist for over
15 20 years, and I am also a PhD trained researcher.
16 I would like to speak to concerns about the
17 administration of the functional outcome measures.

18 The briefing document questioned whether the
19 administration of the outcome measures were
20 identical in this trial and the historical control
21 group. As a researcher, I understand the issues
22 surrounding functional outcome measure performance.

1 To raise the stability and quality of clinical
2 trial outcome measures, a group of international
3 experts formed the Adam [ph] training group several
4 years ago. As a member of this group, I have
5 trained evaluators for almost every clinical trial
6 in DMD, including GSK, PTC, Eli-Lilly for DMD,
7 Biomarin, FibroGen, and others.

8 By establishing inter-rater reliability, our
9 training group can ensure consistent training. We
10 go to individual sites to establish reliability
11 with the evaluators and perform quality reviews on
12 video assessments from trials and perform quality
13 reviews on blinded trial data.

14 The lead author on the publication from the
15 Italian natural history study, Elena Mazzone, is a
16 member of our training team. This means that Elena
17 and I present identical trainings on how to conduct
18 functional outcome measures, including when to stop
19 administering the test. We have trained evaluators
20 worldwide, including in Italy and Belgium, as well
21 as at the CINRG sites.

22 I can assure the committee that consistent

1 instructions and encouragement designed to achieve
2 maximum effort are given on every test, regardless
3 if the boy is a clinic patient, in a natural
4 history study, or part of a clinical trial.

5 One of the voting questions is whether
6 decisions to administer the 6-minute walk versus
7 conclusions that the patient could no longer walk
8 were sufficiently objective to allow for a valid
9 comparison. I would like to also alleviate this
10 concern.

11 In the 2011 Italian Natural History
12 publication, the definition given for two boys who
13 were non-ambulant was that they lost the ability to
14 complete the 6-minute walk test but were still able
15 to take a few steps. Able to take more than a few
16 steps is extremely permissive cutoff for being
17 considered ambulant.

18 In comparison, you have been watching the
19 boys on eteplirsen walk up to the podium.
20 Differences of opinion is one explanation of why
21 boys continue to perform assessments longer than
22 the other boys. Superior ability is another. I

1 can personally attest to the quality of my data
2 that you saw presented, and I encourage you to
3 approve the use of eteplirsen.

4 (Applause.)

5 DR. ALEXANDER: Thank you very much. Will
6 speaker number 12 please come to the podium and
7 introduce yourself? Please state your name and any
8 organization you are representing for the record.

9 DR. WAGNER: Good afternoon. My name is
10 Dr. Kathryn Wagner, and I have no financial
11 interest in the outcome of these proceedings. I am
12 a neurologist at the Johns Hopkins School of
13 Medicine and director of the Center for Genetic
14 Muscle Disorders at Kennedy Krieger in Baltimore,
15 Maryland.

16 I have cared for boys and young men with
17 Duchenne for over 15 years. I have 2 patients who
18 participated in the 201/202 study, 4 subjects in
19 the current 301 study, and 3 subjects in the
20 current advanced stage 204 study. None of these
21 9 boys has experienced any drug-related side
22 effects. They are all doing extremely well with

1 their disease.

2 I cannot say that eteplirsen has definitely
3 benefited every boy, but it has benefited most
4 boys. Duchenne is a profoundly disabling and fatal
5 condition without exception. After the age of 13,
6 there's a progressive downward decline.

7 Individual measurements such as the 6-minute
8 walk test may have small day-to-day variabilities,
9 but the course of the disease is consistently
10 downward in the teenage years. Clinically, we
11 rarely see a teenager remain stable over 6 months,
12 and never over 2 years.

13 Yet to highlight just one subject in the 201
14 trial, 006, his 6-minute walk test has remained
15 stable over 4 years with values of 355, 329, 359,
16 332 meters. He is now over 14 years old and still
17 able to rise from the floor. He had no dystrophin
18 at baseline and now has 20 percent dystrophin
19 positive fibers, and 2.47 percent of normal levels
20 by Western blot.

21 If I were this patient's physician, I would
22 see the stabilization of function over years and

1 want the option to prescribe eteplirsen.

2 Muscular dystrophy physicians routinely
3 monitor timed function tests and weigh the risks
4 and benefits of drugs for our patients. We
5 prescribe corticosteroids and follow the rise from
6 floor, run time and/or walk distance, while
7 monitoring the multiple side effects to behavior,
8 bone, and weight, among others. We discuss our
9 findings with the family with whom we make informed
10 decisions whether to continue, reduce, or withdraw
11 a drug.

12 With corticosteroids, we see much less
13 stabilization of function and much more side
14 effects than what has been demonstrated with
15 eteplirsen. From experience with corticosteroid
16 management, the physicians, families, and
17 communities are well-equipped to make individual
18 assessments of benefit of eteplirsen. As a
19 physician, I want the option to prescribe
20 eteplirsen. We cannot withhold a safe drug from
21 even one boy who may benefit.

22 (Applause.)

1 DR. ALEXANDER: Thank you. Will speaker 13
2 please introduce yourself? Please state your name
3 and any organization you are representing for the
4 record

5 MS. NICHOLS: I'm Jodi Nichols.

6 MS. DUMM: Jen Dumm.

7 MS. NICHOLS: Make Duchenne History
8 Coalition arranged our travel. We represent our
9 boys and all families participating in the limited
10 ambulation safety study of eteplirsen. My son,
11 Andrew, is 10 years old. He has been on eteplirsen
12 for one year. I remember watching Andrew begin to
13 walk as a toddler. It was so exciting.

14 Then it was like watching all over again in
15 reverse. As he grew older, Andrew started holding
16 on to furniture, and we had to stabilize and assist
17 him with walking until one day we knew and he knew
18 that he was done walking for good.

19 I find FDA's assertion that kids who are
20 motivated can walk longer than kids who are not of
21 the highest insult. No one was more motivated than
22 my son to keep walking.

1 (Applause.)

2 MS. NICHOLS: But he didn't have the muscles
3 left or the dystrophin available to continue to do
4 so. Then, on April 2nd of last year, Andrew began
5 getting infusions of eteplirsen as part of the
6 limited ambulation study recommended by the FDA in
7 2014. This has given him back capabilities that we
8 thought were gone forever.

9 In Andrew's words, "Today at school, I
10 carried my tray by myself. My arms are stronger.
11 I can wrestle with my brother. I can lift my legs
12 now, and I can almost kick." Today, Andrew crawls.
13 He climbs out of bed into his wheelchair. He sits
14 up independently. Posture and fine motor skills
15 are improved immensely. Andrew has experienced
16 zero negative side effects on eteplirsen.

17 MS. DUMM: My son, 12-year-old John Owen
18 Dumm, shares the same exact story as Andrew. Both
19 Andrew and Owen stopped walking one decade earlier
20 than what is suggested in the FDA briefing
21 documents. Once his infusions started in April
22 2015, new found strength in every muscle is also

1 our new norm. Many in our community can attest to
2 the strength he now exhibits that we all thought
3 was gone forever. You have heard from many of them
4 in our written testimonies.

5 Like Andrew, Owen has experienced zero
6 negative side effects, zero. Before, Owen had
7 difficulty moving his arms. Today, he can feed
8 himself without the use of his mechanical arm. He
9 can write and draw for hours without assistance.
10 He can even hold his own cards when we play card
11 games on game night and move his own pawns in the
12 game Sorry, all because his upper body strength has
13 returned, and not merely because he put his mind to
14 it.

15 While these small improvements might seem
16 like not much to you, but the return of strength is
17 a massive quality of life improvement. We stand
18 before you not just as two fierce mothers. We
19 stand before you representing a patient community
20 that expects you to do your job.

21 We expect you to recognize the safety and
22 effectiveness of this drug. We expect you and the

1 FDA to use the authority and flexibility in FDASIA
2 to approve eteplirsen because it is [mic off].

3 (Applause.)

4 DR. ALEXANDER: Thank you. Will speaker 14
5 please step to the microphone and introduce
6 yourself? Please state your name and any
7 organization you are representing for the record.

8 DR. HEYDEMANN: My name is Peter Heydemann.
9 I am a pediatric neurologist at Rush Medical Center
10 in Chicago. I have been caring for kids in a
11 muscular dystrophy clinic since the early 1980s.

12 Along with our nurses, I have been
13 administering eteplirsen to patient 004 per a
14 university contract with Sarepta. I've also been
15 paid as a Sarepta advisor at times. The Make
16 Duchenne History consortium funded my travel and
17 hotel here.

18 With my few minutes, I want to convey two
19 main points. I have observed unexpected stability
20 in the one boy who I care for, who mirrors the
21 accumulated data of the eteplirsen boys. Secondly,
22 there were no significant side effects.

1 I first observed 004 at age 10 in September
2 2012 after about 9 months of treatment at
3 Nationwide Children's. He was a spirited boy with
4 mild to moderate waddling and a toe walk gait.
5 Based on his style of movement, I thought he would
6 move slower than he did. He took steroids per
7 study requirements, thyroid hormone for
8 hypothyroidism, and last year transiently, he was
9 treated with growth hormone for about 9 months.

10 My expectation initially was that his
11 walking would substantially worsen in the upcoming
12 year and certainly over the next 2 years. What I
13 found was that he continued to move around at about
14 the same speed with little change in his style of
15 walking over those 2 years.

16 It is only in the past year, his fourth year
17 on eteplirsen, that his walking has substantially
18 weakened, especially in the past several months.
19 These degenerative changes are coming much later
20 than I expected.

21 As a side note, I'd like to point out that
22 004 is the only boy I've ever cared for who scored

1 a basket in a school basket game. My functional
2 observations over time were surprisingly favorable
3 compared to my expectations of untreated similar
4 boys, and my observations seemed to correspond well
5 to European natural history group.

6 In terms of adverse events, 004 experienced
7 none, though we had mild laboratory or family
8 observed side effects, which didn't affect him in
9 the least. The weekly medication infusions were
10 made much easier in his case with the use of a
11 permanent intravenous access port, and then with
12 home infusions.

13 In sum, my experience and observations tell
14 me that 004's progressive course of weakness was
15 substantially slowed by eteplirsen without any
16 serious adverse events. I believe that eteplirsen
17 if started in younger DMD boys, with more savable
18 muscle, would improve the course of disease even
19 more.

20 Furthermore, from listening to today's
21 discussion, I believe that eteplirsen meets
22 criteria being reasonably likely to predict

1 clinical benefit, that it's highly unlikely to
2 produce clinical harm, and that dystrophin is
3 produced, and that the many valid criticisms are
4 not negating of any of this but are reasons for
5 further data collection after granting accelerated
6 approval.

7 (Applause.)

8 DR. ALEXANDER: Thank you very much. Will
9 speaker number 15 please introduce yourself?
10 Please state your name and any organization you are
11 representing for the record.

12 DR. CONNOLLY: I am Ann Connolly. I'm a
13 neurologist at Washington University in St. Louis,
14 and I have worked with children and adults with
15 neuromuscular disorders for 27 years. I have been
16 a consultant for Sarepta but stand to gain nothing
17 financially from approval.

18 Please consider what I have to say from the
19 perspective of a clinical researcher in Duchenne
20 dystrophy, a neuromuscular pathologist, and finally
21 with their permission, I speak for Justin and Cole,
22 who I have followed for 3 and a half years in the

1 extension study.

2 I know well the difference between Duchenne
3 and Becker muscular dystrophy as I have cared for
4 more than 150 boys and men with these disorders.
5 If I have a question whether a boy has Duchenne or
6 Becker, I do in fact assess the number of
7 dystrophin positive fibers.

8 In the recent FDA briefing, it was stated
9 that the percent of positive fibers is not a
10 reliable way to quantify dystrophin. Not only do I
11 disagree with you, I ask you to review those
12 biopsies carefully and note that the fibers with
13 dystrophin are larger and more frequent than any
14 biopsy I've ever seen with revertant fibers.

15 I believe these dystrophin fibers are
16 driving the clinical effect. Furthermore, because
17 Justin and Cole are so much stronger than I would
18 have expected, if I met them for the first time
19 today, I would have suggested they have muscle
20 biopsies. When I consider their post eteplirsen
21 biopsies and their physical examinations, I would
22 have reclassified them as having Becker muscular

1 dystrophy. Thus, I do believe that dystrophin
2 positive fibers are a clear biomarker for strength
3 and rescue of muscle.

4 Now, a minute on behalf of Justin and Cole.
5 I have followed Justin since the age of 3 and
6 treated with intermittent twice weekly steroids.
7 However, at the age of 11 when he entered the
8 study, he had difficulty getting off the ground,
9 and I timed him at 26 seconds, and he subsequently
10 lost the ability to get off the ground.

11 Based on all natural history that you and I
12 have reviewed, he should have stopped walking by
13 age 13. At age 16 and a half, after recovery from
14 a femur fracture, he is still walking.

15 My second patient, Cole, was 10 years old
16 when he started the trial and has also done well,
17 despite a fracture at age 11 and a half requiring a
18 cast and no weight bearing for 8 weeks. He has
19 regained the ability to walk and continues to do so
20 at 14 and three-quarters years.

21 They are both exceptionally bright. These
22 two teenage boys do not require someone to feed

1 them, take notes, or take them to the bathroom.
2 While I am a strong advocate of corticosteroids,
3 make no mistake about this fact, corticosteroids,
4 whatever the regimen, do not explain the data here.
5 Be careful of a type 2 error. Thank you.

6 (Applause.)

7 DR. ALEXANDER: Thank you. Will speaker 15
8 please introduce yourself? Please state your name
9 and any organization you are representing for the
10 record.

11 AUSTIN LECLAIRE: Hi. My name is Austin
12 Leclaire. I'm 17 years old. My brother Max has
13 been on eteplirsen for almost five years, and like
14 many in this room, I know what it feels like to
15 watch the drug work and wait for it. After years
16 of waiting, 18 months ago, I was screening for
17 participation in the safety trial.

18 UNIDENTIFIED FEMALE SPEAKER: All right, the
19 video needs to start over please. It wasn't
20 supposed to be played. Can you start the video
21 over please?

22 AUSTIN LECLAIRE: I want you to know that I

1 knew if I didn't perform well, I may not get into
2 the trial, so what you are seeing is my very best
3 effort in the screening, stacking 4 cans, then
4 stacking the fifth can at 48 weeks, and finally
5 lifting my arm over my head at 62 weeks. What does
6 this mean? This means I can now feed myself
7 easier, reach my own urinal, and also transfer
8 myself. This means independence.

9 My brother and I are Duchenne experts.
10 We've lived with it every day. Before Max started
11 eteplirsen, he was on a sharp decline, and I knew
12 he would be soon in a wheelchair because I remember
13 going through that time when I was 9.

14 Brothers may not progress in exactly the
15 same way, but I do know that once you start to
16 decline, you keep declining, it doesn't stop. Max
17 was declining. We were about to get him a
18 wheelchair, and then he stopped. The DMD
19 progress -- it's not normal DMD progress, and I
20 know it because I live through it.

21 I've been on drug 18 months. Normally, boys
22 decline over that time, and I'm not only not

1 getting worse, I'm getting better. I also know
2 that we are making dystrophin.

3 I feel bad that my brother had to go through
4 4 biopsies to prove this over and over again and
5 that data needs to be used now to review the drug.
6 I hear you say that 0.9 percent is disappointing.
7 In order to use a word like that to describe making
8 dystrophin in a disease like Duchenne, I can only
9 guess that you don't know anything about Duchenne.
10 Making 0.9 --

11 (Applause.)

12 DR. ALEXANDER: Please hold your applause.

13 AUSTIN LECLAIRE: Making 0.9 percent is
14 amazing. It lets me feed myself. It keeps Max
15 walking. It gives us a chance. 0.9 percent is not
16 perfect, but it is life changing. My friend, Jake,
17 needs the next drug, exon 45. He has just had to
18 have a painful spinal surgery that I would like not
19 to have to go through because I am on eteplirsen,
20 and my back is much stronger because of it.

21 It's time to listen to the real experts. So
22 to make that easier for you, we brought them all

1 here today. Please use them.

2 (Laughter.)

3 (Applause.)

4 DR. ALEXANDER: Thank you very much. Once
5 again, please hold your applause until the last
6 speaker has spoken. Thank you very much.

7 Will speaker number 17 please introduce
8 yourself? Please state your name and any
9 organization you are representing for the record.

10 DR. GULATI: My name is Neera Gulati, and
11 I'm representing Suneel's Light. I'm presenting my
12 perspective as a physician. The people best able
13 to assess the efficacy of this drug are the experts
14 who have cared for Duchenne patients. Thirty-six
15 doctors who have cared for over 5,000 patients for
16 15 years have presented their support.

17 The FDA is accustomed to evaluating drugs
18 for common highly prevalent diseases such as
19 hypertension and diabetes. Statistically, it is
20 easier to collect data in such diseases. With
21 Duchenne, due to the rarity, heterogeneity, and the
22 shortened lifespan, this is not possible.

1 Statistics are not an adequate tool to
2 assess ultra-rare diseases. Consequently, Congress
3 passed in 2012 FDASIA, a bill I and others in this
4 room supported. In the FDA briefing documents, it
5 was very disappointing for me to read the FDA
6 declared support for FDASIA and yet still insist on
7 data that cannot be collected for a rare disease.

8 Well-controlled studies as interpreted by
9 the FDA are not easily achieved if at all in orphan
10 disease populations. This is not honoring the
11 spirit of FDASIA. Following FDASIA should not be
12 optional.

13 The FDA feels they can better assess disease
14 trajectory based on data they select, and they have
15 discounted specialists' clinical experience rather
16 than valuing the information provided. If I as a
17 family physician inform my patient there is a new
18 drug specialists are recommending for his rare,
19 terminal, life limiting disease that has no
20 significant side effects, but I am not going to
21 give him access to this drug because my
22 interpretation of the data conflicts with the

1 specialist's, I am certain he would leave my
2 practice and seek expert opinion elsewhere,
3 probably from one of those 36 doctors.

4 I have had the privilege to live in Buffalo,
5 New York next to Roswell Park Cancer Institute and
6 witness the prognosis for cancer change from a
7 death sentence to a treatable disease. I watch my
8 patients try treatments with serious side effects
9 that definitely had mortality risks and uncertain
10 benefits. They wanted these options. Why not for
11 Duchenne?

12 In the 1950s, childhood leukemia had
13 100 percent mortality rate. Clinicians such as
14 James Holland from Roswell Park and [indiscernible]
15 Frei from the NCI were convinced medical orthodoxy
16 had it backwards in regards to treating childhood
17 leukemia. They spearheaded novel combination
18 treatments with serious side effects. This was
19 unheard of in the late '50s. Today, combination
20 drug treatments for cancer is standard, and
21 childhood leukemia has a 90 percent cure rate. Why
22 not for Duchenne?

1 It is clear to me the FDA will never feel
2 comfortable with ultra-rare diseases. It is also
3 clear to me from the experts that exon skipping
4 drugs meet the criteria for FDASIA and are worthy
5 of accelerated approval.

6 I am hoping the advisory committee members
7 will have the insight and judgment to realize that
8 eteplirsen should be granted accelerated approval.
9 I'm hoping that FDASIA will be respected and
10 enforced.

11 (Applause.)

12 DR. ALEXANDER: Thank you very much. Will
13 speaker 18 please introduce yourself? Please state
14 your name and any organization you are representing
15 for the record.

16 MS. ARNOLD: Good afternoon. My name is
17 Louise Crow-Arnold, and the Make Duchenne History
18 Coalition paid for my travel today. The diagnosis
19 of Duchenne to a family is devastating. To know
20 that your child, who has just begun to discover
21 things, will gradually have each development taken
22 away is particularly cruel.

1 With no treatments available in the UK, and
2 with the knowledge that if we were to do nothing,
3 his early death would be inevitable, we sought out
4 the most promising, effective, and safest drug that
5 could treat our son, Leon. We moved our family to
6 the United States to take part in the eteplirsen
7 trial.

8 As parents, we had enough faith in the data
9 that was made public to move across the world so
10 that Leon could be in a clinical trial. This huge
11 upheaval has meant we have left our jobs, home, our
12 son's schools, family, and friends behind.

13 Since taking eteplirsen, Leon has shown
14 increasing signs of strength. He performs the
15 Gowers Maneuver far less when rising, and his falls
16 are less frequent. He enjoys drawing and writing
17 far more as he tires less with these activities,
18 and his hand grip has strengthened.

19 His stamina has increased, and he can cover
20 greater distance before fatigue sets in. His
21 stroller is staying in the garage far more than
22 when we arrived in America eight months ago. Our

1 biggest reward is that Leon can hug us tighter.

2 At no point have we experienced any side
3 effect with eteplirsen, either during the infusion,
4 afterwards, or at any time during the week between
5 doses. When Leon was born, we stared at our
6 sleeping child in wonder, and it is then as a
7 parent that you vow you will always love them and
8 do anything you can for them.

9 That is why we have moved halfway around the
10 world. That is why we are here today, for Leon,
11 and for every other child who has the misfortune to
12 be born with Duchenne.

13 This drug is not a false promise. We have
14 witnessed the efficacy of this drug. We are not
15 just desperate parents, as often described in the
16 media. We have listened to our doctors. Standards
17 of efficacy matter, but flexibility matters too.

18 Eteplirsen patients are experiencing delayed
19 loss of motor milestones. The data is sufficient
20 to approve eteplirsen, and the FDA has the
21 authority to grant approval. Thank you.

22 (Applause.)

1 DR. ALEXANDER: Thank you very much. Will
2 speaker 19 introduce yourself? Please state your
3 name and any organization you are representing for
4 the record.

5 MS. EICHELBERGER: My name is Kim
6 Eichelberger, and my son Cole has Duchenne. Our
7 travel was paid for by the Make Duchenne History
8 Coalition. In August 2011, when Cole was 10 years
9 old, he was selected as one of 12 participants in
10 the eteplirsen 201 trial. He was selected because
11 he appeared to be on the cusp of decline.

12 He walked with lordosis to compensate for
13 quadriceps weakness. He had a wide stance because
14 he needed the support, and he had the typical
15 Duchenne waddle when he walked. In short, he did
16 not look like a child who would be walking for
17 years to come.

18 We now know that for the first 24 weeks he
19 received placebo. During this time, he declined
20 significantly in his 6-minute walk, then he started
21 eteplirsen. The FDA's briefing documents argue
22 that boys on eteplirsen are progressing exactly as

1 one would expect given the natural history of the
2 disease. They argue that several of the boys have
3 reached distances on the 6-minute walk that would
4 suggest they will come off their feet shortly,
5 signaling the drug doesn't work.

6 My son is one of those referenced boys. At
7 the 3-year mark, my son walked right around
8 100 meters on the 6-minute walk test. Six months
9 later, at the 3 and a half year mark, he walked
10 only 50 meters on the 6-minute walk test. Any
11 clinician will tell you based on that trajectory
12 that his walking days were numbered. And then
13 6 months later, at the 4-year mark, my son still
14 walked 50 meters on the 6-minute walk test. And
15 then just a few weeks ago, at the 4 1/2 year mark,
16 my son not only completed the 6-minute walk test
17 once again, but after the visit, he informed us he
18 had walked further than he had on the previous two
19 visits, walking further than he had on the test in
20 over a year.

21 I'll say that again because it needs to be
22 heard. At 14 and a half years old, instead of

1 coming off his feet like the briefing documents
2 predicted would happen, my son improved his
3 distance on the 6-minute walk. His is not the
4 story of a Duchenne outlier who continues to
5 perform better than one would expect. His is the
6 story of a Duchenne patient who was falling off the
7 cliff toward irreversible decline and was somehow
8 yanked back onto the ledge.

9 I should also mention, because it is in the
10 briefing documents, that Cole has never had an
11 intensive physical therapy regimen. In fact, over
12 the last 4 and a half years, he has received
13 physical therapy for a total of about 6 months. In
14 addition, his steroid dose has remained at roughly
15 half of the weight recommended dose of
16 0.9 milligrams per kilogram.

17 Cole will enter high school this year still
18 on his feet, which is something my husband and I
19 could not have imagined possible when we were given
20 his diagnosis. I can say with confidence that the
21 life my family is living would be very different
22 than it is today were it not for eteplirsen.

1 I believe if you were to ask his doctors,
2 Drs. Ann Connolly and Jerry Mendell, both of whom
3 are here today, that they would agree. In fact
4 you've just heard Dr. Connolly's opinion on Cole's
5 progression.

6 This drug should be granted accelerated
7 approval so that anyone who can be helped by it has
8 access and can benefit the way Cole has while we
9 wait for definitive answers from the confirmatory
10 trials. Thank you for the opportunity to speak
11 today.

12 (Applause.)

13 DR. ALEXANDER: Thank you very much. Will
14 speaker 20 please introduce yourself? Please state
15 your name and any organization you are representing
16 for the record.

17 MS. ELLSWORTH: My name is Terri Ellsworth
18 from Pittsburgh, Pennsylvania, and my son Billy,
19 age 15, has been receiving eteplirsen since August
20 2011, receiving 30 mgs/kg of the drug. The Make
21 Duchenne History Coalition arranged for our travel.

22 Instead of spending the most important

1 3 minutes of my life talking about Billy's
2 accomplishments and success on eteplirsen, I have
3 to spend it talking about the misleading briefing
4 documents that were released by FDA's neurology
5 division.

6 In these documents, FDA states that boys on
7 eteplirsen, quote, "Appear to receive optimal care,
8 including intensive physical therapy and intensive
9 steroid regimens," close quote, claiming that PT
10 and steroids are responsible for these boys'
11 stability rather than the eteplirsen.

12 We want the panel to know that the Columbus
13 trial family strongly disagree with these comments.
14 Our boys either received minimal, standard, or no
15 PT throughout the trial. In addition, most of the
16 boys on eteplirsen are massively underdosed with
17 steroids.

18 My son spent the entire trial at
19 21 milligrams of deflazacort, which is nearly half
20 the recommended dose. The advisory committee
21 process is supposed to be an unbiased panel, but
22 with the FDA's briefing package, the committee has

1 been tainted and led astray with misrepresentation
2 in the information that they received.

3 I read posts daily on social media from
4 fellow Duchenne parents about their daily
5 caregiving and challenges that their boys face. I
6 read it, I understand it, I get a lump in my
7 throat, but that is not my life. I don't wake
8 several times a night to turn my son in bed, he
9 turns himself.

10 I don't have to feed my son, he feeds
11 himself, and then carries his dishes and glass to
12 the sink. I don't have to brush my son's teeth, he
13 does it himself. I don't dress my son, he dresses
14 himself, and then comes down the stairs for
15 breakfast. I don't bathe my son, he does it
16 himself.

17 Billy was not and is not an outlier. Before
18 eteplirsen, Billy was an extreme toe walker. He
19 consistently walked with his heels 3 inches off the
20 ground, which typically indicates the end of
21 ambulation is near. Now, almost 5 years later, he
22 is still walking, and his heels are much closer to

1 the ground. This is not placebo effect, this is
2 eteplirsen still at work.

3 MR. ELLSWORTH: My name is Billy, and I have
4 been receiving the eteplirsen drug since I was
5 10 years old. You should approve eteplirsen
6 because I am very strong and still walk a lot. I'm
7 afraid that if you don't approve this drug, I will
8 become very weak and not be as independent like I
9 am now. It makes me sad and afraid that I won't be
10 able to do all the things that I can do now.

11 I see other boys my age and younger that
12 cannot do what I can do, and it makes me mad that
13 they also cannot have the drug. I hardly ever have
14 to ask my parents to help me with anything because
15 I can do most everything in my daily life by
16 myself.

17 I'm going to beat this bloody disease, but I
18 need your help. So please help me and my friends
19 and do the right thing. FDA, please don't let me
20 die early.

21 (Applause.)

22 DR. ALEXANDER: Thank you very much. Once

1 again, please hold your applause until the final
2 speaker has spoken.

3 Will speaker 21 please introduce yourself?
4 Please state your name and any organization you are
5 representing for the record.

6 (Applause.)

7 MS. MILLER: My name is Debra Miller. I'm
8 the founder and CEO of CureDuchenne, which has paid
9 for my travel. CureDuchenne provided funding to
10 Sarepta in 2010 to conduct studies that enabled it
11 to get off clinical hold and move into human
12 clinical trials for eteplirsen.

13 Duchenne, unlike other neuromuscular
14 diseases such as MS, has no ebbs and flows or
15 remissions, only a downward trajectory of loss
16 first of ambulation, then autonomy, and ultimately
17 life. Our kids have been taking steroids, which
18 carry multiple side effects and have uneven
19 benefits. Fortunately, we've been able to use
20 off-label steroids or buy them from other
21 countries, otherwise our children wouldn't not have
22 been able to benefit from them.

1 Exon skipping works. It may not be the
2 complete cure, but it helps many boys extend
3 ambulation and improve their quality of life. We
4 cannot buy it off-label or order it from another
5 country. Your approval is our only hope for
6 access. The current exon skipping trials were
7 designed many years ago with limited knowledge of
8 Duchenne's natural history.

9 You, the FDA, can insist on a perfectly
10 designed trial and sacrifice this current
11 generation of Duchenne boys, or you can allow
12 access to these drugs while we perfect clinical
13 trial designs for the future.

14 CureDuchenne has sponsored cTAP, the first
15 collaboration between biotech and pharma companies
16 created to apply statistical analysis to understand
17 the natural progression of Duchenne and design more
18 informed clinical trials.

19 We encourage the FDA and sponsor companies
20 to take advantage to cTAP and meanwhile use the
21 accelerated approval program to allow the use of
22 eteplirsen. Use your power to remove the drug if

1 it is demonstrated to be unsafe or ineffective
2 post-marketing.

3 To cure Duchenne, we will need a combination
4 of therapies to treat the whole disease. Exon
5 skipping is a cornerstone of this approach.
6 CureDuchenne is funding the development of multiple
7 drugs, but we cannot test drug combinations until
8 the first drugs are approved.

9 I have a son with Duchenne. His name is
10 Hawkin. He is 19 years old and just finishing his
11 freshman year at USC. He's a news editor for the
12 Daily Trojan. He lives independently without an
13 aide. Although he uses a scooter or power chair
14 for distance, he is able to walk and take care of
15 himself and drive his friends around town.

16 He has approximately 3 percent of normal
17 dystrophin. Even small amounts of dystrophin can
18 add years of independence and improve quality of
19 life, but we need to start treatment when they are
20 young to realize the true benefit.

21 I respect the FDA's caution in setting a
22 precedent in approving new drugs, but our kids are

1 not a precedent, they are real live human beings
2 and they are short on time.

3 An FDA official once told me, "The worst
4 thing we can do is approve a drug and then have to
5 pull it off the market." I argue that the worst
6 thing you can do is deny access to a drug and then
7 find out it works too late, after we have lost a
8 generation of boys. Thank you.

9 (Applause.)

10 DR. ALEXANDER: Thank you very much. Will
11 speaker 22 please introduce yourself? Please state
12 your name and any organization you are representing
13 for the record.

14 MS. McSHERRY: Hi. My name is Jordan
15 McSherry. Today, I'm introducing my brother,
16 20-year-old brother, Jett McSherry's video
17 testimony. This video was filmed in his college
18 dorm room. So feel free to laugh. Audio.

19 (Video played and transcribed.)

20 MS. McSHERRY: [Indiscernible] I feel
21 pretty -- I've noticed a few changes since
22 [indiscernible]. I started to take eteplirsen in

1 October of 2014. Right now, it's April 2015, and
2 I've been on it for around about 20 weeks now.

3 I feel pretty -- I've noticed a few changes
4 since I've -- since I've been on this drug. I've
5 noticed that I have more strength than I usually
6 have. I can do more stuff on my own. I can eat by
7 myself a lot easier.

8 I sleep a lot better at night. I don't
9 snore as much anymore. I don't get tired as
10 easily. I don't feel so tired at the end of the
11 day [ph] than I did before. I can also open cans
12 myself, which I couldn't do before pretty easily.

13 AIDE: I've been working with Jett since the
14 beginning of the school year, and one thing that
15 I've noticed [indiscernible] better since he's been
16 on the drug was at first his snoring was really
17 bad, right, could barely fall asleep at first and
18 then after [indiscernible] once he got on the drug,
19 I'd have to say right around probably December,
20 winter break, around that area, he just got a lot
21 better and it's -- I mean every one snores but it's
22 not nearly as bad as it's ever been and it seems to

1 be improving every day.

2 Another thing with him sleeping is he likes
3 to put his leg up when he sleeps but that's
4 something that he asks me to do for him. And then
5 one time I woke up in the middle of the night and
6 he had his leg up himself and he did it himself
7 without anyone asking.

8 Just little things like he used to ask me to
9 get him food, and when he needed food I'd either
10 have to help feed him or open the bag like chips
11 but now he can open a bag of chips by himself.

12 Another example is this water bottle, I used to
13 have to feed him the water bottle, but now he can
14 for the most part grab it himself and put it up to
15 his mouth, but also I can leave it on the desk and
16 he can just come over and grab it by himself.

17 (Laughter.)

18 AIDE: [Indiscernible] And also other
19 things like his laptop, he can -- if I left his
20 laptop on the desk [indiscernible] controller or
21 the video game controller I can just leave it right
22 there and then he -- [mic off].

1 (Applause.)

2 DR. ALEXANDER: Thank you very much. Will
3 speaker 23 please introduce yourself? Please state
4 your name and any organization you're representing
5 for the record.

6 MS. SECKLER: My name is Tracy Seckler, and
7 my son Charlie has Duchenne. I'm the cofounder of
8 Charlie's Fund, a public charity that has directed
9 \$38 million since 2004 into a varied portfolio of
10 medical research and drug development programs,
11 including exon skipping and other therapeutic
12 approaches.

13 Here's a fact that is not in dispute today,
14 not in the medical literature, not in the FDA
15 briefing documents, not among the experts, and not
16 in our personal experience. Two clear warning
17 signs let us know that loss of ambulation is coming
18 soon. When a boy loses the ability to
19 independently rise from the floor, he is highly
20 likely to lose ambulation in 1 to 2 years. And
21 scores of 13 and 9 on the North Star Ambulatory
22 Assessment predict loss of ambulation in 2 and

1 1 years, respectively.

2 These warning signs let us know when we can
3 expect the next loss milestone. Amy, Scott, Lisa,
4 Valerie, and I watch anxiously and fearfully each
5 and every day for those signs, and there is nothing
6 we can do to stop it or slow it down because our
7 children are not on eteplirsen.

8 The boys on eteplirsen who got these warning
9 signs have experienced something different. Based
10 on what we all agree upon about the sequential loss
11 of milestones, many of the eteplirsen boys should
12 be in wheelchairs by now, but they are not.

13 FDA suggests that perhaps these boys are
14 outliers, that all 10 of them would, without
15 treatment intervention, progress relatively late,
16 but the boys selected for the eteplirsen study
17 5 years ago were not the strong ones, the late
18 progressers. The stories you have heard from them
19 and their physicians today, including toe walking,
20 lordosis, and frequent falls prior to starting
21 treatment, support and fit with the data collected
22 in the clinical trial setting.

1 One boy lost the ability to rise from the
2 floor 3 years ago, yet today he can still walk.
3 Another lost the ability to rise from the floor
4 2 years ago; today, he can still walk. A third boy
5 lost the ability to rise from the floor a year and
6 a half ago; today, he's still walking.

7 A look at the North Star scores provides
8 more evidence that these boys should have lost
9 ambulation by now. The three kids who dropped
10 below a score of 13 more than 2 years ago are still
11 on their feet, and the 4 who dropped below a score
12 of 9 more than a year ago, still walking.

13 These boys are deviating significantly from
14 their natural history counterparts who were
15 rigorously selected to provide the closest possible
16 match. Importantly, they are also defined their
17 own predicted natural history based on uncontested
18 signals of rate of disease progression.

19 Later today, you will be asked to consider
20 several questions. Theoretical concerns about the
21 limitations of natural history notwithstanding,
22 this data provides the information you need to

1 answer questions 5 and 6. As for question number
2 7, these boys are the answer. These boys are the
3 substantial evidence of eteplirsen's treatment
4 effect. Thank you.

5 (Applause.)

6 DR. ALEXANDER: Thank you very much. Will
7 speaker number 24 please introduce yourself?
8 Please state your name and any organization you're
9 representing for the record.

10 MS. McNARY: My name is Jenn McNary. My
11 travels were supported by the Make Duchenne History
12 Coalition, and this is Max. I am told that I was
13 the first person that knew the drug now called
14 eteplirsen worked, before any of the data was
15 released.

16 It's not because I'm a scientist or a
17 clinician, it's because one of my sons, Max, was
18 one of the first boys in the U.S. to receive the
19 drug. His older brother, Austin, who you've heard
20 from, had already stopped walking at 10 and a half
21 years old. He was unable to get into the trial
22 because he was unable to walk, forcing me into a

1 situation where there was essentially an open
2 placebo-controlled trial in my own home.

3 At trial start, Max was 9 and a half and on
4 a downward spiral. It was Austin who told me at
5 the time, "Max is falling a lot, Mom. I think he
6 needs a power wheelchair." We ordered one. The
7 FDA states in their briefing document that there's
8 a wide range of loss of ambulation for boys
9 amenable to exon 51 from 8 to 18 years.

10 Those in this room who know Duchenne know
11 most lose ambulation between 10 and 12 years. So
12 why is the FDA so focused on outliers? Our sons
13 were not chosen for the trial because they are
14 outliers, they were typical boys. The boys in the
15 study were chosen because they were declining,
16 typical for Duchenne, until they began the
17 treatment with eteplirsen. This is when their
18 progression became atypical.

19 I was skeptical at first because the trial
20 was blinded and placebo-controlled. I didn't even
21 know if Max was on drug, until the day that I knew.
22 Max opened a milk container at the airport for the

1 first time. His grip has always been weak. He
2 always handed the jug to me to open, but that day
3 he opened it. Small changes turned to bigger
4 changes over time.

5 Max was choosing to ride in his wheelchair
6 less and less until he decided not to use it at
7 all. He was not coming home from school tired,
8 despite abandoning the chair. It had been with him
9 daily since kindergarten. He started participating
10 normally in gym class. And most importantly, he
11 totally stopped collapsing. We cancelled that
12 order for a power chair, and 4 and a half years
13 later, we haven't seen the need.

14 Max is still declining some. Over 4 years,
15 his walk test has remained about the same, which in
16 itself is amazing to have this kid just dangling on
17 the edge of a cliff and stay there for 4 years
18 without falling off.

19 But more importantly, Max's daily life and
20 level of independence has changed. Last week,
21 14 and a half-year-old Max got out of his bed. He
22 got dressed. He put on his shoes and his backpack

1 and he walked out to the school bus unassisted.

2 I am incredibly proud to be standing here
3 saying the same thing I've been saying daily since
4 day 1, eteplirsen works. Only today, I'm happy to
5 be surrounded and supported by sound dystrophin and
6 clinical data, physician, researcher, and patient
7 testimonies similar to my own.

8 I want to impress upon the panel that a
9 recommendation for approval is the only acceptable
10 outcome of today's meeting. And if you ask me,
11 it's incredibly overdue at this point. We are the
12 lucky ones, the boys in orange. So many are still
13 waiting. Let's do the right thing.

14 (Applause.)

15 DR. ALEXANDER: Thank you very much. Will
16 speaker 25 please introduce yourself? Please state
17 your name and any organization you are representing
18 for the record.

19 DR. PARTRIDGE: Yes, I'm Terry Partridge,
20 and I'm currently professor of systematic
21 integrative biology at George Washington medical
22 school here in DC. Before that, I was in London

1 where for about the past 45 years, I've worked on
2 research on muscular dystrophy, and I was head of
3 the Medical Research Council Clinical Sciences
4 Centre muscle group.

5 My main area of interest is the mechanisms
6 of muscle repair and of exon skipping, and I think
7 the two are beginning to become involved with one
8 another. One of the problems that came up today,
9 regularly, was the inconsistency about dystrophin
10 measurement between different studies, and across
11 time, and within the same manual, and between
12 muscles. And I think there's a perfectly good
13 explanation to this, which I think should be taken
14 into account when considering the data.

15 On the screen at the moment is an old slide
16 from Francesco Muntoni's original systematic trial
17 showing perfectly good post-dystrophin, pre-
18 post-dystrophin differences there. One of those is
19 slightly more overloaded than the other, but it's
20 good data. And it shows that there is dystrophin
21 there. And the question is, what does it do?

22 So the problem with the exon skipping is

1 that it works on very small groups of muscle cells.
2 When you look at these biopsies, and I was hoping
3 to put one up, you find tiny groups of muscles,
4 muscle fibers that are affected. These are about a
5 millimeter cubed in size. And if you were to try
6 to find those with the 10 or 20 micrograms of a
7 muscle biopsy, you might find two or three of those
8 in one of your biopsies, in which case you'd find
9 dystrophin, or you might miss all of them, in which
10 case you wouldn't find any dystrophin. And I think
11 this accounts for quite a lot of the lack of
12 consistency.

13 I see I'm running out because my slides are
14 not working. So the other thing I would say is
15 that you need to have something more easily
16 evaluable than the amount of dystrophin that's
17 present. You need to use biomarkers that are
18 beginning to come up that are much less invasive,
19 like urinary proteins that are lost from muscle
20 during the stages of degeneration and regeneration.
21 And you can show quite easily, as I would be doing
22 if the slides were working, that there is a -- it's

1 too late -- that there is a distinctive benefit.

2 Can I go back to that slide or not? Yes. .
3 The last one, that's it. I've lost it. I don't
4 know. [Off mic.]

5 DR. ALEXANDER: I'm sorry. Can you
6 extend -- can you turn on the microphone, please,
7 so the gentleman can have just a second or two more
8 for his comments?

9 (Applause.)

10 DR. PARTRIDGE: So these two slides up there
11 show basically following two proteins in the urine
12 that are lost from muscle fibers when they're
13 damaged, and it shows the effects of a morpholino
14 treatment in the mouse to skip the exons and
15 restore dystrophin. And it shows that -- can you
16 go on to the last one again?

17 Yes, that's the one. It shows that with the
18 treatment, the lower of those curves, in both
19 sides, the treatment takes down those biomarkers in
20 the urine. These are easily accessible biomarkers.
21 They're the same biomarkers as are being used in
22 Duchenne boys, and they would, I'm sure, form the

1 basis of any trial should the committee agree to an
2 accelerated approval for the continuation of
3 eteplirsen.

4 DR. ALEXANDER: Thank you very much.

5 (Applause.)

6 Will speaker 26 please introduce yourself?
7 Please state your name and any organization you are
8 representing for the record.

9 MR. BOWER: Hello. My name is Caden, and
10 I'm one of the 12 boys in Sarepta's eteplirsen --

11 DR. ALEXANDER: Can you speak into the
12 microphone a little bit more, please?

13 MR. BOWER: I ask that you please approve
14 this medicine. If it is not approved, I am scared
15 that I will lose the ability to walk, and I don't
16 want this to happen to me. This medicine is
17 keeping me walking and allowing me to keep up my
18 day-to-day activities and remaining stable. Thank
19 you.

20 MS. PEREZ: Hello. My name is Beth Perez,
21 and the Make Duchenne History Coalition paid for
22 our travel. And my 12-year-old son is one of the

1 12 boys in Sarepta's study. You heard it from him,
2 it is keeping him walking, and he is here standing
3 next to me today.

4 Caden has faithfully devoted nearly five
5 years of his life to this exon skipping drug. He
6 has not been on placebo and has been receiving
7 50 milligrams of the drug throughout the study.

8 Eteplirsen is giving my son a fighting
9 chance. I would have expected him to have more of
10 a physical decline by this stage of his life, and I
11 feel that he would be completely non-ambulatory if
12 it weren't for this life-saving drug. It is safe
13 and effective with zero side effects.

14 One thing I can tell you is that through
15 receiving these eteplirsen treatments, he is able
16 to live a more functional life than that of a
17 12-year-old DMD patient not receiving the drug.
18 For example, a typical DMD boy cannot pedal a
19 bicycle, but Caden is remarkably able to pedal a
20 few feet on a therapeutic tricycle and has less
21 falls since receiving the drug.

22 Caden is receiving below the recommended

1 dose of steroids. Until October 2015, he was on
2 18 milligrams of deflazacort. At that point,
3 Dr. Mendell increased the dose to 24 milligrams.

4 Caden does not receive any intensive
5 physical therapy. He receives therapy as advised
6 for any child with DMD. Caden's therapist has seen
7 and said that he has increased endurance for
8 walking activities without the need of assistive
9 devices.

10 He has participated in aquatic therapy
11 sessions for longer periods without excessive rest
12 breaks, and he has shown drastic improvements in
13 his active range of motion, most notably in his
14 hamstrings and hip flexors.

15 As parents, it's difficult seeing your child
16 struggle, but to witness them tackle life's
17 seemingly simple daily tasks is a heartbreaking
18 battle that any DMD parent can relate to. I don't
19 know want to tell my son that his dreams for a
20 future are going to be taken away from him.

21 The boys fighting DMD are the strongest
22 warriors that I know of, and if this drug helps to

1 make their world a little easier to live, then I
2 don't see any ethical reason as to why this
3 medicine should not be approved.

4 We support Sarepta and eteplirsen one
5 hundred percent. This drug means a future and a
6 promise to my son, our family, and every Duchenne
7 boy. Thank you for your time.

8 (Applause.)

9 DR. ALEXANDER: Thank you very much Will
10 speaker 27 please introduce yourself? Please state
11 your name and any organization you are representing
12 for the record.

13 DR. MICELI: I'm Carrie Miceli, professor of
14 microbiology, immunology, and molecular genetics
15 and co-director of the Center for Duchenne Muscular
16 Dystrophy at UCLA. For the past 10 years, my own
17 laboratory has been well funded to explore
18 mechanisms for boosting the activity of morpholino
19 directed DMD exon skipping in mouse and human
20 models. I'm familiar with measuring and
21 interpreting expression of skipped dystrophin
22 proteins.

1 One stated concern relates to the fact that
2 the pre-treatment control tissues was exhausted,
3 and thus controls from the PROMOVI pre-treatment
4 biopsies were included in analysis of biopsy 4
5 challenging interpretation.

6 It's important to note that two patient
7 pre-treatment samples were included in both
8 assessments of biopsies 1 through 3 and biopsy 4 by
9 immunohistochemistry. These samples should serve
10 as internal controls that allow for the validation
11 of the new set of controls, as typical of the
12 treatment cohort. The findings are interpretable
13 and clearly support induction of dystrophin.

14 Exon skipping uses morpholino and is known
15 to induce patchy dystrophin expression. Therefore,
16 assessment of eteplirsen induced dystrophin
17 requires consideration of both the absolute amount
18 of dystrophin present as well as its distribution.

19 Given the level and distribution of induced
20 dystrophin being observed, it's reasonable to
21 expect that some positive fibers express as much as
22 5 to 12 percent of normal dystrophin, levels

1 clearly predicted to impart some production of
2 myofiber's contraction induced damage.

3 Data from studies in BMD and DMD patients
4 and in mouse and canine models support the
5 suggestion that relatively low levels of dystrophin
6 can be functionally significant even if only
7 expressed in a limited number of fibers.

8 Of note, the number of dystrophin positive
9 fibers is not expected to be equal to the percent
10 of normal dystrophin protein unless each fiber
11 expresses 100 percent of normal levels of
12 dystrophin, which is clearly not the case. There
13 is no inconsistency there.

14 In response to the first set of briefing
15 documents, 36 prominent scientists and physician
16 experts in Duchenne provided FDA with a letter
17 clarifying issues raised. We ask that the letter
18 be made available unredacted to the advisory
19 committee. If you have not seen it in its
20 entirety, we hope you can gain access today.

21 Quoting from that letter, "We conclude that
22 there is strong evidence of induced dystrophin

1 production upon prolonged eteplirsen exposure."
2 The letter goes on to say, "The findings of this
3 trial are sufficiently robust to support the
4 proposed mechanism of action of eteplirsen to
5 provide a plausible explanation for the relative
6 gain in function observed within the treatment
7 group, and serve to bolster confidence that there's
8 a positive treatment effect."

9 I am also the mother of Dillon Miceli Nelson
10 who lives with Duchenne. Given the strong safety
11 profile, I'd be keen for Dillon to be on this drug
12 if it were pertinent.

13 (Applause.)

14 DR. ALEXANDER: Thank you very much. Will
15 speaker 28 please introduce yourself? Please state
16 your name and any organization you are representing
17 for the record.

18 MS. KELLY: Hi. My name is Wendy Kelly, and
19 I'm here today with Susan Patterson. The Make
20 Duchenne History Coalition arranged our travel.
21 We're here today to speak about our children's
22 experience on eteplirsen and how our sons have been

1 performing everyday activities easier since
2 starting the drug.

3 My 8-year-old son, Jackson, has been on
4 eteplirsen since January 2015. Susan's 8-year-old
5 son, David, has been on eteplirsen since July 2015.
6 Both of our boys are part of the confirmatory trial
7 that was clearly guided by the FDA in the April
8 2014 guidance. In that guidance, FDA also guided
9 for eteplirsen safety trials on younger Duchenne
10 patients and those at later stages of the disease.

11 Since they started on eteplirsen last year,
12 our boys have stabilized and they have started
13 doing things that they could not do before,
14 everyday things that normal 8-year-old boys take
15 for granted, like opening car doors, getting off
16 the floor with ease, easily bending over to pick up
17 things off the floor. We truly believe that
18 eteplirsen has changed the trajectory of their
19 disease.

20 Our children may have a future now that
21 might give them the opportunity to walk well into
22 their teens. With that ability comes independence

1 that most boys living with Duchenne lose very
2 quickly after going into a wheelchair.

3 Our observations verify and confirm what
4 Sarepta's data on the original 12 patient study
5 show, that treatment of eteplirsen can cause a real
6 and concrete impact on the lives of Duchenne
7 patients.

8 In addition, it is necessary to note that
9 neither of our boys have experienced a single
10 negative side effect from being on eteplirsen.
11 This drug has our stamp of approval. We believe it
12 is unfair of the FDA to make a comparison to Becker
13 muscular dystrophy. The comparison should be to
14 Duchenne. Eteplirsen is allowing our boys to
15 produce dystrophin.

16 We would love to turn our sons' Duchenne
17 into Beckers, but that should not be the standard
18 of measurement. Any benefit that allows our boys
19 to walk longer, breathe longer, or just make it
20 through the day is worthwhile.

21 The only reason our children were able to
22 receive eteplirsen is because the FDA allowed for

1 confirmatory trials in their 2014 guidance to the
2 company. By the time these confirmatory trials are
3 complete and the data is analyzed, it could be
4 another three years.

5 The human cost of not approving this drug
6 now and waiting up to three years for confirmatory
7 trials to be complete would be massive. Children
8 will have lost the ability to walk, to pick
9 themselves up off the ground, and to feed
10 themselves.

11 We all know what the end result of Duchenne
12 is, and the patient testimony here today should
13 tell you all that you need to know, the benefit of
14 eteplirsen far outweighs its risks. From the
15 Pattersons and the Kellys, please approve this
16 drug.

17 (Applause.)

18 DR. ALEXANDER: Thank you very much. Will
19 speaker 29 please introduce yourself? Please state
20 your name and any organization you are representing
21 for the record.

22 MR. LEFFLER: My name is Mitch Leffler. The

1 Make Duchenne History Coalition arranged my travel
2 here today, and I have a 12-year-old son who has
3 been on drisapersen and is now on eteplirsen.

4 The decision we're facing today would be an
5 easier one if we had a large placebo-controlled
6 data set, but here's the problem with collecting
7 that data set for exon 51. We're already starting
8 with an orphan disease. Then you remove the
9 87 percent of patients that aren't amenable to this
10 exon skip.

11 Out of the remaining 13 percent, you take
12 away the one-third of boys who are too cognitively
13 affected. Then you need to remove the boys who
14 have already participated in an exon-skipping trial
15 and are no longer drug naïve. Then you subtract
16 the families that live too far from a study site to
17 travel once per week. Then we lose the families
18 that have chosen to participate in a less demanding
19 clinical trial.

20 Then you subtract the families that cannot
21 afford clinical trial participation. For example,
22 my own family has spent over \$40,000 in childcare

1 and lost wages to participate in two clinical
2 trials.

3 Lastly, you need to subtract the boys that
4 do not fit the inclusion criteria, that are too old
5 or too young, their pulmonary or cardiac function
6 isn't strong enough, or maybe it's something as
7 simple as elevated white blood cell count during
8 the screening. But they may not fit in the narrow
9 6-minute walk criteria that's necessary to show a
10 treatment effect over a shorter period of time.

11 The result is that you're left with so few
12 boys that you end up relaxing the enrollment
13 criteria in order to get the numbers. And once
14 that happens, if you're using the 6-minute walk,
15 you've introduced so much variability into your
16 trial that you've changed science into
17 randomization roulette.

18 Some may say extend the duration of the
19 trial, keep children on placebo for a longer period
20 of time, but this trial includes muscle biopsies
21 under general anesthesia. If you think that
22 procedure is minor, you should know that my son has

1 a permanent limp from his two muscle biopsies in
2 his quadriceps.

3 So once you introduce this kind of
4 procedure, absolutely a more minor increase over
5 minimal risk, you have to involve the prospect of
6 direct benefit for every participant, a requirement
7 that is not satisfied by participation in a placebo
8 arm.

9 So we all know that a large scale,
10 long-term, placebo-controlled trial would give us
11 some of the answers we're looking here today. But
12 here's the deal. We can't have one. It's not
13 numerically possible, and according to FDA's own
14 guidelines on pediatric clinical trials, it is not
15 ethical.

16 So when we can't have the optimal data we
17 want but we still need to make a decision, what do
18 we do? Do we abandon a promising treatment or do
19 we become more interested in getting at the truth
20 than focusing on methodological concerns?

21 That is a question we're answering today,
22 and it's a question that's going to be asked more

1 and more often with genetic targeting of rare
2 diseases. The world's leading experts are here
3 today telling us that what they're seeing is
4 unusual. Our boys are changing in front of our
5 eyes. It can't be ignored. It can't be explained
6 away. And it needs to be acknowledged today.
7 Thank you.

8 (Applause.)

9 DR. ALEXANDER: Thank you very much. Will
10 speaker 30 please step to the podium and introduce
11 yourself? Please state your name and any
12 organization you are representing for the record.

13 MR. WESLEY: Yes, Mr. Chair, my name is
14 Keith Wesley. Make Duchenne History Coalition paid
15 for my lodging. My son, Jake Wesley, is 15 years
16 old, has Duchenne muscular dystrophy. Jake's not
17 in any current clinical trial. Jake's lack of
18 abilities and limitations due to the unfortunate
19 circumstances are what have brought me before you
20 today. I have slides but they're not coming up.
21 Oh, here you go.

22 DR. ALEXANDER: And I believe you have

1 control of the slides or no?

2 MR. WESLEY: Yes, they are up now. Thank
3 you.

4 DR. ALEXANDER: Very good.

5 MR. WESLEY: Jake lost the ability to walk
6 at 8 years old. After being confined to a
7 wheelchair for several years, Jake developed severe
8 neuromuscular scoliosis, a condition that occurs in
9 a large majority of the boys with the more severe
10 phenotype, those boys that produce little or no
11 dystrophin.

12 Jake underwent an extremely invasive 10 and
13 a half hour spinal fusion surgery this past year.
14 I'd like to draw your attention to those photos.
15 Earlier today scoliosis was mentioned. Here it is.
16 And while pictures tell a thousand words, they
17 don't tell you the fear that these boys endure for
18 months in advance of this surgery.

19 Although Jake is not in the eteplirsen
20 trial, his best friend, Austin Leclaire, is. Jake
21 and our family have known Austin for almost
22 10 years. Prior to Austin being in a trial, his

1 motor skills almost mimicked Jake's. Now Austin
2 can lift his hand above his head. And prior to
3 Jake's surgery he contacted a number of boys with
4 DMD who had spinal fusion surgery.

5 The majority of these boys said their
6 biggest regret was the fact they could no longer
7 feed themselves. It seems like such a small thing
8 to ask, the ability to feed yourself, but to these
9 boys, it means the world.

10 While Austin has regained the ability to
11 raise his arms above his head and transfer to bed
12 independently, Jake can no longer feed himself.
13 While Austin has regained the ability to toilet
14 independently, Jake completely is dependent on us
15 for all his personal care. After years of
16 progressing identically, there should be no reason
17 that Jake and Austin would start to differ in
18 progression unless the drug works.

19 I'm an elected official in the state of
20 Pennsylvania, and I ran for office because I wanted
21 to make a difference. I didn't just want to make a
22 difference, I did make a difference. I like to

1 believe the same of all of you. Why else, if not
2 to make a difference?

3 In closing, my intent is what Congress
4 wants, and voiced through FDASIA, and that is to
5 deliver safe and effective drugs for the treatment
6 of rare and severely life-threatening diseases. I
7 don't know a better candidate for accelerated
8 approval than a drug that apparently its only side
9 effect is extended life.

10 (Applause.)

11 DR. ALEXANDER: Thank you very much. Will
12 speaker number 31 please introduce yourself?
13 Please state your name and any organization you are
14 representing for the record.

15 MR. VAISH: Hi. My name is Ryan, and I have
16 Duchenne. I am 13 years and 10 months old, and I
17 have been on eteplirsen for almost five years
18 without missing a single dose. Ever since I was
19 diagnosed, all the doctors are saying by the time
20 I'm 13, I would be in a wheelchair and not be able
21 to do things I can do now. But since I've been on
22 the medicine, I am still walking, swimming, playing

1 with my friends and my dog, which people say I
2 could not do at this age.

3 If someone asks me if the medicine is
4 working, I say I believe it is because I'm doing
5 stuff I should not be able to do at my age. If you
6 are 100 percent sure that this medicine is not
7 working, don't approve it. But if you're not
8 100 percent sure, then approve this medicine, help
9 other boys who share my struggle. Thank you.

10 (Applause.)

11 DR. ALEXANDER: Thank you. Please hold your
12 applause.

13 MS. VAISH: I am Ana, and Make Duchenne
14 History Coalition arranged for us to be here today.
15 I am Ryan's mother. As he said, he is 13 years and
16 10 months old, and one of the 12 boys getting
17 eteplirsen since 2011. He hasn't missed a single
18 dose and has had no safety issues.

19 When Ryan started the study, he was
20 declining. He walked with lordosis and his toes
21 pointed inwards due to the weakness in his hips,
22 both signs that he would lose ambulation soon.

1 He did not look like a child with Duchenne
2 that you would expect to see walking four years
3 later. However, since 2011, Ryan has maintained
4 the same energy and ability to do day-to-day
5 things, like walk, go to school, play with his
6 friends, go swimming, and shower by himself.

7 We have not given Ryan any more PT or
8 anything other than the recommended care. Before
9 being on the trial, Ryan used to come home from
10 school very tired. Now on eteplirsen, he comes
11 from school and goes straight into the pool. In
12 fact Ryan has been receiving below the recommended
13 dose of steroids.

14 Until March of 2015, he was taking
15 18 milligrams of deflazacort, half of the
16 recommended dose. At that point, Dr. Mendell
17 increased his dose to 24 milligram because it was
18 still very low. That is still below the
19 recommended dose of 33 milligrams according to his
20 weight today.

21 The 0.9 increase in dystrophin may not mean
22 much to the reviewers at FDA, but come, look at the

1 10 boys that are still walking. Come live in the
2 shoes of these children, of my son Ryan, and it is
3 meaningful.

4 Every day that Ryan maintains his ability to
5 walk and live longer matters. Maintaining the
6 ability to do day-to-day things matter. More time
7 matters. More time for our family and hope for
8 even more treatments that will reach your desk soon
9 for approval. The first safe and effective
10 treatment is on your desk today. Please recommend
11 approval of eteplirsen.

12 (Applause.)

13 DR. ALEXANDER: Thank you very much. Will
14 speaker 32 please come to the microphone? Please
15 state your name and any organization you are
16 representing for the record.

17 MS. DWYER WILLIS: My name is Alison Dwyer
18 Willis. I am the mother of Jack and Nolan Willis,
19 patients number 9 and 10 of the original 12 Sarepta
20 clinical trial participants. Before I speak, I
21 think you should hear from them since they are two
22 of the most important voices in the room today.

1 JACK WILLIS: My name is Jack Willis, and I
2 am patient number 9 in the Sarepta trial.

3 NOLAN WILLIS: My name is Nolan Willis, and
4 I am patient number 10 in the Sarepta trial.

5 JACK WILLIS: We have chosen to dedicate the
6 last five years of our lives to this clinical
7 trial, quite willingly. Since we have lost the
8 ability to walk, we have been labeled as the
9 failures of the eteplirsen trial. We come here
10 today not only to show that we are not failures,
11 but to claim victory.

12 NOLAN WILLIS: We claim victory because our
13 lives improved while on drug. Our hearts and lungs
14 performed normally. We had some increase in
15 strength. We noticed when we had to skip a dose we
16 are more tired and lethargic. We know this drug
17 will keep us alive longer.

18 JACK WILLIS: Duchenne patients don't die
19 from not walking, they die from heart and lung
20 failure. We are almost 15 years old with normal
21 function, something which is not necessarily normal
22 for other Duchenne kids our age. We did not have

1 one side effect while we have been on eteplirsen.

2 NOLAN WILLIS: We are not outliers. We have
3 followed the natural progression of Duchenne, which
4 has now changed due to eteplirsen. Even though we
5 stopped walking four years ago, we are still able
6 to pick books off the table, feed ourselves
7 independently, drink without a straw, and brush our
8 teeth without help.

9 JACK WILLIS: We are not failures because we
10 stopped walking. Please stop calling us that.
11 This drug not only preserves the ambulation -- this
12 drug is not only to preserve ambulation, like we
13 said. You don't die from Duchenne by not being
14 able to walk. Maybe had we been on drug sooner, we
15 would still be walking. Why would you make other
16 boys wait when this drug could allow them to walk
17 longer, to feed themselves longer, to hug their
18 parents longer, to live longer?

19 MS. DWYER WILLIS: I was nervous that the
20 boys would not qualify for this trial knowing that
21 Nolan's ambulation was already rapidly declining.
22 Our goal for this trial was not to preserve

1 ambulation. It was to preserve their quality of
2 life and allow them to live longer, period.

3 Nolan took his last steps in February of
4 2012 and Jack joined him in June of that year.
5 They fought hard to stay on their feet as their
6 walking days were really gone before they even
7 started the trial.

8 My boys became known as the kids who were
9 making the data messy, who declined in the 6-minute
10 walk test, who lost ambulation, and everyone began
11 to question if the drug was working.

12 My boys make the data stronger because they
13 are responders, they are making dystrophin. The
14 drug is working in them. The production of
15 dystrophin has changed the trajectory of their
16 disease. My boys regained some upper arm and torso
17 strength, were less fatigued, and regained some of
18 their independence that had been lost.

19 In their case, loss of ability to walk
20 independently has still not preceded a decline in
21 pulmonary function. Thanks to eteplirsen, both of
22 my boys are experiencing a clear deviation from the

1 natural disease course. My sons should give the
2 ad comm panel members confidence that the drug is
3 working in both ambulatory and non-ambulatory boys.
4 Both populations will benefit from the approval of
5 eteplirsen. Thank you.

6 (Applause.)

7 DR. ALEXANDER: Thank you very much. Will
8 speaker 33 please introduce yourself? Please state
9 your name and any organization you are representing
10 for the record.

11 MS. JOHNSON: Our travel was supported by
12 the Make Duchenne History Coalition. My name is
13 Alex Johnson, and I have come here with 42 parents
14 from Britain who have children with Duchenne.
15 We've traveled all this way for 0.9 percent of
16 dystrophin.

17 If eteplirsen gets rightly approved, we
18 would move our family here for 0.9 percent of
19 dystrophin. For those who were disappointed by 0.9
20 of dystrophin or don't know Duchenne well, this may
21 be viewed as an act of desperation. Although the
22 U.S. seems nice enough, we assure you, we would not

1 uproot our entire lives for something trivial.

2 Our decision rests firmly on scientific
3 research. It is well-known in the scientific
4 community that some exon 44 patients have
5 spontaneous exon skipping that results in revertant
6 fibers. This small amount of dystrophin leads to a
7 slower disease progression.

8 Just two days ago, the Bello paper was
9 published revealing that exon 44 patients have a
10 later median loss of ambulation than other
11 deletions on a Kaplan-Meier analysis. Two years
12 more walking is life changing for patients and
13 families.

14 MR. JOHNSON: The FDA calls into question
15 Sarepta's use of a matched natural history control.
16 They claim that the placebo arm of the drisapersen
17 study is a more appropriate control. Most of that
18 data came from European patients.

19 We know there is data from that study for a
20 duration of 2 and a half years, but the FDA has
21 only referenced the first year of data, then looks
22 to other natural history studies on an apparent

1 hunt for a comparator group that appears to
2 diminish eteplirsen's effects.

3 We would like to know when using these
4 untreated cohorts, such as the CINRG data presented
5 today as a comparator, did the agency apply the
6 appropriate filters, such as age greater than 7 and
7 baseline 6-minute walk score, to ensure the closest
8 possible apples to apples comparison.

9 MS. JOHNSON: We know that being in a trial
10 can incentivize functional improvement. Maybe at
11 first, these boys on this study were influenced by
12 what the briefing document describes as expectation
13 bias, motivation, and coaching. Maybe.

14 But this is Duchenne we're talking about,
15 and we want the panel to know that every parent
16 motivates their child to keep walking. Every
17 parent loses that fight. Every parent, except
18 those of the 10 out of 12 boys on this study; yes,
19 they were motivated, but motivation alone cannot
20 account [mic off].

21 (Applause.)

22 DR. ALEXANDER: Thank you very much. Will

1 speaker 34 please introduce yourself? Please state
2 your name and any organization you are representing
3 for the record.

4 MS. FURLONG: My name is Pat Furlong, and I
5 am president and CEO of Parent Project Muscular
6 Dystrophy. I have nothing financial to disclose.

7 On Friday, April 29th, my son Patrick died.
8 He was just 15. He was Billy Ellsworth's age. He
9 stopped walking at 9, and at the time of his death,
10 he couldn't lift his hand to his mouth.

11 I spent those last nights with him
12 attempting to remove secretions from pneumonia. It
13 felt like I was suctioning concrete through a
14 straw. Patrick was tired, and he tried to smile,
15 but we knew it was goodbye.

16 Like my son Christopher, who died 7 months
17 earlier on September 29th, Patrick had no options.
18 None. Christopher and Patrick followed the
19 predicted natural history. They were off their
20 feet at 10 years old, and they died in their teens.

21 Today we're talking about a drug with
22 significant great impact, one that is focused on

1 the fundamental defect in Duchenne, restoring
2 dystrophin. Eteplirsen is safe. Four years of
3 safety data with no adverse effects, no SAEs, none
4 whatsoever. We can argue small numbers. We can
5 argue about the quantification of dystrophin.

6 What is critical to discuss is the impact of
7 an incremental effect. A positive incremental
8 effect has a ripple effect across a lifetime.
9 Extending ambulation, preventing scoliosis,
10 delaying the need for ventilation, improving family
11 stability, decreasing the financial impact in terms
12 of accommodation, school, home, employment, and
13 most of all, improving and preserving the quality
14 of life.

15 We've done a benefit-risk study about
16 incremental benefit. The overwhelming priority of
17 the parents that participated was slowing disease
18 progression. These are important milestones,
19 measures of intermediate endpoints that should
20 serve as a future reference point for all
21 regulators and developers.

22 Your goal, the FDA, is to improve how an

1 individual feels, functions, and survives. If you
2 ask these boys, I think they would say absolutely
3 to that. So that's going to require considerable
4 flexibility for all rare disease assessments.

5 Congress agreed and provided tools such as
6 accelerated approval. In addition, they told you
7 to listen to the patient voice. Inclusion of the
8 patient in decision making and those choices will
9 be best be heard via the more creative approaches
10 to rare disease development, which better capture
11 patient centered outcomes.

12 Patient-focused tools are of limited value
13 if we continue to operate in a rigid and
14 adversarial manner. Today, I'm asking for a
15 paradigm shift for all parties, FDA and industry,
16 to commit themselves to a fundamentally
17 collaborative approach, both in this eteplirsen
18 decision and in hopefully the many future INDs and
19 DNAs that come before you. I urge the committee to
20 exercise maximal flexibility. [mic off].

21 (Applause.)

22 DR. ALEXANDER: Thank you very much. Will

1 speaker 35 please introduce yourself? Please state
2 your name and any organization you are representing
3 for the record. Once again, please hold your
4 applause until all speakers have finished.

5 MS. KELLY: My name is Melanie Kelly, and I
6 have two sons with Duchenne muscular dystrophy,
7 Jacob and Liam.

8 MR. KELLY: My name is John Kelly. I'm
9 Melanie's husband.

10 MS. STELLY: My name is Trina Stelly. I
11 have one son who is 12 with Duchenne, and I have an
12 8-year-old daughter who is a manifesting carrier.

13 MS. PEASE: My name is Katherine Pease. I
14 have one son 8 years old with Duchenne muscular
15 dystrophy.

16 MR. DENGER: My name is Brian Denger. Our
17 group represents those who are amenable in this
18 therapy and relive the agony of missing the
19 threshold for inclusion in this clinical trial. We
20 are living the history of Duchenne muscular
21 dystrophy.

22 We read in the briefing documents how FDA is

1 not impressed by the slowed progress of the
2 eteplirsen patients because boys with Duchenne can
3 lose ambulation between ages 8 and 18. We are
4 concerned the reviewers are confusing something
5 that is possible with something that is common.
6 Are there outliers who are walking at 18? Yes. Is
7 it common? No.

8 I have two sons affected by Duchenne.
9 Matthew stopped walking at 8. His was a steady
10 decline in physical ability leaving him unable to
11 perform activities of daily living by 12. He
12 succumbed to heart failure at 20.

13 His brother, Patrick, who is now 21, stopped
14 walking at age 13. Though he walked longer, his
15 progression followed the same path as his brother,
16 just several years later.

17 We long came to appreciate that preserving
18 function would be important and a life changing
19 breakthrough. The difference in being able to walk
20 longer, Patrick did at age 13, meant he didn't need
21 spinal fusion surgery, unlike his brother who
22 stopped walking at 8 and needed surgery at 13.

1 The level of ability of participants in
2 Sarepta's trial exhibit is far different than what
3 any of our sons experienced. Walking independently
4 at 14, 15 is not the norm for someone who has
5 Duchenne. These patients are walking well.

6 If you witnessed the last months of walking
7 for someone with Duchenne, you'd realize how
8 starkly different this truly is. In the final year
9 of walking, not only do patients tire and have a
10 significantly slower pace, but they fall, and they
11 fall hard regularly.

12 Nearing the end, they need someone to help
13 them stand, hold them upright while they find their
14 balance, only to walk a meter or 2, not 6 minutes,
15 before collapsing into a heap and wait to be picked
16 up. No amount of motivation stops that tree from
17 falling. That's not the same experience we see for
18 the boys in the study. They walk with more balance
19 and confidence.

20 We represent the patients who are amenable
21 to this drug, and not one of our boys walked past
22 the age of 13. As a parent who has lost a son to

1 Duchenne, I don't need a reminder of how time
2 passes so quickly. We wait and watch as function
3 is lost never to be regained. Each of us asks, how
4 much longer. Thank you.

5 (Applause.)

6 DR. ALEXANDER: Thank you very much. Will
7 speaker 36 please introduce yourself. Please state
8 your name and any organization you are representing
9 for the record.

10 DR. NELSON: My name is Stanley Nelson. I'm
11 a professor of human genetics and co-director of
12 the Center for Duchenne Muscular Dystrophy at UCLA,
13 and I have no financial interest in the outcome of
14 the meeting today. I care for children with
15 Duchenne and am an expert in genetic and genetic
16 modifiers. I've served on clinical trials, data
17 monitoring committees, and advisory boards related
18 to Duchenne.

19 DuchenneConnect is the largest online
20 registry, and in 2014, my group published a
21 multivariate analysis looking at all 78 parameters
22 collected and identified that the most strong

1 correlate with age at loss of ambulation was by far
2 the use of steroids. This is using a hard endpoint
3 of age at loss of ambulation. There was a minor
4 difference between daily deflazacort usage and
5 daily prednisone.

6 I'll also comment that the effect of LTBP4,
7 which was brought up by Glen Nuckolls on the
8 advisory committee, would be of minor concern in
9 comparing these sample sets, partly because the
10 LTBP4 allele, the haplotype, seen in a homozygous
11 state would only be present in about 10 percent,
12 and the effect of LTBP4 observed in three
13 independent studies is much smaller than the effect
14 observed by steroids, so controlling for steroids
15 is most important.

16 I can also give you a little bit of a
17 personal take in terms of the hard point of loss of
18 ambulation. I'm also here as the father of Dillon,
19 age 15, living with Duchenne. He lost his ability
20 to walk at age 13 and a half. Most boys that I
21 know socially, and Dillon in particular, are very
22 resistant to this transition and fight hard to push

1 it back as long as possible.

2 This is the case for Dillon and makes age at
3 loss of ambulation actually a rather hard endpoint.
4 You can change it by weeks, maybe months; extending
5 it longer is actually very difficult to do. It
6 makes it also an irreversible and highly
7 undesirable endpoint with substantial consequences
8 to his environment and care needs.

9 I know this well, and this point has been
10 brought up by several in the open public hearing
11 and in the Sarepta presentation, that Dillon lost
12 ambulation at 13 and a half and is therefore on the
13 slightly more mild end of Duchenne, and that's
14 supported by multiple natural history data. And
15 yet, when he was 9, his 6-minute walk distance, as
16 determined by being in a different clinical trial,
17 would have compelled him not to be a part of this
18 clinical trial.

19 So the boys that are at the outlier end,
20 those boys that are still walking at age 14, 15,
21 16, also tend to have better physical measurements
22 at ages 7, 8, 9 and 10, the exact group that

1 Sarepta was hoping to exclude from this.

2 I'll also note that many of these opinions
3 were shared in a letter drafted by 36 experts in
4 Duchenne that actually do support that there is
5 substantial evidence of efficacy for eteplirsen
6 based on the clinical data and based on the
7 reasonable comparison to multiple external
8 data sets. Thank you.

9 (Applause.)

10 DR. ALEXANDER: Thank you very much. Will
11 speaker 37 please introduce yourself? Please state
12 your name and any organization you are representing
13 for the record.

14 MR. PROCKO: We are Bill and Kim Procko, and
15 thank you to CureDuchenne for our travel and
16 lodging arrangements. Our son, Evan, is one of the
17 original 12 participants. During the course of
18 this trial, we have observed profoundly positive
19 changes to his physical condition, each one of them
20 contradicting normal Duchenne disease progression.
21 Here is what 0.9 percent can do.

22 Natural history suggests that once a boy

1 with Duchenne loses the ability to get up off the
2 floor, he will also lose the ability to walk within
3 the next 12 to 24 months. Evan remains walking
4 3 years and 2 months after losing this ability.

5 Prior to eteplirsen, Evan slept fitfully
6 through the night, his fists clenched so tightly we
7 could hardly pry his fingers open, his calves in
8 full contracture. After eteplirsen, Evan's sleep
9 became relaxed, his palms open, calves soft,
10 without contracture. Evan's body now rests and
11 recovers at night as it should.

12 Prior to eteplirsen, Evan fell 2 to 3 times
13 per week. During the course of this trial, Evan's
14 fall frequency has reduced to 1 fall every 2 to
15 3 weeks. The amount of Evan's daily walking has
16 remained nearly the same.

17 Prior to eteplirsen, Evan's digestive
18 process was noticeably slower than it is today,
19 with bowel movements 3 to 4 days apart requiring
20 laxatives. At present, bowel movements occur daily
21 without aid. His diet has always been healthy.
22 The only change has been eteplirsen.

1 On September 6, 2015, Evan suffered a spiral
2 fracture to his right tibia. We knew that a broken
3 leg and subsequent muscle atrophy from weeks in a
4 cast for a 12-year-old with Duchenne more often
5 than now spells the permanent end of ambulation.
6 For Evan, however, after 7 weeks in a cast and
7 boot, he stood up and walked unassisted.

8 According to his UF Schanz orthopedic staff,
9 recovery time was indistinguishable from any non-
10 Duchenne patient, and on November 2nd, only 8 weeks
11 after his fracture, Evan was back in Ohio
12 performing two successful 6-minute walk tests for
13 Sarepta.

14 These observations contradict Duchenne
15 progression. In the last four years, we've done
16 nothing out of the ordinary concerning protocol
17 with Evan's care except for eteplirsen. The FDA's
18 January briefing documents stated that the boys in
19 our study have received intensive physical therapy.
20 The date of Evan's last physical therapy
21 appointment was May 13, 2009. At home, we do a set
22 of stretches 4 to 5 times per week. If anything,

1 this falls below recommended PT regimen.

2 MS. PROCKO: The benefits we have presented
3 from 0.9 percent dystrophin are significant to us.
4 Now, I wonder how many more years does that
5 0.9 percent give Evan independence to pour more hot
6 sauce on his burrito or to wrap his arms around me
7 in a hug.

8 Duchenne has taken away Evan's dystrophin.
9 Eteplirsen has given him some back. Now, it's in
10 your hands to allow him to keep it or take it away
11 from him again.

12 (Applause.)

13 DR. ALEXANDER: Thank you very much. Will
14 speaker 38 please introduce yourself? Please state
15 your name and any organization you are representing
16 for the record.

17 MS. PENROD: My name is Marissa Penrod, and
18 my son Joseph has Duchenne. My son and the sons of
19 the parents standing with me here right now are
20 waiting for a treatment. This was a significant
21 year for Joseph. It was the year that Duchenne
22 stole Joseph's ability to walk. I assure you, he

1 had no choice. He wanted desperately to keep
2 walking. It was not a question of motivation or
3 mindset. Joseph lost ambulation because he has
4 Duchenne.

5 We tend to think of loss of ambulation as
6 the end of something, the end of walking, but
7 really it's just a new beginning. It's the
8 beginning of a new kind of decline. Decline in
9 Duchenne comes in many forms. Dave and Maria's son
10 Ryan, and Kelly's son Jack, demonstrate the immense
11 burden of Duchenne through their struggle with
12 self-image.

13 Anessa's teenage son, Tyler, can no longer
14 go to his friend's house because they're not
15 accessible. Natalie's son, Max, can no longer move
16 his arms to scratch his own face. And Kat's [ph]
17 son, Dusty, has just 12 percent of his lung
18 function remaining. He is literally on his last
19 breaths.

20 I know that Joseph's arm strength will go
21 next. He won't be able to feed himself. I will
22 have to hold a book for him to read, and hugs will

1 be a memory. We will face scoliosis, spinal
2 surgery, pulmonary distress, heart failure. The
3 loss of ambulation matters, but what matters more
4 than losing ambulation is maintaining ambulation.

5 Thanks goodness for eteplirsen. Today
6 should not be a day for uncertainty or fear, it
7 should be a day of celebration. We know that many
8 clinical trials and potential treatments comes with
9 risk. Not this one. We know that some decisions
10 you have to make are clouded by uncertain clinical
11 benefits. Not this one.

12 Today we should celebrate and honor the
13 truth, and we must not be distracted from that
14 truth. Four years later, 4 biopsies later, that
15 surgery under general anesthesia, they're still
16 walking. How much more will you ask of them? When
17 will their sacrifice be enough?

18 The FDA gave guidance to Sarepta in April of
19 2014 urging them to identify matched natural
20 history cohorts. You can't move the target now, it
21 is too late and our sons deserve better. Our kids
22 are not your science experiment. They're not a

1 sample or a cohort or a subject. They're someone's
2 brother and son, someone's grandson, and student,
3 and best friend. Our children are not here to
4 serve the science, but the science must always
5 serve our children, and eteplirsen does that.

6 If not you to acknowledge the evidence that
7 eteplirsen works, if you not honor the tools give
8 to you by Congress and FDASIA to demonstrate
9 flexibility, then who will? It's time to stop
10 talking about flexibility and to show us. We don't
11 hope you do the right thing, we expect you to do
12 the right thing, and the right thing is to say yes.

13 (Applause.)

14 DR. ALEXANDER: Thank you very much. Will
15 speaker 39 please introduce yourself? Please state
16 your name and any organization you are representing
17 for the record.

18 DR. JUHASZ: Hello. My name is Rose Juhasz,
19 from the University of Michigan Medical School,
20 support by Make Duchenne History. My son is in the
21 confirmatory study control arm amenable to exon 53
22 skipping. My comments today are coming both as a

1 parent and as an academic colleague who has worked
2 for nearly 15 years in the study and support of
3 personalized medicine. I currently manage a
4 \$13 million NCI research program on precision
5 medicine in early stage breast cancer.

6 I could stress that precision medicine is
7 also here to treat children, and that we do so by
8 skipping exons. Instead, I refer you to a recent
9 JAMA neurology viewpoint by noted clinician
10 scientist Eva Feldman. She concluded, and I quote,
11 "Exon skipping offers tremendous promise, and the
12 impact on Duchenne patients may alter the practice
13 of neuromuscular medicine by bringing personalized
14 genetic therapies."

15 I could praise the FDA's accelerated
16 approval paths for select treatments in early stage
17 breast cancer. It's helped to render that disease
18 highly survivable and rich with treatments. We
19 desire similar flexibility for just a first
20 treatment in Duchenne. Without it, this is
21 disparity, and our children deserve better.

22 As today is about children, I'll share on a

1 clinical cohort I find relevant. Completing my own
2 doctoral work, I had the privilege to study some of
3 the first deaf kids to receive cochlear implants.
4 They were implanted at relatively old ages after
5 prolonged auditory deprivation. The FDA did not
6 initially favor implanting kids earlier despite
7 known critical periods for speech and language and
8 preserving auditory function.

9 Positive outcomes in those first kids were
10 not immediate. Those who did respond needed years
11 of device use. For others, it was too late to get
12 full benefit from a technology now known as
13 groundbreaking.

14 Those were children failed by the FDA
15 process. The technology was there for years;
16 access was delayed. These are kids who will then
17 live out the rest of their lives knowing that the
18 quality of life could have been quite different had
19 it not been for regulatory disparities and delays
20 for children. Despite those odds and having
21 received the first devices, there were some stand
22 out responders. They became known in our research

1 group as the stars.

2 Today you have met the stars of exon
3 skipping. They have walked up here and stood and
4 told you that this drug is working and important
5 for them. And as I stand here 15 years later,
6 please hear this message.

7 No child should have waited then for the
8 chance to hear, and no child today should be
9 waiting this long to keep walking or to continue to
10 use his limbs. This is a fatal disease. We cannot
11 afford to fail them. Thank you.

12 (Applause.)

13 DR. ALEXANDER: Thank you very much. Will
14 speaker 40 please introduce yourself? Please state
15 your name and any organization you are representing
16 for the record.

17 DR. SHIEH: Good afternoon. Yes, my name is
18 Dr. Perry Shieh, and I'm an associate professor of
19 neurology at UCLA, where I serve as the clinic
20 director of the muscular dystrophy clinic. I would
21 like to ask if somebody could pull up the slides
22 for speaker number 36.

1 It's through this clinic that I currently
2 care for approximately 100 boys and men with
3 Duchenne muscular dystrophy.

4 DR. ALEXANDER: I'm sorry, we're unable to
5 provide those slides at this time.

6 DR. SHIEH: Okay. That's fine. And I'm
7 also an investigator in numerous clinical trials
8 for Duchenne muscular dystrophy, including three
9 ongoing clinical trials involving eteplirsen. I
10 think the most important question today is whether
11 eteplirsen works. Is whether eteplirsen clinically
12 improves Duchenne muscular dystrophy patients. And
13 I do like to thank the FDA for their caution and
14 their extensive discussion about the potential
15 shortcomings of the study data.

16 Nonetheless, I would like to emphasize that
17 the study data do show reasonable substantial
18 evidence of efficacy. I would like to echo the
19 opinions of my colleagues before me that loss of
20 ambulation is truly a hard endpoint. It is not
21 something that is optional.

22 Generally, people who are not able to do

1 6-minute walk test will not be able to do anything
2 very soon. And looking at the study data, looking
3 at loss of ambulation as a function of a drug
4 exposure seems to be the most appropriate way to
5 analyze the data because baseline characteristics
6 and baseline 6-minute walk tests do predict the
7 future outcome, the future course of these boys.

8 Now, one may argue that the 4-year data was
9 not blinded. It was not a placebo-controlled
10 study. However, this is an issue of perhaps
11 placebo effect, and many publications have
12 indicated in the past that placebo effect is
13 generally small, temporary, and relatively
14 subjective.

15 The placebo effect would not prevent
16 Duchenne boys, based on a hard endpoint such as
17 loss of ambulation, from losing ambulation.
18 Placebo effect cannot prevent them from losing the
19 ability to walk. In fact, I believe it is the
20 collection of study data over four years of this
21 very progressive disease that makes this data very
22 convincing and robust, and it would not be possible

1 to perform the double-blind placebo-controlled
2 study over the same amount of time.

3 So although 12 patients may seem like a
4 relatively small number for a clinical trial, the
5 effect observed is still impressive. Of course, we
6 would like the sponsor to complete the confirmatory
7 studies that are already ongoing that will have
8 many more patients, but the data have presented so
9 far are persuasive, and additional safety data from
10 ongoing studies, I do not believe that there's any
11 reason to limit access to this medication.

12 In other words, I would like to be able to
13 prescribe this medication to other Duchenne boys
14 who are amenable exon 51 skipping. The risk of
15 harm appears to be minimal. And with close
16 monitoring, I believe this is the best way to
17 acquire additional information about this effective
18 treatment. Thank you.

19 (Applause.)

20 DR. ALEXANDER: Thank you very much. Will
21 speaker 41 please introduce yourself? Please state
22 your name and any organization you are representing

1 for the record.

2 DR. MCNALLY: Thank you. My name is
3 Elizabeth McNally. I am a physician and scientist.
4 I direct the Center for Genetic Medicine at
5 Northwestern University in Chicago. I'm also a
6 cardiologist who specializes in providing care for
7 those with neuromuscular disease.

8 I'm a physician in the Muscular Dystrophy
9 Association Clinic at Northwestern Medicine, where
10 I work closely with neurology and pulmonary experts
11 caring for those with advanced Duchenne muscular
12 dystrophy. I have no consulting relationship with
13 Sarepta. I have no bias in looking at the data
14 here today.

15 Boys with DMD grow to be men with DMD, and
16 they should not be forgotten here today in this
17 discussion. There's been much focus and emphasis
18 on walking as an endpoint in DMD, but walking is an
19 not an endpoint for a young man with DMD.

20 Retaining upper limb strength is important
21 for being able to eat, drive a wheelchair, type on
22 a keyboard, and hold a job. These are the

1 endpoints that matter. Walking is a surrogate for
2 what happens to many muscles in DMD.

3 We know well from the earliest genetic DMD
4 studies that the amount and quality of dystrophin
5 production is the primary determinant of outcome in
6 this disease. Dystrophin production linearly
7 correlates with outcome. There has never been
8 shown to be a threshold effect under which
9 dystrophin level does not matter. Any increase in
10 dystrophin is meaningful.

11 The goal of exon skipping is to convert the
12 more severe form of disease, DMD, to the milder
13 form of disease, Becker muscular dystrophy, but
14 what does that really mean?

15 I think of the many DMD guys I take care of.
16 I think of Ryan and I think of Joe in particular.
17 They have DMD. They went to college, they
18 graduated, but it was hard to find work with the
19 fact that they had lost so much upper limb
20 strength, and post-college life has been hard for
21 them. With even modest improvement in upper arm
22 strength, they would be able to do so much more.

1 I am also a scientist and an established
2 investigator in the neuromuscular field for more
3 than 20 years. As a scientist, the FDA conclusions
4 regarding dystrophin quantitation presentation are
5 most puzzling. We heard that three independent
6 veterinary pathologists arrived at different
7 quantitative values than the pathologist from
8 Nationwide Children's Hospital, and based on this
9 discrepancy, the immunofluorescence results were
10 devalued.

11 The dismissal of the immunofluorescence data
12 seems to be skipping the critical point that these
13 veterinary pathologists identified a clear
14 difference between treated and untreated patients,
15 17 percent versus less than 1 percent.

16 It is implied that immunoblotting is somehow
17 superior to immunofluorescence microscopy, and this
18 is plainly inaccurate. Blotting methods are
19 hampered by the large size of dystrophin, its high
20 susceptibility to proteolysis, and the challenges
21 in extracting dystrophin adequately from fibrotic
22 muscle.

1 Blotting fails to take into account for the
2 regional distribution of dystrophin expression
3 within a muscle. To be fair and unbiased, both
4 blotting and fluorescence methods should be
5 considered together.

6 Today, we saw data that eteplirsen treated
7 boys walk longer, walk farther, have more
8 dystrophin on blotting, and on fluorescence.
9 Moreover, this drug is safe. It seems prudent to
10 recommend accelerated approval based on the data.

11 (Applause.)

12 DR. ALEXANDER: Thank you. Will speakers
13 number 42 introduce yourselves? Please state your
14 name and any organization you are representing for
15 the record.

16 MR. MARQUEZ: My name is Ethan Marquez. I
17 am joined by Kadee Roden, Christina Burrell, and
18 Sandra Katzin. Each one of us has a son with
19 Duchenne muscular dystrophy and enrolled in the
20 confirmatory trial of eteplirsen.

21 Our boys are between the age of 10 and
22 13 years old and have been taking eteplirsen for

1 approximately one year. We all have noticed our
2 boys doing things they weren't able to do before
3 the trial, and I'm here to share our stories.

4 Before eteplirsen, Sandra's son, Ethan, was
5 extremely lethargic, unable to walk for long
6 distances. Today, he can walk alongside his mother
7 without getting exhausted. His stride is more
8 stable. He does not fall as much as he used to.

9 This is important to note because a
10 reduction of Duchenne falls is a commonly reported
11 result of eteplirsen. This is a massive quality of
12 life improvement because it means he is less likely
13 to fall and injure himself.

14 Christina's son, Xavier, and Kadee's son,
15 Morgan, have also experienced an increase in
16 strength since being on eteplirsen. Since starting
17 the trial, they have the ability to keep up with
18 their friends at school and not come home
19 exhausted. Xavier can independently dress himself,
20 comb his hair, put on his shoes.

21 DR. ALEXANDER: I'm sorry for interrupting.
22 If you're having conversations, can you please have

1 those outside.

2 MR. MARQUEZ: Tie his shoes, and even brush
3 his teeth. These are daily tasks that he could not
4 do before eteplirsen. Since my son, Peyton,
5 started on eteplirsen over a year ago, my wife and
6 I have seen him stabilize, gain his strength, and
7 even move in ways he has never done before. This
8 has not happened to a boy with Duchenne. We've all
9 seen eteplirsen working.

10 Before starting the trial, Peyton could not
11 kick his foot above the air, now he can kick his
12 foot above his waist.

13 (Laughter.)

14 MR. MARQUEZ: Before eteplirsen, he was
15 unable to pull himself out of our pool. He would
16 just barely hang onto the edge. Now he can pull
17 himself out. He used to struggle to climb into our
18 SUV and onto his bed, now he can do both with ease.
19 Before he came home exhausted and needed a nap.
20 Now he has the stamina to participate all day in
21 school and after school activities, and even stay
22 awake until bedtime.

1 Eteplirsen has given us hope for his future.
2 We no longer plan his funeral. Now, when Peyton
3 talks about driving, attending college and becoming
4 a scientist, because of eteplirsen, we believe it's
5 possible.

6 I implore you, recommend this drug. It is
7 clear to us, our sons, our children's teachers,
8 family and friends that eteplirsen works. It is
9 safe and needs approval so many of the boys have a
10 chance. We already know the results without
11 eteplirsen.

12 This committee has the ability to recommend
13 that the FDA approve a drug that will improve the
14 quality of life for our entire community. It will
15 lead to other breakthroughs. To not approve it for
16 many other boys that are suffering, that have
17 suffered, and that will suffer in the future is not
18 only confusing but outright cruel. Substantial
19 evidence of the effectiveness of eteplirsen is
20 clear. Thank you.

21 (Applause.)

22 DR. ALEXANDER: Thank you very much. Will

1 speaker 43 please introduce yourself? Please state
2 your name and any organization you are representing
3 for the record.

4 DR. CHAMBERLAIN: My name is Jeff
5 Chamberlain, and I'm a professor of neurology at
6 the University of Washington. I'm also director of
7 the Senator Paul D. Wellstone Muscular Dystrophy
8 Research Center, and I'm a paid member of the
9 Sarepta scientific advisory board.

10 I've been studying the molecular genetics of
11 DMD for 30 years with a focus on dystrophin
12 expression and the development of gene therapy.
13 For these goals, my lab has developed transgenic
14 mice, we've developed adenoviral vectors,
15 lentiviral vectors, and AAV vectors in order to
16 study how much dystrophin is needed to prevent or
17 to reverse the pathophysiology of DMD.

18 We've also been looking at the relative
19 effects of producing full length Becker-like and
20 micro dystrophin proteins in muscle. These studies
21 have been remarkably consistent in showing that
22 very low levels of dystrophin can have significant

1 effects on muscle function.

2 Now, it was mentioned earlier that
3 dystrophin levels as low as 10 percent of normal
4 can prevent and largely reverse the dystrophic
5 pathology, and our data and animal models certainly
6 agrees with that. However, those levels are
7 essentially what are needed for a cure, and we're
8 not here today talking about a curative therapy.

9 It's very important to emphasize that our
10 studies of animal models also showed that much
11 lower levels of dystrophin have a clear and
12 measurable impact on muscle function, and this is
13 true whether we're expressing full length
14 dystrophin, Becker-like dystrophins, or even the
15 micro dystrophins that were developed in my
16 laboratory.

17 Our studies of dystrophin function have also
18 demonstrated a mechanical role mediating the
19 lateral transmission of force from within a
20 myofiber into the extracellular matrix. And the
21 consequence of this is that a single dystrophin
22 positive myofiber has a clear protective effect on

1 adjacent dystrophin negative myofibers.

2 Thus, the overall protection that's
3 conferred by low dystrophin expression is greater
4 than what you would predict by a simple comparison
5 to normal dystrophin levels, and it's greater than
6 you would see just by looking at the percent of
7 dystrophin positive fibers. We have clear data
8 that even a single dystrophin positive fiber
9 protects adjacent fibers, so patchy or mosaic
10 expression of dystrophin has a wider effect than
11 just counting dystrophin positive fibers. In fact,
12 our studies indicate that any dystrophin expression
13 has a beneficial effect on overall muscle function
14 and physiology.

15 In summary, our data in animal models
16 acquired through a variety of different methods
17 predict that the dystrophin expression patterns
18 that have been observed with eteplirsen are
19 sufficient to achieve a significant increase in
20 muscle function. Thank you.

21 (Applause.)

22 DR. ALEXANDER: Thank you very much.

1 Because we're running over, I'd like to take a
2 break now. So we'll take the afternoon break at
3 this time. So this is going to substitute for the
4 break that would be coming up at the end of the
5 open public hearing. So we'll take a 15-minute
6 break at this time. Thus, we'll come back at 10
7 minutes after 5, 5:10.

8 Panel members, please remember that there
9 should be no discussion of the meeting topic during
10 the break amongst yourselves or with any member of
11 the audience. Once again, we'll resume at 5:10.

12 (Whereupon, at 4:55 p.m., a recess was
13 taken.)

14 DR. ALEXANDER: If you can please take your
15 seats. We're going to be beginning in just a
16 minute with open public hearing speaker number 44
17 in just a minute.

18 (Pause.)

19 DR. ALEXANDER: Okay. Out of respect for
20 those public speakers, if you are still conversing
21 and wish to continue, please do so in the hallways.
22 And we'll be beginning now where we left off which

1 is with speaker number 44.

2 If speaker number 44 could introduce
3 yourself, please state your name or any
4 organization you are representing for the record.

5 MR. WOLF: We appreciate the break, but you
6 can't ice this kicker so thank you.

7 I'm Brian Wolf, and I am joined by exon 45
8 and 53 waiting group, and our travels was arranged
9 by the Make Duchenne History Coalition.

10 Our group consists of Amy Aikens,
11 Chris Daimler and Cindy Quitzau. We represent
12 Duchenne patients in need of access to follow-on
13 drugs, specifically exon skipping 45 and 53, and we
14 fully support the approval of eteplirsen.

15 We are here to support our Duchenne
16 community for exon skipping 51 and believe that
17 future exon skipping drugs will advance with the
18 approval of this first drug. While we wait, our
19 sons continue to get weaker and we are running out
20 of time.

21 Four and a half years ago, we began to hear
22 and see the stories of continued ambulation and

1 increased flexibility and zero side effects in the
2 patients in the eteplirsen 201/202 trial aside from
3 their encouragement. We also see the publicly
4 released data and were encouraged by eteplirsen's
5 unprecedented results. We need to include the rest
6 of our Duchenne family in this huge vehicle of
7 hope.

8 The approval of eteplirsen would be our
9 first critical step in getting this new life-saving
10 technology in the hands of other Duchenne patients,
11 including our sons. The FDA has the authority to
12 approve this drug next month and make a meaningful
13 difference in the lives of families.

14 As parents, we have become advocates,
15 speakers, caregivers, educators, and fighters, and
16 we have passed those traits to our sons and
17 daughters, those with Duchenne and those without.
18 Despite how the media sometimes portrays us, we are
19 not desperate parents. We are educated in the
20 data, the expert scientists and clinicians support
21 us, and we are not willing to give our children a
22 drug that isn't safe or doesn't work.

1 The FDA in this division have wavered with
2 their guidance far too many times, which in turn
3 has delayed the opportunity for our sons to receive
4 the needed exon skipping drug. Today, you have
5 renewed opportunity to follow FDASIA and use the
6 tools Congress has provided FDA to expedite access
7 of life-saving treatments to patients who need
8 them.

9 Today, we ask the committee to consider the
10 total and quality of eteplirsen's data and the
11 patient and expert testimony and please, recommend
12 eteplirsen for accelerated approval.

13 Our community has already experienced many
14 unnecessary delays related to this drug. Do not
15 waste any additional time so that thousands of
16 other waiting Duchenne patients from our group that
17 we represent can make Duchenne history by outliving
18 their diagnosis. Thank you.

19 DR. ALEXANDER: Thank you very much.

20 (Applause.)

21 Will speaker number 45 please come to the
22 podium and introduce yourself? Please state your

1 name and any organization you are representing for
2 the record.

3 MR. KUNKEL: Yes. My name is Lou Kunkel
4 from Boston Children's Hospital in Boston, in the
5 Department of Genetics and Pediatrics at Harvard
6 Medical School. I am a paid member of Sarepta's
7 scientific advisory board, and my travel here was
8 paid for by Make Duchenne History Consortium.

9 My laboratory was the laboratory which
10 identified the gene responsible for Duchenne
11 dystrophy back in 1986. In 1987, we described the
12 encoded protein, dystrophin, and we showed that
13 major mutations at this two-and-a-half megabase
14 locus were deletions in both the severe Duchenne
15 form of dystrophy, as well as the milder form of
16 Becker muscular dystrophy.

17 We proposed, at the time, that the
18 difference between deletions in Duchenne patients
19 and Becker patients were based on the effect they
20 had on the translational reading frame of the
21 encoded protein. We predicted Duchenne patients
22 would make no protein because they would have

1 premature stop because they've disturbed the
2 reading frame, whereas Becker patients would have
3 an internally truncated protein but that it would
4 be made.

5 We showed, in 1988, that protein was not
6 being made in Duchenne biopsies, published in the
7 New England Journal of Medicine. And in that
8 article, we talked about the limit of our
9 detection. This is in 1988, and this is where this
10 3 percent number comes from.

11 Eric Hoffman used both myocin staining
12 post-transfer to estimate underloaded gels and said
13 that he couldn't probably see below 3 percent. But
14 that's a long time ago, and the technology has
15 changed a lot since then. Becker patients were
16 shown to make an abnormal truncated protein of
17 variable degrees of levels of the protein.

18 This led us to propose, as Steve Wilton did,
19 that, potentially, we should try to block the
20 inclusion of exons and convert a Duchenne into a
21 Becker by interchanging the reading frame and
22 producing protein.

1 Sarepta's eteplirsen is designed to block
2 exon 51 in 13 percent of dystrophin deletion
3 patients. They documented that exon skipping 51 is
4 skipped based on RTPCR, so the mechanism of action
5 of that drug is working. They document on
6 immunofluorescence that the protein is being made,
7 albeit at not quantifiable levels but way above
8 what we've ever seen for revertant fibers.

9 But for me, the best evidence was their
10 Western blots, which showed 0.9 percent. We never
11 see 0.9 percent in patient biopsy samples, and so
12 this is really an appreciable amount. Consistent
13 with this was the clinical progression. These make
14 dystrophin, its safe, and I believe there's no
15 reason not to approve.

16 (Appause.)

17 DR. ALEXANDER: Thank you very much. Will
18 speaker number 47, please come to the podium and
19 introduce yourself?

20 MS. LEFFLER: I'm 46.

21 DR. ALEXANDER: I'm sorry, 46. Will speaker
22 46, please introduce yourself? Thank you. Please

1 state your name and any organization you are
2 representing for the record.

3 MS. LEFFLER: My name is Mindy Leffler, and
4 I'm here representing my family. We are listening
5 to two versions of reality today: Sarepta's is
6 that a group of boys who are on the cusp of
7 decline, took an experimental drug, and progressed
8 slower than expected. The FDA's is a group of boys
9 with DMD who frequently walked past the age of 13.
10 Sarepta lucked into a group of them, and everything
11 else you're hearing today in support of efficacy is
12 either wishful thinking or coincidence.

13 Here is my son's story, and you can decide
14 which it supports. Aiden screened for the study
15 we're evaluating today. He walked too far to fit
16 the inclusion criteria and he was not included. We
17 went with plan B, which ended up being the placebo
18 arm for driaspersen, the very data set cited in FDA
19 briefing documents as the most accurate control for
20 eteplirsen.

21 So he was too functional for the eteplirsen
22 study, and yet somehow he's the perfect control for

1 it.

2 When Aiden was on driaspersen, I relied on
3 casual observation to draw my conclusions. By the
4 time he was off drug, I had nothing definitive to
5 say. So at age 11, when Aiden was put on
6 eteplirsen, I was not going to rely on observation.
7 I wanted to be objective about how he was doing
8 because I didn't want him spending any more time on
9 a drug that might not work.

10 I picked the things he struggled with the
11 most: getting off the floor, going upstairs,
12 getting in a car, and spontaneous collapsing. I
13 took a video at regular intervals and I kept a
14 daily log of collapses.

15 So I am not standing up here with anecdotes
16 about how strong my son was on drug and simply
17 asking you to trust me. I'm saying that I put
18 together a perspective PRO program on Aiden when he
19 started eteplirsen, and I captured data regularly
20 in a rigorous way.

21 On eteplirsen, Aiden went from collapsing
22 2 to 5 times per day to not collapsing anymore, at

1 all. On eteplirsen, Aiden regained the ability to
2 pull himself into the car independently for the
3 first time in over a year. As of this morning, he
4 can still do it. I would challenge anyone to find
5 that kind of progression, regaining definitively
6 lost milestones anywhere in the natural history of
7 Duchenne.

8 The briefing documents spend a great deal of
9 time criticizing each piece of data independently,
10 but if you look at the data as a whole, either
11 eteplirsen works or there are a whole lot of
12 coincidences pointing in the same direction.

13 Medical students are often told when they
14 hoof beats to think of horses, not zebras; look to
15 the obvious conclusion rather than searching for
16 the unlikely. It is now time to stop hunting
17 zebras.

18 (Applause.)

19 DR. ALEXANDER: Thank you. Please hold your
20 applause until the last speaker has spoken. Will
21 speaker 47 please introduce yourself? Please state
22 your name and any organization you are representing

1 for the record.

2 DR. DAY: Yes. My name is John Day. I'm a
3 professor of neurology and pediatrics at Stanford
4 University. And I appreciate having the
5 opportunity to address the advisory committee to
6 provide my perspective on the importance of making
7 eteplirsen available for treating Duchenne.

8 I've received financial support from Sarepta
9 for scientific consultation. My travel to the
10 meeting was supported by the Make Duchenne History
11 Coalition, but I have no direct financial interest
12 in the outcome of today's meeting.

13 I direct the Stanford Neuromuscular Program,
14 Stanford Duchenne Comprehensive Care Center, where
15 we see Duchenne patients from a large part of
16 Northern California. For the preceding two decades
17 before moving to Stanford, I was director of the
18 neuromuscular program, the Paul and Sheila
19 Wellstone Muscular Dystrophy Center, and the
20 Duchenne Comprehensive Care Center at the
21 University of Minnesota, where I saw patients from
22 the Upper Midwest and where I also ran my own CLIA

1 certified neuromuscular biopsy lab.

2 I've rewritten my talks to basically focus
3 on specific issues the FDA brought up in their
4 review, so I won't be needing any of the slides.

5 First, regarding the adequacy of the control
6 group, it matches my own experience. During the
7 course of my career, I've diagnosed and cared for
8 250 boys with Duchenne muscular dystrophy, more
9 than 20 of whom had exon 51 skippable mutations.
10 Despite optimal care, none of those boys walked
11 beyond 12 years of age. This clearly differs from
12 the eteplirsen 201/202 experience where boys
13 continued to walk for 3 to 4 years of treatment at
14 ages greater than 12.

15 In addition to my experience with Duchenne
16 natural history, we have 4 subjects at Stanford
17 involved in current eteplirsen studies, all have
18 remained ambulatory, ages 9-11, and are functioning
19 well in multiple respects with no side effects.

20 Second, in terms of questions regarding
21 reliability of age of loss of ambulation, we can
22 agree with Dr. Farkas' contention that a placebo

1 arm differs from a natural history study. But my
2 experience is that boys try to keep walking as long
3 as possible and that the difference of several
4 years between walking and non-walking, by my
5 experience, mirrors the results in the Italian
6 registry, and the eteplirsen's results are striking
7 and meaningful.

8 Furthermore, in a slide of speaker
9 number 36, Stan Nelson, you can see a statistically
10 significant difference in the Duchenne Connect data
11 regarding the Kaplan-Meier curve for loss of
12 function of eteplirsen compared to steroids alone.

13 In essence, I'm convinced that eteplirsen
14 improves the course of Duchenne by multiple
15 measures, and I strongly urge its approval.

16 (Applause.)

17 DR. ALEXANDER: Thank you very much. Will
18 speaker 48 introduce yourself? Please state your
19 name and any organization you are representing for
20 the record.

21 MR. LOPEZ: My name is Roger Lopez, and I
22 represent the International Association of

1 Firefighters as the IAFF MDA national coordinator.
2 We have no financial interest in this.

3 The IAFF is a nonprofit labor organization
4 representing over 300,000 firefighters and
5 emergency medical service providers in the United
6 States and Canada. Our members serve cities,
7 towns, and fire districts in every state and
8 territory. Our members protect the communities
9 that are home to over 85 percent of the population
10 of the United States.

11 The IAFF is based in Washington, DC within a
12 network over 3200 local affiliates. For over
13 60 years, the IAFF has stood shoulder-to-shoulder
14 with the Muscular Dystrophy Association in the
15 ongoing fight against the more than 40
16 neuromuscular diseases that are claiming the lives
17 of our children and our fellow firefighters.

18 Through our Fill the Boot campaigns, the
19 IAFF has helped MDA fund the research that is now
20 resulting in the development of breakthrough
21 therapies for these devastating diseases. To date,
22 we are proud we have contributed over a half

1 billion dollars of funds to help find an end to
2 diseases like Duchenne, \$26 million just last year.

3 Our commitment to this fight is unwavering.
4 This year alone, more than 162,000 of our
5 firefighters volunteered their time in more than
6 3000 events across the country to raise money to
7 support this mission.

8 But our hard work and dedication go beyond
9 our commitment to fill the boot. We are in this
10 fight at a personal level. Every year, many of our
11 firefighters from around the country dedicate a
12 week of their time to volunteer to MDA summer
13 camps. These are wonderful places where kids can
14 go to get a traditional summer camp experience
15 despite the challenges they face.

16 Last summer, many of our firefighters had
17 the chance to share the week with these amazing
18 children. I, myself, have participated every year
19 for the past 13 years. I look forward to it every
20 summer. It is truly a life-changing experience.

21 Through our many years of working with the
22 MDA and the families they serve, we understood the

1 impact of this disease, and we want to see
2 effective options for every one with Duchenne and
3 the other related diseases become available.

4 I am not here today as an expert on the
5 science, but we as firefighters want to take this
6 opportunity to express our support for finding
7 therapies that can improve and save the lives of
8 the people that we love, people living with
9 muscular dystrophy.

10 We have helped lead this fight for more than
11 half a century, and we are proud of the IAFF's many
12 contributions, and will continue this fight to
13 fulfill the promise from our earliest days of our
14 partnership to join forces and fight back until
15 cures are found.

16 I have 16 seconds left, and I want to relate
17 to the families, how important you all are to us
18 and that we've been doing this for 60 years, and
19 we're here for you. And we're going to be here for
20 you until we find a cure. Thank you.

21 (Applause.)

22 DR. ALEXANDER: Thank you very much. Will

1 speaker 49 please introduce yourself? Please state
2 your name and any organization you are representing
3 for the record.

4 DR. CWIK: Good afternoon, I'm
5 Dr. Valerie Cwik, representing the Muscular
6 Dystrophy Association. I have no personal
7 financial relationship with the sponsor, but MDA
8 receives contribution for educational support and
9 conferences from a number of drug companies
10 targeting therapies for muscular dystrophy,
11 including Sarepta. And some of our board members,
12 because they have expertise in this field, from
13 time-to-time are paid to consult with drug
14 companies, again including Sarepta.

15 I'm pleased to be here today on behalf of
16 MDA and the thousands of Duchenne families that we
17 represent. At the outset, I'd like to share MDA's
18 optimism that there will soon be treatment options
19 to change the course of Duchenne muscular dystrophy
20 and that eteplirsen could be the first of what we
21 hope will be many new treatments for MDA families.

22 As chief medical and scientific officer at

1 MDA and as a neurologist and former MDA care center
2 director, I've worked with many families living
3 with Duchenne. I'm reminded that my 25 years of
4 medical specialty in the neuromuscular diseases is
5 about the same amount of time that the average
6 person with Duchenne can expect to survive, and
7 this is a reality that is unacceptable to MDA.

8 MDA has led the search for treatments and
9 cures for Duchenne for more than a half century and
10 will continue to do so until there is a cure.
11 Twenty years ago, we funded foundational exon
12 skipping research and follow-on studies that led to
13 the development of eteplirsen. And while not a
14 cure, the data indicates that the drug could slow
15 disease progression.

16 Many leaders in the Duchenne research and
17 clinical communities have voiced enthusiastic
18 support for eteplirsen, and as a science and
19 evidence-based organization, their support carries
20 great weight with us.

21 All of us at MDA, as well as our sister
22 organizations, scientific community, families and

1 supporters have been working tirelessly to see a
2 time like the present, a time when therapies could
3 be more than just a hope for the future. We are
4 all here for those living with Duchenne and the
5 people who love them.

6 It is time that treatment options shift from
7 being a goal to being reality. While the decision
8 of whether to approve a drug is ultimately a
9 regulatory science determination for the FDA, given
10 the support of Duchenne scientific and clinical
11 leaders, the support of the families we serve, the
12 urgent and unmet medical need, and the strong
13 safety data, we urge you to strongly consider all
14 of the tools available to the FDA to allow the
15 earliest possible access to eteplirsen. Thank you.

16 (Applause.)

17 DR. ALEXANDER: Thank you very much. Will
18 speaker 50 introduce yourself? Please state your
19 name and any organization you are representing for
20 the record.

21 MS. HICKMAN: My name is Chelsie Hickman,
22 and I'm reading a statement on behalf of

1 Shannon Dematteo, the mother of one of the 12 study
2 participants who started in 2011.

3 "On March 3, 2008, at 5 years old, our son,
4 Jack, was diagnosed with Duchenne muscular
5 dystrophy. Jack's doctor never described him as an
6 outlier, and as far as we could tell, he followed
7 the normal progression of Duchenne.

8 "When Jack was 8 years old, we began
9 traveling to Columbus, Ohio from Chicago every
10 Sunday for a Monday infusion in the eteplirsen
11 study.

12 "I've heard that the FDA thinks that the
13 benefit that the boys in the trial with Jack may
14 have seen was because they started steroids early
15 or their steroid dose or standard of care was far
16 better than those in the natural history group.
17 But I would like to let you know that Jack started
18 at age 6 and was dosed correctly for his weight.
19 He received stretching as physical therapy every
20 other week for about an hour and now swims once a
21 week, neither of which could be described as a
22 rigorous, intensive regiment.

1 "Never once, in the three-plus years of Jack
2 receiving eteplirsen has he had an adverse reaction
3 to it, not a fever, not a cough, not a headache,
4 nothing. In fact, most of the time, we noticed
5 that the day after his infusion is often one of the
6 best days of his week as far as his energy level
7 and his physical abilities.

8 "Because we understand Duchenne, we were
9 fully prepared to be taking care of a child who was
10 wheelchair-bound by the time he was 10 or 11. When
11 Jack was 11, he was playing on the school's
12 volleyball team.

13 "Our kids all go to Catholic school in a
14 very old building that's not ADA accessible. He
15 was able to walk up and down the stairs several
16 times a day, every day in school, until he was in
17 5th grade.

18 "Jack, at 13 and a half, is still declining
19 but at a much slower rate than we expected. He
20 needs help getting up from the ground, and he uses
21 a scooter or wheelchair to get around for distance.
22 But for the majority of his life, he is completely

1 independent. Like all of the 7th graders in our
2 neighborhood, he walks around with his friends to
3 go to the park, out to eat or just to hang out.
4 He's on the student council at school, is the
5 assistant coach manager for every one of the school
6 sports teams, and he has more friends than we can
7 count.

8 "Because of eteplirsen, Jack has been able
9 to enjoy a far more normal and active life than we
10 ever could have dreamed. We thank God every day
11 for our good fortune. We know Jack one of the
12 lucky ones, and we know that other boys, like Jack,
13 would benefit from being on this drug." Signed,
14 Shannon and Tom Dematteo.

15 (Applause.)

16 DR. ALEXANDER: Thank you very much. Will
17 speaker 51 introduce yourself? Please state your
18 name and any organization you are representing for
19 the record.

20 MS. LEFFLER: I'm introducing my son's video
21 testimony on his experiences on eteplirsen. We
22 chose to have him submit video testimony because we

1 didn't want him to come here and realize that his
2 access to eteplirsen was at risk.

3 Aiden, you see, is a warrior. In his
4 testimony, you'll see a series of videos of Aiden
5 trying to get into the car. At the start of the
6 study, I did not tell Aiden how long it might take
7 for eteplirsen to work because I did not want to
8 bias his performance.

9 The first video was taken over a month into
10 the study. Aiden is frustrated at this point
11 because he is convinced that the drug doesn't work.

12 Two weeks after this video was taken, in
13 fact, he asked me if he could quit the study
14 because he was tired of hospitals and needles
15 without seeing benefit.

16 Members of the advisory committee, please
17 watch my son regain function with your own eyes.
18 Ask yourself how it could be placebo-controlled or
19 placebo effect if he is convinced the drug doesn't
20 help.

21 Survey what you know about Duchenne and ask
22 yourself how likely this video would be if

1 eteplirsen doesn't work. It is not enough to
2 listen to our words and send us on our way. You
3 are charged with using our words to inform the
4 decisions that you make and hear our Aidens.

5 (Video played and transcribed.)

6 AIDEN LEFFLER: My name is Aiden and I'm 12
7 years old. I have Duchenne muscular dystrophy.
8 I've been on eteplirsen for only a little over a
9 year, 62 visits. I stopped being able to get
10 myself into our car about 9 months before started
11 eteplirsen.

12 I used to wait by the car door, and then mom
13 would pick me up in the arms and lift me into the
14 car. It's embarrassing at school being picked up
15 like that in front of friends. And then it all
16 changed.

17 I would like to show you some clips of how
18 life has treated me since I started this drug, at
19 the beginning of the trial, 5 months in and 7
20 months in. And it really has been changed.

21 (Pause.)

22 AIDEN LEFFLER: My mom was more than scared

1 I wasn't going to be able to walk anymore. But
2 then I started eteplirsen, and now I'm able to do
3 everything I was before.

4 Now, you'll see me downstairs playing soccer
5 for hours at a time. Now, I can use the car ramp,
6 now by myself. I taught myself. Thank you,
7 eteplirsen. Thanks for giving me a chance to be
8 normal, to do what I want to do.

9 I'd like to end my presentation with a video
10 of me playing catch with Russell Wilson,
11 quarterback with Seattle Seahawks.

12 (Laughter.)

13 AIDEN LEFFLER: Thanks to eteplirsen I'm
14 able to enjoy moments like this, moments that every
15 boy waiting for eteplirsen deserves.

16 (Applause.)

17 DR. ALEXANDER: Thank you very much. Our
18 final speaker is speaker number 52. If you could
19 introduce yourself. Please state your name and any
20 organization you are representing for the record.

21 MS. McLINN: My name is Laura McLinn. I
22 paid my own way here, and I have no financial

1 interest in today's outcome.

2 My 6-year-old son, Jordan, is a candidate
3 for exon skipping, but is not yet able to receive
4 the drug. On Thursday, I received a phone call
5 from United State Senator, Joe Donnelly. He asked
6 if I would read a letter that he and three other
7 senators wanted to share with you today. He's in
8 our home state of Indiana today and regrets that he
9 cannot be here personally. I won't have time to
10 read the entire letter, so I will share some key
11 points.

12 "In 2012, Congress provided additional tools
13 to facilitate new therapies intended to treat
14 persons with life-threatening and severely
15 debilitating illnesses, especially when no
16 satisfactory alternative exists.

17 "We write today to underscore the focused
18 efforts of Congress to provide for and encourage
19 accelerated review of promising therapies,
20 prioritize the patient perspective in evaluating
21 new drugs and treatments, and provide regulators
22 with flexibility to expedite evaluations of drugs

1 for life-threatening illnesses for not only
2 Duchenne but all rare and severe diseases.

3 "FDA regulations state that it is
4 appropriate to exercise the broadest flexibility in
5 applying the statutory standards. As members of
6 Congress, representing constituents who are
7 battling rare and severe diseases with unmet
8 medical needs, we wholeheartedly agree with this
9 viewpoint and we urge the FDA to ensure this
10 flexibility is applied in reviewing all candidate
11 therapies.

12 "The cost of unnecessary delays manifests in
13 terms of human lives. And therefore, urgency on
14 this matter to patients and their families is
15 absolute. Thank you for your attention to this
16 important matter."

17 This is signed by four United States
18 senators: Ron Johnson, Thomas Carper,
19 Joe Donnelly, and Dan Coats.

20 As you know, there are similar letters from
21 the United States Congress highlighting these
22 points, especially the requirement that the FDA

1 consider the perspective of patients during
2 regulatory discussions.

3 There seems to be a challenge with measuring
4 dystrophin. That doesn't mean it's not there. It
5 means maybe more work needs to be done in this
6 area, right? I mean really, we don't have a true
7 scientific piece of evidence that explains how we
8 even exist but we do exist, right?

9 (Laughter.)

10 MS. McLINN: Do we need a piece of
11 scientific evidence to proof the amount of
12 dystrophin? Your evidence is right here in this
13 room. And because of FDASIA, you are not only
14 allowed to use that evidence, but you have a lawful
15 and ethical responsibility to do so.

16 Every person in this room has been given a
17 shot at this thing called life. We didn't deserve
18 it, but God gave it to us anyway. There is no
19 lawful, moral, scientific, or ethical reason to
20 deny these well-deserved boys a chance to live
21 their lives and fulfill their own destinies. Let's
22 do the right thing. Let's make Duchenne history

1 today.

2 (Applause.)

3 **Questions to Committee and Discussion**

4 DR. ALEXANDER: Thank you very much,
5 speaker, and for all the speakers that participated
6 in the open public hearing. We'll now proceed with
7 the questions to the committee and panel
8 discussions.

9 I'd like to remind public observers that
10 while this meeting is open for public observation,
11 public attendees may not participate except at the
12 request of the panel.

13 I also want to remind the panel as there's
14 an extraordinary amount of information that we
15 could talk about and lots and lots of interesting
16 areas for discussion, so please, keep your
17 questions crisp. And for those that are responding
18 to questions, either on the part of the FDA or the
19 sponsor, please keep your answers crisp and concise
20 as well. Thank you.

21 So we'll move to the first question at hand,
22 which was provided to all of the panelists. The

1 question itself is to discuss the evidence
2 presented about dystrophin production, including
3 the following: A) the strength of evidence that
4 eteplirsen increased the amount of dystrophin in
5 muscles of treated patients relative to their
6 baseline; and B) the clinical meaning of the amount
7 of dystrophin observed in the muscles of
8 eteplirsen-treated patients, taking into the
9 consideration the range of amounts of dystrophin
10 known to be typically present in patients with DMD
11 and in patients with Becker muscular dystrophy.

12 I'll also point the panelists, there is a
13 little bit of discussion that precedes this actual
14 question that's posed, if that's helpful for you to
15 review again, but I think that we've heard the
16 content of that in the presentations from both the
17 sponsor and the FDA.

18 So with this, we'll open for discussion.
19 The first question, which is a non-voting question,
20 discuss the evidence presented about dystrophin
21 production.

22 Dr. Green?

1 DR. GREEN: Okay. I think there is moderate
2 evidence for dystrophin production. However, I
3 think it's more difficult than that because at the
4 end of the day, we don't really have a clue as to
5 how much is clinically significant.

6 We also, at least I don't, have a clue about
7 this dystrophin that's manufactured, whether it is
8 effective, the same or better than native
9 dystrophin. So I think it's a very difficult
10 biomarker.

11 DR. ALEXANDER: Thank you. I'm sorry.
12 Dr. Onyike?

13 DR. ONYIKE: If I recall from Dr. Farkas'
14 testimony earlier, it would appear that there are
15 some people who have very, very low levels of
16 dystrophin and much better clinical function than
17 you'd anticipate from that -- am I recalling that
18 correctly?

19 So it seems to me, therefore, that there
20 might not even exist the threshold of effect but
21 rather, it's possible that dystrophin couples in
22 some way that is indirect to function.

1 I recall that -- I think it was
2 Dr. Chamberlain and the gentleman also, the
3 investigator from Harvard, also suggested that the
4 levels of -- that it might take very low levels to
5 achieve a significant clinical effect.

6 Now, the question is whether that would be
7 universal or whether it would only apply to a
8 subset of individuals. And if so, what are the
9 other markers that might indicate or that might
10 predict how dystrophy links to clinical effect?

11 So in other words, it's ambiguous. I agree
12 with Dr. Green in that sense, that it's very
13 ambiguous.

14 DR. ALEXANDER: Thank you. And am I
15 understanding you correctly that you're pointing
16 out that it's ambiguous with regard to whether
17 there's a threshold effect or not, but also was
18 there a second part of that, what else may couple
19 with the absolute amount of dystrophin to produce
20 the clinical response that one sees?

21 DR. ONYIKE: Well, first of all, I suspect
22 that there may not be threshold per se or that the

1 threshold may vary widely perhaps on an individual
2 or in the subgroup way, and that we have no idea
3 what that range is. But it may very well dip very
4 low.

5 Does that clarify?

6 DR. ALEXANDER: Yes, thank you.

7 Dr. Kesselheim?

8 DR. KESSELHEIM: To me, a lot of the answer
9 to this question of whether there's an increased
10 amount of dystrophin in the muscles depends to a
11 lot of extent on the methods being used to assay
12 that. I guess I wasn't convinced or I'm still
13 questioning whether the biopsies that were taken
14 were the correct biopsies and why it was that the
15 two different muscle groups were compared. And I
16 was dismayed by some of the inconsistencies and the
17 availability of the comparative evidence.

18 So I think that because of those various
19 things, it makes it pretty hard to draw a firm
20 conclusion about point A.

21 DR. ALEXANDER: Thank you. Other comments?

22 Dr. Hoffman?

1 DR. HOFFMAN: Yes. I think there's plenty
2 of evidence that the mechanism of action for
3 eteplirsen is producing dystrophin. Both the PCR
4 testing, the immunofluorescence, and the Western
5 blot all have indicated, many times in all
6 different species, that mechanism of action.

7 DR. ALEXANDER: Thank you. Yes, I didn't
8 hear Dr. Kesselheim or others question the
9 mechanism of action. What I heard was that
10 conclusions about whether or not there's a large
11 amount produced depends upon the methods used to
12 assess this, and also some concern regarding
13 whether the biopsies were the correct biopsies or
14 not and concern regarding the quality of the
15 comparative evidence.

16 DR. HOFFMAN: I read the question as, is
17 eteplirsen producing --

18 DR. ALEXANDER: Can you speak into the
19 microphone more please?

20 DR. HOFFMAN: Yes. I think the question --

21 DR. ALEXANDER: I'm sorry. State your name
22 also for the record.

1 DR. HOFFMAN: Yes. Richard Hoffman. I
2 think there's plenty of evidence in all those
3 different testing methods that show that the
4 mechanism of action of eteplirsen is to skip
5 exon 51 and produce dystrophin. I don't think
6 there's any question about that. It's not only in
7 humans but in other species.

8 DR. ALEXANDER: Thank you. Dr. Ovbiagele?

9 DR. OVBIAGELE: Perhaps I'm not reading this
10 correctly, but as I understood it, one of the big
11 challenges here was the issue of not enough pre-
12 and post-treatment comparisons on the same
13 patients; so no matched baselines. And that's
14 exactly what the A question is asking.

15 So for me, there isn't the evidence there
16 because the comparisons were with other controls
17 but not necessarily the pre- and post. Is that
18 correct?

19 DR. FARKAS: Yes, that's the concern.

20 DR. ALEXANDER: Thank you. I'm transcribing
21 while we go. Other comments regarding question 1?
22 Ms. Gunvalson?

1 MS. GUNVALSON: I agree with Richard
2 that --

3 DR. ALEXANDER: I'm sorry. Can you please
4 state your name for the record?

5 MS. GUNVALSON: My name is Cheri Gunvalson,
6 and I agree with Richard that the issue was to
7 produce dystrophin, and we did produce dystrophin,
8 or the drug did, as Dr. Kunkel said. And I believe
9 we're seeing clear benefit from it. I know
10 hundreds of boys with Duchenne, my son included,
11 and you just don't see this clinical benefit.

12 DR. ALEXANDER: We will be discussing
13 benefit, but for right now we're focused strictly
14 on the dystrophin production in terms of the
15 strength of evidence, that the drug increased the
16 amount of dystrophin and also the clinical meaning
17 of the amount produced.

18 So do you feel that the amount produced is
19 sufficient to explain the clinical benefit?

20 MS. GUNVALSON: Yes, I do believe. And as
21 the physician down there said, we don't know the
22 exact amount. There are Becker boys that produce

1 very, very trace amounts that look very, very good.
2 We just don't know that.

3 So I don't -- for me, the fact that it
4 produced dystrophin and there are some boys and
5 young men with very scant amounts that do very
6 well, it's difficult to know the clinical benefit.

7 You know, I think we're all learning here,
8 not only the physicians and the FDA. This is a
9 learning process. There's never been a drug
10 approved. So that's my opinion.

11 DR. ALEXANDER: Thank you very much.

12 Dr. Woodcock?

13 DR. WOODCOCK: I would like to talk about
14 the order of this question. Question 1B, all
15 right, whether the clinical meaningfulness, you're
16 going to talk about that next as far as the
17 strength of the clinical data. However, what might
18 influence your assessment of whether the dystrophin
19 is actually clinically meaningful might be the
20 clinical data from the study or studies that were
21 done.

22 So if you're talking about this first,

1 you're going to have to think about what you think
2 about the clinical studies in relation to the
3 amount of dystrophin that has been produced, if you
4 follow me.

5 DR. ALEXANDER: Thank you. Yes.
6 Dr. Kryscio?

7 DR. KRYSCIO: Yes, the other Richard,
8 Richard Kryscio. Would like to ask Richard, since
9 you know these measurement techniques a lot better
10 than I do, where is the dose effect? I didn't see
11 any dose effect when they looked at 50 versus 30.

12 DR. HOFFMAN: Well, you're talking about a
13 dose ranging study, and really that hasn't been
14 accomplished. Maybe there's not enough of a
15 difference between 30 and 50 in animals. As far as
16 I know, in mice, they've gone up to 900 milligrams
17 per kilogram; and in dogs, I think they've gone up
18 as high as 200 milligrams per kilogram. And I
19 think at those higher doses, you would see the dose
20 effect.

21 I think one of the problems here is it's
22 been described by several people, the expression of

1 dystrophin in the muscle is regional or what's been
2 described as patchwork-type fashion that it's
3 produced after exon skipping. So if you're taking
4 a biopsy, it just represents a very, very small
5 part of the total musculature. And that particular
6 biopsy may not show as much, but there might be
7 other areas where there's very high amounts of
8 dystrophin produced, and that's where the
9 beneficial effects would be occurring.

10 That's just my opinion and from what I've
11 read.

12 DR. ALEXANDER: Thank you. Just a comment
13 that I'll make -- Caleb Alexander -- is just
14 the -- I'm surprised that there's not more
15 consensus. I accept that there may not be, but
16 it's surprising to me that there's not more
17 consensus, scientific consensus, regarding what
18 would constitute clinically meaningful levels of
19 dystrophin.

20 I will say that I think that the sponsor
21 question, the adequacy of Western blot data,
22 arguing that it really can't be compared with

1 published reports, but also made the case that in
2 prior reports of BMD, Beckers, that dystrophin
3 levels are between 2 and 100 percent.

4 The fact that there were also -- it sounds
5 as if early in the clinical development program,
6 there were estimates that dystrophin levels may
7 have increased as much as 20 to 50 percent, which I
8 think we would all argue or believe or feel would
9 be incredible results relative to, for example,
10 what we're seeing here.

11 Now, I'm referring to the actual
12 quantification with Western blot, and that clearly
13 was a pivotal event that appears to have had a very
14 profound impact on the subsequent decisions that
15 the sponsor and the FDA reached regarding the next
16 steps in the development program.

17 Dr. Romitti?

18 DR. ROMITTI: Yes. Paul Romitti. So in
19 looking at this and thinking about laboratory
20 methods in general, I think they're constantly
21 evolving. We are what we are today and we have the
22 best methods available.

1 While we may not know enough as we wish we
2 would with regard to dystrophin levels, I think
3 that after the instruction by the FDA to have three
4 blinded reviewers, I felt more confident with those
5 results, study sample aside, than I did with just
6 one reviewer, which I think is not quality science.

7 So I think even though the amount may have
8 been less and it may have been less striking than
9 originally reported by that one reviewer, I still
10 think that there is evidence here that there is a
11 difference. And the evidence may not be high, but
12 I think back to many studies that I'm involved
13 with, which are other studies where we're trying to
14 study biomarkers of exposure, they're challenging.

15 As the laboratory methods get better, we get
16 better at doing it. We can do it better in animals
17 than we can in humans. But we get better and we
18 get better in humans.

19 So I think given the state of the science
20 today, I think that there is enough evidence here
21 to say that with the re-analysis and the rereads,
22 that we do see some difference in dystrophin.

1 (Applause.)

2 DR. ALEXANDER: Dr. Dunn and then
3 Dr. Onyike, and then we may move onto the next
4 question, keeping in mind that we have seven, and
5 we're projected to be about 45 minutes to an hour
6 over at this point.

7 DR. DUNN: Billy Dunn, FDA. You mentioned
8 the difference. I just want to make sure I fully
9 explore that so we understand. When you mention
10 the difference, that obviously implies difference
11 in A and B. Can you just talk a little bit more
12 about what specifically you find the difference
13 between?

14 DR. ROMITTI: I'm referring to the
15 difference in the tables that were shown that
16 showed the single reviewer versus the three blinded
17 reviewers, and there was still a difference, if I
18 recall, of 17. There was a still a total of 17
19 overall as opposed to --

20 DR. DUNN: Right. I'm sorry. I didn't
21 actually mean the data in presentation as much as
22 the change from what dystrophin,

1 where -- obviously, you're referring to the 0.9
2 that was observed. And I think what I really want
3 to try and understand is what change, do you think,
4 that represented, what the comparison is.

5 DR. ROMITTI: From the data that we have
6 been given, the comparison is around 0.08, is what
7 I recall the comparison is.

8 DR. ALEXANDER: Can we see the table,
9 please? I wonder if that would be helpful in
10 clarifying this point.

11 DR. BASTINGS: Yeah. If you can pull
12 Slide 37 of FDA presentation?

13 DR. ALEXANDER: Dr. Nuckolls, do you want to
14 first try -- I'm sorry. Dr. Romitti, do you want
15 to try to address? I think the question was --

16 DR. ROMITTI: Okay.

17 DR. ALEXANDER: What I understood you saying
18 was that you have more confidence in the three
19 blinded reviewers than just one reviewer, and so
20 the amount --

21 DR. ROMITTI: So there are two different
22 measures here of dystrophin. There's the positive

1 fibers and then we have the PCR -- the Western
2 blot, excuse me. So I'm lumping both into my
3 discussion. If you would like me to reserve my
4 discussion for one, that's fine.

5 So this is what I'm meaning here for one and
6 the other is the 0.9 versus the 0.08 with the, what
7 I'll call FDA-accepted method of analysis being the
8 Western blot.

9 DR. ALEXANDER: Okay. Can you try one more
10 time, please? Just to be sure we have it straight
11 on the record, just making the point again.

12 DR. ROMITTI: Okay. I'm taking a look at
13 both measures that were used. The sponsor's
14 original endpoint was positive fibers. And I'm
15 looking at this, and I'm saying I was uncomfortable
16 with the original analysis given it lacks
17 replication. I was more comfortable that there
18 appears to be some kind of change here with the
19 re-analysis by the blinded reviewers for this
20 approach.

21 But I'm also commenting on the FDA's
22 suggestion of using Western blot as well to

1 quantify dystrophin. And with that and with the
2 unknown threshold, if there is one, for what is
3 enough dystrophin to see change, I think both
4 provide evidence there has been some change.

5 DR. ALEXANDER: Okay. Thank you very much.
6 Dr. Onyike?

7 DR. ONYIKE: Yes. I was just intrigued
8 earlier by the commentary. I think it was from a
9 gentleman who is my line of sight about how
10 dystrophin effect might transfer beyond specific
11 fibrils to their neighbors. But I don't fully
12 understand how this might work. So perhaps you
13 might elaborate.

14 DR. ALEXANDER: Who is the question for?

15 DR. ONYIKE: Well, it was a professor in the
16 audience who had talked earlier about evidence that
17 fibrils might generalize -- I mean, sorry, that
18 dystrophin levels --

19 DR. ALEXANDER: I'd like to --

20 DR. ONYIKE: Well, if you can't do it,
21 that's fine.

22 DR. ALEXANDER: Yes, yes. I --

1 DR. ONYIKE: I was intrigued by --

2 DR. ALEXANDER: Sure. Thank you. I mean
3 for the record, I'd like to have the question be
4 known, but I think in the interest of being sure
5 that we give due consideration to the remaining
6 questions, we should move on, unless Dr. Ovbiagele
7 has a final comment on this?

8 DR. OVBIAGELE: No. I just wanted to say,
9 it's one thing to talk about change, but the other
10 thing is I think be asked about the clinical
11 correlation. So whether there's change or not is
12 one issue.

13 But if you remember, if you looked up the
14 four individuals with the best 6-minute walking
15 times, there was actually no correlation. Two of
16 them had the highest levels of dystrophin and two
17 has the lowest levels of dystrophin.

18 So to answer that question, the clinical
19 meaning is not clear based on that.

20 DR. ALEXANDER: Okay. Thank you very much.
21 So my job is to try to summarize what I've heard,
22 and this included the following. There's moderate

1 evidence for production of dystrophin, though we
2 don't have a clue how much is clinically
3 significant, also hard to know if what is produced
4 is as clinically active as natively produced normal
5 dystrophin. There might not be a threshold effect
6 or the threshold may vary wildly among individuals
7 with no idea what the range is, but it may dip very
8 low.

9 The conclusion about whether or not there's
10 a large amount produced depends upon the methods
11 used to assess this, not convinced that the
12 biopsies were correct biopsies or not; dismayed at
13 the quality of some of the comparative evidence;
14 plenty of evidence to support mechanism of action.

15 The big challenge is that there's not enough
16 pre- and post-treatment comparisons on the same
17 patients, and this is what question 1A is focused
18 on. Comparisons were with other patients.

19 The issue was to produce dystrophin, and the
20 drug did do this. Believe that we are seeing clear
21 benefit and that the amount produced is sufficient
22 to account for the clinical benefit observed;

1 whereas, the dose effect, maybe not enough of a
2 range examined in doses, and that might account for
3 the absence of a dose response.

4 The biopsy represents a very small part of
5 the musculature and may not show you as much.
6 There may be other areas where there are very high
7 amounts of dystrophin produced.

8 Surprising that we're not further along in
9 figuring out what amount of dystrophin would
10 constitute a clinically meaningful response and
11 also surprised that there's so little consensus
12 about this.

13 More confidence in the 3 blinded reviewers
14 than just one reviewer. Although the amount made
15 may have been less and less striking than initially
16 reported by the single reviewer, there's still
17 evidence that there is a difference. And this was
18 referring to both the immunofluorescence, as well
19 as the Western blot.

20 Belief that there's a change in the
21 reanalyzed data over time, but comparing that with
22 the Western blot data provided is difficult. And

1 we are asked about the clinical correlation, as
2 well as change, and we're asked to evaluate not
3 only the change in dystrophin levels but also the
4 clinical correlation. And the final point that I
5 heard was that there was no obvious correlation
6 between the dystrophin levels and the change in the
7 6-minute walk test.

8 So Dr. Woodcock?

9 DR. WOODCOCK: Yes. When you move to the
10 next question, I'd like to have a conversation with
11 the committee about what you're voting on, so
12 you're clear about what you're voting on,
13 question 2, in this part of the discussion.

14 DR. ALEXANDER: Thank you. We'll be sure to
15 do that.

16 So for voting questions, we'll first be
17 discussing the questions, subsequently voting on
18 it, but I'll read now for you about the voting
19 process.

20 For voting questions, we'll be using an
21 electronic system. When we begin the vote, the
22 buttons on your microphone will start flashing and

1 will continue to flash even after you have entered
2 the vote.

3 Please press the button firmly that
4 corresponds to your vote. If you are unsure of
5 your vote or you wish to change your vote, you may
6 press the corresponding button until the vote is
7 closed. After everyone has completed their vote,
8 the vote will be locked in.

9 The vote will then be displayed on the
10 screen. The designated federal officer will read
11 the vote from the screen into the record. Next, we
12 will go around the room and each individual who
13 voted will state their name and vote into the
14 record. You're also requested to please state a
15 very brief reason why you voted as you did if you
16 want to. We will continue in the same manner until
17 all questions have been answered or discussed.

18 So the voting question that we're posed with
19 is, has the applicant provided substantial evidence
20 from adequate and well-controlled studies that
21 eteplirsen induces production of dystrophin to a
22 level that is reasonably likely to predict clinical

1 benefit?

2 Dr. Woodcock?

3 DR. WOODCOCK: Yes. This is the standard
4 for accelerated approval. So this would be a vote
5 on whether or not that surrogate endpoint of
6 dystrophin is reasonably likely to predict clinical
7 benefit.

8 So this is a question about approvability,
9 and my point is that you have to factor in the
10 clinical data in this discussion, what weight you
11 think it gives to the reasonably likely decision.
12 So you're talking about, first, whether
13 question 1A, which you already discussed, whether
14 or not dystrophin was increased.

15 Now, reasonably likely, as you've already
16 discussed and I've mentioned in my opening remarks,
17 there is no standard established. And for this
18 condition, there is no threshold established
19 because there's never been a drug to do this.

20 So people don't know. They've looked at
21 natural experiments such as Becker's, and you see
22 that there is a range of response as was said

1 earlier. So the question that you're being posed,
2 if you follow me, is does the clinical experience
3 in these trials, with these patients, lead you to
4 believe, if you believe dystrophin was increased,
5 that that increase is reasonably likely to predict
6 a clinical benefit?

7 Do you follow me? Okay.

8 DR. ALEXANDER: Are there clarifying
9 questions for Dr. Woodcock or other members of the
10 FDA regarding the question?

11 (No response.)

12 Okay. If not, then we'll vote now. So once
13 again, the question is, has the applicant provided
14 substantial evidence from adequate and
15 well-controlled studies that eteplirsen induces
16 production of dystrophin to a level that is
17 reasonably likely to predict clinical benefit?

18 (Vote taken.)

19 DR. ALEXANDER: Please vote again in case
20 you haven't. Although your vote only counts once.

21 DR. CHOI: Everyone has voted. The vote is
22 now complete.

1 DR. ALEXANDER: Thank you.

2 DR. CHOI: For the record, we have 5 yes,
3 8 no, zero abstentions.

4 DR. ALEXANDER: So we'll now go around and
5 briefly state our name and vote into the record, as
6 well as a brief rationale for why you voted as you
7 did. So we'll begin with the first voting member
8 on this side.

9 DR. HOFFMAN: Richard Hoffman. I voted yes
10 because of all the reasons I mentioned earlier.

11 DR. ALEXANDER: Can you briefly state those
12 very succinctly?

13 DR. HOFFMAN: By all the testing methods
14 that were used, PCR, Western blot,
15 immunofluorescence, I believe that there is proof
16 that dystrophin was produced and that eteplirsen
17 was responsible for it.

18 DR. ALEXANDER: Thank you. Please proceed
19 around the room.

20 DR. GREEN: Okay. Mark Green. I voted yes.
21 I believe that dystrophin is made by the drug. As
22 I said before, I'm very troubled by not

1 understanding a clinically significant amount. And
2 I'm not sure at what level I'm supposed to say
3 this, but I've been extraordinarily influenced and
4 impressed by the people who spoke about this drug
5 earlier and their observations.

6 (Applause.)

7 MR. DUPREE: To me --

8 DR. ALEXANDER: State your name please.

9 MR. DUPREE: Benjamin Dupree. Do I state
10 what my vote was? I voted yes, and the reason
11 behind that is that it appears to me, as has been
12 described by Paul Romitti, that there's a change.
13 And I think given the clinical results that were
14 described, it's reasonably likely to predict
15 clinical benefit.

16 DR. ALEXANDER: Please just continue around
17 the room.

18 MS. GUNVALSON: I'm Cheri Gunvalson, and I
19 voted yes. I believe the dystrophin was produced,
20 and that was what the goal was. And I believe it's
21 demonstrated in the clinical abilities of these
22 boys, that you don't regain lost milestones in

1 Duchenne, never.

2 (Applause.)

3 MS. GUNVALSON: And I think that the
4 qualitative data was good, and I would hope that
5 the FDA would require qualitative data on future
6 studies, because as a public health nurse who does
7 studies on populations, we look at quantified data
8 and quality data. And in the trends in the quality
9 data, you can almost find out more. So number of
10 falls I think is tremendous information on how a
11 drug is working.

12 DR. ALEXANDER: Thank you. Dr. Kryscio?

13 DR. KRYSCIO: Richard Kryscio. I voted no.
14 I guess I'm the first no vote. I voted no because
15 I don't think the studies were well controlled. I
16 was concerned with using different tissue samples.
17 I was concerned about a lack of correlation that
18 people who have little or no -- people who had
19 substantial problems clinically may or may not have
20 had a lot of the dystrophin actually produced.
21 Perhaps it's a measurement issue, but that's the
22 reason I voted no.

1 DR. ROMITTI: Paul Romitti. And I hit the
2 wrong button. I apologize.

3 (Applause.)

4 DR. ALEXANDER: I'm sorry. Please hold your
5 comments. Dr. Romitti?

6 DR. ROMITTI: Yes. I'm sorry. I must have
7 hit in between, so I apologize for the -- if I
8 can't change my vote, I understand.

9 DR. ALEXANDER: But just please, state for
10 the record what you intended to vote and your
11 rationale.

12 DR. ROMITTI: It's what I said before. I
13 think we do see some difference. Would I have
14 liked a better controlled study? Yes, but we do
15 see some difference. There was some evidence of
16 improvement in endpoints given the overall size of
17 the study.

18 DR. ALEXANDER: So for the record, your vote
19 is a yes?

20 DR. ROMITTI: Yes.

21 DR. ALEXANDER: Thank you.

22 (Applause.)

1 Dr. Nuckolls?

2 DR. NUCKOLLS: Glen Nuckolls. I voted no.
3 I think that Western blot comparison is the most
4 important for determining dystrophin level. And
5 the samples were done with samples from different
6 patients in different muscles. And I don't find
7 that this fits the definition of an adequate and
8 well-controlled study.

9 DR. FOLEY: Reghan Foley. And I voted yes.
10 I believe that Western blot in combination with
11 immunofluorescence are very important, and that
12 RT-PCR proves that drug was working by its intended
13 mechanism. And there's likely patchy dystrophin
14 expression, but I think the clinical efficacy seen
15 is likely secondary to that increase in dystrophin
16 expression no matter what degree increase was seen.

17 DR. KESSELHEIM: My name is
18 Aaron Kesselheim. I voted no. I wrote this
19 question down into four parts. There was the
20 applicant-provided part, the adequate and
21 well-controlled studies part, the induces
22 production part, and then the reasonably likely

1 part.

2 For me, I felt like the induces production
3 part was the easiest. It clearly does seem, to me,
4 to induce production. I felt like the studies that
5 were provided by the applicant were not adequate
6 and well controlled because of the problems that I
7 discussed earlier in terms of the sampling, and the
8 comparisons that were made, and the lack of
9 adequate comparators before and after, and the
10 staining issues that we went over before.

11 Then the final part is the question of
12 whether it was reasonably likely to predict
13 clinical benefit. I was moved a lot by the lack of
14 association between the findings from the results
15 in some of the clinical findings.

16 I think it is still an open question though,
17 and I think that it is possible that the drug does
18 work, but that the methods being used to test for
19 the drug, in this case, just weren't specific
20 enough to identify that.

21 DR. ALEXANDER: Caleb Alexander. I voted
22 no, and I had concerns about the techniques whereby

1 dystrophin was measured, the relatively modest or
2 very modest absolute amounts of dystrophin
3 produced, as well as the absence of more
4 scientifically rigorous selection and management of
5 controls to allow for, what I felt, would be
6 comparisons that would lead me to be more
7 confident.

8 DR. ONYIKE: Chiadi Onyike. I voted no. I
9 voted no because even granted -- and would be
10 willing to accept -- even if one is willing to
11 accept, and I am willing to accept -- for the
12 purposes of this question anyway -- that eteplirsen
13 led to some dystrophin production, but it's very
14 small. And it's still within the range of what
15 people with the disease have.

16 So with that in mind, it's very important to
17 have some sort of coupling between the dystrophin
18 production and the clinical effect. We don't have
19 that. So I can't get from dystrophin production,
20 even if I accept it, to any kind of clinical effect
21 without some understanding of a threshold or the
22 mechanisms -- if it were large amount, we would

1 have a different conversation but it's a very small
2 amount, too small to just go from dystrophin
3 production to clinical effect.

4 Now, as to whether there was clinical
5 efficacy, I think that's a separate issue in terms
6 of the clinical measures. I think it's a separate
7 question.

8 I do believe it is possible, for example,
9 for a medication to have an effect without you
10 knowing why. We have Tylenol, for example. We
11 have heparin. We don't know how they work. It
12 doesn't mean that we should throw them out.

13 So I'm not entirely sure that one should
14 lock the clinical effect to the dystrophin
15 production.

16 DR. ALEXANDER: Thank you.

17 DR. GONZALES: Nicole Gonzales. I voted no.
18 While I believe it is more likely than not that the
19 drug does produce dystrophin, the clinical data, as
20 presented with the use of historical control, was
21 very problematic for me and does not convince me
22 that whatever dystrophin is being produced is

1 demonstrated in a clear benefit clinically.

2 DR. OVBIAGELE: Bruce Ovbiagele. I voted no
3 for many of the same reasons that have been
4 mentioned. I had problems with the techniques.
5 But even if I give a pass to the techniques and
6 there was some dystrophin production, I don't think
7 the study was well controlled. And most
8 importantly to the question that was asked, whether
9 the level was likely to produce a clinical benefit,
10 there was a lack of correlation between dystrophin
11 levels and the outcome. So that was a no for me.

12 DR. ALEXANDER: Thank you. So I'll briefly
13 summarize this for the record. Some of the votes
14 in favor were influenced by the reports of
15 individuals that provided comments during the open
16 public hearing. There was a comment that a change
17 of levels is present. This was felt to be
18 reasonably likely to predict clinical benefit.

19 There was a comment that dystrophin was
20 produced, and that was the goal and demonstrated in
21 the clinical abilities of boys, and you don't
22 regain lost milestones otherwise; support based on

1 the qualitative data that was provided, number of
2 falls.

3 Those voting no did so in part because of
4 concerns about the studies not being well
5 controlled, using different tissue samples, lack of
6 correlation between clinical progress and changes
7 in dystrophin produced, perhaps a measurement
8 issue.

9 There was a comment that one does see some
10 difference, some evidence of improvement in
11 endpoints based on the size of the population.
12 Western blot comparisons are most important, were
13 felt to be most important by a panelist. Samples
14 were done from different patients with different
15 muscles and doesn't fit the definition of adequate
16 and well-controlled study.

17 PCR suggested the drug is working by
18 intended mechanism, so a belief that the clinical
19 efficacy was likely due to differences in
20 dystrophin seen. Another panelist pointed that
21 there was evidence of induction, or production, I
22 should say, but the studies, once again, that were

1 provided by the applicant were not felt to be
2 adequate and well controlled.

3 With respect to whether or not these were
4 likely to be -- the dystrophin change was
5 reasonably likely to be predict clinically benefit,
6 the panelist was moved by the associations
7 presented but thinks it's an open question,
8 possible that it works, but the methods need to
9 test for this weren't specific enough, and so that
10 panelist voted no.

11 Concern about the quality of dystrophin
12 production data, about the techniques that were
13 used and the absence of more rigorous controls,
14 very small amounts of dystrophin and the range of
15 what people with the disease have untreated,
16 important to have some coupling between dystrophin
17 production and clinical effect.

18 Even if one accepts the dystrophin
19 production, hard to get from there to clinical
20 effect. If it was a very large amount of
21 production, we'd be having a different
22 conversation.

1 Another panelist, once again, more likely
2 than not that the drug produces dystrophin but the
3 clinical data are very problematic and not
4 convinced that the dystrophin that's produced is
5 generating the benefit that we see. And the final
6 panelist commenting problems with techniques, and
7 even if this is accepted, here again, the study
8 wasn't well controlled. And even if so, lack of
9 correlation between levels and outcomes.

10 With this, we'll move on to
11 question number 3, which is a discussion question.
12 Discuss the strengths and weaknesses of the
13 clinical evidence of efficacy provided by
14 study 201/202 with particular consideration of the
15 design of the study, sample size, statistical
16 methods, general concerns regarding comparison to a
17 historical control group, specific concerns with
18 respect to comparability of these two groups; in
19 particular, how motivational factors and
20 differences in assessment of physical performance
21 outcomes may have affected the 6-minute walk
22 endpoint and other endpoints, and any other issues

1 that you think may be important.

2 So we have a few moments for discussion
3 here. Once again, please keep your comments or
4 questions very crisp and focused on this question
5 at hand.

6 Ms. Gunvalson?

7 MS. GUNVALSON: I've seen a lot of 6-minute
8 walk tests, and I can honestly say that these boys
9 know what's going on. They know they're being
10 timed. They know this is a deadly disease.
11 They're on the internet. I can honestly say I've
12 not seen a boy motivated to do his best, and so
13 that's my opinion.

14 As far as -- yes, I just don't -- I know
15 what coaching is about. I have kids and athletes,
16 but you can't coach these kids to walk faster.
17 They have this waddle gait that if you push them to
18 go faster, they fall. It's just not possible. I
19 mean, it's like a balance beam how they do it, and
20 they go to the best of their ability.

21 DR. ALEXANDER: Thank you. Dr. Green?

22 DR. GREEN: Well, I think we all agree that

1 placebo controls are often flawed, but historical
2 controls are worse. And that was so well pointed
3 out in Dr. Temple's discussion on historical
4 controls.

5 So the data, my yes vote had to do with
6 external influences that I believe were
7 significant. But the way the study is designed, it
8 gives me very little comfort.

9 DR. ALEXANDER: Thank you. And I'll just
10 make a comment. Caleb Alexander. One contrast
11 that I wanted to underscore that I noted was the
12 difference and the conclusions that one reaches
13 when one looks at individual trajectory level as a
14 function of age at enrollment. And we saw several
15 analyses, I think three analyses, for the
16 historical controls and then three for the synergy
17 data by the FDA that provided this type of analysis
18 that are following individual patients over time as
19 a function of their age at study enrollment.

20 I did note that the sponsor had at least one
21 slide that had information that wasn't just means
22 or averages but actually allowed for individual

1 level trajectories, although even this slide only
2 looked at the 6-minute walk test as a function of
3 length of treatment, not patient age.

4 So I just wonder whether there's
5 information -- and so that seems, to me, to be a
6 really important set of slides and ones that point
7 in a different direction than if one looks at plots
8 of the primary outcome as a function of study
9 enrollment alone.

10 Dr. Gonzales?

11 DR. GONZALES: Nicole Gonzales. I just had
12 a comment. Just reading the data from Sarepta,
13 every single secondary clinical endpoint seemed to
14 be so positive. And listening to the testimonials
15 and the experiences of the boys and the families,
16 it just seems to me that had there been a true
17 placebo group, that the differences would have been
18 so striking and that the study may have even been
19 stopped soon. I'm trying to understand why there
20 wasn't an adequately powered placebo group.

21 DR. GORDON: Someone else has their mic on.

22 DR. ALEXANDER: Just one minute, please.

1 Does the sponsor want to respond to a
2 particular question about the absence of a placebo
3 group?

4 DR. KAYE: Yes, just to be able to address
5 to that about the placebo. So I think just to be
6 clear, I think when we had initially done the
7 phase 2 study, there wasn't enough drug at that
8 time. We didn't have the ability to manufacture
9 until almost two years later. So this was designed
10 as a phase 2B.

11 When we had enough drug to actually do a
12 placebo-controlled trial, because of the response
13 to the fact that this drug produced dystrophin and
14 also the clinical response, there really wasn't a
15 possibility at that time to be able to really do a
16 formal placebo-controlled trial.

17 This was exactly the same problem I had with
18 my Myozyme that you heard about earlier from
19 Dr. Temple. We had to make a decision at that time
20 what was the in the best interest of patients, and
21 we decided to do the external control, which is the
22 next best thing.

1 If I can have the slide up, one of the
2 things that we did -- and I agree --

3 DR. ALEXANDER: I'd like to move on,
4 actually. Thank you.

5 DR. GORDON: Okay.

6 DR. ALEXANDER: Thank you very much.

7 Dr. Onyike?

8 (Audience groans.)

9 DR. ONYIKE: I think when we have what I
10 perceive as a weakness on the biological
11 plausibility front and you have a small sample and
12 a control group that is not optimal, and when you
13 look at the effect of age corrections on the
14 outcome, the 6-minute walk test, you do want some
15 validity.

16 But when you turn to the 10-minute walk/run
17 results, or to the sit/stand, and to all the other
18 things that should provide convergent validity
19 regarding the outcome, what you find is that you
20 don't find any positive results.

21 So across the board, if a drug is effective,
22 given its pharmacologic effect, it should have

1 effect on multiple outcomes, not just the single
2 one. And that isn't happening in this data, so
3 that's my one problem I have.

4 Now, in terms of the testimony from the
5 families, what really struck me is that a lot of
6 the testimonies were about -- there was a picture.
7 I think it was Austin who is stacking cans, and
8 that's upper limb strength. And you look at -- all
9 the outcomes in this study were about limbs, about
10 the limbs or the trunk. And there is no study
11 outcome that's about upper limb strength or grip,
12 and I think that is a very unfortunate thing about
13 outcomes assessment in this field in general.

14 You want something that's tangible to
15 quality of life. You want something else that
16 accounts for the distribution of effects across the
17 various muscles, and without upper limb testing,
18 you don't have that.

19 DR. ALEXANDER: Can I just ask for you to
20 clarify the first comment that you made? What I
21 understood you to say is that you have concerns
22 about biologic plausibility because the drug isn't

1 having an effect on multiple outcomes. But can you
2 specify what you mean by that?

3 DR. ONYIKE: Let me clarify. When I'm
4 talking about plausibility, I'm going back to the
5 dystrophin. If the dystrophin data is not decisive
6 and you have a clinical outcome that arises from
7 comparisons with a suboptimal control and that
8 wilts under age correction, you need all the other
9 outcomes to line up in the same direction for the
10 single outcome to be considered a valid measure of
11 efficacy.

12 Now, it turns out that none of the other
13 outcomes, as depicted in the FDA analysis, lined up
14 with a positive effect.

15 Now, when you listen to the testimony from
16 the families, one of the things that was
17 highlighted is opening cans, opening packages,
18 lifting things, and none of that is captured by the
19 NSAA, or the 6-minute walk test, or the 10-minute
20 walk test.

21 So you have an unfortunate discrepancy
22 between what the families are describing as

1 tangible benefits and what is actually measured.
2 We're not even talking about negative measurements
3 now. We're talking about non-measurement of areas
4 of function that might have delivered some clarity
5 about the effects of this drug.

6 DR. ALEXANDER: Okay. So you're questioning
7 the biological plausibility and making the point
8 that one doesn't have a lot of dystrophin
9 production, and then reporting that, in that case,
10 that one would want all of the outcomes to line up.

11 But does the sponsor not present a case for
12 the outcomes being consistently positive? By what
13 basis are you deciding or the claiming that the
14 outcomes don't line up?

15 DR. ONYIKE: So when you look at slides 92
16 through 94, and when you look at 87, 88 --

17 DR. ALEXANDER: Can we see one or two of
18 these just to help us, remind us what this covers?

19 DR. ONYIKE: So 87, if we can look at 87, it
20 covers both the NSAA and the 6-minute walk test.
21 Slide 88 covers the rise time. And all of these do
22 not show a difference between the groups when

1 plotted as a function of age of the subjects.

2 So basically, outcome after outcome after
3 outcome is lining up as no effect, when
4 age-corrected. So there's no validity to
5 the -- you can't anchor claims of benefit on one
6 outcome when the rest of them are not falling in
7 line, particularly when your biological
8 plausibility and your control groups are subject to
9 question.

10 DR. ALEXANDER: Okay.

11 DR. ONYIKE: But I feel that there's an
12 inadequate measurement of treatment effect to begin
13 with because there's no measurement of upper limb
14 strength.

15 DR. ALEXANDER: Okay. Thank you. This is
16 Caleb Alexander. If you can leave the slide for a
17 minute, I'd like to give the sponsor a chance,
18 because this is the second time that this type of
19 analysis has been raised during this question
20 discussion.

21 So the question for the sponsor is whether
22 or not you considered or if you could help the

1 panel interpret the data that's presented here or
2 in slide 66, which precedes it, I believe. But
3 these all show a similar analysis of individuals
4 over time stratified by age. And the request is
5 just to help us interpret -- provide for us your
6 interpretation of what these data represent.

7 DR. KAYE: So if we just look at the rise
8 time -- and Dr. McDonald had described it -- what
9 was recorded is when it was really the ability to
10 rise. So those boys with the higher rise times had
11 with support. So that wasn't what we did in the
12 analysis; it was just the ability to rise. And
13 they were all less than 75 seconds.

14 If I could have a slide up --

15 DR. ALEXANDER: I'm sorry. Just --

16 DR. KAYE: Oh.

17 DR. ALEXANDER: This is another example of
18 that, if you could provide -- sort of help us
19 understand how these types of analyses complement
20 those that look at the effect over time rather
21 individuals plotted out over the course of -- based
22 on age.

1 DR. KAYE: Sure. Well, I really think the
2 main difference, though, is we're also looking at
3 the time on treatment. So if we were looking at
4 two external control groups and trying to see what
5 the difference was, then I think the age. What we
6 try to do is match up the baseline ages, 6-minute
7 walk test, all of the other parameters, the steroid
8 use, and then look at what is the time on therapy.

9 What this doesn't really show is what is the
10 ability -- what's the change we see in response to
11 the treatment. And I think when we look at that,
12 that's where we're able to see the treatment
13 benefit.

14 I think getting back to the question as far
15 as what do we see as far as other things, we did do
16 grip strength, both left and right, for 4 years,
17 and we did not see any decrease in that. That was
18 one of the exploratory measurements that we used.

19 We also looked at pulmonary function over
20 4 years, and as you heard, that's an important
21 event. And the pulmonary function should go down
22 anywhere from 5 to 8 percent per year. Every study

1 that's ever been done, that's with or without
2 steroids.

3 This study showed 2.5 percent per year. And
4 again, if we look that cumulative data and looking
5 at all of the information about -- looking at the
6 number of boys -- slide up please -- again, looking
7 at the treatment difference, if we look at this in
8 regards to what we see, we always see it in
9 benefit of treatment.

10 So 6-minute walk test, you heard about.
11 Loss of ambulation, it's even more. There was a
12 difference, but it was always in favor of
13 eteplirsen or the North Star and the ability to
14 rise, and then also what I just mentioned was the
15 pulmonary function.

16 So if we look at it from that
17 perspective -- and I think it is important not to
18 just look at the difference of ages because you
19 can't judge the boy at an age, what you've heard
20 from Dr. McDonald. It's how long are they walking,
21 what is their ability to rise, all of those
22 factors, how much steroids were they on.

1 So I think it's not a fair comparison to
2 just look at the age because a boy at age 11 who's
3 walking 600 meters is very different from a boy at
4 age 11. So what we try to do is make this
5 comparison at baseline when we started the
6 treatment. That's how every study is always done
7 because you have to look at what's the time on
8 drug. And I think when you do that, it's always in
9 favor of eteplirsen. And I think that's the
10 important thing that has to be done.

11 We appreciate the small size of the study,
12 but I think if you look at the totality of the
13 data, including the upper extremity function, it's
14 always in favor of eteplirsen.

15 DR. ALEXANDER: Thank you very much.

16 Dr. Gordon, did you have comment? And then
17 I think we'll just have one more, and we'll move
18 on.

19 DR. GORDON: The sponsor wanted to make an
20 additional comment.

21 DR. ALEXANDER: Can you speak into the
22 microphone? I'm sorry. Your comment?

1 DR. GORDON: Sure. The sponsor had asked me
2 to make a comment.

3 DR. ALEXANDER: I see. Dr. Bastings and
4 then Dr. Kesselheim.

5 DR. BASTINGS: Yes, I think I heard Dr. Kaye
6 make a comment that the kids were helped when they
7 were attempting to rise. You mentioned that there
8 was some help provided. I would like him to expand
9 on that a little bit.

10 DR. KAYE: Yes. So when we looked at the
11 rise time, I think one of the things that obviously
12 we wanted to make sure is that we did it exactly
13 the same way. So when the rise time was done, it
14 was the ability to rise independently, because if
15 you're hanging on to a chair or if you're hanging
16 on to the wall and you're getting up, it will take
17 a longer period of time.

18 So we specifically wanted to make sure that
19 we did the rise time from the external control to
20 our eteplirsen-treated boys in exactly the way. So
21 when you look at that -- and again, all of these
22 boys who got up did it in less than 25 seconds;

1 they all did it unaided. And then when you do that
2 exact comparison, then it's over half of the boys,
3 55 percent, were able to do that unaided compared
4 to 12 percent.

5 What was shown in that graph is the boys
6 from the external control who had lost the ability,
7 their rise time wasn't included, so it was just the
8 boys who -- so we actually tried to measure the
9 boys who could walk unaided, so it was a
10 difference.

11 I think that's really the focus, is that
12 what is the difference. When you do an apples-to-
13 apples comparison, you do see a difference.

14 DR. ALEXANDER: Okay. So just to clarify,
15 were the boys -- do the rise times uniformly
16 reflect unaided rise times or is some of them
17 aided --

18 DR. KAYE: Yes, that's correct. All of them
19 that are unaided that are used in this analysis.

20 DR. ALEXANDER: So does that answer your
21 question, Dr. Bastings?

22 DR. BASTINGS: Yes. So you're referring to

1 the rise time that were shown on slide 88 of the
2 FDA presentation?

3 DR. KAYE: That's correct.

4 DR. BASTINGS: Like when we have 40-,
5 45-second rise times, there was no help provided?

6 DR. KAYE: No, no. Those 45-second rise
7 times, they were using external support. That's
8 the difference. So in other words, when we looked
9 at the boys, what we looked at here is could they
10 walk unaided, and that wasn't recorded for the boys
11 in the external control. And maybe Dr. McDonald
12 can just explain it.

13 DR. BASTINGS: I don't think this
14 information was provided in the NDA.

15 DR. ALEXANDER: Okay.

16 DR. McDONALD: Could I just clarify this
17 data? This data is based on the North Star
18 subscore of whether you can perform the rise
19 ability independently or in an impaired fashion, or
20 if you cannot perform it independently; you've lost
21 the function.

22 So at 3 years, 55 percent of eteplirsen

1 treated patients have continued independent ability
2 to perform the rise ability, whereas only 8 percent
3 of the external controls.

4 Now, we made the point that as a prognostic
5 endpoint, it's really the loss of rise ability;
6 it's not how long it takes you to do the rise test.
7 It doesn't matter whether you're zero to 5 seconds,
8 5 to 10 seconds, or even greater than 10 seconds;
9 that's not prognostic for loss of ambulation. It's
10 the loss of rise ability, which this data captures
11 based on the North Star subscore of independent
12 rise time.

13 DR. ALEXANDER: Okay. Thank you very much.

14 I'll try to summarize what I've heard
15 regarding question number 3. There was a
16 comment -- and the record will reflect a more
17 accurate capture of everything because there was a
18 fair amount that was discussed.

19 But there was a comment regarding boys
20 knowing what's going on, a comment regarding
21 concerns about placebo controls often being flawed,
22 concern with regarding historical controls often

1 even being more flawed as represented by or
2 demonstrated by Dr. Temple's presentation.

3 There was a comment regarding the fact that
4 every secondary clinical endpoint seemed so
5 positive and listening to the experience of boys
6 and their families so positive. And if there had
7 been a placebo group, the panelist felt that the
8 study would have been stopped, yet they queried why
9 a placebo wasn't done.

10 The answer provided was that there wasn't
11 enough study drug available, and then at the point
12 when there was enough available, it wasn't possible
13 because of conclusions that had been reached
14 regarding the assays on dystrophin at the time.

15 There was a comment regarding the results
16 not being biologically plausible because we don't
17 have a lot of dystrophin. And especially in that
18 setting, one would want all of the other outcomes
19 to line up with very clear evidence of efficacy,
20 and that one doesn't have this, based on the FDA's
21 analyses such as in slides 87, 92-94, all of which
22 raise concerns or failed to show a

1 significant -- I'm saying not statistically
2 significant but rather failed to show a large or
3 observable qualitatively significant difference
4 between the groups.

5 The family testimony includes outcomes that
6 were not captured by the measures assessed, and
7 this was felt to be unfortunate and an unfortunate
8 discrepancy between what families were reporting
9 and what was actually measured.

10 There was encouragement to -- the sponsor
11 was queried regarding the analyses, but that the
12 FDA provides examined patients over time stratified
13 by the age at which they started treatment or
14 entered the historical control, and the sponsor
15 felt that these analyses don't show the change that
16 we see in the response-to-treatment; that one can't
17 just look at the patient age but has to look at the
18 time on therapy.

19 The sponsor also commented that pulmonary
20 function should go down 5 to 8 percent a year, but
21 didn't. I presume I was understanding correctly.
22 And the same with grip strength, and that these do

1 support the variety of additional outcomes that
2 were assessed.

3 The sponsor provided their analyses
4 suggesting that NSAA, the North Star assessment,
5 and ability to rise, and 6-minute walk test, all in
6 favor of the study drug based on their analyses,
7 and that kids were helped.

8 Then there's some uncertainty, a little bit
9 of unclarity on my part regarding whether or not
10 assistance was provided to kids and what
11 constitutes assistance, whether this was mechanical
12 devices or human help and the like, but that can be
13 clarified. And I'll just note that ambiguity in my
14 mind for the record.

15 With that said, we'll move to question 4,
16 which is a voting question. Were decisions to
17 administer the 6-minute walk test versus
18 conclusions that the patient could no longer walk
19 sufficiently objective and free of bias and
20 subjective decision-making by patients, their
21 caregivers, and/or healthcare professionals to
22 allow for a valid comparison between study patients

1 in studies 201/202 and an external control group?

2 So we'll move to voting on that now.

3 Once voting is concluded, we'll begin again
4 with -- well, why don't we begin at this side of
5 the table this time, to my left, once voting is
6 concluded. And just for the sake of time, rather
7 than my calling on you, please just state your name
8 into the record and your vote, and a brief
9 rationale after the person immediately to your left
10 has provided their information.

11 DR. HOFFMAN: [Inaudible - off mic.]

12 DR. ALEXANDER: Yes, C is -- I'm sorry.
13 D is abstain. So yes is B, like boy; no is C, like
14 Charlie; and D, like dog is abstain.

15 DR. HOFFMAN: [Inaudible - off mic.]

16 DR. ALEXANDER: So let me just read the
17 question just to be clear. The voting question is,
18 were decisions to administer the 6-minute walk test
19 versus conclusions that the patient could no longer
20 walk sufficiently objective and free of bias and
21 subjective decision-making by patients, their
22 caregivers, and/or healthcare professionals to

1 allow for a valid comparison between patients in
2 studies 201/202 and an external control group?

3 So if you believe that the decisions were
4 sufficiently objective and free of bias and
5 subjective decision-making, you would vote yes.
6 And if you believe they were not sufficiently
7 objective and free of bias and subjective
8 decision-making, you would vote no.

9 (Vote taken.)

10 DR. ALEXANDER: Please enter your vote one
11 final time. Press the button firmly.

12 DR. CHOI: Everyone has voted. The vote is
13 now complete. For the record, we have 5 yes, 7 no,
14 1 abstention.

15 DR. ALEXANDER: So we'll begin with
16 Dr. Ovbiagele.

17 DR. OVBIAGELE: Bruce Ovbiagele. I voted
18 no. I'll just be quick. Two reasons. Number 1,
19 of course, it was open label. I would have loved
20 to see a blinded adjudication of the outcome. That
21 would have at least helped a little bit.

22 Then, the other issue was in the control

1 groups themselves, it seemed as if in some
2 situations, patients were deemed unable to do the
3 6-minute walk test, which was not necessarily
4 appropriate in some situations. So I didn't think
5 it was necessarily objective.

6 DR. ALEXANDER: I'm sorry. Can you repeat
7 the second point? The first you made was about
8 open label and blinded adjudication. But what was
9 the second point?

10 DR. OVBIAGELE: The second point was about
11 in some situations, for the control patients, they
12 were deemed not able to do the 6-minute walk test.
13 And in those cases, it might not have been
14 appropriate for them to have been deemed
15 unable [sic] to do that -- unable to do that.

16 DR. GONZALES: Nicole Gonzales. I voted no.
17 For me, this has nothing to do with motivation. I
18 think it's crystal clear to me that boys are
19 extremely motivated to walk. And for me, this has
20 to do with the difficulties with using a historical
21 control, as has been demonstrated, not just in the
22 neurology but in all of medicine and all of the

1 biases that we cannot measure.

2 DR. ONYIKE: Chiadi Onyike. I voted yes. I
3 believe that what -- even though it's true that one
4 can't say that it was very systematic with respect
5 to looking at the study versus looking external
6 controls or that you can argue uniformity and
7 ascertainment of the scores, I don't think that the
8 magnitude of error would be enough to have
9 distorted the study outcomes if it were not for the
10 small sample size and other key problems.

11 DR. ALEXANDER: Caleb Alexander. I voted
12 no. I had concerns primarily about the -- well,
13 concerns both about the potential ways that the
14 controls may not have been exchangeable, comparable
15 with the treated patients, and these can be very
16 subtle.

17 Really, the impact of this is unknowable at
18 this point, so it's not so much that I'm convinced
19 that they're different as that it's unknowable, the
20 magnitude of difference that may have been present.
21 So that was my primary concern.

22 DR. KESSELHEIM: Aaron Kesselheim. I

1 abstained. With all due respect, I didn't think
2 this was a very good question, the way it was
3 written, and I had trouble interpreting it in order
4 to make a firm yes or no answer.

5 I felt like I was convinced through the
6 course of the day today that the 6-minute walk
7 test, though it is a subjective measure, it could
8 be a valid intermediate endpoint. But I had
9 trouble with the context in which it was used and
10 the results that came up in regard to the
11 historical control. I felt like it was more
12 appropriate to address that in the seventh question
13 as opposed to this question.

14 So because I couldn't exactly -- because I
15 agree with part of the question but not another
16 part of the question, I chose to abstain.

17 DR. FOLEY: Reghan Foley. I voted no due to
18 the problems with historic controls and seeing that
19 there were patients for whom there had been times
20 were at 10-meter walk or run but no time for the
21 6-minute walk.

22 I just think that the most important issue,

1 really, is the preserved ambulation and ability to
2 rise, which is kind of, to me, incontrovertible
3 evidence. But with this data with historic
4 controls, it was hard to control for other sites
5 and historically.

6 DR. NUCKOLLS: Glen Nuckolls. I voted no.
7 The predetermined selection criteria for the
8 control group were not sufficient to control for
9 biases. And since it's an open label, and I also
10 agree with your point about subjects that had a
11 12-second, 10-meter walk but were listed as
12 non-ambulatory, these caused me to question the
13 objectivity and comparability of a 6-minute walk
14 test.

15 DR. ROMITTI: Paul Romitti. I wavered
16 between yes and abstain. Just for the record, I
17 did push the correct button this time. Reason
18 is -- a couple of reasons, one, a fellow panel
19 member talked about upper body strength, but I
20 heard testimonies from more than one child who said
21 they were still walking after being on the drug.
22 So there was also measures of lower strengths, so I

1 do think there was consistency there.

2 The biggest problem I have with this -- and
3 I took the question literally, which is why I gave
4 it a yes. After working for a decade with a
5 30-year cohort of patients with Duchenne and Becker
6 muscular dystrophy, I believe these patients will
7 do anything they can to maintain their mobility,
8 and I don't think there are any extra motivated to
9 do so.

10 I think the other thing is, is I think we're
11 just losing a bit of grasp here on the
12 heterogeneity of this condition. And so in
13 analyzing data by age of the subject I think is
14 inappropriate.

15 I think it's more appropriate to look at
16 disease progression. After seeing after symptom
17 onset can happen at 2 years for some and 5 years
18 for others, I don't think that's the way to go. So
19 I was not convinced by the evidence that the FDA
20 presented by year, and I think it's more
21 appropriate to go by the stage of development where
22 the child is.

1 DR. KRYSICIO: Richard Kryscio. I voted no.
2 I was disappointed that the data was not analyzed;
3 the way the subjects were randomized, its
4 delay-start designed. They introduced historical
5 controls; I'm not convinced that they are
6 necessarily comparable. They had problems, as were
7 mentioned, throughout the day.

8 My real problem is the endpoint itself. I
9 mean, it just looks at the lower body; it doesn't
10 look at the upper body. And we've heard many
11 comments about upper body strength versus lower
12 body strength.

13 There are a lot of better measures. There
14 are diseases where you have more of a functional
15 rating scale. Take a look at ALS, which has
16 similar problems with people losing ambulatory
17 status. They have well-designed trials with lots
18 and lots of patients with a well-accepted endpoint.

19 This is not a good primary endpoint where
20 you have a floor effect when people can't walk, and
21 statistically, it just doesn't make sense to try to
22 average those numbers in the plots. Those are

1 called spaghetti plots in the statistical
2 literature.

3 MS. GUNVALSON: I'm Cheri Gunvalson, and I
4 voted yes. I believe that there was a
5 differential, and it has also demonstrated in the
6 boys that showed us upper body and lower body
7 increases.

8 I think the FDA should require a
9 non-ambulatory arm in every Duchenne trial because
10 there are a lot of things that need to be studied.
11 If a drug is approved, and non-ambulatory boys who
12 are on a cohort of cardiac meds and things like
13 that, that should be looked at in a trial setting
14 for safety, not after a drug is approved. And
15 also, there are things you can measure but safety
16 is a main factor too.

17 I agree with Dr. Day who spoke about -- he's
18 a neurologist who's seen hundreds of boys with
19 Duchenne. His data is similar to the historical as
20 how boys decline, which there was a study done by
21 UCLA. So I --

22 DR. ALEXANDER: Thank you. Thank you.

1 MR. DUPREE: Benjamin Dupree. I voted yes.

2 DR. ALEXANDER: Can you just speak into the
3 microphone a little bit more? Thank you.

4 MR. DUPREE: Sorry. Benjamin Dupree. I
5 voted yes, the reasoning being that, specifically,
6 with the 6-minute walk test, I think that given how
7 much boys with muscular dystrophy want to continue
8 to walk, that I just don't see that there would
9 bias in deciding to not take the test per se.

10 DR. GREEN: Mark Green. I voted no. I
11 don't believe that these assessments give a full
12 and adequate assessment of the disabilities of the
13 condition.

14 DR. HOFFMAN: Richard Hoffman. I voted yes.
15 I think there was plenty of potential for bias but
16 no real evidence of any bias, so we really don't
17 know. And I would say that it's just speculation
18 that there was.

19 DR. ALEXANDER: Thank you very much. Those
20 are very helpful comments.

21 So there were comments regarding the fact
22 that this was open label and the panelists would

1 have loved to have seen a blinded adjudication of
2 outcome. There were concerns regarding the fact
3 that some control patients were deemed unable to do
4 a 6-minute walk test and concerns regarding whether
5 or not they were truly unable to do so.

6 Another panelist felt there were no concerns
7 about motivation for the boys and more concern
8 about difficulty of using historical controls and
9 all of the biases that we cannot measure.

10 One panelist felt that there were concerns
11 about the question itself and had trouble knowing
12 how to interpret this to make a firm yes or no
13 answer.

14 The effect of historical controls is
15 unknowable, also concerns about the potential
16 motivational bias that may be present. More than
17 one panelist commented -- again, we're back to the
18 fact that there was a 6-minute walk time or no
19 6-minute walk time for a few subjects that had
20 10-meter data present, and so panelists questioned
21 the objectivity and comparability of the 6-minute
22 walk test.

1 One felt a predetermined selection criteria
2 were not sufficient to control for biases as open
3 label. One wavered between yes and abstain but
4 didn't believe that patients were extra motivated
5 to maintain mobility, that is that they're
6 sufficiently motivated and thus less of a concern
7 regarding motivational bias.

8 One felt that there were concern that we're
9 losing grasp with heterogeneity of disease
10 progression, and they felt that it isn't
11 appropriate to analyze the data based on patient's
12 age, and felt that it was more appropriate to
13 analyze based on children's stage of development.

14 One was disappointed with the data that was
15 analyzed and felt that patients weren't randomized
16 and wasn't convinced that historical controls were
17 comparable, but the real problems is the endpoint
18 itself. It doesn't look at upper body; it only
19 looks at lower body. There are better measures
20 such as for ALS.

21 One felt there was a differential and
22 believes the FDA should require non-ambulatory arms

1 in every DMD trial, lots of things to be studied.

2 Another voted yes because the 6-minute walk
3 test was felt to be sufficient. And given how much
4 patients with DMD want to continue walk, the
5 panelist didn't see how there could bias in terms
6 of not taking the test.

7 One felt that the assessments didn't provide
8 a full and adequate assessment of the condition.
9 And the final panelist mentioned as support for
10 their vote that, yes, that they didn't believe that
11 there was any real evidence of any bias.

12 So we'll move on to the next question. So
13 I'll read the question, but I also want to provide
14 the panelists a chance to ask clarifying questions
15 of the FDA prior to the vote.

16 So the question is, question number 5, What
17 is the impact of the North Star Ambulatory
18 Assessment Results on the persuasiveness of the
19 findings in study 201/202?

20 Does the NSAA, the North Star Ambulatory
21 Assessment Results, does the NSAA strengthen the
22 persuasiveness of the findings in study 201/202?

1 Does it weaken the persuasiveness of the findings
2 or is there no effect?

3 So are there any clarifying questions on the
4 part of the panelists for the FDA regarding the
5 wording of this question and its meaning?

6 Yes, Dr. Gonzales?

7 DR. GONZALES: Nicole Gonzales. Are we
8 supposed to use of all of the data presented by
9 both Sarepta and the FDA or use one or the other?

10 DR. ALEXANDER: I think you'd be using the
11 totality of evidence that's been discussed and
12 presented today and provided in the briefing packet
13 to you.

14 Dr. Gordon?

15 DR. GORDON: The sponsor is asking for
16 permission to clarify something for the record
17 regarding the 6-minute walk test.

18 DR. ALEXANDER: If there is a specific
19 question on the part of a panelist seeking
20 clarification, then we can pursue that. But if
21 not, I'd like to proceed with this vote unless
22 there are questions of clarification for the FDA

1 regarding the wording of question 5.

2 Yes, Dr. Nuckolls?

3 DR. NUCKOLLS: So not regarding the wording,
4 but I see on slide, whatever, 85, 86, the
5 comparison of the slope of North Star in the
6 treated and control, and the standard deviation
7 error bars look like they're completely
8 overlapping. But I'm wondering is there any
9 evidence of a statistically significant difference
10 between --

11 DR. BASTINGS: The answer is no.

12 DR. ALEXANDER: Are there any further
13 questions of clarification for the FDA regarding
14 the wording of question 5?

15 (No response.)

16 DR. ALEXANDER: If not, we'll proceed to
17 vote.

18 So once again, what is the impact of the
19 North Star Ambulatory Assessment Results on the
20 persuasiveness of the findings in study 201/202?
21 Do these results, A) strengthen -- I'm sorry. I
22 guess it is A, B and C.

1 So do these results, A, strengthen the
2 persuasiveness; B) weaken the persuasiveness; or
3 C) no effect?

4 (Vote taken.)

5 DR. CHOI: Everyone has voted. The vote is
6 now complete.

7 DR. ALEXANDER: Thank you. So why don't we
8 begin with the first --

9 DR. CHOI: For the record, we have 2 votes
10 for A, strengthen; 5 votes for B, weaken; and
11 6 votes for C) no effect.

12 DR. ALEXANDER: Thank you. So we'll begin
13 with the first voting member on this side, and
14 please state your name, your vote, and a very brief
15 explanation of why you voted as you did.

16 DR. HOFFMAN: Richard Hoffman, and I voted
17 no effect, C, basically because there was a
18 complete difference of opinion on this matter
19 between the sponsor and the FDA. And it's kind of
20 who do you believe and how do you interpret the
21 data.

22 DR. ALEXANDER: Please continue.

1 DR. GREEN: Yes. Mark Green. Mine also is
2 an error. I wanted C as well. Please change my
3 vote because I don't think it had any persuasive
4 evidence either direction.

5 DR. ALEXANDER: Okay. So for the record,
6 Dr. Green is voting C, that it had no effect.

7 MR. DUPREE: Benjamin Dupree. I voted C. I
8 just don't see one way or the other that it
9 influences the persuasiveness.

10 MS. GUNVALSON: I'm Cheri Gunvalson. I
11 voted A. I felt the sponsor had a strong point.

12 DR. ALEXANDER: Can you just specify the
13 basis for that?

14 MS. GUNVALSON: Well, when Dr. McDonald
15 explained the findings, as others have said, there
16 are two sets of data. I mean, I wavered between C
17 and A, but that's where I'm at.

18 DR. KRYSCIO: Richard Kryscio. I voted on
19 the weakened side because of the graph I saw
20 produced by the FDA, two parallel lines, one line
21 below the other, indicating that that the
22 historical control group was not comparable.

1 It helped convince me the historical control
2 group is not comparable to the randomized patients.
3 And there's a large variability in there showing no
4 statistical difference between the two parallel
5 lines. And finally, that has to do with the sample
6 size that was chosen, I'm sure. And this
7 measurement, NSAA, is closer to a functional rating
8 scale than is the 6-minute walk test.

9 DR. ROMITTI: Paul Romitti. I voted C, no
10 effect and for reasons discussed.

11 DR. NUCKOLLS: Glen Nuckolls. I voted B,
12 weakened. So the North Star test measures function
13 of many of the same muscle groups as the 6-minute
14 walk. And since there is no statistically
15 significant difference between the treated and
16 control groups, that in my mind weakens the
17 strength of the 6-minute walk data.

18 DR. FOLEY: Reghan Foley. I voted C, no
19 effect. For me, it didn't lessen or weaken or
20 strength the results. For me, the main issue to
21 preserve ambulation.

22 DR. KESSELHEIM: Aaron Kesselheim. I voted

1 C, no effect. I was also moved by the slides with
2 the really, really large error bars, again,
3 indicating probably just the small numbers of
4 patients in this comparison.

5 But, these are all sort of historical
6 control comparisons performed after the trial had
7 already sort of been started and going along, so
8 some of them might turn out positive; some of them
9 negative. And for me, this ended up being one of
10 the many different things that were tested, and
11 therefore, to me, overall had no effect.

12 DR. ALEXANDER: Caleb Alexander. I felt
13 that it weakened the evidence that was presented
14 primarily because the NCAA, as I understand it,
15 assesses -- is comprised of many more measures than
16 a single dimensionality. So I guess that leads me
17 to feel a little bit more confident in it as an
18 overall assessment.

19 There was also a difference at baseline,
20 which I guess raised concerns for me about the
21 comparability of the two groups at baseline. But
22 the trajectories, the trend lines are virtually

1 indistinguishable, and the confidence intervals
2 overlap.

3 So for me, I think I would have been more
4 convinced about the evidence in 201 and 202 even
5 though those studies, the primary endpoints, as I
6 understood them, were not achieved. I would have
7 been more confident about the longer term follow-up
8 data that was presented and the open label had the
9 NSAA been more compelling.

10 DR. ONYIKE: Chiadi Onyike. I voted no. As
11 already mentioned, the NSAA is a more comprehensive
12 measure than the 6-minute walk test or the
13 10-minute test. But in any case, neither the FDA,
14 nor the sponsor is claiming a statistically
15 significant difference between the groups on this
16 measure.

17 DR. GONZALES: Nicole Gonzales. I voted no
18 for reasons already mentioned.

19 DR. OVBIAGELE: Bruce Ovbiagele. I voted no
20 for reasons already mentioned.

21 DR. ALEXANDER: Okay. Thank you very much.
22 So for those that voted no effect primarily felt

1 that they didn't see that this influenced things
2 one way or another.

3 They were moved by -- one was moved -- one
4 panelist mentioned being influenced by the slides
5 with the large error bars, probably indicating
6 small numbers of patients within the comparisons.

7 These are all historical comparisons
8 performed after the trial had been started as some
9 might turn out to be positive, some negative. But
10 it turned out as one of many things that were
11 tested.

12 Those that felt that the NSAA data
13 strengthened the results of studies 201 and 202
14 felt that the sponsor had a strong point. One
15 panelist mentioned having wavered between no effect
16 and strengthens.

17 Those that felt that the data weakened the
18 results of the 201 and 202 felt that there were two
19 parallel lines; one was lower than the other. This
20 helped convinced one panelist that the historical
21 control was not comparable.

22 The results of large variability, no

1 statistically significant difference, large
2 variation was felt partly due to sample size. NSAA
3 was felt to be closer to a functional rating scale
4 than the 6-minute walk test. It measures function
5 of many of the muscle groups as a 6-minute walk
6 test, so since no difference, this was felt to
7 weaken the association.

8 It was also pointed out that this was a more
9 comprehensive measure and that neither the FDA or
10 the sponsor is claiming that there was a
11 significant difference between groups on this
12 measure.

13 So thank you very much for that. And moving
14 right along, we'll move to question 6, which is,
15 what is the impact of the other tests of physical
16 performance such as rise time, 10-meter run/walk on
17 the persuasiveness of findings in study 201/202?

18 So a very similar question, but in this
19 case, we're discussing not the North Star
20 Ambulatory Assessment but the other test of
21 physical performance: rise time and 10-meter
22 run/walk as two examples of those.

1 Are there any questions clarifying this
2 question for the FDA; that is, do the panelists
3 have any questions for the FDA about what's being
4 asked?

5 (No response.)

6 DR. ALEXANDER: Okay. Very good. So we'll
7 move to voting then. Once again, the question is,
8 What is the impact of the other test of physical
9 performance such as rise time or 10-meter run/walk
10 on the persuasiveness of findings in study 201 and
11 202?

12 Does it strengthen the persuasiveness of the
13 findings, does it weaken the persuasiveness of the
14 findings, or is there no effect?

15 (Vote taken.)

16 DR. CHOI: Everyone has voted. The vote is
17 now complete. For the record, we have 1 vote for
18 A, strengthen; 2 votes for B, weaken; 10 votes for
19 C, no effect.

20 DR. ALEXANDER: Thank you. So why don't we
21 begin with Dr. Hoffman? If you could state your
22 name, and your vote and a brief justification or

1 explanation of why you voted as you did for the
2 record.

3 DR. HOFFMAN: Richard Hoffman. And I voted
4 C, no effect because of the same reasons from the
5 previous question.

6 DR. ALEXANDER: And those reasons were?

7 DR. HOFFMAN: Well, in my opinion, there
8 were differences of opinion between the FDA and the
9 sponsor. And I really didn't think one or the
10 other proved the case one way or the other for that
11 particular testing.

12 DR. ALEXANDER: Thank you. Dr. Green?

13 DR. GREEN: Yes. I voted C too because I
14 think these represent too small of a sampling error
15 to be convincing about the disability caused by the
16 condition.

17 DR. ALEXANDER: Just so I understand you
18 that they represented too small a sampling error?

19 DR. GREEN: Sampling the -- there's a lot of
20 overlap between the muscles involved in those two
21 tests, so I think they don't represent the totality
22 of the muscle disorder.

1 DR. ALEXANDER: Thank you. Mr. Dupree?

2 MR. DUPREE: Benjamin Dupree. I voted C, no
3 effect. I don't really see that these influence
4 persuasiveness one way or the other because, based
5 on the testimony, it seems like -- I can't see a
6 real correlation between these and the 6-minute
7 walk test.

8 MS. GUNVALSON: Cheri Gunvalson. I voted A.
9 I believe Dr. McDonald gave a good presentation on
10 how rise time affects ability to walk, and I
11 thought it strengthened it.

12 DR. KRYSCIO: Richard Kryscio. I voted no
13 effect. These, I viewed as secondary outcomes and
14 it didn't factor into my opinions on this. And
15 there was certainly disagreement between sponsor
16 and the FDA.

17 DR. ROMITTI: Paul Romitti. I voted C, no
18 effect for the same reasons just explained.
19 There's agreement on how to handle rise time
20 between the FDA and the sponsor. And also,
21 10-meter walk run, I don't think really adds much
22 to the outcome assessment here.

1 DR. NUCKOLLS: Glen Nuckolls. I voted no
2 effect. So I get Craig McDonald's point that its
3 ability to rise and not time to rise, but that's
4 just one component of the North Star. But I give
5 that kind of a little bit of strengthen. And then
6 the data from the FDA, it showed there's really no
7 difference in 10-meter walk with the other way, so
8 they kind of cancelled out.

9 DR. FOLEY: Reghan Foley. I voted C, no
10 effect for reasons already stated. These are
11 secondary outcomes. It didn't really strengthen or
12 weaken the results, in my eyes.

13 DR. KESSELHEIM: Aaron Kesselheim. I also
14 voted no effect because the secondary outcomes
15 didn't clearly show evidence one way or other. And
16 given the very small sample size, I don't think
17 that there is much that they add one way or other
18 on the main question.

19 DR. ALEXANDER: Caleb Alexander. I felt
20 that they weakened the results or conclusions one
21 reaches about studies 201/202 primarily because I
22 think the -- in this type of setting where there's

1 questions about the adequacy of the historical
2 controls and the -- I mean, the amount of
3 dystrophin produced, the adequacy of the historical
4 controls and the relationship between the
5 dystrophin production and outcomes assessed, I
6 would have liked to have seen more convincing
7 evidence of the effect of the study drug on these
8 outcomes.

9 I think in particular, looking at the
10 experience of individuals over time by age
11 influenced me to feel that these weaken the
12 findings.

13 DR. ONYIKE: Chiadi Onyike. I voted weaken
14 as well for the reasons -- firstly, for the reasons
15 that Dr. Alexander has explained. But also taking
16 into account Dr. McDonald's explanation, I think
17 that at the end of the day, you still have to
18 control for either age at baseline or age at
19 illness onset if you wish to account for illness
20 duration.

21 I don't think that you can look at these
22 time-dependent measures independent of some

1 adjustment for age. And unfortunately, the sample
2 is not large enough to successfully do that. But I
3 think anyone would agree that in a large enough
4 sample, you would be remiss not to control for age.

5 DR. GONZALES: Nicole Gonzales. I voted no
6 effect. In the absence of a concurrent control
7 group, it makes it very difficult for me to
8 interpret the results of any of the secondary
9 outcome measures.

10 DR. OVBIAGELE: Bruce Ovbiagele. I voted no
11 effect even though I thought it slightly diminished
12 the effect. But I think there's enough conflict
13 about the interpretation of how to look at this
14 that I thought on balance overall, the effect, if
15 anything, was very minimal.

16 DR. ALEXANDER: Okay. So those that felt
17 that it strengthened the association felt that rise
18 time affects the ability to walk and that there was
19 a good rationale for why these might be linked.

20 Panelists that felt that this weakens the
21 persuasiveness of the associations, I should say in
22 studies 201/202, felt that a collateral information

1 is very important, especially in this setting where
2 questions have been raised about the primary
3 endpoints and the 6-minute walk test results.

4 There was a comment that at the end of the
5 day, you have to control for age at baseline or
6 illness onset and that one can't look at these
7 measures without adjustment for age. But the
8 sample isn't large enough to do so, that is to
9 adjust for age.

10 Then, for those that felt there was no
11 effect, reasons to support that included that there
12 are differences in opinion between the FDA and the
13 sponsor. Neither proved a case one way or the
14 other for that particular testing. A lot of muscle
15 is involved between these two tests so that they
16 don't represent the totality of muscles involved in
17 this disorder.

18 Panelists felt that they don't see that
19 these tests influence the persuasiveness one way or
20 the other, that there was disagreement with how to
21 handle the rise time between the FDA and the
22 sponsor, that the 10-meter test doesn't add much to

1 the outcome.

2 Another panelist made the point that they
3 get the point that it's the ability to rise, not
4 time to rise that give some strength in the data
5 that was provided by the FDA.

6 Panelists felt that these are secondary
7 outcomes and therefore didn't strengthen or
8 weakened the associations -- or the persuasiveness
9 of the findings of studies 201/202, that the
10 evidence regarding these outcomes didn't clearly
11 show evidence one way or another; that there was a
12 small sample size that didn't add much; that in the
13 absence of a concurrent control group, difficult to
14 interpret any of these secondary outcome measures.

15 So those were some of the rationales for
16 those panelists that felt that there was no effect
17 here.

18 The last question is a voting question,
19 which is whether or not the clinical results of the
20 single historically-controlled study, that is
21 study 201/202 provide substantial evidence, i.e.,
22 evidence from adequate and well-controlled studies

1 or evidence from a single highly persuasive,
2 adequate and well-controlled study that is
3 accompanied by independent findings, that
4 substantiate efficacy that eteplirsen is effective
5 for the treatment of DMD.

6 So here again, are there questions to
7 clarify this for the FDA?

8 (No response.)

9 DR. ALEXANDER: Are there clarifying
10 questions on the part of the panelist?

11 (No response.)

12 DR. ALEXANDER: If not, then we'll move to
13 voting. Once again, the question is, do the
14 clinical results of the single historically-
15 controlled study, study 201 -- I'm sorry. There's
16 a question? Yes?

17 DR. ONYIKE: Yes. Forgive me.

18 DR. ALEXANDER: Can you identify yourself
19 please?

20 DR. ONYIKE: My name is Chiadi Onyike. To
21 what extent are we to incorporate into this
22 question the testimony of the families, the boys

1 and their families?

2 (Applause.)

3 DR. ONYIKE: From my reading of the
4 question, it would seem narrowly worded towards the
5 actual statistical results. So I just want some
6 clarification on that point.

7 DR. ALEXANDER: Can the FDA address that
8 question, please?

9 DR. WOODCOCK: Well, we are instructed, as
10 people said, to take the use of the patient
11 community into account, more on the benefit and the
12 risk.

13 (Applause.)

14 DR. WOODCOCK: So the statutory standard is
15 more or less as described there, but there is
16 flexibility, and that's where we should take the
17 views of the community into account.

18 DR. ONYIKE: Sorry. If I might just follow
19 on. So if I understand you correctly, this
20 question, as worded, is really about statistics; is
21 that correct?

22 DR. ALEXANDER: Would it be fair to suggest

1 that you should take into account the totality of
2 information in the briefing packet and what's been
3 discussed today?

4 DR. WOODCOCK: I think that's fair. The
5 standard is adequate and well-controlled trials.
6 That's what's in the statute. But we are
7 instructed to have flexibility in how we interpret
8 that based on the medical need. So I think,
9 Dr. Alexander, that's a fair summation.

10 Bob wants to say something.

11 DR. TEMPLE: There are lots of questions
12 raised about the study, whether there was improper
13 influence of the fact that people knew what the
14 study was and all that kind of stuff.

15 You heard testimony from patients who said
16 very explicitly that they didn't think that would
17 alter the level of effort that people made. So
18 those kinds of factors are certainly things that
19 are up for discussion.

20 You know, whether it's persuasive or not,
21 whether the study is persuasive enough, that has a
22 lot to do with the study design and what was

1 measured, size of the treatment effect and all
2 those things. But you heard testimony that might
3 affect your views on the quality of the endpoints,
4 on the importance of lack of blinding, and all
5 kinds of stuff like that.

6 DR. ALEXANDER: Dr. Unger?

7 DR. UNGER: I think with the majority of the
8 patients here, we have an incredible advantage that
9 we -- I mean, in my time with the FDA, it's
10 unprecedented to have basically all of the patients
11 here. So that's an important advantage that we
12 have.

13 One of the things that you can do is try to
14 reconcile what you've heard from the patients with
15 the data that you've seen presented by the company.
16 We're hearing patients are improving, doing things
17 next year that they didn't do last year. And you
18 have to figure out if you can reconcile that with
19 the actual hard data that you've been analyzing
20 today.

21 DR. ALEXANDER: Yes? Please state your name
22 and question for the record for the FDA clarifying

1 this question.

2 DR. ROMITTI: Paul Romitti. This is
3 directed to Dr. Woodcock because when I look at
4 this question and I think of the first one we
5 discussed, you're talking about two
6 different -- there are some overlap in subjects,
7 but you're talking about two different groups,
8 particularly with the controls.

9 So I want to understand if we are to
10 consider the dystrophin results, which were tested
11 on some different people than in the one or two, or
12 we just talking about the other part of the study?

13 DR. WOODCOCK: This is the full approval
14 question, and that is based on the empirical
15 results in the clinic. I agree with what Dr. Unger
16 said. They're not based on the persuasiveness of a
17 surrogate endpoint. They're based on the
18 persuasiveness of the trial that was done.

19 DR. ALEXANDER: Thank you. One more
20 question of clarification. Please state your name
21 for the record.

22 DR. OVBIAGELE: Bruce Ovbiagele. Because I

1 would have two different answers to the questions.
2 One would be objective; one would be subjective.
3 And it's how to reconcile both in the same question
4 here that I guess is the issue.

5 DR. ONYIKE: This is Chiadi Onyike. If I
6 may quickly add to that, the question twice
7 mentions "well controlled," and as you've heard
8 repeatedly, people have said that they have trouble
9 the control. So this "well controlled" phrase, in
10 a sense, tips or constrains the question.

11 DR. TEMPLE: I understand a lot of people
12 don't like historically-controlled trials. They're
13 not sure they believe they're well controlled. Our
14 regulations since 1970 have said that a
15 historical-controlled trial can be a
16 well-controlled study, an adequate and
17 well-controlled study.

18 The question here goes to, do you think,
19 under the circumstances, that it was? Do you think
20 the way they selected them was right? Do you think
21 the way analyzed them was right; good enough to
22 make it an adequate and well-controlled study?

1 That's the question.

2 DR. DUNN: Yes --

3 DR. TEMPLE: Historically-controlled trials
4 have been the basis for approval, sometimes in sort
5 of obvious cases; sometimes in cases that aren't
6 quite as obvious.

7 DR. DUNN: Yes. Billy Dunn. I want to
8 reiterate all of these issues. I think it's very
9 important to take into account the testimony you
10 heard here today because you heard half of the
11 comparison. You heard from the patients in the
12 201/202 trials.

13 They're being compared to a historical
14 control. One of the reasons that I opened up the
15 meeting, and many others reiterated the issues that
16 I abruptly spent so much time talking about what
17 substantial evidence is and what adequate and
18 well-controlled studies are, so that you can sort
19 out whether or not the evidence provided from this
20 study, with the information that you have at hand
21 here from the patients as well as what's provided
22 by the -- what you referred to as more objective

1 results, rises to the standard that it creates
2 substantial evidence of effectiveness, which again
3 most traditionally is provided by two adequate and
4 well-controlled trials.

5 We did not set out to refute the notion that
6 the historical control was unacceptable by design.
7 I think we took pains to actually illustrate that
8 that was potentially acceptable.

9 What we've done is describe to you the
10 concerns that the team had that have to do with the
11 comparability of that control, the acceptability of
12 the use of that control.

13 So the issue here is that substantial
14 evidence question of whether or not in comparison
15 with the group, with all the issues that we've
16 heard and everything you've heard today, it serves
17 to reach that level of evidence.

18 DR. ALEXANDER: Thank you. Are there any
19 other final questions clarifying this question
20 before we move to voting?

21 (No response.)

22 DR. ALEXANDER: Okay. So we'll move to

1 voting then, and I'll read the question. If you've
2 voted once, please do so again. And the question
3 is as follows:

4 Do the clinical results of the single
5 historically-controlled study, study 201/202,
6 provide substantial evidence, that is evidence from
7 adequate and well-controlled studies or evidence
8 from a single highly persuasive adequate and
9 well-controlled study that is accompanied by
10 independent findings that substantiate efficacy,
11 that eteplirsen is effective for the treatment of
12 DMD?

13 (Vote taken.)

14 DR. CHOI: Everyone has voted. The vote is
15 now complete. We have 3 yes, 7 no, 3 abstentions.

16 DR. ALEXANDER: Thank you. Why don't we
17 begin with Dr. Hoffman? If you can state your name
18 and your vote for the record and a brief
19 explanation of why you voted as you did.

20 DR. HOFFMAN: Richard Hoffman. And I voted
21 to abstain and the reason was, is I was basically
22 just torn between my mind and my heart. And I

1 don't want to make type 1 error, and I don't make a
2 type 2 error.

3 DR. ALEXANDER: Thank you. Dr. Green?

4 DR. GREEN: Mark Green. I also abstained
5 because I'm uncomfortable by the language of the
6 question because I think it's a bit leading even
7 though I recognize that's the answer that's
8 requested of us, because I don't believe that an
9 external control is customary in a study like this
10 at all, so I can't say I'm in favor of that.

11 But I'm very fearful that we'll leave here
12 with some sort of stalemate between the FDA and the
13 panel, where I'm still quite sympathetic and
14 persuaded by the public's presentations.

15 MR. DUPREE: Benjamin Dupree. I voted yes
16 because I can't really reconcile the difference
17 between the testimony that was given suggesting
18 that the boys' recovering abilities, I
19 don't -- living with Duchenne, I don't understand
20 how that's even possible.

21 But at the same time, this study doesn't
22 prove from a -- like it doesn't provide what I

1 think is adequate evidence to support all this
2 testimony that I'm seeing and hearing.

3 MS. GUNVALSON: Cheri Gunvalson. I voted
4 yes. I believe there's substantial evidence in
5 supporting this.

6 (Applause.)

7 DR. KRYSCIO: Richard Kryscio. I voted no.
8 It's not a well-controlled study. I was not
9 convinced that the data was there to basically
10 approve something on the basis of one poorly
11 controlled trial.

12 DR. ROMITTI: Paul Romitti. I voted to
13 abstain. Like the other panelists before me, I was
14 conflicted with this vote because I do see
15 limitations. And as a scientist, I cannot say that
16 this study -- and answer the question as
17 written -- was adequate and well controlled for a
18 number of reasons.

19 But I also was moved by the testimony, the
20 public testimony as well. And I'm also concerned
21 that we keep getting more and more information
22 about why there wasn't a placebo-controlled trial.

1 I'd asked for clarification earlier on in
2 the meeting about when Sarepta was told or asked to
3 do a placebo-controlled trial and received a date
4 of several years ago. And I'm surprised
5 that -- and I feel like maybe that they needed to
6 consider that. Now, we hear maybe they didn't have
7 enough drug.

8 So more information keeps coming out, so I'm
9 uncomfortable -- as much as I'd like to say yes,
10 I'm uncomfortable with the evidence to date to say
11 yes. I'm moved by the public testimony, but I'm
12 not as uncomfortable to just say no. I think
13 there's still room to work here.

14 DR. NUCKOLLS: Glen Nuckolls. I voted no.
15 I thought that there were significant concerns
16 regarding the ability to draw valid conclusions
17 from this design of an externally-controlled
18 comparison.

19 DR. FOLEY: Reghan Foley. I voted yes. As
20 a pediatric neuromuscular specialist, for me,
21 there's substantial evidence that there's
22 amelioration of the clinical phenotype of Duchenne

1 dystrophy. I believe that more data is needed, and
2 I also believe that looking at other biomarkers, as
3 Professor Partridge pointed out, would very helpful
4 as well. But I did feel that the phenotype was
5 clearly ameliorated.

6 DR. KESSELHEIM: Aaron Kesselheim. I voted
7 no. I felt like a historically-controlled study
8 could provide substantial evidence, but this one
9 did not both in its results and its design. I felt
10 like it could therefore be used potentially as
11 supportive. But the original controlled study,
12 placebo-controlled study, the 12 patients was
13 negative. So if it was going to be supportive or
14 secondary, it was going to be secondary to
15 something that did not show an effect.

16 Then I was also confused -- I was also
17 confused a little bit by the fact that there did
18 appear to be evidence from the audience from more
19 patients that were presented here from some of
20 these newer studies and some of these extension
21 studies.

22 So I think that there is still information

1 to learn about this drug. But as the data
2 currently stand, it doesn't appear to me that this
3 historically-controlled study provides substantial
4 evidence.

5 DR. ALEXANDER: Caleb Alexander. I voted
6 no. I just felt that this wasn't a well-controlled
7 study and that the ways that the controls were
8 selected and analyzed didn't meet the threshold
9 that I would consider to be adequate and well
10 controlled.

11 We heard criteria for what constitutes a
12 well-controlled study. And even if the study was
13 well controlled, I have concerns regarding the
14 conclusions reached about the efficacy of
15 eteplirsen.

16 DR. ONYIKE: Chiadi Onyike. I voted no.
17 Basically, the findings do not support a conclusion
18 of yes, at least on the statistical grounds and
19 scientific grounds. And unfortunately, what I
20 would consider meaningful evidence or testimony
21 from the families is not properly measured in the
22 study.

1 So I hope that in the future that the field
2 will incorporate measures of function. Someone
3 alluded to ALS fields. There are other fields.

4 I work also in the dementia field where
5 caregiver outcomes are routinely included in the
6 clinical trials. I think there needs to be a move
7 in that direction so what you report are not
8 considered soft outcomes. I also hope you would
9 consider, as a community, participating fully in
10 controlled trials so that you're not in this
11 position in the future.

12 (Audience interrupts.)

13 DR. ALEXANDER: I'm sorry, please. We have
14 to continue with the explanation.

15 DR. ONYIKE: My apologies. I don't mean --

16 (Audience interrupts.)

17 DR. ALEXANDER: I'm sorry. The audience --

18 DR. ONYIKE: Let me speak to that, please.

19 DR. ALEXANDER: No, actually, I'd like to
20 move on.

21 DR. ONYIKE: Let me speak to it. I made the
22 comment, please. Please.

1 DR. ALEXANDER: No.

2 (Audience interrupts.)

3 DR. ONYIKE: I'm sorry. I didn't mean to be
4 critical or lecturing. What I meant to say -- what
5 I meant to address was the --

6 DR. ALEXANDER: Thank you. May we have
7 the -- Dr. Gonzales?

8 DR. GONZALES: Nicole Gonzales. I voted no.
9 The placebo portion of the study wasn't positive on
10 the primary outcome measures, and I had issues with
11 the historical control for secondary clinical
12 endpoints.

13 DR. OVBIAGELE: Bruce Ovbiagele. I voted
14 no. I thought it wasn't a well-controlled study at
15 all. If I had to vote based on the testimony I
16 heard, if this was a before and after question,
17 definitely based on all that I heard, the drug
18 definitely works, but the question was framed
19 differently.

20 DR. ALEXANDER: Thank you. So I'd like to
21 just for the record summarize the comments that
22 I've heard.

1 (Audience interrupts.)

2 DR. ALEXANDER: I'd like to try to get this
3 entered in to the record and not adjourn the
4 meeting prematurely. So out of respect for all of
5 the individuals that are here, I request that you
6 allow for me to summarize briefly the comments that
7 we've heard thus far.

8 So those that voted yes felt that one
9 couldn't reconcile the differences between
10 testimony that was given suggesting boys were
11 recovering abilities, didn't understand how that
12 was possible, but the study didn't provide what was
13 felt to be adequate evidence to support all of this
14 testimony that the panelists were seeing.

15 They felt that there was substantial
16 evidence that the phenotype clearly improved, but
17 there was an encouragement for the collection of
18 more data, including biomarkers.

19 Individuals that voted no felt that it was
20 not a well-controlled study, that the data wasn't
21 there to approve something on the basis of one
22 poorly controlled trial. There were significant

1 concerns raised about the ability to draw valid
2 conclusions from this type of external comparison.

3 One panelist commented that the historical
4 control could provide sufficient information but
5 that this one did not and was also confused by the
6 fact there appear to be evidence from newer studies
7 or extension studies. And the panelist felt that
8 more information would be helpful to learn about
9 this product.

10 One felt that there wasn't -- that this
11 wasn't a well-controlled study, so here again that
12 the ways the controls were selected and analyzed
13 didn't meet the threshold that they felt would
14 constitute to be adequate and well controlled.

15 We heard criteria for what constitutes a
16 well-controlled study. A panelist commented that
17 even if it was well controlled, that there was
18 reason to question the conclusions regarding
19 efficacy that were reached.

20 A panelist commented that based on
21 scientific and statistical grounds, what they would
22 consider meaningful testimony from the families was

1 not optimally assessed in the study and that
2 caregiver outcomes are routinely included in
3 randomized trials in dementia, and that this might
4 be pursued in DMD. And one panelist also commented
5 that the placebo portion of the study was not
6 positive on outcome measures.

7 Those that abstained, one panelist felt that
8 he was torn between his mind and his heart. He
9 doesn't want to make a type 1 error but doesn't
10 want to make a type 2 error either.

11 One panelist was uncomfortable by the
12 language of the question and felt that it was a
13 little leading and didn't feel that external
14 control is -- that having an external control is
15 customary, wouldn't favor that; but one panelist
16 noted that they feared that we would leave with a
17 stalemate between the FDA, and they said the panel,
18 but I imagine they meant the sponsor, maybe not.

19 One panelist noted that they do see
20 limitations, that they didn't feel that they could
21 answer the question affirmatively, but they were
22 also moved by the public testimony and also

1 concerned that more and more information -- they
2 were concerned with the additional information
3 about why there wasn't a placebo-controlled trial
4 and that they had asked for that information early
5 in the meeting and then told that the date was, I
6 believe, in 2011 that Sarepta was encouraged to
7 pursue an RCT. That panelist felt uncomfortable
8 with evidence to-date to say yes but they were
9 moved by the public testimony.

10 Before we adjourn, I would like to give the
11 opportunity to the FDA, if there are any final
12 comments from the FDA?

13 DR. DUNN: Billy Dunn, FDA. The emotion and
14 passion in the room during the discussion is clear.
15 And I mentioned at the beginning of the day that we
16 listen and we listen carefully. And although I
17 recognize there's great concern about the
18 discussion and the results of the votes, I assure
19 you that we listened very carefully.

20 We've heard some very meaningful testimonies
21 today, and we've observed the panel be highly
22 influenced by that testimony. I assure you that we

1 will take the information we've learned here today
2 under very serious consideration as we adjourn this
3 meeting.

4 **Adjournment**

5 DR. ALEXANDER: Thank you. And I'd just
6 like to add my thank you to the patients and
7 friends and family, the members of the general
8 public. Many of you exerted a tremendous effort to
9 get here, and I appreciate your participation.

10 Also, I'd like to thank the FDA staff and
11 scientists, the sponsor for the enormous amount of
12 work that all of you and your colleagues have
13 performed in order to make today possible. I'd
14 also like to thank the conference center staff as
15 well for helping to host this event.

16 Once again, thank you for your contribution
17 to today's meeting. The meeting is now adjourned.
18 Panel members, please take all your personal
19 belongings with you as the room is cleaned at the
20 end of the meeting today. All materials left on
21 the table will be disposed of.

22 Please also remember to drop off your name

1 badge at the registration table on your way out so
2 that they may be recycled. Thank you again for
3 your participation.

4 (Whereupon, at 7:37 p.m., the meeting was
5 adjourned.)

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Smith, Celeste

From: Unger, Ellis
Sent: Wednesday, July 13, 2016 3:19 PM
To: Woodcock, Janet
Cc: Jenkins, John K; Dunn, Billy; Bastings, Eric
Subject: RE: MEMO

Janet,

I've canvassed the Division, and we have no additional comments.

Thanks for sharing,

Ellis

From: Woodcock, Janet
Sent: Monday, July 11, 2016 7:21 PM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy; Bastings, Eric
Subject: MEMO

Here is a draft version of my decisional memo. I welcome comments on it. An appeal can't be done until I finalize this, I am told. Thanks. jw

Smith, Celeste

From: Unger, Ellis
Sent: Tuesday, July 05, 2016 3:37 PM
To: Woodcock, Janet
Cc: Jenkins, John K; Temple, Robert
Subject: eteplirsen NDA

Janet,

I don't have to tell you how difficult the eteplirsen decision has been for many of us in ODE-I. As you know, we have reached different scientific conclusions on the strength of the data, and in particular, the likelihood that the small increase observed in Becker-type dystrophin is reasonably likely to predict clinical benefit. This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed "reasonably likely to predict clinical benefit." Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated.

I know that Dr. Jenkins has mentioned the possibility of involving Dr. Califf in the eteplirsen decision on at least one occasion, and I would like to request a formal appeal to the Commissioner on this matter.

I'm aware that the Commissioner's official role is to consider the administrative aspects of review decisions and not the science. But given the potential for setting a precedent here, I think he should be aware of the various points of view and consider the potential ramifications of the matter at hand.

I'm also aware that you advised Sarepta that we would be prepared to grant accelerated approval of their NDA within 4 business days of receiving their new data, but there was a provision in the letter that the increase in dystrophin had to be meaningful, and we do not have agreement on this point. Thus, it is my hope that a Commissioner Briefing can be held before an action is taken.

I have discussed the above with Dr. Jenkins, and he supports this course of action.

I propose that we reserve a few minutes at the briefing tomorrow to discuss this matter.

Thank you for your consideration,

Ellis

Eteplirsen-- IND 077429 ; NDA 206488

<i>Date</i>	<i>Brief Background/Supplemental Information</i>	<i>Meeting Forum</i>
July 17, 2013	Discussed the suitability to file NDA for Subpart H approval	Center Director Briefing
October 18, 2013	Overview and background Application Review General Discussion	Center Director Briefing
October 28, 2013	Continuation of meeting that occurred on Oct. 18	Center Director Follow Up Briefing
December 19, 2013	Follow up to the Nov. 15 meeting to discuss the study design of a clinical trial for eteplirsen (Study 4658-301)	Sponsor (Type A Meeting) with Sarepta Therapeutics
January 17, 2014	Follow up discussion on GSK-IND 105284 Drisapersen data findings	Center Director Follow Up Briefing
February 6, 2014	Update on DMD drugs study design (drisapersen-eteplirsen)	Center Director Briefing
March 5, 2014	OND team meeting on biomarker data findings and discussion on inviting Sarepta in for a brainstorming discussion	Division Meeting re: IND 77429 eteplirsen/biomarker data
March 19, 2014	Sponsor meeting to discuss study design and path forward	Refer to background
April 2, 2014	Post- Brainstorming Debrief	Refer to background
July 14, 2014	Sarepta Clinical Site Inspection Report	Center Director Briefing

<i>Date</i>	<i>Brief Background/Supplemental Information</i>	<i>Meeting Forum</i>
December 9, 2015	Discussed the current status of eteplirsen review in advance of the AC meeting that occurred on April 25, 2016	Center Director Briefing
January 13, 2016	Reviewed slide presentation for the upcoming AC meeting	Center Director Briefing
February 10, 2016	Discussed the ongoing review of eteplirsen NDA and reviewed what will be presented at the AC meeting	Center Director Briefing
April 15, 2016	Statistician subgroup presented CINRG data analysis prior to the April 25 AC meeting	Center Director Briefing
April 25, 2016	Advisory Committee Meeting	
May 4, 2016	Discussed outcome and plan of action(s) for eteplirsen application	Center Director Briefing
May 24, 2016	Meeting to discuss eteplirsen decision	One-on-one discussion between Drs. Woodcock & Unger
May 31, 2016	<p>Discussed reviews conducted by the review team and senior leadership along with any additional information obtained from the sponsor for the eteplirsen application.</p> <p>First draft memo from Dr. Woodcock was discussed at this meeting with the division.</p> <p>Comments were also received back from the division</p> <p style="text-align: center;">  Sarepta dct.docx </p>	Center Director Briefing

<i>Date</i>	<i>Brief Background/Supplemental Information</i>	<i>Meeting Forum</i>
July 6, 2016	<p>Ongoing review of the NDA for eteplirsen (e.g. levels of dystrophin, PMR trials and description of the clinical data in the drug label if approved). Meeting notes transcribed by Dr. Woodcock are attached.</p> <p style="text-align: center;">  Eteplirsen application notes-7-6-16.pdf </p>	Meeting with the division on eteplirsen
July 7, 2016	Meeting with Commissioner to discuss regulatory review issues and potential formal appeal	Commissioner's Briefing with Unger, Temple, Jenkins
July 11, 2016	<p>Draft version of second decisional memo sent to division via email. Comments were also received back from the division</p> <p style="text-align: center;">  Sarepta dct.docx </p>	N/A
July 14, 2016	Finalized Center Director Review Decisional Memo (signed and uploaded into DARRTS)	N/A
July 16, 2016	Finalized Office Director's Decisional Memo (signed and uploaded into DARRTS)	N/A
July 18, 2016	Finalized Office Director Unger's formal appeal submitted under SMG 9010.1	N/A

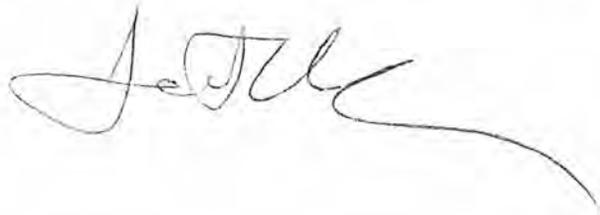
7/6/16
Meeting between Janet Woodcock
and OND on Sandoz Rempevir
etelivon application

OND attendees - John Jenkins
Ellis Unger
Robert Teple
Billy Dunn
Eric Barling (by phone)

I indicated to the review team that I had read their memoranda that had been updated to reflect the new WB data, and that I maintained my position that the application should receive accelerated ~~by~~ approval based on Wyeth's production. My reasoning is attached, and was discussed.

The team disagreed with this position. After a discussion, Dr. Unger indicated that the team would appeal this matter to the FDA Commissioner.

We discussed the mechanics of such an appeal.



Reasoning behind "reasonably likely"

- ① Substantial evidence - weekly dystrophenin
- ② Means useful for statistical comparison - but not ~~to~~ provide all information
- ③ # of pts non-responders at 180 weeks = 42 weeks. Unlike many drugs, not likely they drug works thru other MDA
- ④ Responders achieved levels 1-2% of normal control
- ⑤ Disparate deletions in mix
It is known that the "Becker" protein in a β gene produces a dramatically ameliorated phenotype
- ⑥ The protein-expression-response characteristics of the disease are not known at this level and over time due to lack of careful analytical techniques available. That small β not enough is conjecture
- ⑦ Any small improvement in maintaining function meaningful in this group - even moving a finger
- ⑧ Can't prove that 1-2% levels are meaningful, can't prove that they are not
- ⑨ Natural history studies can be criticized, but also consist of some responders
- ⑩ Correlation between rate of decline in MDA + % dystrophenin in WB
 $r^2 = ?$

CENTER DIRECTOR DECISIONAL MEMO

NDA# 206488
Drug Name EXONDYS 51 (eteplirsen)
Indication Duchenne Muscular Dystrophy (DMD)
Sponsor Sarepta
Author Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research (CDER),
Food and Drug Administration

SUMMARY

This memorandum explains the CDER's final decision on the above application. I have read the reviews and recommendations by Drs. Unger (Office level), Bastings (Division level), Farkas (Cross-Discipline Team Lead), Breder and Rao (Clinical Reviewers), Ling (Statistical Reviewer), and Bhattaram, Wu, and Rogers (Clinical Pharmacology Reviewers). In addition to the review memoranda, I have also reviewed the Advisory Committee briefing materials, pertinent portions of the sponsor's submission, and multiple scientific statements submitted by the public, including a letter from a large number of DMD experts.

The review team has done an exemplary job in performing a detailed evaluation of the data submitted with the application. Nevertheless, I disagree with certain of their findings and come to a different conclusion, as discussed below.

I find that the data contained in NDA 206488 meet the standard for accelerated approval under 21 CFR 314.510 based on the surrogate endpoint of increased dystrophin protein production, a surrogate endpoint that I conclude is reasonably likely to predict clinical benefit.

DISCUSSION

Extensive analyses have been performed by the team on the clinical results of the long-term experience of 12 patients administered the drug, and I will not recapitulate these.

Approval under 314.510 is based, among other things, on adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Below, I discuss how both of parts of this standard are met.

A. Are the Data on Dystrophin Protein Production From One or More Adequate and Well-Controlled Studies?

The characteristics of adequate and well-controlled studies are laid out in 21 CFR 314.126. Three lines of evidence are pertinent to the conclusion that eteplirsen results in increased dystrophin production.

- Production of an appropriate mRNA transcript
- Quantitative assessment of dystrophin content in muscle biopsies by Western blot
- Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry (IHC) techniques

The sponsor provided data demonstrating an increase in mRNA expression following treatment with eteplirsen. The drug's proposed mechanism of action is to bridge a section of the pre-RNA to result in a shorter mRNA with an open reading frame, e.g., "exon skipping." In this case, the production of an appropriate mRNA transcript has been documented by PCR and Sanger sequencing. Although this establishes proof of mechanism, it does not mean that there is increased protein production.

In the following, I discuss the assessments related to dystrophin protein production (2. and 3.) in some detail. Much of the controversy over the adequacy of these assessments relates to the fact that rigorously validated assays were not used to evaluate the initial 3 muscle biopsies, apparently resulting in overestimation of the various readouts and some irreproducibility of IHC and Western blot dystrophin assays. For these reasons, I do not discuss or rely upon the results of these earlier assays, or on re-reads of them. With FDA's assistance, the sponsor improved the design and conduct of the assays and performed repeat biopsies on 11 of 12 patients at week 180. The control samples for these week 180 biopsies were stored baseline tissue (in 3 of 11 subjects) and baseline biopsies from subjects with exon 51 amenable mutations enrolled in another trial by the sponsor. FDA reviewers had the following concerns about these controls, leading them to conclude that the studies were not adequate and well controlled.

1. Most of the baseline biopsies were not from the same subjects as the week 180 biopsies (as the original tissue had been used up for the previous assays). Given this, the control subjects could differ in unknown ways from the test subjects.
2. The biopsies taken at week 180 were from different muscles in the upper extremity than the baseline biopsies, including subjects with baseline tissue as well as for control samples. It is hypothesized that there may be differences in dystrophin protein content among various muscles in DMD patients.
3. The existing baseline biopsies for the three subjects with 180 week data had been stored frozen for several years and may have changed (apparent decrease in dystrophin protein content) over time.

In my judgment, these issues increase the uncertainty around the results, but do not necessarily render them an inadequate basis on which to draw a conclusion. The non-treated control subjects were very similar in age and dystrophin mutation site to the treated subjects (sponsor Appendix 10, AC briefing package). The single deltoid muscle biopsy in the untreated control group (subject 7, sponsor Appendix 14, AC briefing package) had replicate dystrophin levels of 0.3% and below the limit of quantification, averaging out at below 0.3%, and not different than biceps biopsy results in other patients, suggesting

that variations in upper extremity biopsy site (concern b above) did not result in large differences in the findings. There was little difference in the dystrophin protein content found in the stored baseline samples and the frozen samples, as discussed below.

The data submitted with the original application, supporting the finding that eteplirsen increases the production of dystrophin protein, come from the quantitative assessment of (internally truncated) dystrophin in muscle tissue by Western blot using the controls described above. Much of the controversy around this method relates to the fact that the apparently achieved dystrophin levels are very much lower than originally hoped (and previously claimed by the sponsor and investigators).

In the 180 week assessment, the three subjects with baseline biopsies available had baseline dystrophin levels (reported as % of normal) below the level of quantification of the assay used (0.25%). These results were similar in magnitude to the baselines of the six additional control biopsies drawn from subjects in another study (highest level 0.37%). At week 180, two treated subjects had (an average of replicate) dystrophin levels above 2%, two had over 1%, and two additional had about 1%. Of these individuals, two subjects having both baseline and week 180 samples had clearly increased levels at week 180 compared to baseline. (The third subject with a baseline sample did not consent to a week 180 biopsy). Unsurprisingly, some subjects had week 180 dystrophin levels similar to the overall baseline control levels. Not all individuals are expected to respond to a drug intervention. The issue is whether the dystrophin levels found at 180 weeks were within the variability expected for this assay in such patients and, thus, could have arisen by chance, or whether they could have been caused by differences from the controls or from sample storage as outlined above, or whether they reflected a drug effect, and, thus, whether these data could be seen as adequate and well-controlled. The following data are relevant to this issue.

Because the original data on the presence of dystrophin by Western blot suffered some difficulties in interpretation because of lack of availability of baseline samples from most patients, the sponsor of this application submitted, subsequent to the Advisory Committee meeting on this drug, additional Western blot data from 12 patients with baseline and 48 week eteplirsen exposure, using baseline and post-treatment muscle biopsies from the same patients and muscle groups. This experiment clearly shows, using adequate controls, that the drug increases dystrophin protein production in some of the patients. The mean baseline dystrophin values in this study were very similar to the mean baseline values in the 180 week study. The achieved levels of dystrophin in these patients are lower than those seen in the Western blots from the week 180 patients. Only 2 of 12 patients achieved a level over 1% of normal control. It is not known if this result is due to a shorter duration of drug exposure or to other factors. Putting together the 180 week data and the additional 48 week data, I conclude that there is substantial evidence from Western blot experiments of increased dystrophin protein production, albeit at a low level.

A finding of increased dystrophin was also seen in several IHC assays performed by the sponsor. Both assays were originally performed with baseline and several pre-180 week assays by the sponsor as a part of the clinical trial. The validity of the results of these assays were questioned by FDA because of methodological problems in their conduct, as documented in the primary clinical review and in the inspection report. Therefore, I will not further consider the results of these original assays. As discussed for the Western blot above, the sponsor responded by performing an additional 180 week biopsy and repeating the assays. Baseline tissue was available, as for Western blot, from recut samples

in only three cases. In one of these, the subject did not consent to a biopsy at 180 weeks. To supplement the three baseline samples the sponsor included six other untreated patients from a different trial, as discussed above for the Western blot. In both assays, greater staining or intensity was observed after drug exposure at week 180 compared to controls. The results are described in more detail below.

A Percent Dystrophin Positive Fibers analysis was a semi-automated evaluation performed at 180 weeks and compared to the controls used for the 180 week study as discussed above. The percentage of positive fibers was assessed using a blinded read by Nationwide Children's Hospital and by three independent pathologists through Flagship Biosciences. The technique used to assess percent positive fibers was modified from the original assay in the following ways:

1. A computer algorithm (MuscleMap from Flagship) that performs non-linear mapping of all fibers was used for consistent and automated analysis of low intensity values, in contrast to a manual and non-standardized fiber counting technique in the prior assay.
2. The images were inverted and amplified to score the total fibers (the denominator for the percent positive fiber scoring).
3. An isotype matched secondary antibody staining step was incorporated to confirm lack of non-specific staining and reduce background noise. The background signal was subtracted from test sample values in calculation of percent intensity.
4. 8% of the images for re-analysis were blinded, renamed, randomized, and rotated 180 degrees.
5. A rejection factor for the inter-rater analysis score of <4 was established.
6. The images were acquired in a more systematic and random fashion to minimize bias, with predefined rules for random sampling of fields and avoiding artifacts.

These changes were likely to result in a more conservative reading of Percent Dystrophin Positive Fibers, and indeed the results, including the new untreated baseline controls, were read at 1.1% positive fibers (in contrast to a higher result in the prior baseline using the original technique). The 180 week cohort had a score, using this technique, of 17.4% positive fibers, showing a statistically significant difference. Now, these results are subject to the same caveats as discussed for the Western blot (1-3 above), in that there were only two baseline to 180 week pairs, that the baseline samples had been frozen for years, and that the external controls might differ in some way. So, these results cannot stand alone.

Other reviewers have pointed out that the (much higher) baseline values for Percent Positive Fibers from the original experiment are not very different from the 180 week values in this new experiment. However, I would point out that experimental conditions changed quite a bit, and very low values for all the external controls, statistically comparable to the frozen baseline results, were obtained in this recent experiment, suggesting that it returned a more conservative result. I do not believe that comparison of the original baseline data, obtained under one set of experimental conditions, can be compared to the later 180 week results, done under different, more optimized conditions and yielding very different results for new (external control) baseline samples.

The sponsor also performed a Mean Relative Fluorescence Intensity assay for dystrophin. This assay is commonly performed by laboratories evaluating DMD patients and is intended to be a semi-quantitative evaluation of dystrophin content. Using the six external baseline samples and the three stored study patient baseline samples, the mean intensity approximately doubled from baseline to 180 weeks. The technique for this assay did not change significantly from the technique used in the assay done as part of

the original protocol, and the baseline means for the patient samples were roughly comparable to the baseline means obtained in the new experiment.

Although the IHC assays provide only semi-quantitative assessments of dystrophin content, they do support an effect of eteplirsen on the proposed surrogate endpoint (an increase of dystrophin production as a result of drug exposure). The accompanying microscopy images also demonstrate correct localization of the molecule within the muscle fibers, a very important factor in any translation to clinical benefit.

In summary, I conclude that there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells.

B. Is the Effect on the Surrogate Endpoint “Reasonably Likely to Predict Clinical Benefit”?

In this case, the standard for clinical benefit does not require “cure” or “conversion to Becker MD (BMD) phenotype.” Clinical benefit encompasses improvements (including slowing of disease progression) in how an individual feels or functions, or an improvement in survival. There is no question that, for DMD patients and their families, small improvements in function or delays in loss of function are meaningful benefits. Therefore, the question is:

What amount of increase in dystrophin production is reasonably likely to predict clinical benefit (even small benefits)?

The usual way to address this question would be to rigorously evaluate what is known about the correlation between dystrophin levels in muscle and expression of disease. The following summarizes the existing scientific literature on this topic and the challenges in interpreting it.

1. The clinical classification of disease severity (i.e., phenotype) in the literature appears broad, variable, and somewhat subjective.

Experts usually classify patients clinically as DMD (severely affected at a young age); intermediate MD (also called DMD/BMD); or BMD, which can range from severe BMD to asymptomatic individuals with biochemical abnormalities, usually increased creatine phosphokinase (CPK). There is clearly a wide spectrum of disease wherein the ends of the spectrum are easily distinguishable, but the zone of real interest for this discussion, between DMD and intermediate presentations, is not rigorously categorized. In part, this is because “intermediate muscular dystrophy” (IMD) is less common, due to the consequences of having either in-frame mutations with a truncated protein expressed (leading to BMD) or out-of-frame mutations with little-to-zero protein expressed (leading to DMD), as discussed below.

2. Much of the prior data reporting the relationship of dystrophin protein levels to phenotype have been from IHC studies using a variety of techniques and antibodies.

Anthony, et al., (*Neurology*, 83, 2014) in a collaborative cross-laboratory study, investigated the variability of techniques used to quantify dystrophin in individuals with muscular dystrophy. Blinded tissue sections from three DMD and three BMD muscle biopsies were tested in five

different laboratories accustomed to performing dystrophin quantification. Estimates of dystrophin expression using a somewhat standardized IHC technique were about 20%, 11% and 10% of normal for the three DMD samples, on average among the laboratories. Corresponding estimates of dystrophin content by Western blot, using an actin antibody to normalize for loading, but not a serially diluted standard control, resulted in dystrophin estimates of about 11%, 0, and 0.4% respectively, with fairly high CV's. Therefore, in this small sample, repeated across five experienced laboratories, IHC estimates were about 10 percentage points higher than Western blot estimates.

Significantly higher estimates by IHC by fluorescence intensity (overall about 23% of normal) than by Western blot were also seen in the evaluation of week 180 muscle biopsies in the Sarepta trial. Because much of the historical data on protein content vs phenotype has been reported using IHC analysis, extrapolating these findings to the current trial data is challenging. Additionally, Anthony et al., found that the inter-laboratory variability was greatest for the low levels of dystrophin found in the DMD patients. Western blot data in the literature quantifying dystrophin and relating it to phenotype is often from experiments that were not designed to distinguish among dystrophin levels below 10% of normal. These may have been reported out as "less than 10%." From this sponsor's well-controlled studies, the analytically accurate dystrophin baseline for many DMD patients might be in the range of 0.02-0.35 % normal, hence previous estimates of 5-10% might be an over-estimation using non-standardized and semi-quantitative methods.

3. Both IHC analyses and WB results are influenced by the anti-dystrophin antibodies used, as well as other experimental conditions

Significantly, if the epitope recognized by the antibody is modified by the deletion, the dystrophin isoform may not be recognized and a result read out as zero. For this reason, recent studies use multiple antibodies against known regions. Additionally, muscle biopsies in patients with BMD and DMD may be quite variable in degree of fibrosis and fatty replacement; this may decrease the reproducibility and representativeness of muscle biopsy estimates of dystrophin content by Western blot. Additionally, imaging methods, choices for normalization, biopsy handling, background standing, and a multitude of other experimental conditions can influence results.

4. The phenotype is significantly influenced by *dystrophin isoform quality* as well as *dystrophin quantity*.

Dystrophin is a very large protein with multiple functional domains. Generally, DMD results from an out-of-frame mutation (often a deletion) that leads to an unstable or unreadable mRNA transcript. Thus, DMD patients usually have zero or very low levels of dystrophin, but the DMD phenotype can also result from in-frame mutations that result in a unstable transcript or dysfunctional dystrophin isoform. BMD usually results from an in-frame mutation (often an exon deletion) that affects the functional quality of the protein and also the quantity produced. It remains unclear what role protein function plays vs quantity in leading to the wide range of variability in BMD phenotypes. There are a vast number of mutations that can lead to each of these phenotypes (Tuffery-Giraud, et al., *Hum Mutat*, 30, 2009), all of which can have different effects on protein function as well as protein production. This micro-heterogeneity is common in genetic diseases and is highly germane to

evaluation of interventions targeting the gene, gene expression, or protein function. There are also non-dystrophin-related factors that can modulate phenotype.

5. The literature contains various findings on the relationship of dystrophin expression to clinical status, including the low levels of dystrophin protein of interest in this case.

I note that in the decades since 1988, much technical progress has been made in standardizing Western blot techniques, and the results from early studies may not be fully comparable to those from recent experiments.

- a. The seminal 1988 paper on this subject (Hoffman et al., *NEJM*, 318(21)) found that the majority of patients with DMD had undetectable levels of dystrophin using their Western blot technique and that 35 of 38 had levels below 3% in their assay. They also reported that one of seven “intermediate” patients had dystrophin levels below 3% of normal, as did one of the 18 patients with a BMD phenotype.
- b. Beggs et al., (*Am J Hum Genet*, 49, 1991) published one of the early studies on the correlation between the level of dystrophin on Western blot and clinical features of BMD. Western blot was performed using a polyclonal serum and had about a 20% variability between blots according to the authors. In this study a number of patients with BMD or intermediate phenotype (DMD/BMD) were found to have dystrophin contents that overlapped with those of the DMD patients. Of four patients included with DMD phenotype, two had less than 5% dystrophin, and two had 10%, by their assay. Of patients with BMD/DMD phenotypes, eight were found to have 10% of normal dystrophin, two had 15%, one had 50%, and one had 100%. Three BMD patients with dystrophin levels of 10% were found; two of these had relatively mild disease.
- c. Nicholson et al., (*J Med Genet*, 30, 1993) studied patients across a wide range of DMD and BMD phenotypes. They used loss of ambulation as a criterion to establish five functional groups, grouped from one (most severe, LOA before age 9) to five (LOA past age 40) (pre-steroid era). *They found a linear relationship overall between dystrophin levels (Western blot with Dy4/6D3 antibody, using myosin for a loading control) and their five categories, with more dystrophin protein translating to better function. They found no significant difference between any two adjacent groups however, which they interpreted as showing considerable overlap, as reflected in their patient level data (Appendix 1), which showed a number of less severe patients (e.g., Group 2 or 3) registering no or very low dystrophin abundance on their Western blot assay.* Of note, they reported a higher average level of dystrophin protein in severe DMD patients than other investigators, partly resulting from 5 of their 21 severe patients reported to have dystrophin protein levels above 20.
- d. Neri et al., (*Neuromuscular Disorder* 17, 2007) reported on families with X-linked Dilated Cardiomyopathy. In these families, mutations give rise to absent dystrophin in heart muscle, but only reduced levels of nearly normal dystrophin in muscle tissue. One patient in their series had a normal neurological exam at age 23, an elevated CPK, and 29% of normal dystrophin protein in skeletal muscle by Western blot. This example can contribute to understanding the role of abundance of dystrophin protein vs compromised function.

- e. Anthony et al., (*JAMA Neurology*, 71, 2014) evaluated the correlation between phenotype and mRNA and protein expression in patients with both in-frame and out-of-frame mutations amenable to exon 44 or 45 skipping. Studying a group of patients with closely related deletions could diminish variability due to differences in function of the truncated protein. Five samples from patients with clinical “mild” BMD and in-frame mutations underwent Western blot analysis using the Dys-2 antibody. Their mean protein expression was 17% (normalized to actin) with a standard deviation of 7.5%. Two of the “mild” patients had dystrophin levels in this assay of around 10%. Based on comparisons of IHC experiments with various antibodies, the authors found “*no clear correlation between the level of dystrophin transcript or protein expression with clinical severity*” in 13 patients with in-frame mutations leading to BMD. The finding of Neri et al., above, along with this report, reinforce the concept that protein function (i.e., quality) is an important determinant of clinical severity and undermine the concept that 10% dystrophin protein content is a threshold, since these patients had “mild” BMD.
- f. Van den Bergen et al., (*J Neurol Neurosurg Psychiatry*, 85, 2014) compared dystrophin levels by Western blot with clinical severity in 27 patients with a clinical diagnosis of BMD. Dystrophin expression ranged from 4-71% and 3-78%, depending on the antibody used. *The authors found no linear relationship between dystrophin expression by Western blot using newly acquired muscle biopsies and clinical severity, muscle strength, or fatty infiltration on MRI.* Although this was the case for the majority of the patients, who had dystrophin levels above 20% of normal, four patients had levels at or below 10%. These patients generally had a more severe phenotype: one patient with a dystrophin level of 10% was wheelchair dependent at 45 years; one patient with a level of 7% developed trouble with stair walking at age 21; one patient with a level of 4% had a DMD phenotype with wheelchair dependency at age 10, one patient with a level of 3% had wheelchair dependency at age 25.
- g. Anthony et al., (*Brain*, 134, 2011) studied 17 BMD patients with exon 51 or 53 skipping-amenable mutations by IHC methods. These patients primarily had very mild or asymptomatic disease; the one patient classified as severe was ambulatory at age 25 but unable to run. *There was a statistically significant difference in dystrophin expression by IHC when patients classified as mild disease were compared to asymptomatic patients.*
- h. Bello et al., (*Neurology* 87, 2016) published a detailed study of loss of ambulation in DMD patients with particular exon deletions, using the CINRG-DNHS, a prospective natural history study. They found patients with exon 44 amenable mutations to have a two-year delay in loss of ambulation compared to the overall comparison group. This finding had previously been reported by another group (van den Bergen, et al., *J Neuromuscul Dis*, 1, 2014). The mutations studied (primarily single-exon deletion of exon 45) are known to undergo spontaneous skipping with production of some dystrophin. According to the Bello report, of six patients previously tested by IHC, three showed traces of dystrophin production and 0/four (possibly other patients) had dystrophin detectable by Western blot. These authors suggest that the observed differences in loss of ambulation (LOA) could be due to small amounts of spontaneously induced dystrophin that slightly ameliorate the ordinary DMD phenotype.

- i. Cirak et al., (*Lancet*, 378, 2011) published a study (AVI-4658) using intravenously administered eteplirsen that showed a detectable increase in dystrophin protein levels using both Western blot and immunofluorescence in 3/19 patients. The authors reported that the functional properties of restored dystrophin were confirmed by assessing increased levels and co-localization of neuronal nitric oxide synthase (nNOS) and sarcoglycan with dystrophin. Such a protein assembly is suggested to be indicative of functional restoration of the dystrophin-associated glycoprotein complex in muscle fibers (Molza et al., *JBC*, 290, 2015; Wells KE et al., *Neuromuscul Disord*, 2003). Cirak et al., reported that the restoration was more so in patients with exon 49-50 deletions than in those with 45-50 deletions, which is consistent with a previous observation that nNOS binding domain is located in dystrophin exons 42-45 (Lai Y et al., *J Clin Invest*, 2009). These studies suggest that important functional domains are included in the dystrophin protein induced by eteplirsen.

To summarize what is known about the association between dystrophin levels and phenotype, dystrophin content above about 10% on Western blot is usually associated with a BMD phenotype, except in patients with higher levels of dystrophin (including above 50%) who potentially have functionally deficient protein leading to a DMD phenotype. Within the BMD phenotype, a proportional inverse relationship between disease severity and protein expression has not generally been demonstrated (i.e., between 10-100%), although there may be a broad association, as seen in the Anthony study (*Brain*, 134, 2011). This may be due to the fact that protein quality, rather than quantity, plays a key role in determining phenotype in BMD. Patients with DMD are usually found to have no detectable, or very low levels of, dystrophin. Dystrophin content in the 3-10% range has been associated with DMD, DMD/BMD, and BMD phenotypes. I find no evidence of a threshold value for protein content and expression of a DMD phenotype, although the majority of DMD patients reported in the literature have dystrophin that is undetectable by the Western blot assays used. Generally, the divide between DMD and BMD, in terms of protein, is the result of the consequences of an OOF or an in-frame mutation, respectively. I believe that the conventional threshold, at or below 10% protein, was derived from the IHC data that seem to estimate low-level protein content about 10% percentage points higher on IHC than on Western blot, so that the majority of DMD patients would read out at 10% of normal dystrophin on IHC. I believe that evidence from Western blot and other experiments discussed above show that protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation, all other things being equal, i.e., mutation status and non-dystrophin-related factors affecting phenotype.

These findings are germane to the determination of “reasonably likely to predict clinical benefit.” The broad phenotypic distinctions made in the clinic (e.g., DMD vs IMD vs BMD) are different from the prediction of benefit to an individual patient who has a specific baseline dystrophin level and whose mutation and external factors do not change pre- and post-drug. For example, extending ambulation by six months to a year would not normally move a patient from one to another of these categories, but could be very important to quality of life (e.g., as suggested in the Bello study). This is also true for other functional improvements.

For these reasons, incorporating the analysis of dystrophin content discussed above, I conclude that the biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit.

Additional support for “reasonably likely” comes from the long-term experience with the drug. The sponsor’s comparison of the experience of the treated cohort to natural history data does not reach the level of substantiation required for traditional approval based on the clinical data. However, it is highly suggestive of improvement in some parameters, in some patients, over natural history. My conclusion is informed by all the caveats expressed in the reviews about the pitfalls of non-randomized comparisons. Given that the two exon 52 deletion patients in the study had fairly good long-term results in terms of rate of disease progression, the question arises as to whether exon 52 is a prognostic factor that could have skewed the results.

Several facts militate against this conclusion. First, one of the exon 52 deletion trial subjects (subject 6) had a fairly low score on the 6MWT at entry and a very low score on the NSAA, compared to other subject around his age. He also was the only subject in the trial noted to be unable to rise without external support at baseline. Additionally, the Italian external cohort had exon 52 deletion representation.

Questions have been raised about the correlation of dystrophin levels from Western blot with clinical outcomes. The 6 Minute Walk Test does not show a strong correlation. I evaluated the NSAA in children who could still walk (because the NSAA primarily scores activities related to walking) and who also had a dystrophin result at 180 weeks (Table 1). I did this because the NSAA includes multiple measures and therefore might have some noise averaged out. I looked at the absolute decline in NSAA in patients since study initiation, and did not correct for the initial time some patients spent on placebo. I only evaluated patients who were ambulatory. There was a positive (inverse) correlation between dystrophin by Western blot and rate of decline in NSAA score, . (Figure 1) This adds additional support to the idea that dystrophin production is “reasonably likely to predict clinical benefit.” In totality, I find that the comparative disease course data provide additional support for the use of the surrogate endpoint of an increase in dystrophin expression as “reasonably likely to predict clinical benefit.”

Therefore, both the biochemical data and the clinical data lead me to conclude that an “increase in dystrophin production” is reasonably likely to predict clinical benefit in DMD.

CONFIRMATORY TRIALS

The sponsor is currently conducting a nonrandomized, concurrently controlled trial in patients with mutations amenable to exon 51 skipping compared to untreated DMD patients with other exon deletions. Because of the relatively low level of protein induced, additional doses should be aggressively pursued and, if successful, a dose-comparison trial could be confirmatory. The sponsor has also planned to initiate a randomized trial with a related compound in other exons. The clinical results from these trials can inform the predictive value of the surrogate endpoint.

EXPLORATION OF ADDITIONAL DOSES, REGIMENS, AND DRUG-MUTATION INTERACTION

The dystrophin levels achieved in this development program are well below those initially hoped for. I agree with Dr. Farkas and other reviewers that the sponsor should aggressively explore higher doses or more frequent administration of eteplirsen. It appears that this is possible given the toxicology data and the clinical safety profile observed to date.

Because patients in the Sarepta 180 week cohort had a range of deletions in the dystrophin gene, variability in the pharmacodynamic response among deletions is of great interest. The two patients with over 2% dystrophin in the 180 week Western blot both had exon 52 deletions. These patients also fared fairly well, clinically. This raises the question of whether patients with this exon deletion naturally produce more dystrophin. One of these subjects had a baseline sample available. It was found to be below the limit of quantitation. There was an exon 52 subject included in the added baseline controls. This subject's assay had replicate results of 0.3% and below the limit of quantification, respectively, as discussed above. This suggests that baseline dystrophin levels are not higher in exon 52 deletion subjects and that there may be a drug-deletion interaction, wherein subjects with this deletion may have a more robust pharmacodynamic response to the drug. There were a number of apparent non-responders to the drug. It will be important to find out if this is mutation specific. It is likely that more detailed knowledge about each patient's specific mutation will have to be generated to study this in detail.

COMMENTS ON THE DEVELOPMENT PROGRAM AND REVIEW

The development program for eteplirsen was seriously deficient in a number of respects that may have led to delay in broad access and certainly led to difficulties in regulatory review. In my assessment, the most egregious flaw was the lack of robust and high-quality assays early in the development program. Inaccurate conclusions from the assays used led to a flawed development program. Additionally, the entire drug development field must recognize that there is no such thing as an "exploratory study" for a serious, life-threatening illness without therapeutic options. Randomization should be performed very early in the development program, and open-label studies should be avoided. When possible, seamless adaptive dose-finding and early efficacy studies should be carried out with the goal of most efficiently generating the data needed to demonstrate safety and effectiveness.

The flaws in the eteplirsen development program led to severe challenges in regulatory review. 21 CFR 312.80, concerning drugs intended to treat life-threatening or severely-debilitating illness, states that FDA has determined "that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness...Physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses than they would accept from products that treat less serious illnesses." I note that the acceptable risks include greater uncertainty about the effects of the drug. The Peripheral and Central Nervous System Drugs Advisory Committee met on this application on April 25, 2016. There was a split vote (7 against, 6 for) on the question of accelerated approval for this drug, reflecting the greater than usual uncertainty about the application. This vote was taken before the additional data on protein expression were submitted.

To conclude, the studies used in this analysis to support the effect of eteplirsen on dystrophin were adequate and well-controlled as specified in 314.126. In addition, the surrogate of increased dystrophin production is reasonably likely to predict clinical benefit. Given the deficiencies that have been identified in the development program, my conclusion to rely on the surrogate endpoint described above represents the greatest flexibility possible for FDA while remaining within its statutory framework. In this case, the flexibility is warranted because of several specific factors, including: the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a fatal disease in children. Of note, the therapy has been relatively safe in the clinic, although intravenous administration always carries risk. In addition, adequate confirmatory studies are underway and planned and are capable of further refining our understanding of the biomarker and providing evidence about the nature of the clinical benefit. The approval does not create any risk of compromising the confirmatory trials because of their nature. Therefore, I find that the probable benefits outweigh the foreseeable risks and that this application should be approved under 21 CFR 314.510.

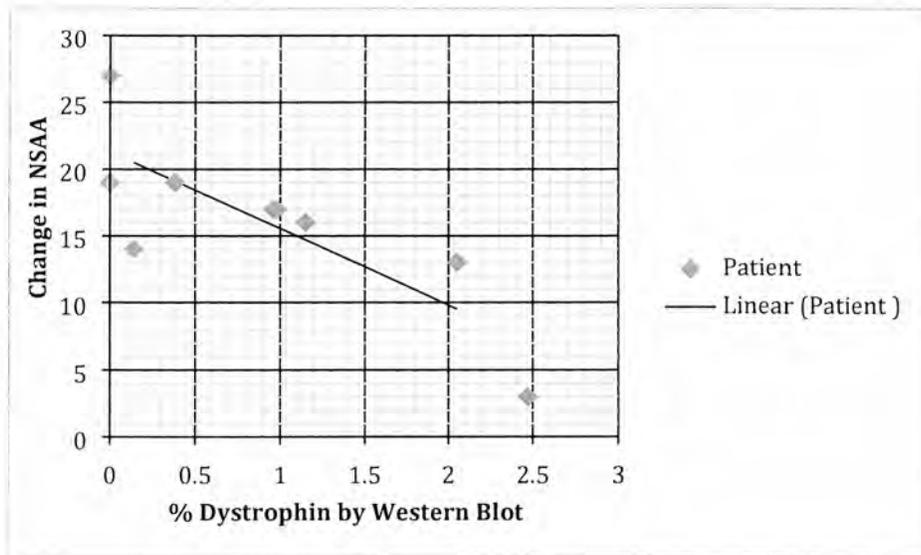
Table 1 Patient Data on Change from Baseline in 6MWT and NSAA

180 Weeks
Change from
Baseline

Subject	Baseline WB	180 Week WB	Fiber Intensity	PDPF	Δ 6MW	Δ NSAA
002	N/A	0.14	MD	4.54	-67	-14
003	N/A	0	7	1.42	-174	-27
004	N/A	0.96	28	29	-168	-17
005	0	N/A	N/A	N/A	-231	-19
006	N/A	2.47	29	21	-23	-3
007	N/A	0	12	7	-197	-19
008	N/A	0.98	26	12	-291	-17
009	N/A	0.52	23	22	0	0
010	N/A	1.62	21	24	0	0
012	N/A	0.38	26	33	-114	-19
013	0	1.15	32	19	-170	-16
015	0	2.05	30	18	-1	-13

Data from Sarepta
Therapeutics, Inc. PCNSD
Advisory Committee Briefing
Document, Appendix 5, p.
149 (6MW and NSAAO
Appendix 11, p. 155, (Percent
Positive Dystrophin Fibers
(PPDF), Appendix 12 p. 156
(fiber intensity) 14, p. 159.
(Western blot),

Figure 1. Decline in NSAA by % Dystrophin on Western blot



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET WOODCOCK
07/14/2016

Agency Scientific Dispute – Appeal

Date: July 18, 2016

To: **G. Matthew Warren**
Director
Office of Scientific Integrity, FDA

From: **Ellis F. Unger, M.D. (initiator)**
Director
Office of Drug Evaluation-I
Office of New Drugs
Center for Drug Research and Evaluation
U.S. Food and Drug Administration

Re: **NDA #** 206488
Drug: eteplirsen (Exondys 51)
Applicant: Sarepta Therapeutics
Indication: Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping

1. **Background**

The Office of New Drugs within the Center for Drug Evaluation and Research (CDER) oversees regulation of new drugs, and is responsible for making regulatory decisions for approval/non-approval of new molecular entities. Within the Office of New Drugs, there are 6 sub-offices, including the Office of Drug Evaluation-I. The Office of Drug Evaluation-I oversees the Division of Neurology Products, which regulates drugs for the central and peripheral nervous systems, as well as drugs for muscular disorders. Typically, a new drug application (NDA) for a new molecular entity for a neurology indication is reviewed by the Division of Neurology Products in concert with review staff from other offices in CDER.¹ The regulatory decision is typically rendered by Office of Drug Evaluation-I, i.e., the signatory authority.

NDA 206488 for eteplirsen was reviewed by the Division of Neurology Products, and members of the review team reached the unanimous conclusion that the NDA should receive a *complete response* action. This view was shared by the Office of Biometrics, which performed the statistical review, as well as the Office of Clinical Pharmacology, which performed the pharmacology review. Dr. John Jenkins, Director, Office of New Drugs, also supports a *complete response* action for this NDA (verbal communication).

This memo is meant to explain the salient arguments around the scientific disagreement here; additional details are available in my memo recommending a complete response and Dr. Woodcock's memo recommending approval, and the reader is referred to those memoranda.

Disease Background:

¹ Reviews are typically provided by Office of New Drug Quality Assessment, Division of Medication Error Prevention and Analysis, Office of Biometrics, Office of Scientific Investigations, and others.

Duchenne muscular dystrophy is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene. These mutations disrupt the messenger ribonucleic acid (mRNA) reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells. The disorder affects 1 in ~3,600 boys.

Dystrophin protein is thought to maintain the structural integrity of the muscle cell, cushioning it from the stress and strain of repeated contraction and relaxation. Absence of dystrophin leads to muscle damage, with replacement by fat and collagen. With progressive degeneration of skeletal muscle (including breathing muscles) and cardiac muscle, there is loss of physical function in childhood and adolescence, with premature death from respiratory and/or cardiac failure in the second to fourth decade.

No specific therapies are approved for DMD. Steroids are currently the cornerstone of management, widely believed to delay loss of ambulation and respiratory decline by several years.

Drug Background:

Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. Theoretically, by restoring of the mRNA reading frame, a 'truncated' but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, delaying disease progression. Similar truncated dystrophin is found in a less severe form of muscular dystrophy, Becker Muscular Dystrophy (BMD). In essence, the drug is hoped to induce production of sufficient Becker-type dystrophin to slow the progression of the disease. This drug is specific for exon 51 mutations, a subset of the mutations that cause DMD. If approved, the drug would be indicated for ~13% of the overall DMD patient population. Eteplirsen has not received marketing authorization from any regulatory authority, and no similar drugs are approved.

Drug Development Background:

Three studies are germane to the issues here. Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202. Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from 13 patients in this study (see below).

The endpoints for these studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle – the surrogate endpoint. Dystrophin was quantified in this development program using two methods: Western blot and immunohistochemistry.

2. Description of How My Position Differs from the Center's Perspective

Dr. Janet Woodcock, Director, CDER, disagrees with some of the findings of the review team, and has reached the conclusion that the NDA should be approved. She finds that the data meet the standard for accelerated approval under 21 CFR 314. 510, based on the change in a surrogate endpoint of dystrophin protein production – a change she concludes is reasonably likely to predict clinical benefit. The disagreement is over the question of whether the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit. The decision of *approval vs. complete response* hinges on this question.

a. Clinical/Statistical Efficacy

Accelerated Approval:

Dr. Woodcock has reached the conclusion that eteplirsen should receive accelerated approval based on a small effect on the surrogate endpoint of dystrophin production.

The relevant statutory and regulatory framework (section 506(c) of the FD&C Act and 21 CFR part 314, subpart H) states that a drug can receive accelerated approval if 3 factors are satisfied:

1. If the drug treats a serious or life-threatening disease or condition,
2. if FDA takes into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments, and
3. if the drug demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit OR demonstrates an effect on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. As noted in section 506(c)(1)(B) of the FD&C Act, the evidence to support the concept "...that an endpoint is reasonably likely to predict clinical benefit may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

In terms of the prospect for accelerated approval for eteplirsen, DMD is clearly a serious, severe, and rare condition with no approved treatments; therefore, factors 1 and 2, above, are satisfied. There is no disagreement.

The critical issue is whether factor 3 is satisfied, and factor 3 can be subdivided into three parts: 1) whether the surrogate endpoint is appropriate for the disease; 2) whether there is substantial evidence of an effect on the surrogate endpoint; and 2) whether the effect demonstrated meets the test of being "reasonably likely" to predict clinical benefit. Importantly, there is no regulatory definition of "reasonably likely."

For the first part of factor 3, whether the surrogate endpoint is appropriate for the disease, the review team has agreed that the near-lack of dystrophin is the proximal cause of DMD, and that the level of dystrophin in skeletal muscle is an appropriate surrogate endpoint that could predict efficacy. There is no disagreement here.

The second part of factor 3 is whether an effect has been demonstrated; the legal standard is 'substantial evidence' based on adequate and well-controlled clinical investigations. Typically, such evidence would be two studies, both achieving a p -value < 0.05 , but in some situations FDA has the flexibility to interpret data from a single trial, or a single trial with supporting evidence, as substantial evidence of effectiveness.² Dr. Woodcock believes that "...there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells." I agree that there is evidence from a single adequate and well controlled trial, Study 301, that eteplirsen induces dystrophin production in muscle cells, but do not agree that there is reliable quantitative evidence from the other trial, Study 201/202.

The third part of factor 3, the conclusion that the demonstrated effect is "reasonably likely" to predict clinical benefit, is where there is disagreement.

A. Are the Data on Dystrophin Protein Production from One or More Adequate and Well-Controlled Studies?

Dr. Woodcock cites 3 lines of evidence pertinent to the conclusion that eteplirsen increases dystrophin production:

1. Production of an appropriate mRNA transcript
2. Quantitative assessment of dystrophin content in muscle biopsies by Western blot
3. Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry

1. Production of an appropriate mRNA transcript

I agree that the applicant has shown expression of mRNA following treatment with eteplirsen. As noted by Dr. Woodcock, this finding establishes proof of concept, but does not by itself mean that there is increased dystrophin production.

2. Quantitative assessment of dystrophin content in muscle biopsies by Western blot

Western blot is a standard laboratory technique used to quantify proteins in body tissues. In Sarepta's development program, Western blot was used to assess dystrophin protein levels in skeletal muscle in Study 201, in Study 202 (again, these were Study 201 patients who were maintained on treatment), and finally in Study 301.

a. Study 201:

The original Western blot analyses from Study 201 were intended to show that dystrophin levels were greater in eteplirsen-treated patients than in patients in the placebo group, and analyses were planned to compare the effects of the lower vs. higher eteplirsen doses on dystrophin production. The Western blots submitted by the applicant for Study 201 were oversaturated, unreliable, and uninterpretable.

b. Study 202:

² See: "Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products;" May, 1998.

With FDA's assistance, the applicant improved the assays and performed repeat biopsies on 11 of 12 patients of the Study 201/202 patients at Week 180. These were to be compared to stored baseline (pre-treatment) samples; however, evaluable tissue was available for only 3 of the 11 patients. The baseline samples are germane to the determination of the treatment effect because the Week 180 biopsies showed only a small quantity of dystrophin (mean = 0.93% of normal). Thus, for the purpose of computing the *change* in dystrophin resulting from eteplirsen treatment, even small differences in the baseline level are critical.

As noted by Dr. Woodcock, the review team and I had concerns about these controls, leading us to conclude that Study 201/202 was not adequate and well controlled:

1. The goal was to assess the change in dystrophin with treatment, i.e., pre-treatment vs. post-treatment, but most of the baseline biopsies were obtained from subjects external to Study 201/202, who could differ in unknown ways from subjects in Study 201/202.
2. For all patients, the Week 180 biopsies were obtained from different muscles than the baseline biopsies, and studies of both normal human muscle and non-clinical DMD models have shown that dystrophin levels vary among muscles.
3. The baseline biopsies for the three subjects with Week 180 data had been stored for several years and the protein may have degraded, leading to a falsely low baseline value, and a greater apparent increase from baseline, accordingly.

Dr. Woodcock believes that "...these issues increase the uncertainty around the results, but do not necessarily render them an inadequate basis on which to draw a conclusion." She notes that the external control patients were similar in age and mutation site to the patients in Study 201/202. She found little difference between dystrophin results across different muscle groups, and little difference based on storage time, leading her to believe that these factors "...did not result in large differences in the findings."

Although I agree that these factors are not likely to lead to large differences, even small differences would affect the calculation of the *change* in dystrophin at Week 180, because the Week 180 values were quite small (mean only 0.93% of normal). At issue is how much of the dystrophin detected at Week 180 was newly produced, vs present at baseline. For example, a difference in the baseline level of only 0.30%, although minute, is substantial compared to 0.93%.

Dr. Woodcock notes that at Week 180, 2 subjects had dystrophin levels between 2 and 3%, 2 had a level between 1 and 2%, and 2 had a level of ~1%. She notes that 2 of these subjects had both baseline and Week 180 samples, and there were clear increases in dystrophin in these 2 patients. Of note, Dr. Woodcock points out that although some subjects had Week 180 dystrophin levels similar to the baseline (i.e., close to zero), she would expect this because she would not predict that all individuals would respond to a drug intervention.

She explains that the issue "...is whether the dystrophin levels found at 180 weeks were within the variability expected for this assay in such patients and, thus, could have arisen by chance, or whether they could have been caused by differences from the controls or from sample

storage as outlined above, or whether they reflected a drug effect, and, thus, whether these data could be seen as adequate and well-controlled.”

In the end, taking Dr. Woodcock's arguments into consideration, my view is that the data from Study 202 are *suggestive* of an increase in dystrophin in response to eteplirsen, but the study was not adequate and well controlled. If we accept that there *is* a difference, Study 202 does not reliably speak to the *amount* of dystrophin produced by eteplirsen, given the concerns above. There is only certainty that the largest *possible* amount was 0.93% of normal (on average), and <3% in any individual (if we assume that the quantity was zero at baseline).

Below I will present another concern that leads me to question the veracity of the Western blot data from the Week 180 biopsies from Study 202, based on an issue that Dr. Woodcock did not address in her memo.

c) Study 301:

With the May 26, 2016 goal date approaching, OND and CDER could not reach agreement on the regulatory action for this NDA. In order to gain additional information that might provide evidence of an effect on a surrogate marker that was reasonably likely to predict clinical benefit, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in an ongoing study (Study 301, PROMOVI). These samples were originally planned to be analyzed at the end of the study; however, we requested an interim analyses of a subset of samples. Western blot analyses were performed on paired biceps samples from 13 of the patients. For each of these patients, samples obtained at baseline (prior to treatment) were compared to those obtained at Week 48, after 48 weekly infusions of eteplirsen 30 mg/kg.

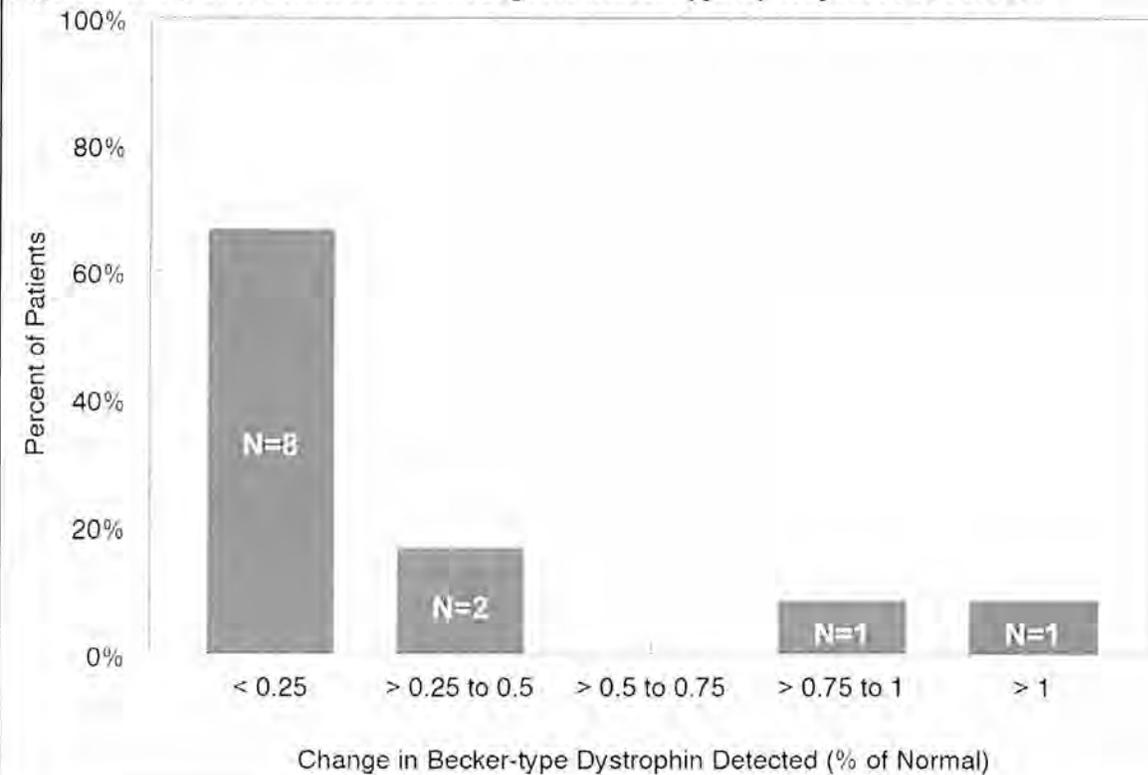
The data are shown in Table 1 and the distribution of these changes is shown graphically in Figure 1. Of these 12 patients, 8 (two-thirds) had a change of 0.25% or less; only 1 patient (8%) had a change greater than 1%. The applicant used 3 methods to consider the numerous values below the limit of quantification, but irrespective of the method used, the mean treatment effect was similar, ranging from 0.22% to 0.32% of normal, a change of approximately 2 to 3 parts per thousand that was nevertheless statistically significant.

Patient	Time	status	value (%)	mean (%)	delta (%)	Patient	Time	status	value (%)	mean (%)	delta (%)
1	Baseline	pass	0.15	0.13	0.13	8	Baseline	fail	0.08	0.05	
		pass	0.11					fail	0.14		
	Week 48	pass	0.22	0.26			Week 48	fail	0.08		
		pass	0.29					fail	0.05		
2	Baseline	pass	0.35	0.35	0.01	9	Baseline	fail	0.14	0.24	1.33
		fail	0.26					pass	0.24		
	Week 48	pass	0.36	0.36			Week 48	fail	1.17		
		fail	0.12					pass	1.57		
3	Baseline	pass	0.06	0.06	0.31	10	Baseline	pass	0.11	0.11	0.01
		pass	0.06					fail	0.05		
	Week 48	pass	0.5	0.37			Week 48	pass	0.12		
		pass	0.24					fail	0.11		
4	Baseline	pass	0.04	0.04	0.06	11	Baseline	pass	0.01	0.05	0.43
		fail	0.06					pass	0.08		
	Week 48	pass	0.1	0.1			Week 48	pass	0.31		
		fail	0.19					pass	0.63		
5	Baseline	fail	0.1	0.17	0.85	12	Baseline	pass	0.02	0.02	0.07
		pass	0.17					fail	0		
	Week 48	fail	0.92	1.02			Week 48	pass	0.09		
		pass	1.02					fail	0.01		
6	Baseline	pass	0.37	0.37	-0.07	13	Baseline	fail	0.34	0.18	0.03
		fail	0.46					pass	0.18		
	Week 48	pass	0.3	0.3			Week 48	fail	0.34		
		fail	0.29					pass	0.21		
7	Baseline	fail	0.04	0.17	0.25						
		pass	0.17								
	Week 48	fail	0.22	0.42							
		pass	0.42								

All parties agree that these data were obtained from an adequate and well controlled study, and that there is a statistically significant effect of eteplirsen. The disagreement is whether or not the dystrophin production is at a meaningful level that is reasonably likely to predict clinical benefit.

To the extent that one can compare results across studies, these changes in dystrophin are even lower than the values obtained from Study 201/202 (the latter represent the quantity detected at Week 180, not the treatment effect). Dr. Woodcock wrote that "Only 2 of 12 patients achieved a level over 1% of normal control." Her characterization refers to the amount of protein *detected* at Week 48, not the *change* in protein. In fact, only a single patient out of 12 had a *treatment effect* that exceeded 1%.

Figure 1: Study 301: Distribution of Changes in Becker-type Dystrophin in 12 Patients



3. Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry

Study 201/202 – Data through Week 48

Dystrophin production was assessed in Study 201 using immunohistochemistry, a standard laboratory procedure used primarily to localize proteins in tissue sections, but also used as a semi-quantitative method to measure dystrophin levels. Muscle samples were analyzed at baseline, and at Weeks 12, 24, and 48.

Dr. Woodcock notes “A finding of increased dystrophin was also seen in several IHC assays performed by the applicant.” She explains that several baseline and other pre-Week 180 assays were performed (from Study 201/202), but the validity of the results was questioned at the FDA inspection because of methodological issues, and so she does not consider these data further.

I do not agree with Dr. Woodcock's outright rejection of these data. In fact, FDA requested a re-reading of the stored images by 3 masked pathologists under improved viewing conditions. We did not request any changes in immunohistochemistry methods or techniques, other than a different approach for selecting microscopic fields for image capture and analysis. Thus, we stressed that their stored images could provide useful data if properly read. The re-read

showed a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group, but not the high dose group. (The p -value is nominal because the type-I error rate was not controlled for multiplicity.) Moreover, for the 4 patients who had received placebo through Week 24 and then switched to eteplirsen, there was no increase in dystrophin at Week 48.

Study 201/202 – Week 180 Data

The applicant performed immunostaining along with Western blot analyses from the skeletal muscle biopsies obtained at Week 180.

Importantly, prior to performing these analyses, the applicant made changes to the immunohistochemistry protocol with the intent of decreasing non-specific staining. Dr. Woodcock details the technical factors in her memo. Their aim was to determine the treatment effect for each patient, by comparing dystrophin levels at baseline and Week 180. Frozen archived baseline tissue was available for only 3 of the patients, however, and so the applicant supplemented these samples with muscle tissue from 6 untreated external DMD patients, together to be compared to the Week 180 levels. Images were read by the same 3 pathologists, masked to treatment group.

Because external controls were used, the comparison of pre- vs. post-treatment values suffers from the same problems described for the Western blot analyses (i.e., different patients, different muscles, and possible loss of immunoreactive dystrophin with long-term storage).

These concerns notwithstanding, the applicant claimed a remarkable increase in dystrophin immunostaining at Week 180: the 9 baseline samples (from 3 patients in Study 201/202 and 6 external controls) showed $1.1\% \pm 1.3\%$ positive fibers (mean \pm SD), whereas the Week 180 samples (from 11 patients in Study 201/202) showed $17.4\% \pm 10.0\%$ positive fibers. I will note that FDA made no attempt to inspect or oversee these analyses.

Given that the original analysis showed, at baseline, 13% positive fibers for patients in Study 201/202, it is important to understand why the results from a new immunostaining protocol provided results of 1.1%, an order of magnitude lower.

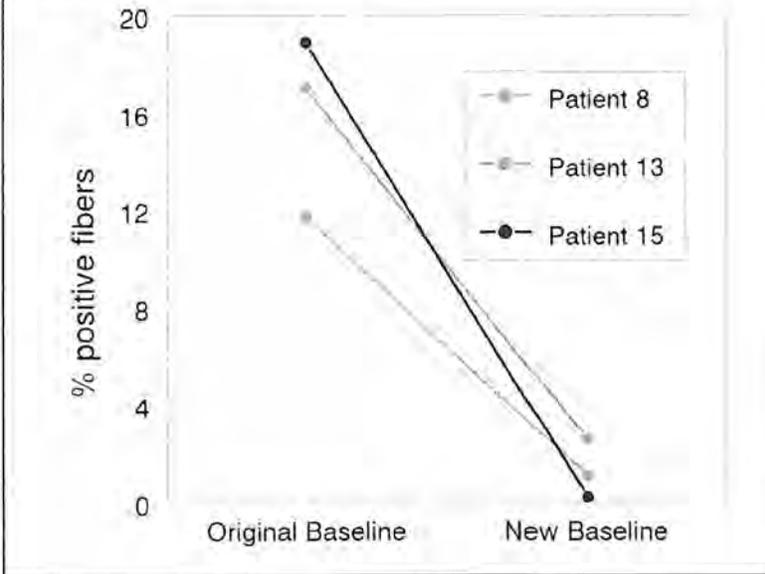
As noted above, there were 3 patients in Study 201/202 with adequate archived tissue from baseline, which permitted a new immunohistochemistry analysis and a comparison of results between the old and new methods. Figure 2 shows how the two methods compare.

These are essentially replicate analyses of a single tissue sample using the two immunohistochemistry methods. There is an inexplicable difference of more than an order of magnitude between results of the old and new immunohistochemistry protocols. Such marked differences raise concerns with respect to the validity of the applicant's methods, and make interpretation impossible.

The disparity also underscores the difficulty of comparing results of immunohistochemical analyses for dystrophin across laboratories, or, for that matter, within the same laboratory.

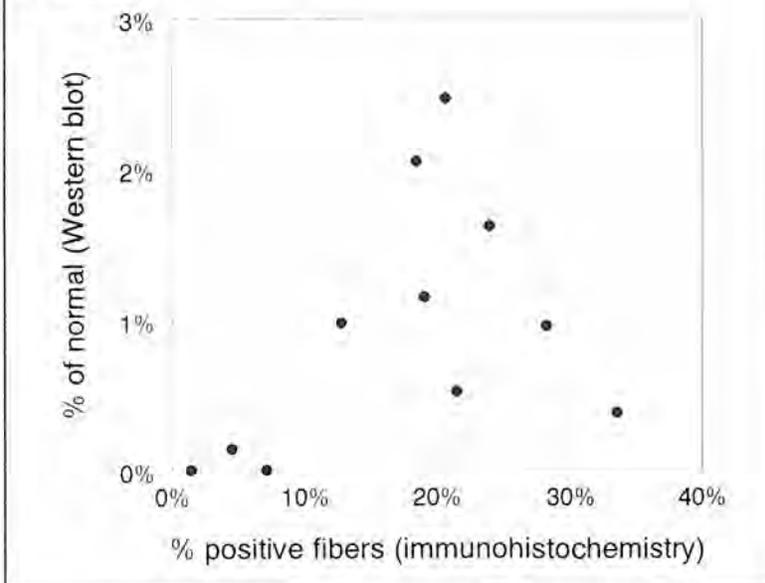
The integrity of the applicant's data is further called into question by lack of agreement between the immunohistochemistry and Western blot methods, i.e., a lack of internal consistency. The applicant claims to have enhanced both the immunohistochemistry methods and the Western blot methods in preparation for processing the Week 180 biopsies. Following these methodological improvements, single tissue blocks were subjected to both analyses – analyses considered to be complementary. Yet the lack of concordance between these two assessments of dystrophin levels is striking (Figure 3).

Figure 2: Comparison of Results from the New and Old Immunohistochemistry Protocols – Lack of Agreement for 3 Patients in Study 201/202



It is simply not possible to determine whether the immunohistochemistry methods are inaccurate, the Western blot methods are inaccurate, or both methods are inaccurate. In light of the discordance between methods, the issues with the control samples, and the order-of-magnitude discrepancy between the old and new immunohistochemistry protocols, these data provide little confidence that the study was designed well enough so as to be able "to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation" (§314.126).

Figure 3: Study 201/202 Week 180 Dystrophin Assessment – Lack of Agreement between Immunohistochemistry and Western Blot



A critical point is that results of immunohistochemistry analyses are method-dependent, and results from different laboratories are not directly comparable. Here we see a striking difference between results of different methods within a single laboratory.

Dr. Woodcock concluded "Although the IHC assays provide only semi-quantitative assessments of dystrophin content, they do support an effect of eteplirsen on the proposed surrogate endpoint (an increase of dystrophin production as a result of drug exposure)."

Although this statement does not constitute an important part of her argument in favor of dystrophin production, I do not agree that the immunohistochemistry data show an increase in dystrophin as a result of drug exposure. Given that changes in the immunohistochemistry protocol led to remarkably disparate results, and in light of the lack of correlation between dystrophin results as determined by immunohistochemistry and Western blot, I question the accuracy and interpretability of the Week 180 immunohistochemistry data. Moreover, the results from the properly blinded re-reading of the original data through the first 48 weeks of Study 201/202 are negative. I do agree, however, that the immunohistochemistry images appear to show dystrophin in the proper location, which helps support proof-of-concept.

In summary, I agree that there are data on dystrophin production from one adequate and well controlled study, Study 301, by Western blot. The amount of dystrophin produced and the likelihood of a clinical effect are discussed below.

B. Is the Effect on the Surrogate Endpoint "Reasonably Likely to Predict Clinical Benefit?"

As noted by Dr. Woodcock, "The usual way to address this question would be to rigorously evaluate what is known about the correlation between dystrophin levels in muscle and expression of disease."

Without restating the details of Dr. Woodcock's discussion, I generally agree with her basic summary of the many challenges of interpretation (quoted below). Most of her discussion speaks to the *uncertainties* inherent in correlating dystrophin levels with disease severity. I strongly agree that we lack a sound basis upon which to relate dystrophin levels observed in this development program to observations in the literature.

"1. The clinical classification of disease severity (i.e., phenotype) in the literature appears broad, variable, and somewhat subjective."

I agree. And importantly, as Dr. Woodcock notes, "the zone of real interest for this discussion, between DMD and intermediate presentations, is not rigorously categorized."

"2. Much of the prior data reporting the relationship of dystrophin protein levels to phenotype have been from immunohistochemistry studies using a variety of techniques and antibodies."

I will add that the applicant's own data show a striking difference between results of two somewhat different immunohistochemistry protocols conducted at the same laboratory (Figure 2). Thus, it would be treacherous to try to relate various levels of dystrophin, determined by immunohistochemical methods at various laboratories, to a particular clinical course.

“3. Both IHC analyses and WB results are influenced by the anti-dystrophin antibodies used, as well as other experimental conditions”

Agree. Thus, is not feasible to relate levels of dystrophin determined by older Western blot methods, which lacked, for example, appropriate internal controls, to levels of dystrophin reported in these eteplirsen studies.

“4. The phenotype is significantly influenced by dystrophin isoform quality as well as dystrophin quantity.”

Agree. It is difficult to predict a protein's function from its structure; even small changes in dystrophin structure can be important.

“5. The literature contains various findings on the relationship of dystrophin expression to clinical status, including the low levels of dystrophin protein of interest in this case.”

Agree. There is little consensus on the relationship between dystrophin expression and clinical course at the low levels observed in eteplirsen-treated patients.

I also agree with Dr. Woodcock on the following points, and I paraphrase here:

- Dystrophin levels >10% on Western blot are usually associated with a BMD phenotype. Within the BMD phenotype, the relation between disease severity and protein expression is not clear. Protein quality, rather than quantity, may play a key role in determining phenotype in BMD.
- Patients with DMD are usually found to have undetectable levels of dystrophin, or very low levels. Dr. Woodcock notes that she believes the conventional threshold of <10% protein resulting in DMD was based on immunohistochemistry data. She tries to make a conversion between values observed from immunohistochemistry (~10% points higher on immunohistochemistry than Western blot in DMD) and those observed from Western blot, but I caution that immunohistochemistry results, in particular, are highly method-dependent, as noted above.
- Rarely, dystrophin levels in the 3 to 10% range have been associated with Becker Muscular Dystrophy phenotypes. Dr. Woodcock found no evidence of a threshold value for protein content and expression of a DMD phenotype.

Despite the absence of reliable data, Dr. Woodcock concluded that evidence from Western blot and other experiments shows that protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation, all other things being equal, i.e., mutation status and non-dystrophin-related factors affecting phenotype.

Because of the lack of reliable evidence, I do not agree that the small increase in dystrophin shown in Study 301 is 'reasonably likely' to predict clinical benefit. This is the central issue in this appeal.

The “reasonably likely” question hinges on whether the protein is functional, and whether the quantity is adequate.

These two uncertainties, protein function and protein quantity, are separate issues that must be considered in series. The function of the Becker-type dystrophin detected in Study 301 cannot be assessed. Nevertheless, the review team has been willing to assume that whatever Becker-type dystrophin is produced would function as well as it does in the Becker form of the disease. Although there can be no certainty on this point, the question of function seems small relative to the uncertainty regarding the adequacy of the quantity of protein, and so function is less germane to the question of "reasonably likely." In short, it is the quantity of Becker-type dystrophin produced that is central to the question of 'reasonably likely,' and central to the approvability of this NDA under accelerated approval.

At the outset, it must be stated that the minimum quantity of Becker-type dystrophin that is reasonably likely to predict clinical benefit in patients with DMD is unknown.

There are two ways to consider the quantity of dystrophin produced: as a binary responder analysis and as a mean response. The former has the advantage of considering the possibility that some patients may respond to the treatment whereas others do not; the latter does not allow for this type of consideration.

The problem with a responder analysis is that there are no data upon which to define a threshold for a 'response.' Various cut-points could be selected, but their selection would be arbitrary, and the particular threshold chosen would have a major influence on the effect size.

Here I provide 3 lines of reasoning to support my view that there is not an adequate basis to believe that the small increase in dystrophin shown in Study 301 is reasonably likely to predict clinical benefit: 1) the treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications; 2) the effect size is inadequate on its face; and 3) no evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.

1) *The treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications.*

In order to place these small quantities of Becker-type dystrophin into a clinical perspective, many have considered publications from laboratories that attempt to relate particular levels of Becker-type dystrophin protein to clinical course, e.g., maintenance of physical function, age at loss of ambulation. Ideally, as suggested by Dr. Woodcock, there would be reliable data showing that Becker-type dystrophin levels in excess of a particular level are associated with a more benign clinical course.

Realistically however, the use of such a framework would be contingent on the ability to make interpretable cross-laboratory comparisons of dystrophin levels, which would require standardized methods to measure dystrophin levels in muscle specimens. Unfortunately, the methods have differed greatly, and the methods in the literature have lacked critical internal controls such as dilution-series. As stressed above, comparison of dystrophin values across laboratories seems unreliable.

With respect to immunohistochemistry analyses, Figure 2 provides ample basis for concern regarding comparability of results using different methods. Results of separate immunohistochemical analyses of skeletal muscle dystrophin, conducted by the same laboratory on single blocks of tissue, differ by more than an order of magnitude. These results underscore the inherent methodological variability of immunohistochemistry assays, and the futility of attempting to compare dystrophin levels across assays/laboratories.

Even with respect to more recent Western blot methods, reproducibility across laboratories is low. As discussed by Dr. Woodcock, Anthony K *et al* (*Neurology* 2014;83;2062) compared results of Western blot analyses from 6 patients (3 with DMD; 3 with Becker Muscular Dystrophy) across 5 experienced laboratories, and found a high degree of variability. Only one of the 5 laboratories had a coefficient of variation (CV = SD/mean X 100) below 0.3%. The authors found that variability was particularly pronounced with low levels of dystrophin – precisely the area of interest here.

During the applicants' presentation at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Dr. Kaye, a pediatric neurologist and interim Chief Executive Officer of Sarepta, could not have been more clear in warning us not to make comparisons between their Western blot results and reported data in the literature:

"Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation. Furthermore, samples were randomized, blinded and run in duplicate on separate gels. In contrast, the Western blot methods in the majority of historical publications referenced by FDA were performed using older methodology that is semi-quantitative at best. Given these significant methodological differences, it is inappropriate to compare our data to literature approximations." (Source: Official transcript of the meeting; underlining for emphasis.)

In summary, the field has not achieved adequate standardization of methods for dystrophin quantification at the very low levels observed in eteplirsen-treated patients; therefore, it is not valid to compare an increase in Becker-type dystrophin of, at best, 2 to 3%, with dystrophin values cited in the literature for other mutations/patient populations, assessed at other laboratories. *If the applicant's results cannot be compared to results in historical publications, then there is simply no way to determine whether the low dystrophin levels in eteplirsen-treated patients are reasonably likely to predict clinical benefit.*

2) *The effect size is inadequate on its face.*

If one were to assume that it is possible to make cross-laboratory comparisons of dystrophin levels, the *largest* change reliably demonstrated in Study 301, 1.3%, is an order of magnitude less than the minimum dystrophin levels cited to be important in affecting the course of patients with Becker muscular dystrophy (at least 10%).

Some of the better data come from Van den Bergen *et al*, who studied the relation between dystrophin levels (quantified by Western blot) and clinical severity in 33 patients with Becker Muscular Dystrophy (*J Neurol Neurosurg Psychiatry* 2014; 85:747). Although the authors did not find a linear relationship between dystrophin levels and disease severity, all 4 of their

patients with dystrophin levels <10% showed poor muscle strength and early symptom onset. As discussed by the review team, DMD experts have proposed that "induction of approximately 10% of normal dystrophin levels sets a minimum level to confer measurable clinical benefit."

Initially, the applicant reported results from immunohistochemistry analyses purportedly demonstrating that eteplirsen caused 50 to 60% positive staining of muscle fibers for dystrophin. This seemingly unprecedented achievement aroused much excitement in the field of DMD research and in the DMD patient community. Upon proper re-analysis, however, the numbers were far lower, and rigorous statistical analyses showed that the changes weren't statistically significant. The Western blot analysis from Study 201/202 showed a mean dystrophin level of only 0.93% (range 0 to 2.5%), but these values are of questionable reliability. Finally, an adequate and well controlled study (Study 301) showed a mean change of 3-tenths of a percent (range 0 to 1.3%). Given that dystrophin is a structural protein, it seems highly unlikely that such changes would translate to a clinical effect.

Here are Dr. Woodcock's assertions on this topic:

"The broad phenotypic distinctions made in the clinic (e.g., DMD vs IMD vs BMD) are different from the prediction of benefit to an individual patient who has a specific baseline dystrophin level and whose mutation and external factors do not change pre- and post-drug. For example, extending ambulation by six months to a year would not normally move a patient from one to another of these categories, but could be very important to quality of life (e.g., as suggested in the Bello study). This is also true for other functional improvements.

For these reasons, incorporating the analysis of dystrophin content discussed above, I conclude that the biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit."

I agree that broad phenotypic distinctions made in the clinic (e.g., Duchenne vs. Intermediate vs Becker Muscular Dystrophy) are different than trying to predict benefit to an individual patient on the basis of a particular change in dystrophin. And I agree that extending ambulation by 6 months to a year (or similar improvements in other functional areas) would be extraordinarily important.

But Dr. Woodcock never provides a rational argument – based on reliable data – to support the concept that "...low-level increases in dystrophin production are reasonably likely to predict clinical benefit." She provides no rationale – no link between a mean increase in dystrophin of 3 parts per thousand and clinical benefit.

3) *No evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.*

Dr. Woodcock states:

"Additional support for "reasonably likely" comes from the long-term experience with the drug. The sponsor's comparison of the experience of the treated cohort to natural history data does not reach the level of substantiation required for traditional approval

based on the clinical data. However, it is highly suggestive of improvement in some parameters, in some patients, over natural history. My conclusion is informed by all the caveats expressed in the reviews about the pitfalls of nonrandomized comparisons. Given that the two exon 52 deletion patients in the study had fairly good long-term results in terms of rate of disease progression, the question arises as to whether exon 52 is a prognostic factor that could have skewed the results.”

The review team analyzed the clinical data in great detail, and could not reach the conclusion that there was any reliable evidence of improvement relative to the expected natural history of the disease. Study 201 did not show a treatment effect on its 1^o clinical endpoint, change in 6-minute walk distance at Week 24. Study 202 failed on the same endpoint at 48 weeks. The course of these Study 201/202 patients, having received eteplirsen for some 3.5 years, was not distinguishable from external control patients (see my review memorandum for more details).

The Advisory Committee voted (7 to 3 with 3 abstentions) that the clinical results of Study 201/202 did not provide substantial evidence that eteplirsen is effective for the treatment of DMD, and their vote was in the face of extraordinary pressure from patients and patient advocates to vote for approval. Two of the 3 “yes” votes were from patient representatives.

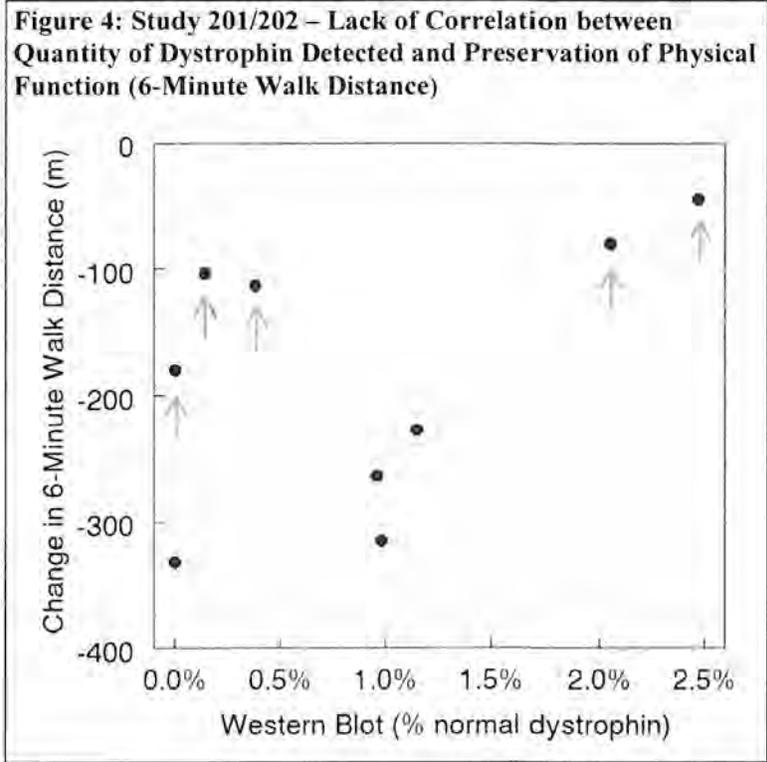
Correlation between dystrophin production and clinical effect

A correlation between dystrophin production (or with less certainty – dystrophin *detected*) and clinical function could provide some support for a conclusion that dystrophin production is reasonably likely to predict clinical benefit.

The applicant collected data on both dystrophin production and physical performance in Study 201/202. On the basis of the data presented in the NDA, the Division concluded that no patient in Study 201/202 clearly deviated from the natural history of the disease. The Division reasoned, therefore, that whatever the quantity of Becker-type dystrophin detected, it did not predict clinical benefit. Thus the Division opined that the clinical data weaken, and do not strengthen, the “reasonably likely” argument.

The Division's view notwithstanding, it is worth considering patients on an individual basis to assess the correlation between the quantity of Becker-type dystrophin detected and changes in physical performance.

As noted by Dr. Woodcock, the 6-minute walk test results do not show a strong correlation (Figure 4). For the 9 patients in Study 201/202 who remained ambulatory at Week 180 and agreed to undergo a fourth muscle biopsy, the figure shows little correlation between the quantity of dystrophin detected (x-axis) and preservation of physical function as assessed by the change in 6-minute walk distance from baseline (y-axis) after weekly infusions of eteplirsen for 3 to 3.5 years.



For the 5 patients whose 6-minute walk performance was best preserved (red arrows), 2 had the highest dystrophin levels detected in the study (upper right), but 3 had levels that were near-zero (upper left).

Dr. Woodcock also evaluated the North Star Ambulatory Assessment (NSAA) as a function of dystrophin detected in boys who could still walk and who had a dystrophin result at Week 180. She obtained the data from the applicant's briefing document for the Advisory Committee meeting, and found a correlation between dystrophin detected at Week 180 by Western blot and rate of decline in NSAA score through 180 weeks. Her graph is reproduced below:

With respect to the correlation, Dr. Woodcock explained: "This adds additional support to the idea that dystrophin production is "reasonably likely to predict clinical benefit."

Given that the correlation was driven by the patient depicted at the lower right (blue arrow; dystrophin level =

~2.5%; change in NSAA = 3), I considered the NSAA data from that patient (Figure 6). I found that his course was less benign than would be inferred from a change in NSAA of only 3 units. Specifically, using linear regression (red line in Figure 6), his NSAA score has, instead, worsened by a mean of 2.7 units per year.

I reasoned that inclusion of all of the NSAA data for each patient would provide a more reliable representation of their course than calculating the change between single pre-treatment and post-treatment data points, because of the test-to-test variability (e.g., short-term swings of 4 to 5 points for patient 006). Thus, using linear regression, I calculated the slope of the relationship between NSAA and time for each patient (as per the red line in Figure 6) and plotted the slopes as a function of the dystrophin detected at Week 180. (Slopes were calculated as loss of NSAA units per year.)

Using this method, there was no correlation ($R^2 = 0.36$), Figure 7. Importantly, the slight trend apparent here is driven by one or two data points.

Figure 5: Study 201/202: Analysis of Change in NSAA vs. Expression of Becker-type Dystrophin by Western Blot (Analysis by Dr. Woodcock)

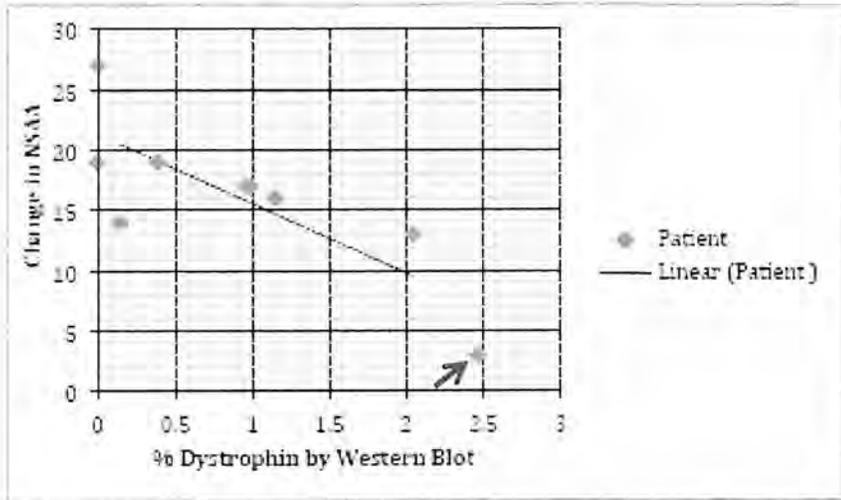
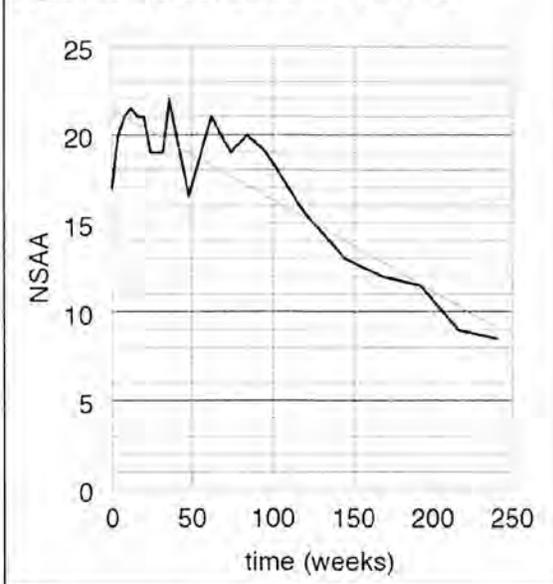


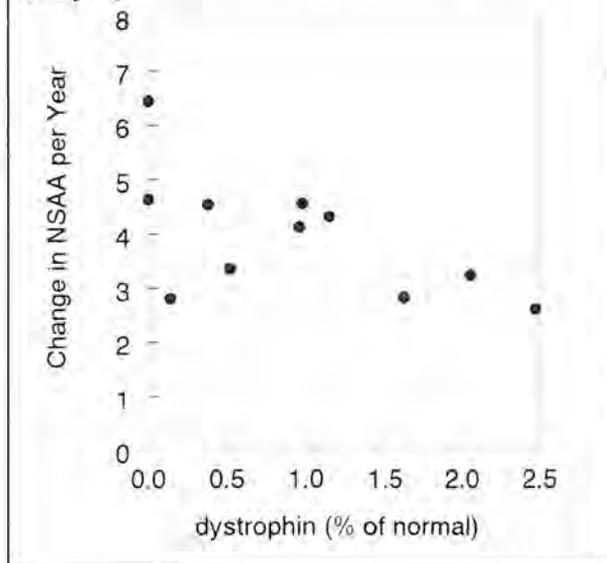
Figure 6: Patient 006: NSAA vs Time



Summary

In summary, I find no evidence that the increase in dystrophin demonstrated in Study 301 is reasonably likely to predict clinical benefit (mean 0.3%, range 0 to 1.3%). The levels of dystrophin linked to various Becker Muscular Dystrophy phenotypes in publications are largely not comparable to dystrophin levels measured in this development program. The applicant's interim CEO correctly urged us not to compare data from their Western blot analyses to historical approximations from the literature. And extremely low levels of dystrophin, as found here, seem particularly difficult to quantify and compare across laboratories. Nevertheless, to the degree that findings can be compared across studies, dystrophin levels of 10% or more would need to be achieved to impact the clinical course. The finding in Study 301 is an order of magnitude below this level.

Figure 7: Study 201/202: Analysis of Change in NSAA (Linear Regression) vs. Expression of Becker-type Dystrophin by Western Blot (My Analysis)



Based on protein levels in other deficiency diseases, the effect size here appears to be too small to provide benefit. If dystrophin were an enzyme that catalyzed a biochemical reaction in myocytes, one might posit that a very small quantity could produce a substantial proportion of the minimum necessary reaction product, and that the increase over baseline might be important because levels are so low in untreated patients. But given that dystrophin is a structural support protein that helps prevent myocyte injury due to stress and strain, I find it difficult to conceive how a treatment effect of 3 parts per thousand could confer clinical benefit. If there were 10 inches of snow on a sidewalk that needed to be cleared, 3 parts per thousand would amount to 1/32nd of an inch. We must also recognize that a treatment that increases dystrophin by 0.3% would seemingly have far less impact than being born with 0.3% more dystrophin, and even *that* seems unlikely to matter.

I can find no precedent of an accelerated approval for a marketing application where the effect size on the surrogate endpoint is as small as 0.3%.

Dr. Woodcock concludes:

"...my conclusion to rely on the surrogate endpoint described above represents the greatest flexibility possible for FDA while remaining within its statutory framework. In this case, the flexibility is warranted because of several specific factors, including: the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a fatal disease in children. Of note, the therapy has been relatively safe in the clinic, although intravenous administration always carries risk.... Therefore, I find that the

probable benefits outweigh the foreseeable risks and that this application should be approved under 21 CFR 314.510."

As noted in 506(f)(1), the amendments made by the Food and Drug Administration Safety and Innovation Act (FDASIA) "...are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs."

Some have interpreted this "flexibility" as a lower standard for demonstration of effectiveness, but this is not true.

Section 506(f)(2) of the FD&C Act specifically notes that drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval, notably the substantial evidence standard of section 505(d) with respect to the drug's claimed effect on a surrogate or intermediate endpoint. These facts have not been altered by FDASIA.

To be clear, 506(f)(2) states: "Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act or under section 351(a) of the Public Health Service Act. Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective. Nothing in this section alters the ability of the Secretary to rely on evidence that does not come from adequate and well controlled investigations for the purpose of determining whether an endpoint is reasonably likely to predict clinical benefit as described in subsection (b)(1)(B)."

I believe the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her July 14, 2016 memo makes this case. I believe that the available evidence leaves open the possibility that some patients *could* benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit.

Finally, there was no clinical benefit demonstrated in the development program, and the correlation between dystrophin and clinical effect was poor – not surprising given that the applicant provided analyzable data from only 11 patients.

3. Assessment of Possible Impact to Public Health Should My Position Not be Adopted

The approval of this NDA in its present form would have far reaching negative consequences for the public health.

1. Eteplirsen's risks are certain, whereas its efficacy is not. Having considered Dr. Woodcock's line of reasoning and her desire to approve eteplirsen, the position of the review team in the Division of Neurology Products, the Office of Biometrics, the Office of Clinical Pharmacology, the Office of Drug Evaluation-I, and the Office of New Drugs (verbal acknowledgement from Dr. John Jenkins) is that the applicant has not provided evidence that this drug is effective at the dose studied.

Dr. Woodcock notes that "...the therapy has been relatively safe in the clinic."

The reality is that only a few dozen patients have been exposed to the drug, such that the safety profile is not well characterized. A closely related drug being studied under a

(b) (4)

With

additional experience, important toxicity may emerge for eteplirsen. It is known that many patients in these studies are now receiving infusions through indwelling catheters. Maintenance of vascular access in patients on chronic corticosteroids poses a certain risk of infections. Although we are not yet aware of any infection-related adverse reactions, there would definitely be serious infections and possibly deaths if this drug is marketed, yet evidence of efficacy is lacking.

2. By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk. I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs – if not to patients, to society.

The prospect of providing false hope to desperate patients from a promising but ineffective therapy recalls the experience with *transmyocardial laser revascularization* (TMLR). In the 1990s, patients with coronary atherosclerosis and severe angina who were poor candidates for conventional revascularization procedures ("no-option" patients) underwent a thoracotomy (opening of the chest cavity) to enable use of a laser to create channels through the heart muscle. Ostensibly, these channels provided conduits for blood to flow from inside the left ventricle to the myocardium. Conduct of sham-controlled studies was impossible; studies were essentially baseline-controlled or historically-controlled. Large treatment effects were reported by a number of investigators, generally from small studies. There were marked increases in treadmill exercise time and relief of angina, with effects sustained for more than a year in some cases. Although many in the cardiology community raised concerns about expectation bias and were highly skeptical of the results, to some the effects seemed larger and more durable than could possibly be explained by expectation bias, i.e., a placebo effect. Thousands of patients underwent this invasive procedure with the hope of angina relief. Some years later, with improvements in technology, the conduct of sham-controlled studies became feasible, and TMLR was not found to be effective. The false hope was ultimately dispelled with the publication of two Cochrane Reviews.³ These reviews found the appearance of a marked treatment effect, but 30-day mortality was 6.8% in the TMLR group vs. 0.8% in the no-treatment group. They noted "The assessment of subjective outcomes, such as improvement in angina, was affected by a high risk of bias and this may explain the differences found." In this case, the cost of false hope was ~6% mortality in the first 30 days post-op.

I will also note that the primary endpoint of these laser studies was generally exercise capacity – the same type of endpoint used in the eteplirsen DMD development program, also for "no option" patients.

3. The accelerated approval pathway is designed to expedite the availability of promising new therapies to patients with serious conditions, especially when there are no satisfactory

³ Cochrane Database of Systematic Reviews 2015, Issue 2, Art. No.: CD003712, DOI: 10.1002/14651858.CD003712.pub3

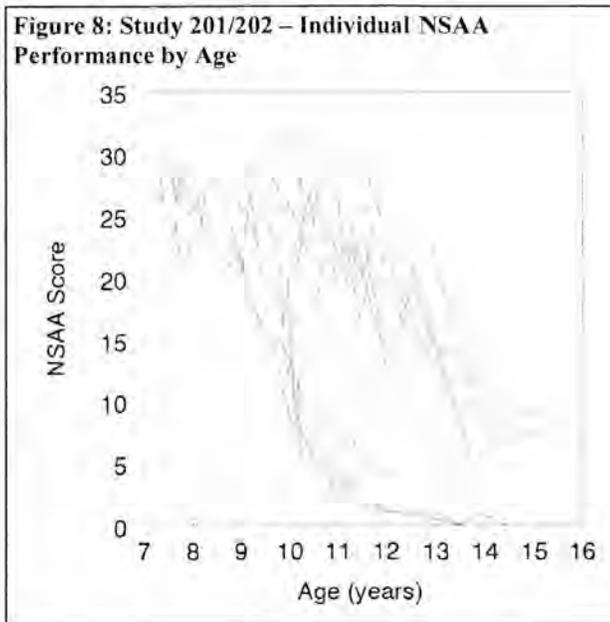
alternative therapies, while preserving standards for safety and effectiveness. For drugs granted accelerated approval, postmarketing confirmatory trials are required to verify and describe the anticipated clinical benefit, and FDA may withdraw approval of a drug if a trial required for verification of the predicted clinical benefit fails.

In reality, it is difficult to withdrawal a drug that is deemed to be effective, or possibly effective, by patients with severe diseases and limited treatment options. FDA has not succeeded in withdrawing the marketing of a single drug for lack of verification of clinical benefit following accelerated approval. The reality is that if eteplirsen is given accelerated approval, it is highly likely to remain on the market indefinitely, irrespective of whether or not efficacy is verified.

4. With the false perception that eteplirsen is effective, patients who are gaining benefit from steroids but experiencing untoward side effects might be inclined to taper or stop them, which could lead to more rapid disease progression.
5. False scientific conclusions have the potential to mislead the field of medicine, slowing progress in finding and developing therapies that actually *are* effective. For example, consider the scenario of a related drug with far greater potential to promote dystrophin production in patients with DMD. In order for a sponsor to study such a drug, patients would likely have to agree to discontinue eteplirsen, and few patients may be willing to do so. In short, approval of an ineffective therapy has the potential to discourage or inhibit the development of other drugs that *are* effective, and this impact can be significant.
6. Accelerated approval would lower the evidentiary standard for effectiveness to an unprecedented nadir. The amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin. In other words, if a statistically significant change of 0.3% – a mere 3 parts out of a thousand – is considered adequate to support accelerated approval here, then the question arises as to whether there would be any statistically significant change that would be too small to be considered “reasonably likely” to support accelerated approval. Similarly, if a ‘responder’ had been defined as a patient with an increase in dystrophin of $\geq 1\%$ (and there is no basis to accept such a low threshold), there would have been only a single responder in Study 301. If we were to adopt the concept that, for rare diseases, accelerated approval could be supported by any statistically significant change in an appropriate surrogate, or a response in a single patient, we would enable accelerated approval of a myriad of drugs for rare diseases. No doubt there are some who would applaud this as an advance. But a standard this low would undercut FDA’s ability to ensure that drugs that are approved are effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.
7. With accelerated approval of this NDA, there would be highly detrimental effects on drug development. Traditional drug development for rare diseases might be replaced by a system where small, baseline-controlled, proof-of-concept studies designed to show any change in a surrogate marker would provide a basis for accelerated approval, assuming that the pathogenesis of the disease was well understood and that the surrogate was directly on the causal path. There would be little reason to pursue adequately controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of

failure would provide a disincentive to conduct such trials. For example, a gene therapy designed to produce a missing clotting factor could receive accelerated approval on the basis of a tiny yet inconsequential change in levels of the factor, or a more robust response in a single patient. In short, the precedent set here could lead to the approval of drugs for rare diseases without substantial evidence of effectiveness.

8. Even if the 30 mg/kg/week dose were considered to have a meaningful effect on the surrogate endpoint, we already know this dose is sub-therapeutic. We know this because patients who have been receiving this eteplirsen dose for some 3.5 years have been progressing at a rate that is similar to that expected, based on the natural history of the disease (Figure 8). I question the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic, when the consequence of a sub-therapeutic dose is clinical deterioration and death. The figure shows the unremitting progression in the patients in Study 201/202, based on changes in NSAA.



9. Approval of this NDA would send the signal that political pressure and even intimidation – not science – guides FDA decisions, with extremely negative consequences (See Grainger D., 11/30/15. "DMD Drugs: an existential threat to FDA," *Forbes*⁴). The public is well aware of this development program: the meager size of the study population, the marginal (at best) effect size, the Division's dim view of the efficacy data, and the robust activism of some members of the DMD community. Many would be amazed at an approval action, because other DMD drugs, recently turned down for approval, appeared to provide stronger evidence of efficacy.

FDA and Congress were bombarded with correspondence – pleas urging approval of this NDA. More than 50 speakers registered to speak at the April Advisory Committee meeting. I received 2,792 emails urging approval. Here is an example of the body of an email I received last week:

"Dear Dr. califf: How is it that everyone in and around DMD understands this simple Idea and the science geniuses at FDA don't? You stupid f___ers are costing each and every DMD kids days of their lives with your Moronic Dystrophin dance. Time to get a

⁴ downloaded 7/18/16 at <http://www.forbes.com/sites/davidgrainger/2015/11/30/dmd-drugs-an-existential-threat-to-the-fda/#5ffc71245517>

f...ing clue! (b) (6)
(b) (6)

The ramifications here are profound. The public will perceive that it was their unprecedented lobbying efforts that made the difference and earned eteplirsen its accelerated approval. For the future, this will have the effect of strongly encouraging public activism and intimidation as a substitute for data, which is one of the worse possible consequences for communities with rare diseases. This type of activism is not what was envisioned for patient-focused drug development.

4. Detailed Description of the History of the Dispute, Including My Description of the Center SDR Procedures Followed and/or Not Followed, Dates of Meetings, and Decisions Rendered Throughout the Process

The following table shows the dates and main activities for 15 Center Director Briefings associated with the development of this drug: 8 Center Director Briefings took place during the IND phase of development, *prior to submission of the NDA*, and 7 Center Director Briefings took place during review of this NDA.

DATE	MEETING	DETAILS
7/17/2013	Center Director Briefing	Follow up on Action Item from 3/13/13 EOP2 Meeting: Sarepta has submitted a comprehensive discussion of the issues from the EOP2 mtg. To discuss the suitability to file the NDA for Subpart H approval.
10/18/2013	Center Director Briefing	Dr. Unger presented an overview and Dr. Farkas had a slide presentation on drisapersen and eteplirsen data. Discussion: 1. Plan to have a manufacturing facility visit by ONDQA - to observe process and obtain yield calculation. Sponsor is expecting to have 2nd batch in Dec 2013. Determine how much product the sponsor has. 2. OBP: recommended to establish specificity of the antibody and variability of the assay. 3. Next trial - plan to have OCL group to observe the conduct. 4. Need data from the (b) (4) trial. DNP has previously requested the (b) (4) data from (b) (4) but did not get any response. Dr. Woodcock will initiate an inquiry to the sponsor (raw data). 5. The Agency needs to assist Sarepta (characterize biomarker, CMC facility, observe 6MWT, etc.) 6. 2nd Internal Meeting (Drs. Woodcock, Temple, Jenkins, Unger and Neuro) before the 11/8/13 sponsor meeting. Discuss further what to convey to Sarepta.
10/28/2013	Center Director Briefing (continuation of 10/18/13 meeting)	Suggestions/Recommendations for DNP to Consider: -- We have concluded that we will not ask for biopsy until (we understand the histopathology and are) we're certain what is a quantitative measure and identified the surrogate marker for the study. -- Tell the sponsor that we have changed our view for the quantitative measure of truncated dystrophin as a surrogate PD marker used in their study, because of the recent natural history

		<p>study and (b) (4)</p> <p>-- Dr. Woodcock wants to have a comprehensive literature review to fully understand what's this mean of the deletions, mutations, or duplications in the dystrophin gene, or this exon 51 of dystrophin mRNA ((Office of Translational Science) believe this task was assigned to a different group).</p> <p>-- To ask the Sponsor to provide their production schedule. I believe Dr. Woodcock wants to understand the amount of production and determine if the company can provide the drugs to those DMD patients in the future.</p> <p>-- To suggest that the Sponsor consider enrolling patients younger in age (like starting with 5yrs) in their clinical study.</p> <p>-- To ask the Sponsor if they could provide drugs for compassionate use to patients (who are very sick or those were in the drisapersen trial previously).</p> <p>-- Schedule a T-con with (b) (4) to discuss (b) (4) data</p>
1/17/2014	Center Director Briefing	Request: Team to present DMD drugs study design to Dr. Woodcock – Path forward for Sarepta (& (b) (4))
2/6/2014	Center Director Briefing	DMD drugs study design (Discuss Sarepta path forward) Action items: (a) Request biomarker data from the sponsor - done TC on 2/7/14(b) If data interpretable, meet with sponsor for a brainstorming session. Then follow-up with Advice Letter
3/5/2014	Center Director Briefing	Dr. Ash Rao presented biomarker data findings (including Drs. Woodcock, Jenkins, Temple, Unger, Moscicki) Team discussed path forward. Action Item: to invite Sarepta for a brainstorming discussion.
3/19/2014	Sponsor Meeting, with Center Director	brainstorming discussion - study design and path forward Action: Sarepta to submit proposed studies and next steps
4/2/2014	Center Director Briefing	Drs. Woodcock, Moscicki, Temple, Unger Discuss proposal & comments to sponsor ~Advice Letter-include previous meeting discussions ~FDA workshop – biomarker ~Work w/ sponsor on dystrophin biomarker ~Natural history raw data - primary investigators
6/26/2015		SUBMISSION OF NDA
12/9/2015	Center Director Briefing	To brief on the current status of eteplirsen review in advance of the planned Jan 22, 2016 AC meeting. To discuss the application and the plan of action.
1/13/2016	Center Director Briefing	To review the slide presentation and plan of action for eteplirsen, that will be presented during the Advisory Committee Meeting on January 22, 2016 to senior leadership.
2/10/2016	Center Director Briefing	To discuss the ongoing review of the NDA, and what will be presented during the Advisory Committee Meeting in April. To discuss the strengths, limitations, and uncertainties of the data, particularly with respect to the comparison between the open-label eteplirsen group and a contemporary untreated external control group.
4/15/2016	Center Director Briefing	To discuss the statistical review of the CINRG data. To discuss the review of data on DMD that was conducted by the Cooperative International Neuromuscular Research Group
4/25/2016	Advisory Committee Meeting	
5/4/2016	Center Director Briefing	Discuss the outcome and plan of actions for the application post advisory committee meeting

5/31/2016	Center Director Briefing	Discuss reviews conducted by the review team and leadership along with any additional information obtained from the sponsor. Discussed Dr. Woodcock's memo. Timeline for reviews due to Dr. Woodcock.
7/6/2016	Center Director Briefing	<ol style="list-style-type: none"> 1. The levels of dystrophin observed in 12 DMD patients from the recent interim analysis of an ongoing trial and whether the levels seen can be interpreted to be "reasonably likely to predict clinical benefit" and used as a surrogate endpoint to support accelerated approval. 2. The design of one or more PMR trials to confirm clinical benefit of eteplirsen if it is approved under accelerated approval. 3. Description of the available clinical data in the drug label if approved.

Based on my years of experience in Office of Drug Evaluation-I, the Center Director's direct involvement with this drug, compared to other development programs, has been unprecedented. She also attended the April meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, where she spoke and interjected a number of important comments.

There is no question that there has been adequate time and place for the discussion of various views. I will note, however, that I found it unfortunate that the Center Director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division's final review memorandum or my review memorandum. Prior to reading our reviews, Dr. Woodcock stated that she had already "...reached a different conclusion..." than the review team.

5. Action, Decision or Remedy Sought

Although the above paragraph could be considered grounds for an appeal based on process, I seek instead a scientific review on the matter of whether or not there is substantial evidence of a quantitative effect on dystrophin protein that is reasonably likely to predict clinical benefit. I maintain, along with the Division of Neurology Products, Office of Biometrics, Office of Clinical Pharmacology, Office of New Drugs, and the majority of the members of the Peripheral and Central Nervous System Drugs Advisory Committee, that substantial evidence is lacking to support either a conventional or accelerated approval, and that a *complete response* should be issued for this NDA.

The unprecedented finding of an increase in dystrophin protein in response to eteplirsen establishes proof-of-concept and provides great promise that this drug, or other therapies, will eventually be capable of ameliorating the fundamental genetic defect of DMD, but the effect size here is insufficient at the tested doses.

6. Path Forward

Based on the quantity of Becker-type dystrophin produced in Study 301 and the clinical findings in Study 201/202, additional studies at this dose are unlikely to support any type of approval, i.e., the data obtained for eteplirsen at doses of 30 and 50 mg/kg/week are fairly solid, but they do not support efficacy.

I remain comfortable with the concept that substantial evidence of dystrophin production from adequate and well controlled trials could support accelerated approval, but it is clear that higher doses are needed, and greater quantities of dystrophin would need to be produced. The path to a conventional approval would require a double-blind, placebo-controlled (or multi-dose) study, at least one year in duration, using some measure of physical performance as the primary endpoint, again, testing higher doses.

The applicant is continuing to enroll Study 301 (PROMOVI), an open-label, multicenter, 48-week study in patients with DMD amenable to skipping exon 51. All patients are receiving eteplirsen, 30 mg/kg/week as an IV infusion.

My suggestion for a path to approval is to randomize patients in the ongoing Study 301 to:

- 1) either remain on 30 mg/kg/week; or
- 2) have their dose significantly increased. This could be done through use of a higher dose, through more frequent dosing intervals (with dummy infusions), or both. Given that many patients receive eteplirsen through indwelling IV lines and no significant infusion reactions have occurred, perhaps these infusions could be performed at home. For example, the study could compare 30 mg/kg weekly to 30 mg/kg daily. Patients who do not tolerate more frequent dosing could have their doses decreased, as needed. Based on non-clinical findings, monitoring would need to be in place to assess renal toxicity.

Patients and investigators would be blinded to treatment group. For accelerated approval, the primary endpoint would be dystrophin production, comparing the higher and lower doses. For standard approval, the primary endpoint would be a test(s) of physical performance such as NSAA or rise time.

Such a trial would be methodologically sound and ethical. Virtually everyone, patients and physicians alike, would want to know whether higher eteplirsen doses would increase dystrophin production, and would have equipoise for participation. Although there is concern regarding performance of muscle biopsies in patients randomized to placebo, this would not be a concern here with all patients receiving active drug. And I would recommend that the applicant forego immunohistochemistry studies in favor of Western blot analyses, such that needle biopsies with local anesthesia would be sufficient (rather than open biopsies with more intensive anesthesia and greater morbidity).

I also believe that it would be desirable for the company to provide access to eteplirsen for DMD patients through expanded access programs, with cost recovery, while an adequate dose-finding study is conducted.

FDA is charged with the responsibility of ensuring that drugs are shown to be effective prior to marketing, based on substantial evidence. If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients, in essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope. If we were to turn the clock back to the days prior to the 1962 Kefauver Harris Amendments to the Federal Food, Drug, and Cosmetic Act, the damage to society and the field of evidentiary medicine would be enormous.



NDA 206488

GENERAL ADVICE

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exondys 51 (eteplirsen) injection, 50 mg per mL.

This letter is in response to your email of June 2, 2016, to Janet Woodcock, M.D., in which you agreed to perform Western blots on baseline and Week 48 biopsies from eteplirsen-treated patients to assess dystrophin content. We will work with you on the protocol and analysis plan, and on the dates for FDA observers to be present during the procedures.

We agree to have an FDA observer present at the Iowa site to monitor tissue sampling and blinding procedures, and to have an observer present at the Corvallis site during performance of the Western blot procedure. We also understand that Corvallis is not a GLP facility.

We understand that a new normal control will need to be established to generate the standard curve of a serially-diluted normal comparator as part of these procedures. Please confirm the healthy dystrophin genotype and phenotype of this new control and compare side-by-side with the limited previous healthy control you have available. Confirm that the validation parameters and acceptance criteria for the new healthy control are comparable to those for the previous healthy control used with the Week 180 samples (e.g., linearity of the serially diluted sample, %RSD).

You should provide each of the relevant protocols for our review that describe the methods you propose to use for testing dystrophin, including those related to tissue acquisition at the clinical site(s), processing, blinding, and shipping procedures at the University of Iowa or elsewhere, tissue quality control before analysis, validation of the new normal control, and Western blotting at the Corvallis location.

You should implement appropriate quality control measures including strict blinding procedures to ensure that the integrity of the other primary and secondary assessments is not compromised as a result of this specific dystrophin investigation.

If you are successful in showing, to FDA's satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to

grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable).

To allow for prompt approval, should your dystrophin analysis prove successful, we will work with you over the next several weeks on completing labeling negotiations to the degree possible and on necessary postmarketing requirements and commitments.

We request that you not publicly communicate the specific details of this plan until after completion in order to allow maximum procedural efficiency.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

(See attached electronic signature page)

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET WOODCOCK
06/03/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20903

Subject: Agreement to utilize FDA Staff Manual Guide 9010.1 for internal appeal related to NDA 206488, eteplirsen injection

Date: July 16, 2016

From: Virginia L. Behr
Ombudsman, FDA Center for Drug Evaluation and Research (CDER)

To: Matt Warren, Director, Office of Scientific Integrity, Office of the Commissioner
NDA 206488 administrative file

Summary: This memorandum requests that you hear an appeal under Staff Manual Guide (SMG) 9010.1 *Scientific Dispute Resolution at FDA*. In my role as the CDER Ombudsman, I serve as an advisor to CDER staff regarding dispute resolution processes. Review officials within CDER's Office of New Drugs (OND) sought my assistance in determining the most appropriate dispute resolution pathway to resolve differences of opinion concerning the official action to be taken on NDA 206488. After thorough analysis of the available dispute resolution processes, my conclusion is that SMG 9010.1 is the most appropriate process for resolving the dispute. The involved parties agree with my recommendation and have waived rights to alternate CDER dispute resolution processes.

Background: On June 26, 2015, Sarepta Therapeutics submitted NDA 206488, eteplirsen injection for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. In CDER, the appropriate Office of Drug Evaluation (ODE) Director – in this case, Ellis Unger, MD, ODE I Director – has the delegated authority for action on NDAs with a new molecular entity. Dr. Unger's final memo dated July 16, 2016, asserts his position that this NDA should receive a complete response letter (i.e., eteplirsen cannot be approved for marketing at this time) because the amount of dystrophin (surrogate endpoint) produced by eteplirsen administration is not reasonably likely to predict a clinical benefit. John Jenkins, MD, OND Director, agrees with Dr. Unger's final conclusions. Janet Woodcock, MD, CDER Director, disagrees with Dr. Unger's final conclusions and issued her final memo dated July 14, 2016, stating her intention to approve the NDA and overrule Dr. Unger's decision. Dr. Unger plans to formally appeal Dr. Woodcock's decision.

Applicable Policies and Procedures: CDER's Manual of Policies and Procedures (MAPP 4151.1) *Scientific / Regulatory Dispute Resolution for Individuals Within a Management Chain* details how a CDER employee whose position on an issue does not align with a higher official in their management chain may submit a formal appeal. The appeal is submitted up the supervisory chain of command, potentially up to the Center Director. In this case, the chain of command is ODE I Director → OND Director → CDER Director.

Because this dispute is between the ODE I Director and the CDER Director, the process outlined in MAPP 4151.1 does not apply. Therefore, one may refer to MAPP 4151.2 *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director* to appeal. CDER MAPP

4151.2 describes a formal process by which individuals in this situation can ensure that their views are heard. These individuals are given an opportunity to request a review of the dispute by the Center Director and an Ad Hoc panel. CDER MAPP 4151.2 “should be used only if an individual expects that an Agency action, or inaction, will have a significantly negative public health impact and 1) the mechanisms detailed in CDER MAPP 4151.1 have been utilized to their full extent, i.e., up to the highest management official or 2) are unlikely to lead to a timely resolution.” The difference of opinion between Drs. Unger and Woodcock could be considered to meet the criteria for filing an appeal under MAPP 4151.2 because the drug indication sought is one for a serious and life-threatening disease that has limited treatment options.

I question the utility of using MAPP 4151.2 in this dispute for two reasons: 1) the CDER Director has already fully evaluated the issues and is one of the parties involved in the dispute, and 2) utilizing this MAPP could potentially extend this already lengthy NDA action another 50 business days. Further appeal beyond MAPP 4151.2 follows the Agency SMG 9010.1 *Scientific Dispute Resolution at FDA* which is handled by FDA’s Office of the Commissioner.

Agreement on Appeal Process: I asked Drs. Unger and Woodcock their opinion about waiving the use of MAPP 4151.2 and allowing the appeal to be heard under SMG 9010.1. I received written affirmation from Dr. Unger via email on July 8, 2016 and verbal agreement from Dr. Woodcock on that same date. Therefore, the disputing parties agree to have Dr. Unger’s appeal submitted to FDA’s Office of the Commissioner under SMG 9010.1 *Scientific Dispute Resolution at FDA*. Their agreement is indicated by their signatures below.

Ellis F.
X Unger -S

Digitally signed by Ellis F. Unger -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Ellis F. Unger -
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Date: 2016.07.16 15:00:05 -04'00'

Ellis Unger, MD
Office of Drug Evaluation 1 Director

Janet
X Woodcock -S

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DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Janet Woodcock -S,
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Date: 2016.07.16 08:56:26 -04'00'

Janet Woodcock, MD
Center for Drug Evaluation and Research Dire...

cc:

Matt Warren, Director, Office of Scientific Integrity, Office of the Commissioner
Elizabeth Dickinson, Director, Office of Chief Counsel
Janet Woodcock, CDER Director
John Jenkins, Director, Office of New Drugs
Ellis Unger, Director, Office of Drug Evaluation 1
Administrative file for NDA 206488

NDA 206488

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIRGINIA L BEHR
07/18/2016

From: [Pennington, Caitlin](#)
To: [Califf, Robert](#)
Subject: FW: Reminder: Proposed CDER/OC Monthly Leadership Agenda Items for August 11
Date: Tuesday, August 09, 2016 9:16:52 AM
Attachments: [CDER OC Leadership Monthly Meeting Memorandum of Meeting 7-20-16 FINAL.doc.docx](#)

Hi Dr. Califf,

Here are the proposed agenda items for this Thursday's meeting with CDER:

1. UFA updates
2. Opioids
3. Unfinished guidance update

Do you want to add anything to this agenda?

Thanks!

Caitlin

From: Moran, Kristy
Sent: Tuesday, August 09, 2016 9:15 AM
To: Kraus, Tom; Auchincloss, Kalah
Cc: Pennington, Caitlin; Sennett, Antonia Monique
Subject: Reminder: Proposed CDER/OC Monthly Leadership Agenda Items for August 11

Good afternoon,

The OC/CDER Monthly Leadership meeting has been moved up to August 11th from 3 – 4 pm.

Reminder: Let me know if you have any additional agenda items you would like to discuss at this meeting. NOTE: Per Alyson Saben, 8/8/16 Jeremy did not have any additional items to add.

-
I will finalize and send out the agenda tomorrow for Thursday's meeting.

Thank you,
Kristy Moran
OC/Office of the Executive Secretariat

From: Moran, Kristy
Sent: Thursday, August 04, 2016 1:12 PM
To: Califf, Robert; Sharp, Jeremy; Kraus, Tom; Auchincloss, Kalah
Cc: Varnado, Martina; O'Neill, Jeff; Saben, Alyson L
Subject: Proposed CDER/OC Monthly Leadership Agenda Items for August 17

Good morning,

Below are the suggested topics that CDER/Dr. Woodcock would like to discuss at the CDER/OC Monthly Leadership meeting scheduled for August 17 at 10:00 a.m. Please let me know if there additional topics that you would also like to include on the agenda to discuss.

I've also attached the discussion/action items from CDER's meeting on July 20.

CDER Proposed topics:

There may be additional items to add by CDER as the meeting approaches. Agenda items 1 & 2 are really standing topics Dr. Woodcock wants to make sure we keep on the agenda, but there isn't anything specific to cover as of now.

1. UFA updates
2. Opioids
3. Unfinished guidance update

Kindly,
Kristy Moran
OC/Office of the Executive Secretariat

MEMORANDUM OF MEETING
OC/CDER Leadership Meeting
July 20, 2016
4:30 pm – 5:30 pm

Subject: General Updates from the July 2016 OC/CDER Leadership Meeting

Participants: Robert Califf, Tom Kraus, Kalah Auchincloss (by phone), Jeremy Sharp (by phone), Luciana Borio (by phone), Janet Woodcock, Heather Brown, Deborah Roth, Liz Dickinson (by phone), Katie Conover, Deborah Roth, Rosemary Roberts, Brad Leissa, Andrei Nabakoski, Mark Russo, and Kristy Moran

Decision/Action Items:

General Updates

- B. cepacia Outbreak
 - Concern about who is in charge in center specific or multi-center product investigation.
 - Next Steps: Some key issues may need to be updated in the Emergency Operations Plan of 2014. Changes can be made on a page by page basis without updating the entire plan.
 - Tom Kraus will follow up on updating the procedures in the Emergency Operations Plan.
- Update on Opioids - CDER will be talking to the state boards next week about implementing the mandatory training on opioids. CDER will make decisions on next steps when they get intelligence on what the state's plan to do. A possible next step may be a public meeting.
- Cough Syrup – CDER is going to communicate with drug sponsors telling them that CDER is opening a drug safety issue to identify any new drug safety issues with these products; this will be followed up by sending drug safety letters to the sponsors. CDER will also call to urge them to remove the pediatric indication from the codeine cough syrups; CDER believes that sponsors will comply with the request. CDER's goal is to have a draft document in approximately 2 weeks that will identify findings as to why the benefits no longer outweigh the risks.
- Update Generics
 - No rescission.
 - CDER will be involving a 3rd party to take a look at the IT system to identify some inconsistencies in flagging data.

- OTC User Fee Negotiations
 - Started July 6, 2016.
 - CHPA issued a statement announcing their participation in the OTC program.
 - CDER will be talking to congressional staff on July 21 about the legislative revision of the monograph system.
 - CDER has issued one set of minutes on the user fee meeting. These minutes could be used for CDER's public talking points since there was agreement not to talk about user fees until further along in the process.

- Eteplirsen
 - An appeal has been filed.
 - Next steps: Lou Borio will follow up on the timeframe for action from the Commissioner's office.

- Committee for the Advancement of Clinical and Therapeutic Professional Education (CACTPE)
 - CDER and OSPD are proposing to realign the Committee for Advanced Scientific Education (CASE) with the Office of Scientific Professional Development, Office of the Chief Scientist.
 - The CASE is a multidisciplinary committee of members who represent major scientific disciplines from various offices within CDER. The Seminar and Curriculum courses provided by the CASE are of high interest to a broad Agency-wide regulatory and scientific target audience and are cross-cutting in nature.
 - The CASE will become the Committee for the Advancement of Clinical and Therapeutic Professional Education (CACTPE) with representation from OCS, CBER, CDER, CDRH, CTP and CFSAN.
 - CDER Scientific Rounds will remain with CDER given that the educational activity is CDER-specific and designed for the CDER target audience.

- Ethics - An OGE audit will be made public soon regarding confidential filers.
Next Steps: CDER is working with FDA Ethics on this issue.

- Unfinished Draft Guidances – the Commissioner urges the Center to complete unfinished draft guidances.

Next meeting:

Wednesday, August 17, 2016, 10:00 am – 11:00 am

Executive Secretariat Contact: Kristy Moran, 301-796-4678

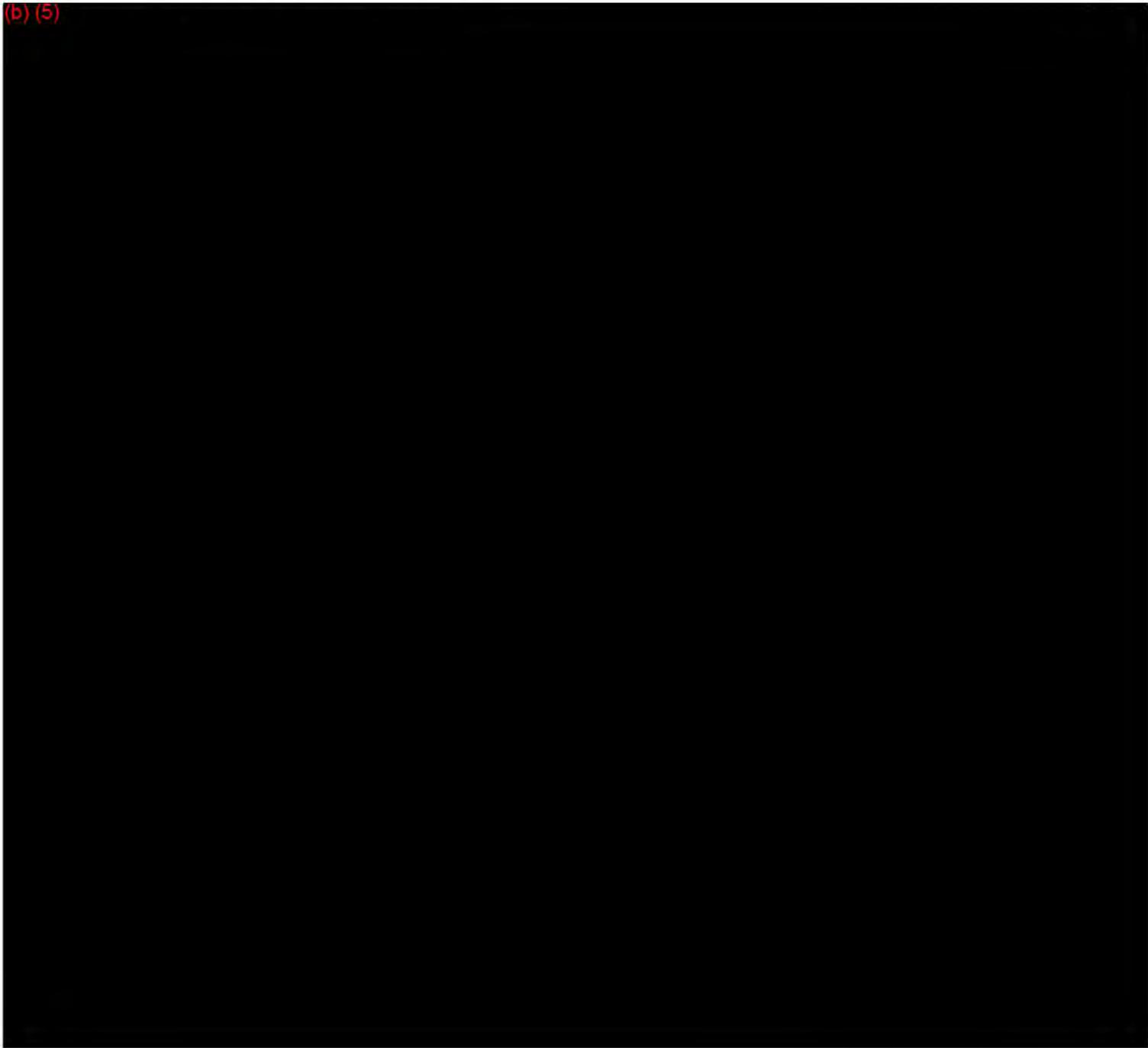
From: [Sherman, Rachel](#)
To: [Califf, Robert](#)
Subject: Personal and confidential
Date: Wednesday, August 10, 2016 8:41:10 AM
Attachments: [Sarepta dctrscm.docx](#)

I've attached my edits to the JW memo for your information.

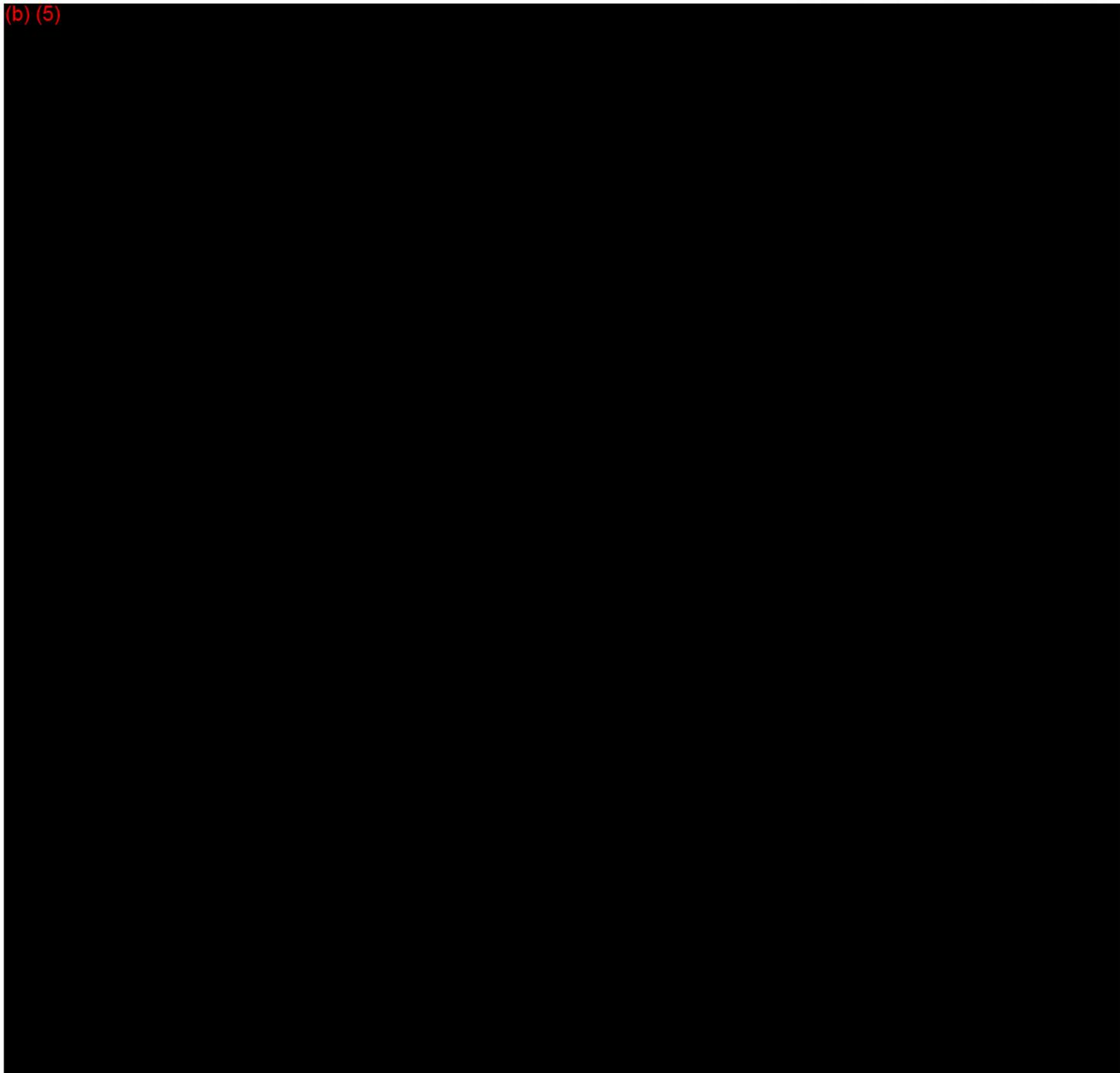
Also, she has repeatedly asked me about CF. I have reminded her I am recused and only discussed personnel matters (her concerns about the super office, office and division directors). We have also had discussions about approaches to labeling – my opinions were not product specific.

Center Director Decisional Memo

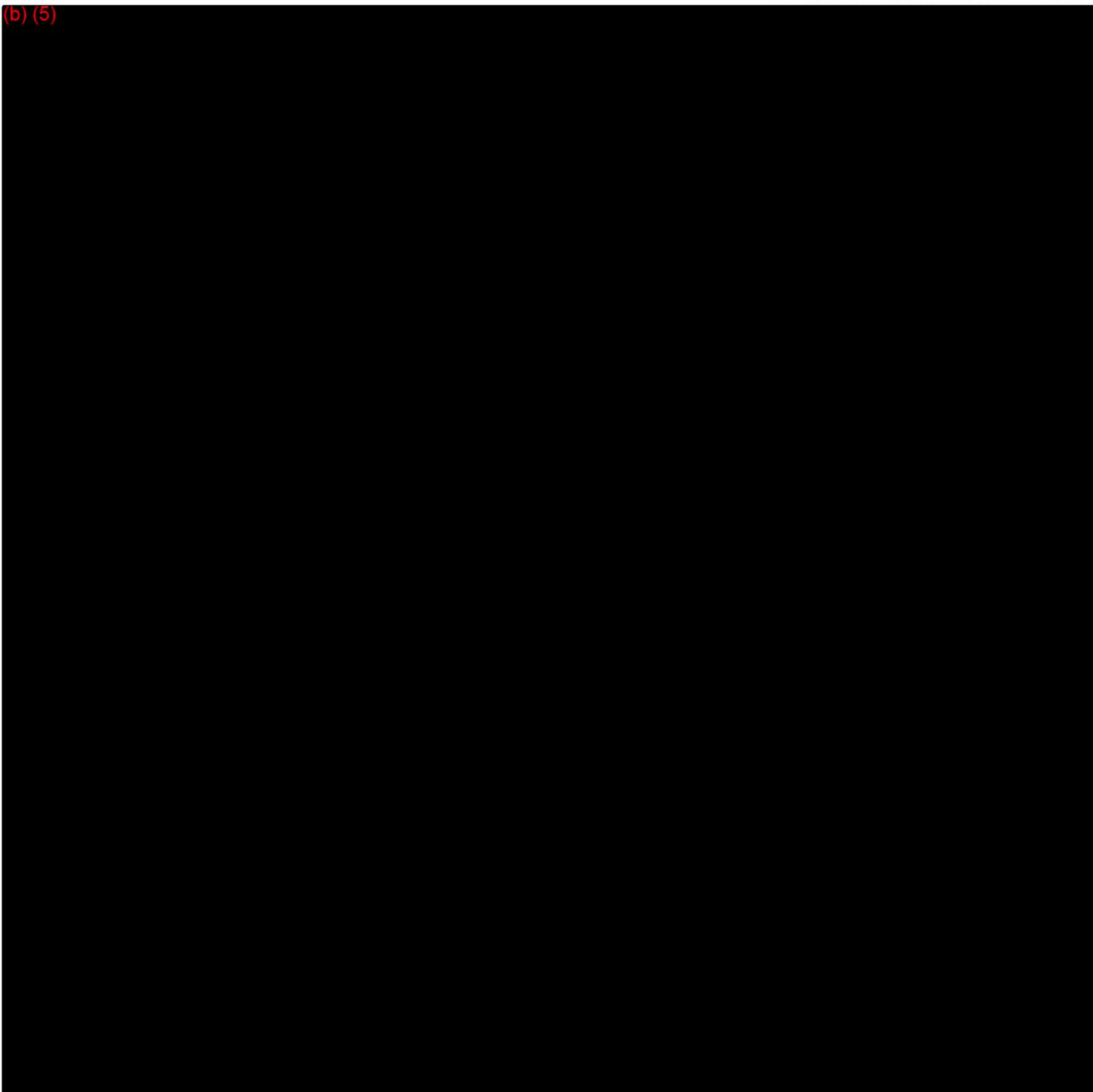
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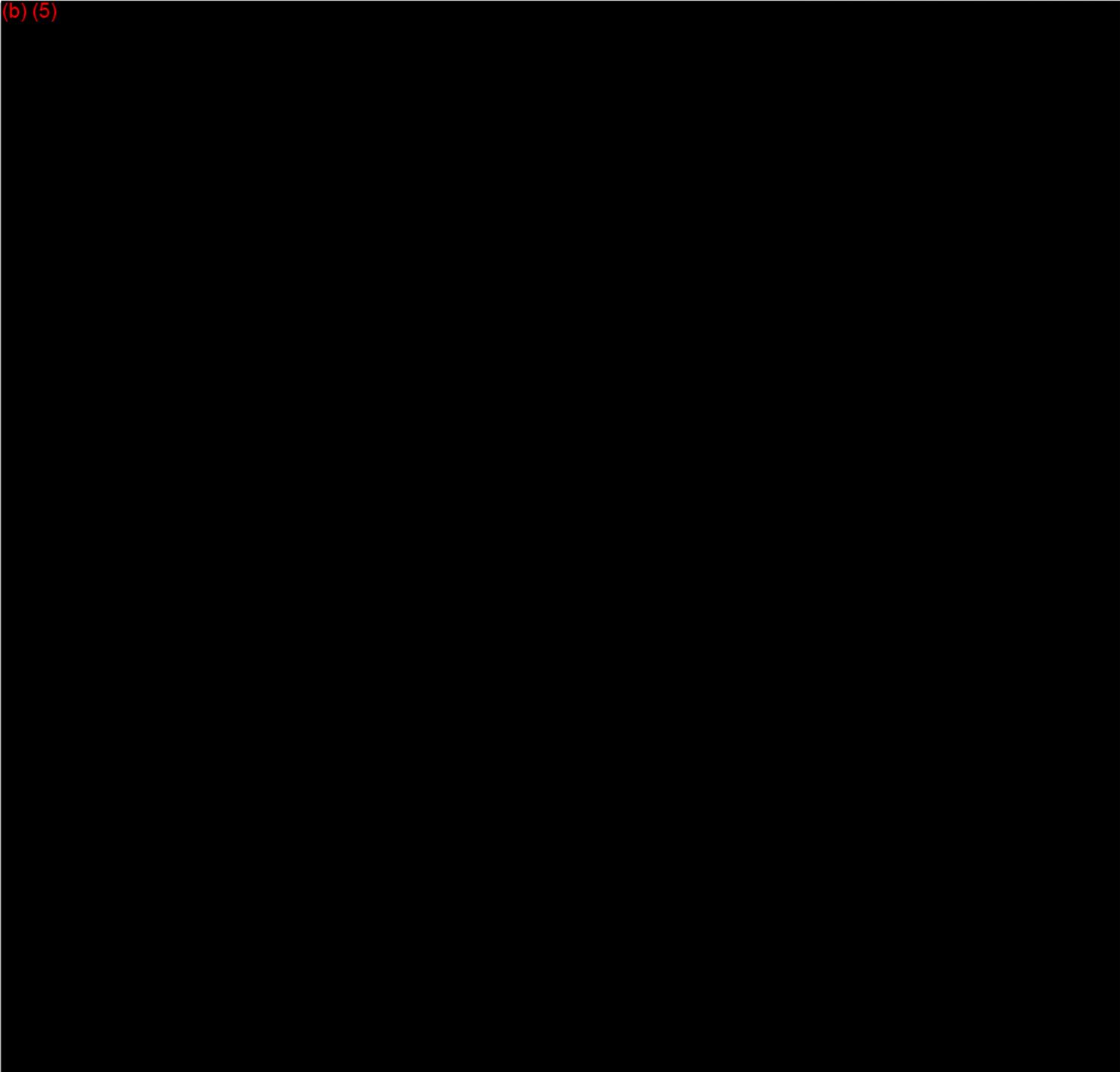
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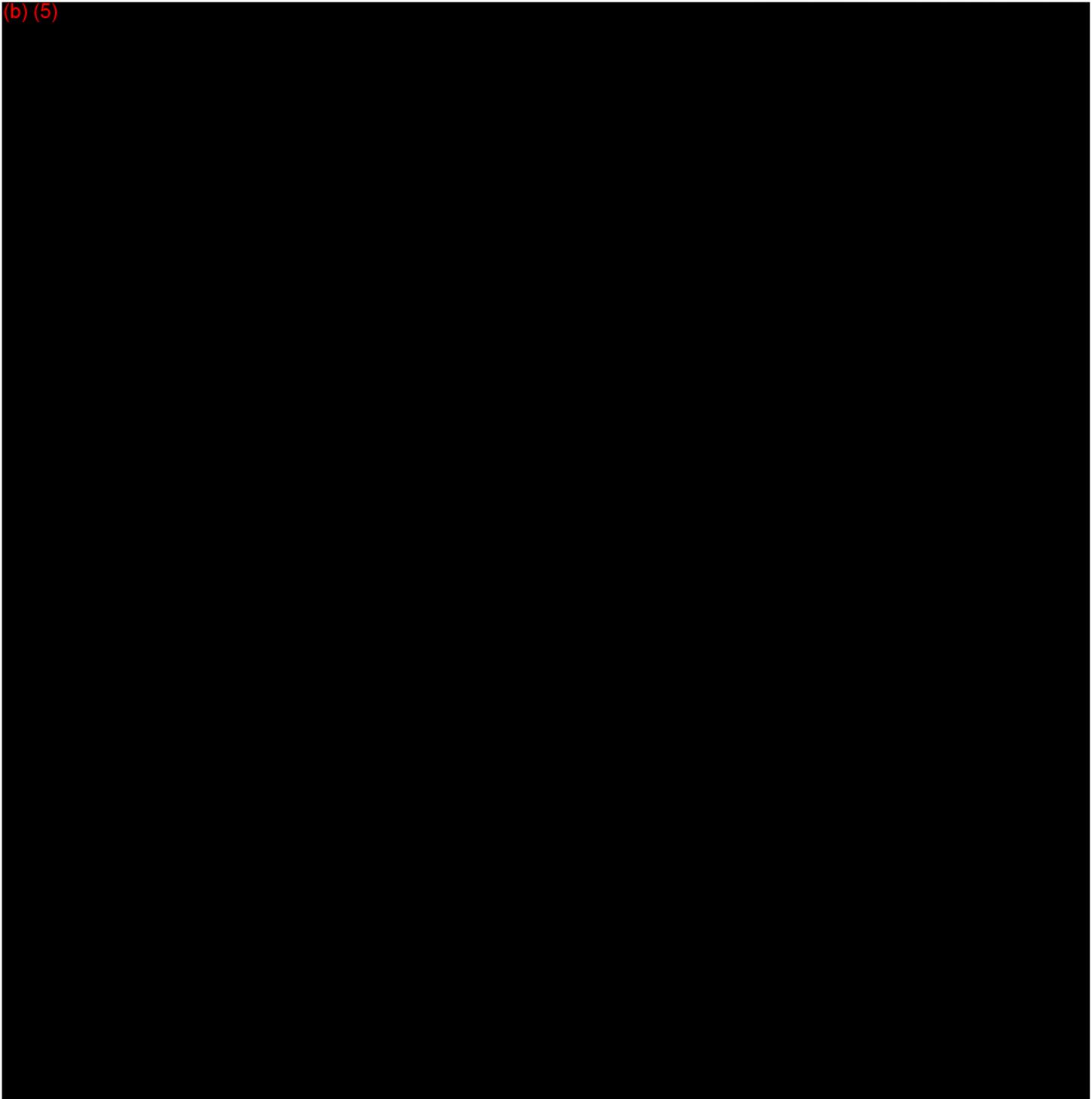
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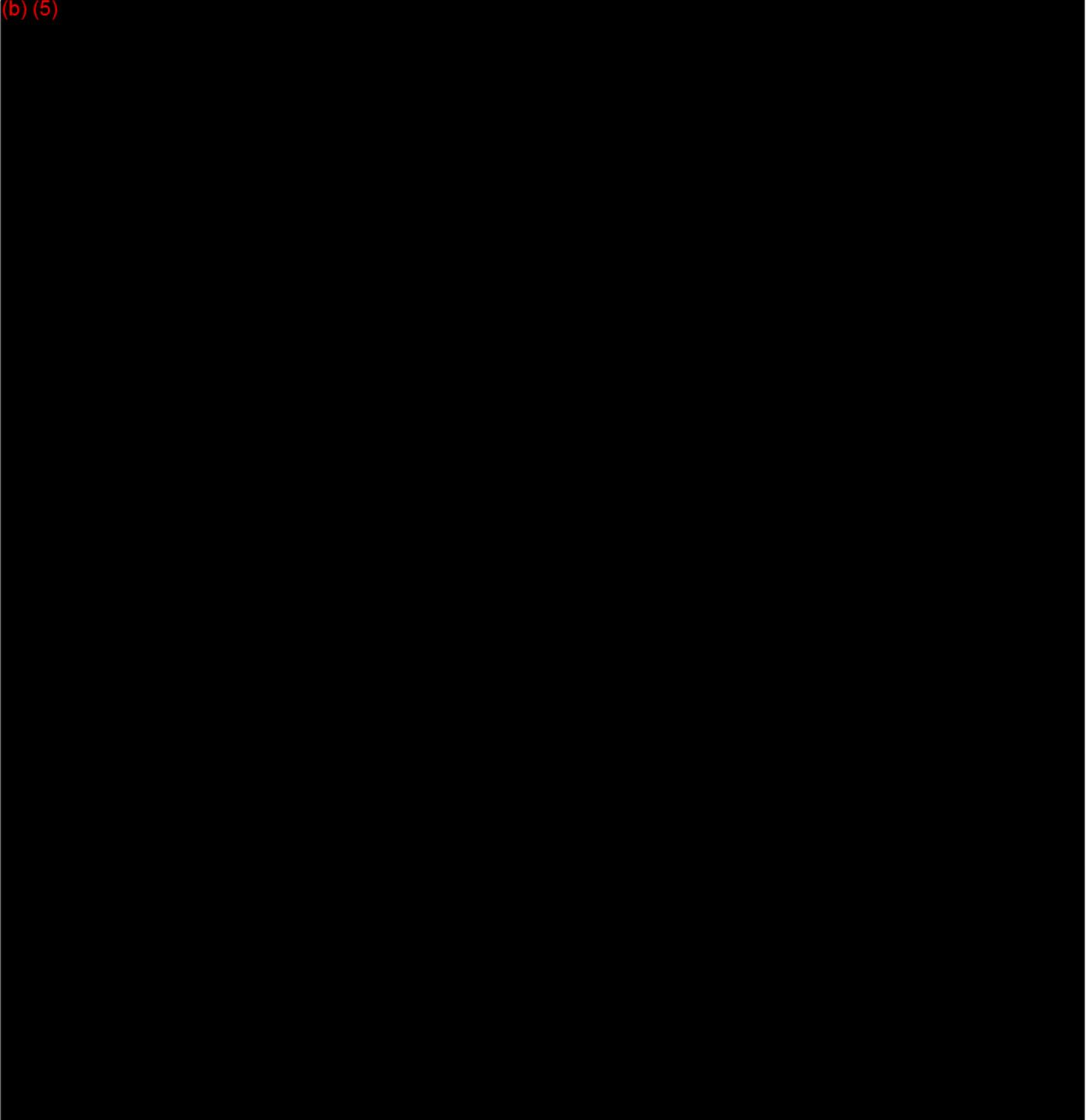
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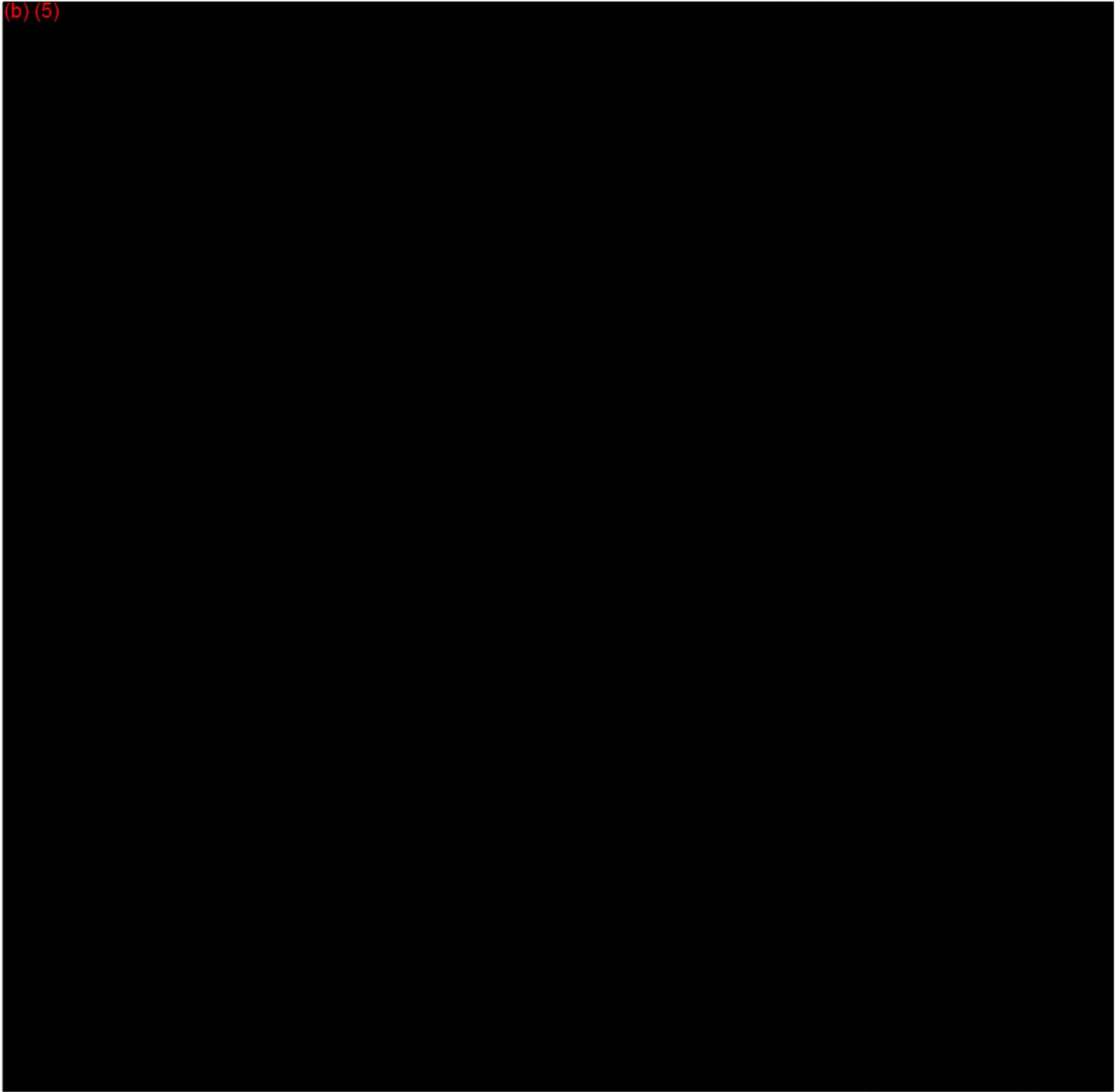
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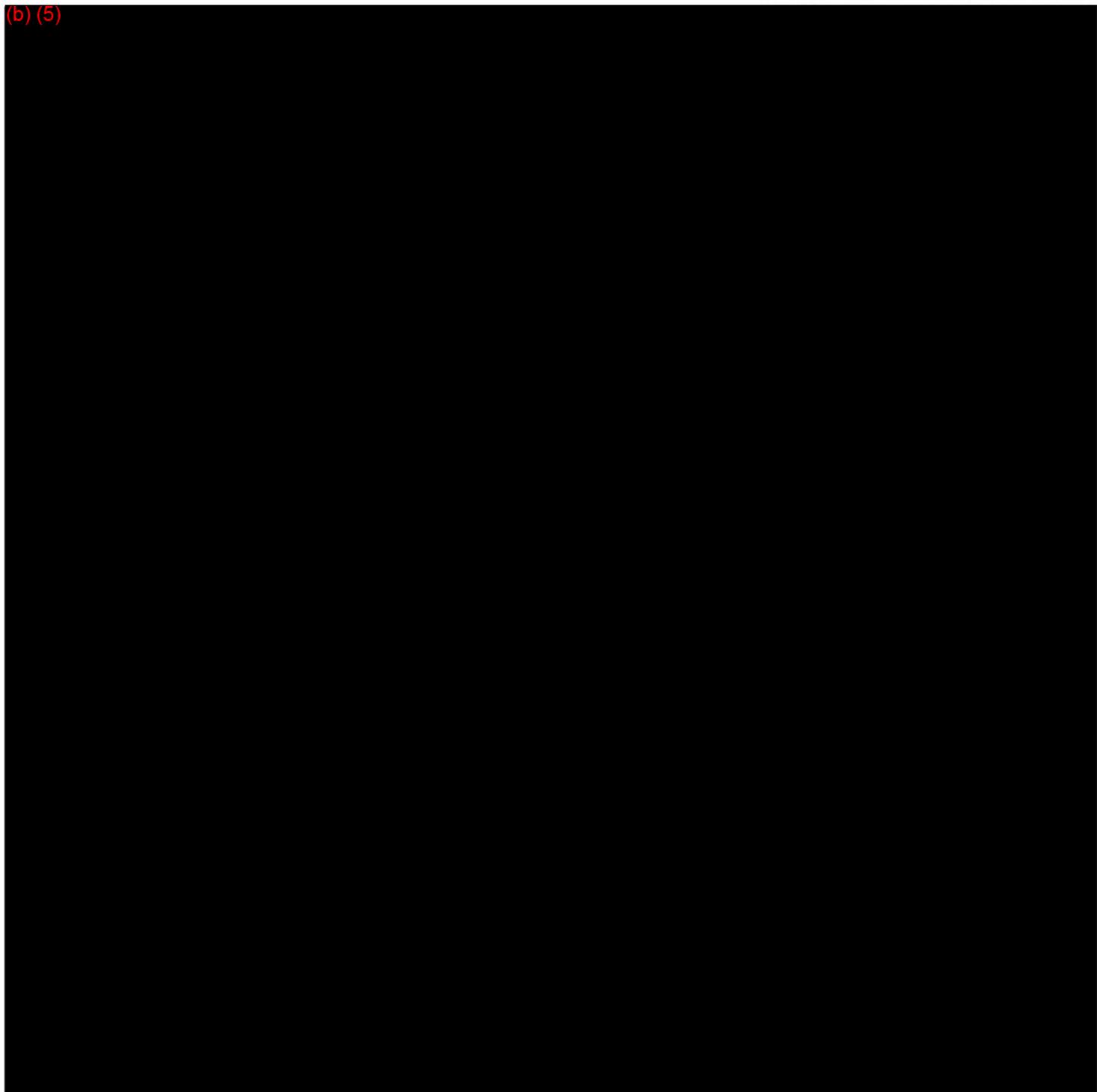
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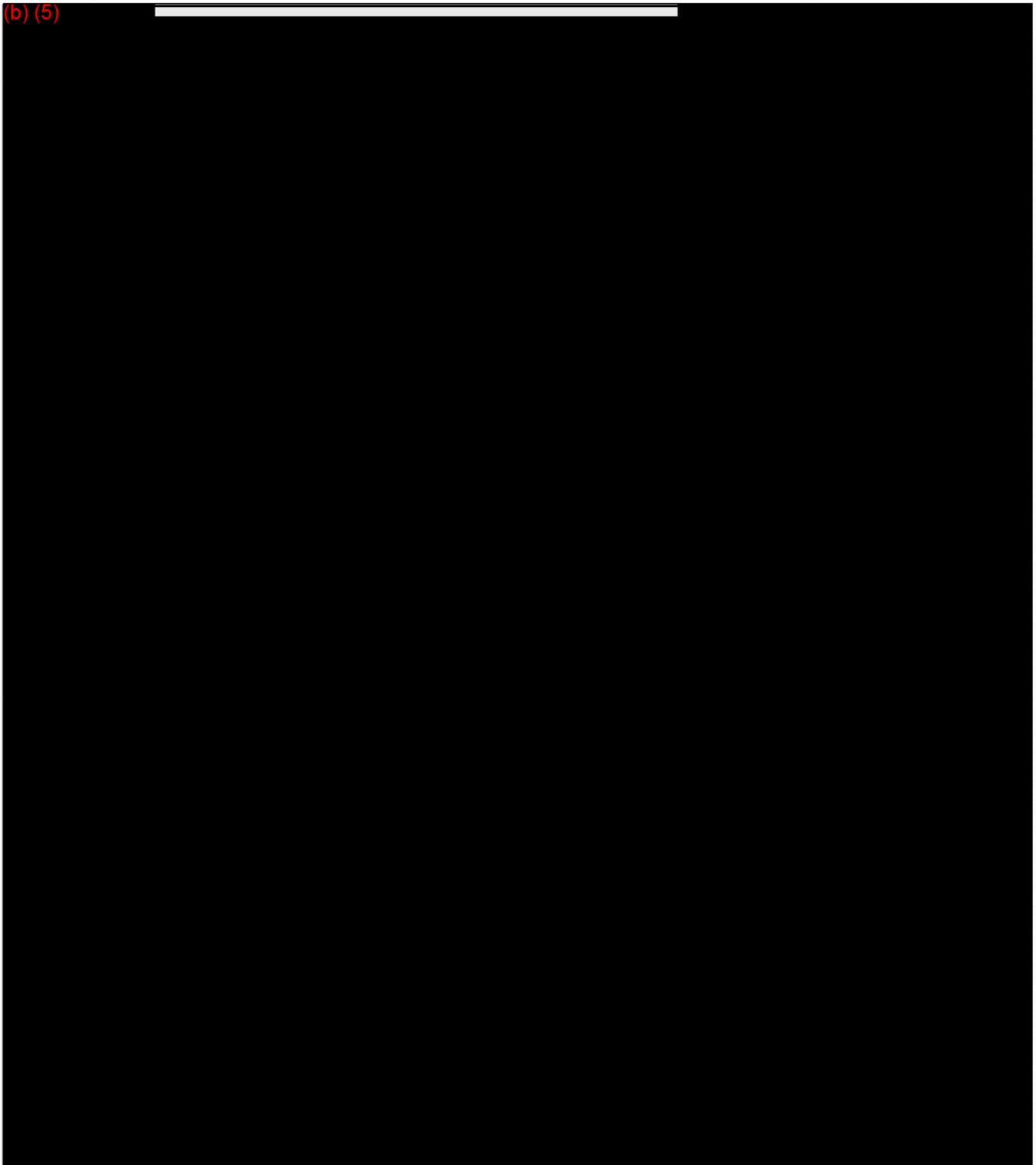
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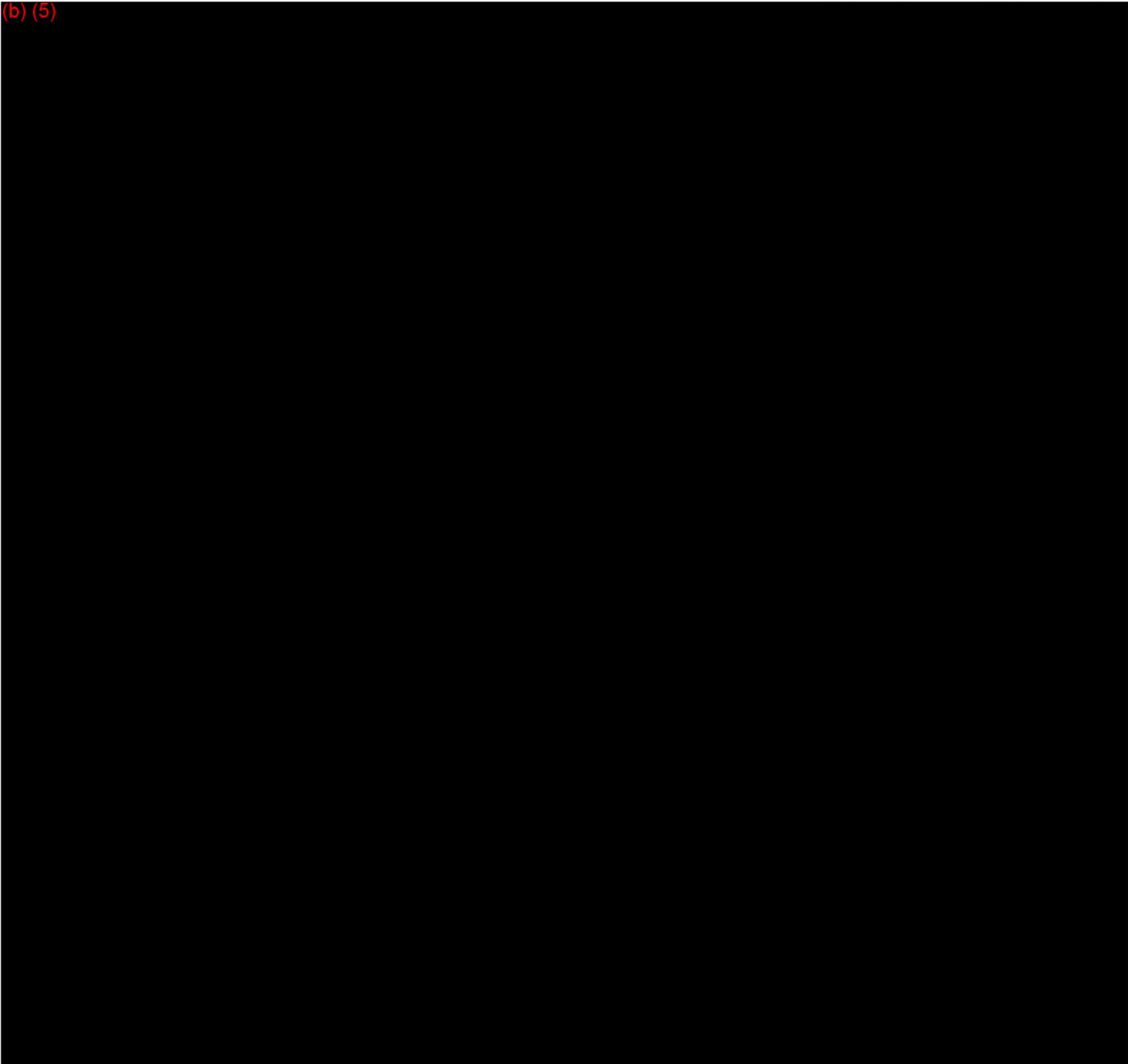
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From: [Califf, Robert](#)
To: [Sherman, Rachel](#)
Subject: confidential
Date: Wednesday, August 10, 2016 6:33:07 AM
Attachments: [20150809 Eteplirsen Appeal Unger 7-18-16.pdf](#)

Here is the first document. Let me know if you can talk at 715. Liz agreed that bringing you in in your OMPT role was appropriate, but need to avoid any further distribution.

rmc

Agency Scientific Dispute – Appeal

Date: July 18, 2016

To: **G. Matthew Warren**
Director
Office of Scientific Integrity, FDA

From: **Ellis F. Unger, M.D. (initiator)**
Director
Office of Drug Evaluation-I
Office of New Drugs
Center for Drug Research and Evaluation
U.S. Food and Drug Administration

Re: **NDA #** 206488
Drug: eteplirsen (Exondys 51)
Applicant: Sarepta Therapeutics
Indication: Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping

1. Background

The Office of New Drugs within the Center for Drug Evaluation and Research (CDER) oversees regulation of new drugs, and is responsible for making regulatory decisions for approval/non-approval of new molecular entities. Within the Office of New Drugs, there are 6 sub-offices, including the Office of Drug Evaluation-I. The Office of Drug Evaluation-I oversees the Division of Neurology Products, which regulates drugs for the central and peripheral nervous systems, as well as drugs for muscular disorders. Typically, a new drug application (NDA) for a new molecular entity for a neurology indication is reviewed by the Division of Neurology Products in concert with review staff from other offices in CDER.¹ The regulatory decision is typically rendered by Office of Drug Evaluation-I, i.e., the signatory authority.

NDA 206488 for eteplirsen was reviewed by the Division of Neurology Products, and members of the review team reached the unanimous conclusion that the NDA should receive a *complete response* action. This view was shared by the Office of Biometrics, which performed the statistical review, as well as the Office of Clinical Pharmacology, which performed the pharmacology review. Dr. John Jenkins, Director, Office of New Drugs, also supports a *complete response* action for this NDA (verbal communication).

This memo is meant to explain the salient arguments around the scientific disagreement here; additional details are available in my memo recommending a complete response and Dr. Woodcock's memo recommending approval, and the reader is referred to those memoranda.

Disease Background:

¹ Reviews are typically provided by Office of New Drug Quality Assessment, Division of Medication Error Prevention and Analysis, Office of Biometrics, Office of Scientific Investigations, and others.

Duchenne muscular dystrophy is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene. These mutations disrupt the messenger ribonucleic acid (mRNA) reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells. The disorder affects 1 in ~3,600 boys.

Dystrophin protein is thought to maintain the structural integrity of the muscle cell, cushioning it from the stress and strain of repeated contraction and relaxation. Absence of dystrophin leads to muscle damage, with replacement by fat and collagen. With progressive degeneration of skeletal muscle (including breathing muscles) and cardiac muscle, there is loss of physical function in childhood and adolescence, with premature death from respiratory and/or cardiac failure in the second to fourth decade.

No specific therapies are approved for DMD. Steroids are currently the cornerstone of management, widely believed to delay loss of ambulation and respiratory decline by several years.

Drug Background:

Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA. Theoretically, by restoring of the mRNA reading frame, a 'truncated' but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, delaying disease progression. Similar truncated dystrophin is found in a less severe form of muscular dystrophy, Becker Muscular Dystrophy (BMD). In essence, the drug is hoped to induce production of sufficient Becker-type dystrophin to slow the progression of the disease. This drug is specific for exon 51 mutations, a subset of the mutations that cause DMD. If approved, the drug would be indicated for ~13% of the overall DMD patient population. Eteplirsen has not received marketing authorization from any regulatory authority, and no similar drugs are approved.

Drug Development Background:

Three studies are germane to the issues here. Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202. Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from 13 patients in this study (see below).

The endpoints for these studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle – the surrogate endpoint. Dystrophin was quantified in this development program using two methods: Western blot and immunohistochemistry.

2. Description of How My Position Differs from the Center’s Perspective

Dr. Janet Woodcock, Director, CDER, disagrees with some of the findings of the review team, and has reached the conclusion that the NDA should be approved. She finds that the data meet the standard for accelerated approval under 21 CFR 314. 510, based on the change in a surrogate endpoint of dystrophin protein production – a change she concludes is reasonably likely to predict clinical benefit. The disagreement is over the question of whether the findings on the dystrophin surrogate endpoint are reasonably likely to predict clinical benefit. The decision of *approval vs. complete response* hinges on this question.

a. Clinical/Statistical Efficacy

Accelerated Approval:

Dr. Woodcock has reached the conclusion that eteplirsen should receive accelerated approval based on a small effect on the surrogate endpoint of dystrophin production.

The relevant statutory and regulatory framework (section 506(c) of the FD&C Act and 21 CFR part 314, subpart H) states that a drug can receive accelerated approval if 3 factors are satisfied:

1. If the drug treats a serious or life-threatening disease or condition,
2. if FDA takes into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments, and
3. if the drug demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit OR demonstrates an effect on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. As noted in section 506(c)(1)(B) of the FD&C Act, the evidence to support the concept “...that an endpoint is reasonably likely to predict clinical benefit may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.”

In terms of the prospect for accelerated approval for eteplirsen, DMD is clearly a serious, severe, and rare condition with no approved treatments; therefore, factors 1 and 2, above, are satisfied. There is no disagreement.

The critical issue is whether factor 3 is satisfied, and factor 3 can be subdivided into three parts: 1) whether the surrogate endpoint is appropriate for the disease; 2) whether there is substantial evidence of an effect on the surrogate endpoint; and 2) whether the effect demonstrated meets the test of being “reasonably likely” to predict clinical benefit. Importantly, there is no regulatory definition of “reasonably likely.”

For the first part of factor 3, whether the surrogate endpoint is appropriate for the disease, the review team has agreed that the near-lack of dystrophin is the proximal cause of DMD, and that the level of dystrophin in skeletal muscle is an appropriate surrogate endpoint that could predict efficacy. There is no disagreement here.

The second part of factor 3 is whether an effect has been demonstrated; the legal standard is ‘substantial evidence’ based on adequate and well-controlled clinical investigations. Typically, such evidence would be two studies, both achieving a p -value < 0.05, but in some situations FDA has the flexibility to interpret data from a single trial, or a single trial with supporting evidence, as substantial evidence of effectiveness.² Dr. Woodcock believes that “...there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells.” I agree that there is evidence from a single adequate and well controlled trial, Study 301, that eteplirsen induces dystrophin production in muscle cells, but do not agree that there is reliable quantitative evidence from the other trial, Study 201/202.

The third part of factor 3, the conclusion that the demonstrated effect is “reasonably likely” to predict clinical benefit, is where there is disagreement.

A. Are the Data on Dystrophin Protein Production from One or More Adequate and Well-Controlled Studies?

Dr. Woodcock cites 3 lines of evidence pertinent to the conclusion that eteplirsen increases dystrophin production:

1. Production of an appropriate mRNA transcript
2. Quantitative assessment of dystrophin content in muscle biopsies by Western blot
3. Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry

1. Production of an appropriate mRNA transcript

I agree that the applicant has shown expression of mRNA following treatment with eteplirsen. As noted by Dr. Woodcock, this finding establishes proof of concept, but does not by itself mean that there is increased dystrophin production.

2. Quantitative assessment of dystrophin content in muscle biopsies by Western blot

Western blot is a standard laboratory technique used to quantify proteins in body tissues. In Sarepta’s development program, Western blot was used to assess dystrophin protein levels in skeletal muscle in Study 201, in Study 202 (again, these were Study 201 patients who were maintained on treatment), and finally in Study 301.

a. Study 201:

The original Western blot analyses from Study 201 were intended to show that dystrophin levels were greater in eteplirsen-treated patients than in patients in the placebo group, and analyses were planned to compare the effects of the lower vs. higher eteplirsen doses on dystrophin production. The Western blots submitted by the applicant for Study 201 were oversaturated, unreliable, and uninterpretable.

b. Study 202:

² See: “Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products;” May, 1998.

With FDA's assistance, the applicant improved the assays and performed repeat biopsies on 11 of 12 patients of the Study 201/202 patients at Week 180. These were to be compared to stored baseline (pre-treatment) samples; however, evaluable tissue was available for only 3 of the 11 patients. The baseline samples are germane to the determination of the treatment effect because the Week 180 biopsies showed only a small quantity of dystrophin (mean = 0.93% of normal). Thus, for the purpose of computing the *change* in dystrophin resulting from eteplirsen treatment, even small differences in the baseline level are critical.

As noted by Dr. Woodcock, the review team and I had concerns about these controls, leading us to conclude that Study 201/202 was not adequate and well controlled:

1. The goal was to assess the change in dystrophin with treatment, i.e., pre-treatment vs. post-treatment, but most of the baseline biopsies were obtained from subjects external to Study 201/202, who could differ in unknown ways from subjects in Study 201/202.
2. For all patients, the Week 180 biopsies were obtained from different muscles than the baseline biopsies, and studies of both normal human muscle and non-clinical DMD models have shown that dystrophin levels vary among muscles.
3. The baseline biopsies for the three subjects with Week 180 data had been stored for several years and the protein may have degraded, leading to a falsely low baseline value, and a greater apparent increase from baseline, accordingly.

Dr. Woodcock believes that "...these issues increase the uncertainty around the results, but do not necessarily render them an inadequate basis on which to draw a conclusion." She notes that the external control patients were similar in age and mutation site to the patients in Study 201/202. She found little difference between dystrophin results across different muscle groups, and little difference based on storage time, leading her to believe that these factors "...did not result in large differences in the findings."

Although I agree that these factors are not likely to lead to large differences, even small differences would affect the calculation of the *change* in dystrophin at Week 180, because the Week 180 values were quite small (mean only 0.93% of normal). At issue is how much of the dystrophin detected at Week 180 was newly produced, vs present at baseline. For example, a difference in the baseline level of only 0.30%, although minute, is substantial compared to 0.93%.

Dr. Woodcock notes that at Week 180, 2 subjects had dystrophin levels between 2 and 3%, 2 had a level between 1 and 2%, and 2 had a level of ~1%. She notes that 2 of these subjects had both baseline and Week 180 samples, and there were clear increases in dystrophin in these 2 patients. Of note, Dr. Woodcock points out that although some subjects had Week 180 dystrophin levels similar to the baseline (i.e., close to zero), she would expect this because she would not predict that all individuals would to respond to a drug intervention.

She explains that the issue "...is whether the dystrophin levels found at 180 weeks were within the variability expected for this assay in such patients and, thus, could have arisen by chance, or whether they could have been caused by differences from the controls or from sample

storage as outlined above, or whether they reflected a drug effect, and, thus, whether these data could be seen as adequate and well-controlled.”

In the end, taking Dr. Woodcock’s arguments into consideration, my view is that the data from Study 202 are *suggestive* of an increase in dystrophin in response to eteplirsen, but the study was not adequate and well controlled. If we accept that there *is* a difference, Study 202 does not reliably speak to the *amount* of dystrophin produced by eteplirsen, given the concerns above. There is only certainty that the largest *possible* amount was 0.93% of normal (on average), and <3% in any individual (if we assume that the quantity was zero at baseline).

Below I will present another concern that leads me to question the veracity of the Western blot data from the Week 180 biopsies from Study 202, based on an issue that Dr. Woodcock did not address in her memo.

c) Study 301:

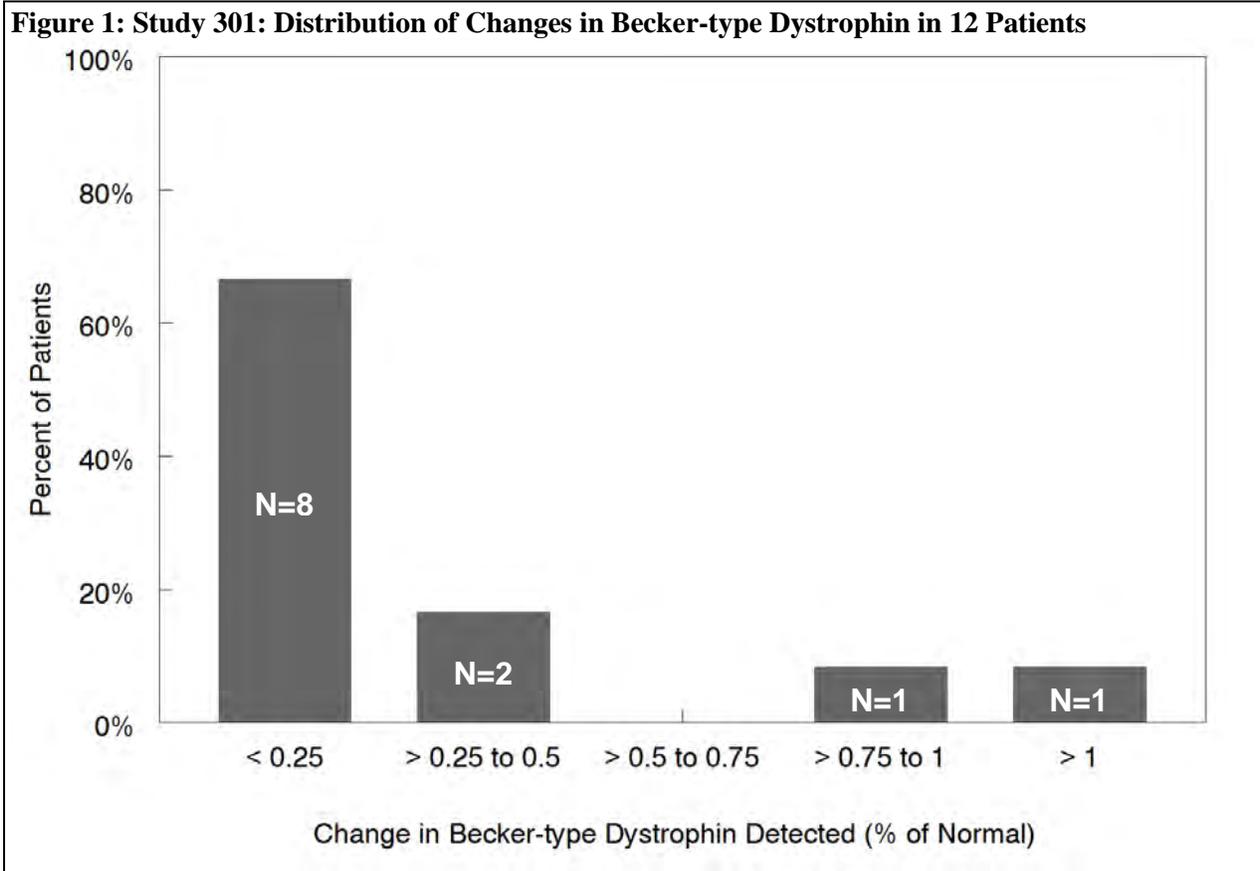
With the May 26, 2016 goal date approaching, OND and CDER could not reach agreement on the regulatory action for this NDA. In order to gain additional information that might provide evidence of an effect on a surrogate marker that was reasonably likely to predict clinical benefit, we requested that the applicant perform Western blot analyses of skeletal muscle biopsy samples that had been obtained in an ongoing study (Study 301, PROMOVI). These samples were originally planned to be analyzed at the end of the study; however, we requested an interim analyses of a subset of samples. Western blot analyses were performed on paired biceps samples from 13 of the patients. For each of these patients, samples obtained at baseline (prior to treatment) were compared to those obtained at Week 48, after 48 weekly infusions of eteplirsen 30 mg/kg.

The data are shown in Table 1 and the distribution of these changes is shown graphically in Figure 1. Of these 12 patients, 8 (two-thirds) had a change of 0.25% or less; only 1 patient (8%) had a change greater than 1%. The applicant used 3 methods to consider the numerous values below the limit of quantification, but irrespective of the method used, the mean treatment effect was similar, ranging from 0.22% to 0.32% of normal, a change of approximately 2 to 3 parts per thousand that was nevertheless statistically significant.

Patient	Time	status	value (%)	mean (%)	delta (%)	Patient	Time	status	value (%)	mean (%)	delta (%)
1	Baseline	pass	0.15	0.13	0.13	8	Baseline	fail	0.08	0.24	1.33
		pass	0.11					fail	0.14		
	Week 48	pass	0.22	0.26			Week 48	fail	0.08		
		pass	0.29					fail	0.05		
2	Baseline	pass	0.35	0.35	0.01	9	Baseline	fail	0.14	1.57	0.01
		fail	0.26					pass	0.24		
	Week 48	pass	0.36	0.36			Week 48	fail	1.17		
		fail	0.12					pass	1.57		
3	Baseline	pass	0.06	0.06	0.31	10	Baseline	pass	0.11	0.11	0.01
		pass	0.06					fail	0.05		
	Week 48	pass	0.5	0.37			Week 48	pass	0.12		
		pass	0.24					fail	0.11		
4	Baseline	pass	0.04	0.04	0.06	11	Baseline	pass	0.01	0.05	0.43
		fail	0.06					pass	0.08		
	Week 48	pass	0.1	0.1			Week 48	pass	0.31		
		fail	0.19					pass	0.63		
5	Baseline	fail	0.1	0.17	0.85	12	Baseline	pass	0.02	0.02	0.07
		pass	0.17					fail	0		
	Week 48	fail	0.92	1.02			Week 48	pass	0.09		
		pass	1.02					fail	0.01		
6	Baseline	pass	0.37	0.37	-0.07	13	Baseline	fail	0.34	0.18	0.03
		fail	0.46					pass	0.18		
	Week 48	pass	0.3	0.3			Week 48	fail	0.34		
		fail	0.29					pass	0.21		
7	Baseline	fail	0.04	0.17	0.25	13	Baseline	fail	0.34	0.18	0.03
		pass	0.17					pass	0.21		
	Week 48	fail	0.22	0.42			Week 48	fail	0.34		
		pass	0.42					pass	0.21		

All parties agree that these data were obtained from an adequate and well controlled study, and that there is a statistically significant effect of eteplirsen. The disagreement is whether or not the dystrophin production is at a meaningful level that is reasonably likely to predict clinical benefit.

To the extent that one can compare results across studies, these changes in dystrophin are even lower than the values obtained from Study 201/202 (the latter represent the quantity detected at Week 180, not the treatment effect). Dr. Woodcock wrote that “Only 2 of 12 patients achieved a level over 1% of normal control.” Her characterization refers to the amount of protein *detected* at Week 48, not the *change* in protein. In fact, only a single patient out of 12 had a *treatment effect* that exceeded 1%.



3. Semi-quantitative assessment of dystrophin in muscle tissue by immunohistochemistry

Study 201/202 – Data through Week 48

Dystrophin production was assessed in Study 201 using immunohistochemistry, a standard laboratory procedure used primarily to localize proteins in tissue sections, but also used as a semi-quantitative method to measure dystrophin levels. Muscle samples were analyzed at baseline, and at Weeks 12, 24, and 48.

Dr. Woodcock notes “A finding of increased dystrophin was also seen in several IHC assays performed by the applicant.” She explains that several baseline and other pre-Week 180 assays were performed (from Study 201/202), but the validity of the results was questioned at the FDA inspection because of methodological issues, and so she does not consider these data further.

I do not agree with Dr. Woodcock’s outright rejection of these data. In fact, FDA requested a re-reading of the stored images by 3 masked pathologists under improved viewing conditions. We did not request any changes in immunohistochemistry methods or techniques, other than a different approach for selecting microscopic fields for image capture and analysis. Thus, we stressed that their stored images could provide useful data if properly read. The re-read

showed a nominally statistically significant increase in dystrophin in response to eteplirsen for the low dose group, but not the high dose group. (The p -value is nominal because the type-I error rate was not controlled for multiplicity.) Moreover, for the 4 patients who had received placebo through Week 24 and then switched to eteplirsen, there was no increase in dystrophin at Week 48.

Study 201/202 – Week 180 Data

The applicant performed immunostaining along with Western blot analyses from the skeletal muscle biopsies obtained at Week 180.

Importantly, prior to performing these analyses, the applicant made changes to the immunohistochemistry protocol with the intent of decreasing non-specific staining. Dr. Woodcock details the technical factors in her memo. Their aim was to determine the treatment effect for each patient, by comparing dystrophin levels at baseline and Week 180. Frozen archived baseline tissue was available for only 3 of the patients, however, and so the applicant supplemented these samples with muscle tissue from 6 untreated external DMD patients, together to be compared to the Week 180 levels. Images were read by the same 3 pathologists, masked to treatment group.

Because external controls were used, the comparison of pre- vs. post-treatment values suffers from the same problems described for the Western blot analyses (i.e., different patients, different muscles, and possible loss of immunoreactive dystrophin with long-term storage).

These concerns notwithstanding, the applicant claimed a remarkable increase in dystrophin immunostaining at Week 180: the 9 baseline samples (from 3 patients in Study 201/202 and 6 external controls) showed $1.1\% \pm 1.3\%$ positive fibers (mean \pm SD), whereas the Week 180 samples (from 11 patients in Study 201/202) showed $17.4\% \pm 10.0\%$ positive fibers. I will note that FDA made no attempt to inspect or oversee these analyses.

Given that the original analysis showed, at baseline, 13% positive fibers for patients in Study 201/202, it is important to understand why the results from a new immunostaining protocol provided results of 1.1%, an order of magnitude lower.

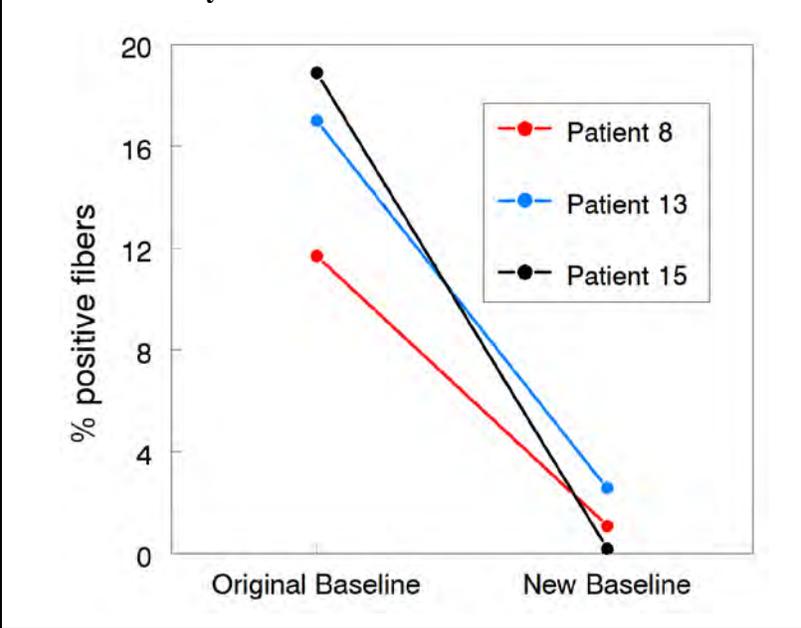
As noted above, there were 3 patients in Study 201/202 with adequate archived tissue from baseline, which permitted a new immunohistochemistry analysis and a comparison of results between the old and new methods. Figure 2 shows how the two methods compare.

These are essentially replicate analyses of a single tissue sample using the two immunohistochemistry methods. There is an inexplicable difference of more than an order of magnitude between results of the old and new immunohistochemistry protocols. Such marked differences raise concerns with respect to the validity of the applicant's methods, and make interpretation impossible.

The disparity also underscores the difficulty of comparing results of immunohistochemical analyses for dystrophin across laboratories, or, for that matter, within the same laboratory.

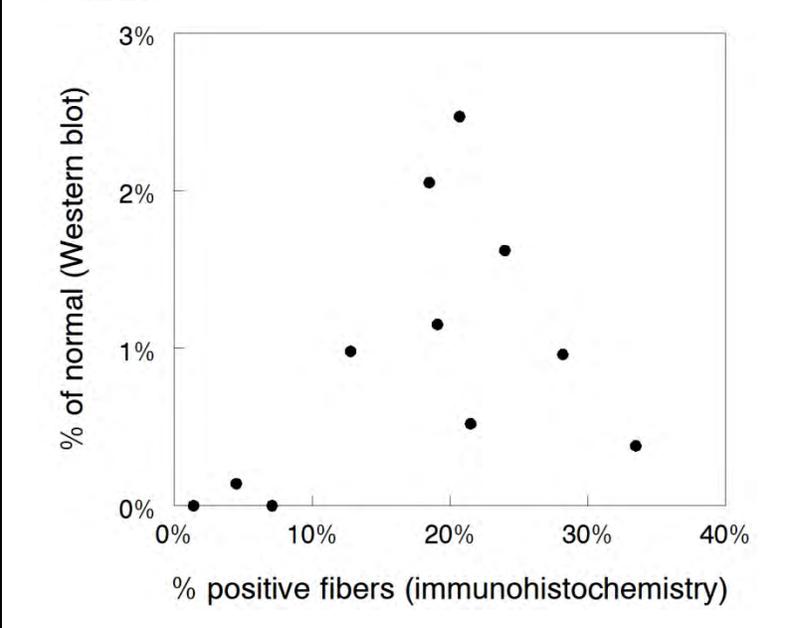
The integrity of the applicant's data is further called into question by lack of agreement between the immunohistochemistry and Western blot methods, i.e., a lack of internal consistency. The applicant claims to have enhanced both the immunohistochemistry methods and the Western blot methods in preparation for processing the Week 180 biopsies. Following these methodological improvements, single tissue blocks were subjected to both analyses – analyses considered to be complementary. Yet the lack of concordance between these two assessments of dystrophin levels is striking (Figure 3).

Figure 2: Comparison of Results from the New and Old Immunohistochemistry Protocols – Lack of Agreement for 3 Patients in Study 201/202



It is simply not possible to determine whether the immunohistochemistry methods are inaccurate, the Western blot methods are inaccurate, or both methods are inaccurate. In light of the discordance between methods, the issues with the control samples, and the order-of-magnitude discrepancy between the old and new immunohistochemistry protocols, these data provide little confidence that the study was designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation” (§314.126).

Figure 3: Study 201/202 Week 180 Dystrophin Assessment – Lack of Agreement between Immunohistochemistry and Western Blot



A critical point is that results of immunohistochemistry analyses are method-dependent, and results from different laboratories are not directly comparable. Here we see a striking difference between results of different methods within a single laboratory.

Dr. Woodcock concluded “Although the IHC assays provide only semi-quantitative assessments of dystrophin content, they do support an effect of eteplirsen on the proposed surrogate endpoint (an increase of dystrophin production as a result of drug exposure).”

Although this statement does not constitute an important part of her argument in favor of dystrophin production, I do not agree that the immunohistochemistry data show an increase in dystrophin as a result of drug exposure. Given that changes in the immunohistochemistry protocol led to remarkably disparate results, and in light of the lack of correlation between dystrophin results as determined by immunohistochemistry and Western blot, I question the accuracy and interpretability of the Week 180 immunohistochemistry data. Moreover, the results from the properly blinded re-reading of the original data through the first 48 weeks of Study 201/202 are negative. I do agree, however, that the immunohistochemistry images appear to show dystrophin in the proper location, which helps support proof-of-concept.

In summary, I agree that there are data on dystrophin production from one adequate and well controlled study, Study 301, by Western blot. The amount of dystrophin produced and the likelihood of a clinical effect are discussed below.

B. Is the Effect on the Surrogate Endpoint “Reasonably Likely to Predict Clinical Benefit?”

As noted by Dr. Woodcock, “The usual way to address this question would be to rigorously evaluate what is known about the correlation between dystrophin levels in muscle and expression of disease.”

Without restating the details of Dr. Woodcock’s discussion, I generally agree with her basic summary of the many challenges of interpretation (quoted below). Most of her discussion speaks to the *uncertainties* inherent in correlating dystrophin levels with disease severity. I strongly agree that we lack a sound basis upon which to relate dystrophin levels observed in this development program to observations in the literature.

“1. The clinical classification of disease severity (i.e., phenotype) in the literature appears broad, variable, and somewhat subjective.”

I agree. And importantly, as Dr. Woodcock notes, “the zone of real interest for this discussion, between DMD and intermediate presentations, is not rigorously categorized.”

“2. Much of the prior data reporting the relationship of dystrophin protein levels to phenotype have been from immunohistochemistry studies using a variety of techniques and antibodies.”

I will add that the applicant’s own data show a striking difference between results of two somewhat different immunohistochemistry protocols conducted at the same laboratory (Figure 2). Thus, it would be treacherous to try to relate various levels of dystrophin, determined by immunohistochemical methods at various laboratories, to a particular clinical course.

“3. Both IHC analyses and WB results are influenced by the anti-dystrophin antibodies used, as well as other experimental conditions”

Agree. Thus, is not feasible to relate levels of dystrophin determined by older Western blot methods, which lacked, for example, appropriate internal controls, to levels of dystrophin reported in these eteplirsen studies.

“4. The phenotype is significantly influenced by dystrophin isoform quality as well as dystrophin quantity.”

Agree. It is difficult to predict a protein’s function from its structure; even small changes in dystrophin structure can be important.

“5. The literature contains various findings on the relationship of dystrophin expression to clinical status, including the low levels of dystrophin protein of interest in this case.”

Agree. There is little consensus on the relationship between dystrophin expression and clinical course at the low levels observed in eteplirsen-treated patients.

I also agree with Dr. Woodcock on the following points, and I paraphrase here:

- Dystrophin levels >10% on Western blot are usually associated with a BMD phenotype. Within the BMD phenotype, the relation between disease severity and protein expression is not clear. Protein quality, rather than quantity, may play a key role in determining phenotype in BMD.
- Patients with DMD are usually found to have undetectable levels of dystrophin, or very low levels. Dr. Woodcock notes that she believes the conventional threshold of <10% protein resulting in DMD was based on immunohistochemistry data. She tries to make a conversion between values observed from immunohistochemistry (~10% points higher on immunohistochemistry than Western blot in DMD) and those observed from Western blot, but I caution that immunohistochemistry results, in particular, are highly method-dependent, as noted above.
- Rarely, dystrophin levels in the 3 to 10% range have been associated with Becker Muscular Dystrophy phenotypes. Dr. Woodcock found no evidence of a threshold value for protein content and expression of a DMD phenotype.

Despite the absence of reliable data, Dr. Woodcock concluded that evidence from Western blot and other experiments shows that protein in the range between undetectable and 10% of normal is likely to be very important for clinical presentation, all other things being equal, i.e., mutation status and non-dystrophin-related factors affecting phenotype.

Because of the lack of reliable evidence, I do not agree that the small increase in dystrophin shown in Study 301 is ‘reasonably likely’ to predict clinical benefit. This is the central issue in this appeal.

The “reasonably likely” question hinges on whether the protein is functional, and whether the quantity is adequate.

These two uncertainties, protein function and protein quantity, are separate issues that must be considered in series. The function of the Becker-type dystrophin detected in Study 301 cannot be assessed. Nevertheless, the review team has been willing to assume that whatever Becker-type dystrophin is produced would function as well as it does in the Becker form of the disease. Although there can be no certainty on this point, the question of function seems small relative to the uncertainty regarding the adequacy of the quantity of protein, and so function is less germane to the question of “reasonably likely.” In short, it is the quantity of Becker-type dystrophin produced that is central to the question of ‘reasonably likely,’ and central to the approvability of this NDA under accelerated approval.

At the outset, it must be stated that the minimum quantity of Becker-type dystrophin that is reasonably likely to predict clinical benefit in patients with DMD is unknown.

There are two ways to consider the quantity of dystrophin produced: as a binary responder analysis and as a mean response. The former has the advantage of considering the possibility that some patients may respond to the treatment whereas others do not; the latter does not allow for this type of consideration.

The problem with a responder analysis is that there are no data upon which to define a threshold for a ‘response.’ Various cut-points could be selected, but their selection would be arbitrary, and the particular threshold chosen would have a major influence on the effect size.

Here I provide 3 lines of reasoning to support my view that there is not an adequate basis to believe that the small increase in dystrophin shown in Study 301 is reasonably likely to predict clinical benefit: 1) the treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications; 2) the effect size is inadequate on its face; and 3) no evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.

- 1) *The treatment effect observed cannot be compared or related to levels of dystrophin measured by other laboratories and reported in various publications.*

In order to place these small quantities of Becker-type dystrophin into a clinical perspective, many have considered publications from laboratories that attempt to relate particular levels of Becker-type dystrophin protein to clinical course, e.g., maintenance of physical function, age at loss of ambulation. Ideally, as suggested by Dr. Woodcock, there would be reliable data showing that Becker-type dystrophin levels in excess of a particular level are associated with a more benign clinical course.

Realistically however, the use of such a framework would be contingent on the ability to make interpretable cross-laboratory comparisons of dystrophin levels, which would require standardized methods to measure dystrophin levels in muscle specimens. Unfortunately, the methods have differed greatly, and the methods in the literature have lacked critical internal controls such as dilution-series. As stressed above, comparison of dystrophin values across laboratories seems unreliable.

With respect to immunohistochemistry analyses, Figure 2 provides ample basis for concern regarding comparability of results using different methods. Results of separate immunohistochemical analyses of skeletal muscle dystrophin, conducted by the same laboratory on single blocks of tissue, differ by more than an order of magnitude. These results underscore the inherent methodological variability of immunohistochemistry assays, and the futility of attempting to compare dystrophin levels across assays/laboratories.

Even with respect to more recent Western blot methods, reproducibility across laboratories is low. As discussed by Dr. Woodcock, Anthony K *et al* (*Neurology* 2014;83;2062) compared results of Western blot analyses from 6 patients (3 with DMD; 3 with Becker Muscular Dystrophy) across 5 experienced laboratories, and found a high degree of variability. Only one of the 5 laboratories had a coefficient of variation (CV = SD/mean X 100) below 0.3%. The authors found that variability was particularly pronounced with low levels of dystrophin – precisely the area of interest here.

During the applicants' presentation at the April 25, 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, Dr. Kaye, a pediatric neurologist and interim Chief Executive Officer of Sarepta, could not have been more clear in warning us not to make comparisons between their Western blot results and reported data in the literature:

“Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation. Furthermore, samples were randomized, blinded and run in duplicate on separate gels. In contrast, the Western blot methods in the majority of historical publications referenced by FDA were performed using older methodology that is semi-quantitative at best. Given these significant methodological differences, it is inappropriate to compare our data to literature approximations.” (Source: Official transcript of the meeting; underlining for emphasis.)

In summary, the field has not achieved adequate standardization of methods for dystrophin quantification at the very low levels observed in eteplirsen-treated patients; therefore, it is not valid to compare an increase in Becker-type dystrophin of, at best, 2 to 3%, with dystrophin values cited in the literature for other mutations/patient populations, assessed at other laboratories. *If the applicant's results cannot be compared to results in historical publications, then there is simply no way to determine whether the low dystrophin levels in eteplirsen-treated patients are reasonably likely to predict clinical benefit.*

2) *The effect size is inadequate on its face.*

If one were to assume that it is possible to make cross-laboratory comparisons of dystrophin levels, the *largest* change reliably demonstrated in Study 301, 1.3%, is an order of magnitude less than the minimum dystrophin levels cited to be important in affecting the course of patients with Becker muscular dystrophy (at least 10%).

Some of the better data come from Van den Bergen *et al*, who studied the relation between dystrophin levels (quantified by Western blot) and clinical severity in 33 patients with Becker Muscular Dystrophy (*J Neurol Neurosurg Psychiatry* 2014; 85:747). Although the authors did not find a linear relationship between dystrophin levels and disease severity, all 4 of their

patients with dystrophin levels <10% showed poor muscle strength and early symptom onset. As discussed by the review team, DMD experts have proposed that “induction of approximately 10% of normal dystrophin levels sets a minimum level to confer measurable clinical benefit.”

Initially, the applicant reported results from immunohistochemistry analyses purportedly demonstrating that eteplirsen caused 50 to 60% positive staining of muscle fibers for dystrophin. This seemingly unprecedented achievement aroused much excitement in the field of DMD research and in the DMD patient community. Upon proper re-analysis, however, the numbers were far lower, and rigorous statistical analyses showed that the changes weren't statistically significant. The Western blot analysis from Study 201/202 showed a mean dystrophin level of only 0.93% (range 0 to 2.5%), but these values are of questionable reliability. Finally, an adequate and well controlled study (Study 301) showed a mean change of 3-tenths of a percent (range 0 to 1.3%). Given that dystrophin is a structural protein, it seems highly unlikely that such changes would translate to a clinical effect.

Here are Dr. Woodcock's assertions on this topic:

“The broad phenotypic distinctions made in the clinic (e.g., DMD vs IMD vs BMD) are different from the prediction of benefit to an individual patient who has a specific baseline dystrophin level and whose mutation and external factors do not change pre- and post-drug. For example, extending ambulation by six months to a year would not normally move a patient from one to another of these categories, but could be very important to quality of life (e.g., as suggested in the Bello study). This is also true for other functional improvements.

For these reasons, incorporating the analysis of dystrophin content discussed above, I conclude that the biochemical data strongly support the idea that low-level increases in dystrophin production are reasonably likely to predict clinical benefit.”

I agree that broad phenotypic distinctions made in the clinic (e.g., Duchenne vs. Intermediate vs Becker Muscular Dystrophy) are different than trying to predict benefit to an individual patient on the basis of a particular change in dystrophin. And I agree that extending ambulation by 6 months to a year (or similar improvements in other functional areas) would be extraordinarily important.

But Dr. Woodcock never provides a rational argument – based on reliable data – to support the concept that “...low-level increases in dystrophin production are reasonably likely to predict clinical benefit.” She provides no rationale – no link between a mean increase in dystrophin of 3 parts per thousand and clinical benefit.

3) *No evidence of a clinical effect was demonstrated in the eteplirsen development program, and there is no correlation between dystrophin levels as determined by Western blot and clinical outcome.*

Dr. Woodcock states:

“Additional support for “reasonably likely” comes from the long-term experience with the drug. The sponsor's comparison of the experience of the treated cohort to natural history data does not reach the level of substantiation required for traditional approval

based on the clinical data. However, it is highly suggestive of improvement in some parameters, in some patients, over natural history. My conclusion is informed by all the caveats expressed in the reviews about the pitfalls of nonrandomized comparisons. Given that the two exon 52 deletion patients in the study had fairly good long-term results in terms of rate of disease progression, the question arises as to whether exon 52 is a prognostic factor that could have skewed the results.”

The review team analyzed the clinical data in great detail, and could not reach the conclusion that there was any reliable evidence of improvement relative to the expected natural history of the disease. Study 201 did not show a treatment effect on its 1° clinical endpoint, change in 6-minute walk distance at Week 24. Study 202 failed on the same endpoint at 48 weeks. The course of these Study 201/202 patients, having received eteplirsen for some 3.5 years, was not distinguishable from external control patients (see my review memorandum for more details).

The Advisory Committee voted (7 to 3 with 3 abstentions) that the clinical results of Study 201/202 did not provide substantial evidence that eteplirsen is effective for the treatment of DMD, and their vote was in the face of extraordinary pressure from patients and patient advocates to vote for approval. Two of the 3 “yes” votes were from patient representatives.

Correlation between dystrophin production and clinical effect

A correlation between dystrophin production (or with less certainty – dystrophin *detected*) and clinical function could provide some support for a conclusion that dystrophin production is reasonably likely to predict clinical benefit.

The applicant collected data on both dystrophin production and physical performance in Study 201/202. On the basis of the data presented in the NDA, the Division concluded that no patient in Study 201/202 clearly deviated from the natural history of the disease. The Division reasoned, therefore, that whatever the quantity of Becker-type dystrophin detected, it did not predict clinical benefit. Thus the Division opined that the clinical data weaken, and do not strengthen, the “reasonably likely” argument.

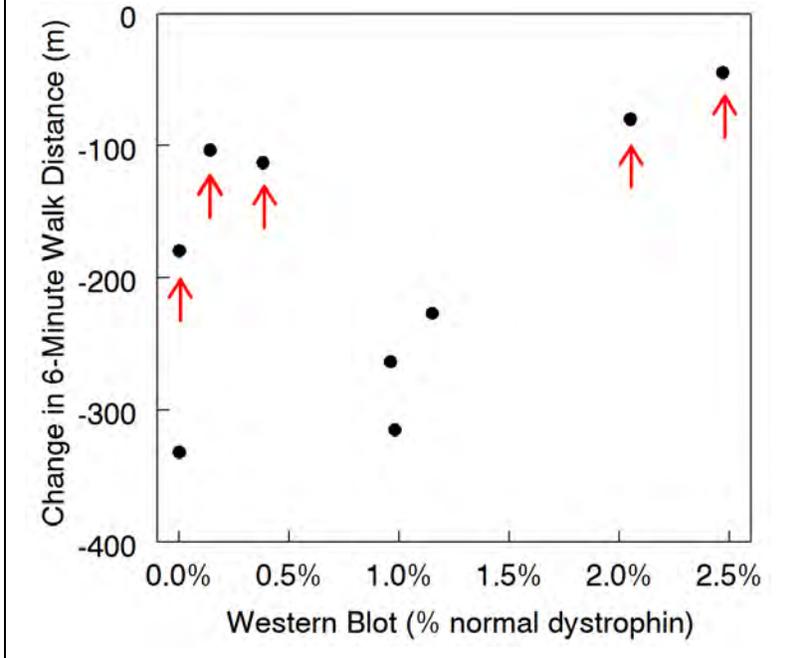
The Division's view notwithstanding, it is worth considering patients on an individual basis to assess the correlation between the quantity of Becker-type dystrophin detected and changes in physical performance.

As noted by Dr. Woodcock, the 6-minute walk test results do not show a strong correlation (Figure 4). For the 9 patients in Study 201/202 who remained ambulatory at Week 180 and agreed to undergo a fourth muscle biopsy, the figure shows little correlation between the quantity of dystrophin detected (x-axis) and preservation of physical function as assessed by the change in 6-minute walk distance from baseline (y-axis) after weekly infusions of eteplirsen for 3 to 3.5 years.

For the 5 patients whose 6-minute walk performance was best preserved (red arrows), 2 had the highest dystrophin levels detected in the study (upper right), but 3 had levels that were near-zero (upper left).

Dr. Woodcock also evaluated the North Star Ambulatory Assessment (NSAA) as a function of dystrophin detected in boys who could still walk and who had a dystrophin result at Week 180. She obtained the data from the applicant's briefing document for the Advisory Committee meeting, and found a correlation between dystrophin detected at Week 180 by Western blot and rate of decline in NSAA score through 180 weeks. Her graph is reproduced below:

Figure 4: Study 201/202 – Lack of Correlation between Quantity of Dystrophin Detected and Preservation of Physical Function (6-Minute Walk Distance)



With respect to the correlation, Dr. Woodcock explained: “This adds additional support to the idea that dystrophin production is “reasonably likely to predict clinical benefit.”

Given that the correlation was driven by the patient depicted at the lower right (blue arrow; dystrophin level =

~2.5%; change in NSAA = 3), I considered the NSAA data from that patient (Figure 6). I found that his course was less benign than would be inferred from a change in NSAA of only 3 units. Specifically, using linear regression (red line in Figure 6), his NSAA score has, instead, worsened by a mean of 2.7 units per year.

I reasoned that inclusion of all of the NSAA data for each patient would provide a more reliable representation of their course than calculating the change between single pre-treatment and post-treatment data points, because of the test-to-test variability (e.g., short-term swings of 4 to 5 points for patient 006). Thus, using linear regression, I calculated the slope of the relationship between NSAA and time for each patient (as per the red line in Figure 6) and plotted the slopes as a function of the dystrophin detected at Week 180. (Slopes were calculated as loss of NSAA units per year.)

Using this method, there was no correlation ($R^2 = 0.36$), Figure 7. Importantly, the slight trend apparent here is driven by one or two data points.

Figure 5: Study 201/202: Analysis of Change in NSAA vs. Expression of Becker-type Dystrophin by Western Blot (Analysis by Dr. Woodcock)

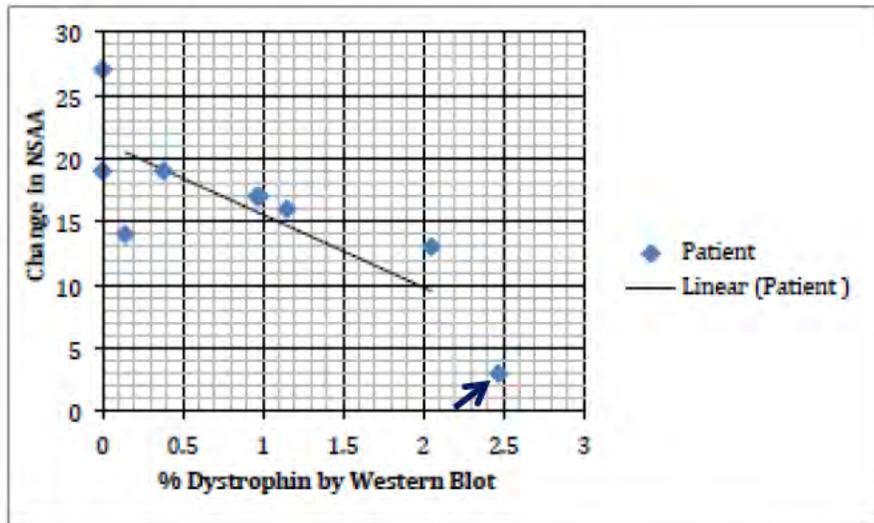
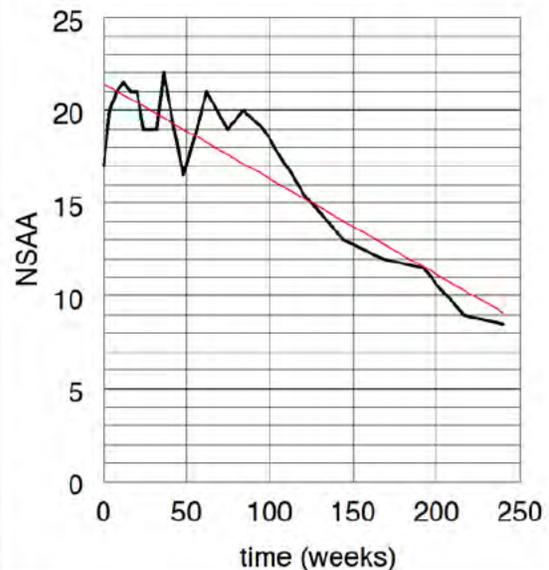


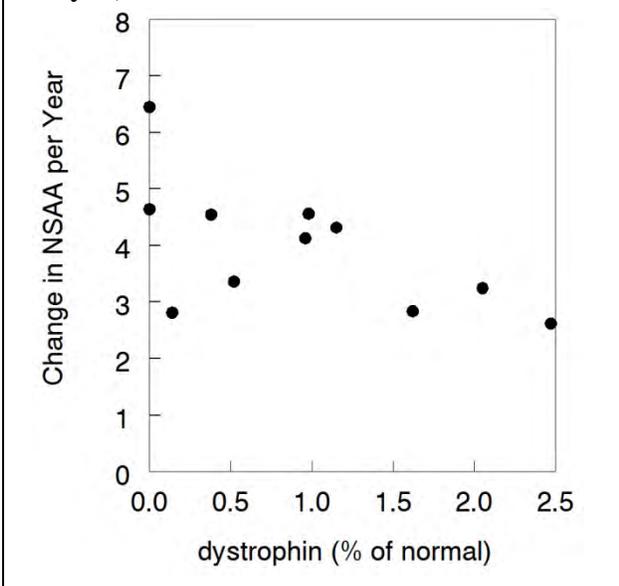
Figure 6: Patient 006: NSAA vs Time



Summary:

In summary, I find no evidence that the increase in dystrophin demonstrated in Study 301 is reasonably likely to predict clinical benefit (mean 0.3%, range 0 to 1.3%). The levels of dystrophin linked to various Becker Muscular Dystrophy phenotypes in publications are largely not comparable to dystrophin levels measured in this development program. The applicant's interim CEO correctly urged us not to compare data from their Western blot analyses to historical approximations from the literature. And extremely low levels of dystrophin, as found here, seem particularly difficult to quantify and compare across laboratories. Nevertheless, to the degree that findings can be compared across studies, dystrophin levels of 10% or more would need to be achieved to impact the clinical course. The finding in Study 301 is an order of magnitude below this level.

Figure 7: Study 201/202: Analysis of Change in NSAA (Linear Regression) vs. Expression of Becker-type Dystrophin by Western Blot (My Analysis)



Based on protein levels in other deficiency diseases, the effect size here appears to be too small to provide benefit. If dystrophin were an enzyme that catalyzed a biochemical reaction in myocytes, one might posit that a very small quantity could produce a substantial proportion of the minimum necessary reaction product, and that the increase over baseline might be important because levels are so low in untreated patients. But given that dystrophin is a structural support protein that helps prevent myocyte injury due to stress and strain, I find it difficult to conceive how a treatment effect of 3 parts per thousand could confer clinical benefit. If there were 10 inches of snow on a sidewalk that needed to be cleared, 3 parts per thousand would amount to 1/32nd of an inch. We must also recognize that a treatment that increases dystrophin by 0.3% would seemingly have far less impact than being born with 0.3% more dystrophin, and even *that* seems unlikely to matter.

I can find no precedent of an accelerated approval for a marketing application where the effect size on the surrogate endpoint is as small as 0.3%.

Dr. Woodcock concludes:

“...my conclusion to rely on the surrogate endpoint described above represents the greatest flexibility possible for FDA while remaining within its statutory framework. In this case, the flexibility is warranted because of several specific factors, including: the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a fatal disease in children. Of note, the therapy has been relatively safe in the clinic, although intravenous administration always carries risk....Therefore, I find that the

probable benefits outweigh the foreseeable risks and that this application should be approved under 21 CFR 314.510.”

As noted in 506(f)(1), the amendments made by the Food and Drug Administration Safety and Innovation Act (FDASIA) “...are intended to encourage the Secretary to utilize innovative and flexible approaches to the assessment of products under accelerated approval for treatments for patients with serious or life-threatening diseases or conditions and unmet medical needs.”

Some have interpreted this “flexibility” as a lower standard for demonstration of effectiveness, but this is not true.

Section 506(f)(2) of the FD&C Act specifically notes that drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval, notably the substantial evidence standard of section 505(d) with respect to the drug’s claimed effect on a surrogate or intermediate endpoint. These facts have not been altered by FDASIA.

To be clear, 506(f)(2) states: “Nothing in this section shall be construed to alter the standards of evidence under subsection (c) or (d) of section 505 (including the substantial evidence standard in section 505(d)) of this Act or under section 351(a) of the Public Health Service Act. Such sections and standards of evidence apply to the review and approval of products under this section, including whether a product is safe and effective. Nothing in this section alters the ability of the Secretary to rely on evidence that does not come from adequate and well controlled investigations for the purpose of determining whether an endpoint is reasonably likely to predict clinical benefit as described in subsection (b)(1)(B).”

I believe the burden is on Dr. Woodcock to show or explain why production of a near-zero quantity of dystrophin (0.3%) is reasonably likely to predict clinical benefit, and I do not believe her July 14, 2016 memo makes this case. I believe that the available evidence leaves open the possibility that some patients *could* benefit from a small increase in dystrophin, but this possibility does not reach the threshold of being reasonably likely to predict a clinical benefit.

Finally, there was no clinical benefit demonstrated in the development program, and the correlation between dystrophin and clinical effect was poor – not surprising given that the applicant provided analyzable data from only 11 patients.

3. Assessment of Possible Impact to Public Health Should My Position Not be Adopted

The approval of this NDA in its present form would have far reaching negative consequences for the public health.

1. Eteplirsen’s risks are certain, whereas its efficacy is not. Having considered Dr. Woodcock’s line of reasoning and her desire to approve eteplirsen, the position of the review team in the Division of Neurology Products, the Office of Biometrics, the Office of Clinical Pharmacology, the Office of Drug Evaluation-I, and the Office of New Drugs (verbal acknowledgement from Dr. John Jenkins) is that the applicant has not provided evidence that this drug is effective at the dose studied.

Dr. Woodcock notes that "...the therapy has been relatively safe in the clinic."

The reality is that only a few dozen patients have been exposed to the drug, such that the safety profile is not well characterized. A closely related drug being studied under a (b) (4) [REDACTED] With additional experience, important toxicity may emerge for eteplirsen. It is known that many patients in these studies are now receiving infusions through indwelling catheters. Maintenance of vascular access in patients on chronic corticosteroids poses a certain risk of infections. Although we are not yet aware of any infection-related adverse reactions, there would definitely be serious infections and possibly deaths if this drug is marketed, yet evidence of efficacy is lacking.

2. By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk. I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs – if not to patients, to society.

The prospect of providing false hope to desperate patients from a promising but ineffective therapy recalls the experience with *transmyocardial laser revascularization* (TMLR). In the 1990s, patients with coronary atherosclerosis and severe angina who were poor candidates for conventional revascularization procedures ("no-option" patients) underwent a thoracotomy (opening of the chest cavity) to enable use of a laser to create channels through the heart muscle. Ostensibly, these channels provided conduits for blood to flow from inside the left ventricle to the myocardium. Conduct of sham-controlled studies was impossible; studies were essentially baseline-controlled or historically-controlled. Large treatment effects were reported by a number of investigators, generally from small studies. There were marked increases in treadmill exercise time and relief of angina, with effects sustained for more than a year in some cases. Although many in the cardiology community raised concerns about expectation bias and were highly skeptical of the results, to some the effects seemed larger and more durable than could possibly be explained by expectation bias, i.e., a placebo effect. Thousands of patients underwent this invasive procedure with the hope of angina relief. Some years later, with improvements in technology, the conduct of sham-controlled studies became feasible, and TMLR was not found to be effective. The false hope was ultimately dispelled with the publication of two Cochrane Reviews.³ These reviews found the appearance of a marked treatment effect, but 30-day mortality was 6.8% in the TMLR group vs. 0.8% in the no-treatment group. They noted "The assessment of subjective outcomes, such as improvement in angina, was affected by a high risk of bias and this may explain the differences found." In this case, the cost of false hope was ~6% mortality in the first 30 days post-op.

I will also note that the primary endpoint of these laser studies was generally exercise capacity – the same type of endpoint used in the eteplirsen DMD development program, also for "no option" patients.

3. The accelerated approval pathway is designed to expedite the availability of promising new therapies to patients with serious conditions, especially when there are no satisfactory

³ Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD003712. DOI: 10.1002/14651858.CD003712.pub3

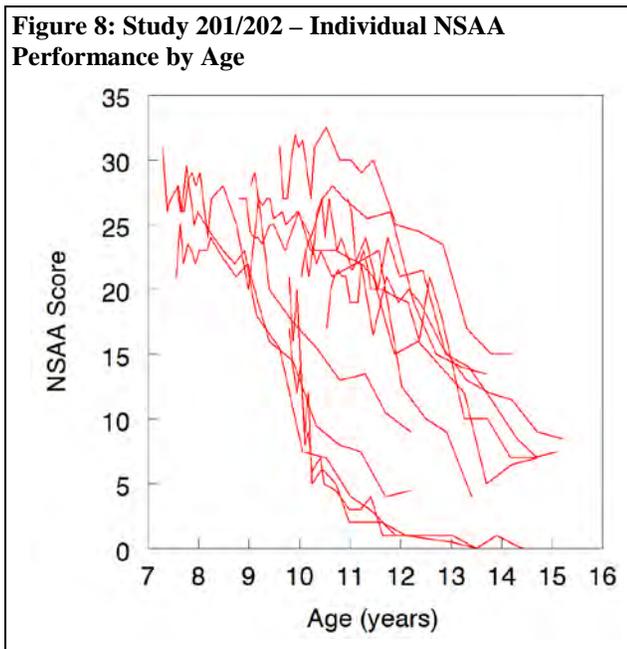
alternative therapies, while preserving standards for safety and effectiveness. For drugs granted accelerated approval, postmarketing confirmatory trials are required to verify and describe the anticipated clinical benefit, and FDA may withdraw approval of a drug if a trial required for verification of the predicted clinical benefit fails.

In reality, it is difficult to withdrawal a drug that is deemed to be effective, or possibly effective, by patients with severe diseases and limited treatment options. FDA has not succeeded in withdrawing the marketing of a single drug for lack of verification of clinical benefit following accelerated approval. The reality is that if eteplirsen is given accelerated approval, it is highly likely to remain on the market indefinitely, irrespective of whether or not efficacy is verified.

4. With the false perception that eteplirsen is effective, patients who are gaining benefit from steroids but experiencing untoward side effects might be inclined to taper or stop them, which could lead to more rapid disease progression.
5. False scientific conclusions have the potential to mislead the field of medicine, slowing progress in finding and developing therapies that actually *are* effective. For example, consider the scenario of a related drug with far greater potential to promote dystrophin production in patients with DMD. In order for a sponsor to study such a drug, patients would likely have to agree to discontinue eteplirsen, and few patients may be willing to do so. In short, approval of an ineffective therapy has the potential to discourage or inhibit the development of other drugs that *are* effective, and this impact can be significant.
6. Accelerated approval would lower the evidentiary standard for effectiveness to an unprecedented nadir. The amount of dystrophin produced in Study 301 is so meager that it could be considered to be tantamount to any increase in dystrophin. In other words, if a statistically significant change of 0.3% – a mere 3 parts out of a thousand – is considered adequate to support accelerated approval here, then the question arises as to whether there would be any statistically significant change that would be too small to be considered “reasonably likely” to support accelerated approval. Similarly, if a ‘responder’ had been defined as a patient with an increase in dystrophin of $\geq 1\%$ (and there is no basis to accept such a low threshold), there would have been only a single responder in Study 301. If we were to adopt the concept that, for rare diseases, accelerated approval could be supported by any statistically significant change in an appropriate surrogate, or a response in a single patient, we would enable accelerated approval of a myriad of drugs for rare diseases. No doubt there are some who would applaud this as an advance. But a standard this low would undercut FDA’s ability to ensure that drugs that are approved are effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.
7. With accelerated approval of this NDA, there would be highly detrimental effects on drug development. Traditional drug development for rare diseases might be replaced by a system where small, baseline-controlled, proof-of-concept studies designed to show any change in a surrogate marker would provide a basis for accelerated approval, assuming that the pathogenesis of the disease was well understood and that the surrogate was directly on the causal path. There would be little reason to pursue adequately controlled clinical trials to support efficacy prior to accelerated approval; in fact, the possibility of

failure would provide a disincentive to conduct such trials. For example, a gene therapy designed to produce a missing clotting factor could receive accelerated approval on the basis of a tiny yet inconsequential change in levels of the factor, or a more robust response in a single patient. In short, the precedent set here could lead to the approval of drugs for rare diseases without substantial evidence of effectiveness.

8. Even if the 30 mg/kg/week dose were considered to have a meaningful effect on the surrogate endpoint, we already know this dose is sub-therapeutic. We know this because patients who have been receiving this eteplirsen dose for some 3.5 years have been progressing at a rate that is similar to that expected, based on the natural history of the disease (Figure 8). I question the ethics of approving or prescribing a drug for a fatal disease at a dose that is very likely to be sub-therapeutic, when the consequence of a sub-therapeutic dose is clinical deterioration and death. The figure shows the unremitting progression in the patients in Study 201/202, based on changes in NSAA.



9. Approval of this NDA would send the signal that political pressure and even intimidation – not science – guides FDA decisions, with extremely negative consequences (See Grainger D., 11/30/15. “DMD Drugs: an existential threat to FDA,” *Forbes*⁴). The public is well aware of this development program: the meager size of the study population, the marginal (at best) effect size, the Division’s dim view of the efficacy data, and the robust activism of some members of the DMD community. Many would be amazed at an approval action, because other DMD drugs, recently turned down for approval, appeared to provide stronger evidence of efficacy.

FDA and Congress were bombarded with correspondence – pleas urging approval of this NDA. More than 50 speakers registered to speak at the April Advisory Committee meeting. I received 2,792 emails urging approval. Here is an example of the body of an email I received last week:

“Dear Dr. califf: How is it that everyone in and around DMD understands this simple Idea and the science geniuses at FDA don't? You stupid f__ _ers are costing each and every DMD kids days of their lives with your Moronic Dystrophin dance. Time to get a

⁴ downloaded 7/18/16 at <http://www.forbes.com/sites/davidgrainger/2015/11/30/dmd-drugs-an-existential-threat-to-the-fda/#5ffc712455f7>

f...ing clue! (b) (6)

The ramifications here are profound. The public will perceive that it was their unprecedented lobbying efforts that made the difference and earned eteplirsen its accelerated approval. For the future, this will have the effect of strongly encouraging public activism and intimidation as a substitute for data, which is one of the worse possible consequences for communities with rare diseases. This type of activism is not what was envisioned for patient-focused drug development.

4. Detailed Description of the History of the Dispute, Including My Description of the Center SDR Procedures Followed and/or Not Followed, Dates of Meetings, and Decisions Rendered Throughout the Process

The following table shows the dates and main activities for 15 Center Director Briefings associated with the development of this drug: 8 Center Director Briefings took place during the IND phase of development, *prior to submission of the NDA*, and 7 Center Director Briefings took place during review of this NDA.

DATE	MEETING	DETAILS
7/17/2013	Center Director Briefing	Follow up on Action Item from 3/13/13 EOP2 Meeting: Sarepta has submitted a comprehensive discussion of the issues from the EOP2 mtg. To discuss the suitability to file the NDA for Subpart H approval.
10/18/2013	Center Director Briefing	Dr. Unger presented an overview and Dr. Farkas had a slide presentation on drisapersen and eteplirsen data. Discussion: 1. Plan to have a manufacturing facility visit by ONDQA - to observe process and obtain yield calculation. Sponsor is expecting to have 2nd batch in Dec 2013. Determine how much product the sponsor has. 2. OBP: recommended to establish specificity of the antibody and variability of the assay. 3. Next trial - plan to have OSI group to observe the conduct. 4. Need data from the (b) (4) trial. DNP has previously requested the (b) (4) data from (b) (4), but did not get any response. Dr. Woodcock will initiate an inquiry to the sponsor (raw data). 5. The Agency needs to assist Sarepta (characterize biomarker, CMC facility, observe 6MWT, etc.) 6. 2nd Internal Meeting (Drs. Woodcock, Temple, Jenkins, Unger and Neuro) before the 11/8/13 sponsor meeting. Discuss further what to convey to Sarepta.
10/28/2013	Center Director Briefing (continuation of 10/18/13 meeting)	Suggestions/Recommendations for DNP to Consider: -- We have concluded that we will not ask for biopsy until (we understand the histopathology and are) we're certain what is a quantitative measure and identified the surrogate marker for the study. -- Tell the sponsor that we have changed our view for the quantitative measure of truncated dystrophin as a surrogate PD marker used in their study, because of the recent natural history

		<p>study and (b) (4)</p> <p>-- Dr. Woodcock wants to have a comprehensive literature review to fully understand what's this mean of the deletions, mutations, or duplications in the dystrophin gene, or this exon 51 of dystrophin mRNA ((Office of Translational Science) believe this task was assigned to a different group).</p> <p>-- To ask the Sponsor to provide their production schedule. I believe Dr. Woodcock wants to understand the amount of production and determine if the company can provide the drugs to those DMD patients in the future.</p> <p>-- To suggest that the Sponsor consider enrolling patients younger in age (like starting with 5yrs) in their clinical study.</p> <p>-- To ask the Sponsor if they could provide drugs for compassionate use to patients (who are very sick or those were in the drisapersen trial previously).</p> <p>-- Schedule a T-con with (b) (4) to discuss (b) (4) data</p>
1/17/2014	Center Director Briefing	Request: Team to present DMD drugs study design to Dr. Woodcock – Path forward for Sarepta (& (b) (4))
2/6/2014	Center Director Briefing	DMD drugs study design (Discuss Sarepta path forward) Action items: (a) Request biomarker data from the sponsor - done TC on 2/7/14(b) If data interpretable, meet with sponsor for a brainstorming session. Then follow-up with Advice Letter
3/5/2014	Center Director Briefing	Dr. Ash Rao presented biomarker data findings (including Drs. Woodcock, Jenkins, Temple, Unger, Moscicki) Team discussed path forward. Action Item: to invite Sarepta for a brainstorming discussion.
3/19/2014	Sponsor Meeting, with Center Director	brainstorming discussion - study design and path forward Action: Sarepta to submit proposed studies and next steps
4/2/2014	Center Director Briefing	Drs. Woodcock, Moscicki, Temple, Unger Discuss proposal & comments to sponsor ~Advice Letter-include previous meeting discussions ~FDA workshop – biomarker ~Work w/ sponsor on dystrophin biomarker ~Natural history raw data - primary investigators
6/26/2015		SUBMISSION OF NDA
12/9/2015	Center Director Briefing	To brief on the current status of eteplirsen review in advance of the planned Jan 22, 2016 AC meeting. To discuss the application and the plan of action.
1/13/2016	Center Director Briefing	To review the slide presentation and plan of action for eteplirsen, that will be presented during the Advisory Committee Meeting on January 22, 2016 to senior leadership.
2/10/2016	Center Director Briefing	To discuss the ongoing review of the NDA, and what will be presented during the Advisory Committee Meeting in April. To discuss the strengths, limitations, and uncertainties of the data, particularly with respect to the comparison between the open-label eteplirsen group and a contemporary untreated external control group.
4/15/2016	Center Director Briefing	To discuss the statistical review of the CINRG data. To discuss the review of data on DMD that was conducted by the Cooperative International Neuromuscular Research Group
4/25/2016	Advisory Committee Meeting	
5/4/2016	Center Director Briefing	Discuss the outcome and plan of actions for the application post advisory committee meeting

5/31/2016	Center Director Briefing	Discuss reviews conducted by the review team and leadership along with any additional information obtained from the sponsor. Discussed Dr. Woodcock's memo. Timeline for reviews due to Dr. Woodcock.
7/6/2016	Center Director Briefing	<ol style="list-style-type: none"> 1. The levels of dystrophin observed in 12 DMD patients from the recent interim analysis of an ongoing trial and whether the levels seen can be interpreted to be "reasonably likely to predict clinical benefit" and used as a surrogate endpoint to support accelerated approval. 2. The design of one or more PMR trials to confirm clinical benefit of eteplirsen if it is approved under accelerated approval. 3. Description of the available clinical data in the drug label if approved.

Based on my years of experience in Office of Drug Evaluation-I, the Center Director's direct involvement with this drug, compared to other development programs, has been unprecedented. She also attended the April meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, where she spoke and interjected a number of important comments.

There is no question that there has been adequate time and place for the discussion of various views. I will note, however, that I found it unfortunate that the Center Director made clear her intent to approve the drug at a briefing with the review team on May 4, 2016, before she had seen drafts of the Division's final review memorandum or my review memorandum. Prior to reading our reviews, Dr. Woodcock stated that she had already "...reached a different conclusion...." than the review team.

5. Action, Decision or Remedy Sought

Although the above paragraph could be considered grounds for an appeal based on process, I seek instead a scientific review on the matter of whether or not there is substantial evidence of a quantitative effect on dystrophin protein that is reasonably likely to predict clinical benefit. I maintain, along with the Division of Neurology Products, Office of Biometrics, Office of Clinical Pharmacology, Office of New Drugs, and the majority of the members of the Peripheral and Central Nervous System Drugs Advisory Committee, that substantial evidence is lacking to support either a conventional or accelerated approval, and that a *complete response* should be issued for this NDA.

The unprecedented finding of an increase in dystrophin protein in response to eteplirsen establishes proof-of-concept and provides great promise that this drug, or other therapies, will eventually be capable of ameliorating the fundamental genetic defect of DMD, but the effect size here is insufficient at the tested doses.

6. Path Forward

Based on the quantity of Becker-type dystrophin produced in Study 301 and the clinical findings in Study 201/202, additional studies at this dose are unlikely to support any type of approval, i.e., the data obtained for eteplirsen at doses of 30 and 50 mg/kg/week are fairly solid, but they do not support efficacy.

I remain comfortable with the concept that substantial evidence of dystrophin production from adequate and well controlled trials could support accelerated approval, but it is clear that higher doses are needed, and greater quantities of dystrophin would need to be produced. The path to a conventional approval would require a double-blind, placebo-controlled (or multi-dose) study, at least one year in duration, using some measure of physical performance as the primary endpoint, again, testing higher doses.

The applicant is continuing to enroll Study 301 (PROMOVI), an open-label, multicenter, 48-week study in patients with DMD amenable to skipping exon 51. All patients are receiving eteplirsen, 30 mg/kg/week as an IV infusion.

My suggestion for a path to approval is to randomize patients in the ongoing Study 301 to:

- 1) either remain on 30 mg/kg/week; or
- 2) have their dose significantly increased. This could be done through use of a higher dose, through more frequent dosing intervals (with dummy infusions), or both. Given that many patients receive eteplirsen through indwelling IV lines and no significant infusion reactions have occurred, perhaps these infusions could be performed at home. For example, the study could compare 30 mg/kg weekly to 30 mg/kg daily. Patients who do not tolerate more frequent dosing could have their doses decreased, as needed. Based on non-clinical findings, monitoring would need to be in place to assess renal toxicity.

Patients and investigators would be blinded to treatment group. For accelerated approval, the primary endpoint would be dystrophin production, comparing the higher and lower doses. For standard approval, the primary endpoint would be a test(s) of physical performance such as NSAA or rise time.

Such a trial would be methodologically sound and ethical. Virtually everyone, patients and physicians alike, would want to know whether higher eteplirsen doses would increase dystrophin production, and would have equipoise for participation. Although there is concern regarding performance of muscle biopsies in patients randomized to placebo, this would not be a concern here with all patients receiving active drug. And I would recommend that the applicant forego immunohistochemistry studies in favor of Western blot analyses, such that needle biopsies with local anesthesia would be sufficient (rather than open biopsies with more intensive anesthesia and greater morbidity).

I also believe that it would be desirable for the company to provide access to eteplirsen for DMD patients through expanded access programs, with cost recovery, while an adequate dose-finding study is conducted.

FDA is charged with the responsibility of ensuring that drugs are shown to be effective prior to marketing, based on substantial evidence. If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients, in essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope. If we were to turn the clock back to the days prior to the 1962 Kefauver Harris Amendments to the Federal Food, Drug, and Cosmetic Act, the damage to society and the field of evidentiary medicine would be enormous.

From: [Califf, Robert](#)
To: [Sherman, Rachel](#)
Subject: draft thoughts
Date: Sunday, August 14, 2016 5:54:00 PM
Attachments: [20160814 eteplirsen draft thoughts.doc](#)

Rachel,

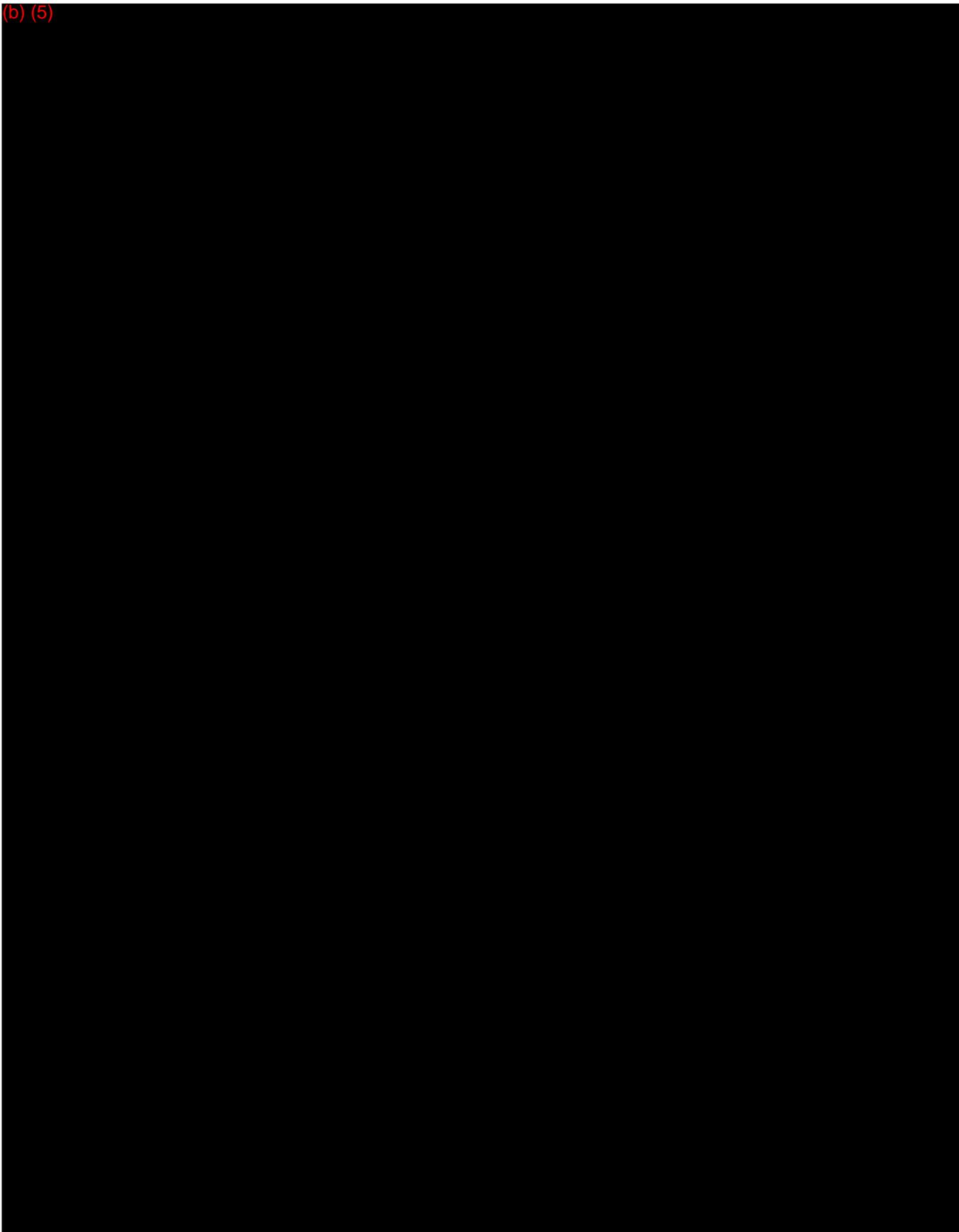
These are draft thoughts and in no way a final decision. I'm interested in your critique and reaction. I know that you have met with both Dr. Woodcock and Dr. Jenkins in your OMPT role and welcome your views as I formulate my final decision.

Thanks for your help with this delicate matter.

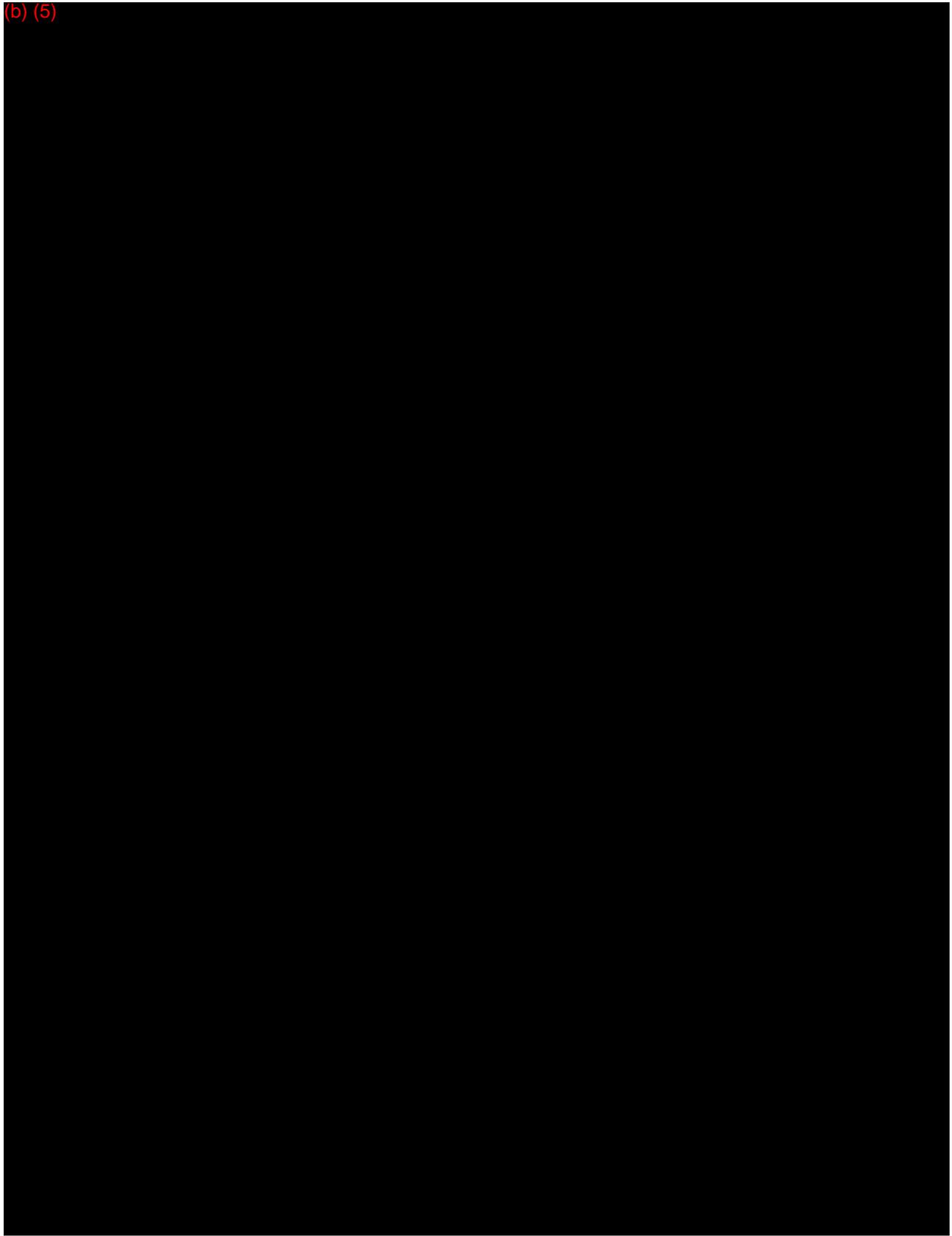
rmc

Robert M Califf MD
Commissioner of Food and Drugs

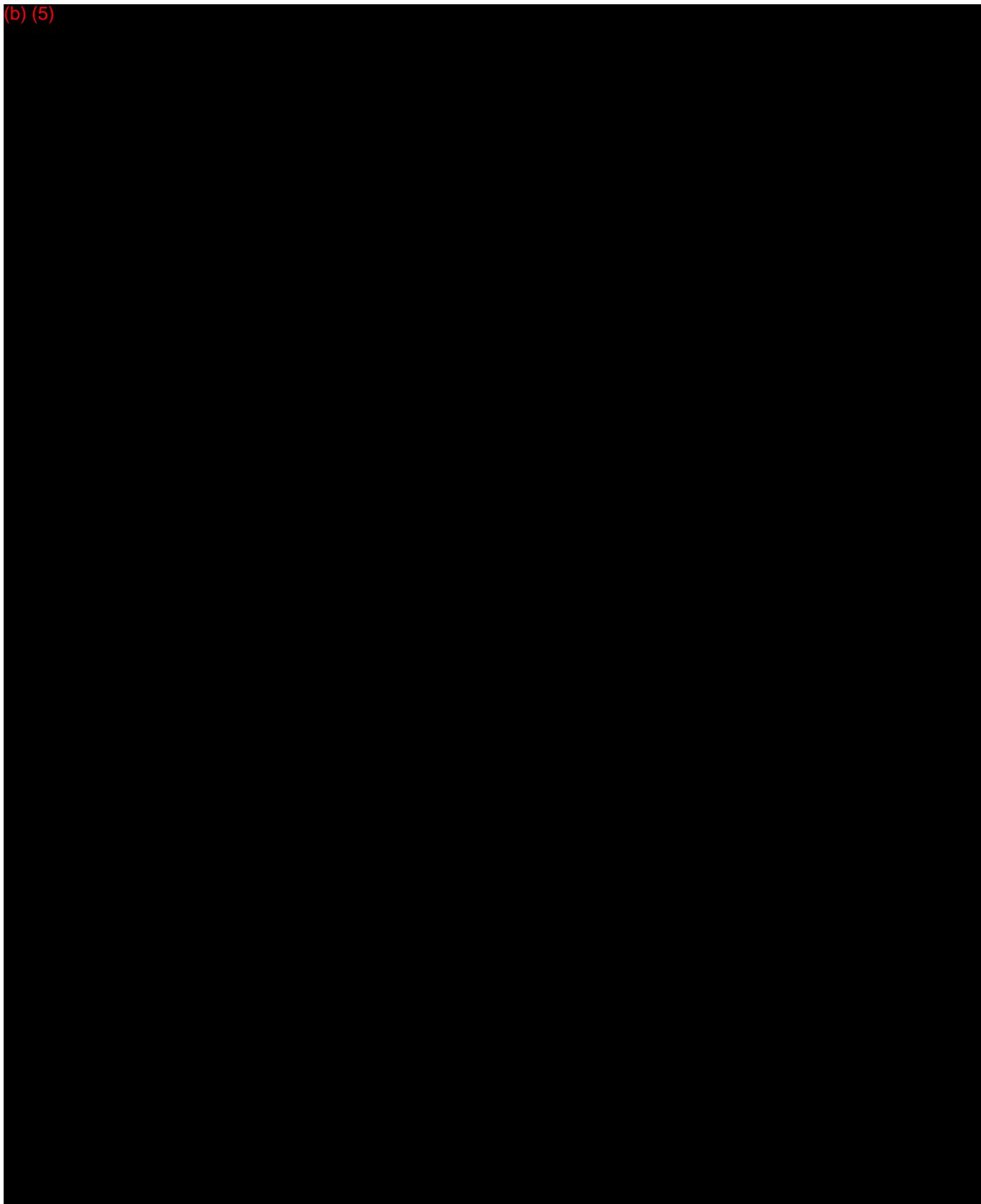
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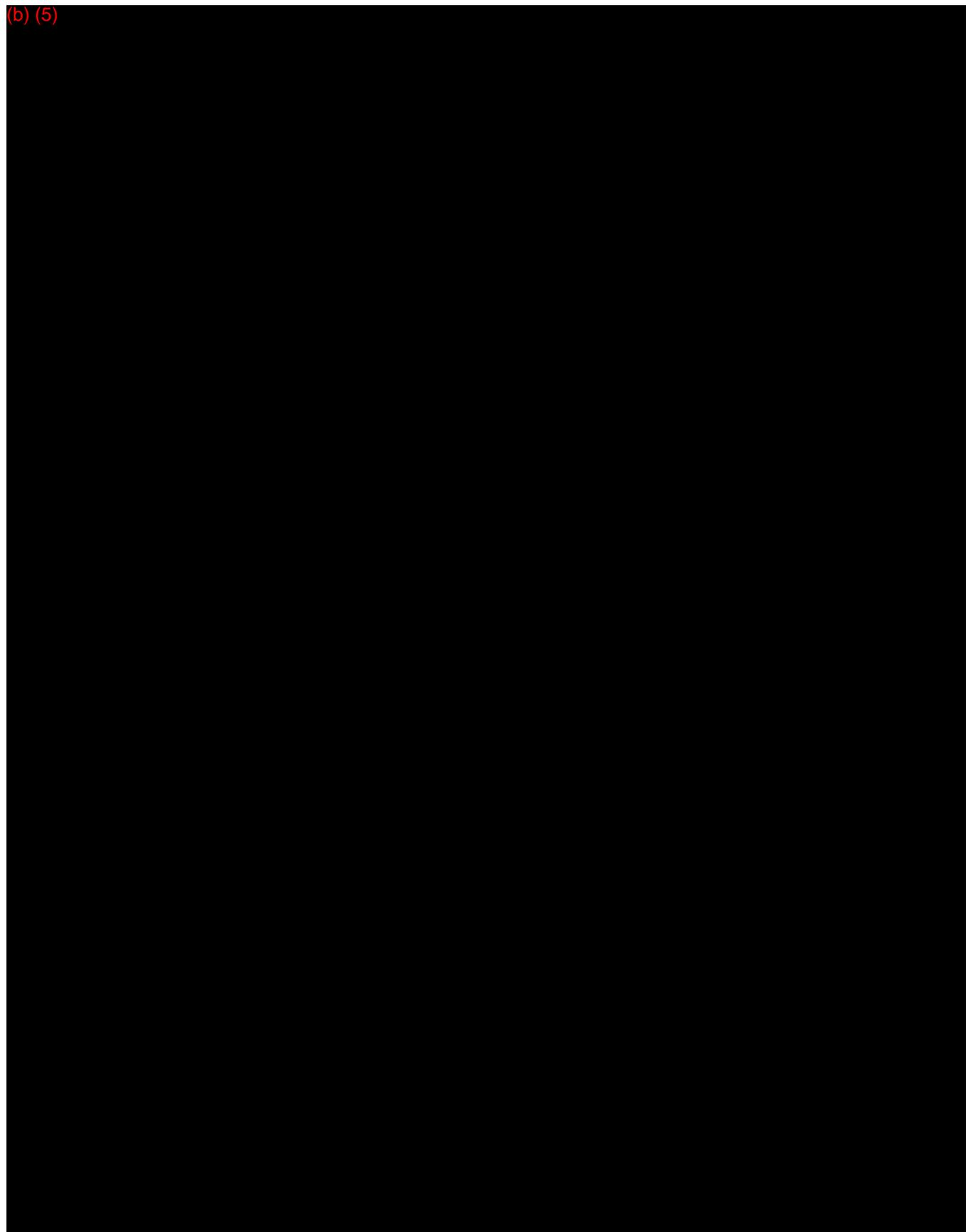
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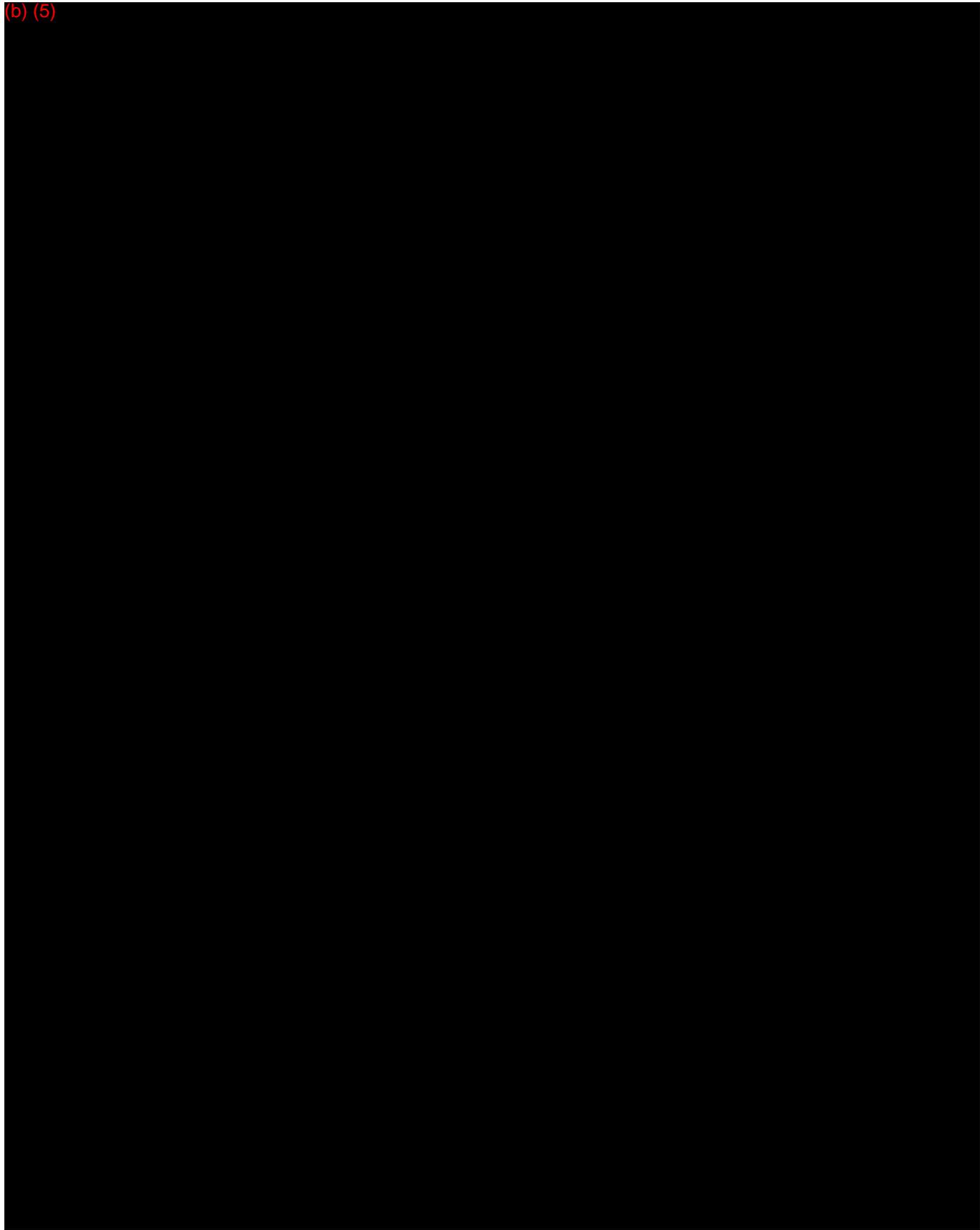
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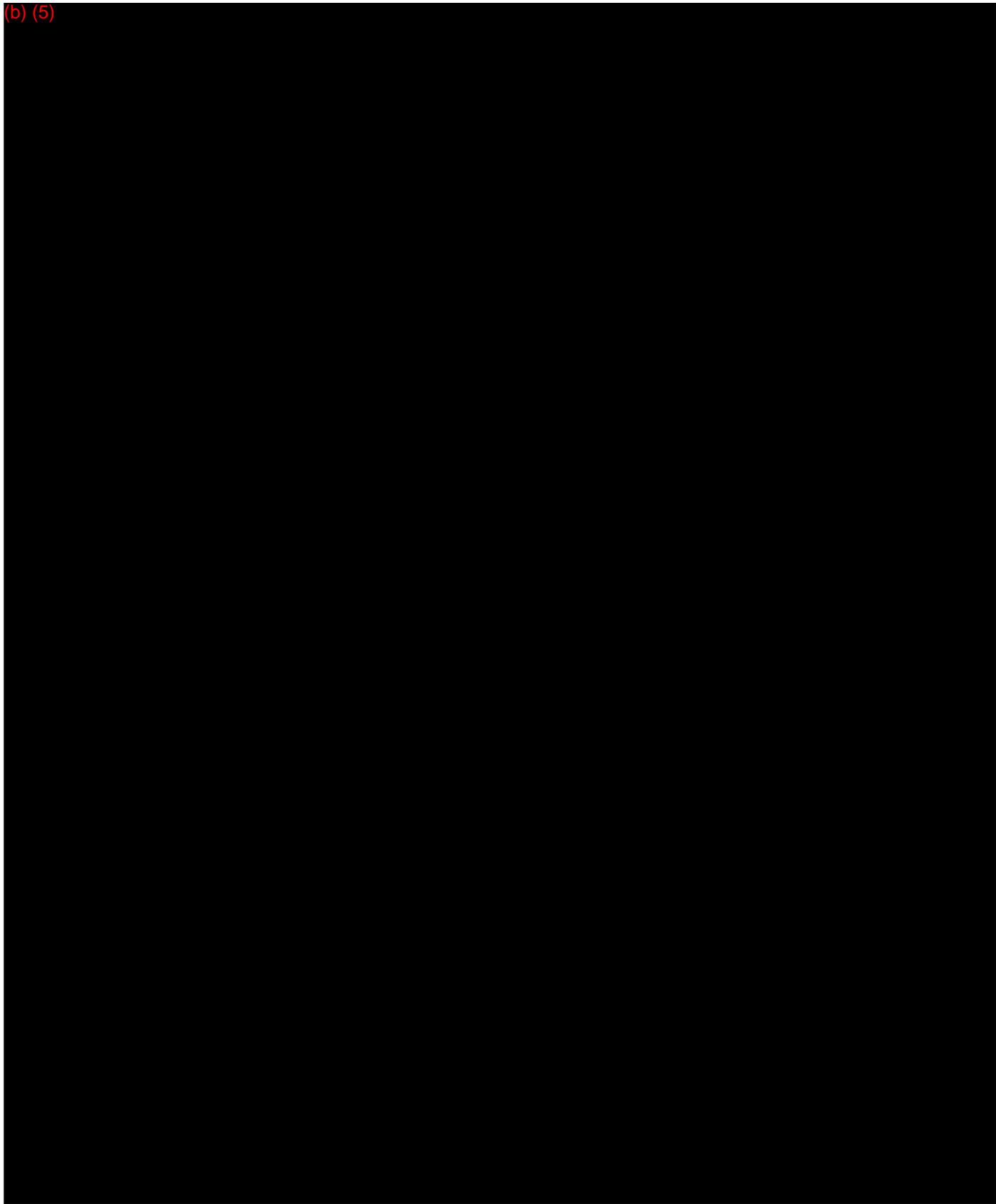
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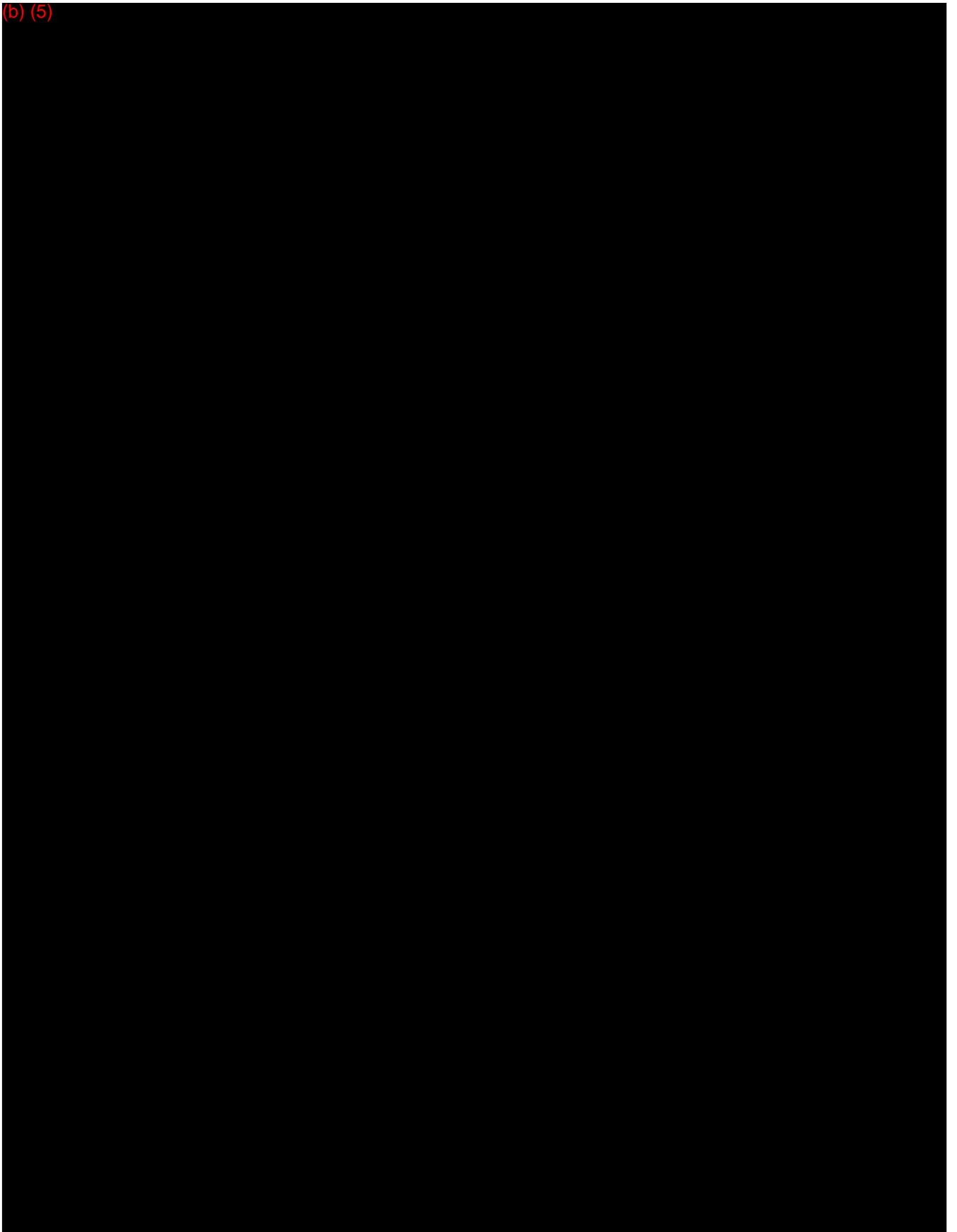
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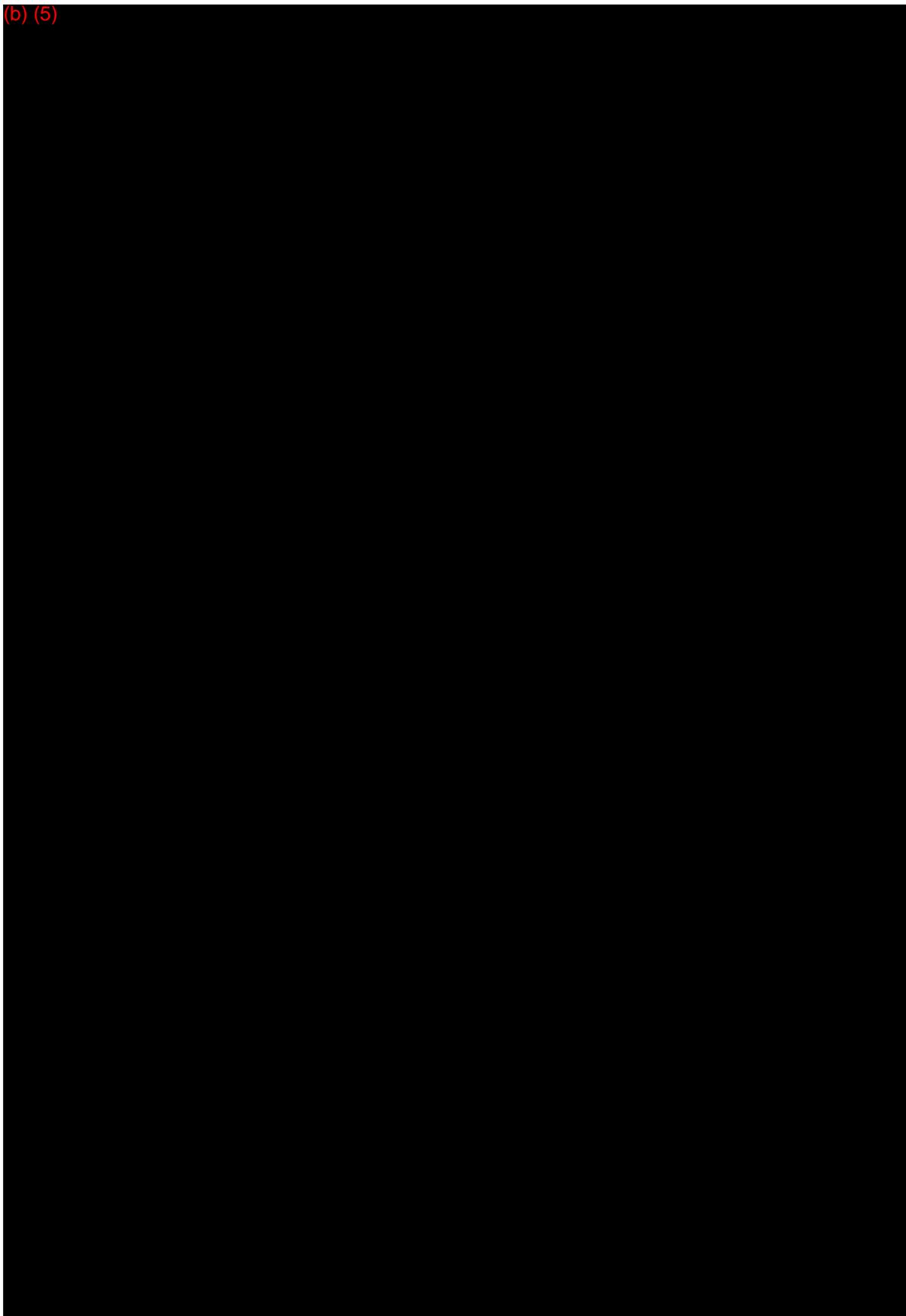
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From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#)
Subject: initial draft thoughts
Date: Sunday, August 14, 2016 5:56:00 PM
Attachments: [20160814 eteplirsen draft thoughts.doc](#)

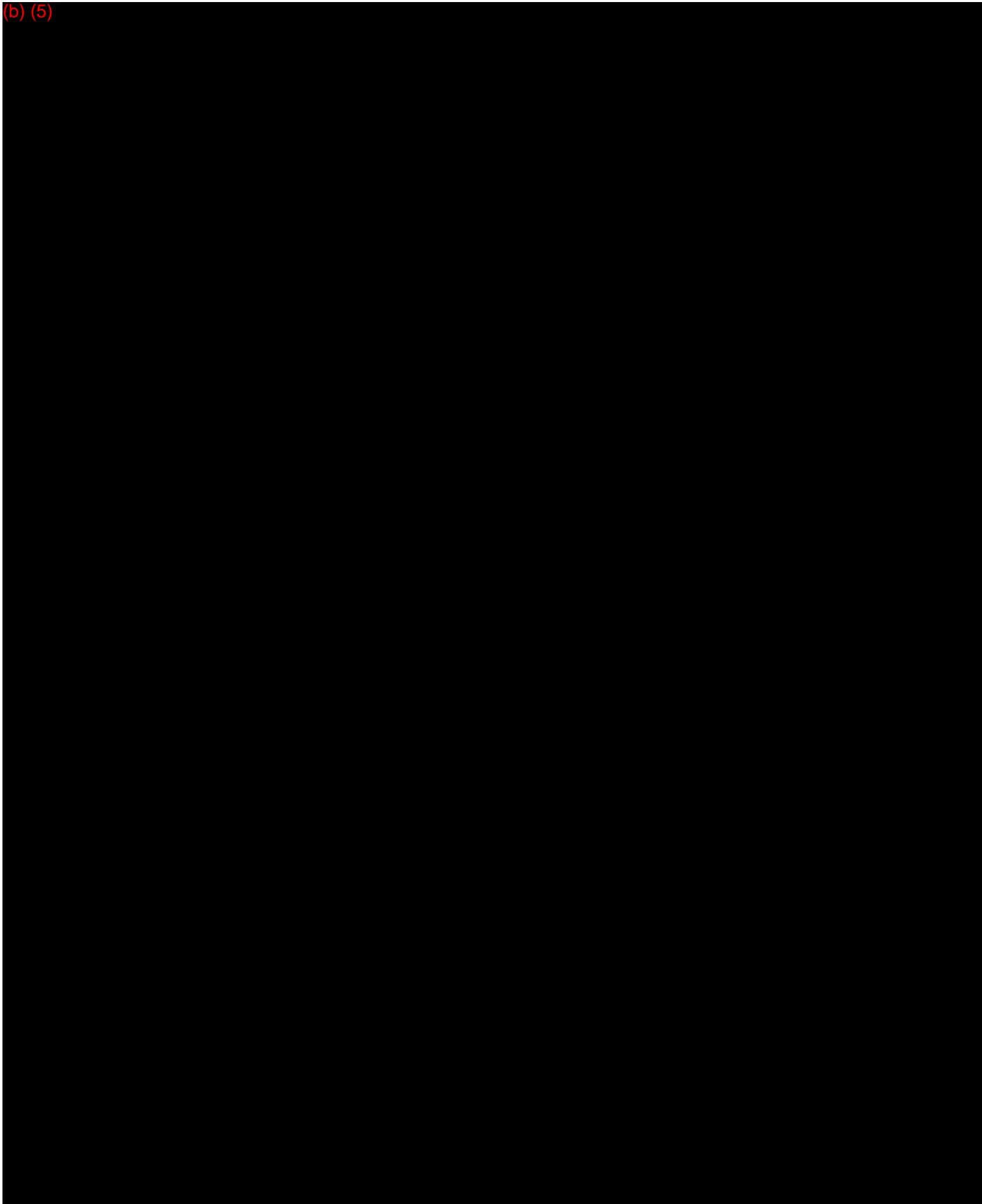
Liz,

These are relatively free flowing initial thoughts and in no way represent a final decision. I welcome suggestions as I formulate my final decision.
Thanks for your help with this tough matter.

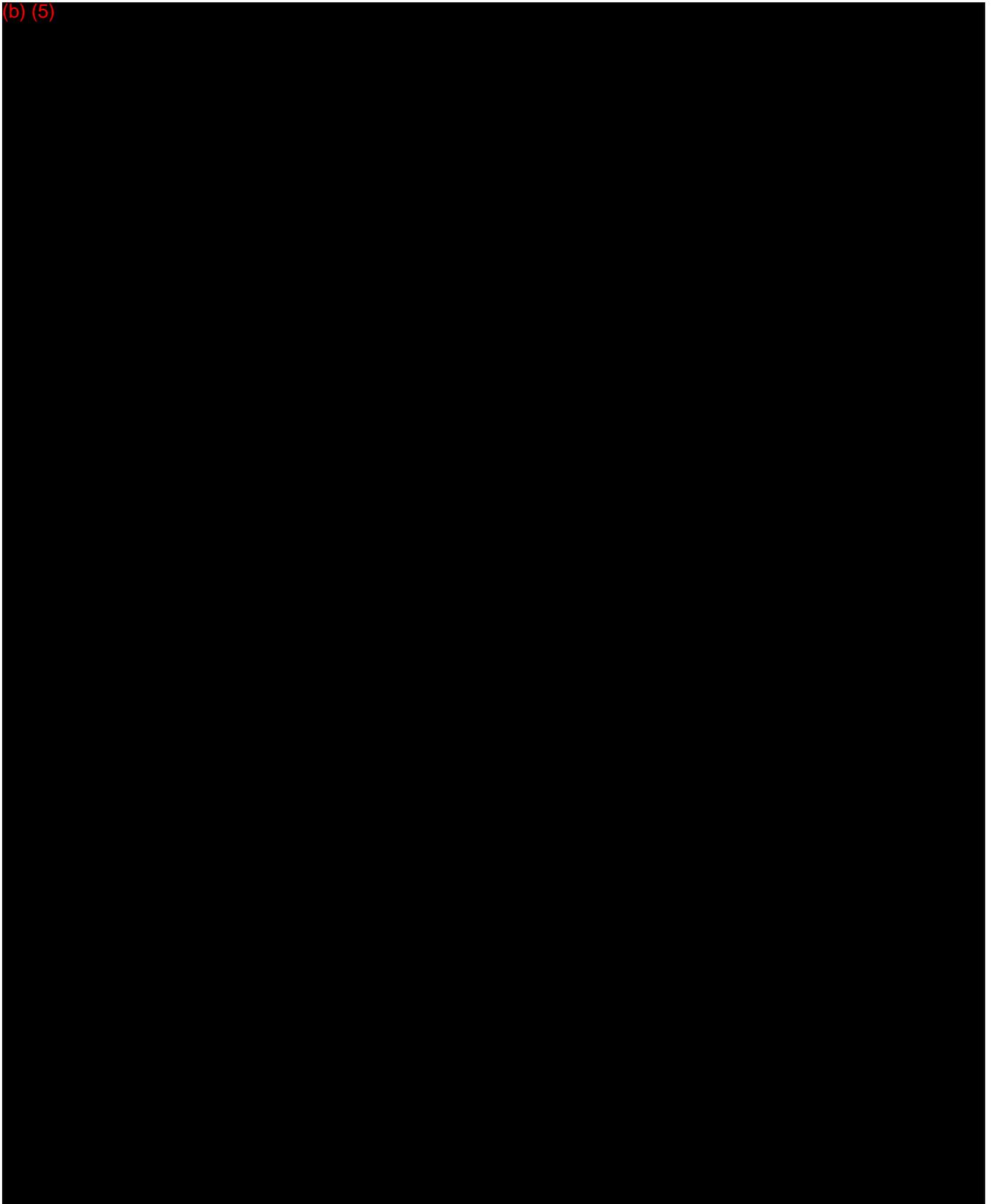
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Robert M Califf MD
Commissioner of Food and Drugs

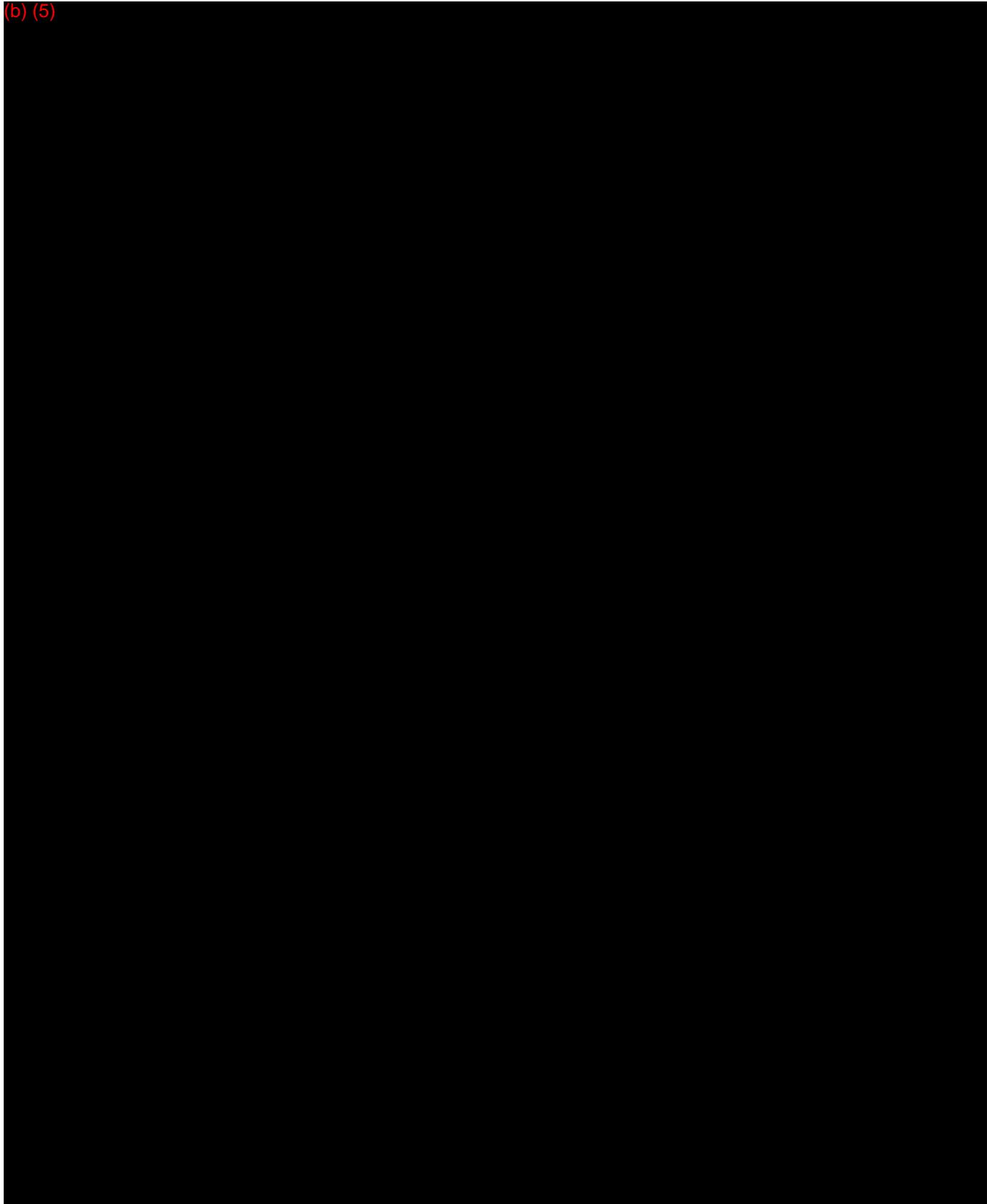
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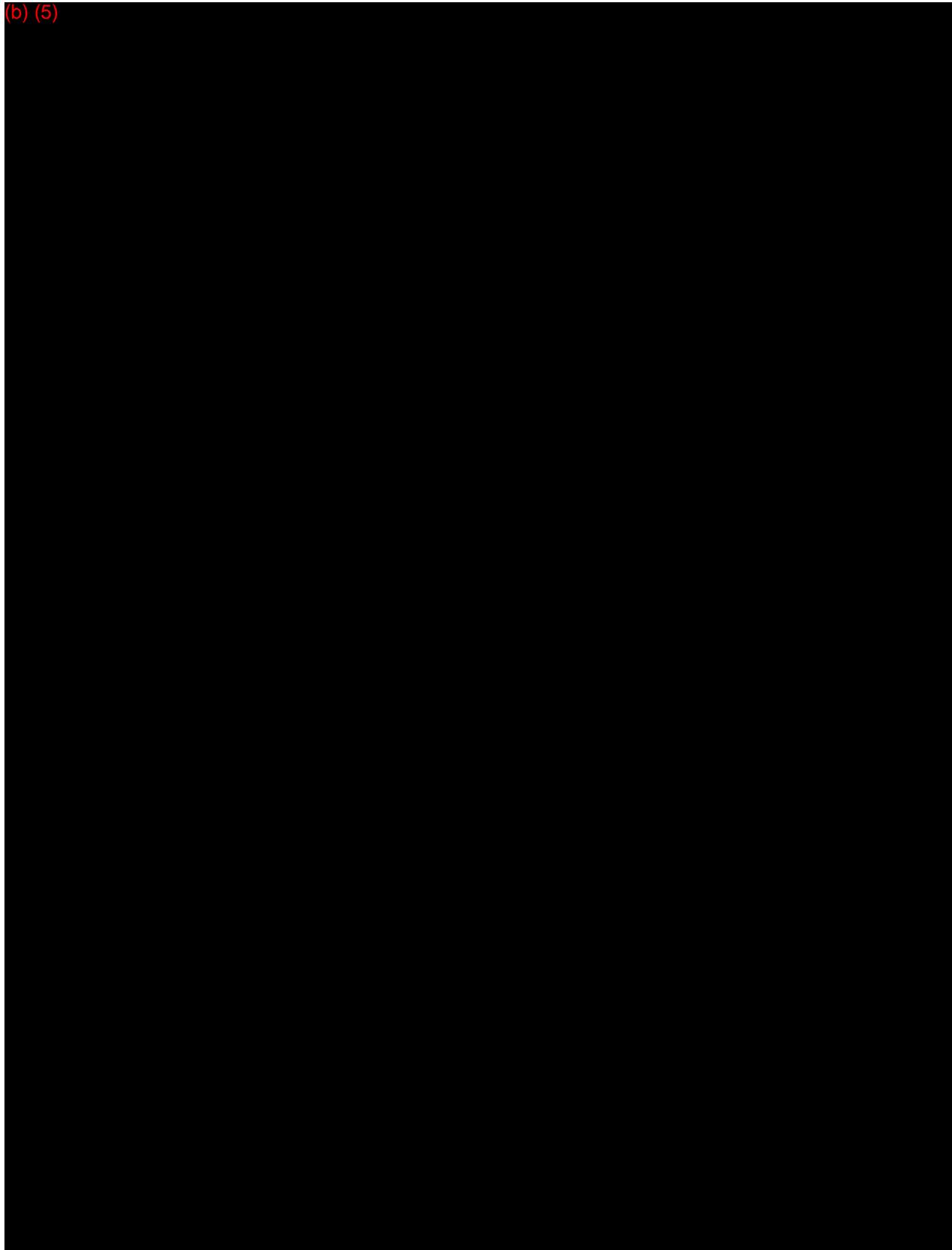
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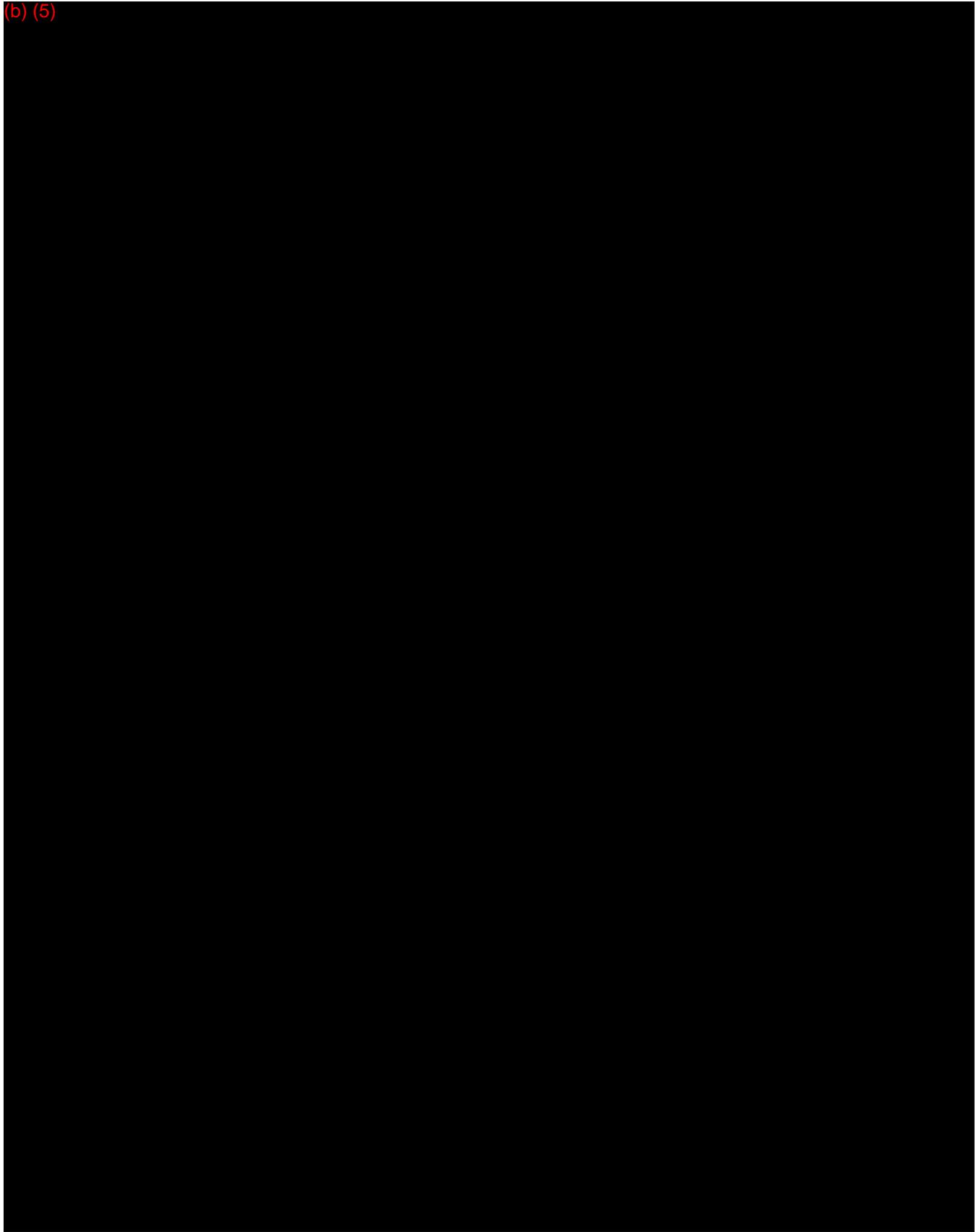
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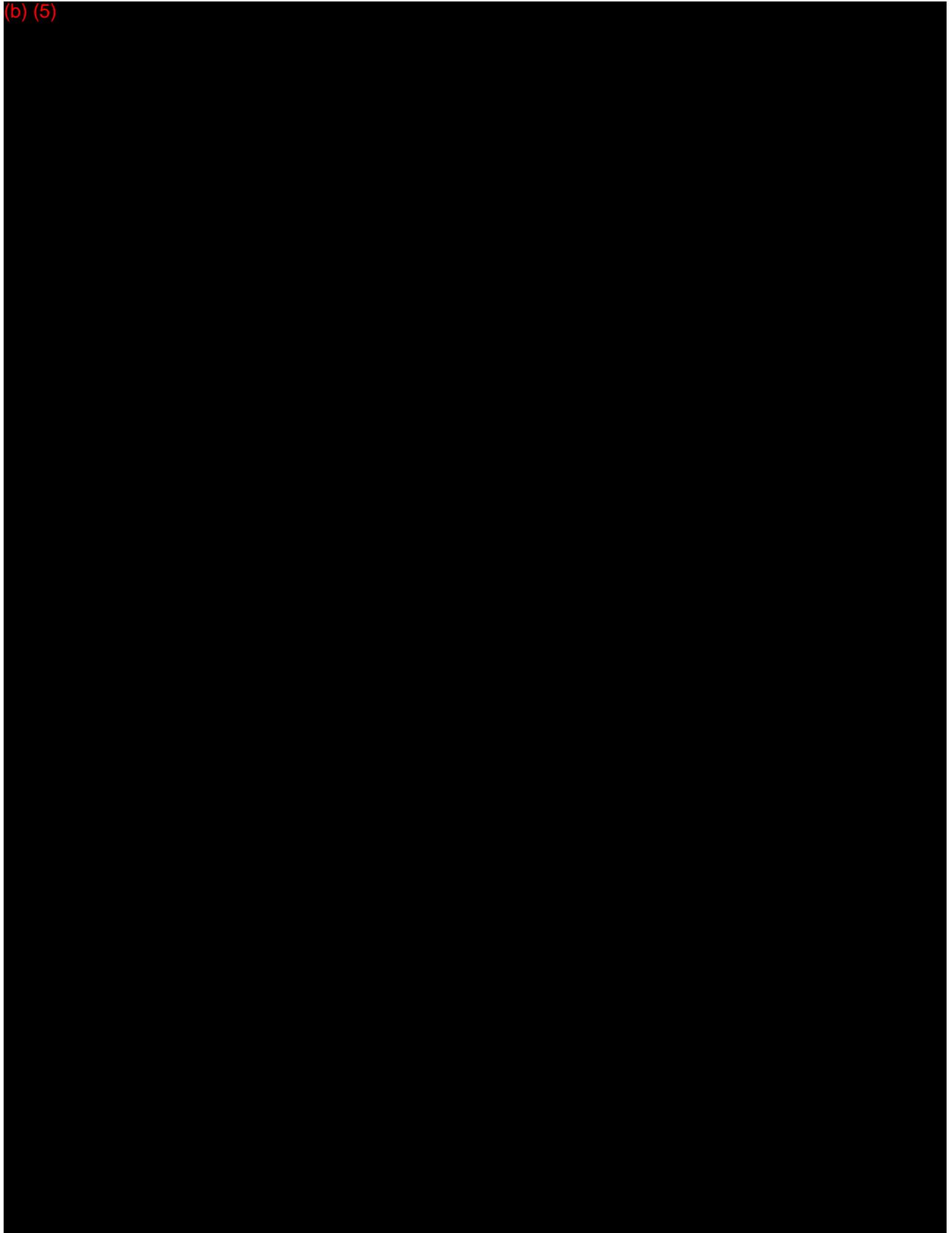
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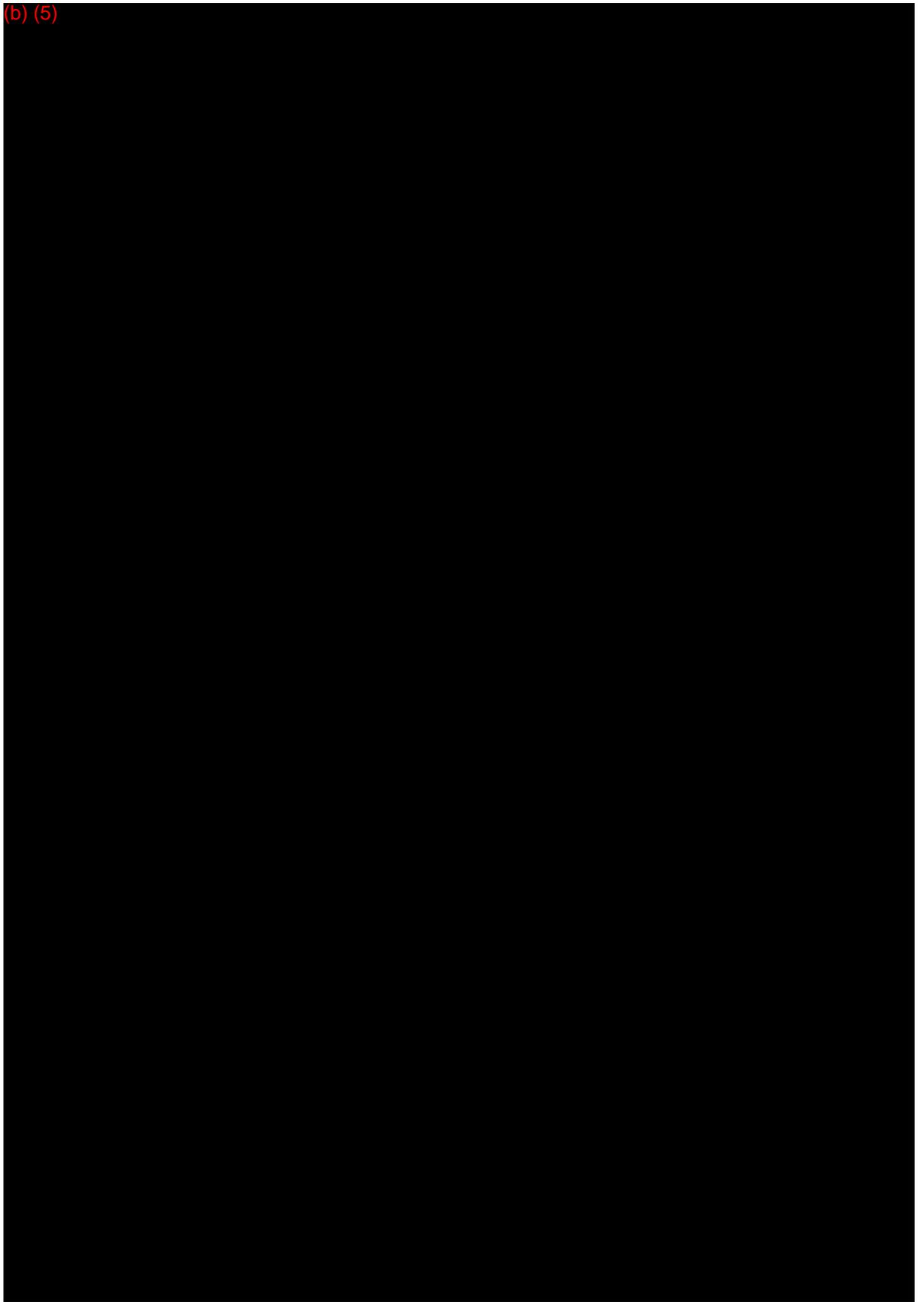
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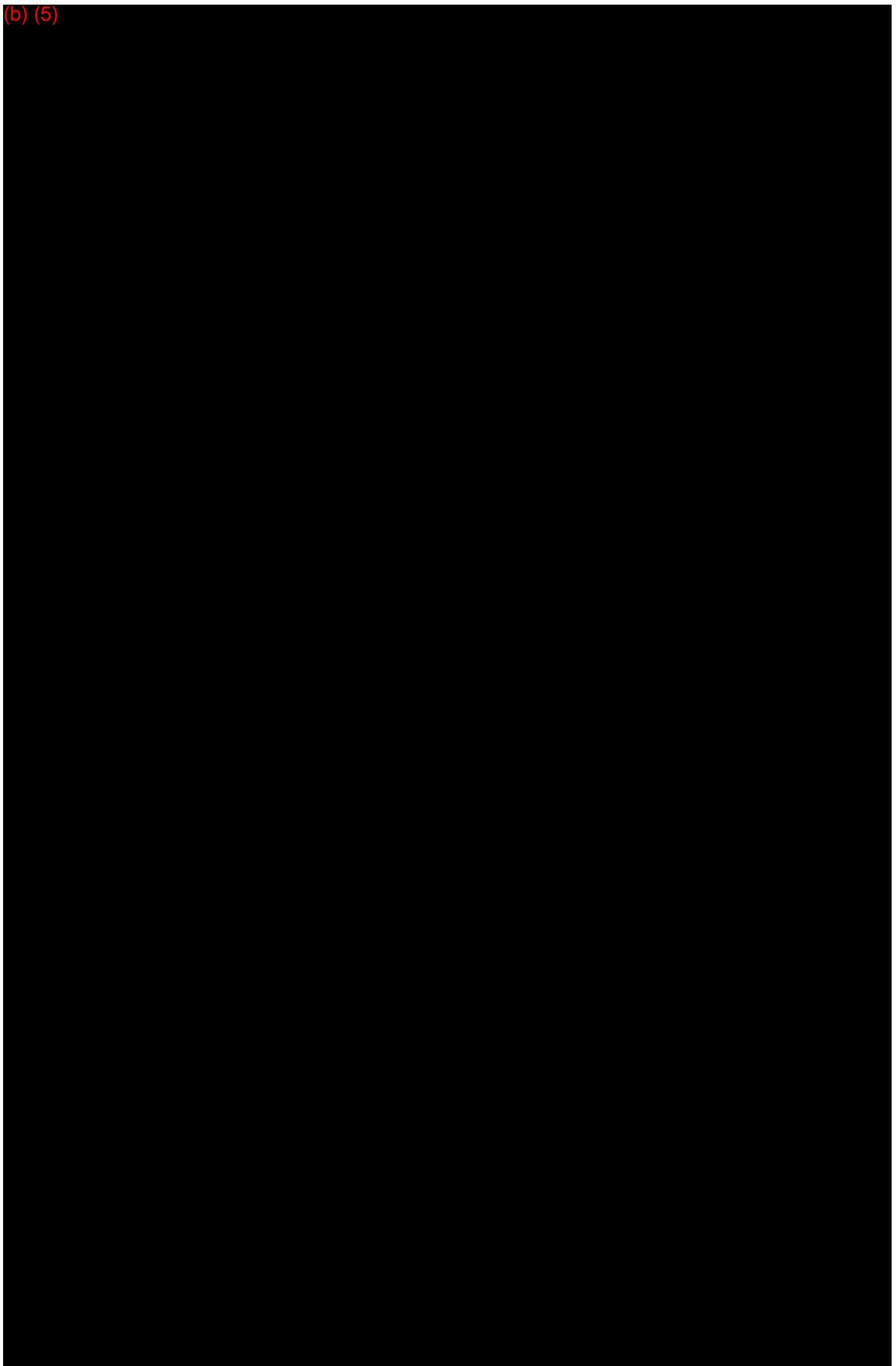
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(b) (5)



(b) (5)



From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#)
Subject: FW: draft thoughts
Date: Monday, August 15, 2016 11:16:00 AM
Attachments: [20160814 eteplirsen draft thoughtsrscom.doc](#)

Liz,

Please see Rachel's thoughts. (b) (5)



Thanks for your help with this.

rmc

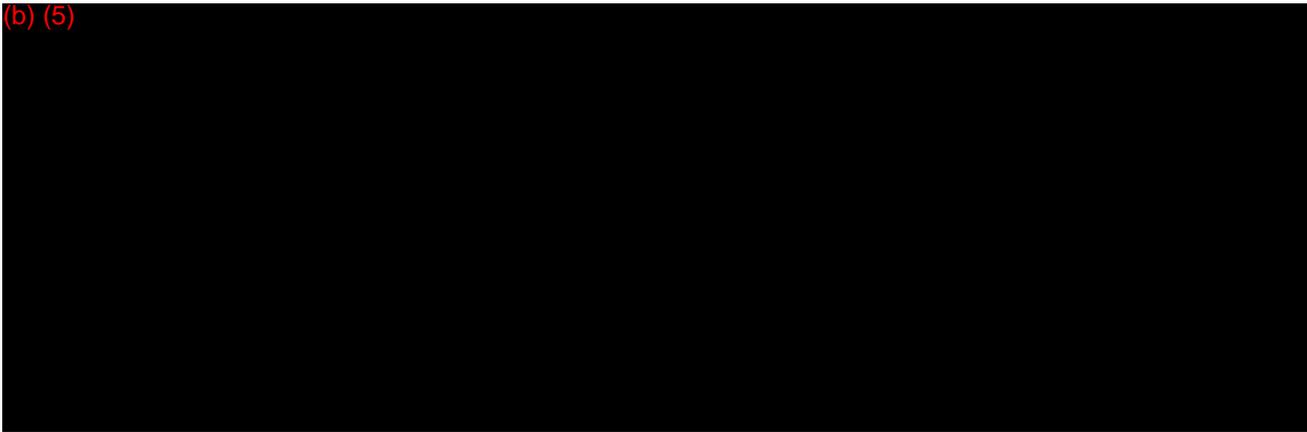
Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Monday, August 15, 2016 9:49 AM
To: Califf, Robert
Subject: RE: draft thoughts

Rob,

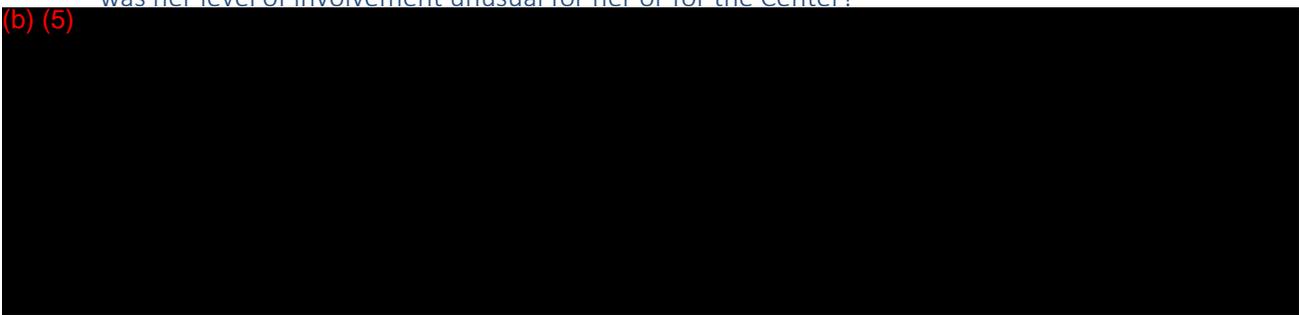
I have attached some initial thoughts, and suggestions, as comments to your document.

(b) (5)



1. Did Dr. Woodcock overstep her bounds and become “too” involved in this application – and was her level of involvement unusual for her or for the Center?

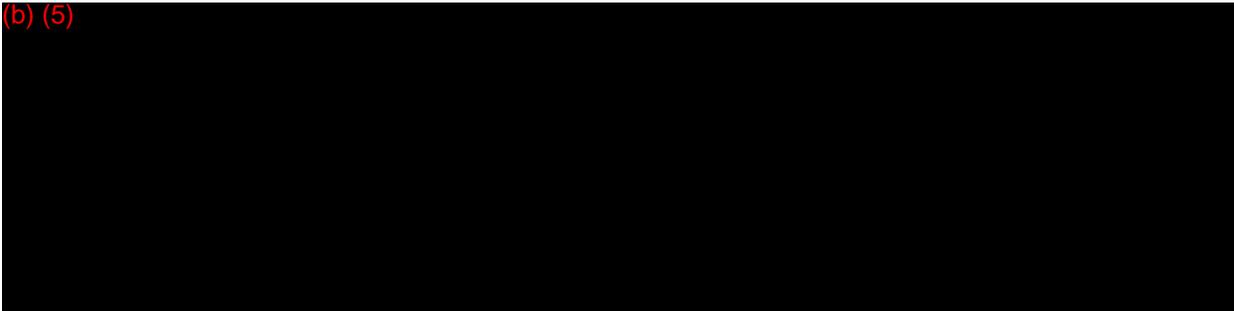
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Center policies.

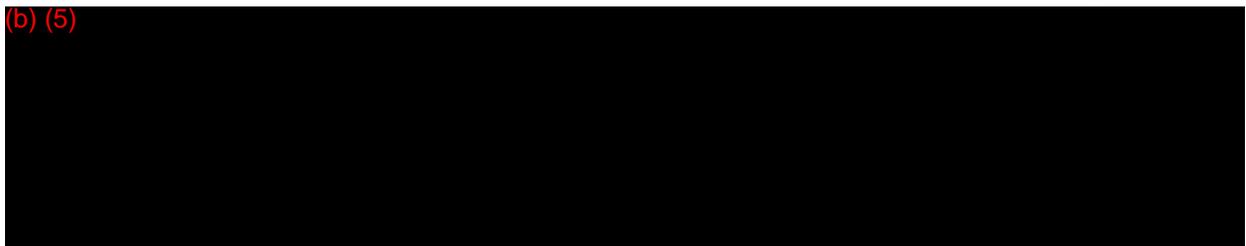
2. Was Dr. Woodcock unduly influenced by patient advocates?

(b) (5)

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3. Was there a repressive atmosphere that inhibited free and open scientific exchange?

(b) (5)

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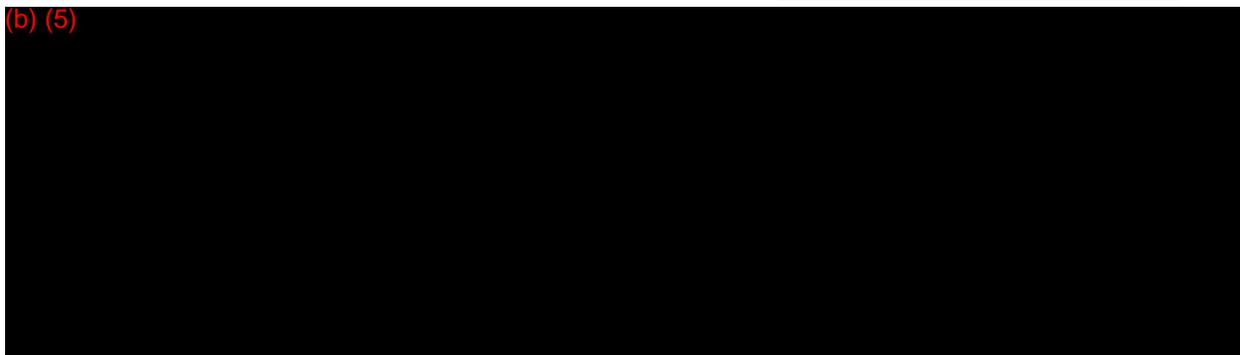
4. Should this product be approved, does it set a “low bar” or encourage sloppy drug development?

(b) (5)

A large black rectangular redaction box covering the entire answer to question 4.

There are several additional important points yet to be raised. (b) (5)

(b) (5)

A large black rectangular redaction box covering the entire answer to the additional points section.

On a personal note, I have spent the bulk of my career on expedited development. These conversations are strikingly similar to those we had in the late 1980s and early 1990s. The first “reasonably likely” approval was taken on the basis of subpart E; subpart H, with its safeguards, patterned after that action, was promulgated the following year. In the very early days we had only very immature development plans; as the entire community became more sophisticated the products, and the data to support their use, improved in quality. Some therapies are no longer used – some remain important. But the most striking lesson is that HIV is now a chronic disease and HCV

is curable.

I believe the overarching lesson is that in the end, when faced with uncertainty of this magnitude, one makes the best possible decision that best serves the public. These decisions, optimally done in an atmosphere of consensus, are never straightforward.

I hope these thoughts are helpful. I am, of course, happy to discuss.

Rachel

From: Califf, Robert
Sent: Sunday, August 14, 2016 5:55 PM
To: Sherman, Rachel
Subject: draft thoughts

Rachel,

These are draft thoughts and in no way a final decision. I'm interested in your critique and reaction. I know that you have met with both Dr. Woodcock and Dr. Jenkins in your OMPT role and welcome your views as I formulate my final decision.

Thanks for your help with this delicate matter.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: [Califf, Robert](#)
To: [McCall, Jonathan *](#)
Subject: FW: Comments
Date: Tuesday, August 16, 2016 1:17:18 PM
Attachments: [20160814 eteplirsen draft thoughts occ suggestions_rmc.doc](#)

Jonathan,

Sorry to bug you, but this is very high priority. Please start with this one. The only major change to be made is to insert the (b) (5)




Next e mails will have Rachel's comments and my responses and changes made due to her comments.

In general I think it would be good to keep all comments for now.

Thx and hope you're having a good time.

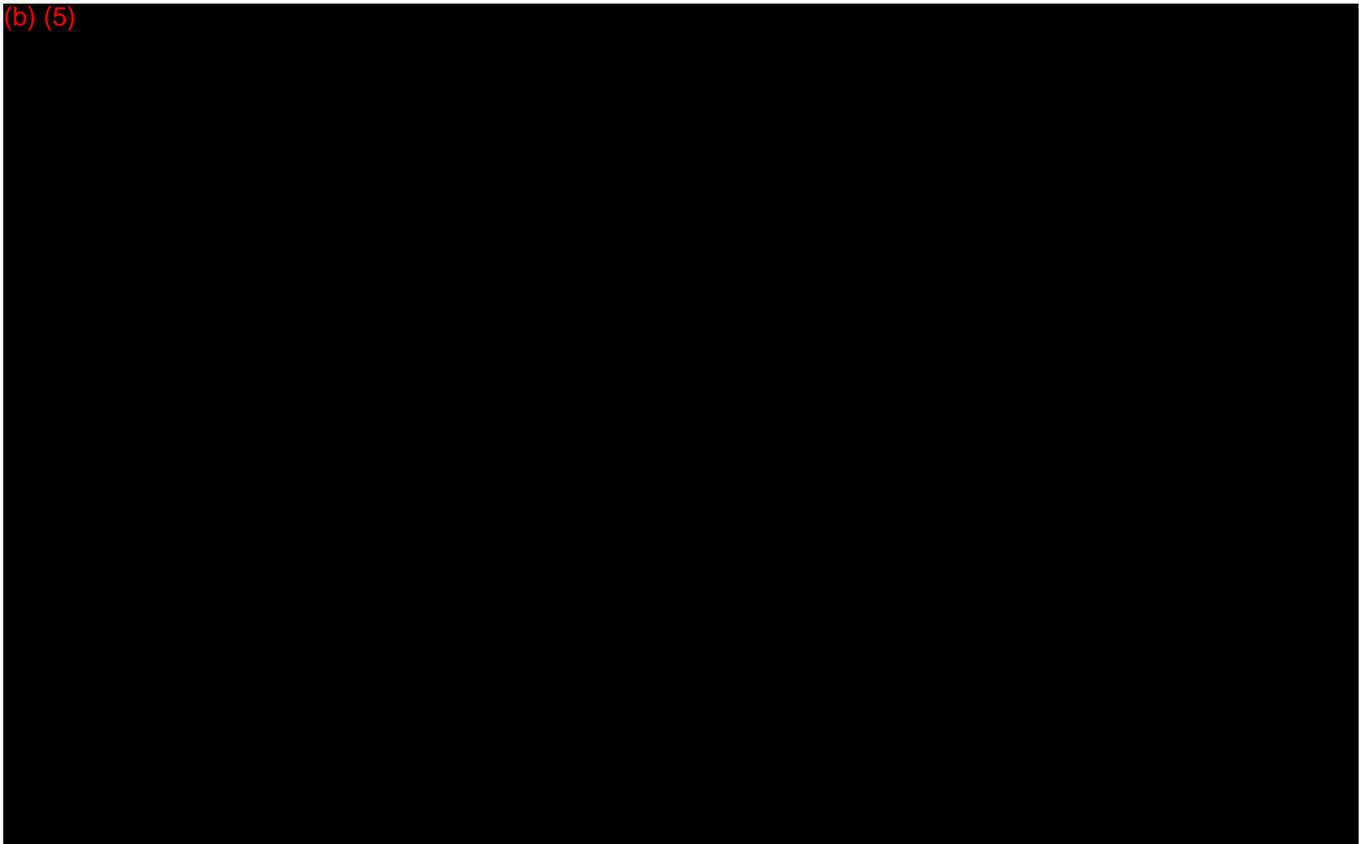
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Robert M Califf MD
Commissioner of Food and Drugs

From: Dickinson, Elizabeth (FDA)
Sent: Monday, August 15, 2016 7:13 PM
To: Califf, Robert
Subject: Comments

Rob,

(b) (5)



(b) (5)

I am headed home for dinner, but can be available later or tomorrow early to answer questions, etc.

I hope your day was alright – sounded tough.

Liz

Elizabeth H. Dickinson
Food and Drug Division, OGC
elizabeth.dickinson@fda.hhs.gov
Food and Drug Administration
Office of the Chief Counsel
White Oak 31 Room 4536
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
(301) 796-8616

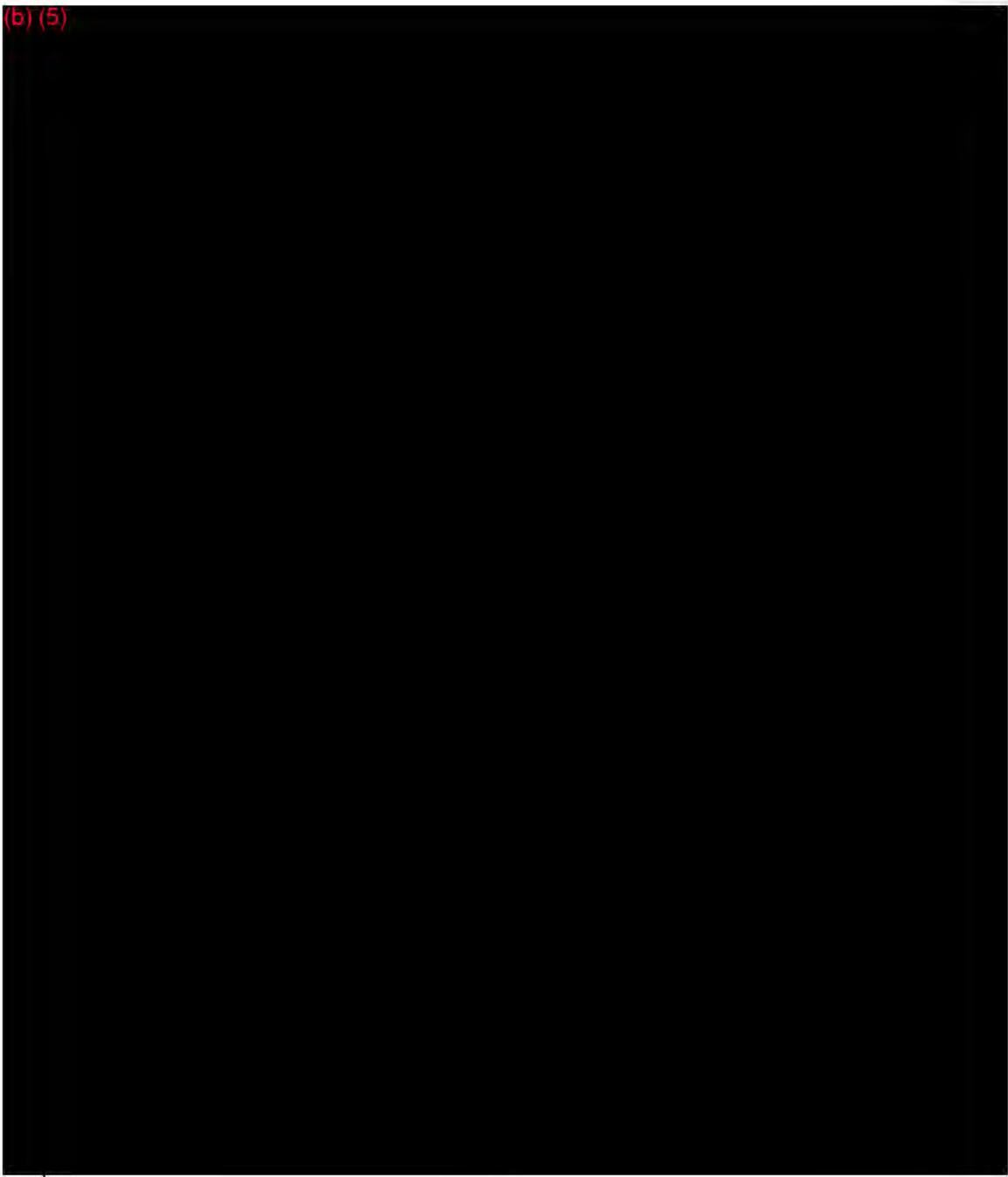
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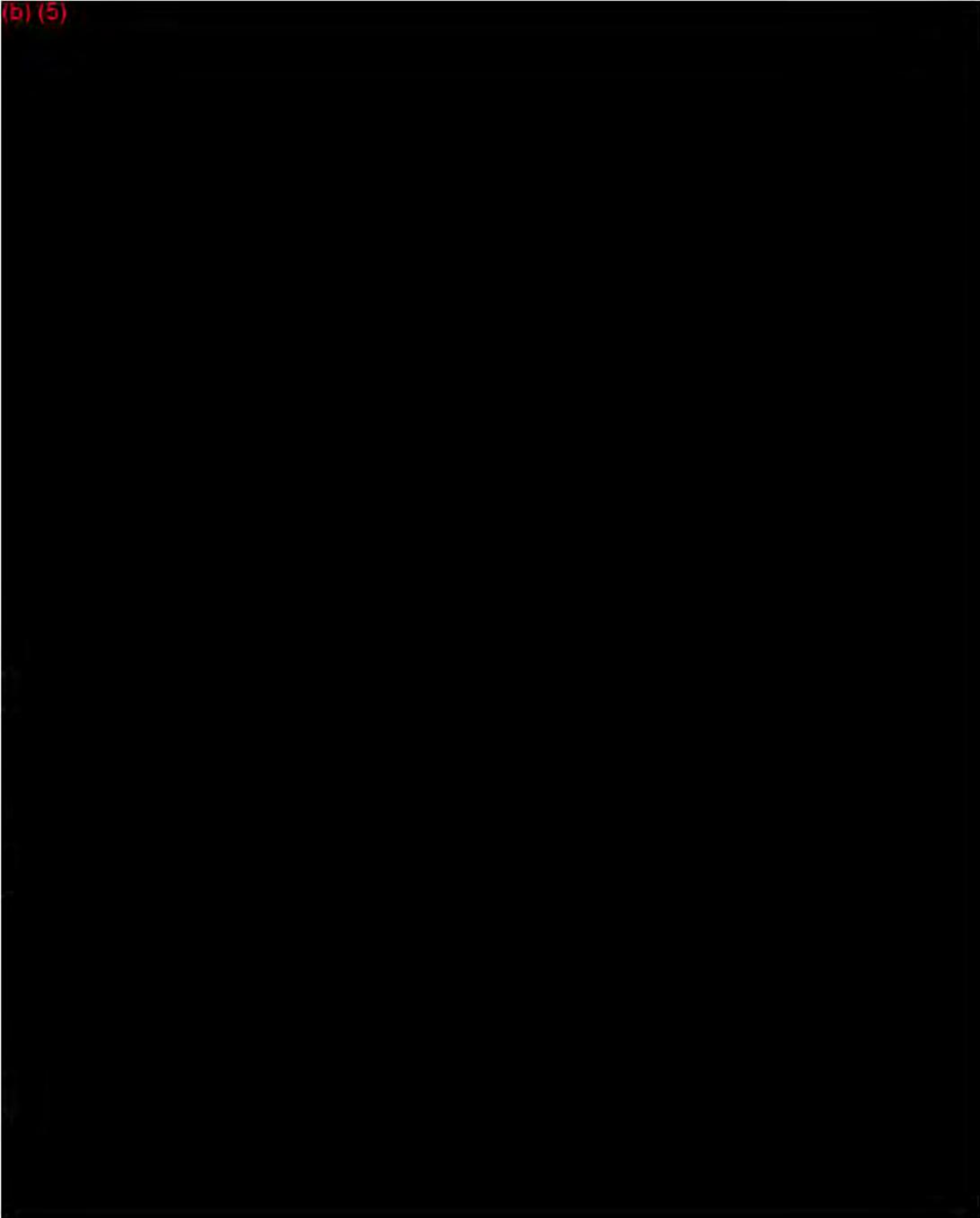
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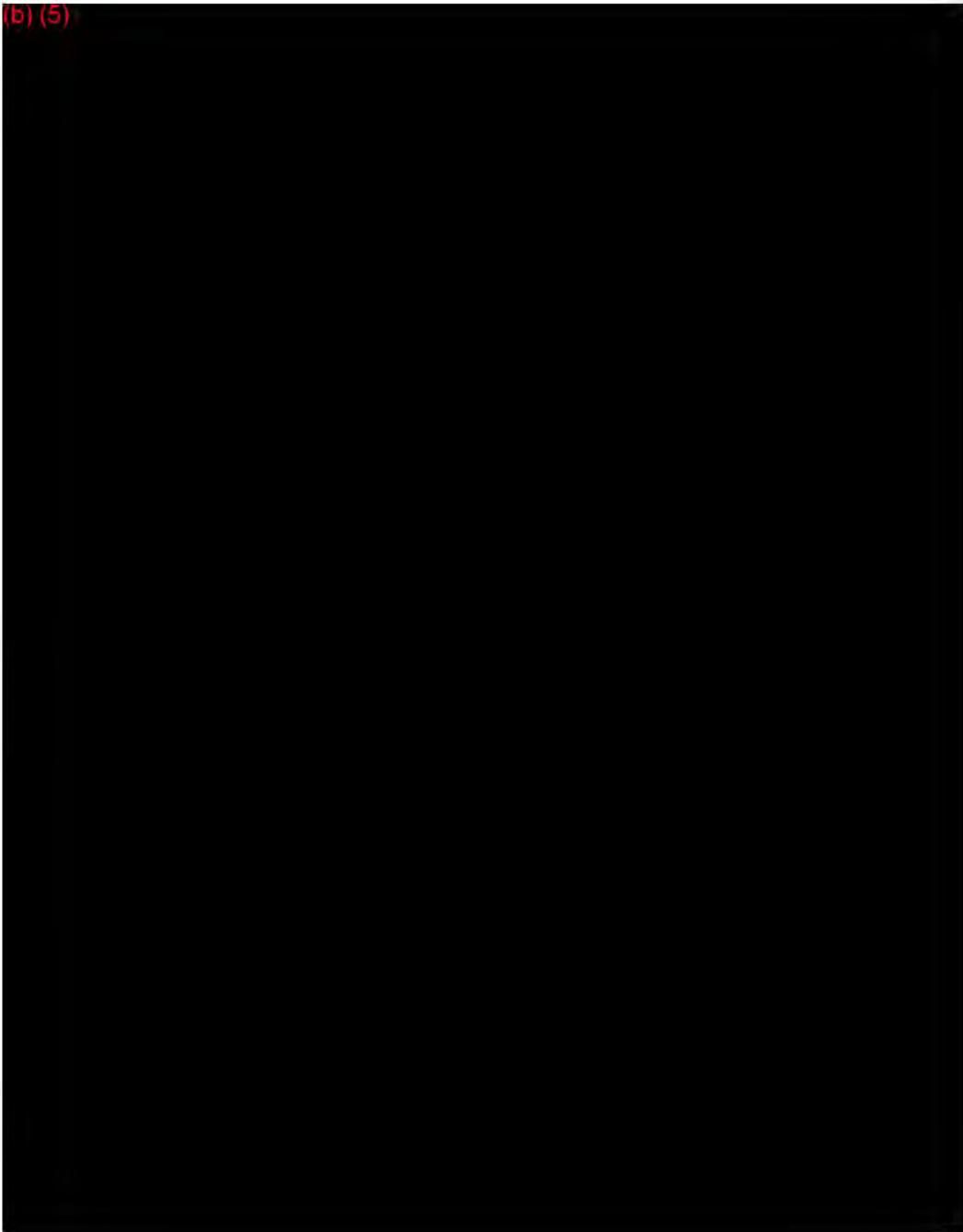
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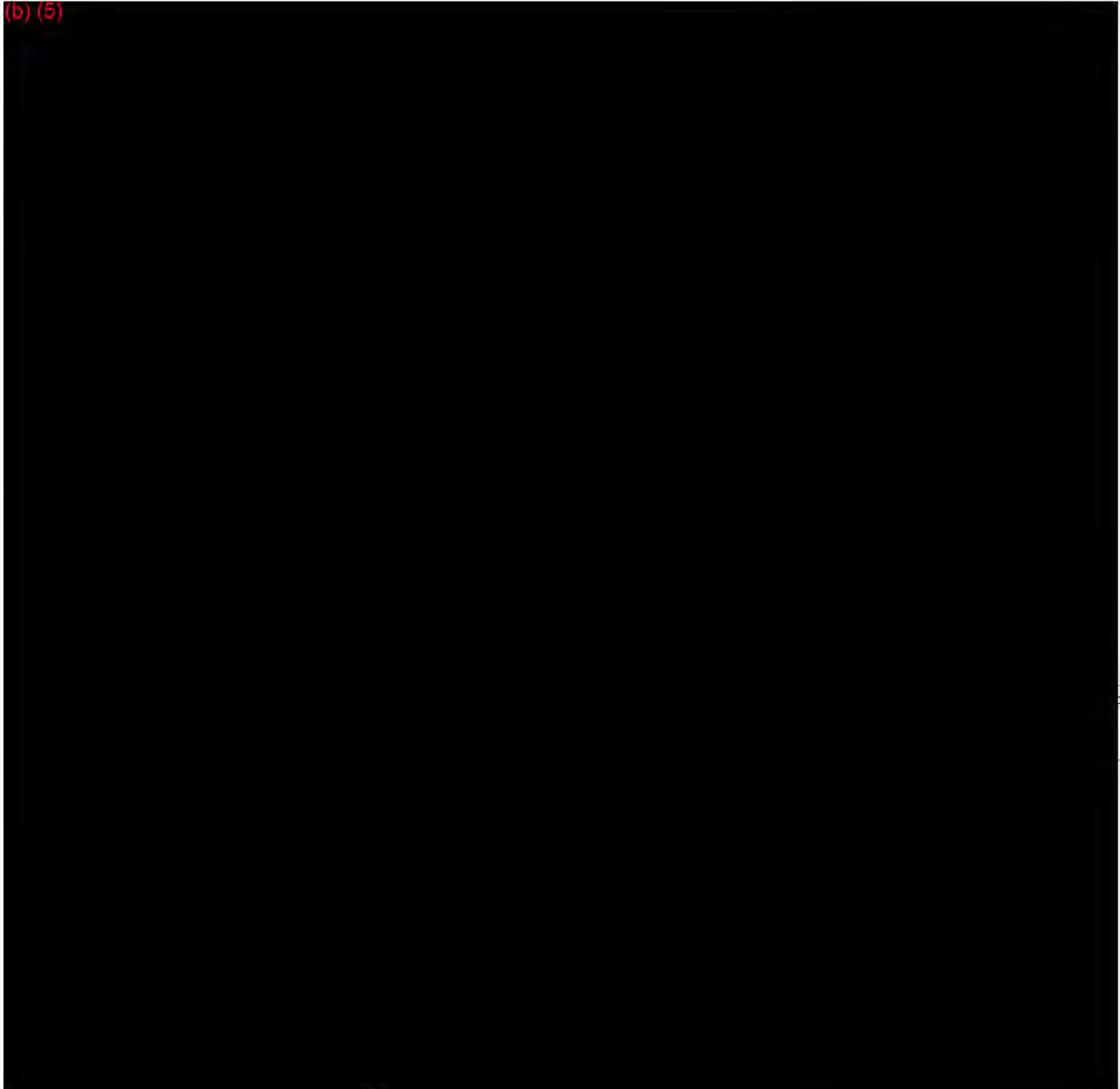
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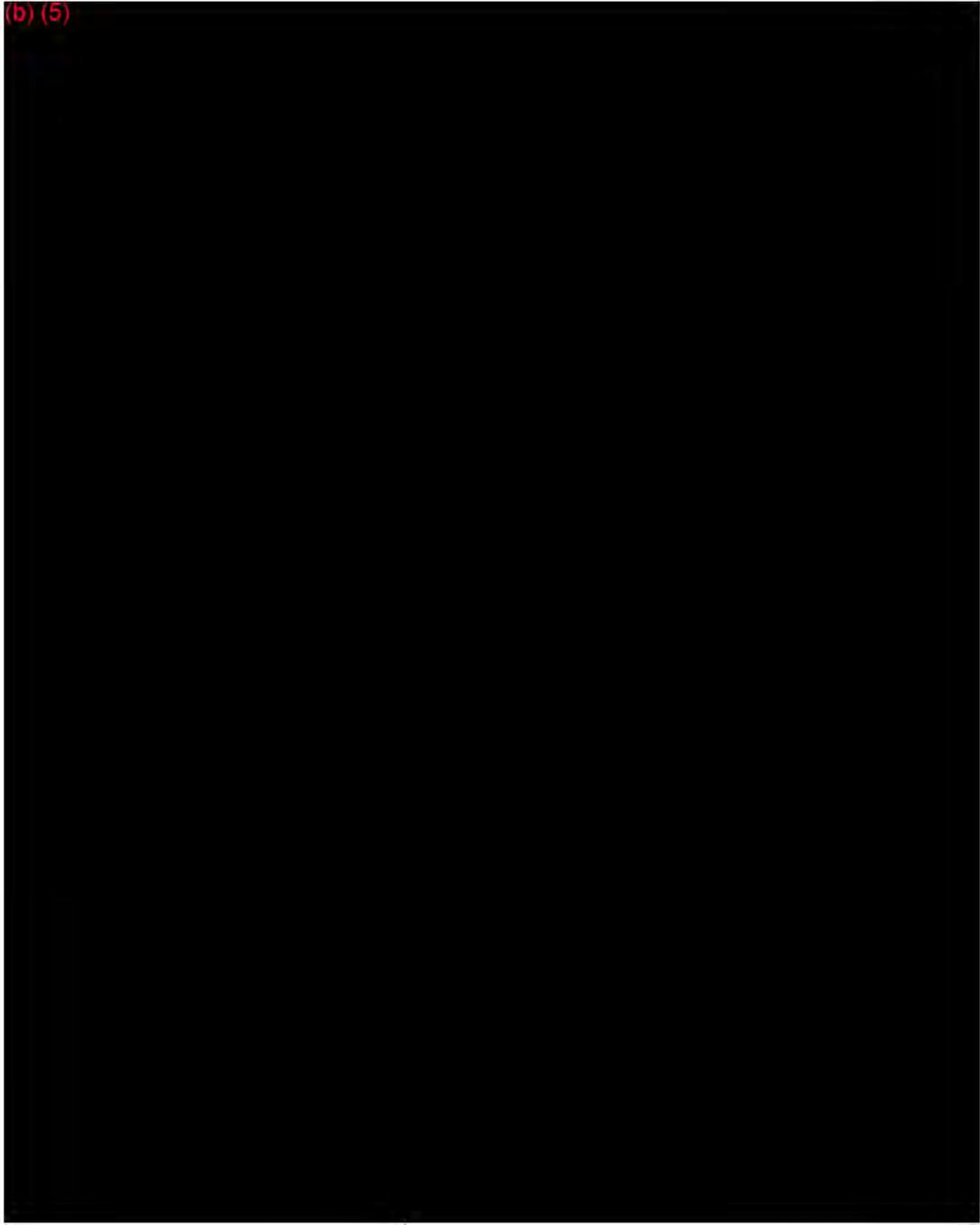
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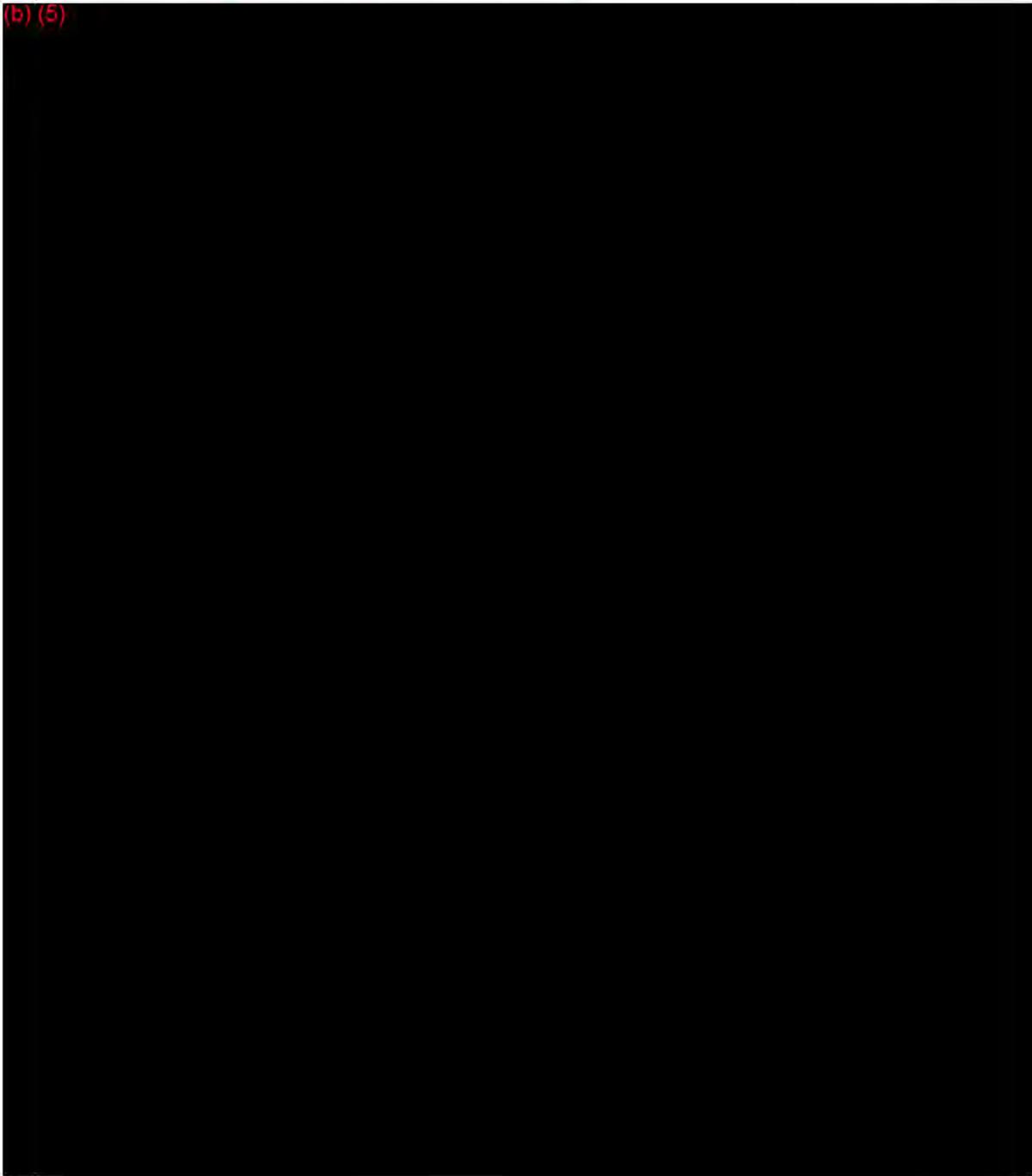
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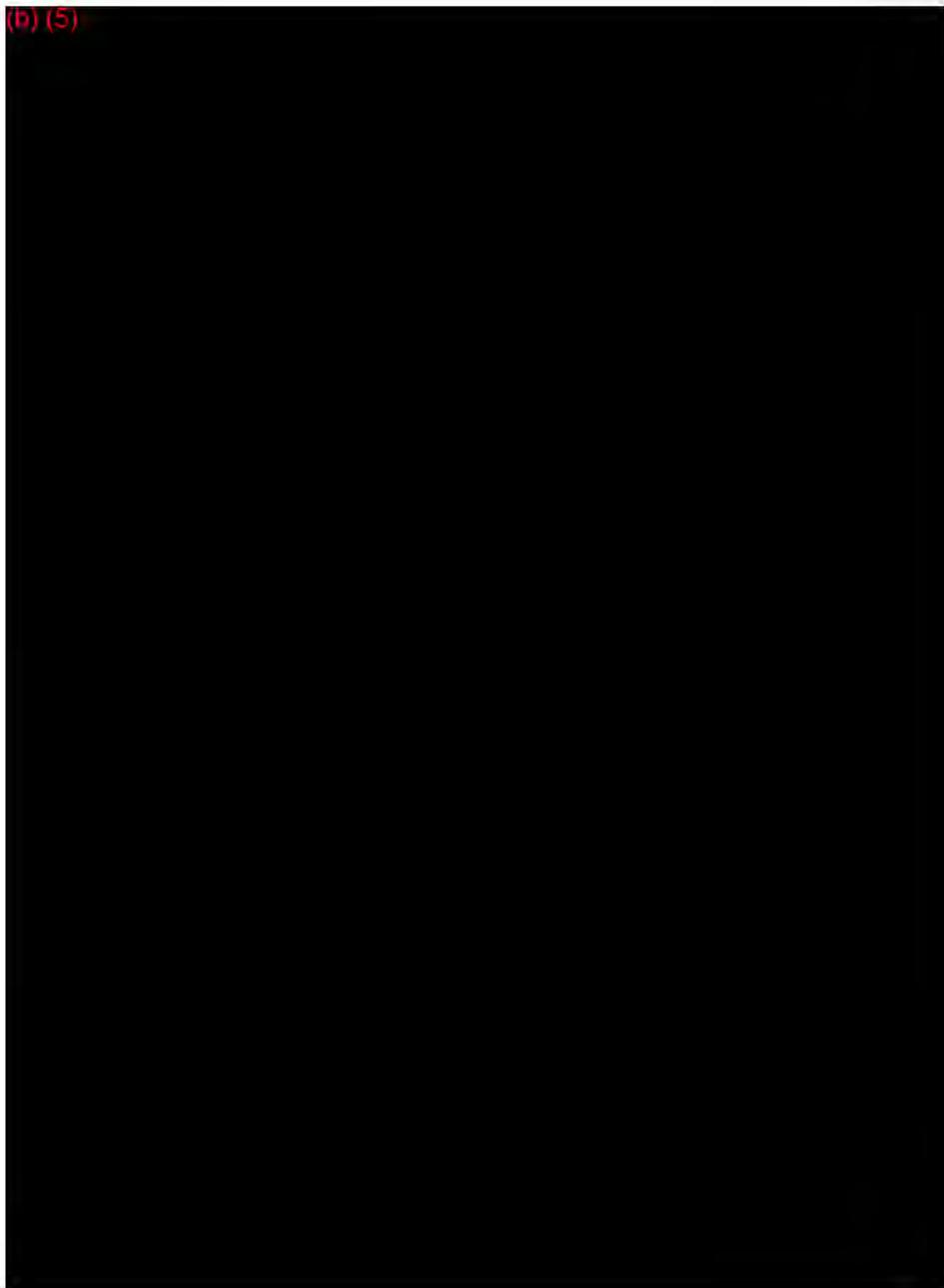
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(b) (5)



(b) (5)



From: [Califf, Robert](#)
To: [McCall, Jonathan *](#)
Subject: FW: draft thoughts
Date: Tuesday, August 16, 2016 1:19:00 PM
Attachments: [20160814 eteplirsen draft thoughtsrscom_rmc.doc](#)

Now here are my reactions to Rachel's comments and changes. As I said before, what I'd like is one document with all the comments included but changes made as indicated.

I'm available by phone if needed at (b) (6).

Thx

rmc

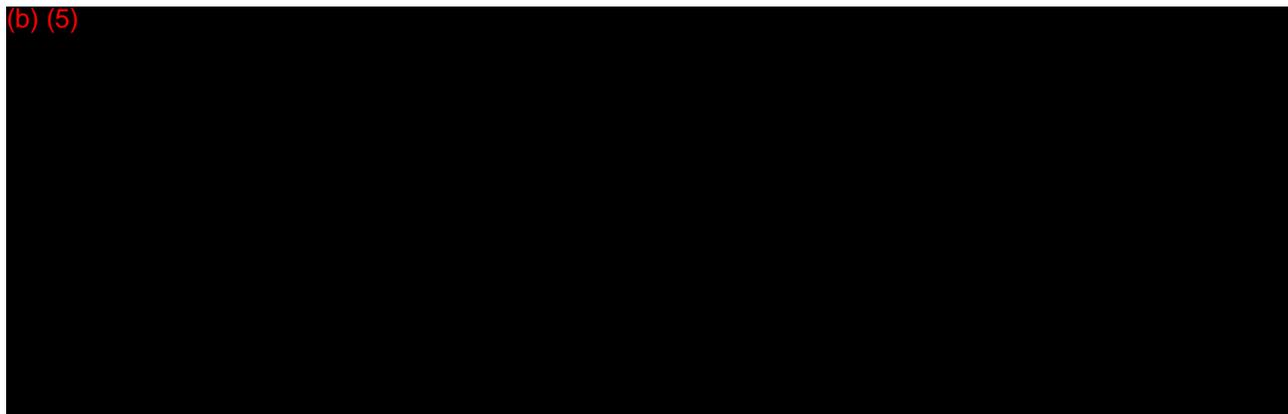
Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Monday, August 15, 2016 9:49 AM
To: Califf, Robert
Subject: RE: draft thoughts

Rob,

I have attached some initial thoughts, and suggestions, as comments to your document.

(b) (5)



1. Did Dr. Woodcock overstep her bounds and become "too" involved in this application – and was her level of involvement unusual for her or for the Center?

(b) (5)



2. Was Dr. Woodcock unduly influenced by patient advocates?

(b) (5)



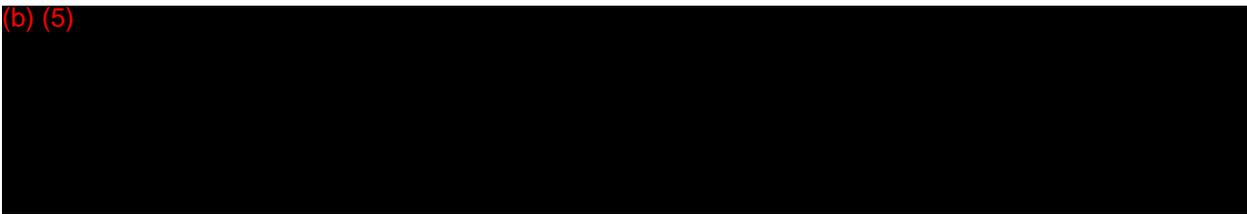
3. Was there a repressive atmosphere that inhibited free and open scientific exchange?

(b) (5)



4. Should this product be approved, does it set a “low bar” or encourage sloppy drug development?

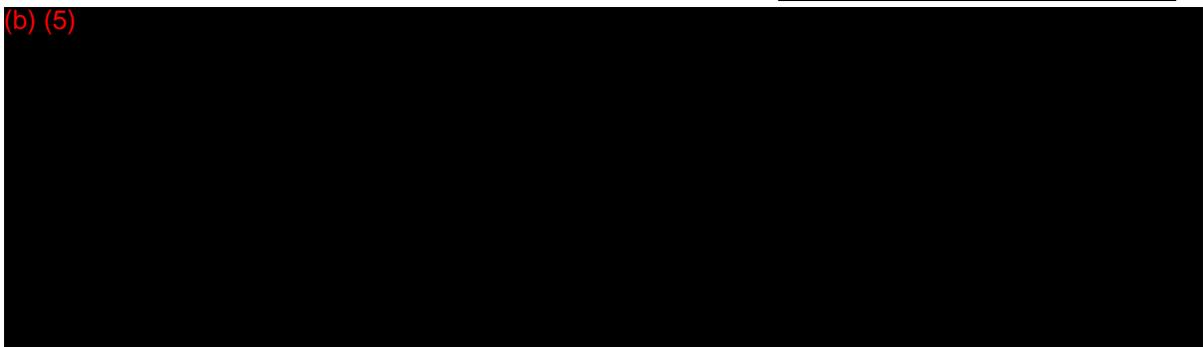
(b) (5)



There are several additional important points yet to be raised. (b) (5)



(b) (5)



On a personal note, I have spent the bulk of my career on expedited development. These conversations are strikingly similar to those we had in the late 1980s and early 1990s. The first “reasonably likely” approval was taken on the basis of subpart E; subpart H, with its safeguards, patterned after that action, was promulgated the following year. In the very early days we had only very immature development plans; as the entire community became more sophisticated the products, and the data to support their use, improved in quality. Some therapies are no longer used – some remain important. But the most striking lesson is that HIV is now a chronic disease and HCV is curable.

I believe the overarching lesson is that in the end, when faced with uncertainty of this magnitude, one makes the best possible decision that best serves the public. These decisions, optimally done in an atmosphere of consensus, are never straightforward.

I hope these thoughts are helpful. I am, of course, happy to discuss.

Rachel

From: Califf, Robert
Sent: Sunday, August 14, 2016 5:55 PM
To: Sherman, Rachel
Subject: draft thoughts

Rachel,

These are draft thoughts and in no way a final decision. I'm interested in your critique and reaction. I know that you have met with both Dr. Woodcock and Dr. Jenkins in your OMPT role and welcome your views as I formulate my final decision.

Thanks for your help with this delicate matter.

rmc

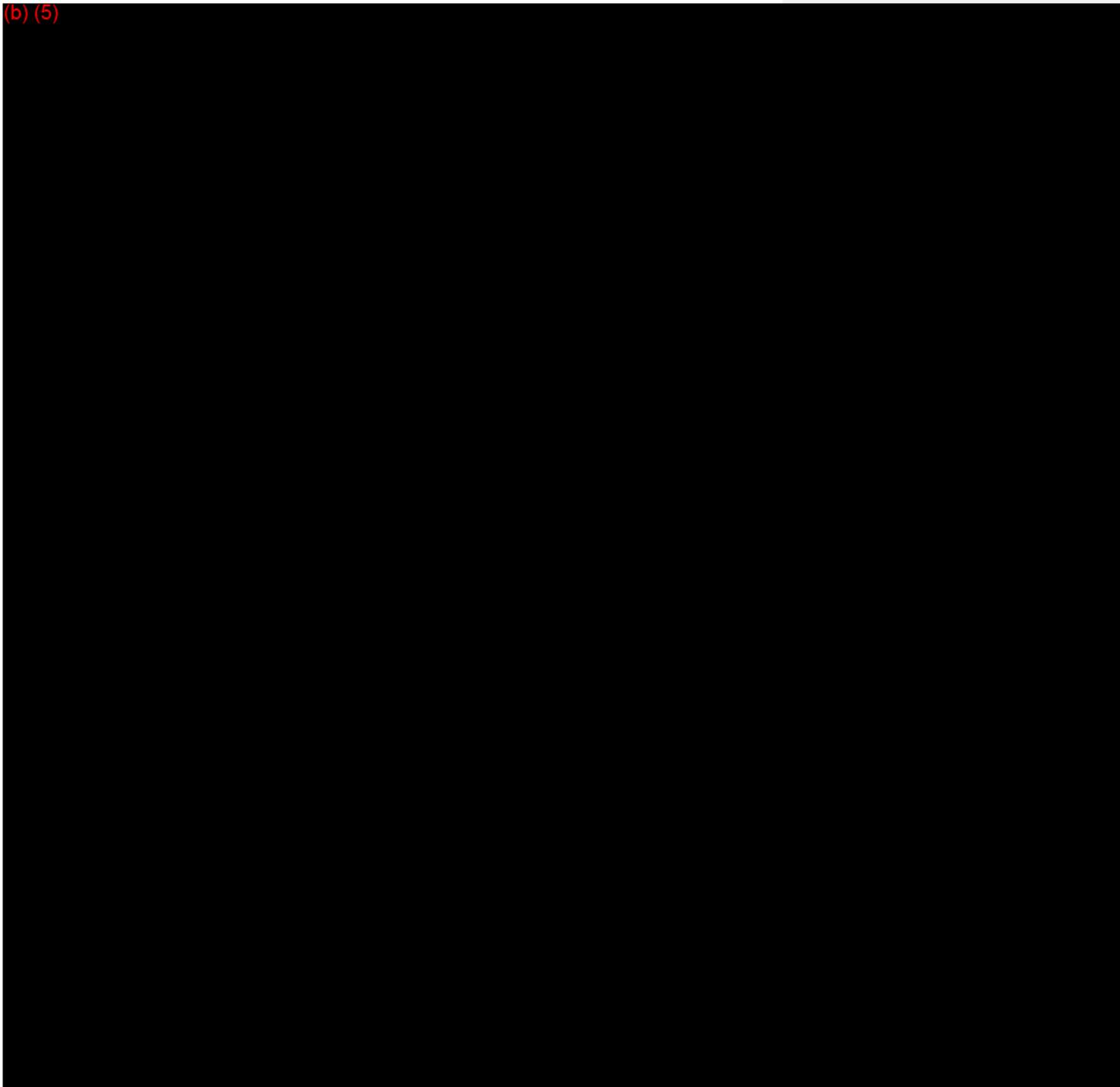
Robert M Califf MD
Commissioner of Food and Drugs

(b) (5)

(b) (5)

(b) (5)

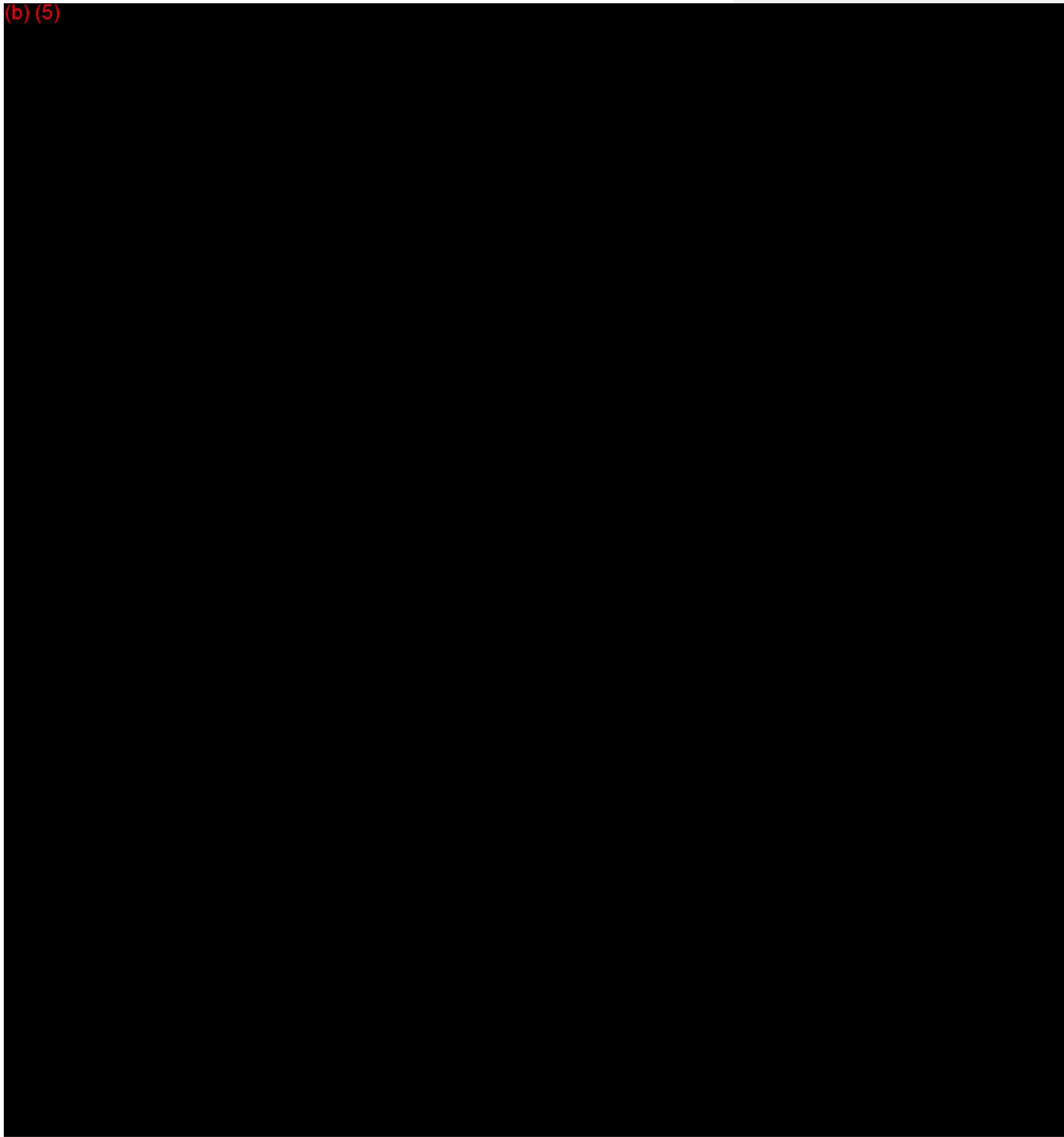
(b) (5)



(b) (5)

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(b) (5)

(b) (5)

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From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#)
Subject: FW: any time today for a quick checkin?
Date: Tuesday, August 16, 2016 3:46:00 PM
Attachments: [Eteplirsen_combined-comments_8-16-2016_rmc.doc](#)

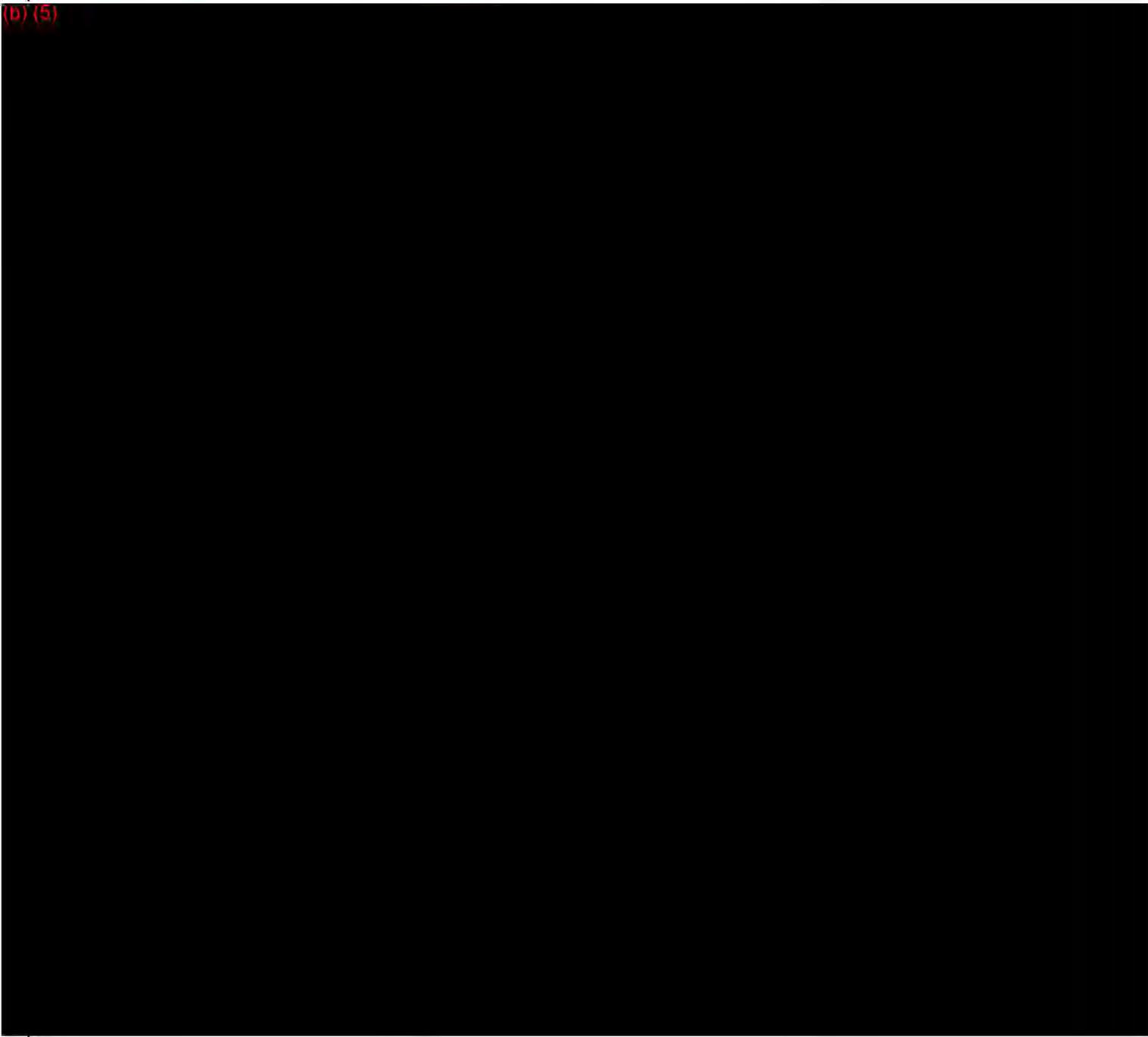
Here is where I am. I've kept all the comments. I plan to go back early in the AM and edit with some of Rachel's input. Also will add a conclusion. Need to (b) (5) [REDACTED] [REDACTED] from other.

My editor, Jonathan McCall is working with it to keep version control and make sure there is a record.

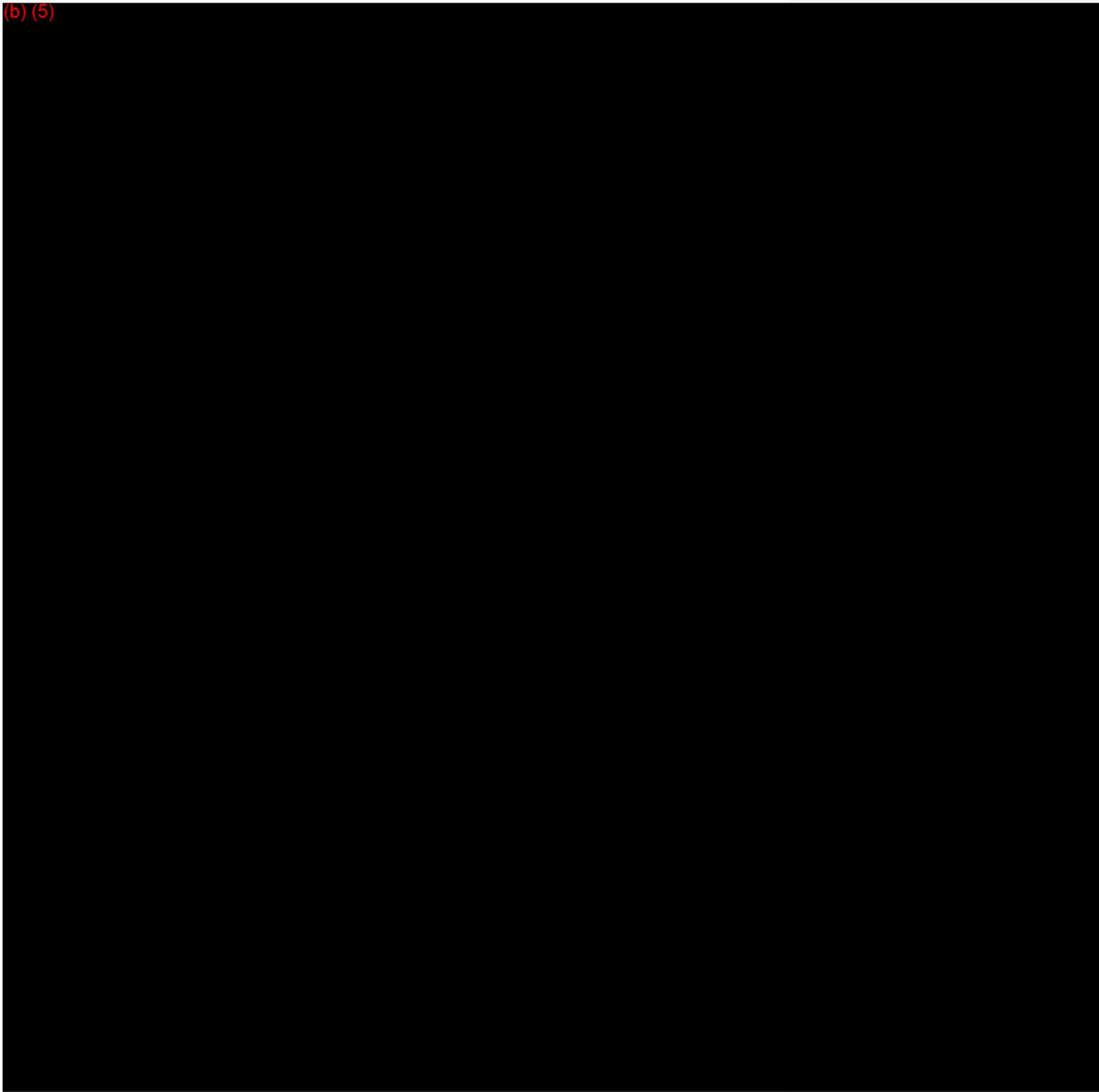
rmc

Robert M Califf MD
Commissioner of Food and Drugs

(b) (5)



(b) (5)



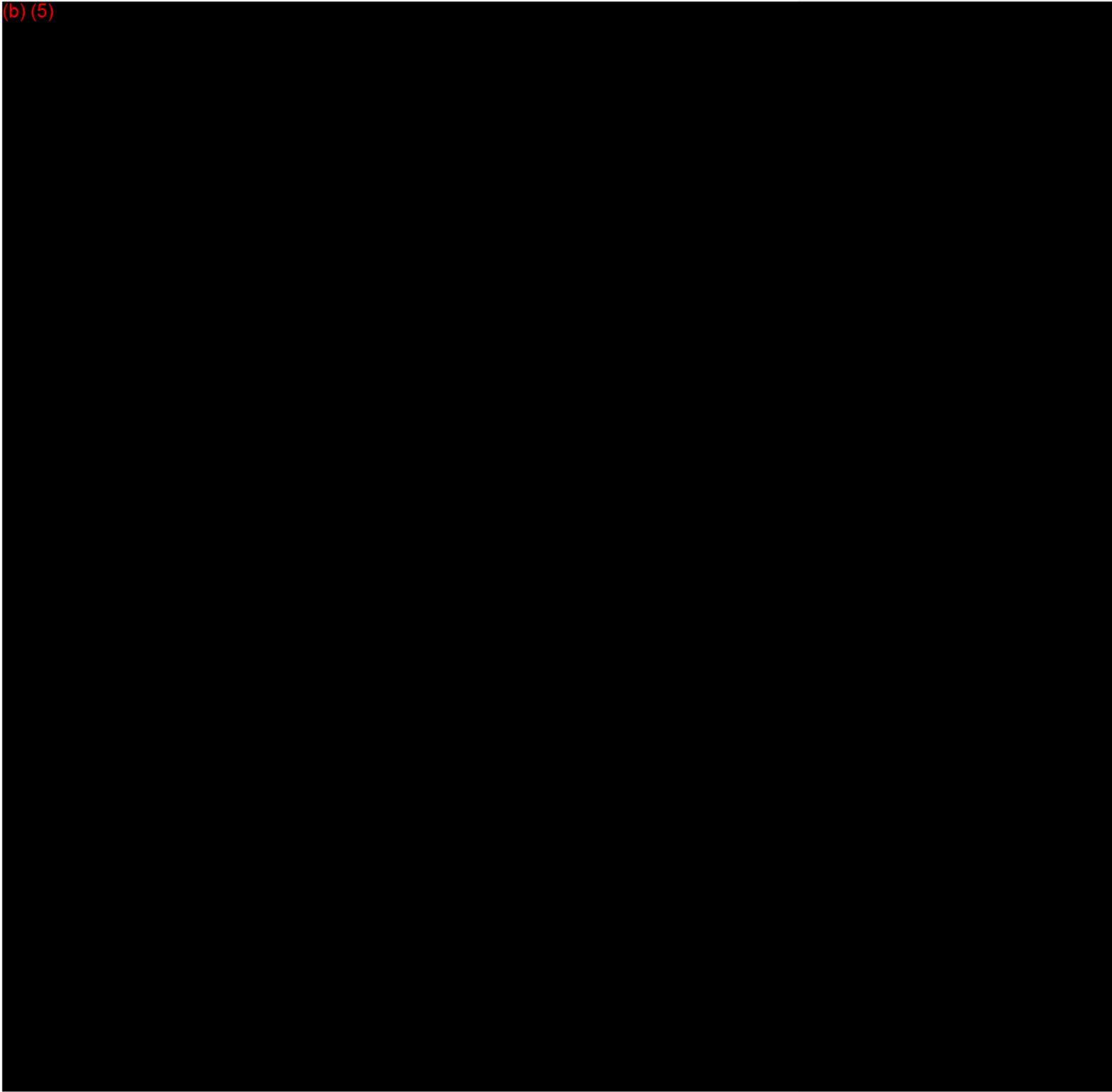
(b) (5)

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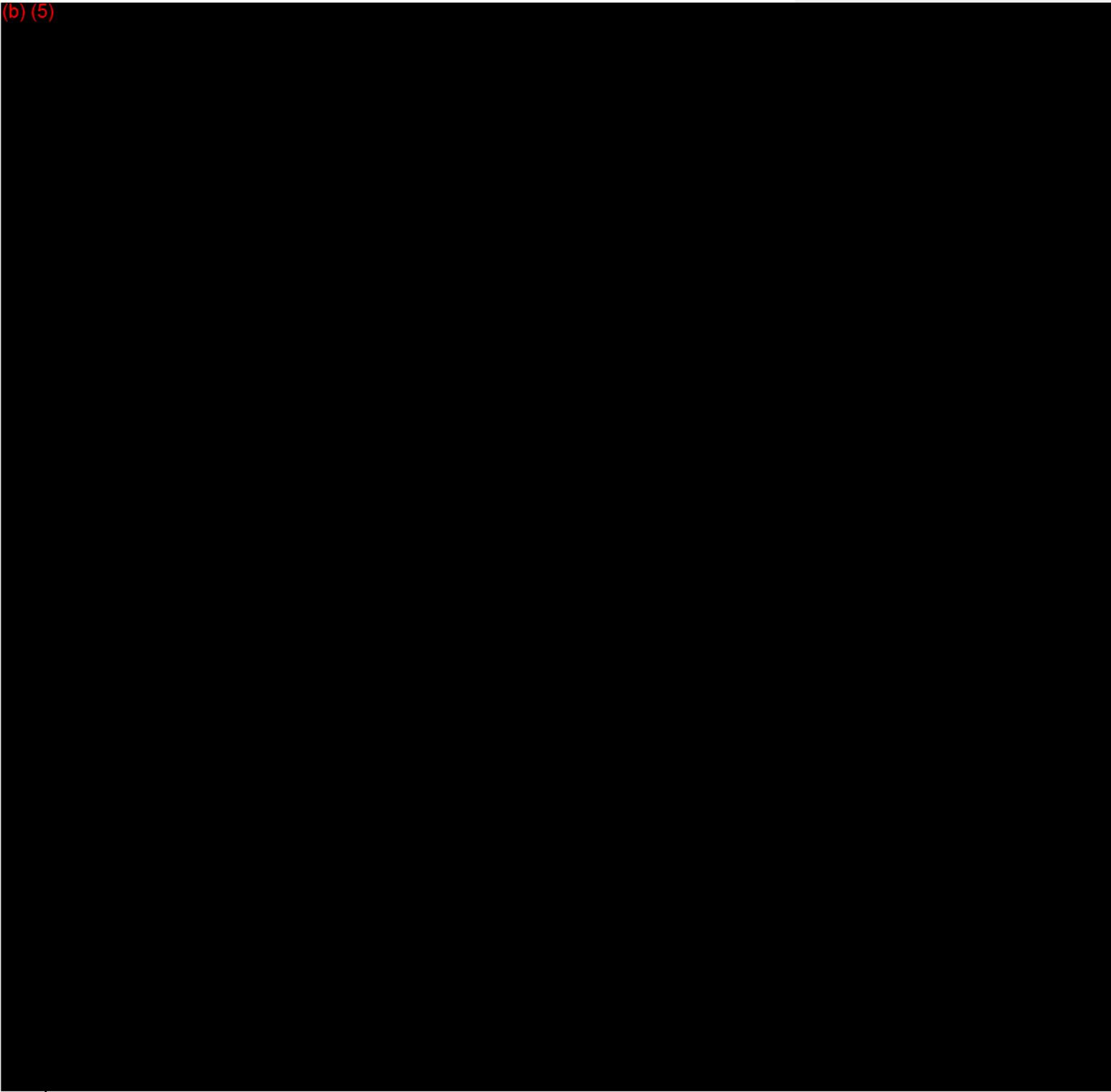


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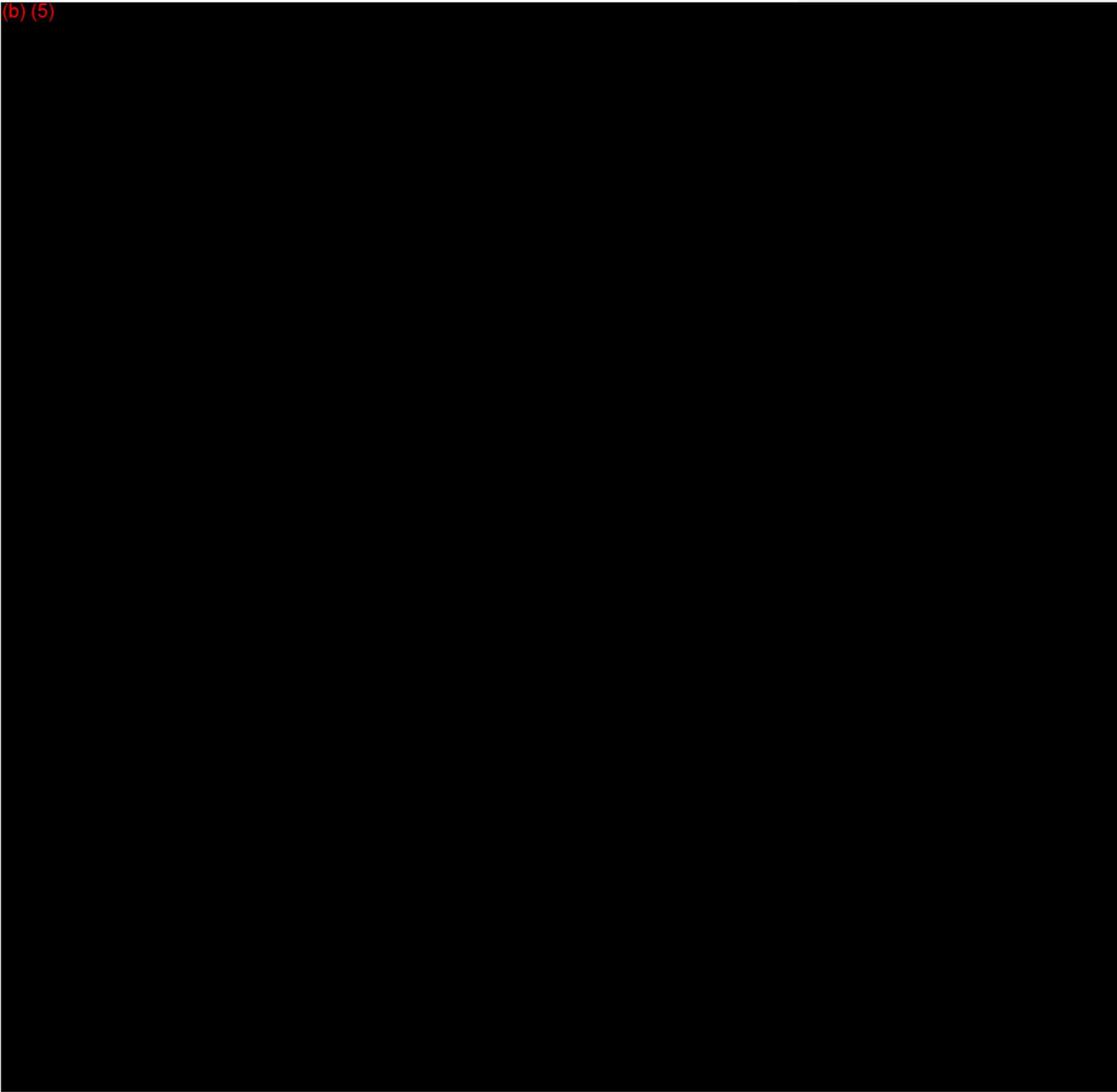


(b) (5)

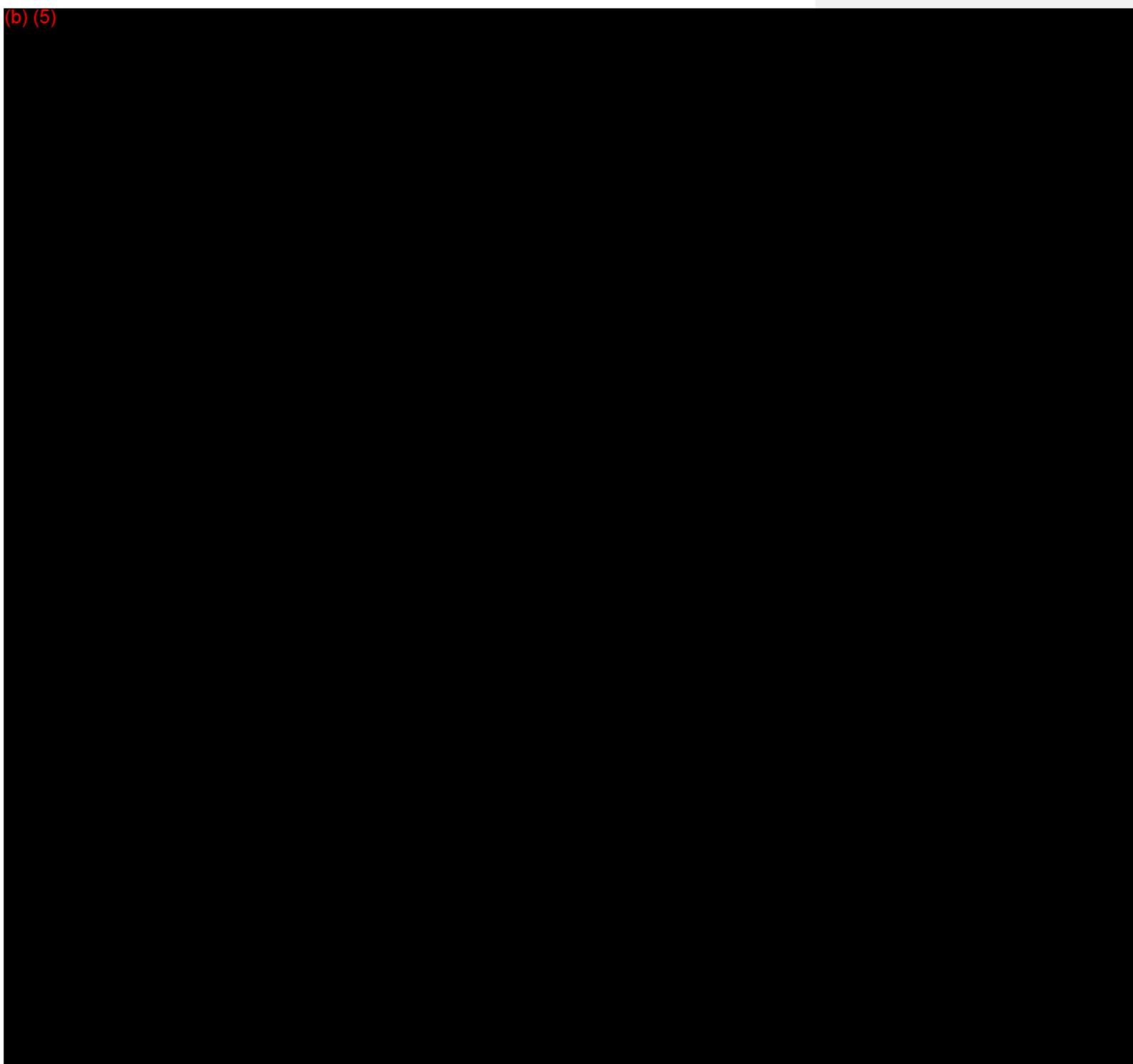
(b) (5)



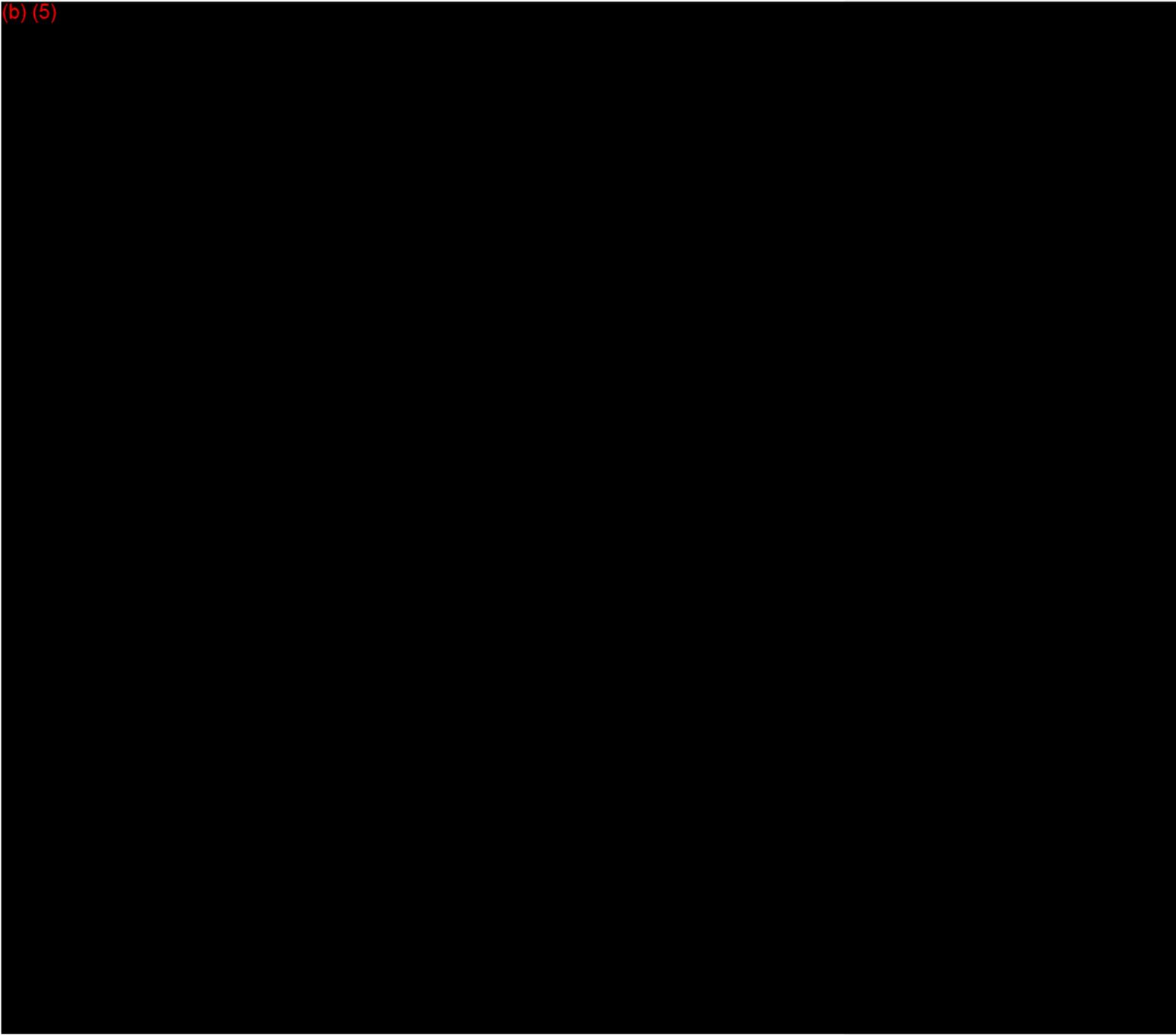
(b) (5)



(b) (5)



(b) (5)



From: [Califf, Robert](#)
To: [Sherman, Rachel](#)
Subject: FW: any time today for a quick checkin?
Date: Tuesday, August 16, 2016 4:10:00 PM
Attachments: [Eteplirsen_combined-comments_8-16-2016_rmc.doc](#)

Current version. Call when you can at (b) (6). I plan to go through and edit to the tune of your retained comments in the AM. Jonathan is now helping out.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

(b) (5)

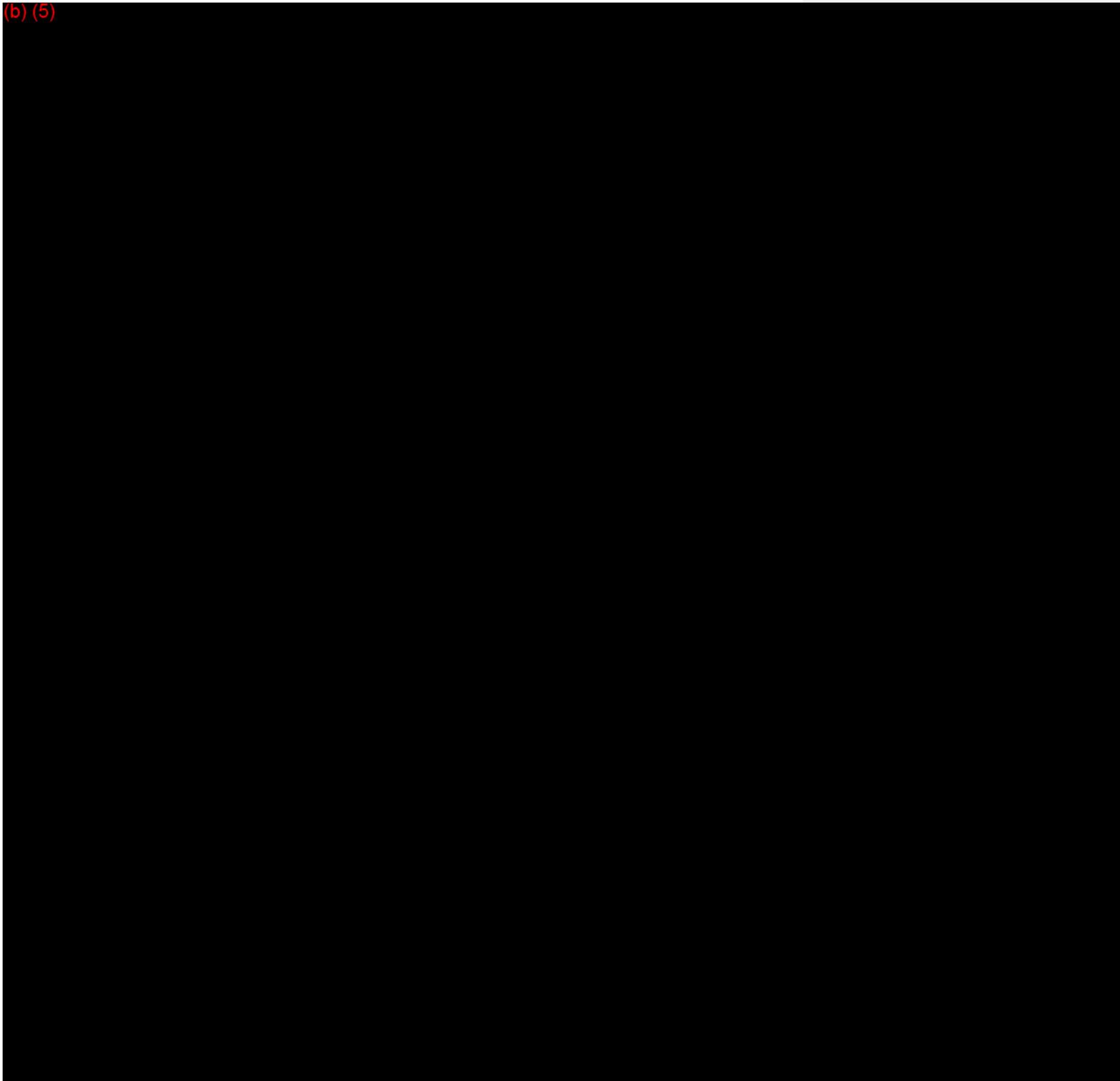


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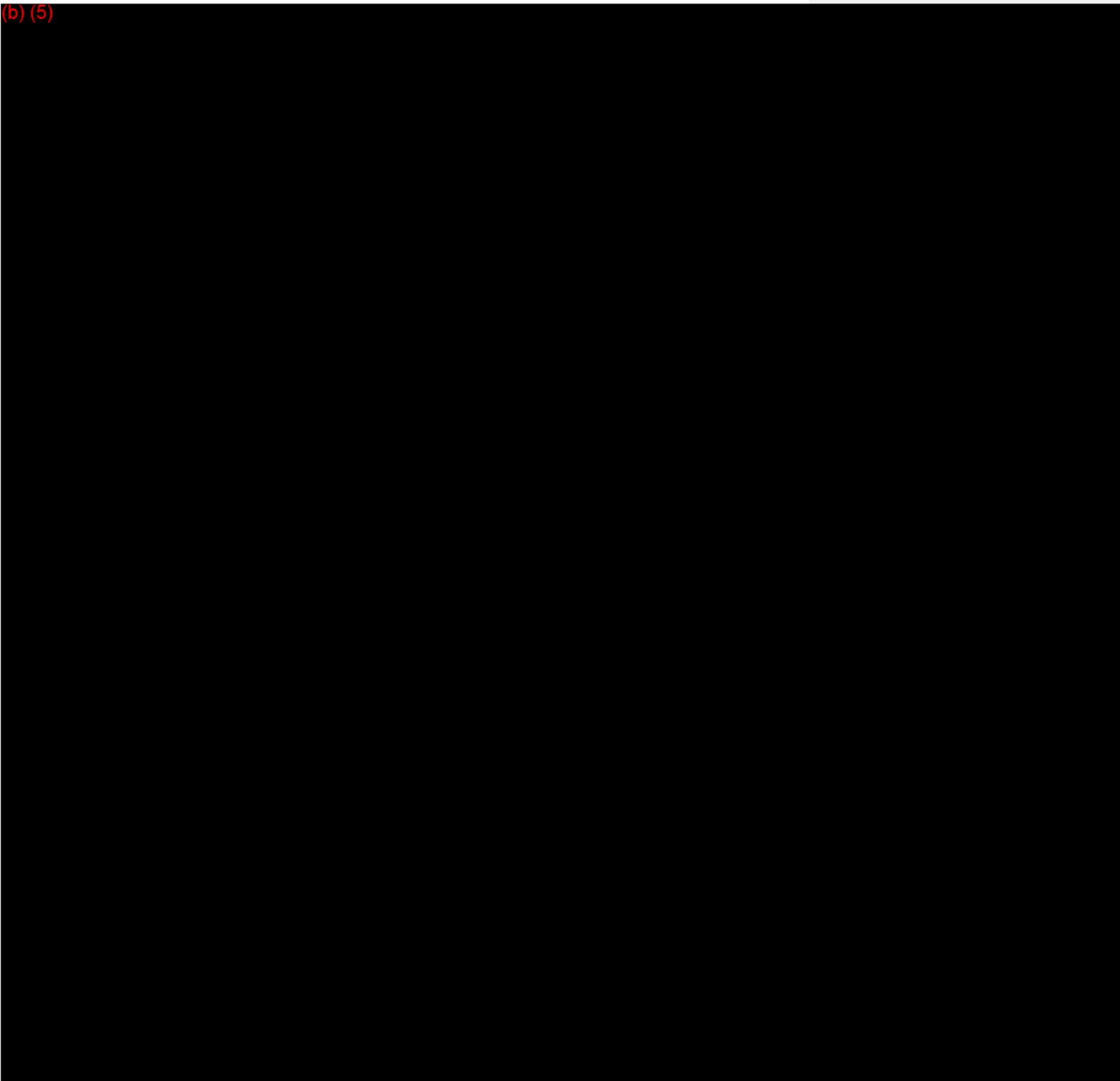


(b) (5)

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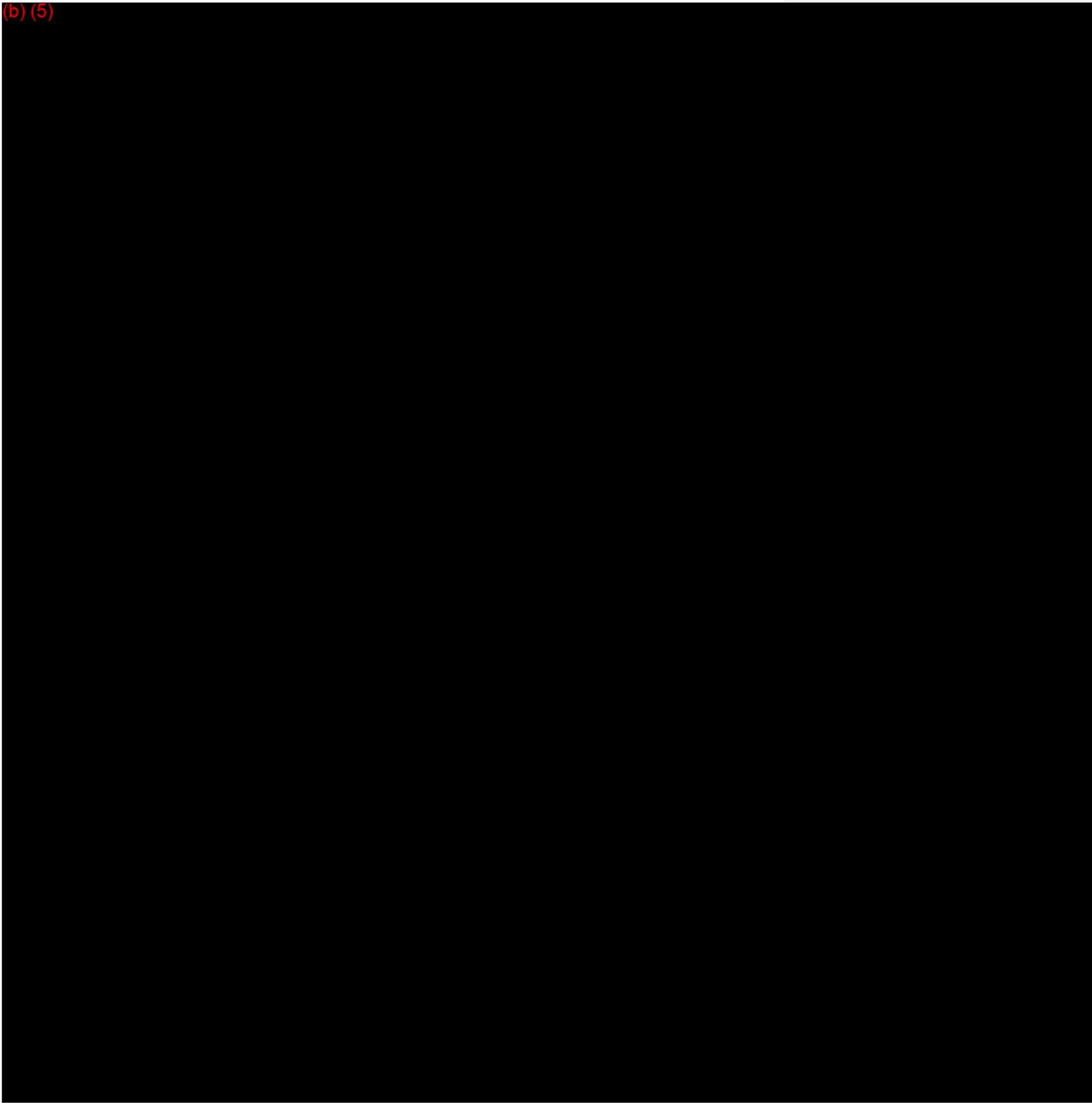


(b) (5)

(b) (5)



(b) (5)



(b) (5)

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(b) (5)



(b) (5)

From: [Califf, Robert](#)
To: [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [McCall, Jonathan *](#)
Subject: RE: next draft
Date: Thursday, August 18, 2016 8:29:00 AM

I can't go that far. But I'm not writing this to agree or disagree with Janet. I'm deferring to her proper role and not over-ruling her. In doing so I need to justify that her behavior was ok (since it was challenged) and ensure that her argument is rational and supportable.

An example where this couldn't possibly be right is (b) (5)

[REDACTED]

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Thursday, August 18, 2016 8:26 AM
To: Dickinson, Elizabeth (FDA); McCall, Jonathan *; Califf, Robert
Subject: RE: next draft

Yes and no. Because Janet does not agree that the quantity matters.

I'm on the fence about your first point. Does everyone agree that (b) (5)

[REDACTED]

From: Dickinson, Elizabeth (FDA)
Sent: Thursday, August 18, 2016 8:18 AM
To: Sherman, Rachel; McCall, Jonathan *; Califf, Robert
Subject: RE: next draft

Would this work? Not elegant, but clarifies the precise issue right up front.

(b) (5)

[REDACTED]

From: Sherman, Rachel
Sent: Thursday, August 18, 2016 8:03 AM
To: Dickinson, Elizabeth (FDA); McCall, Jonathan *; Califf, Robert
Subject: RE: next draft

Hi all,

I like Liz's edits. I'm not going to mark anything up – probably better if we discuss on the phone.

Thanks,
Rachel

From: Dickinson, Elizabeth (FDA)
Sent: Thursday, August 18, 2016 7:54 AM
To: Sherman, Rachel; McCall, Jonathan *; Califf, Robert
Subject: RE: next draft

I have added OCC's comments over Rachel's. In a few places I have made suggestions to address (b) (5) and should be the subject of further discussion between Rob and Rachel.

Happy to discuss.

Liz

From: Sherman, Rachel
Sent: Wednesday, August 17, 2016 6:40 PM
To: McCall, Jonathan *; Califf, Robert
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: next draft

Hi Liz,

Please find attached the "clean" version with my high level comments.

Rachel

From: McCall, Jonathan *
Sent: Wednesday, August 17, 2016 2:42 PM
To: Califf, Robert
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA)
Subject: RE: next draft

Hello all –

A tracked/commented version and a "clean" version with all changes accepted are attached. In addition to Dr. Califf's most recent additions, I've made minor edits for grammar, clarity, and flow (reflected in tracked version).

Please let me know if you have any questions!

Best,

Jonathan

From: Califf, Robert
Sent: Wednesday, August 17, 2016 11:51 AM
To: McCall, Jonathan *
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA)
Subject: next draft

Jonathan,

I think I'd like to:

1. Have you produce a new clean version.
2. Retain the version with all the suggestions and edits so we don't lose the thinking.

My major change here is adding a conclusion and "path forward". But I've also editorialized more based on Rachel's comments which were very helpful.

I will do another edit this afternoon. I'm currently re-reading the supporting material. AS you look at Jonathan's product please pay special attention to the degree to which my comments can be useful

(b) (5)

(b) (5)

Thanks for your help.

Rmc,

Robert M Califf MD
Commissioner of Food and Drugs

From: [Califf, Robert](#)
To: [Kraus, Tom](#)
Cc: [Palmer, Kelly](#)
Subject: RE: Rob's Report - for your review & clearance
Date: Friday, August 19, 2016 5:29:00 AM

Tom,

The change is good (b) (5)

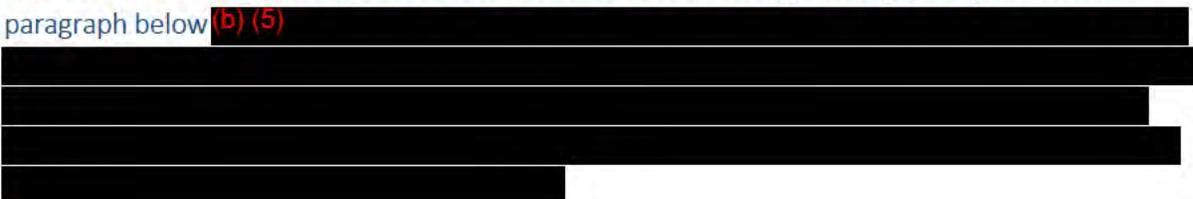


rmc

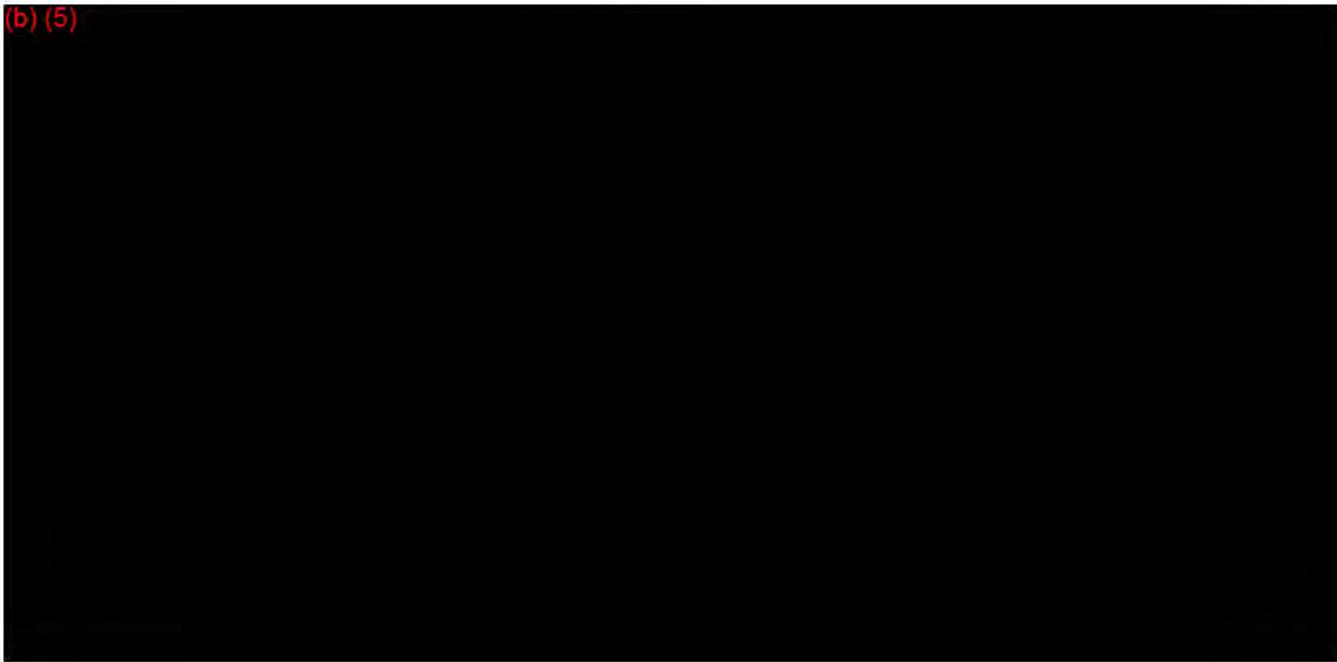
Robert M Califf MD
Commissioner of Food and Drugs

From: Kraus, Tom
Sent: Thursday, August 18, 2016 10:48 PM
To: Califf, Robert
Cc: Palmer, Kelly
Subject: FW: Rob's Report - for your review & clearance

Rob. I was reviewing Rob's report for this week and wanted to flag a thought for you. I think the paragraph below (b) (5)



(b) (5)



From: Koplow, Bret
Sent: Thursday, August 18, 2016 3:17 PM
To: Riley, Karen; Palmer, Kelly; Kraus, Tom
Cc: Raza, Mark
Subject: RE: Rob's Report - for your review & clearance

I've added a minor comment.

From: Riley, Karen
Sent: Thursday, August 18, 2016 3:07 PM
To: Palmer, Kelly; Koplow, Bret; Kraus, Tom
Subject: RE: Rob's Report - for your review & clearance

[Here you go.](#)

From: Palmer, Kelly
Sent: Thursday, August 18, 2016 2:59 PM
To: Riley, Karen; Koplow, Bret; Kraus, Tom
Subject: Rob's Report - for your review & clearance

Attached is this week's Rob's Report for your review and clearance. Please let me know if you have any edits/concerns. Thanks!

Non-legal comment: There is a risk that some may construe this phrase to mean that on occasion the Agency makes decisions based only on poor-quality evidence. Such a statement could be used to criticize the Agency. Perhaps this could be reworded to avoid this risk.

From: [Califf, Robert](#)
To: [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Cc: [McCall, Jonathan *](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: next draft
Date: Monday, August 22, 2016 3:31:00 PM

OK, I've looked it over. Seems like we're in striking distance. Will respond to all of these by this evening.

rmc

From: Sherman, Rachel
Sent: Monday, August 22, 2016 12:57 PM
To: Chasan-Sloan, Deborah (FDA); Califf, Robert
Cc: McCall, Jonathan *; Dickinson, Elizabeth (FDA)
Subject: RE: next draft

Hi,

To move things along I took a peak.

I removed a few more comments and added a couple in response to Deborah's edits.

(b) (5)

Rob, if you feel strongly that a reference should be retained Deborah has created a footnote that works.

Note I did not correct update the header, just the file name.

Rob, I think you're next after your meetings.

Rachel

From: Chasan-Sloan, Deborah (FDA)
Sent: Monday, August 22, 2016 12:34 PM
To: Califf, Robert
Cc: McCall, Jonathan *; Dickinson, Elizabeth (FDA); Sherman, Rachel
Subject: RE: next draft

All,

Attached are the consolidated comments from Rachel and me. For ease of review, I've deleted the comments that I believe to be resolved and have left in those that still require some consideration. Happy to discuss any of the comments and suggested edits.

Let me know when there's another draft you'd like us to review, perhaps after you've had the opportunity to speak with Drs. Borio, Woodcock, and Unger.

Thanks,

Deborah

From: Sherman, Rachel
Sent: Monday, August 22, 2016 9:28 AM
To: Chasan-Sloan, Deborah (FDA)
Cc: Califf, Robert; McCall, Jonathan *
Subject: RE: next draft

You will see a change a "(b) (5)" where we describe that SE is a matter of judgement.

Liz and I struggled with how to say something without making it sound as if we forgot. We were very close but I think this one last change make us even closer.

Everything else is highlighted mostly for Rob (unless we you agree with me...), except the comment about "(b) (5)". I think it will take Jonathan to clean up that sentence.

Happy to discuss.

From: Chasan-Sloan, Deborah (FDA)
Sent: Monday, August 22, 2016 9:24 AM
To: Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA); McCall, Jonathan *
Subject: Re: next draft

Thanks, Rachel. I'll take a look shortly.

From: Sherman, Rachel
Sent: Monday, August 22, 2016 9:13 AM
To: Califf, Robert; Dickinson, Elizabeth (FDA); McCall, Jonathan *
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: next draft

Hi all,

A few comments and questions inserted and one edit that tracks something Liz and I were pondering.

Deborah, you're up next.

Rachel

From: Califf, Robert
Sent: Monday, August 22, 2016 7:51 AM
To: Dickinson, Elizabeth (FDA); Sherman, Rachel; McCall, Jonathan *
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: next draft

OK, I think we're almost there. Not sure what the order for editing and reading should be.

I'm meeting with Dr. Borio this afternoon and will meet with Dr. Woodcock and Dr. Unger in next 48

FDAOC0001526

hours. At that point I can genuinely edit the section on the (b) (5)

Perhaps we should peg early next week to put this out.

Deborah, perhaps you should have first go at this?

rmc

From: Dickinson, Elizabeth (FDA)
Sent: Thursday, August 18, 2016 3:07 PM
To: Sherman, Rachel; McCall, Jonathan *; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: next draft

Rob (and Jonathan),

As promised, attached is a semi-clean revised draft incorporating the points on which we had agreement per the discussion earlier today, leaving in comments about revisions Dr. Califf will be making, and reorganizing slightly as discussed. Rachel has looked at this briefly already and I have incorporated her comments.

I hope it captures what we discussed.

Liz

From: Sherman, Rachel
Sent: Thursday, August 18, 2016 8:03 AM
To: Dickinson, Elizabeth (FDA); McCall, Jonathan *; Califf, Robert
Subject: RE: next draft

Hi all,

I like Liz's edits. I'm not going to mark anything up – probably better if we discuss on the phone.

Thanks,
Rachel

From: Dickinson, Elizabeth (FDA)
Sent: Thursday, August 18, 2016 7:54 AM
To: Sherman, Rachel; McCall, Jonathan *; Califf, Robert
Subject: RE: next draft

I have added OCC's comments over Rachel's. In a few places I have made suggestions to address (b) (5) and should be the subject of further discussion between Rob and Rachel.

Happy to discuss.

Liz

From: Sherman, Rachel
Sent: Wednesday, August 17, 2016 6:40 PM
To: McCall, Jonathan *; Califf, Robert
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: next draft

Hi Liz,

Please find attached the “clean” version with my high level comments.

Rachel

From: McCall, Jonathan *
Sent: Wednesday, August 17, 2016 2:42 PM
To: Califf, Robert
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA)
Subject: RE: next draft

Hello all –

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Please let me know if you have any questions!

Best,

Jonathan

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Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA)
Subject: next draft

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I think I’d like to:

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My major change here is adding a conclusion and “path forward”. But I’ve also editorialized more based on Rachel’s comments which were very helpful.

I will do another edit this afternoon. I’m currently re-reading the supporting material. AS you look at Jonathan’s product please pay special attention to the degree to which my comments can be useful

(b) (5)



Thanks for your help.

Rmc,

Robert M Califf MD
Commissioner of Food and Drugs

From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [Sherman, Rachel](#); [McCall, Jonathan *](#)
Cc: [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: RE: next draft
Date: Monday, August 22, 2016 7:51:00 AM
Attachments: [Eteplirsen_combined-comments_8-18-2016_reorganized_and_adopts_someRSOCCRCcomments_SEMI_CLEANrscm_rmc.doc](#)

OK, I think we're almost there. Not sure what the order for editing and reading should be.

I'm meeting with Dr. Borio this afternoon and will meet with Dr. Woodcock and Dr. Unger in next 48 hours. At that point I can genuinely edit the section on the (b) (5).

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rmc

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Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA)
Subject: next draft

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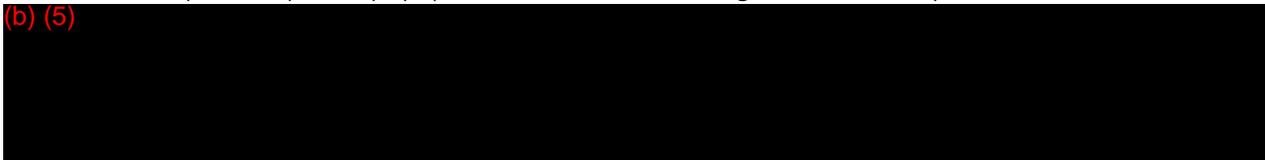
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(b) (5)

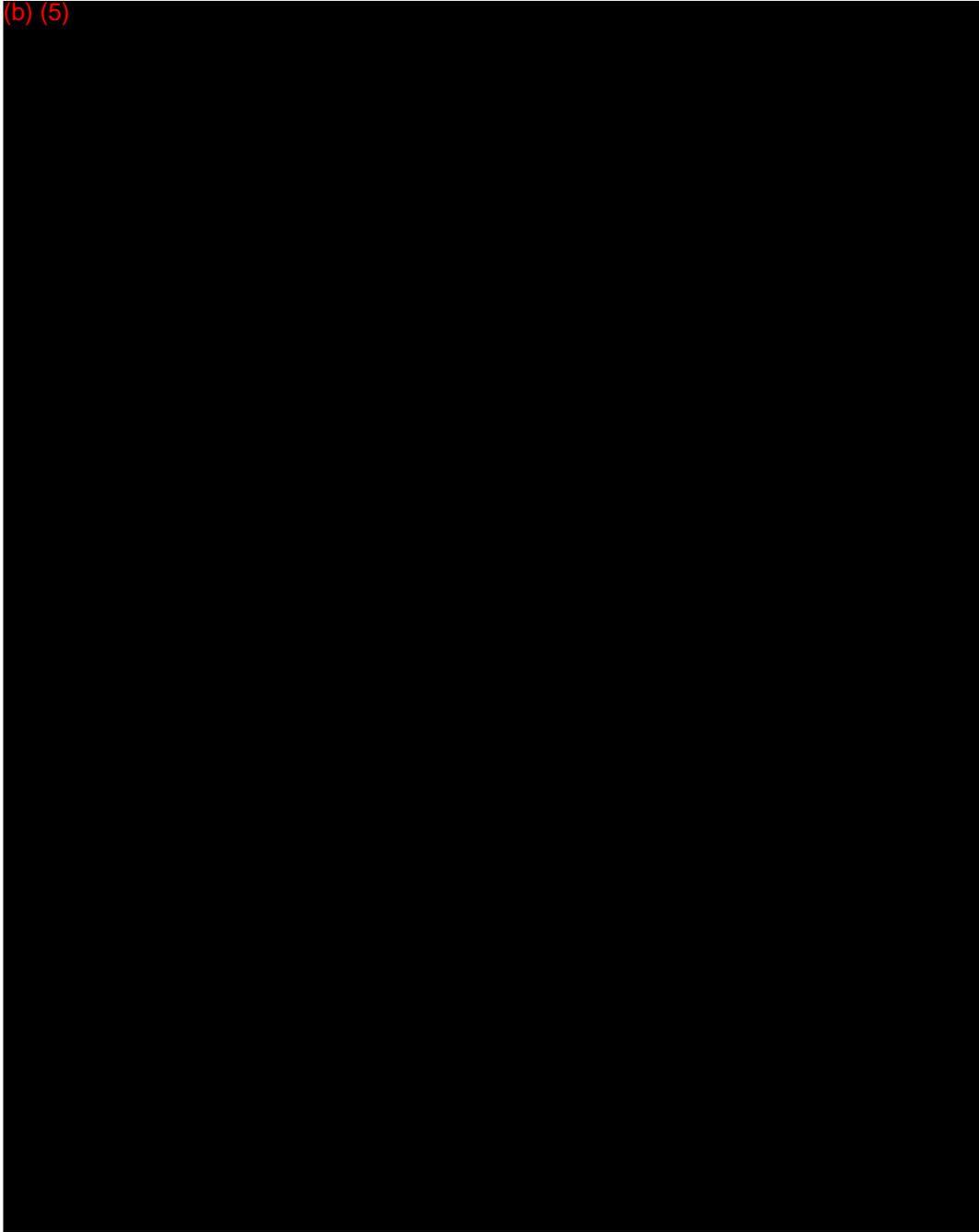


Thanks for your help.

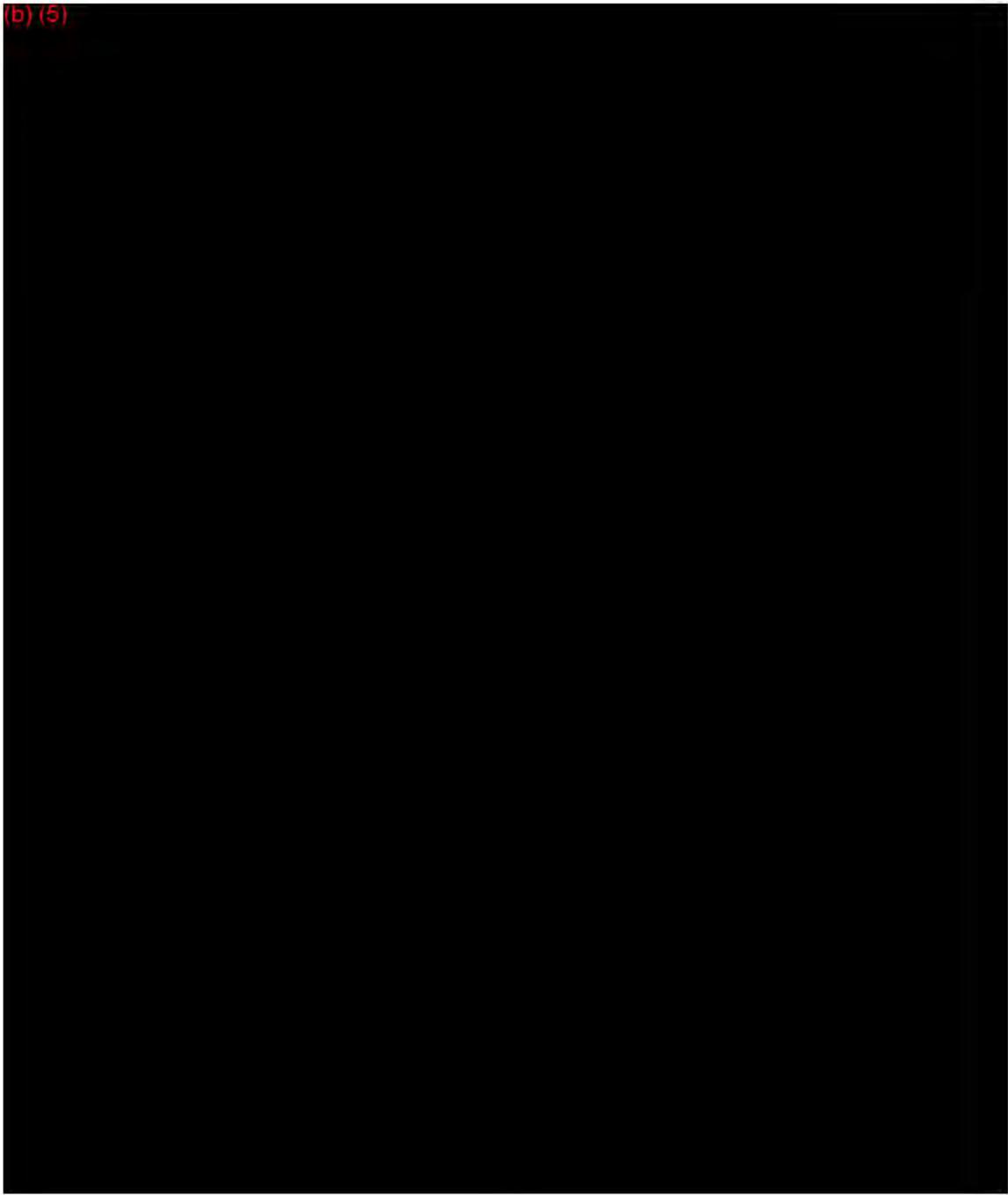
Rmc,

Robert M Califf MD
Commissioner of Food and Drugs

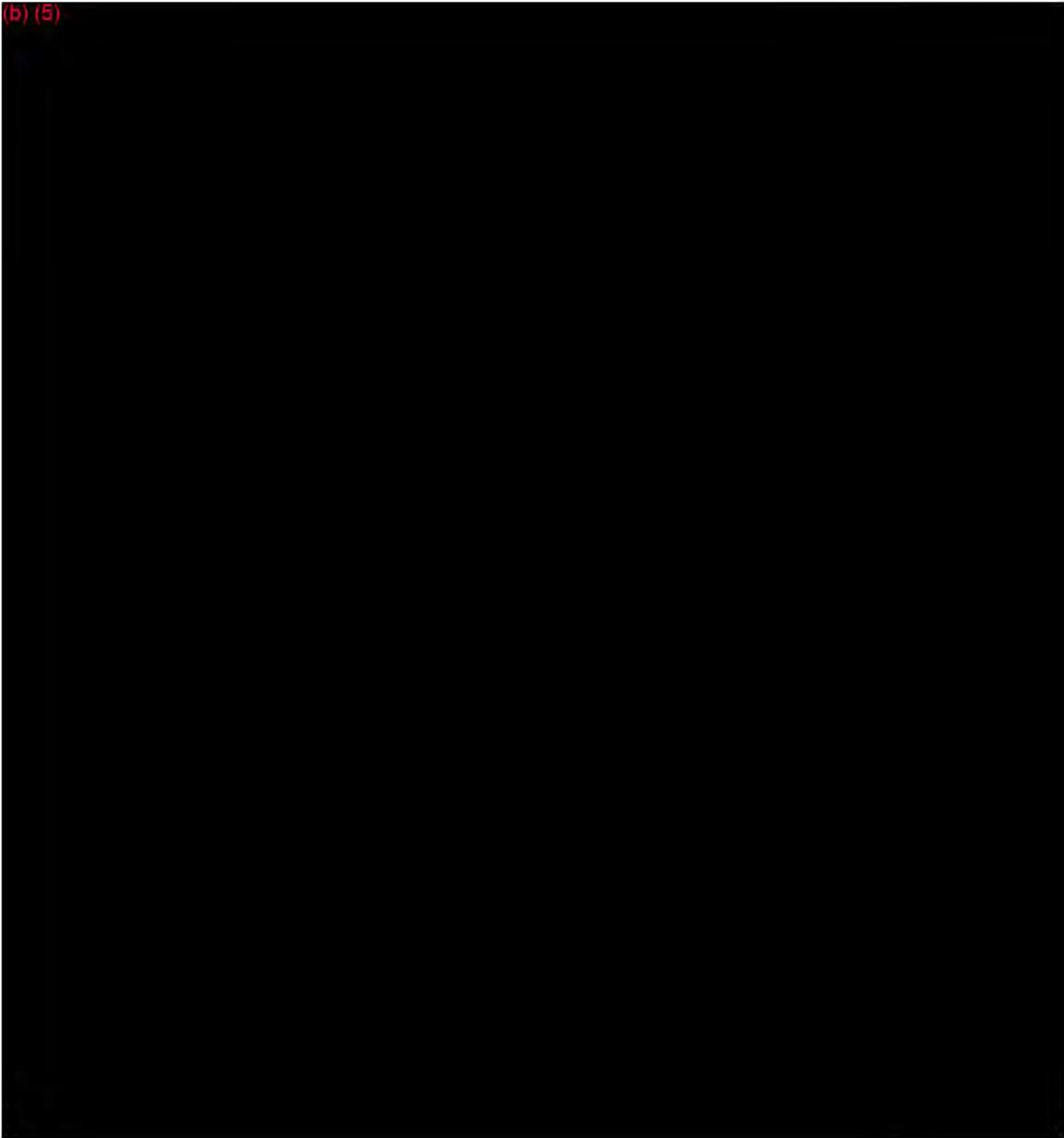
(b) (5)



(b) (5)



(b) (5)



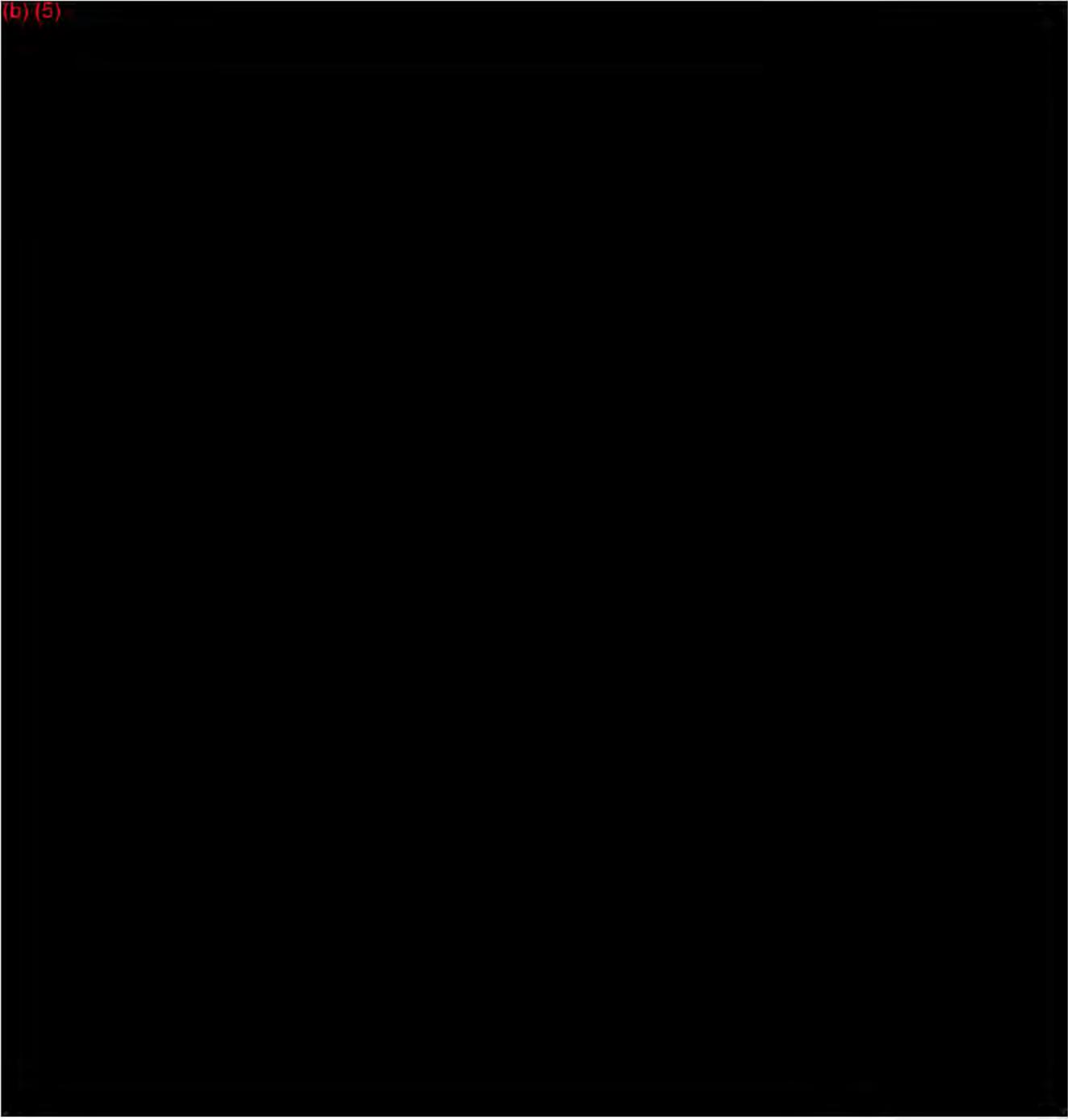
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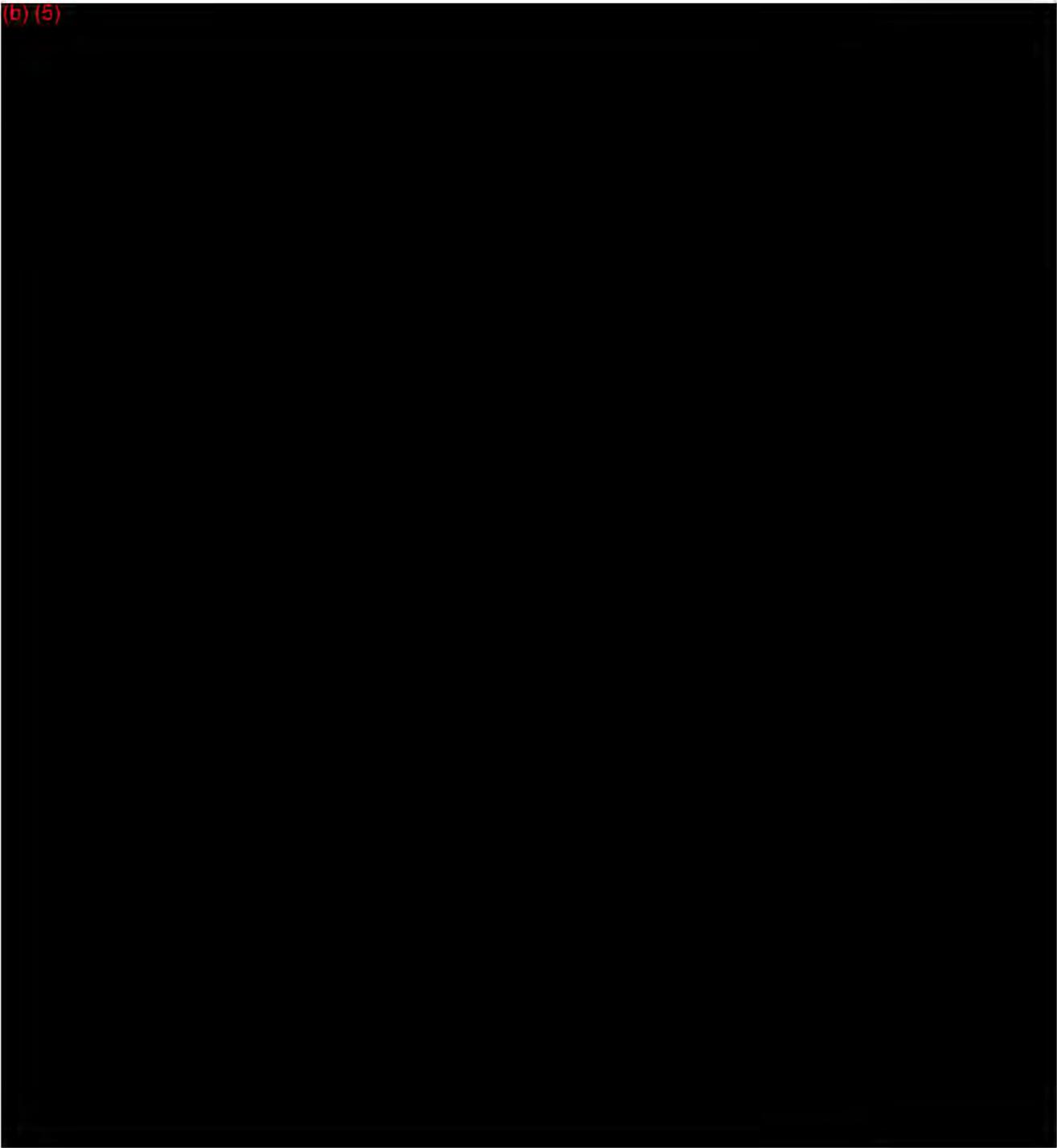
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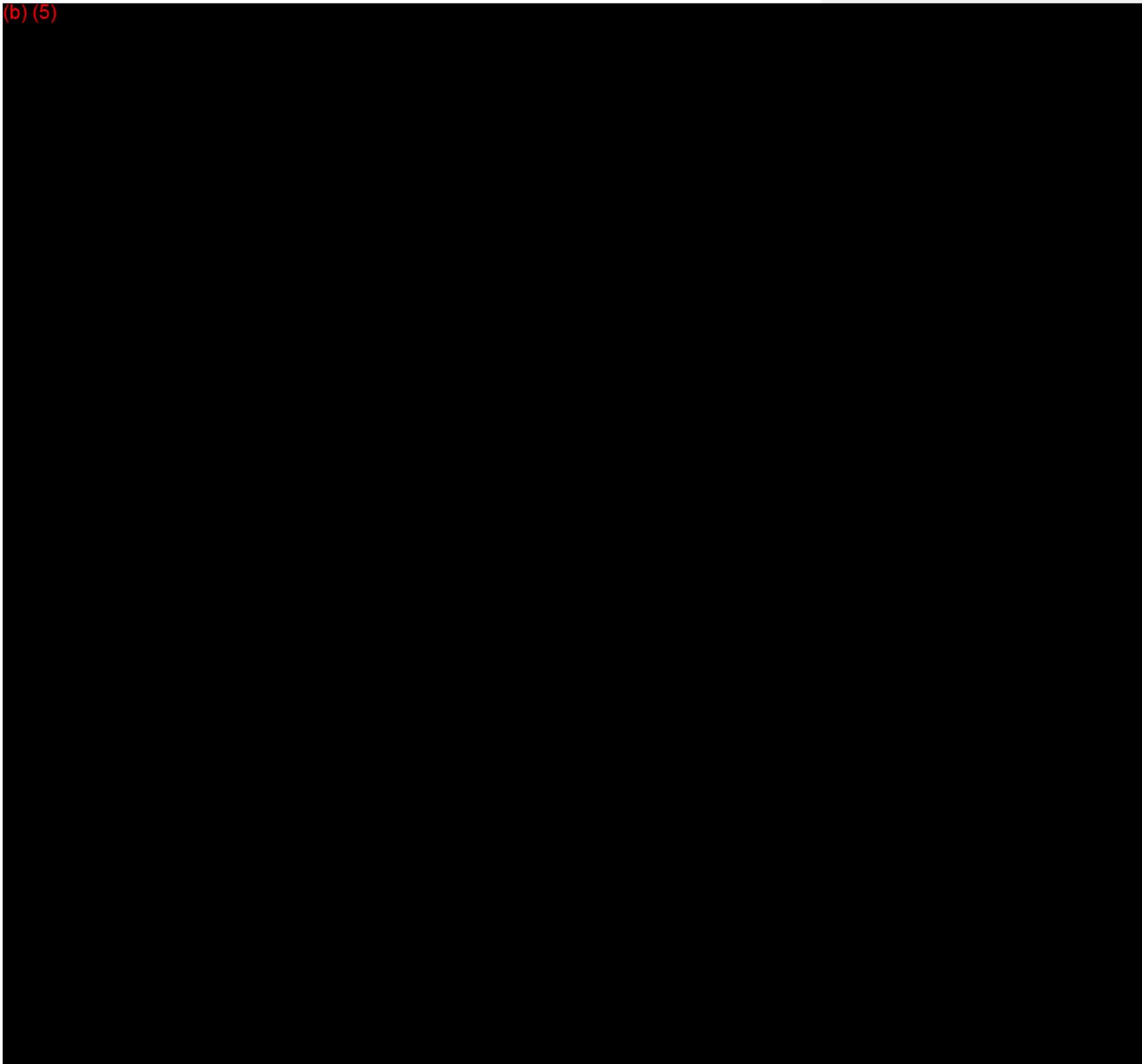
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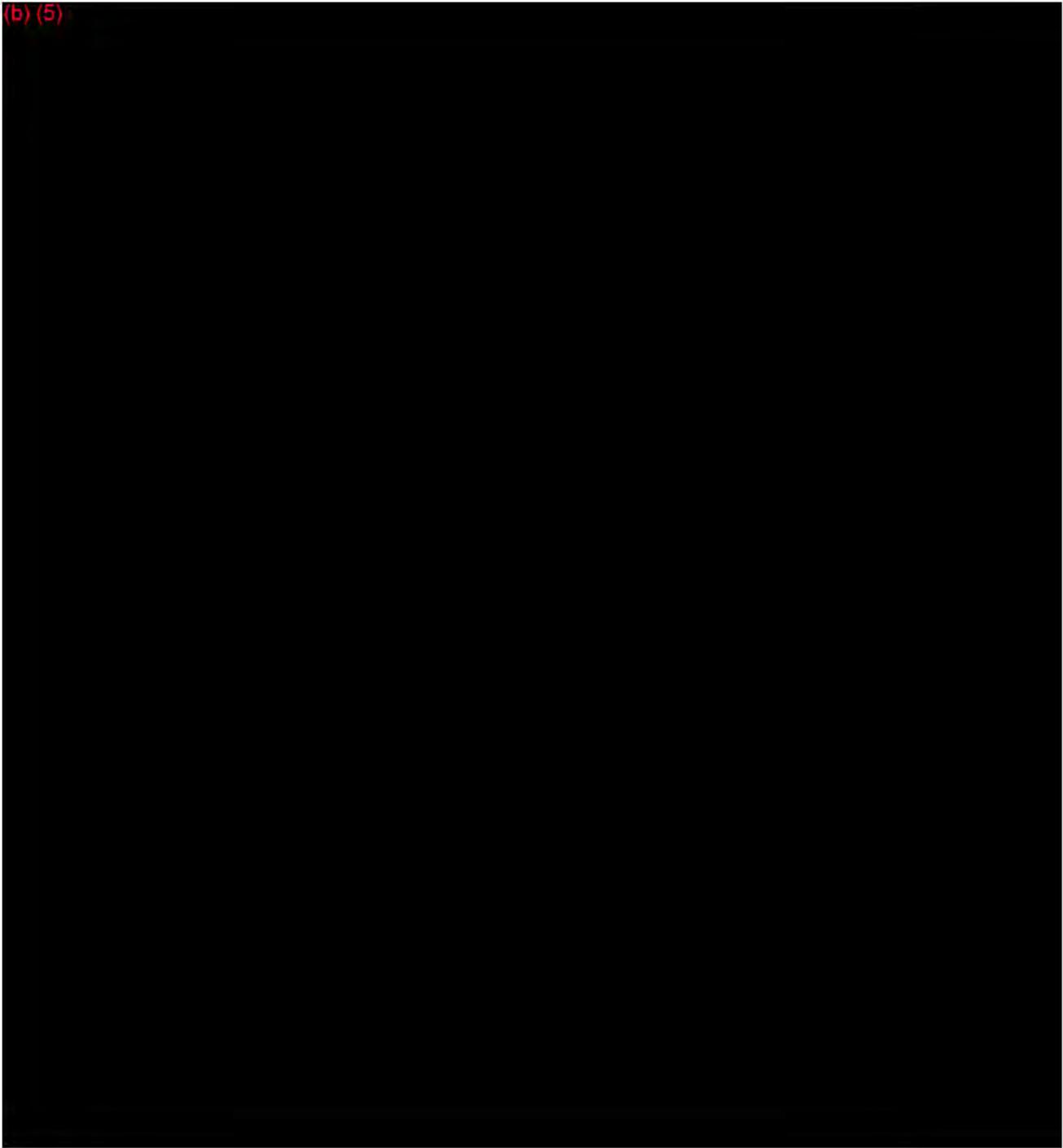
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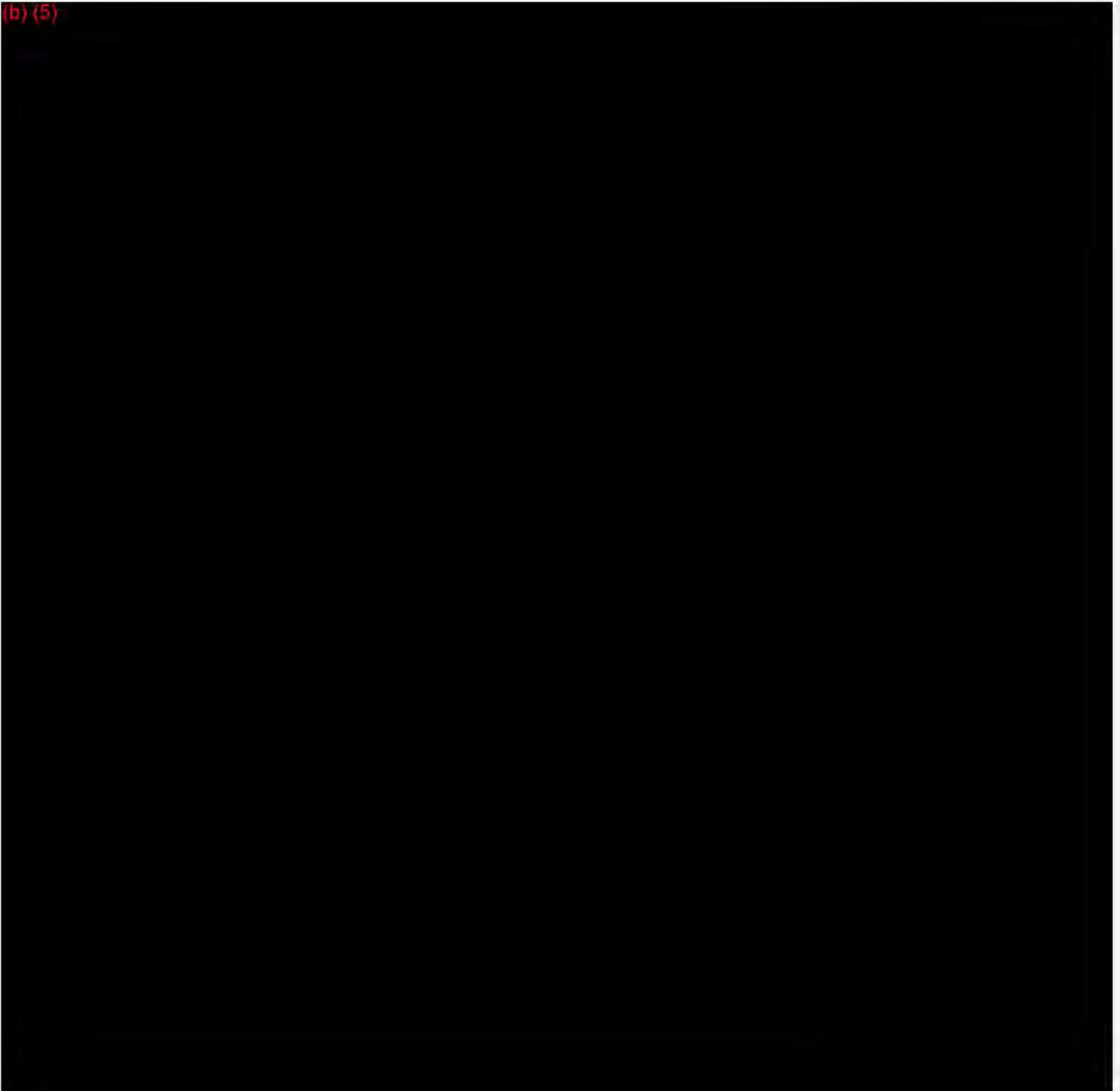
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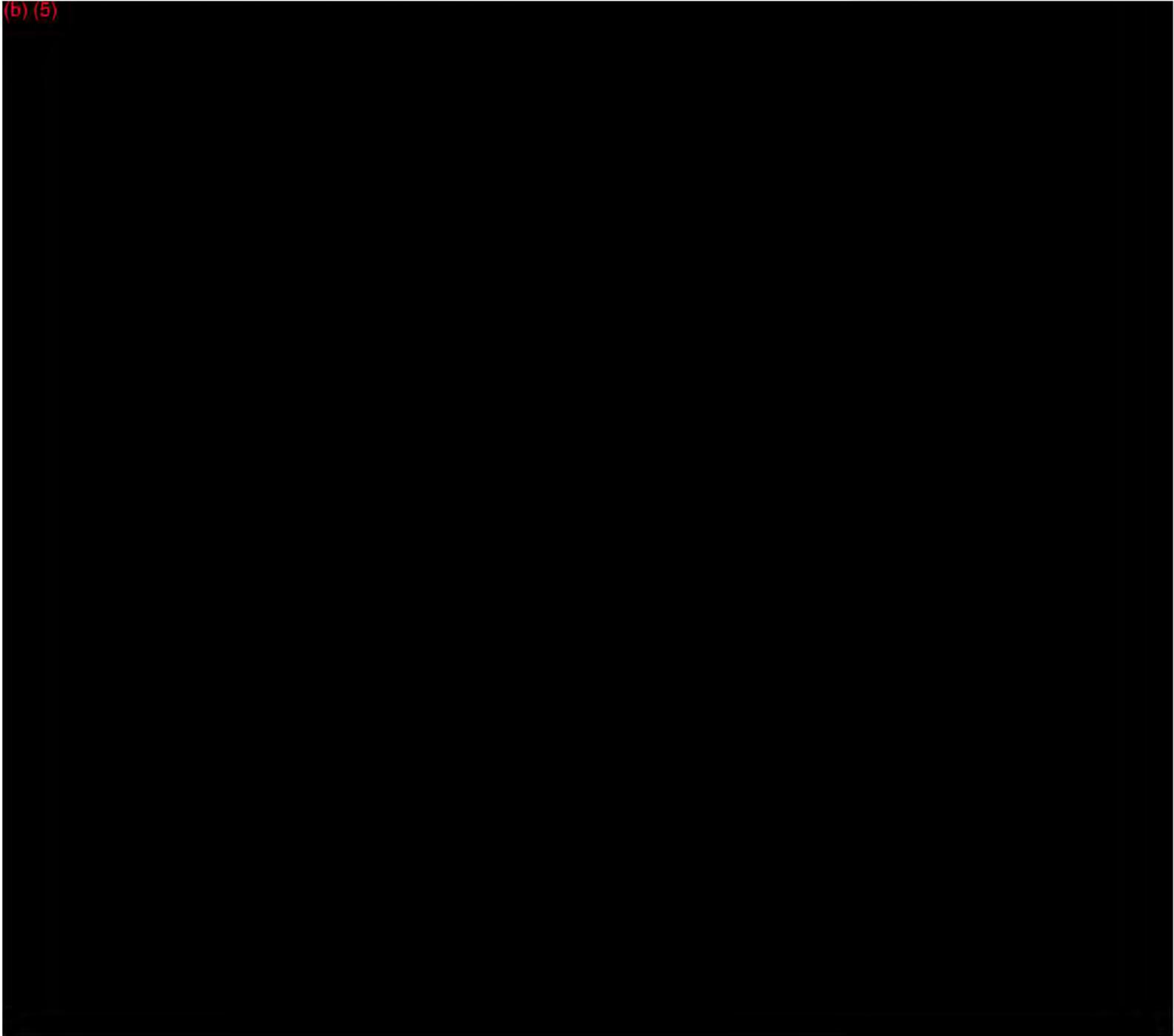
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(b) (5)



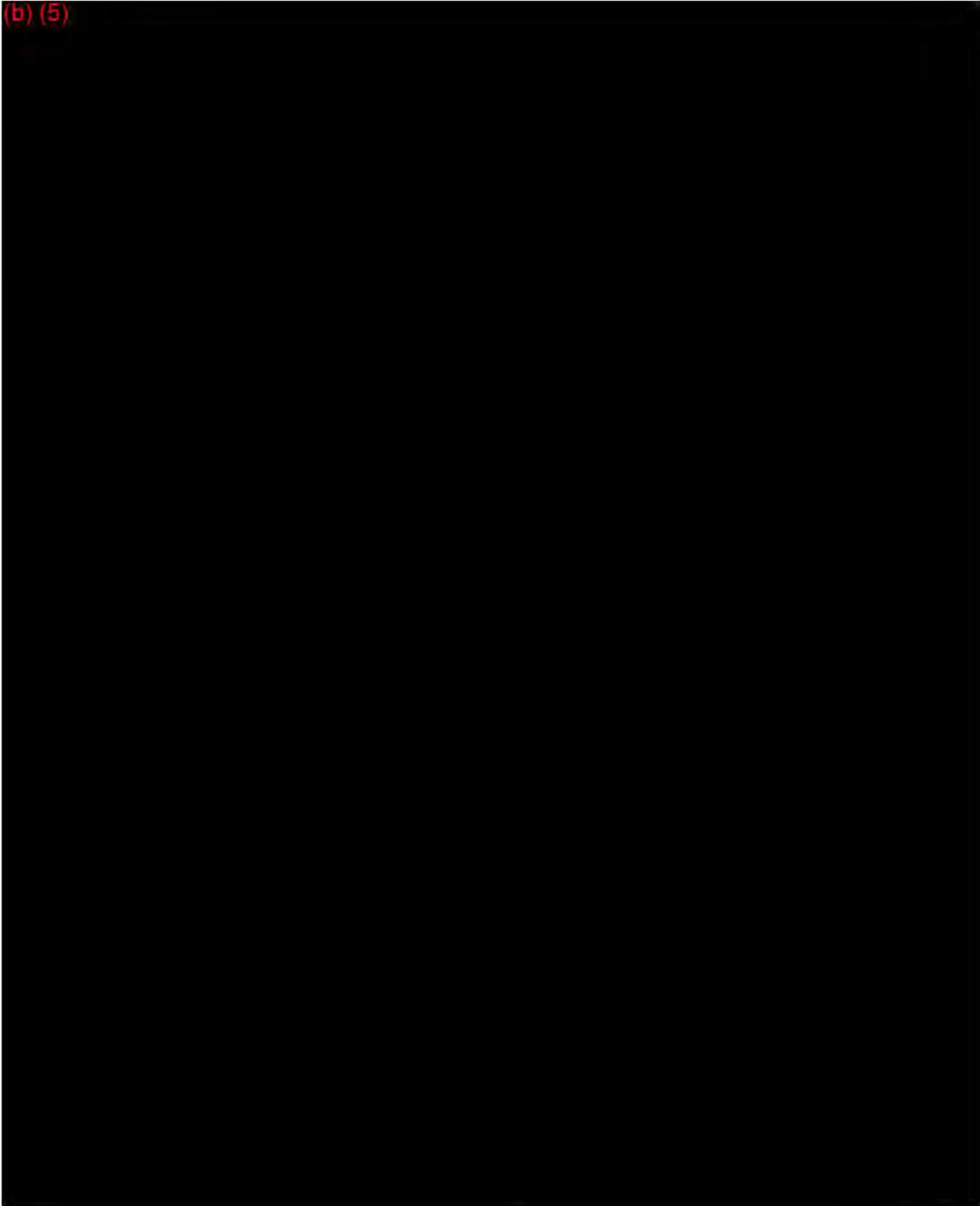
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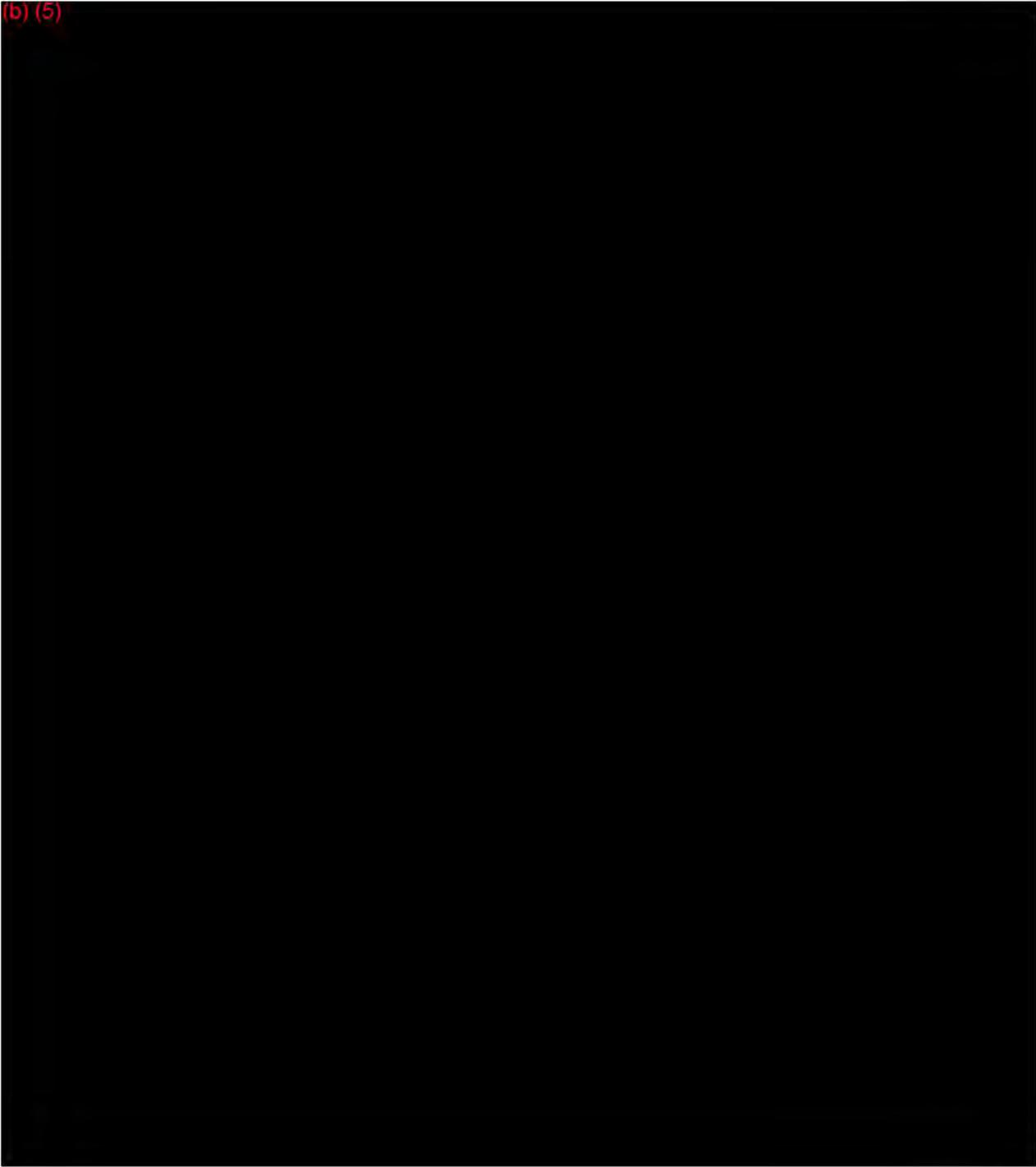
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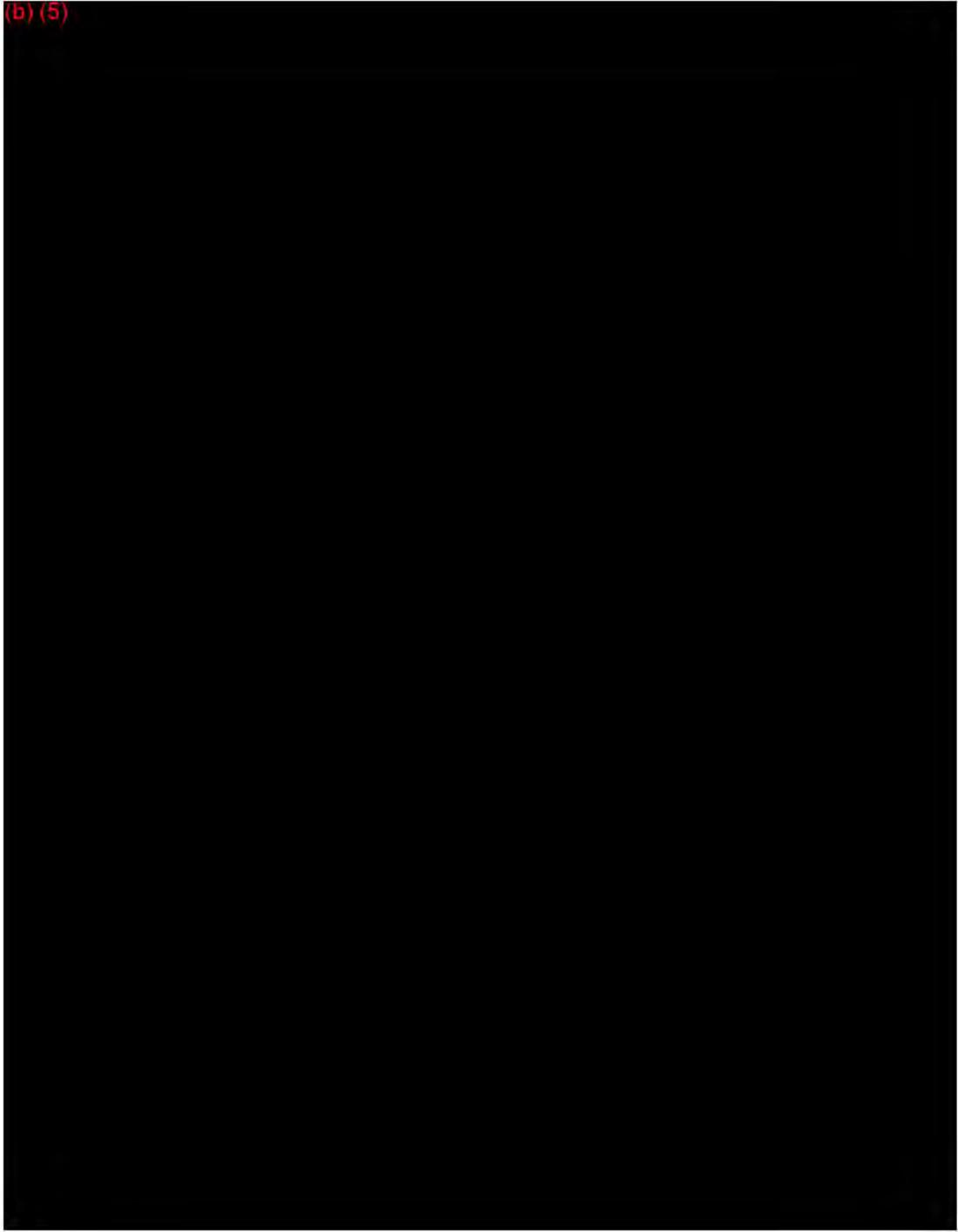
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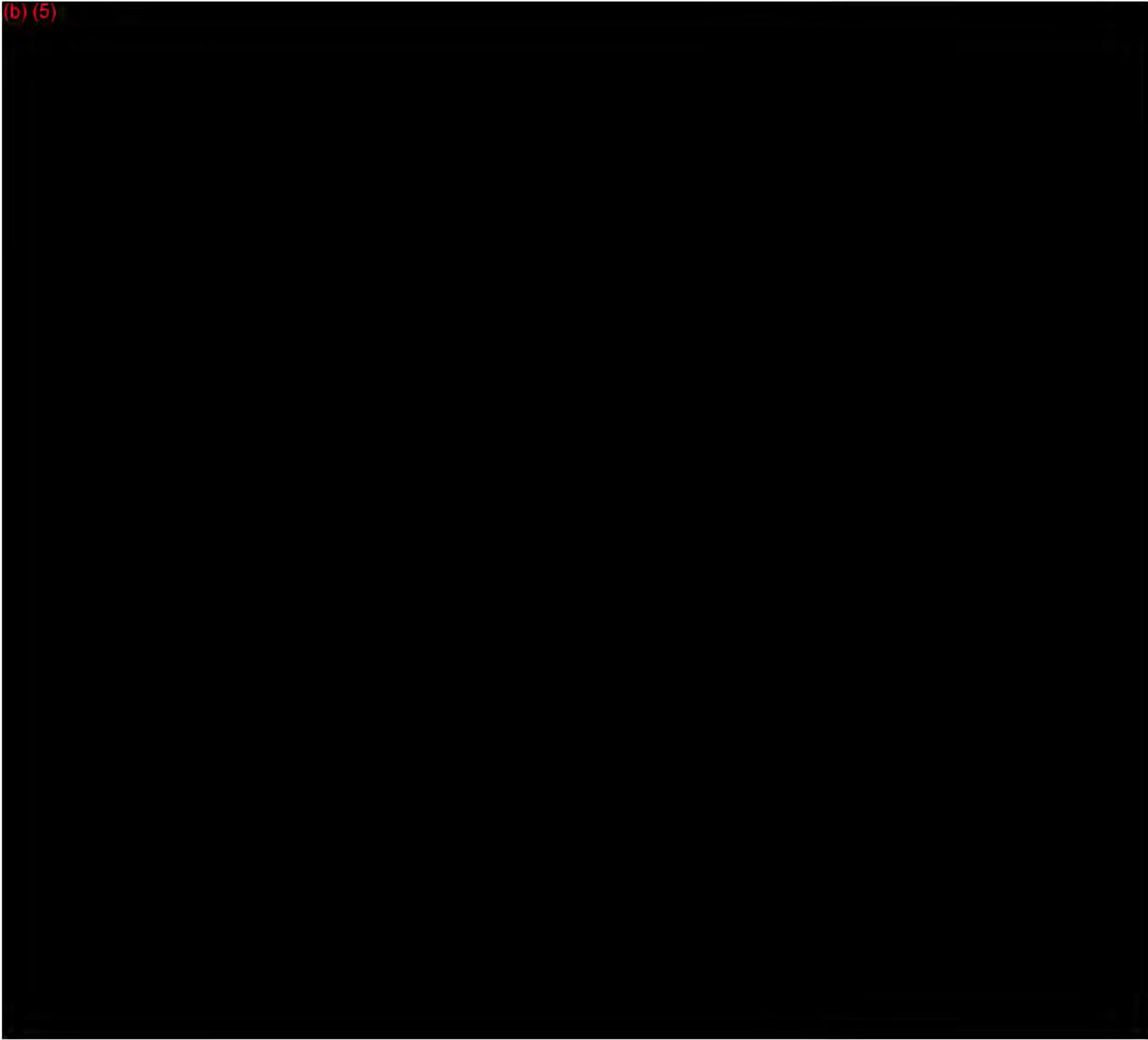
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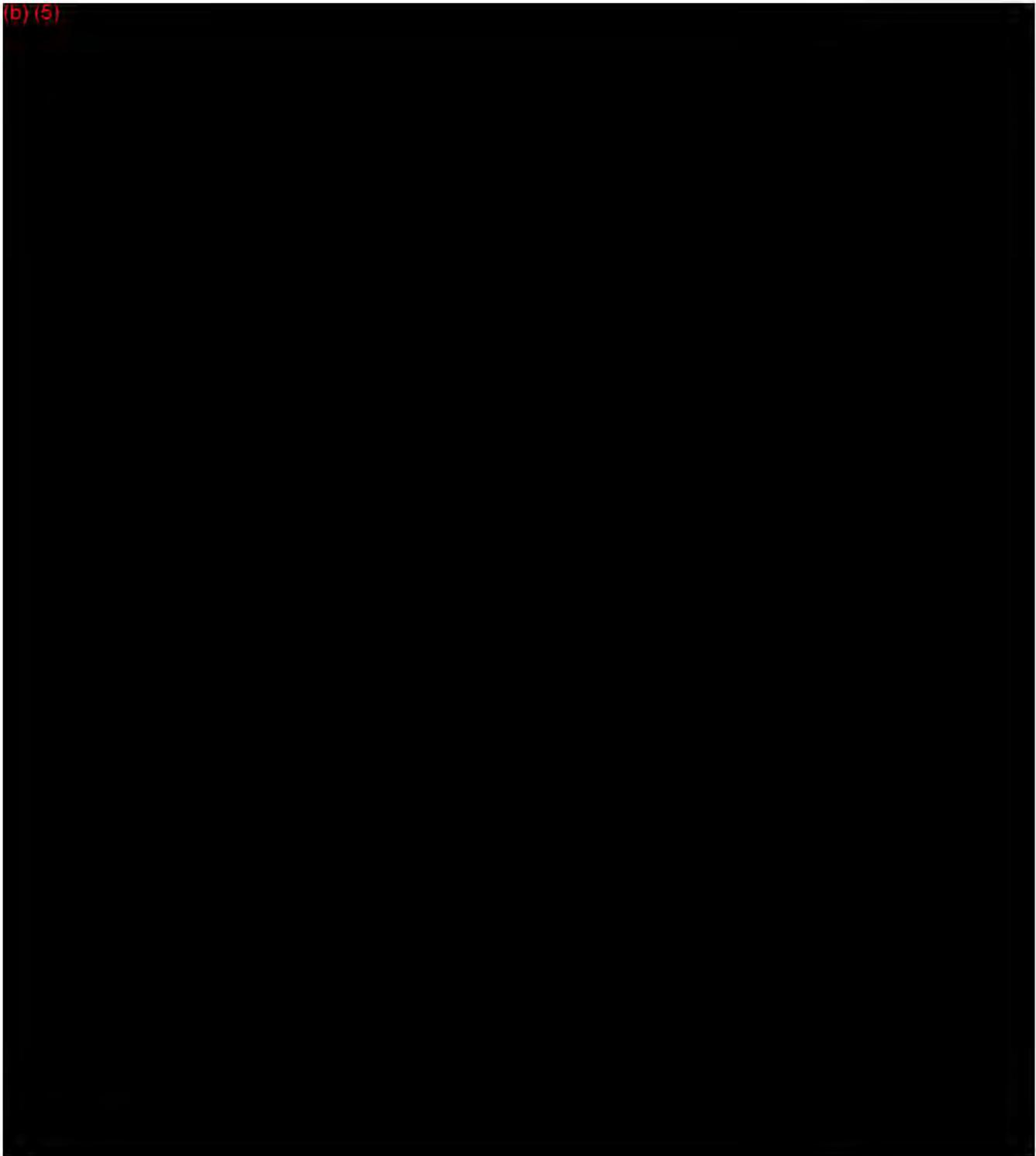
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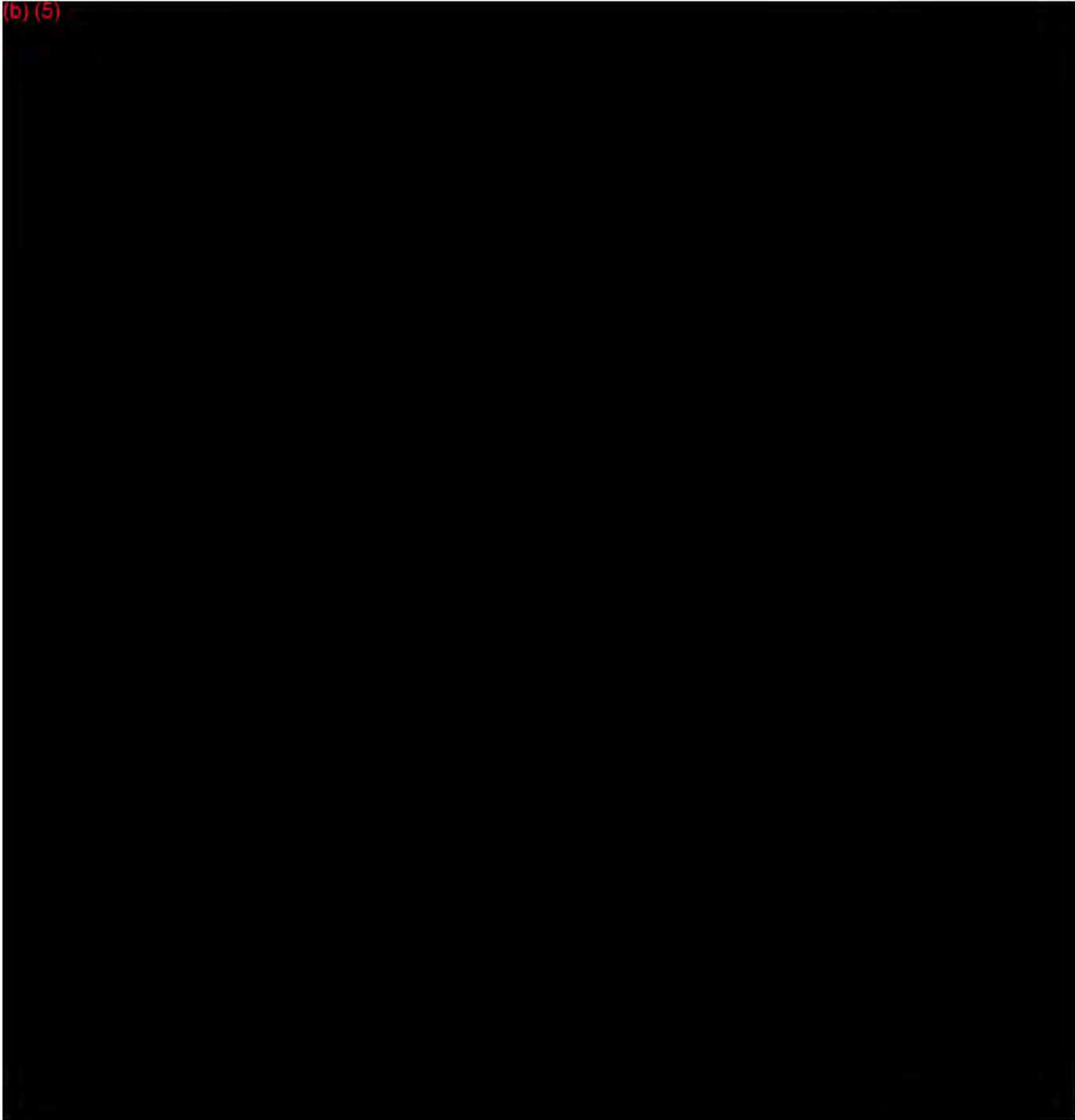
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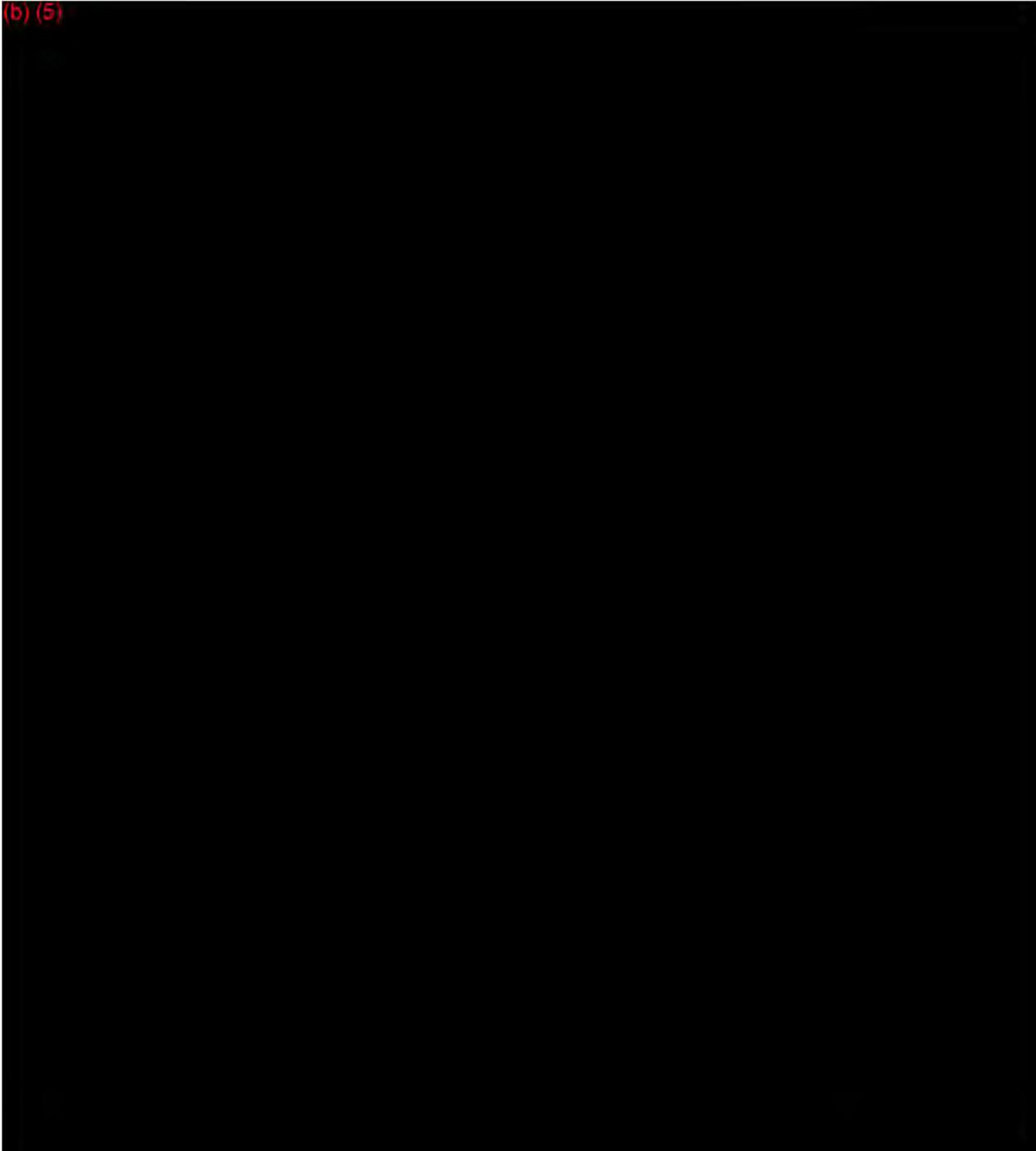
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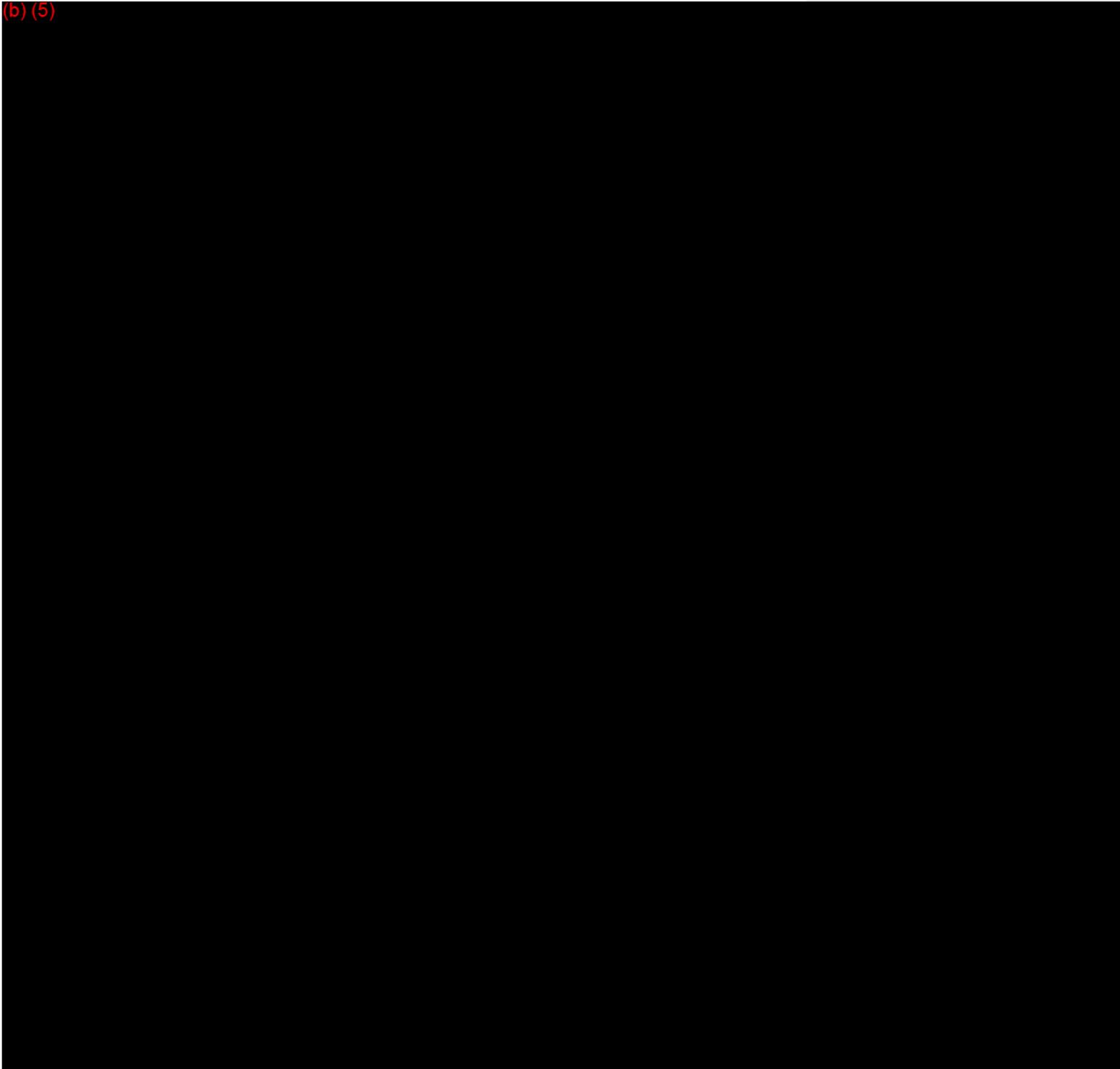
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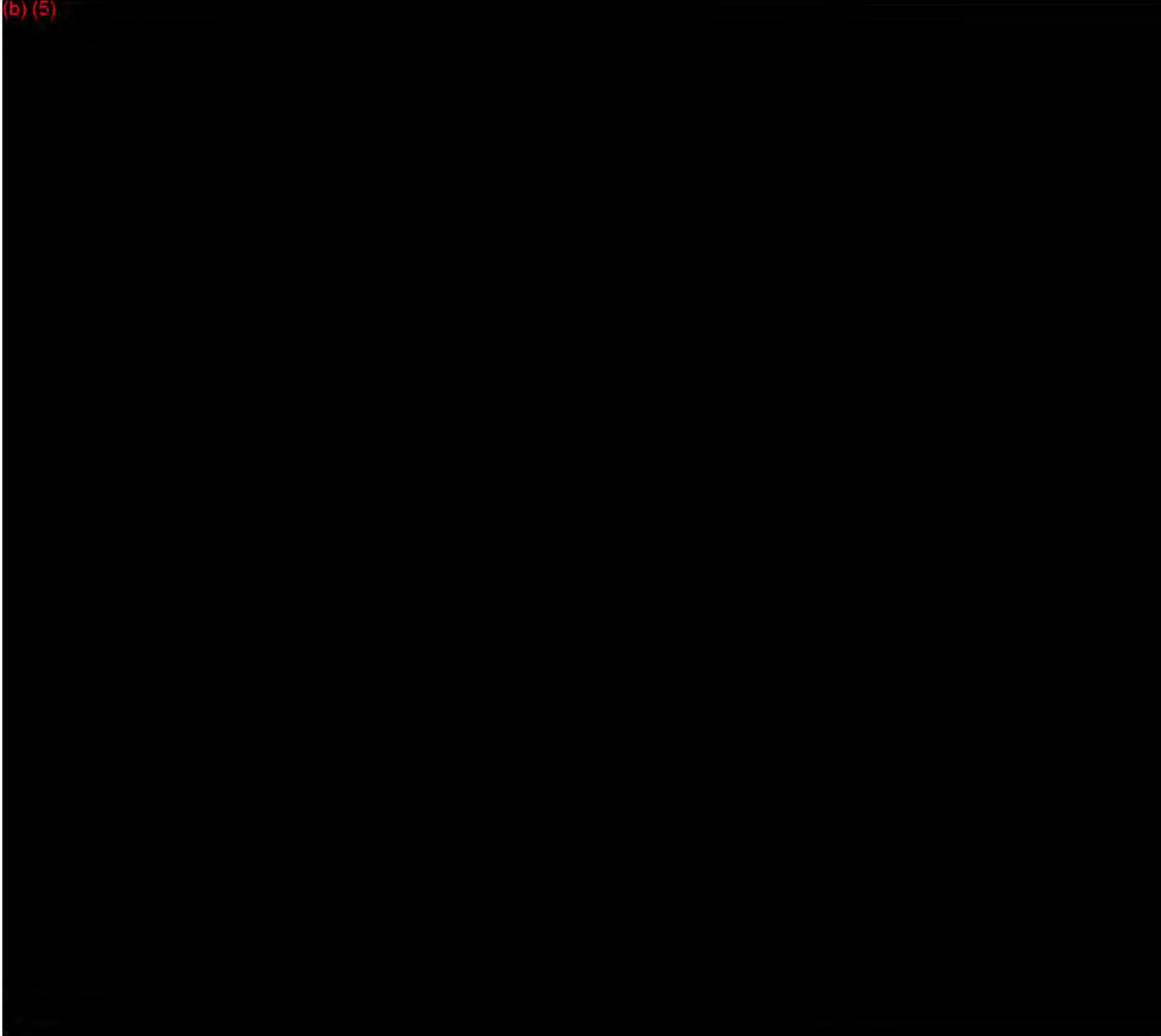
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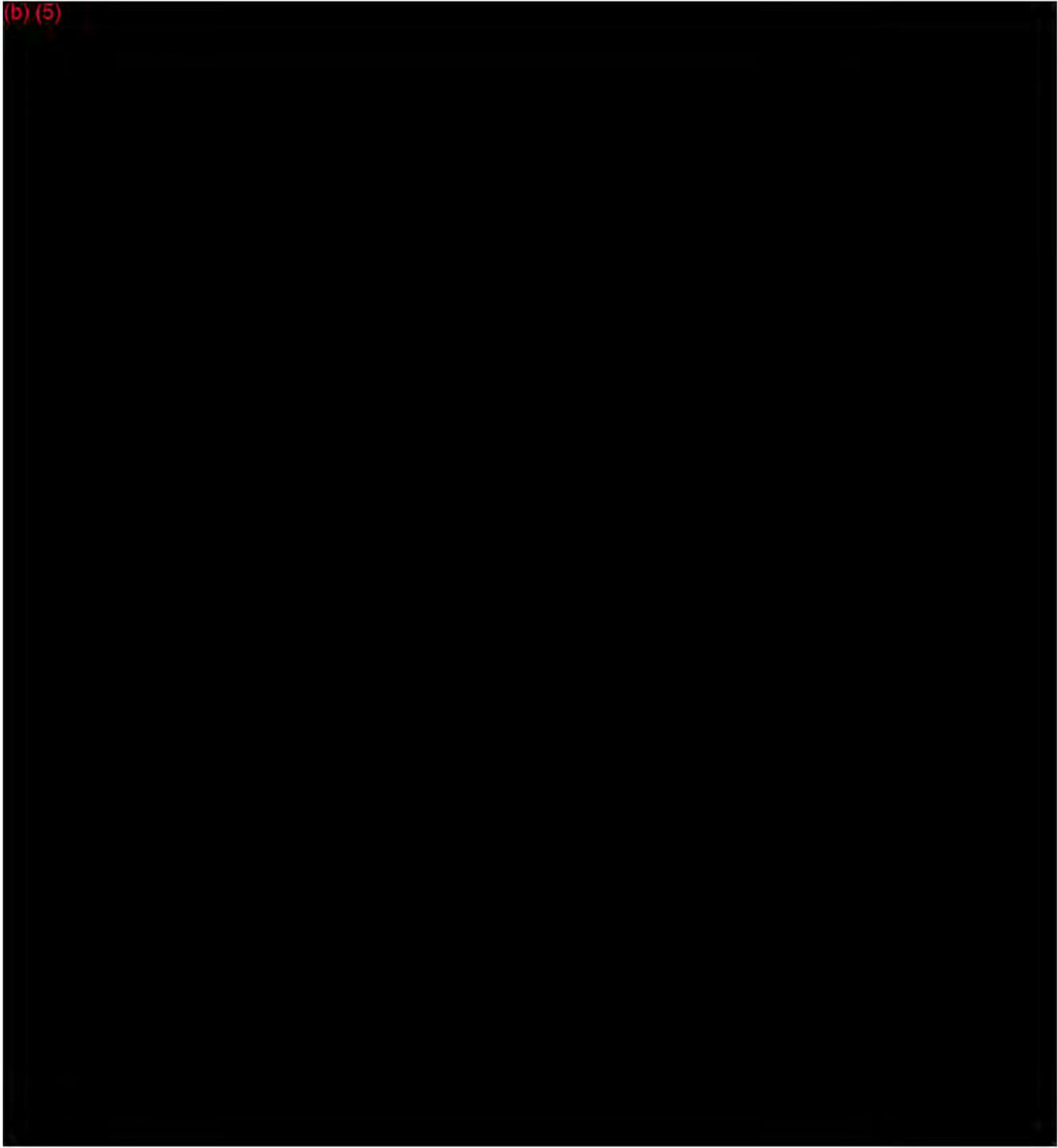
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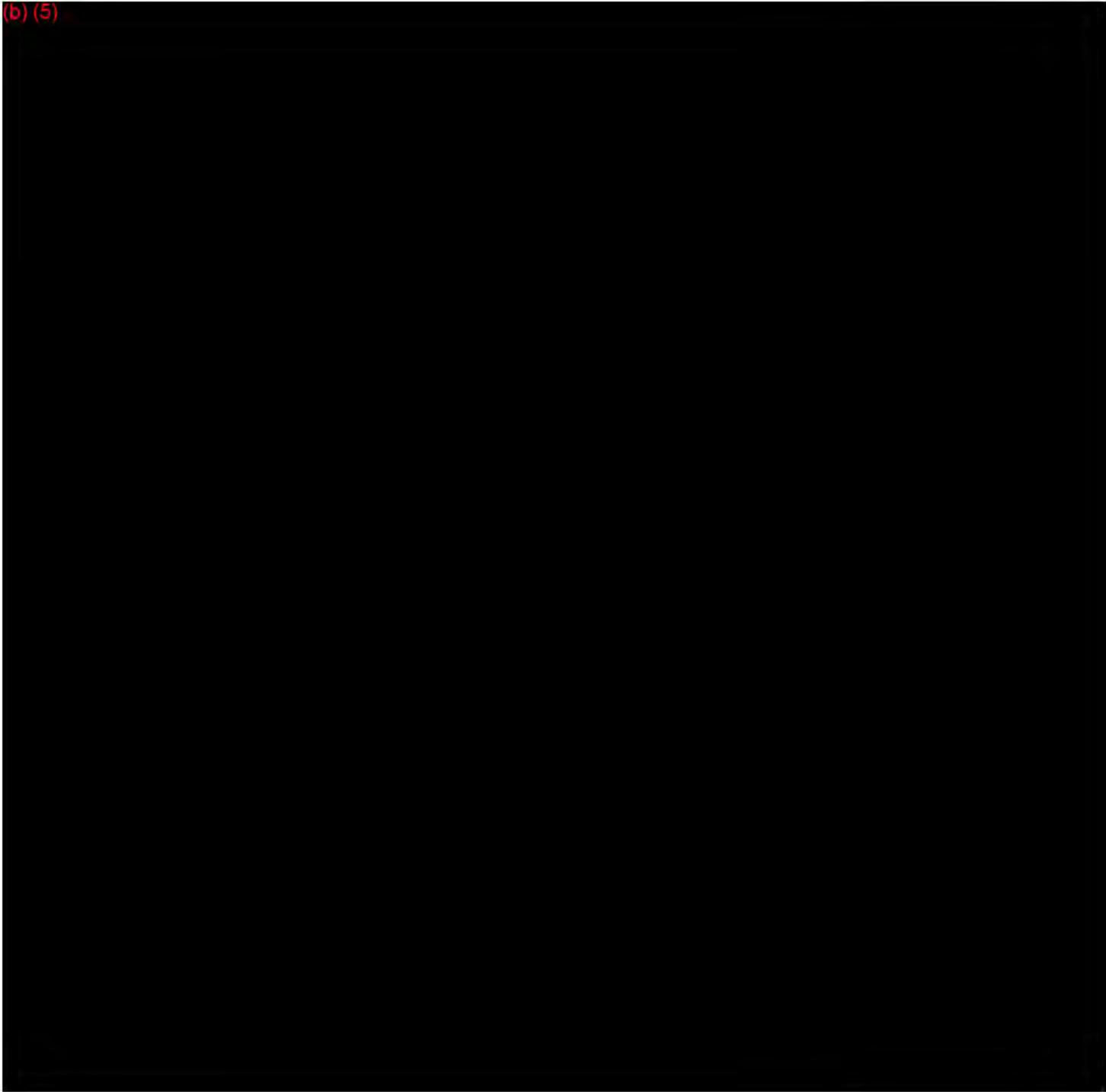
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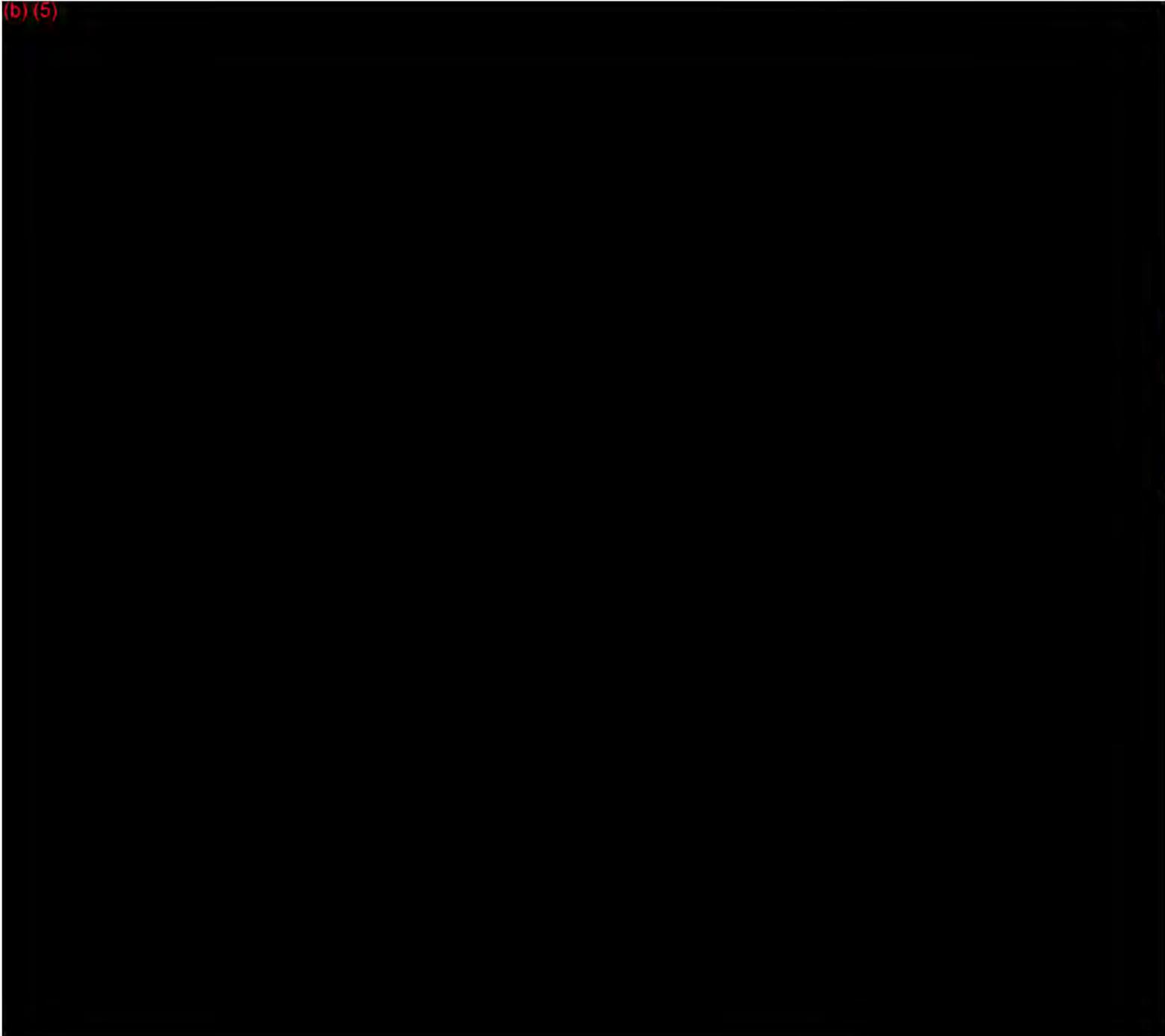
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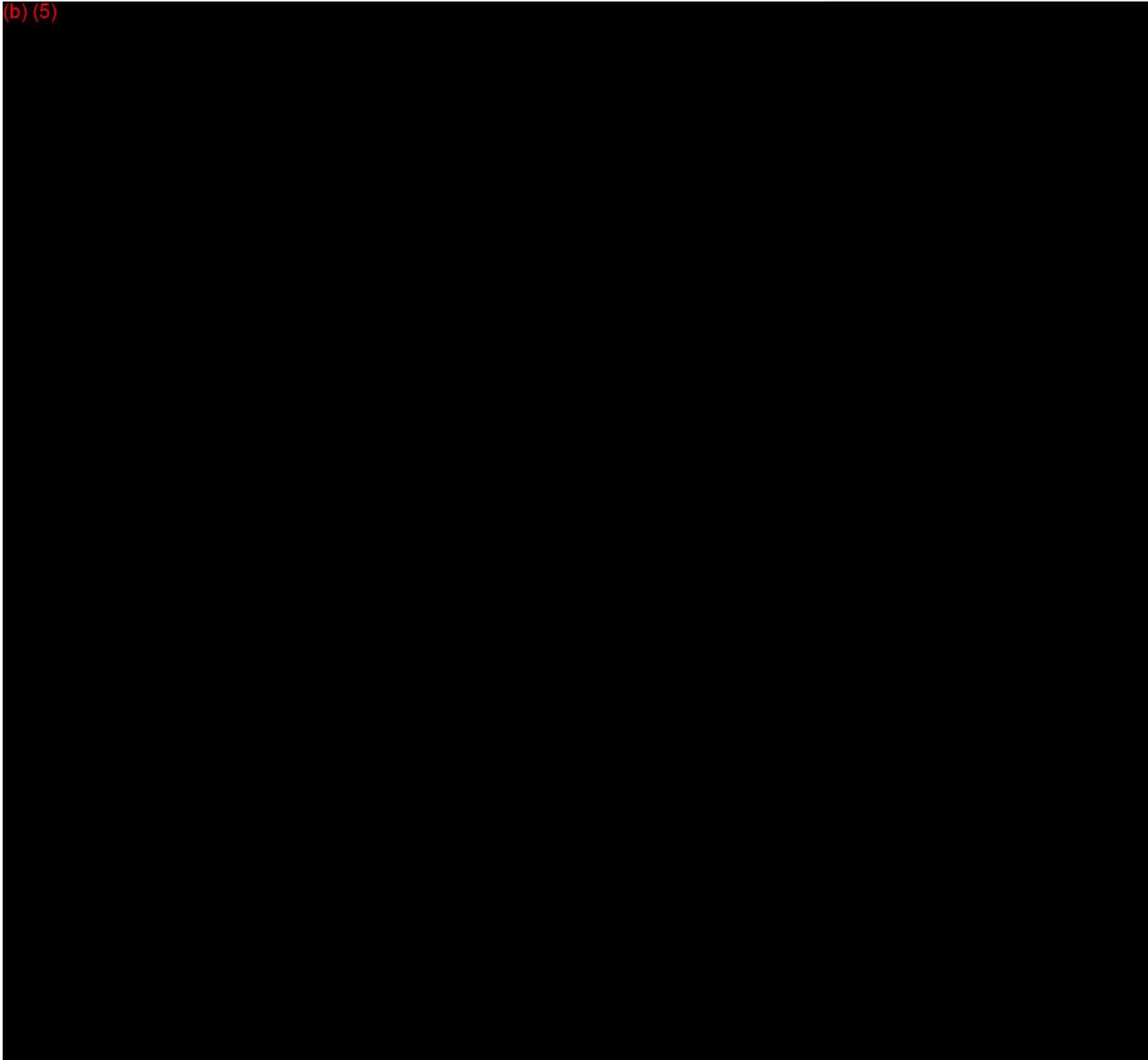
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(b) (5)



From: [Califf, Robert](#)
To: [Ligon, Sharnell \(CDER\)](#)
Subject: Re: Sarepta communication
Date: Wednesday, August 24, 2016 8:29:35 AM

Perfect. Thx

Rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sharnell Ligon <Sharnell.Ligon@fda.hhs.gov>
Date: Wednesday, August 24, 2016 at 8:28 AM
To: apple <rmc1@fda.hhs.gov>
Subject: RE: Sarepta communication

Good Morning Dr. Califf,

I followed up with Dr. Woodcock regarding your query and she wanted me to let you know that the letter was drafted and signed off on by the review group, but went out under her signature. There was a consensus between her and the division except for a small issue about how many days after receipt of the action we would act. Please let me know if this is helpful or if you require additional information.

Kind Regards,

Sharnell

From: Califf, Robert
Sent: Wednesday, August 24, 2016 8:03 AM
To: Ligon, Sharnell (CDER)
Subject: Re: Sarepta communication

Sharnell,

This is a letter from Janet. She had referred to a previous letter that was signed by the review group as I understood it.

Thx

Rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sharnell Ligon <Sharnell.Ligon@fda.hhs.gov>

Date: Tuesday, August 23, 2016 at 2:33 PM

To: apple <rmc1@fda.hhs.gov>

Subject: Sarepta communication

Dear Dr. Califf,

Per your request, attached is the letter that was sent to Sarepta.

Kind Regards,

Sharnell

From: [Califf, Robert](#)
To: [Woodcock, Janet](#)
Subject: RE: Also
Date: Thursday, August 25, 2016 5:27:00 PM

Thanks. I know this isn't easy!

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Woodcock, Janet
Sent: Thursday, August 25, 2016 3:28 PM
To: Califf, Robert
Subject: Also

I believe the premise that I should not be “involved” in the detailed activities of the Center is incorrect. I am ultimately held accountable for everything CDER does, and often have to defend such actions in front of Congress and the media. I am routinely involved in most of the controversial actions and problematic processes. I think that Lu, from what you told me, is conflating “involvement” with something else---

In contradistinction, I do not, and did not in this case, try to suborn or pressure any review scientist to change their analysis or point of view. In fact, I repeatedly reminded the staff that their opinion was their own and that they are required (by regulation) to set down their own analysis and sign it. I stated that I had a different analysis, but did not pressure anyone to change theirs. I also did not interfere in any way in the design of the Advisory Committee meetings, including the briefing materials. I made a brief presentation to the meeting, which summarized my views of how FDA should approach rare fatal diseases. During the AC, I only offered brief clarifying comments, not any opinion on approvability etc. I am very aware that pressuring a reviewer or team is inappropriate, and I went out of my way to avoid doing this.

However, it would have been bizarre of me to wait until the last minute to share my differing opinion with the team, after they had been moving toward a particular action.

As far as the letter, we had been discussing whether the original WB data represented substantial evidence and so after a call with Rich and me, the firm agreed to do more biopsies. They send us a letter and sought a response. The new drugs folks (John Jenkins, Ellis Unger, and Bob T) were at a retreat with me, and agreed on doing the letter, I drafted it that afternoon per our discussion and then it was worked on by the Division, running it by John, Ellis, and Bob (who were still at the retreat), and then getting it to me at the end of the day. I made one slight modification (shortening the review timeline by 2 days) and then signed and sent it. So they were (reluctantly) on board with this plan. When the WB data came back and were low, OND felt they did not meet the “meaningful” level, even though they were statistically significant and thus met the “substantial evidence” test. So OND had been prepared to go along with the approval, but the low amounts of dystrophin on the biopsies gave them too much pause. Same with John.

jw

From: [Califf, Robert](#)
To: [Temple, Robert](#)
Subject: RE:
Date: Sunday, August 28, 2016 7:16:00 AM

Time to touch base today on this and tomorrow's diabetes meeting?

rmc

From: Temple, Robert
Sent: Thursday, August 25, 2016 2:59 PM
To: Califf, Robert
Subject:

Forgot to mention. If you wanted to discuss eteplirsen (not that you don't have all the data and analyses), I'd be glad to.

From: [Califf, Robert](#)
To: [McCall, Jonathan *](#)
Cc: [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: eteplirsen
Date: Sunday, August 28, 2016 7:58:00 AM
Attachments: [20160828 Eteplirsen combined 8-24-2016 CLEAN-COMMENTED.doc](#)

Friends,

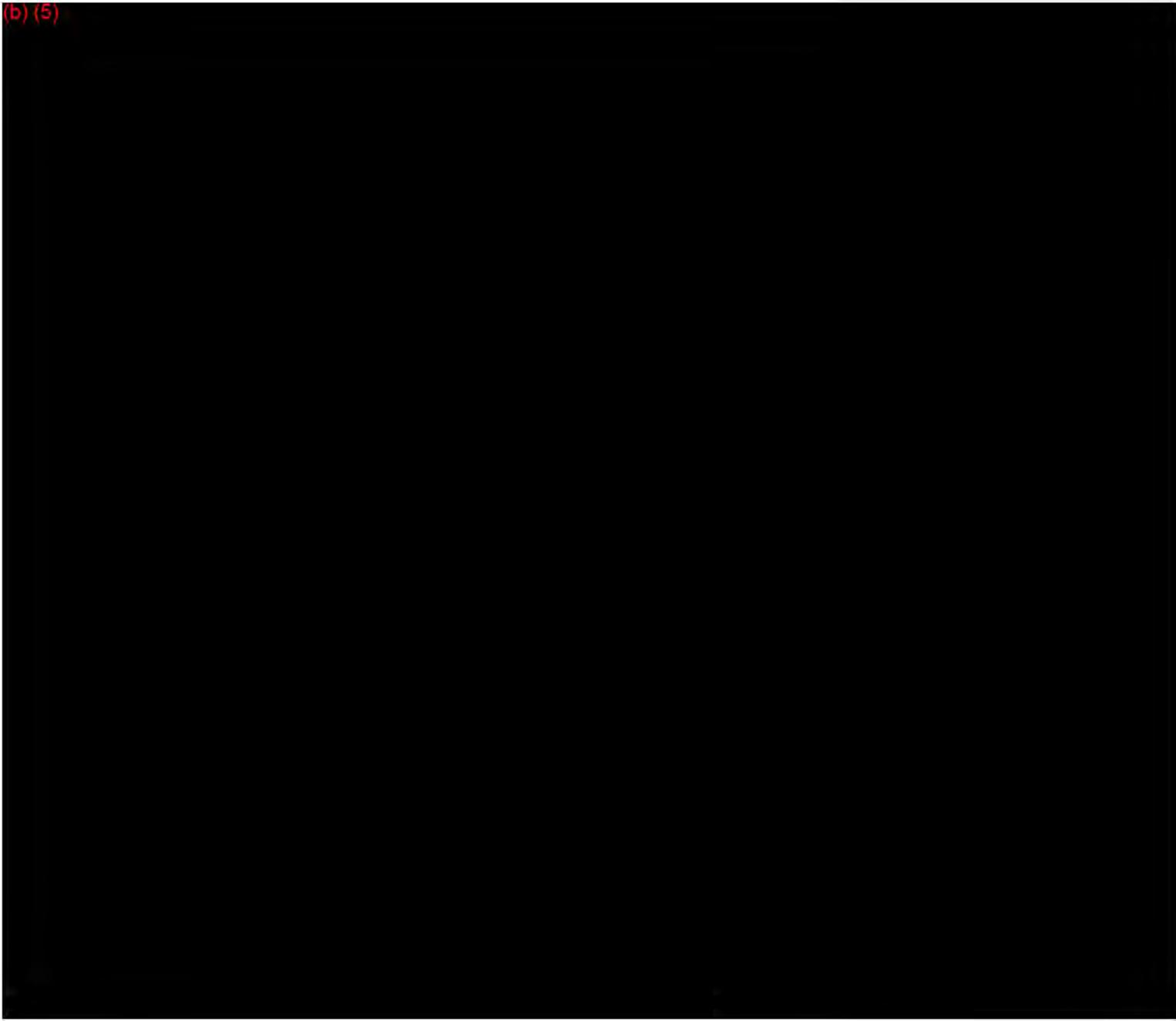
I think I've addressed all the comments and read it thoroughly. I want to make sure we've covered the post-marketing orders. I've also re-read the documents and I don't believe I've left anything unaddressed.

Jonathan, can you produce a clean version?

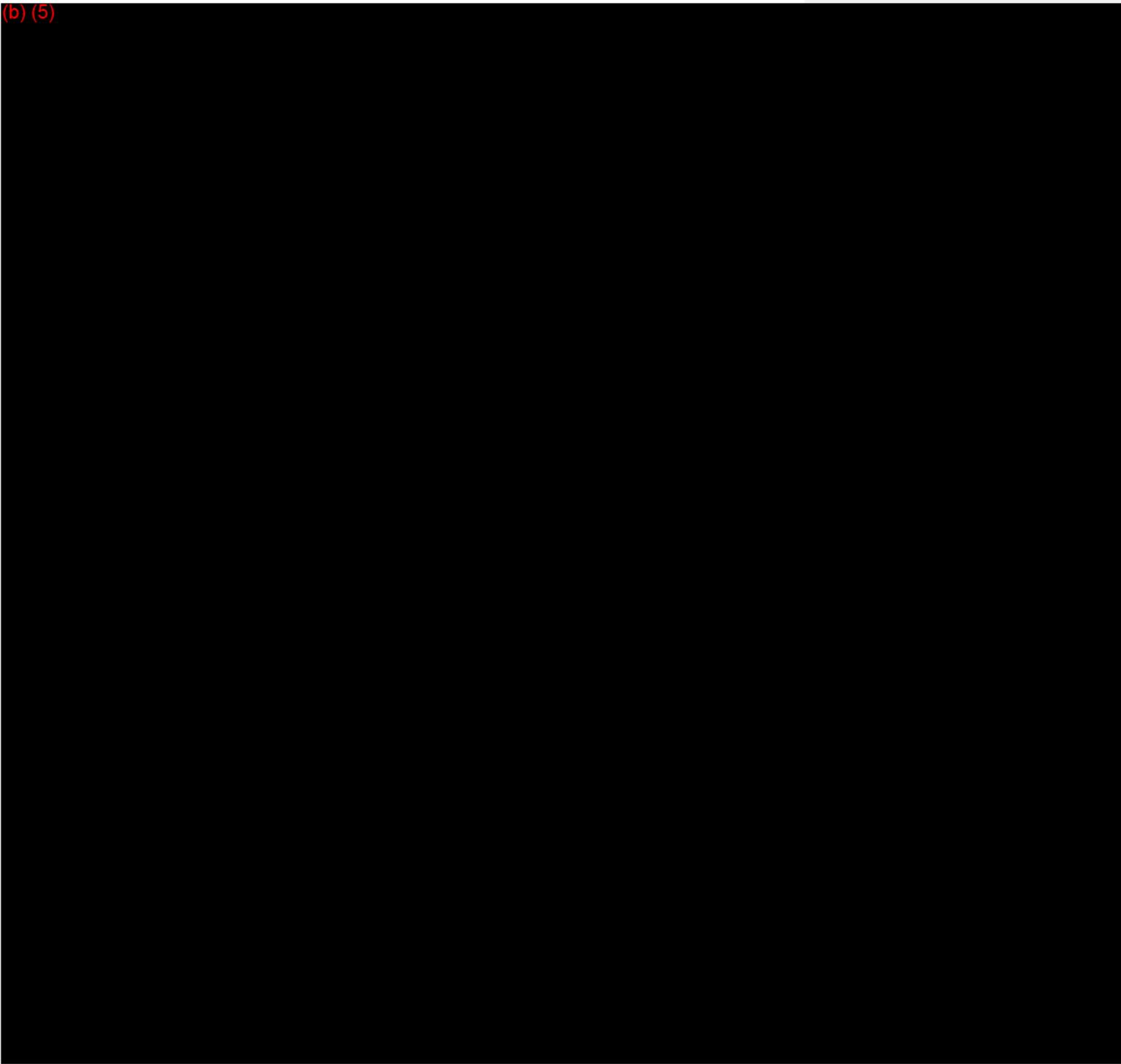
thx

rmc

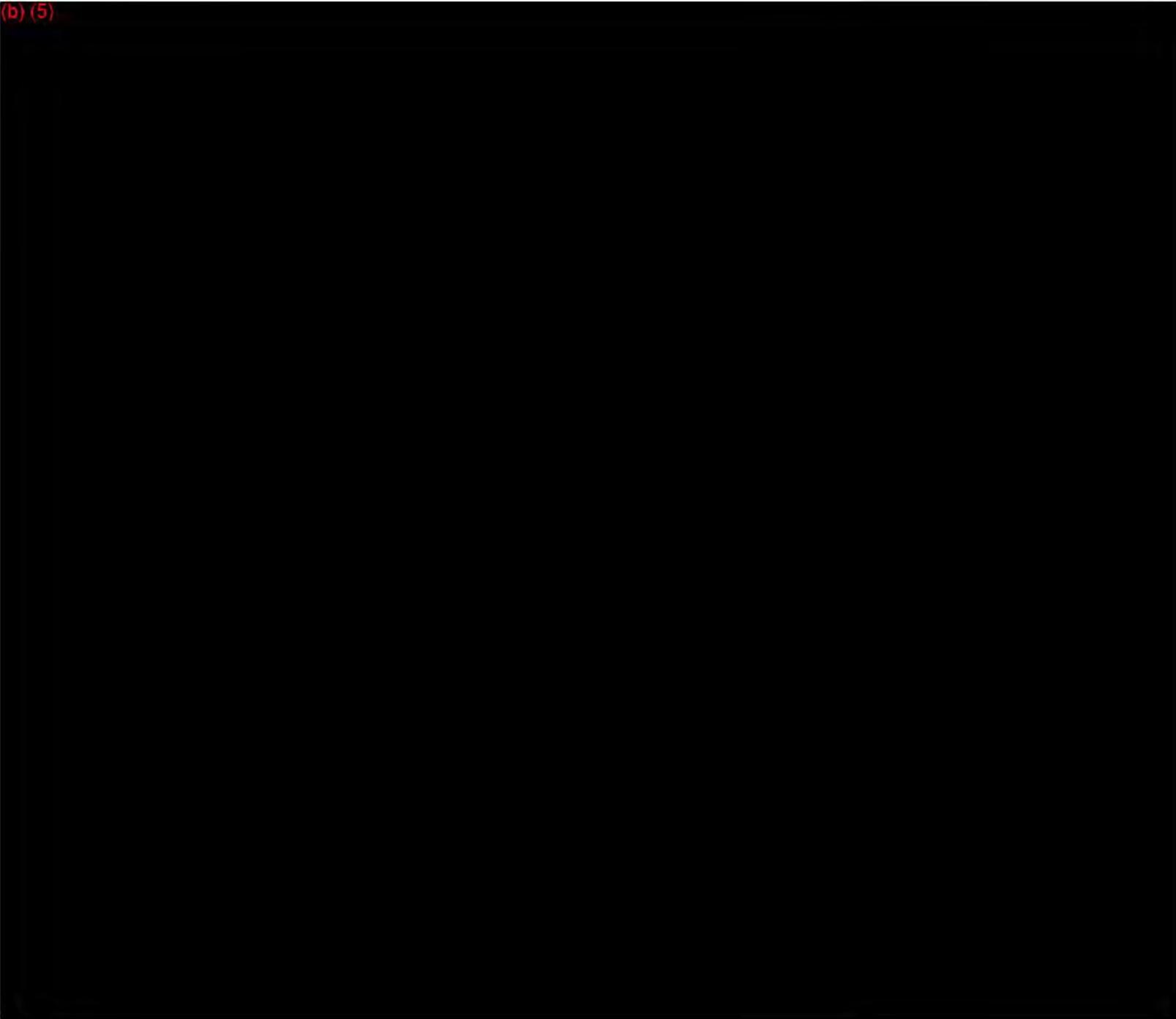
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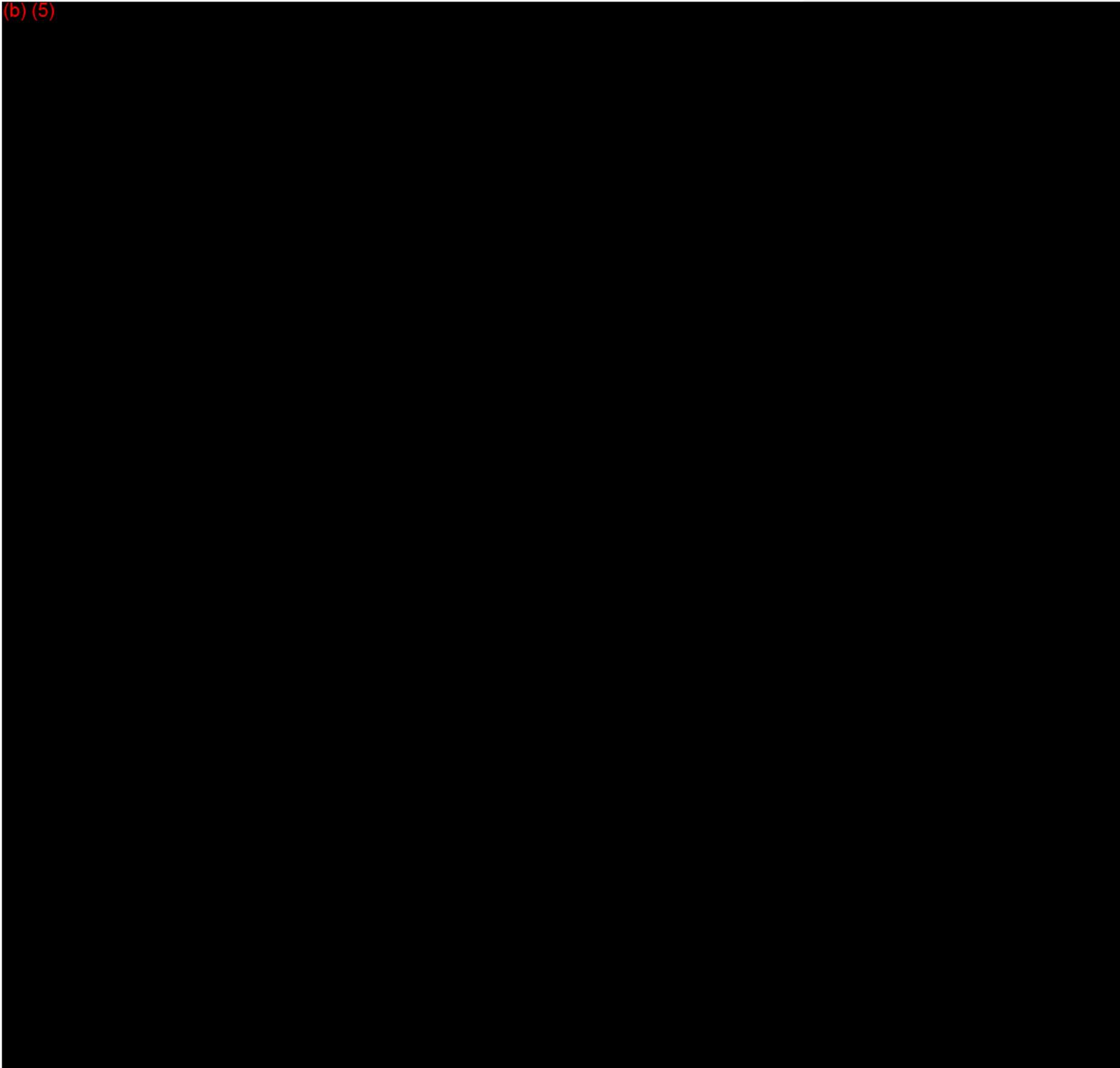
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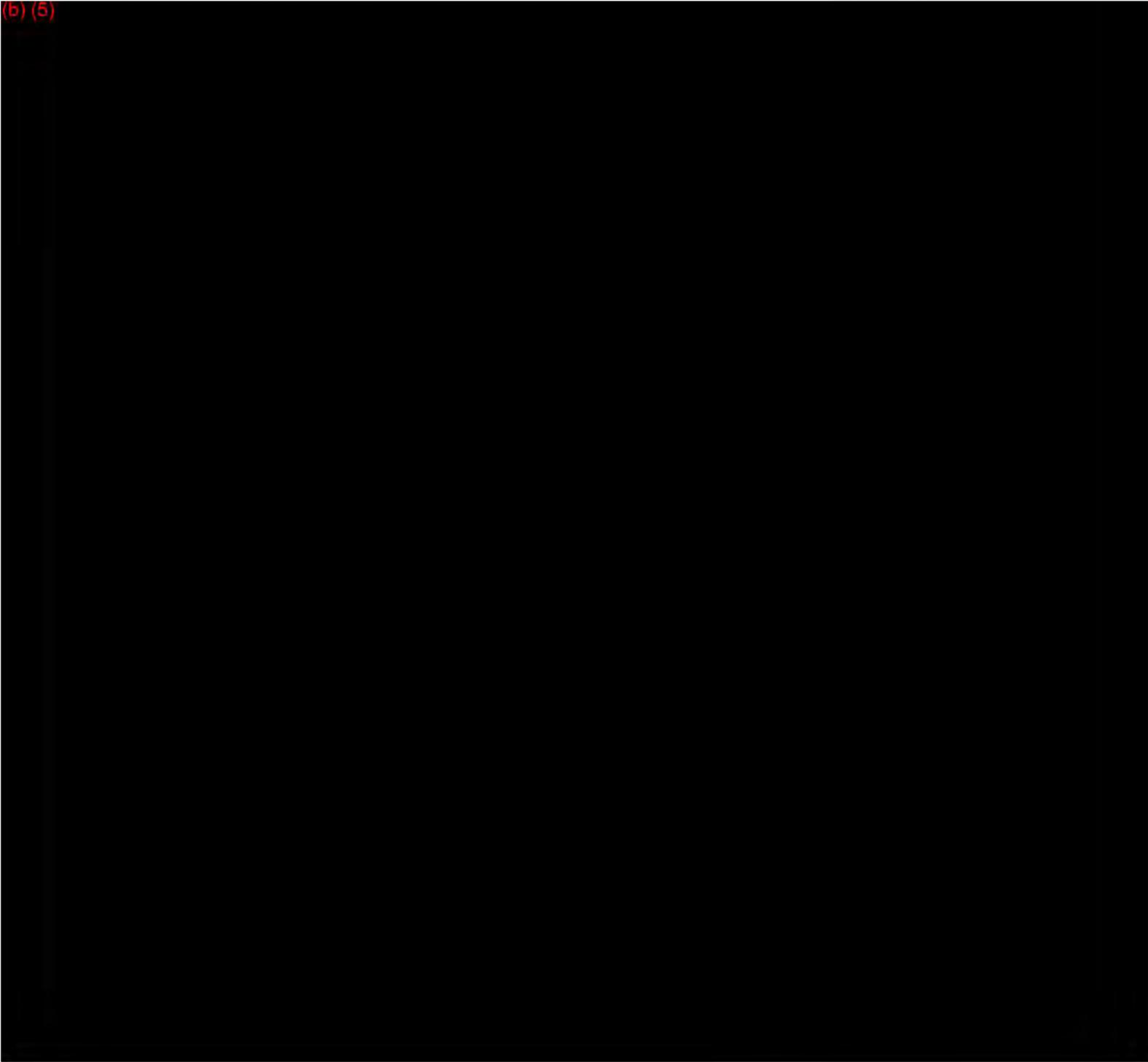
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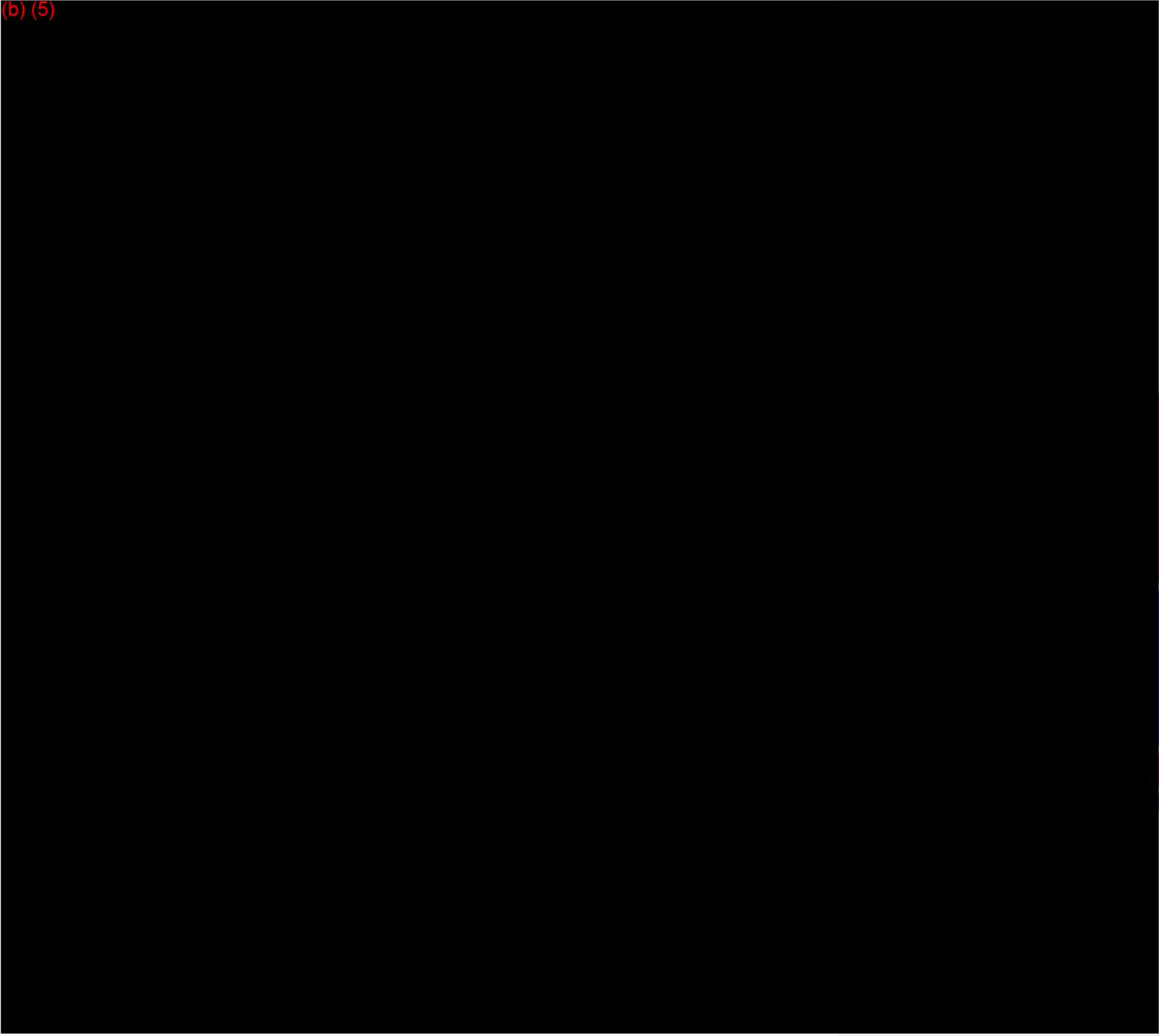
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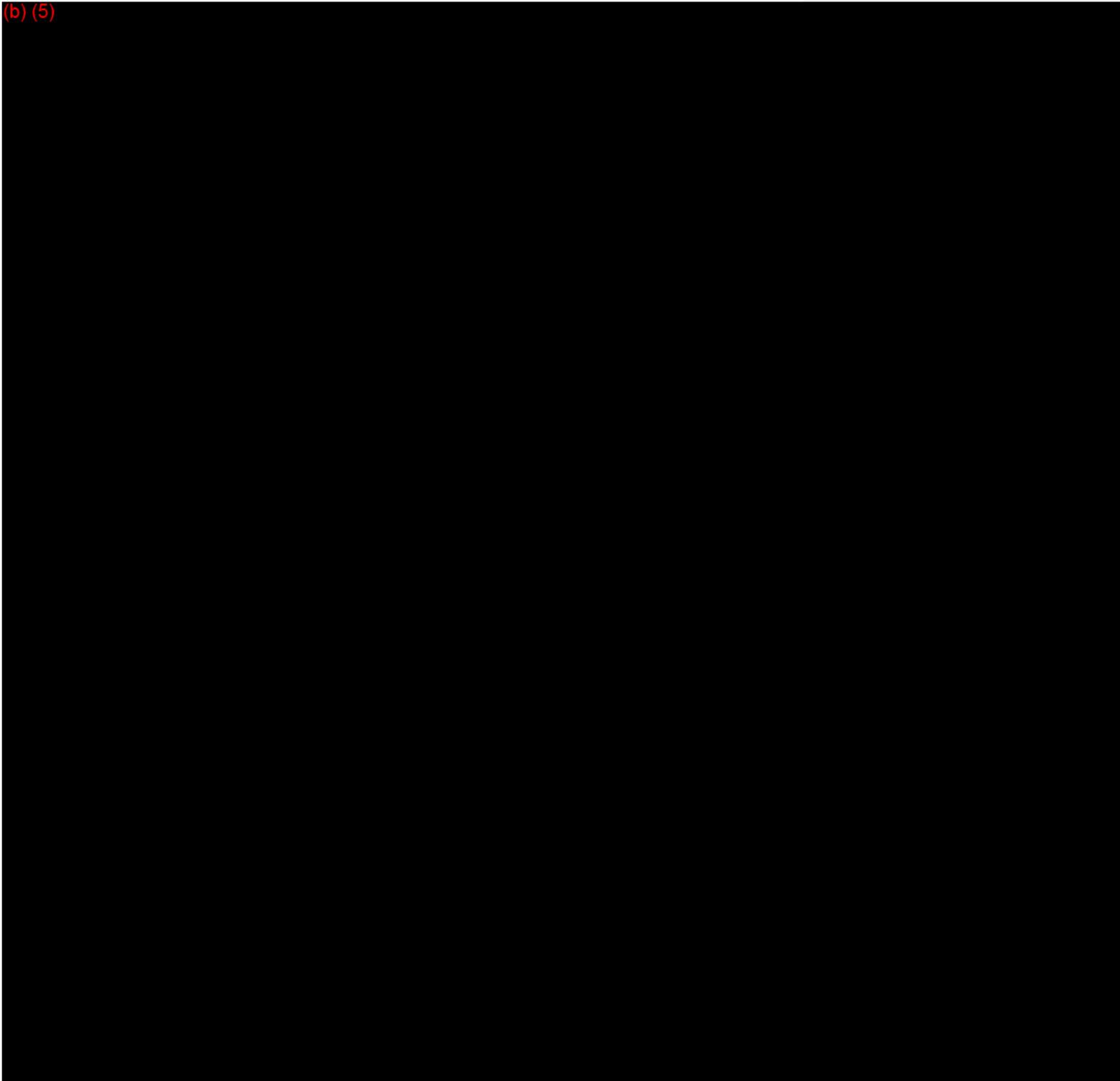
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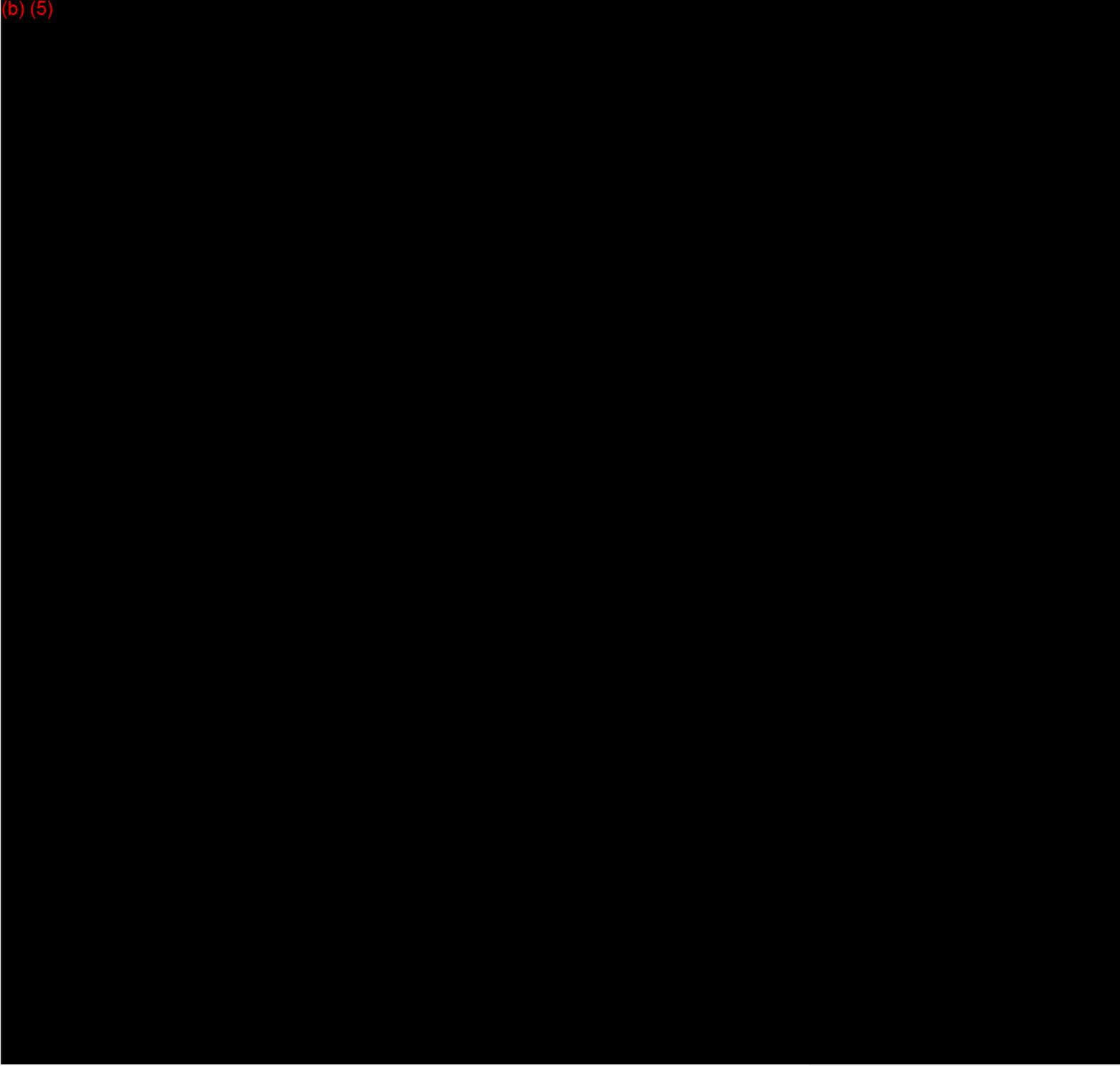
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From: [Califf, Robert](#)
To: [Chasan-Sloan, Deborah \(FDA\)](#); [Sherman, Rachel](#); [McCall, Jonathan *](#)
Cc: [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: eteplirsen
Date: Sunday, August 28, 2016 9:44:00 AM

thx

Robert M Califf MD
Commissioner of Food and Drugs

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, August 28, 2016 9:15 AM
To: Sherman, Rachel; McCall, Jonathan *; Califf, Robert
Cc: Dickinson, Elizabeth (FDA)
Subject: Re: eteplirsen

I should be able to review this tonight. If there's a clean version by then, I'll plan to work off of that.

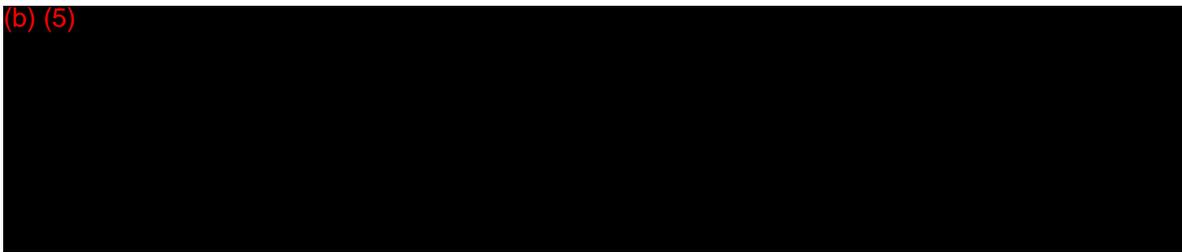
FYI, Liz returns to the office on Tuesday.

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Sherman, Rachel
Sent: Sunday, August 28, 2016 8:23 AM
To: McCall, Jonathan *; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: Re: eteplirsen

I'm working off a phone so can't edit, sorry.

(b) (5)



Otherwise looks good to me.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: August 28, 2016 at 7:58:54 AM EDT
To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Cc: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Sherman, Rachel

<Rachel.Sherman@fda.hhs.gov>

Subject: eteplirsen

Friends,

I think I've addressed all the comments and read it thoroughly. I want to make sure we've covered the post-marketing orders. I've also re-read the documents and I don't believe I've left anything unaddressed.

Jonathan, can you produce a clean version?

thx

rmc

From: [Califf, Robert](#)
To: [Chasan-Sloan, Deborah \(FDA\)](#); [McCall, Jonathan *](#); [Sherman, Rachel](#)
Cc: [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: eteplirsen
Date: Sunday, August 28, 2016 10:21:00 PM

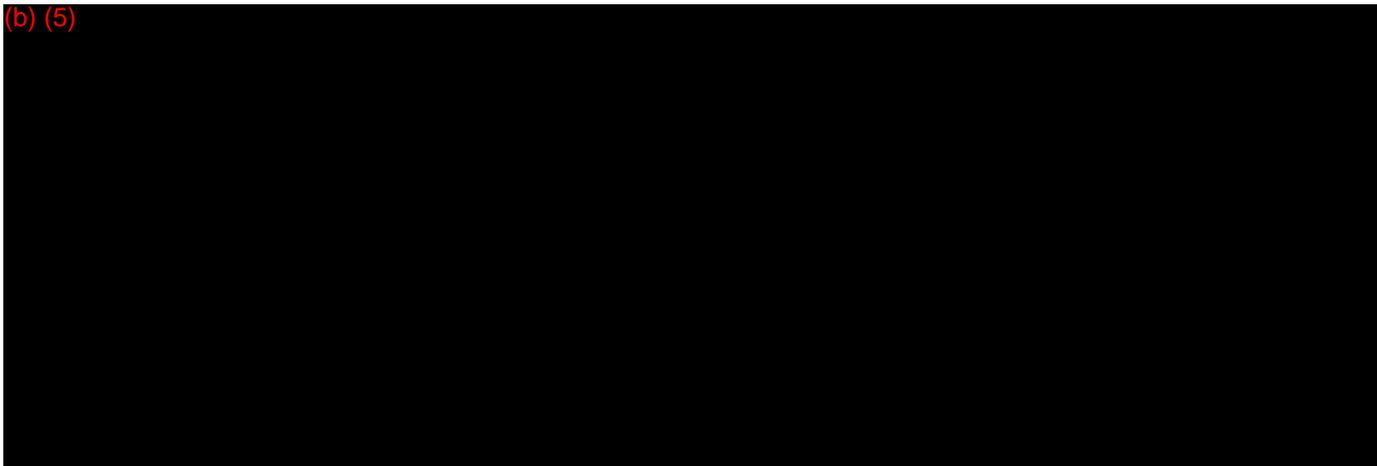
Thanks. I guess we'll need citations for quotes, and I think it would be good if OCC can help. I appreciate your help with all this.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, August 28, 2016 10:16 PM
To: McCall, Jonathan *; Sherman, Rachel; Califf, Robert
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

(b) (5)



Thanks,
Deborah

From: McCall, Jonathan *
Sent: Sunday, August 28, 2016 2:22 PM
To: Sherman, Rachel; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

Hello all –

I've attached clean and tracked versions that incorporate Rachel's suggestions below.

Please let me know if you need anything else!

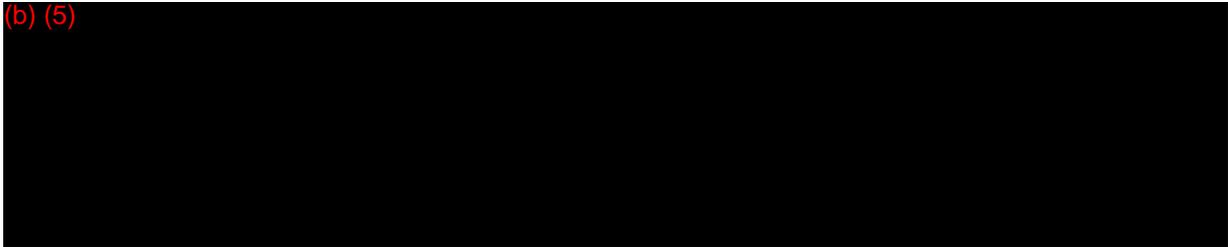
Thanks!

--
J

From: Sherman, Rachel
Sent: Sunday, August 28, 2016 8:23 AM
To: McCall, Jonathan *; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: Re: eteplirsen

I'm working off a phone so can't edit, sorry.

(b) (5)



Otherwise looks good to me.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: August 28, 2016 at 7:58:54 AM EDT
To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Cc: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: eteplirsen

Friends,

I think I've addressed all the comments and read it thoroughly. I want to make sure we've covered the post-marketing orders. I've also re-read the documents and I don't believe I've left anything unaddressed.

Jonathan, can you produce a clean version?

thx

rmc

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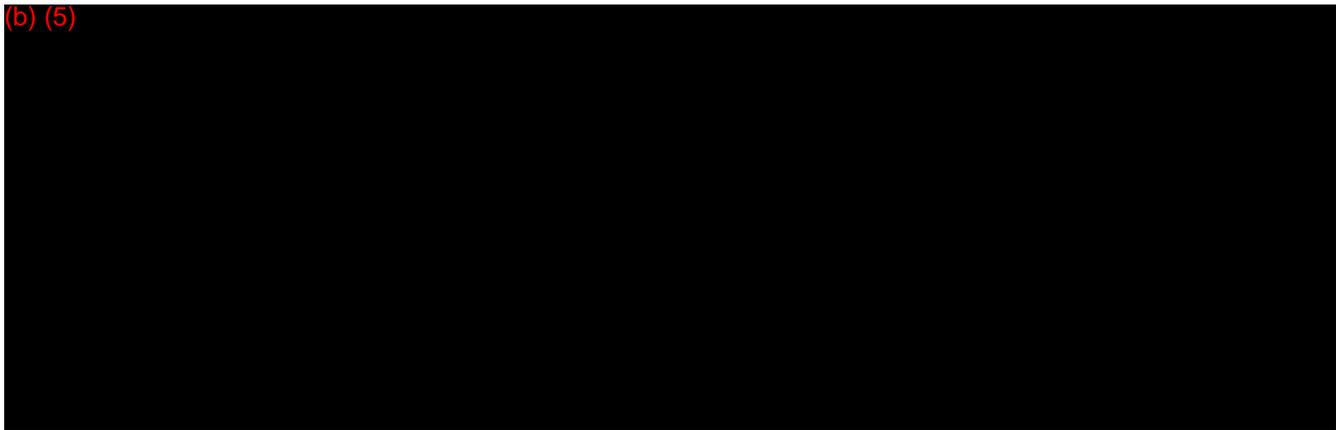
From: [Califf, Robert](#)
To: [Chasan-Sloan, Deborah \(FDA\)](#); [McCall, Jonathan *](#); [Sherman, Rachel](#)
Cc: [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: eteplirsen
Date: Sunday, August 28, 2016 10:28:00 PM
Attachments: [20160828 Eteplirsen_CLEAN\(occ\)_rnc.doc](#)

Agreed with all comments and suggestions. I think its looking good.

rmc
Robert M Califf MD
Commissioner of Food and Drugs

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, August 28, 2016 10:16 PM
To: McCall, Jonathan *; Sherman, Rachel; Califf, Robert
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

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Thanks,
Deborah

From: McCall, Jonathan *
Sent: Sunday, August 28, 2016 2:22 PM
To: Sherman, Rachel; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

Hello all –

I've attached clean and tracked versions that incorporate Rachel's suggestions below.

Please let me know if you need anything else!

Thanks!

--
J

From: Sherman, Rachel
Sent: Sunday, August 28, 2016 8:23 AM
To: McCall, Jonathan *; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: Re: eteplirsen

I'm working off a phone so can't edit, sorry.

(b) (5)



Otherwise looks good to me.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: August 28, 2016 at 7:58:54 AM EDT
To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Cc: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: eteplirsen

Friends,

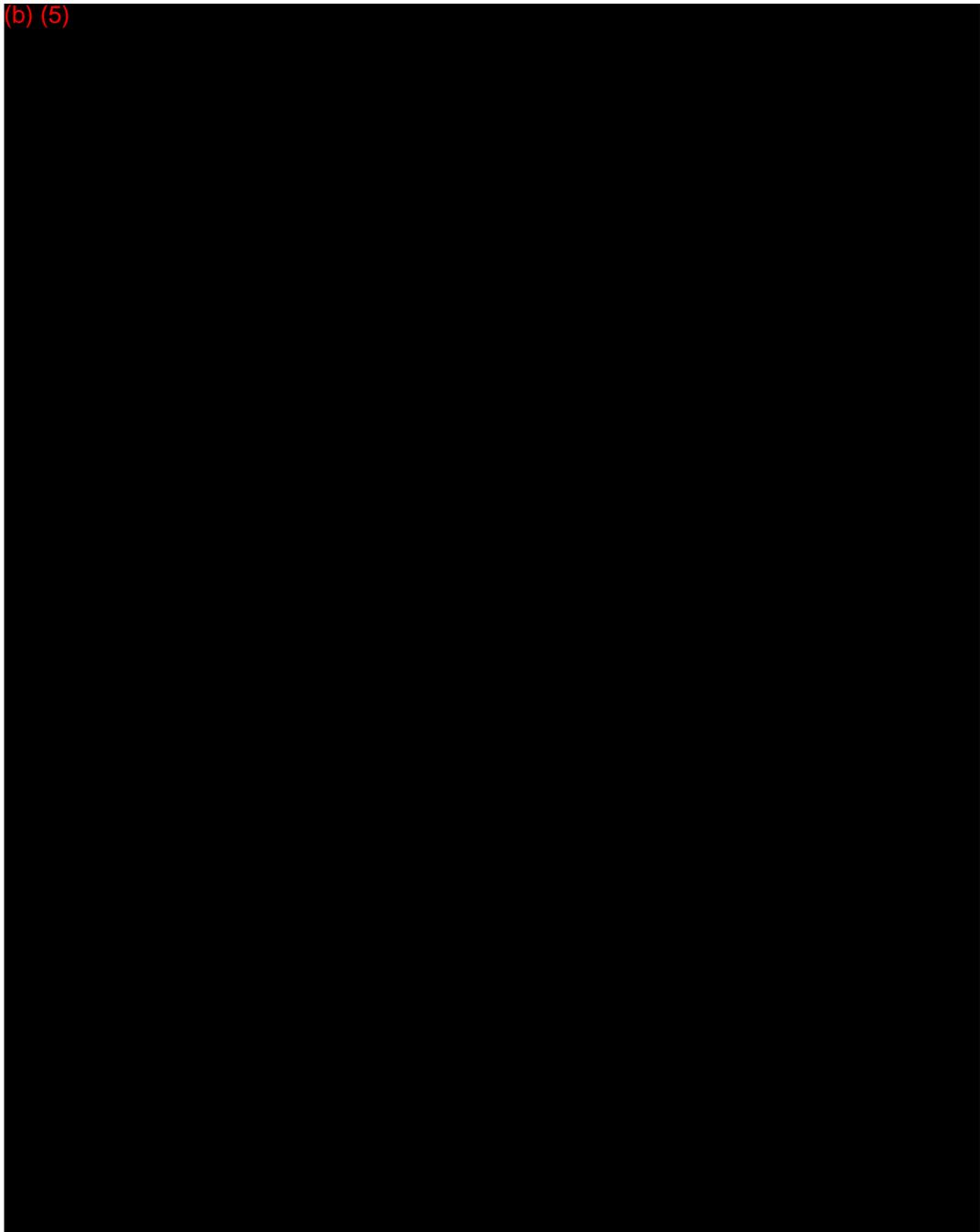
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Jonathan, can you produce a clean version?

thx

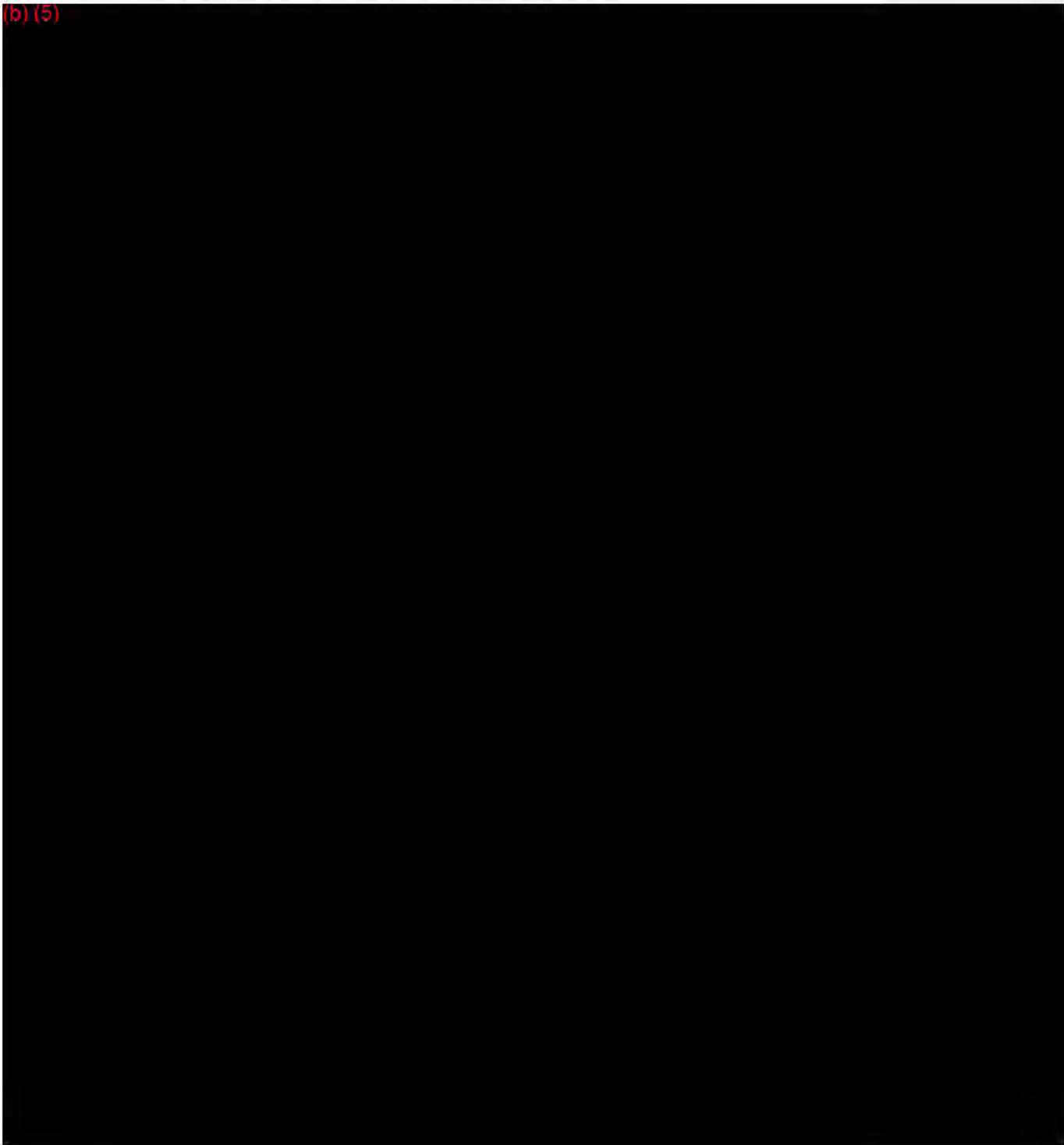
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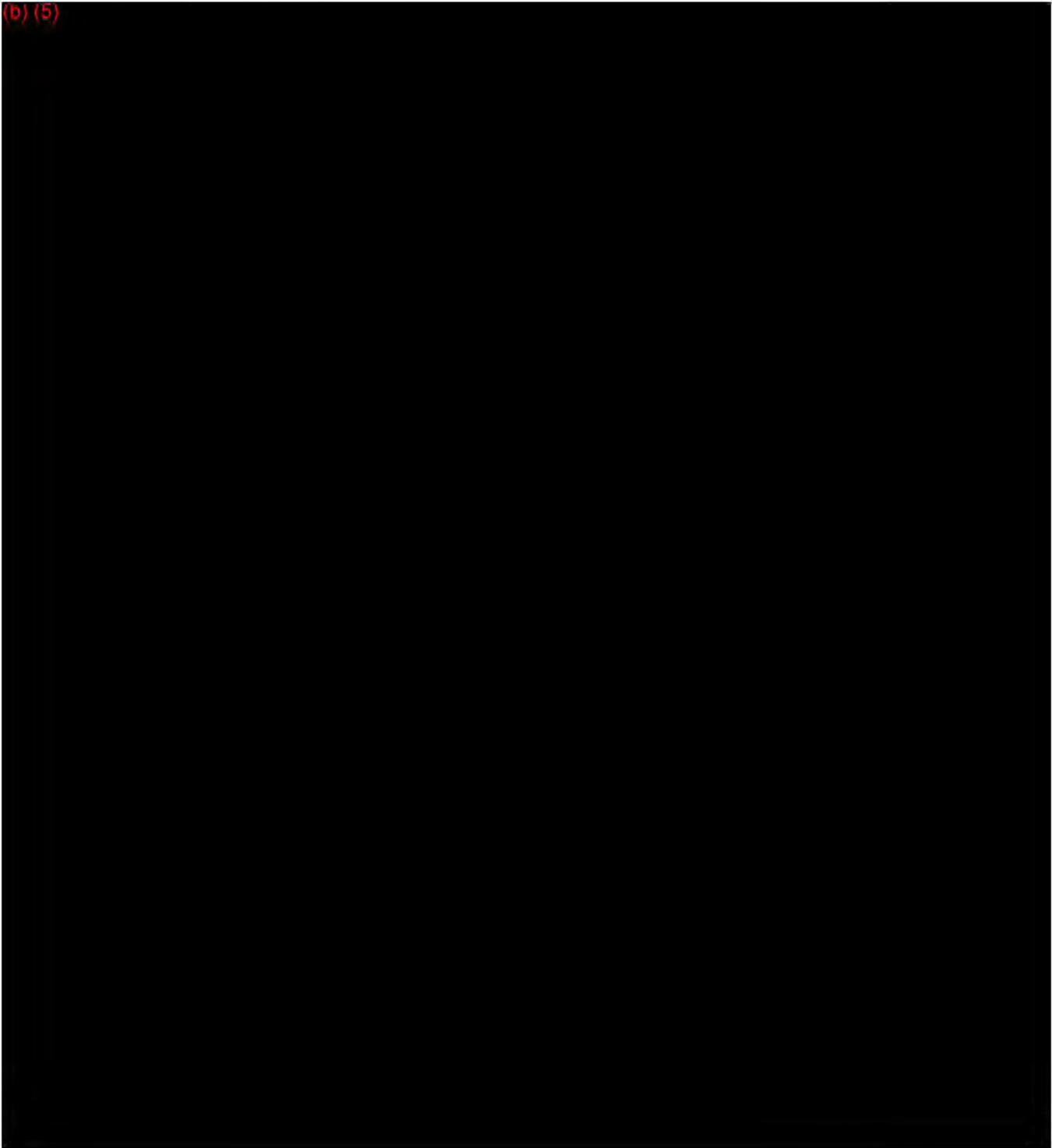


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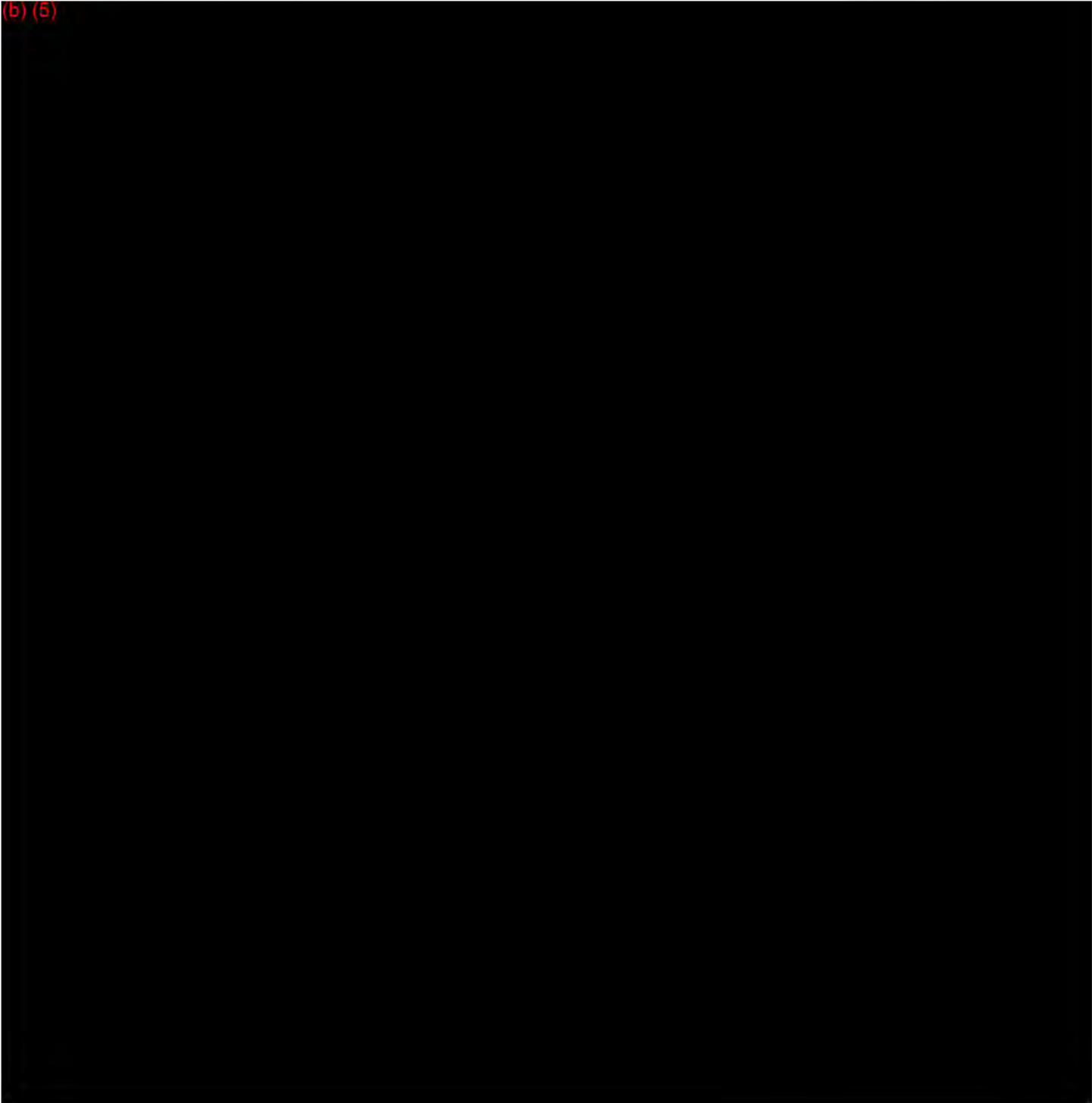
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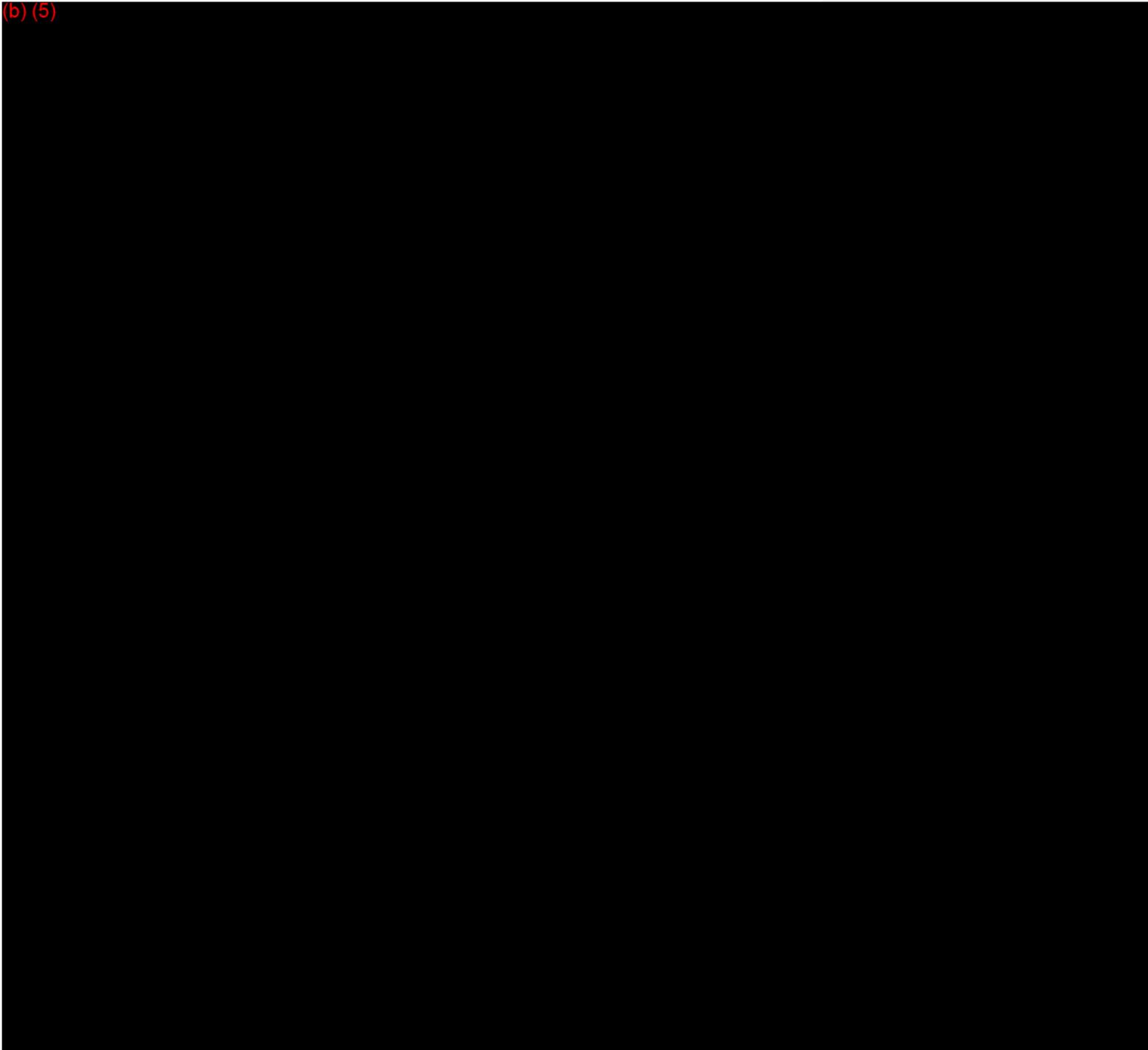
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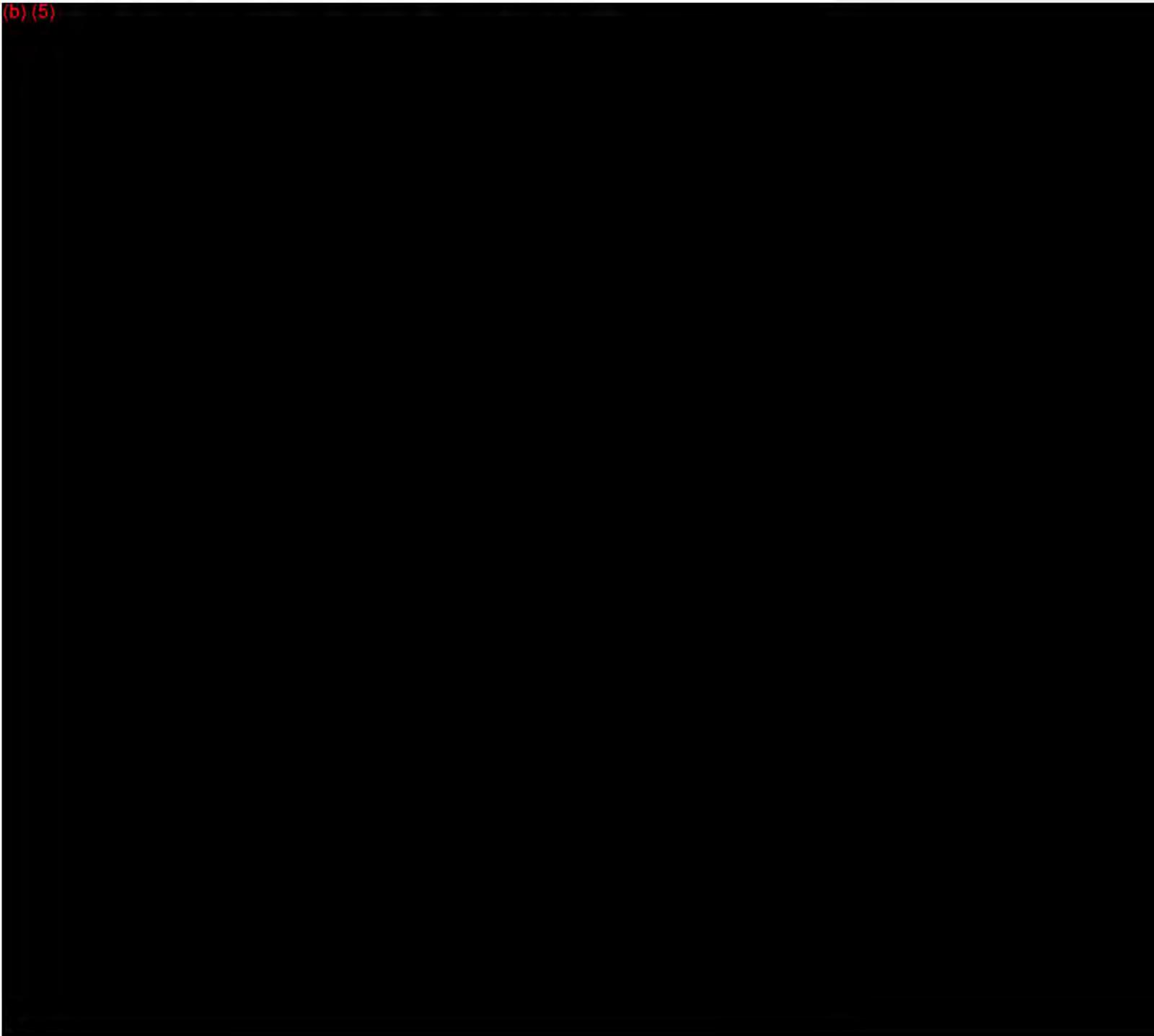
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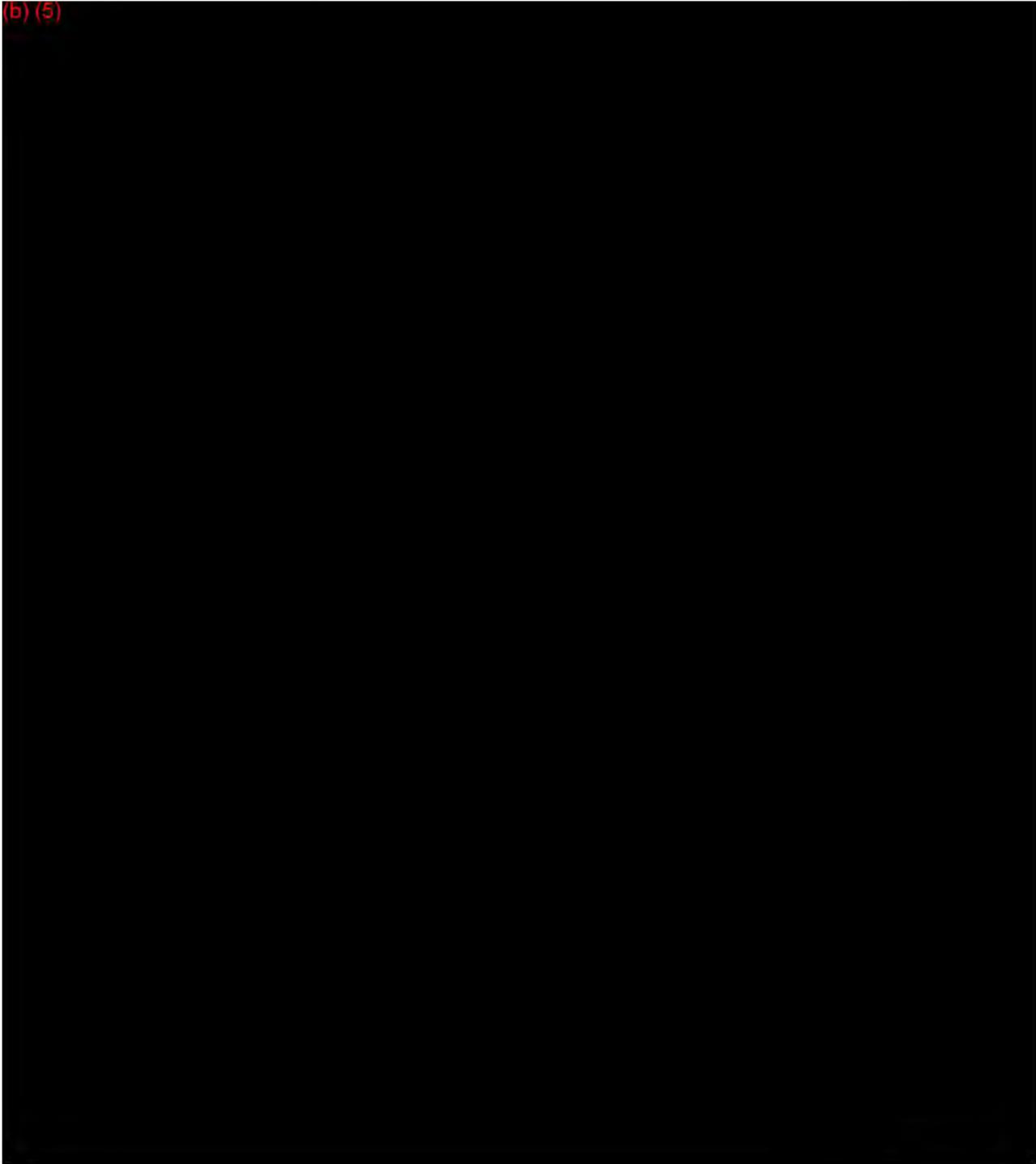
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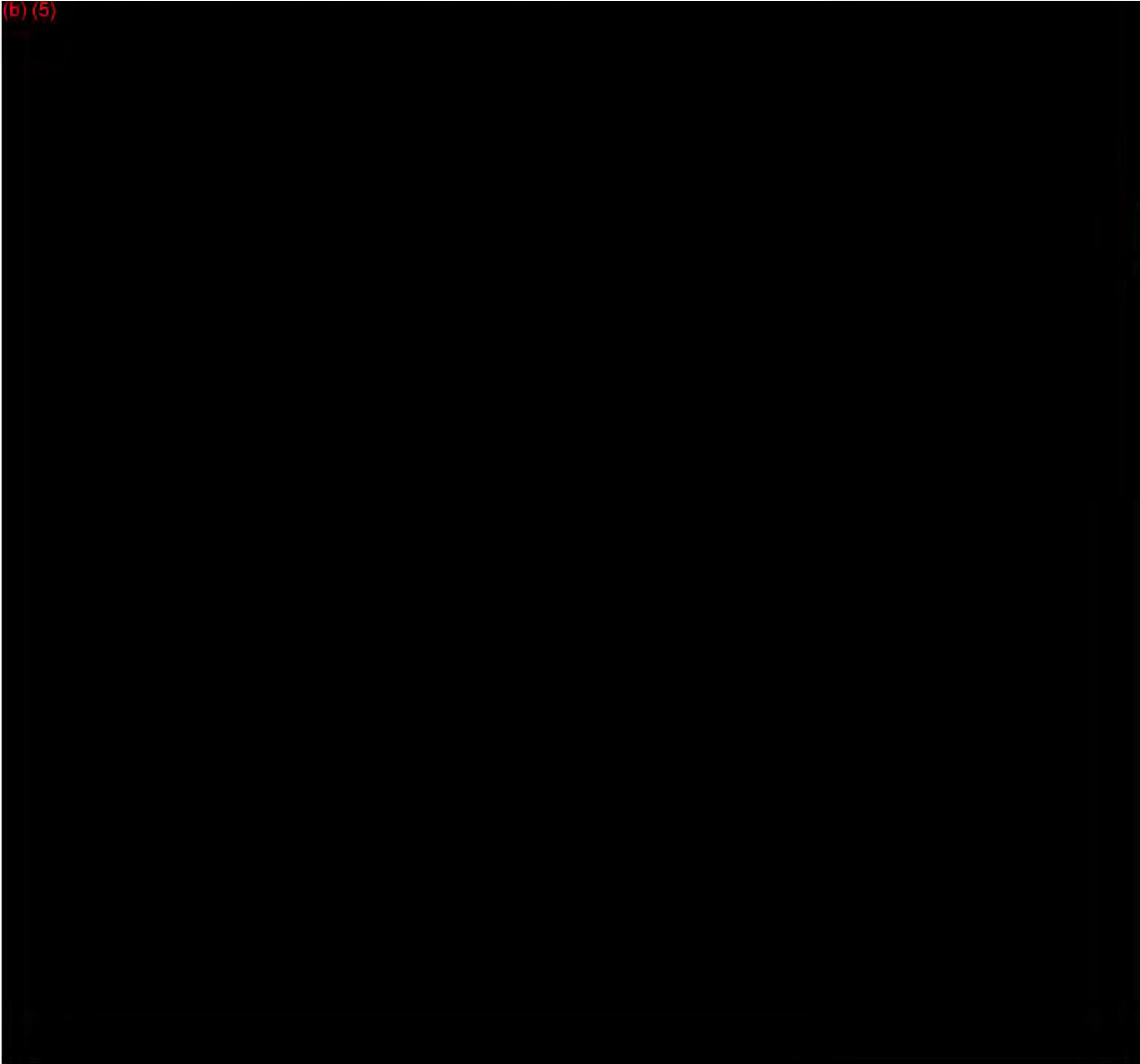
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From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: Tuesday Morning
Date: Tuesday, August 30, 2016 7:17:00 AM

Talk to you soon. I'm in the office and best # is (b) (6)

Rmc

From: Dickinson, Elizabeth (FDA)
Sent: Monday, August 29, 2016 7:03 PM
To: Califf, Robert
Subject: Tuesday Morning

Hello, Dr. C,

I am just back from Colorado. We had snow in Leadville.

You and I have an 8:15 meeting on the calendar tomorrow. I will plan to call you at that time on your cell, unless I hear otherwise.

I will not have read the most recent draft of the eteplirsen memo, but will do so after we talk. Hope all is well.

Liz

From: [Conover, Katie](#)
To: [Califf, Robert](#)
Subject: Review of materials for drug approval
Date: Thursday, September 01, 2016 11:33:04 AM
Attachments: [eteplirsen KMQA \(occ\) 8.9.16 \(occ 8-15\) oma83016.doc](#)
[eteplirsen PR draft occ reviewed Aug2016.doc](#)
[image013.png](#)
Importance: High

Hi Dr. Califf,

In anticipation of our discussion this afternoon, attached please find a draft press release and KMQA to support communications around the approval of the drug. We have not yet sent these materials to Liz – but I am sharing with you now so that you can see what we are envisioning.

I have asked Jen Rodriguez, who has been working on these materials and communications plans, to join me for the call as well. We look forward to speaking with you and providing additional context regarding our communications recommendations.

Best,

Katie

Katie Conover

Acting Associate Commissioner

Office of External Affairs

U.S. Food and Drug Administration

Tel: 240-402-2402 / Cell: 301-512-9120

priscilla.conover@fda.hhs.gov

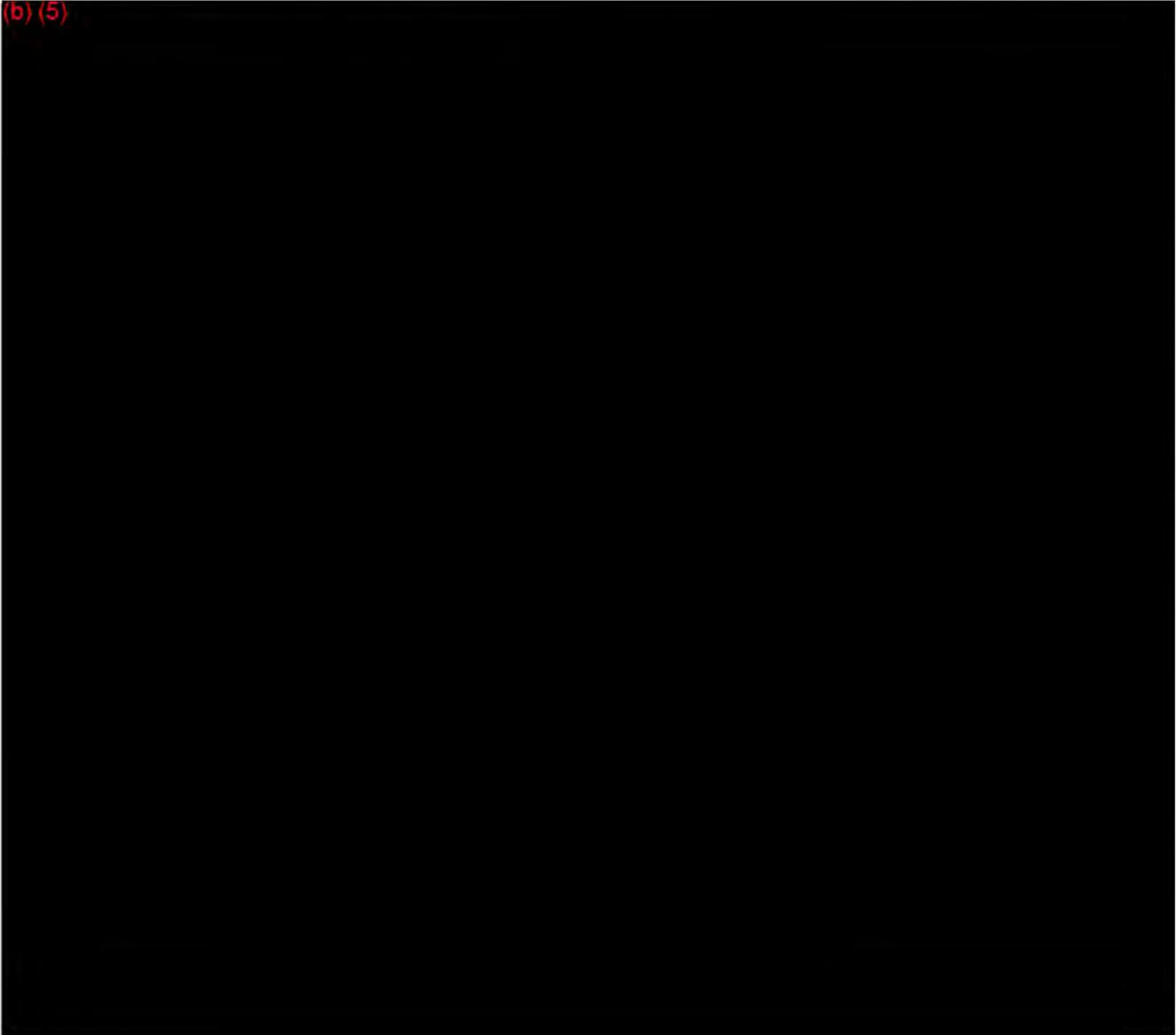


Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

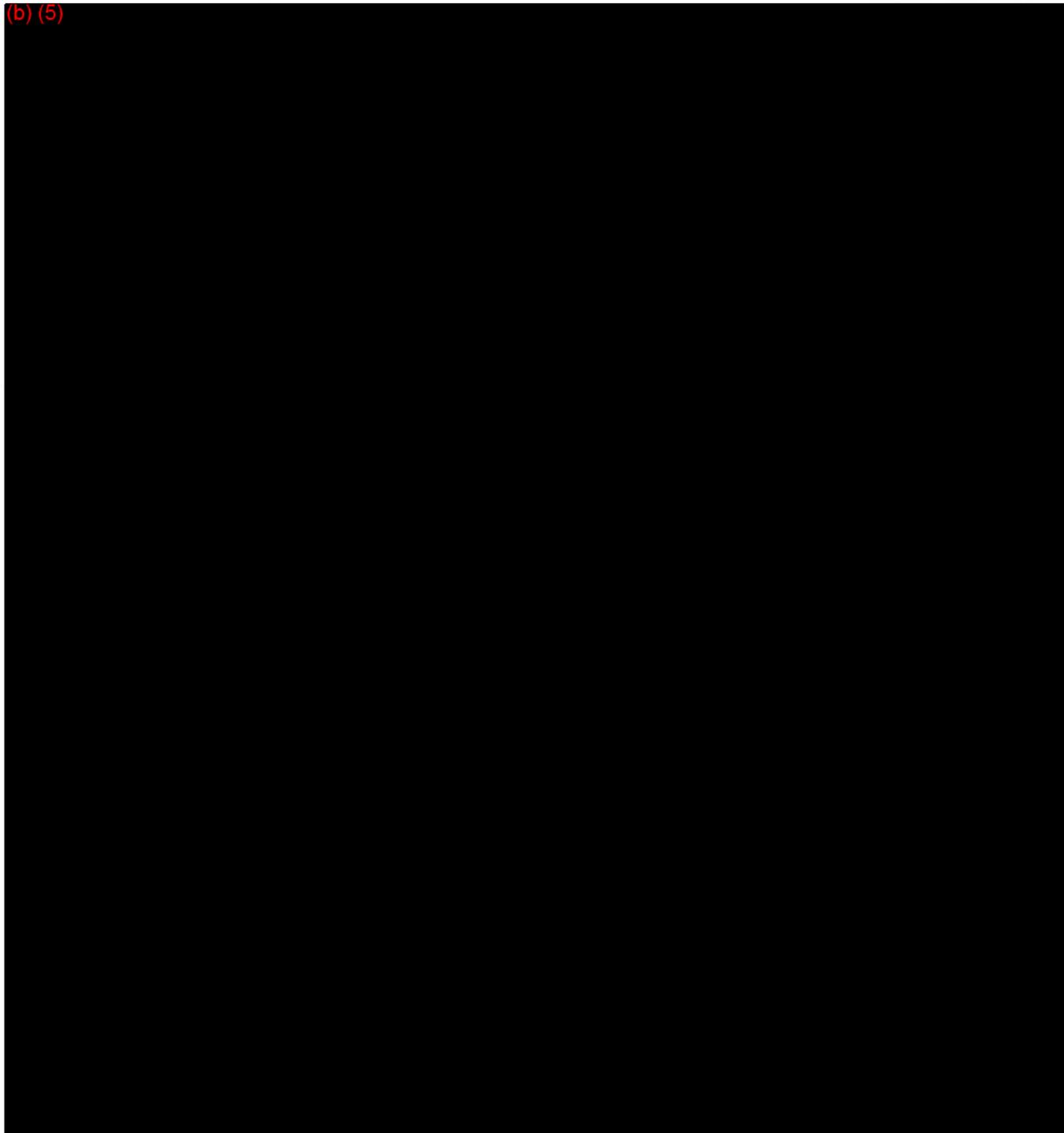
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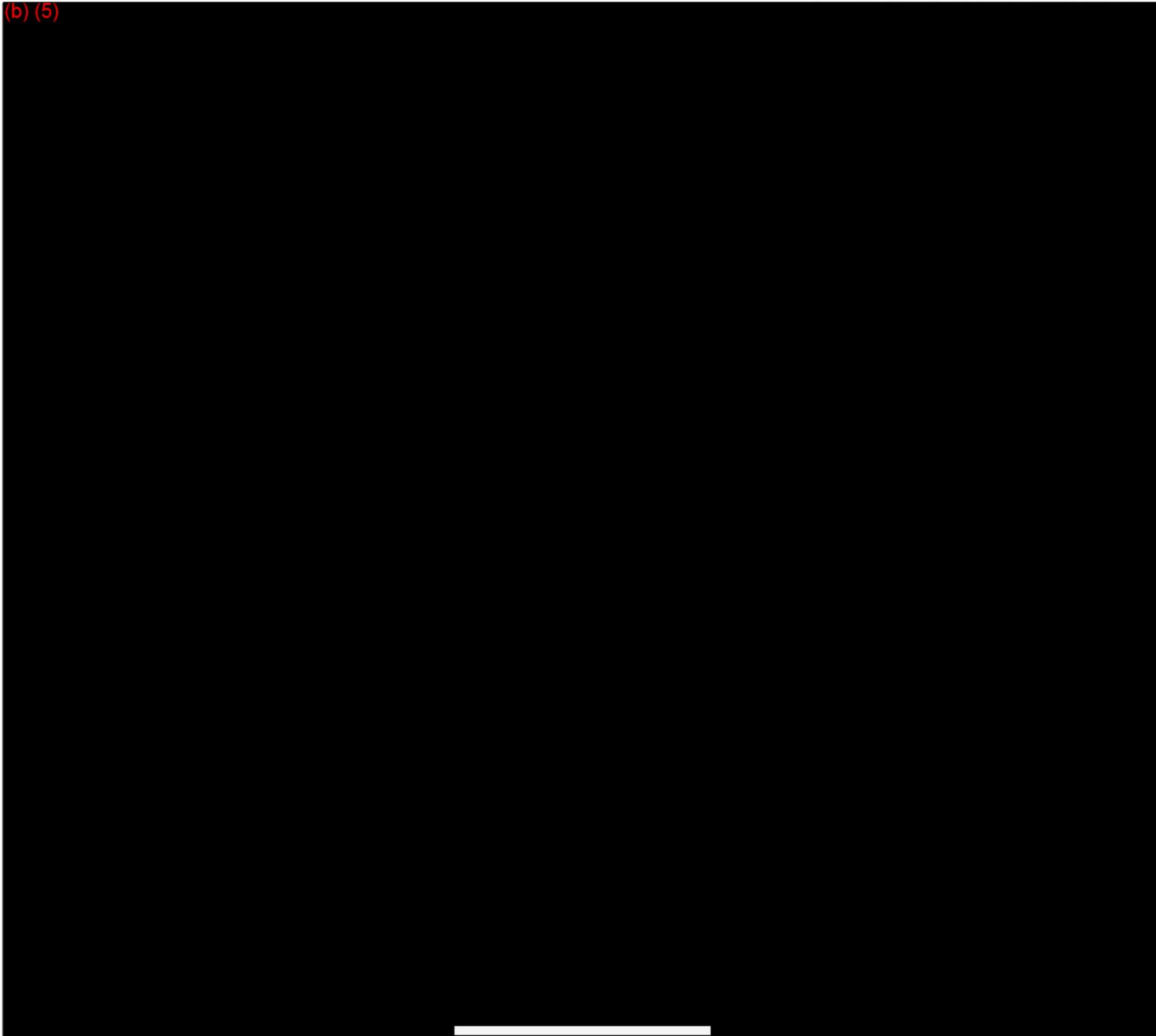
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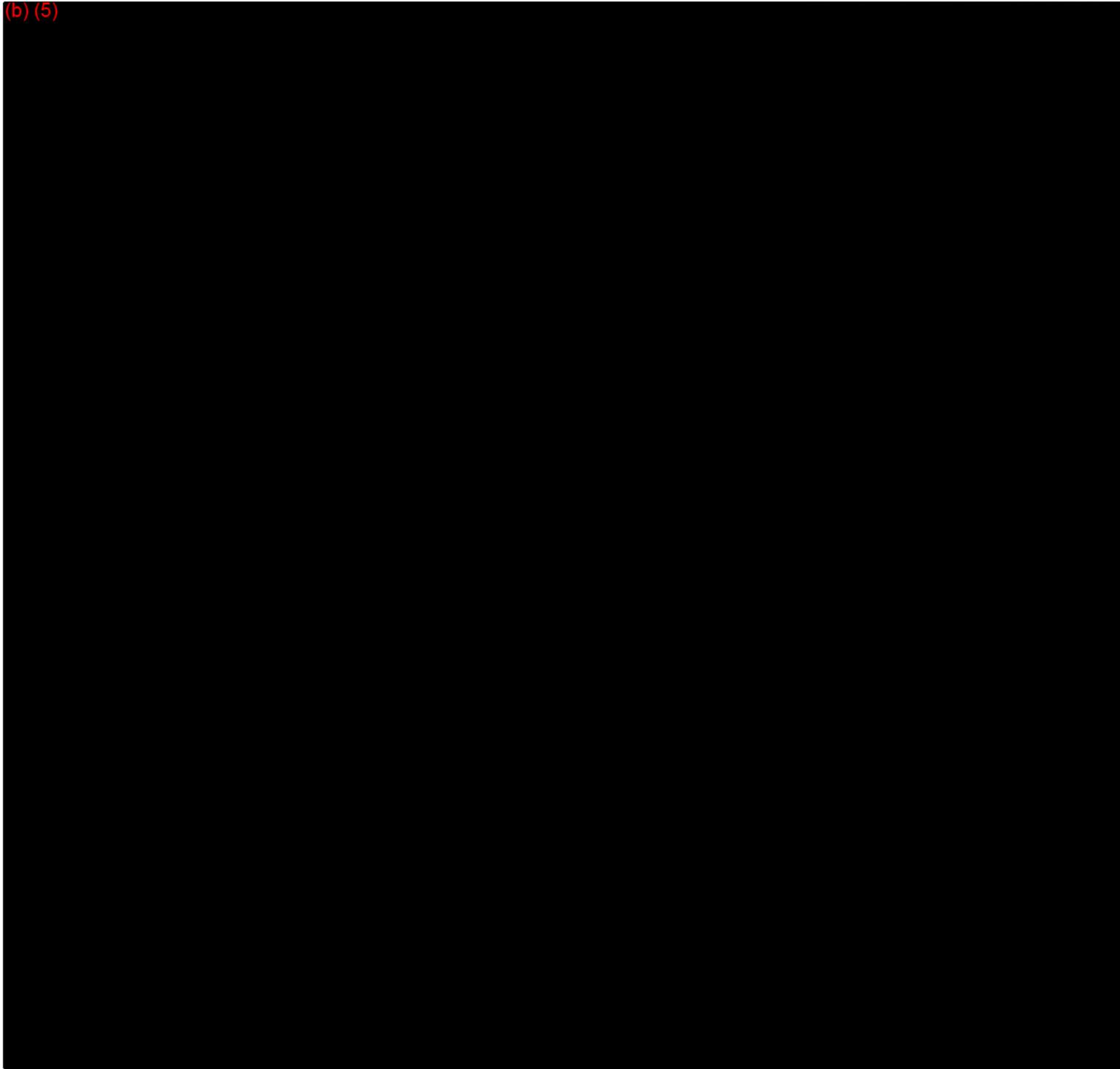


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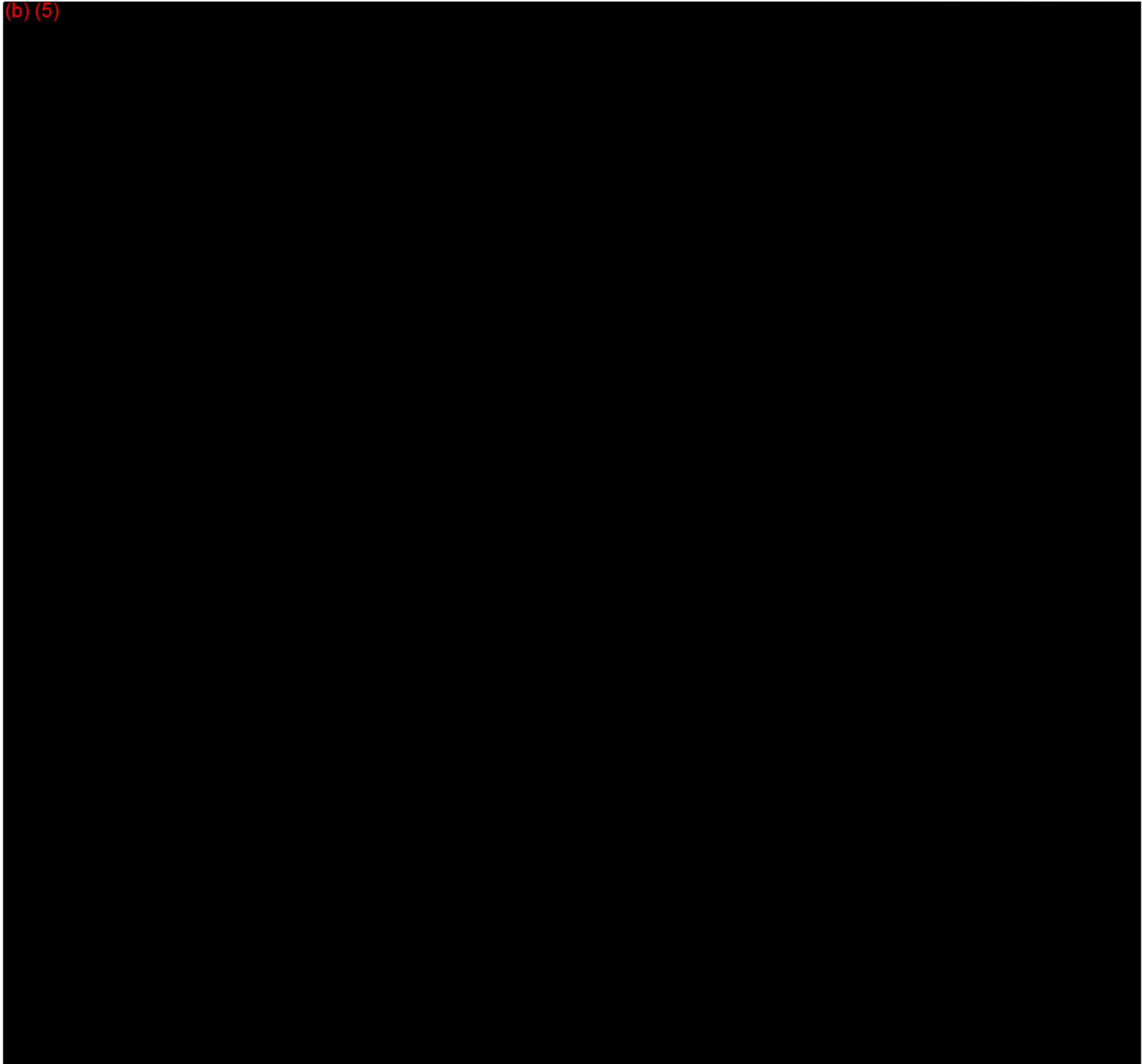


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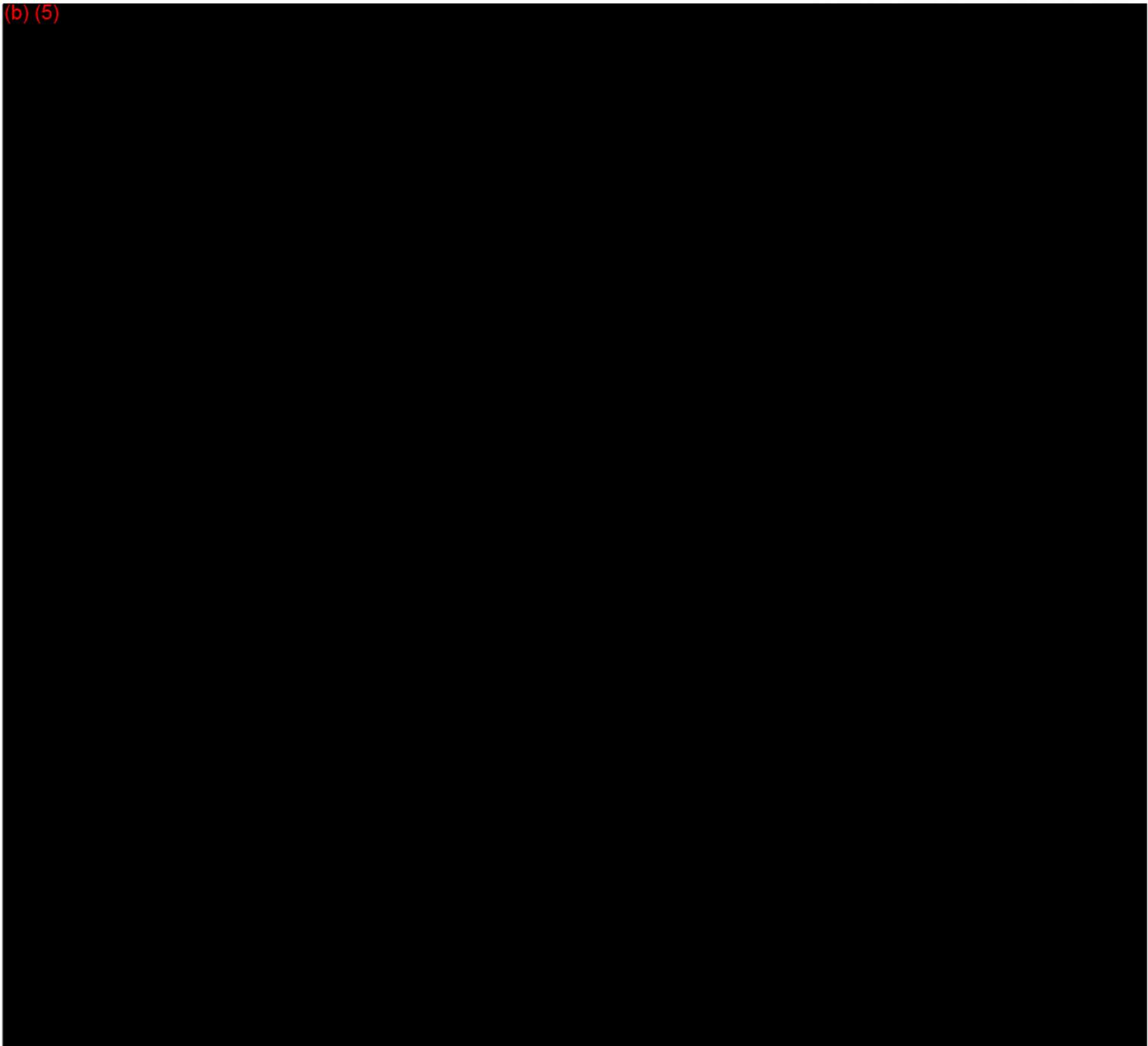
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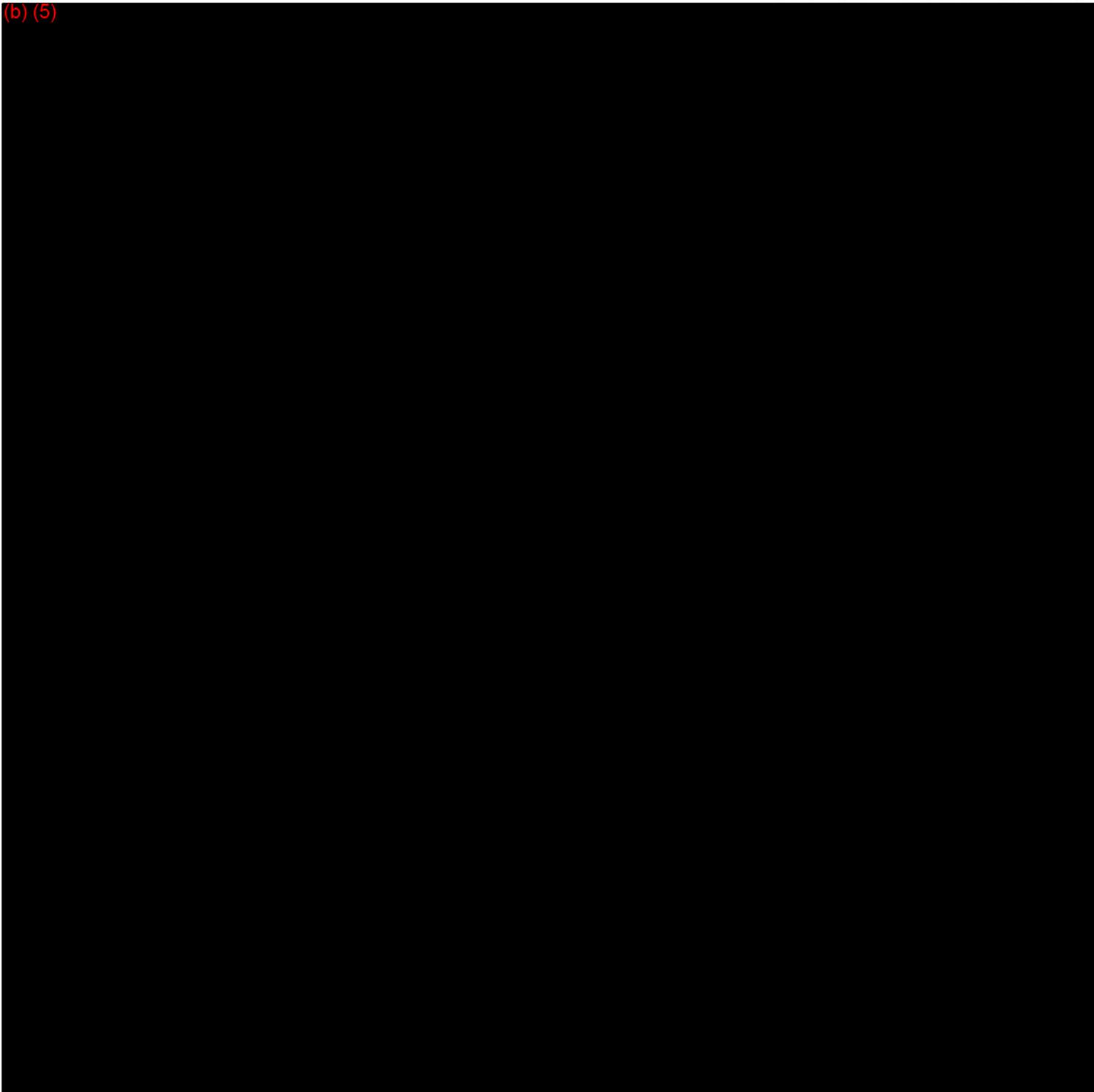
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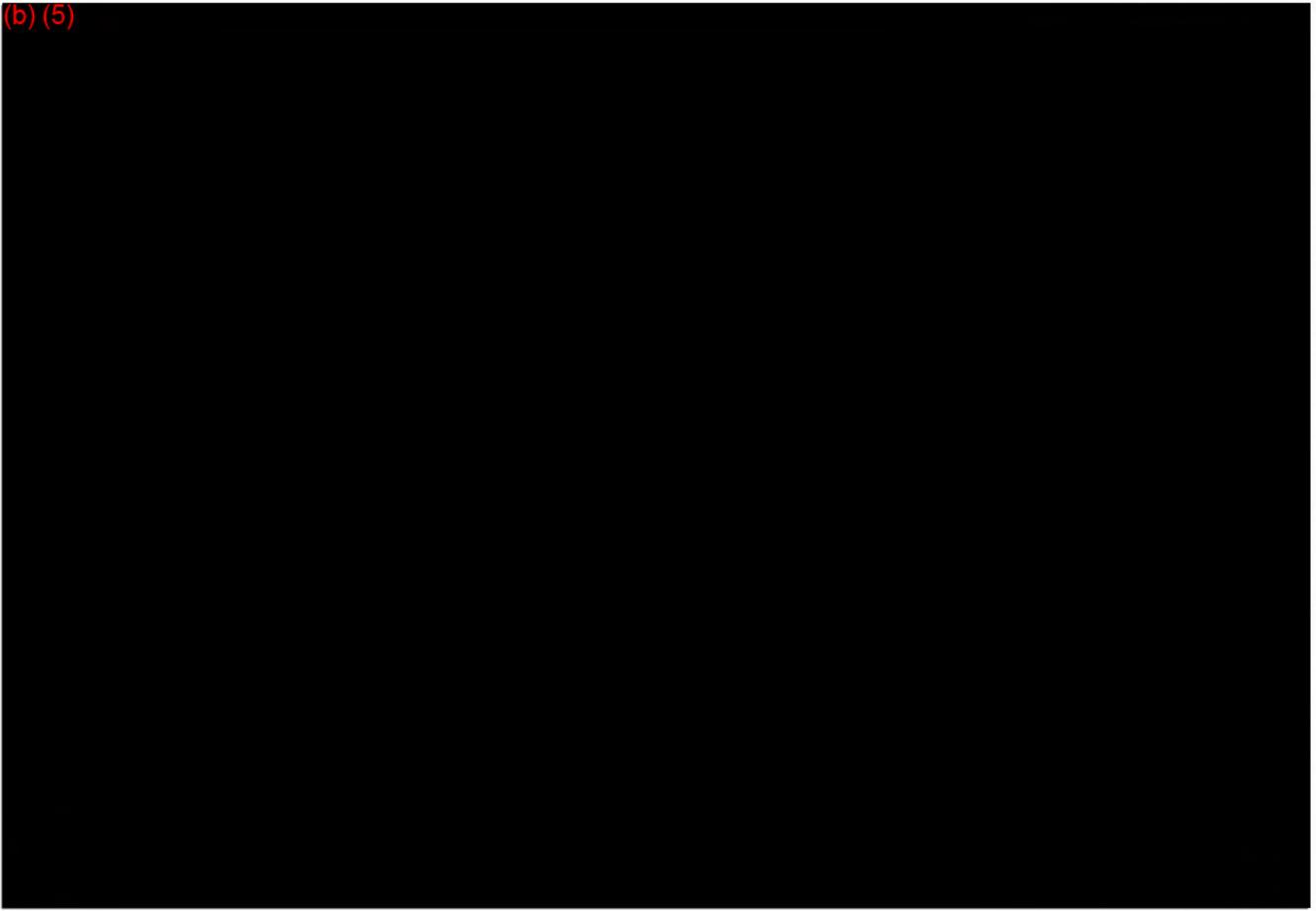
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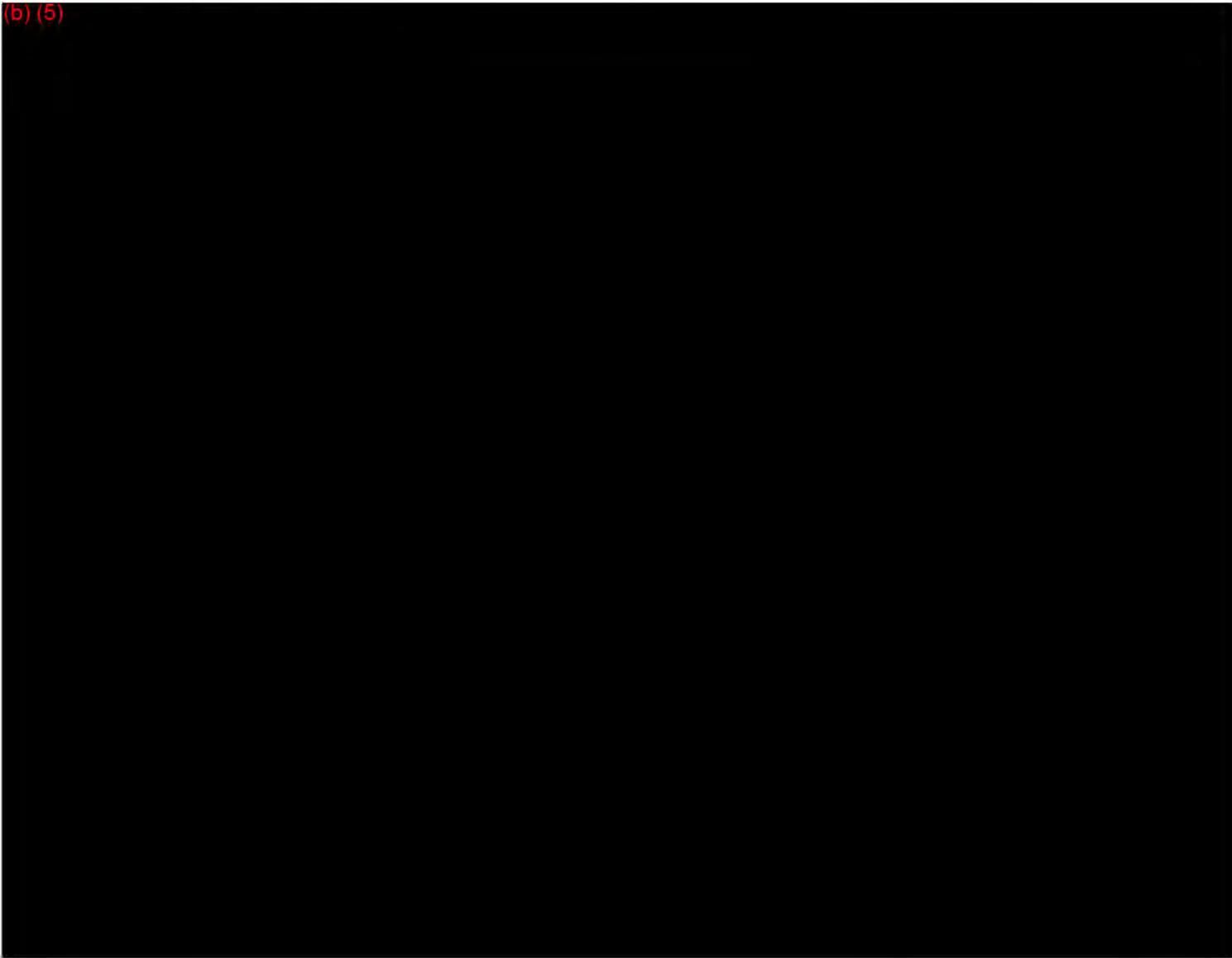
FDA NEWS RELEASE

For Immediate Release: September xx, 2016

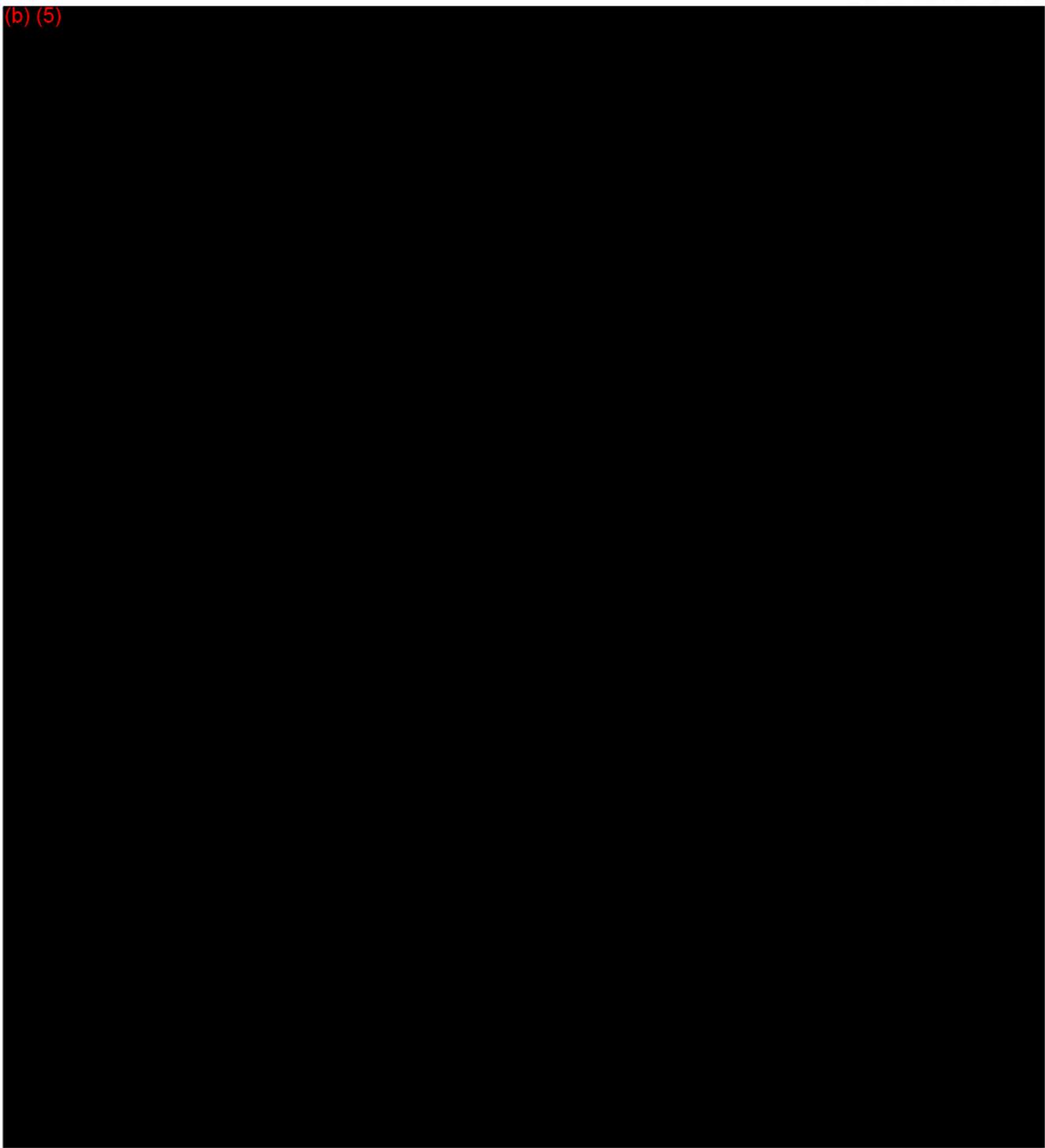
Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

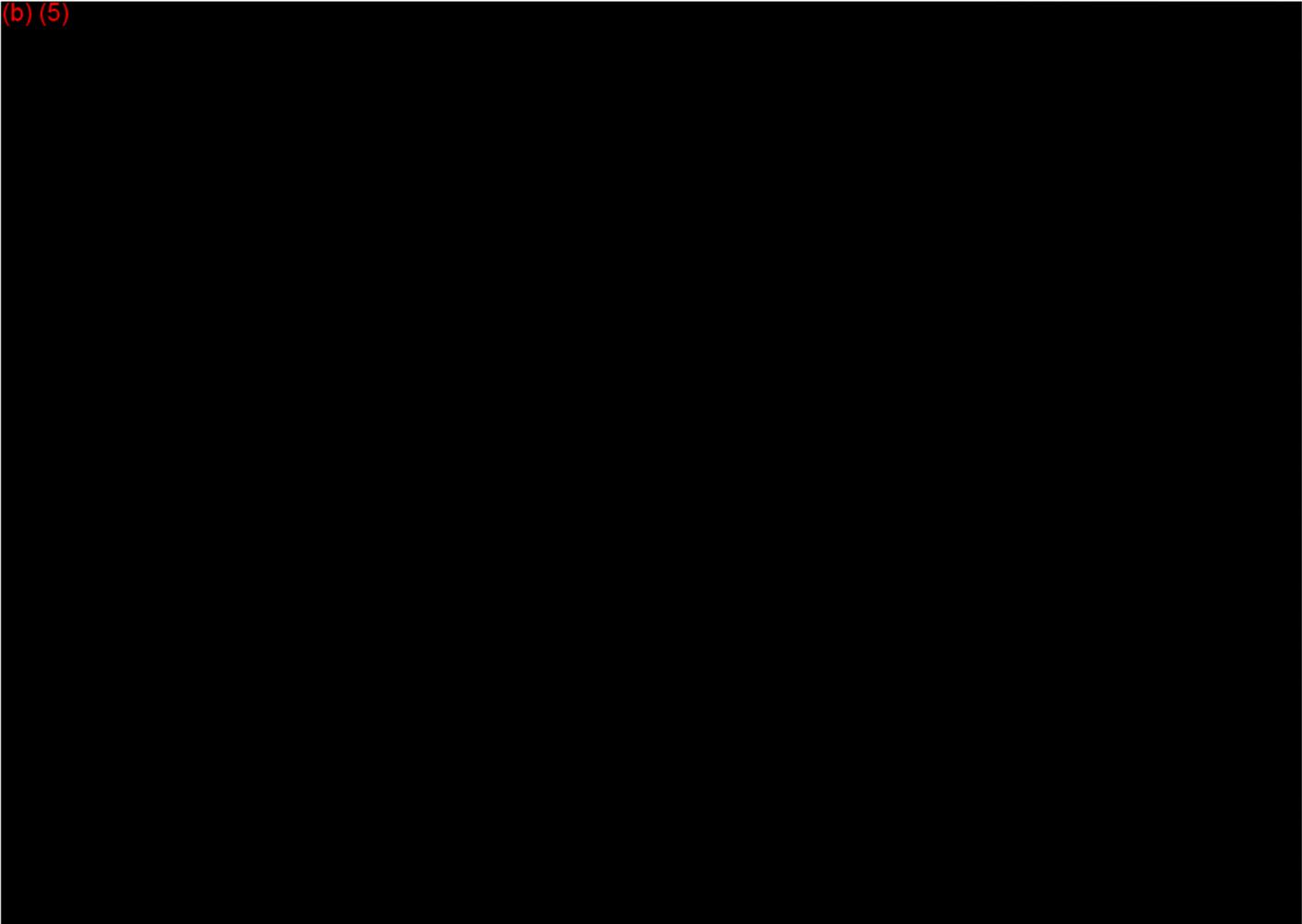
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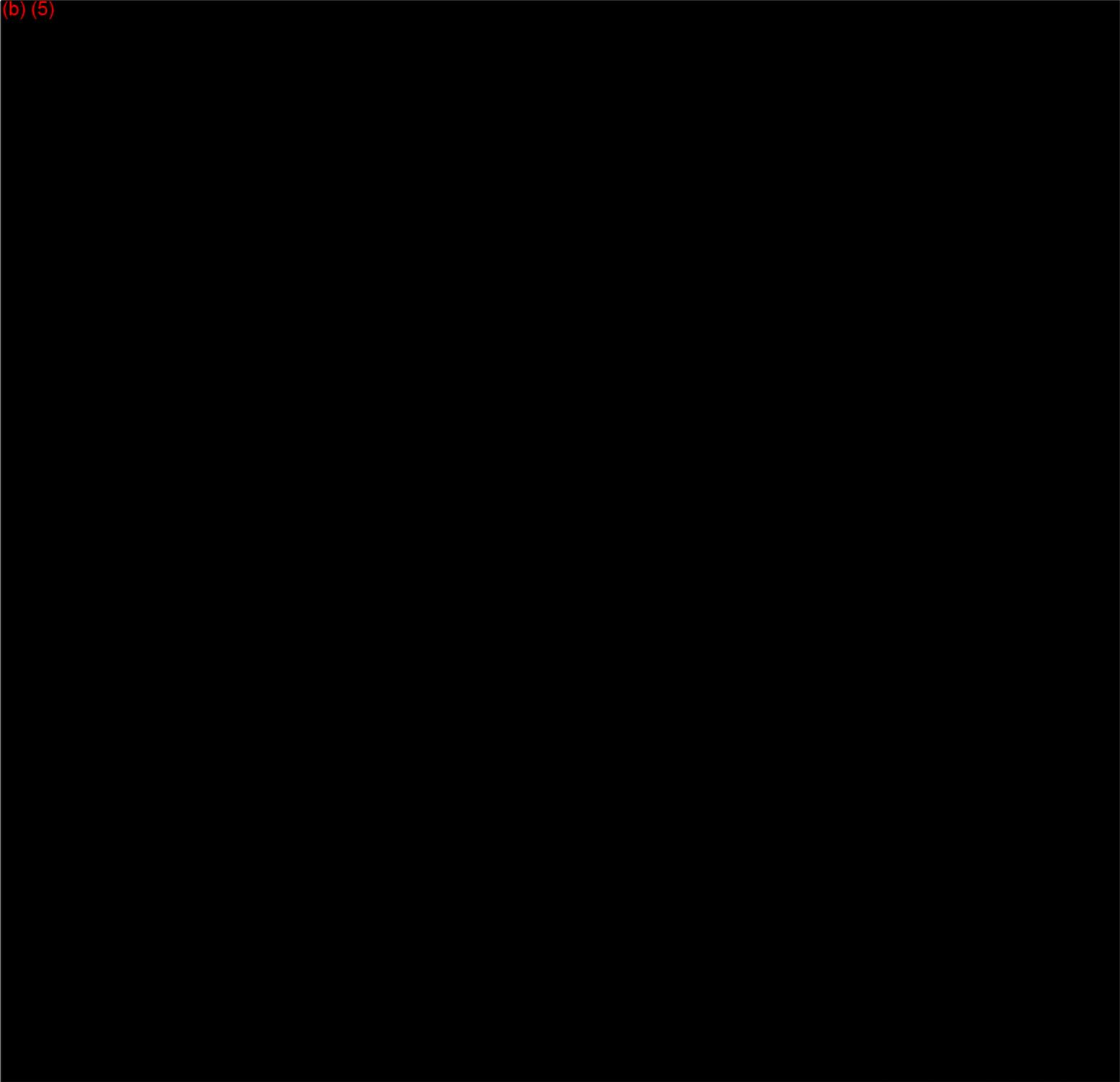
Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

Target date: September 2016

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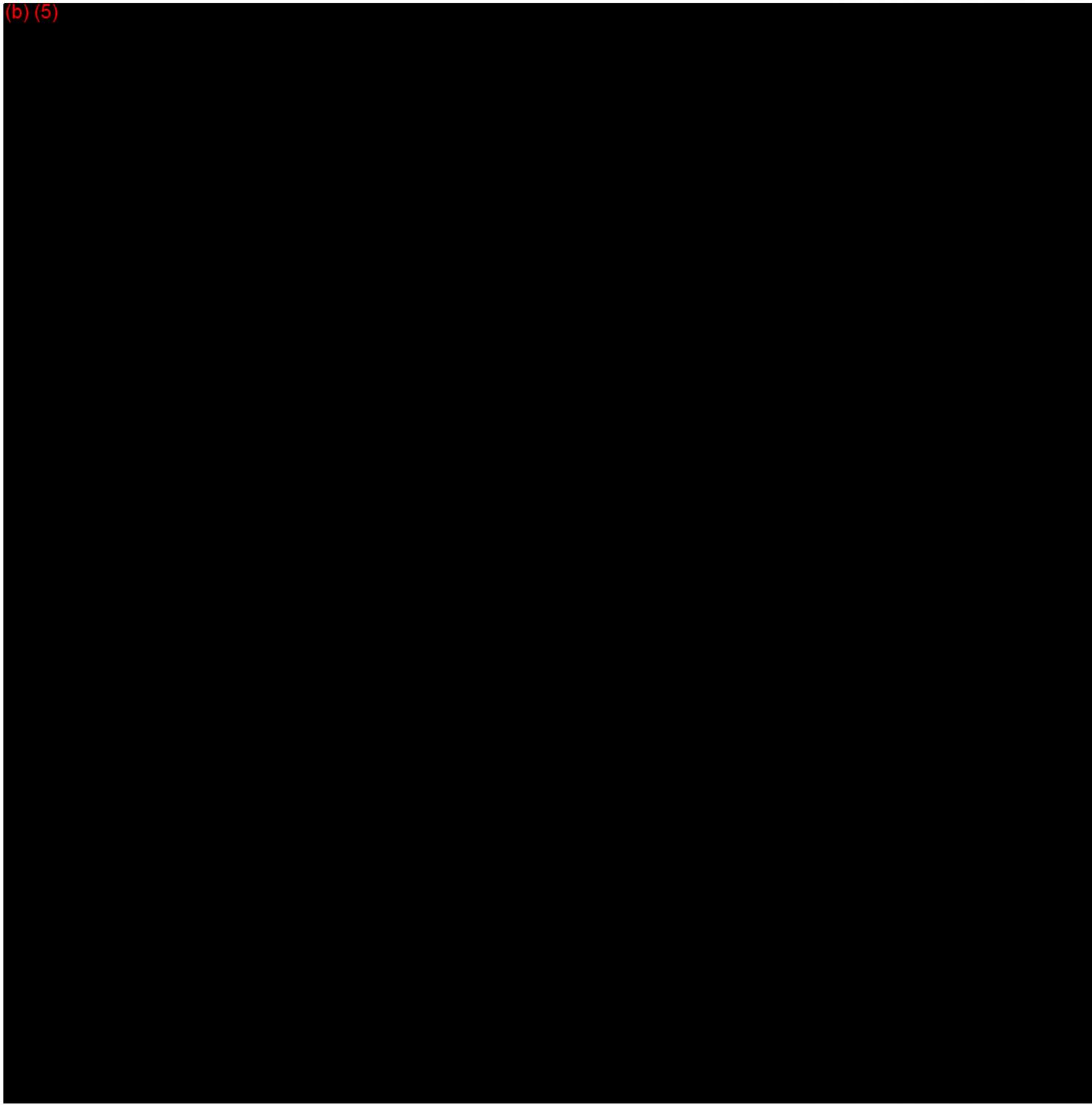
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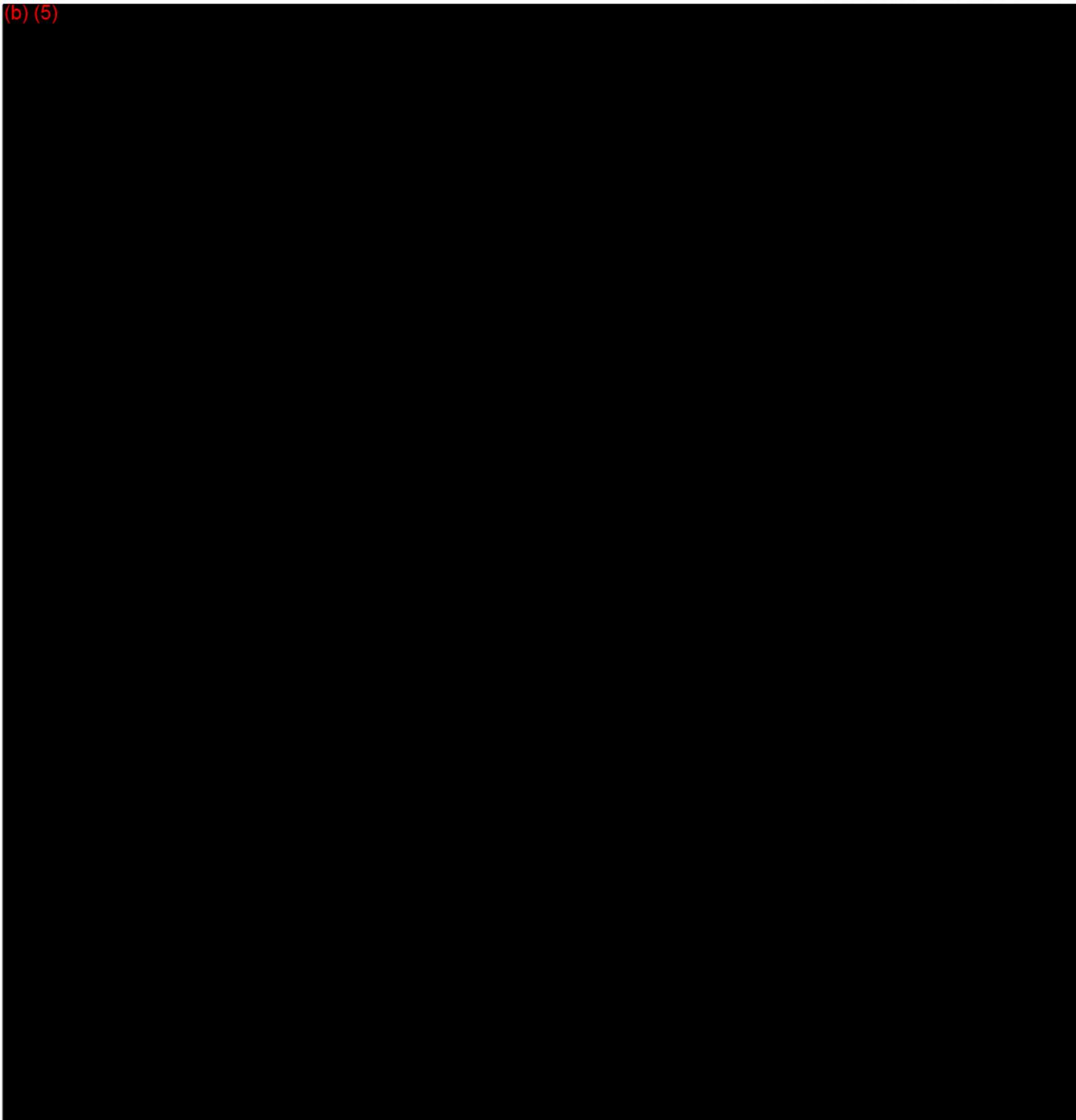
(b) (5)



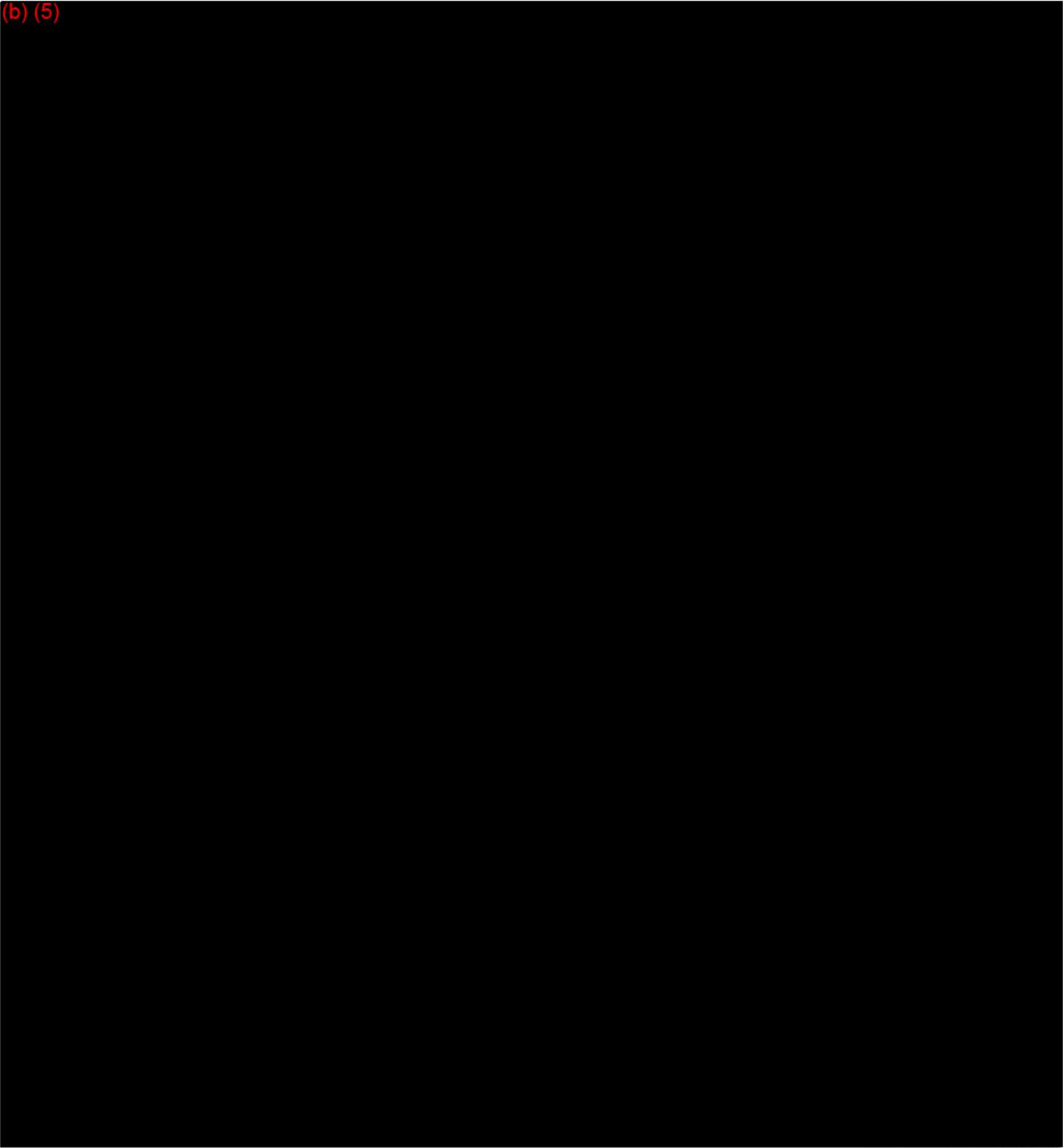
(b) (5)



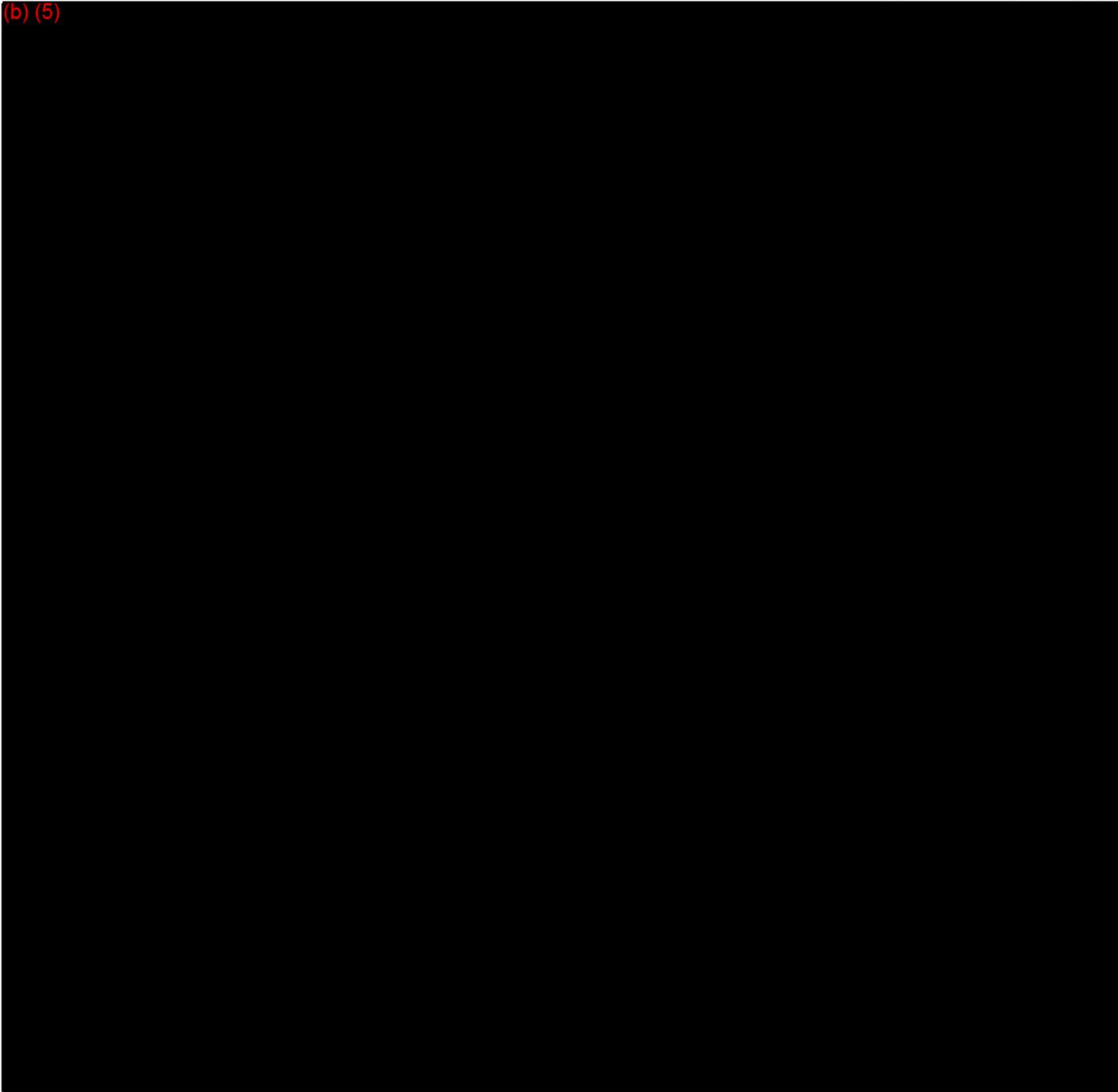
(b) (5)



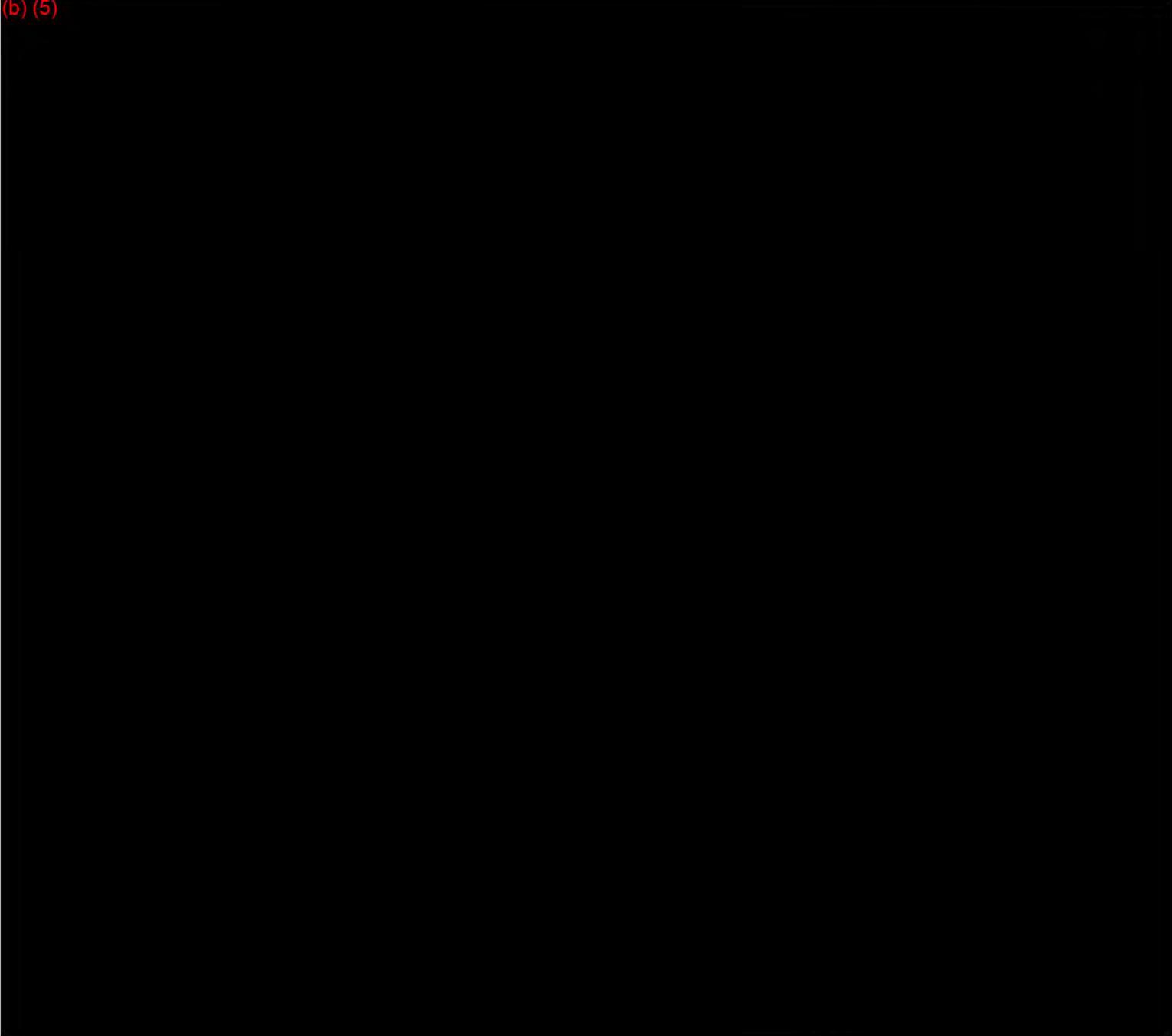
(b) (5)



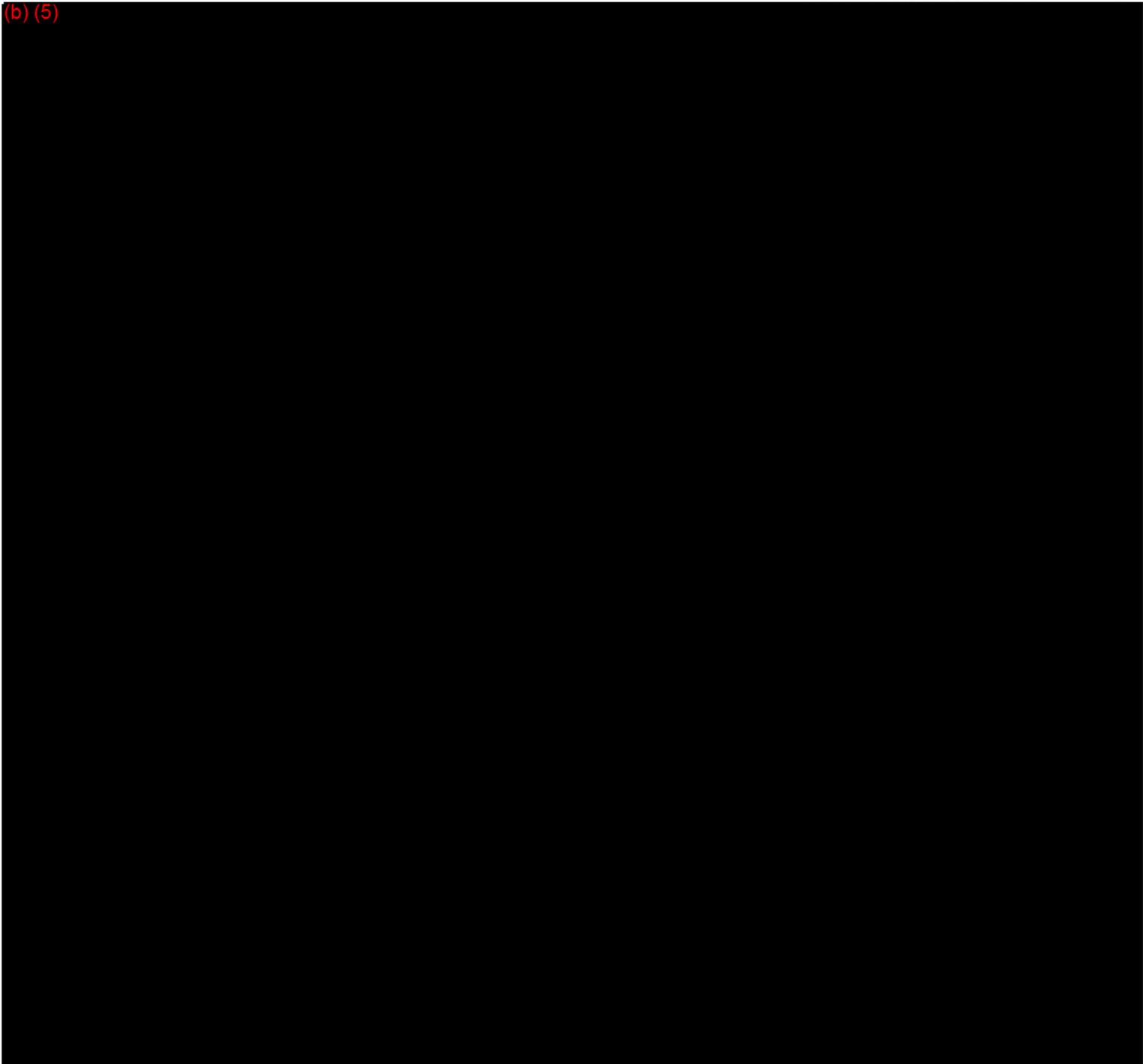
(b) (5)



(b) (5)



(b) (5)



**Reactive Statement and QA: Posting of review documents for approval of
Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy**

Target date: September 2016

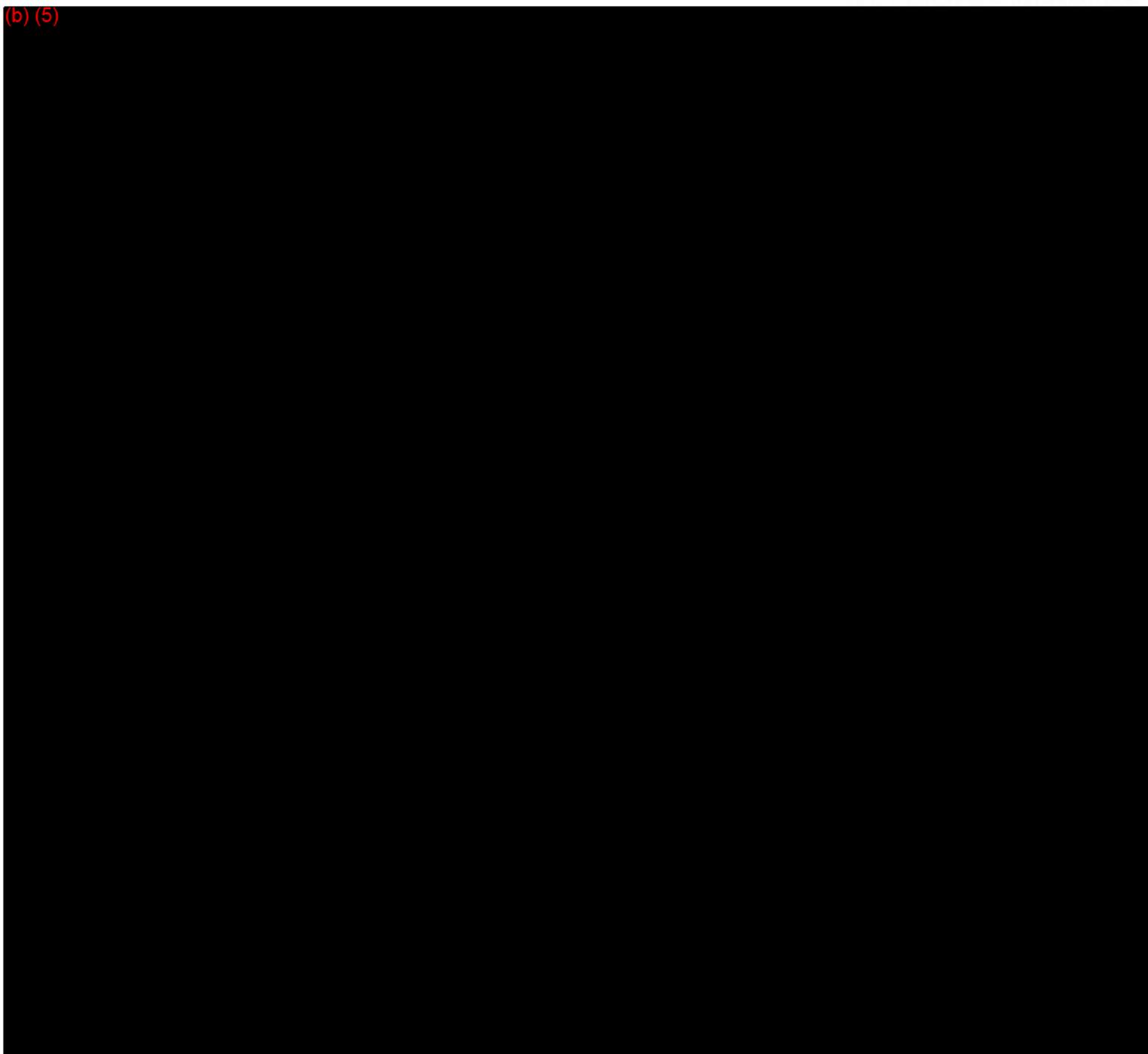
(b) (6)



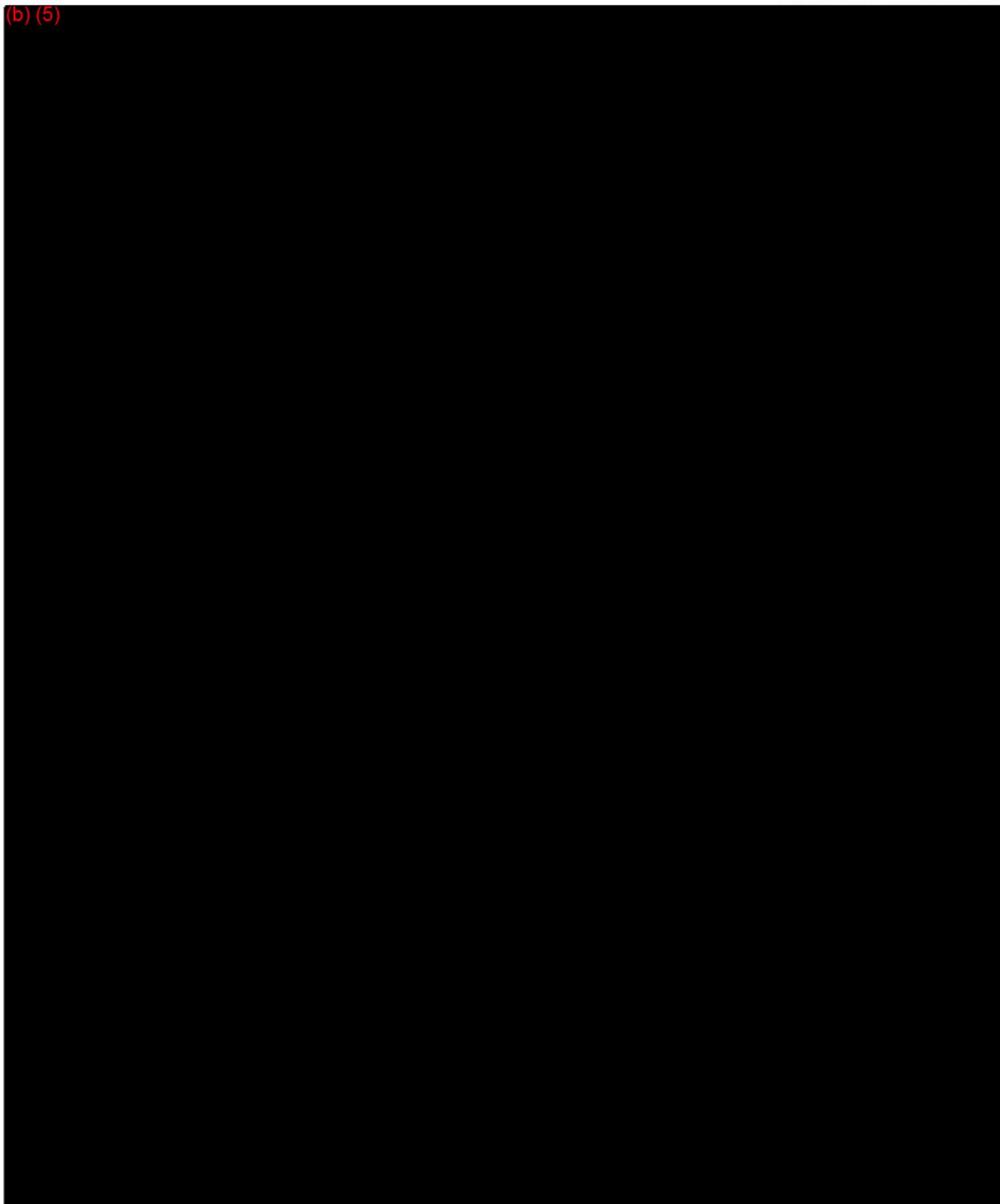
(b) (5)



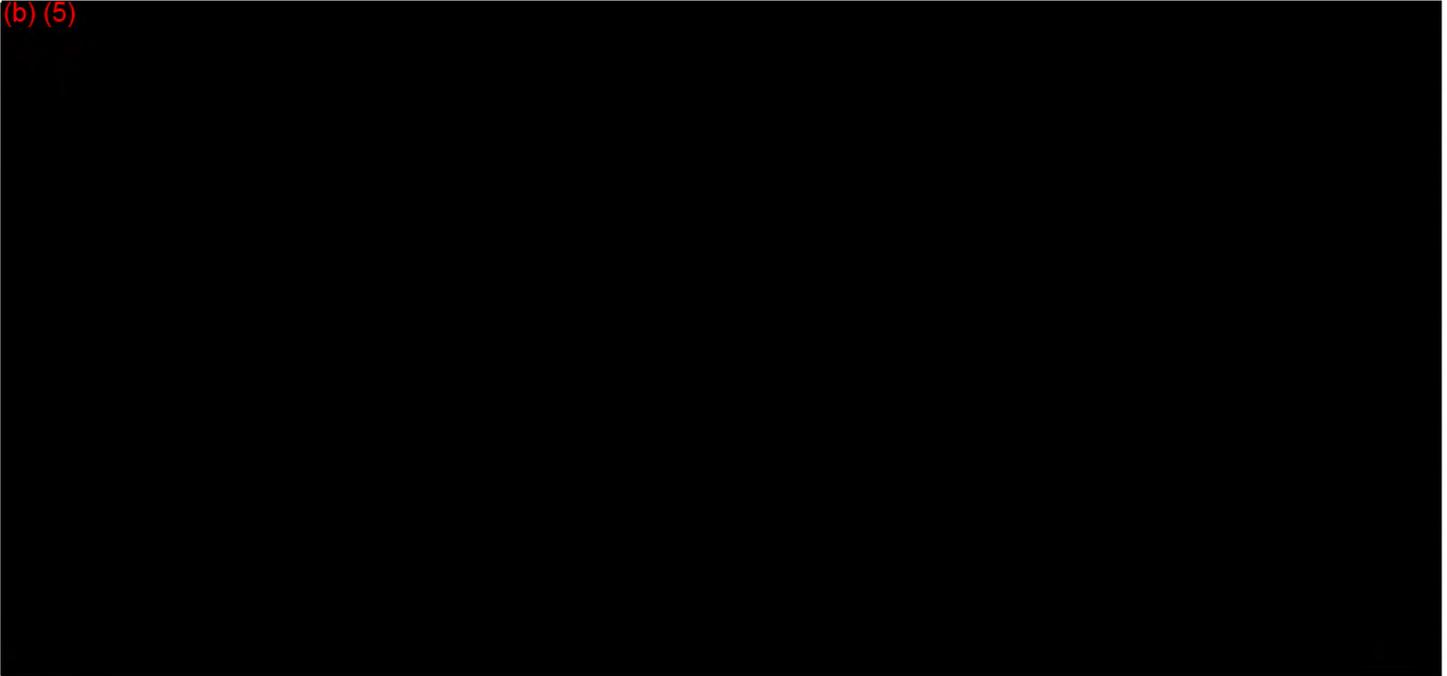
(b) (5)



(b) (5)



(b) (5)



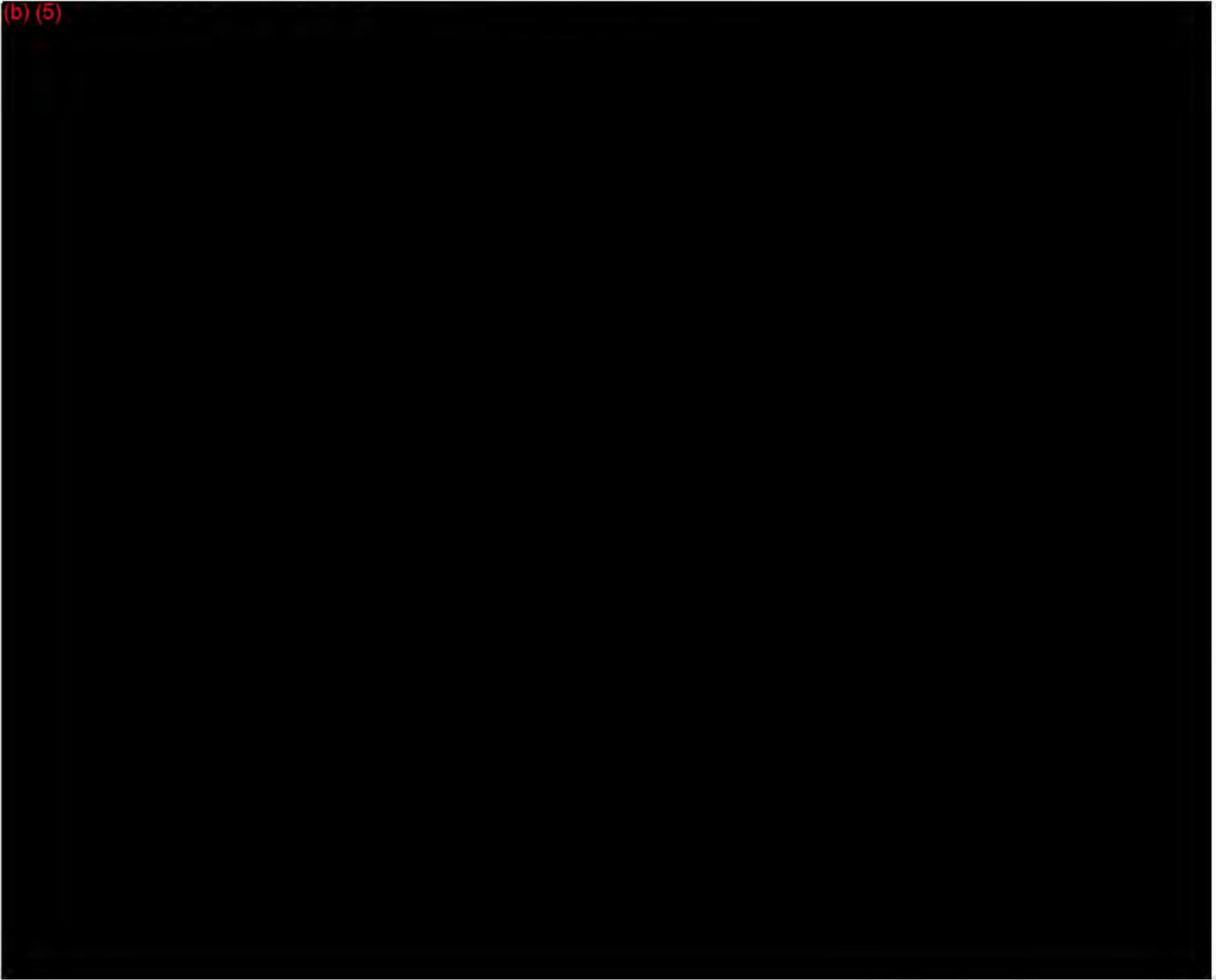
FDA NEWS RELEASE

For Immediate Release: September xx, 2016

Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

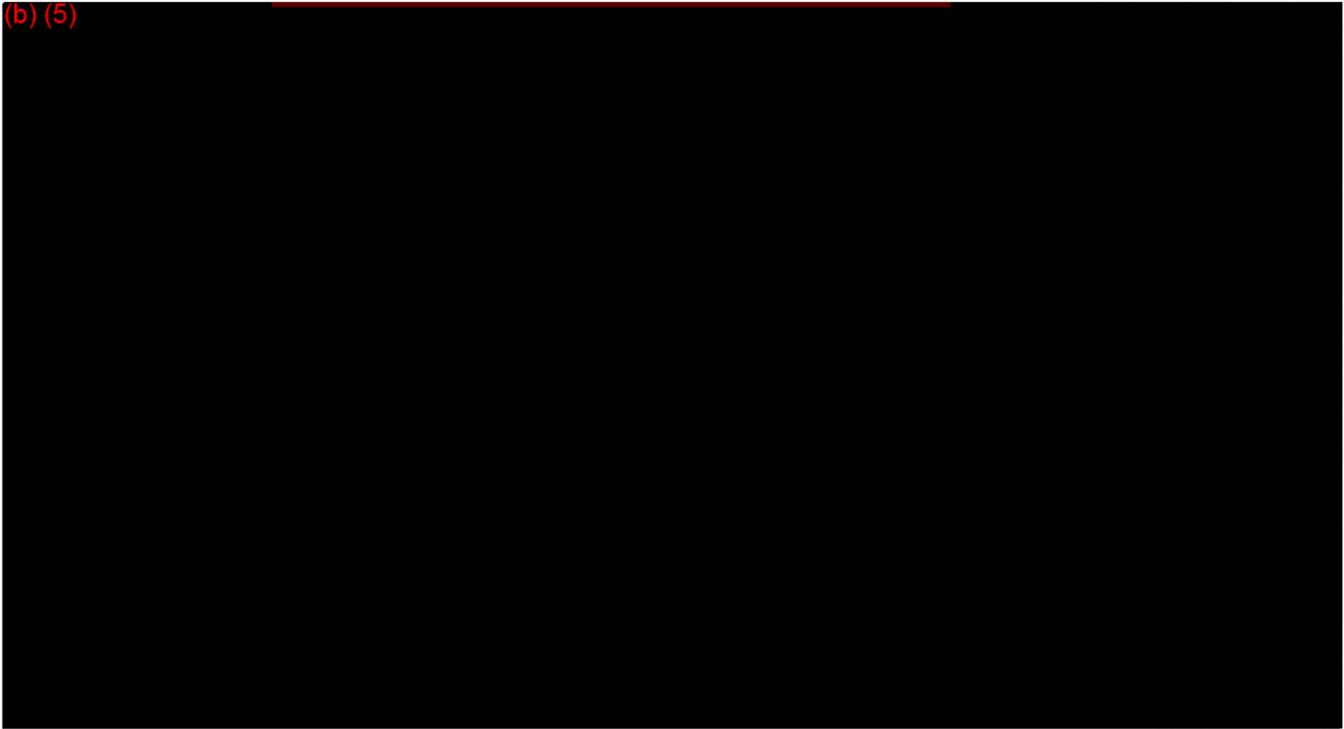
Consumer Inquiries: 888-INFO-FDA

(b) (5)



(b) (5)

(b) (5)



From: [Califf, Robert](#)
To: [Woodcock, Janet](#)
Subject: RE: I spoke to the firm
Date: Friday, September 02, 2016 11:50:00 AM

Let's discuss over weekend. I need to understand some nuances on this part. Let me know your availability.

thx

From: Woodcock, Janet
Sent: Friday, September 02, 2016 11:01 AM
To: Califf, Robert
Subject: I spoke to the firm

And got a much better idea of what is going on. There are a number of studies, but the dose comparison study is not started, they need to reach agreement on the details of the protocol with the division. Of course, they have agreed to do this study.

The ongoing studies with eteplersin on exon 51 amenable:

"PROVMOVI" study: 2yr open label almost at full enrollment. Will use new validated method for dystrophin WB and will use an automated method for ICH that has been validated. Around 70 patients. (b) (4)

204: 45 patient. Overenrolled. Open label safety study in non-ambulatory boys. No biopsies.

203: Open label 1 year with extension. MRI studies in age 4-6. Overenrolled already.

Studies on another molecule:

Exon 45/53 amenable Randomized concurrent open label control study. Ethical problems encountered in doing weekly IV therapy in a placebo group of children. Our ethics people in the Peds group said they could do weekly Ivs, probably non-feasible for a 2 year study in children. Apparently Europe was ok w Ports, not sure how this was worked out. Initiated. Patients enrolled, currently in 4-week pre-dosing observation period. 2 sites open. Will also have sites in Europe. This study could shed light on the surrogate. jw

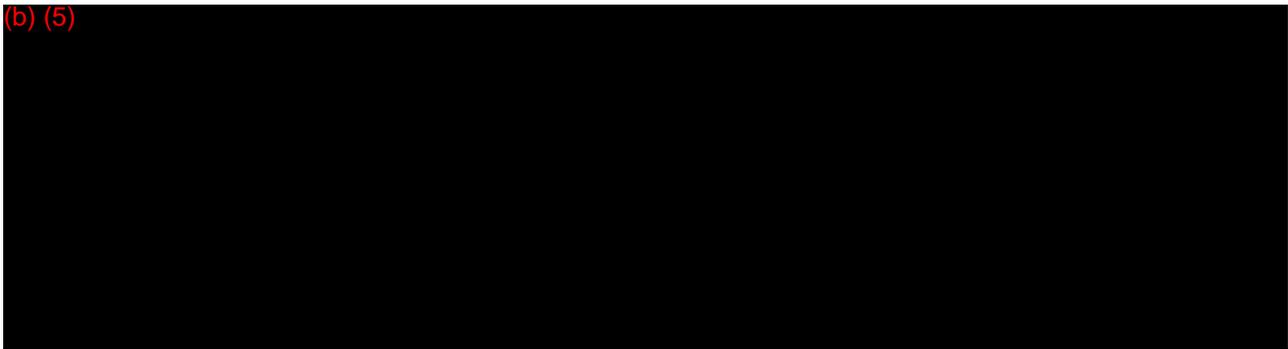
From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [McCall, Jonathan *](#); [Sherman, Rachel](#)
Cc: [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: RE: eteplirsen
Date: Friday, September 02, 2016 12:50:00 PM

This looks good as far as I can tell. Will find cites tonight or tomorrow. Out of action now for Denver lab visit.

Thx
rmc

From: Dickinson, Elizabeth (FDA)
Sent: Thursday, September 01, 2016 6:37 PM
To: McCall, Jonathan *; Califf, Robert; Sherman, Rachel
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: eteplirsen

(b) (5)

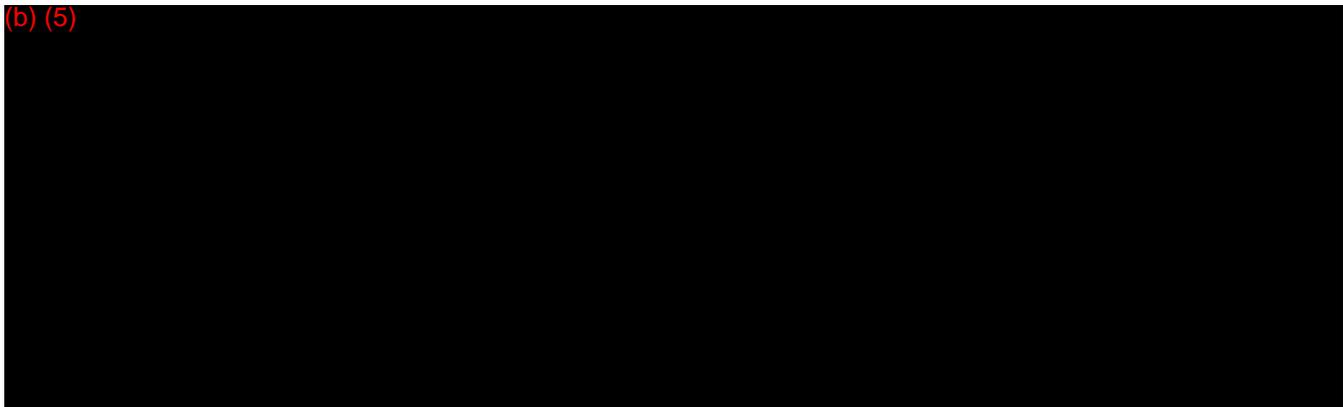


Liz

From: McCall, Jonathan *
Sent: Monday, August 29, 2016 10:06 AM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

I wasn't sure if anyone needed a further clean copy of this, but here are tracked and clean versions. I've made two modifications that I wanted to highlight:

(b) (5)



(b) (5)

Please let me know if you have any questions!

Thanks!

--

J

From: Califf, Robert
Sent: Sunday, August 28, 2016 10:28 PM
To: Chasan-Sloan, Deborah (FDA); McCall, Jonathan *; Sherman, Rachel
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

Agreed with all comments and suggestions. I think its looking good.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, August 28, 2016 10:16 PM
To: McCall, Jonathan *; Sherman, Rachel; Califf, Robert
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

(b) (5)

Thanks,
Deborah

From: McCall, Jonathan *
Sent: Sunday, August 28, 2016 2:22 PM
To: Sherman, Rachel; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

Hello all –

I've attached clean and tracked versions that incorporate Rachel's suggestions below.

FDAOC0001630

Please let me know if you need anything else!

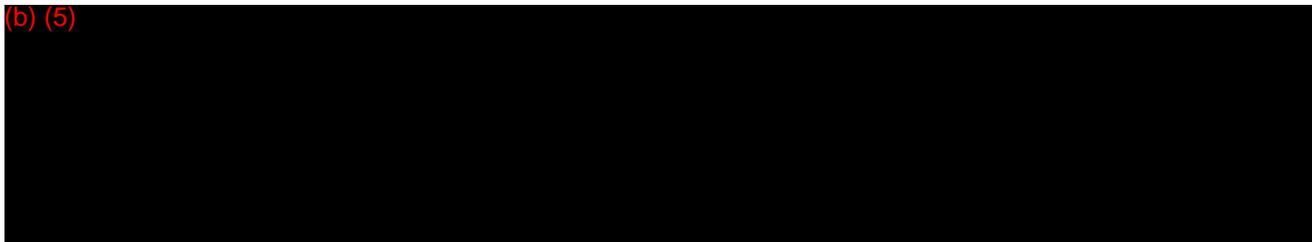
Thanks!

--
J

From: Sherman, Rachel
Sent: Sunday, August 28, 2016 8:23 AM
To: McCall, Jonathan *; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: Re: eteplirsen

I'm working off a phone so can't edit, sorry.

(b) (5)



Otherwise looks good to me.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: August 28, 2016 at 7:58:54 AM EDT
To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Cc: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: eteplirsen

Friends,

I think I've addressed all the comments and read it thoroughly. I want to make sure we've covered the post-marketing orders. I've also re-read the documents and I don't believe I've left anything unaddressed.

Jonathan, can you produce a clean version?

thx

rmc

FDAOC0001631

From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#); [McCall, Jonathan *](#)
Subject: RE: eteplirsen
Date: Saturday, September 03, 2016 11:36:00 AM

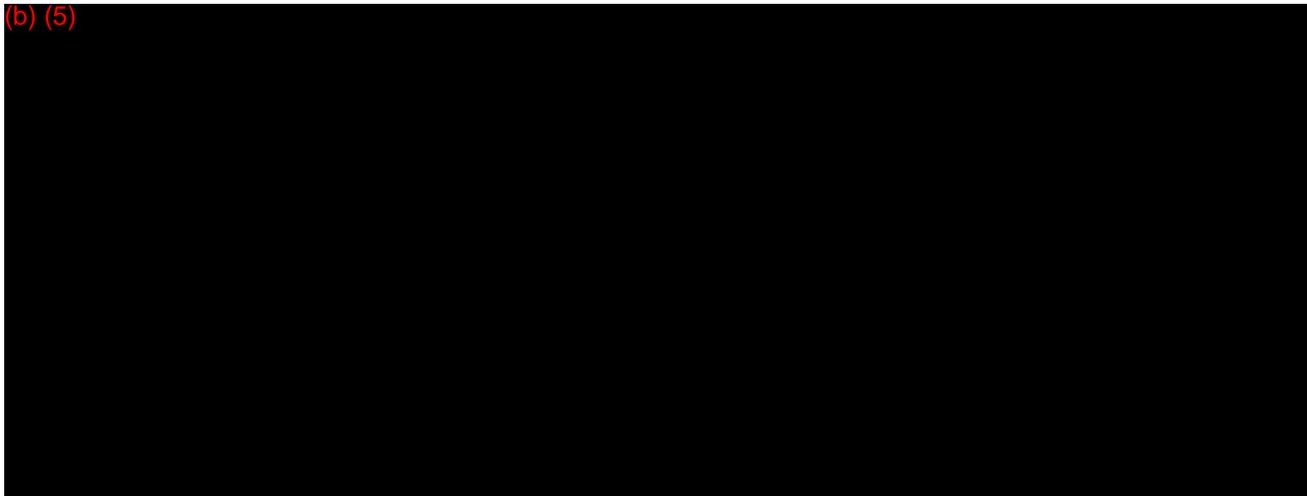
Thanks. Trying to catch up this morning after the Ark./Denver trip. I think I've got the latest version of everything.

rmc

From: Dickinson, Elizabeth (FDA)
Sent: Saturday, September 03, 2016 11:08 AM
To: Sherman, Rachel; Chasan-Sloan, Deborah (FDA); McCall, Jonathan *; Califf, Robert
Subject: RE: eteplirsen

Thanks, Rachel.

(b) (5)

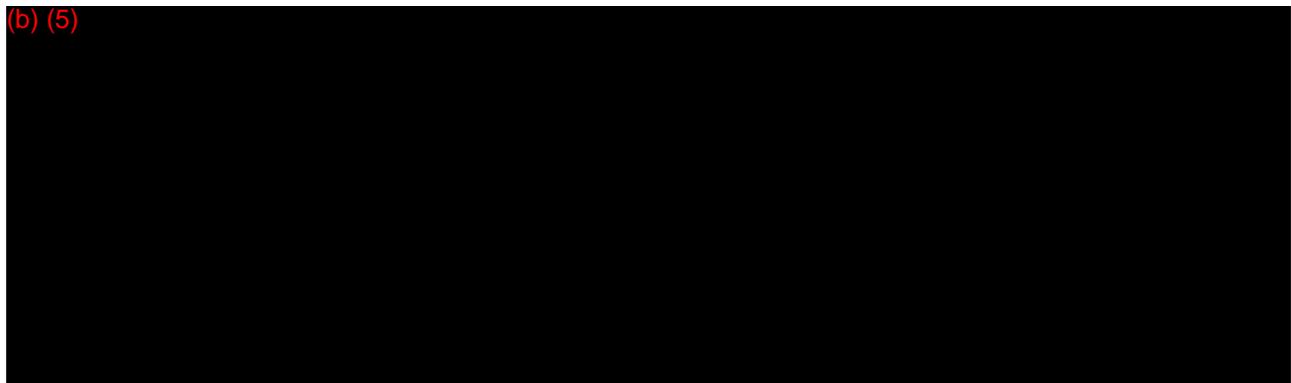


Liz

From: Sherman, Rachel
Sent: Saturday, September 03, 2016 8:47 AM
To: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); McCall, Jonathan *; Califf, Robert
Subject: RE: eteplirsen

Hi,

(b) (5)



(b) (5)

Once Deborah and Liz comment, Rob it's your turn.

Rachel

From: Chasan-Sloan, Deborah (FDA)
Sent: Friday, September 02, 2016 6:26 PM
To: Sherman, Rachel; Dickinson, Elizabeth (FDA); McCall, Jonathan *; Califf, Robert
Subject: RE: eteplirsen

(b) (5)

From: Sherman, Rachel
Sent: Friday, September 02, 2016 6:02
To: Dickinson, Elizabeth (FDA); McCall, Jonathan *; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: eteplirsen

I can look on Monday if no one beats me to it. But we will only be searching the appeal documents, not the entire submission.

That said, these are Rob's points so he may well know what prompted him to include them.

(b) (5)

From: Dickinson, Elizabeth (FDA)
Sent: Friday, September 02, 2016 4:06 PM
To: McCall, Jonathan *; Califf, Robert; Sherman, Rachel
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: eteplirsen

(b) (5)

From: McCall, Jonathan *
Sent: Friday, September 02, 2016 2:13 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: eteplirsen

See comments in the attached – I found a citation for (b) (5)

(b) (5)

(b) (5)

Only changes here are addition of my comments with citation info.

Thanks!

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J

From: Califf, Robert
Sent: Friday, September 02, 2016 12:51 PM
To: Dickinson, Elizabeth (FDA); McCall, Jonathan *; Sherman, Rachel
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: eteplirsen

This looks good as far as I can tell. Will find cites tonight or tomorrow. Out of action now for Denver lab visit.

Thx
rmc

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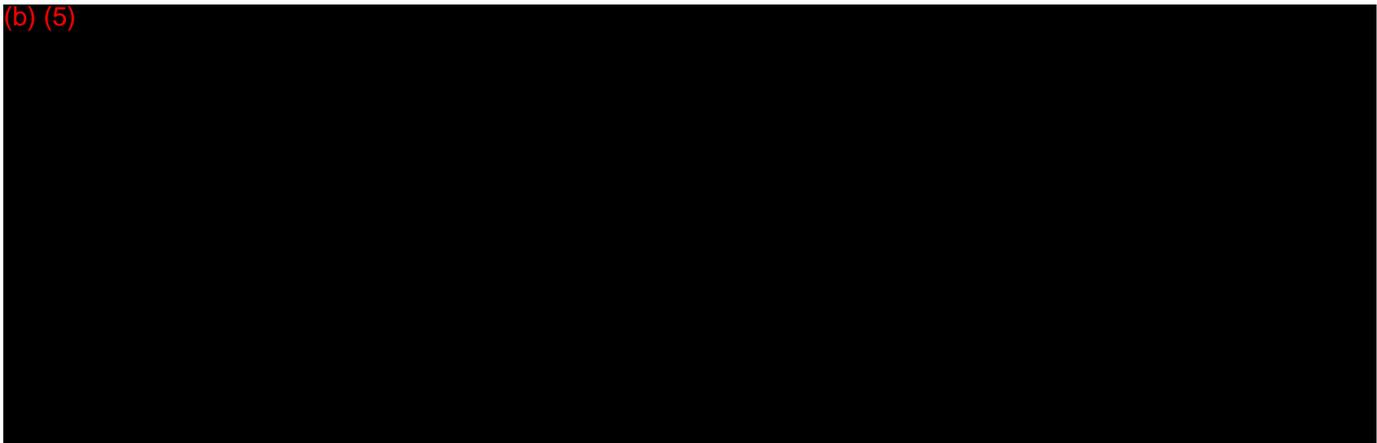
(b) (5)

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Sent: Monday, August 29, 2016 10:06 AM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

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I've made two modifications that I wanted to highlight:

(b) (5)



Please let me know if you have any questions!

Thanks!

--

J

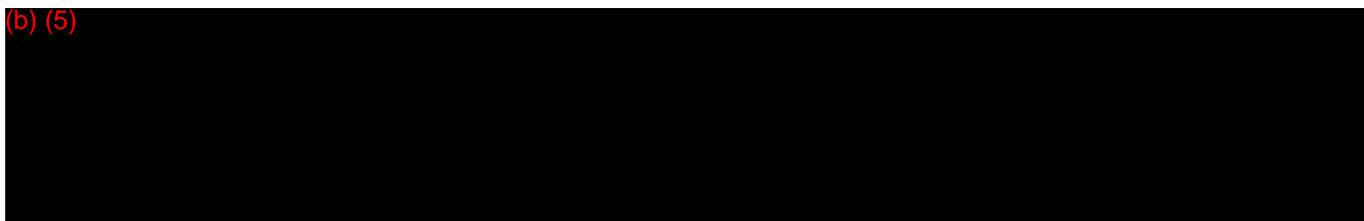
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Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

Agreed with all comments and suggestions. I think its looking good.

rmc
Robert M Califf MD
Commissioner of Food and Drugs

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, August 28, 2016 10:16 PM
To: McCall, Jonathan *; Sherman, Rachel; Califf, Robert
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

(b) (5)



(b) (5)

Thanks,
Deborah

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Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
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Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: Re: eteplirsen

I'm working off a phone so can't edit, sorry.

(b) (5)

Otherwise looks good to me.

From: Califf, Robert <RMC1@fda.hhs.gov>

FDAOC0001636

Date: August 28, 2016 at 7:58:54 AM EDT

To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>

Cc: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>

Subject: eteplirsen

Friends,

I think I've addressed all the comments and read it thoroughly. I want to make sure we've covered the post-marketing orders. I've also re-read the documents and I don't believe I've left anything unaddressed.

Jonathan, can you produce a clean version?

thx

rmc

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To: [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Dickinson, Elizabeth \(FDA\)](#); [McCall, Jonathan *](#)
Subject: RE: eteplirsen
Date: Sunday, September 04, 2016 8:50:00 AM

OK, on these matters:

(b) (5)



There are ample references,

Clinical development success rates:

(b) (5)



See next email.

Thx for all you've done with this. we're close.

rmc

From: Sherman, Rachel
Sent: Saturday, September 03, 2016 8:47 AM
To: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); McCall, Jonathan *; Califf, Robert
Subject: RE: eteplirsen

Hi,

(b) (5)

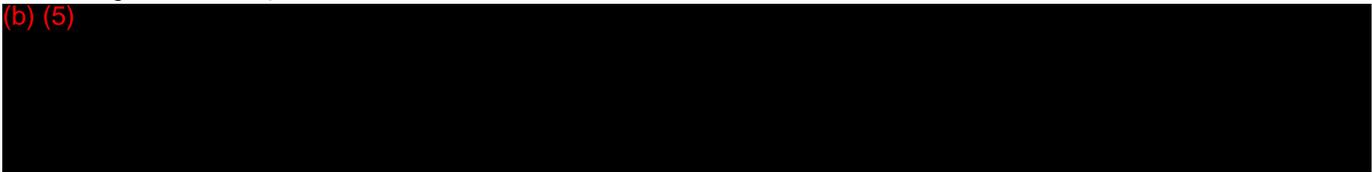


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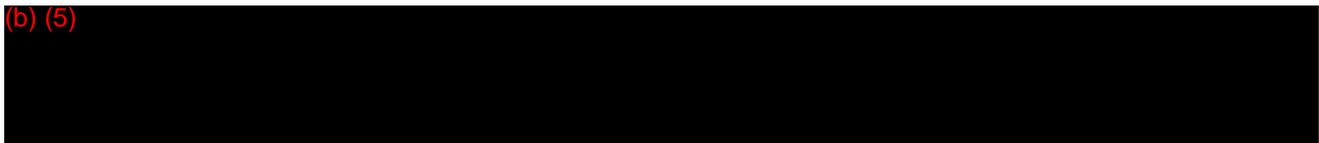


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(b) (5)



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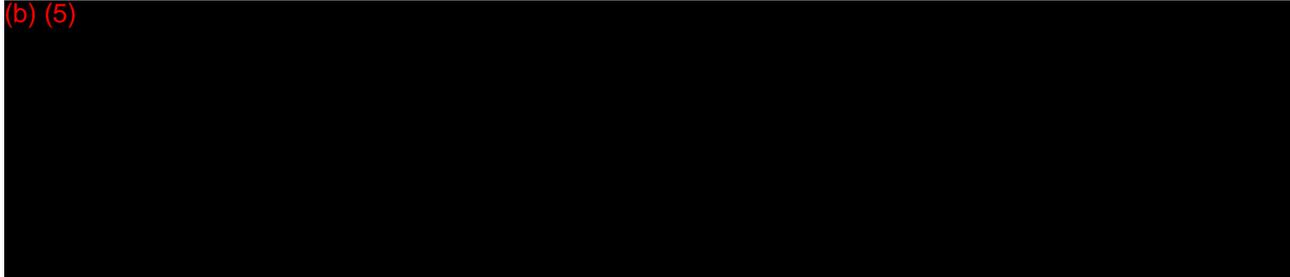
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(b) (5)

(b) (5)

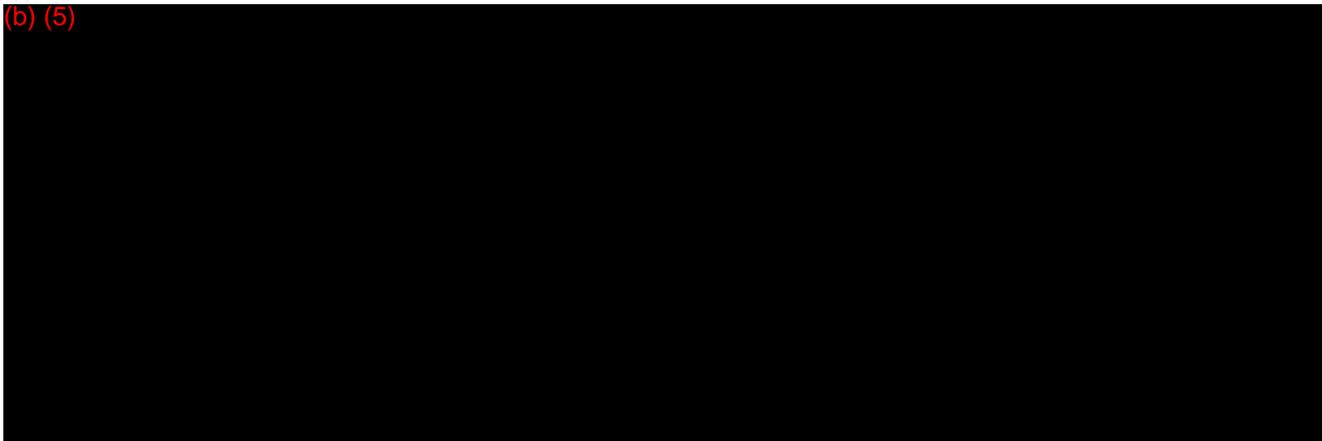


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To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel
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(b) (5)



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To: Chasan-Sloan, Deborah (FDA); McCall, Jonathan *; Sherman, Rachel
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

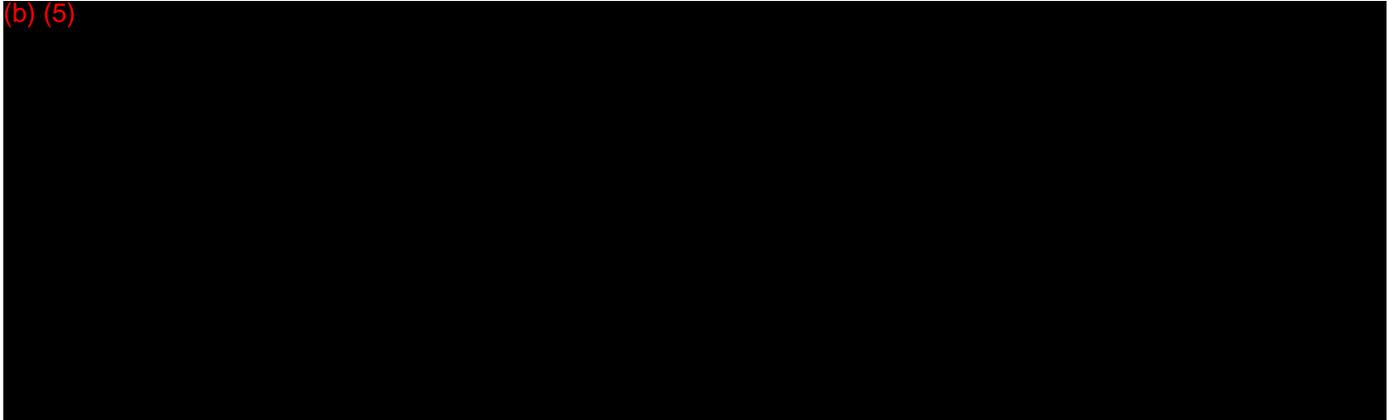
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rmc
Robert M Califf MD
Commissioner of Food and Drugs

FDAOC0001641

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, August 28, 2016 10:16 PM
To: McCall, Jonathan *; Sherman, Rachel; Califf, Robert
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

(b) (5)



Thanks,
Deborah

From: McCall, Jonathan *
Sent: Sunday, August 28, 2016 2:22 PM
To: Sherman, Rachel; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

Hello all –

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Thanks!

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To: McCall, Jonathan *; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: Re: eteplirsen

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(b) (5)



(b) (5)

Otherwise looks good to me.

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Date: August 28, 2016 at 7:58:54 AM EDT

To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>

Cc: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>

Subject: eteplirsen

Friends,

I think I've addressed all the comments and read it thoroughly. I want to make sure we've covered the post-marketing orders. I've also re-read the documents and I don't believe I've left anything unaddressed.

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rmc

From: [Califf, Robert](#)
To: [McCall, Jonathan *](#); [Dickinson, Elizabeth \(FDA\)](#); [Sherman, Rachel](#)
Cc: [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: RE: eteplirsen
Date: Sunday, September 04, 2016 9:05:00 AM
Attachments: [20160828 Eteplirsen CLEAN\(occ\) rmc JM CLEAN \(cites added\) JM rmc.doc](#)

Friends,

I have made only a few edits, and it seems like the only unresolved issues are the citations and making sure the “next .steps” squares with CDER. We also have materials from Katie Conover and a preferred strategy of “roll out”. Jonathan, can you tidy this up and Liz, Deborah and Rachel, please weigh in on whether I’m wrong in my thinking that I want to frame this in a way that not only is clear about what I’ve done and why I’ve done it, but also will shape the discussion in a way that is productive. I truly believe that there is little in this particular decision that is relevant to the future of drug development/FDA, but there is a lot in the generalizable issues.

Thanks again for all your help with this. I hope I’m being open enough to your input as “FDA veterans”.

Jonathan, let me know if there are residual issues that you are detecting as you package this up.

rmc

From: McCall, Jonathan *
Sent: Friday, September 02, 2016 2:13 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: eteplirsen

See comments in the attached – I found a citation for (b) (5)

[REDACTED]

[REDACTED]

[REDACTED]

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Thanks!

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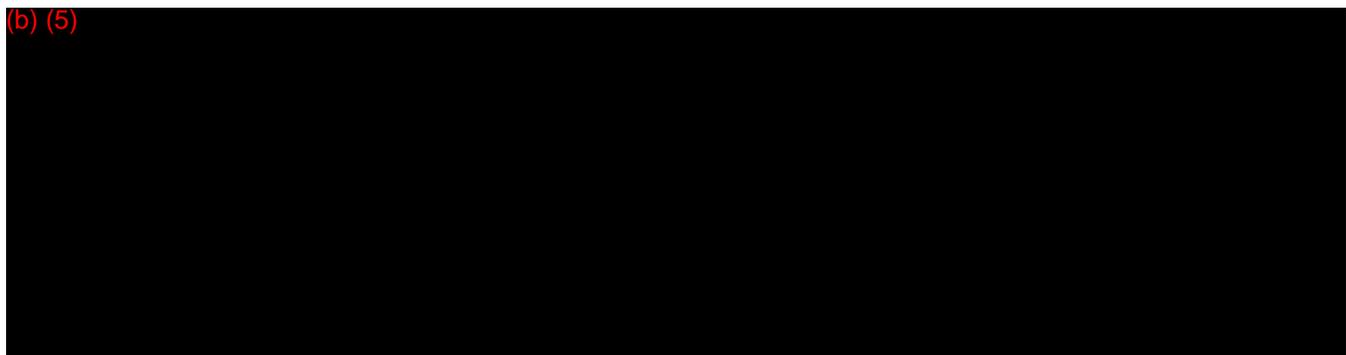
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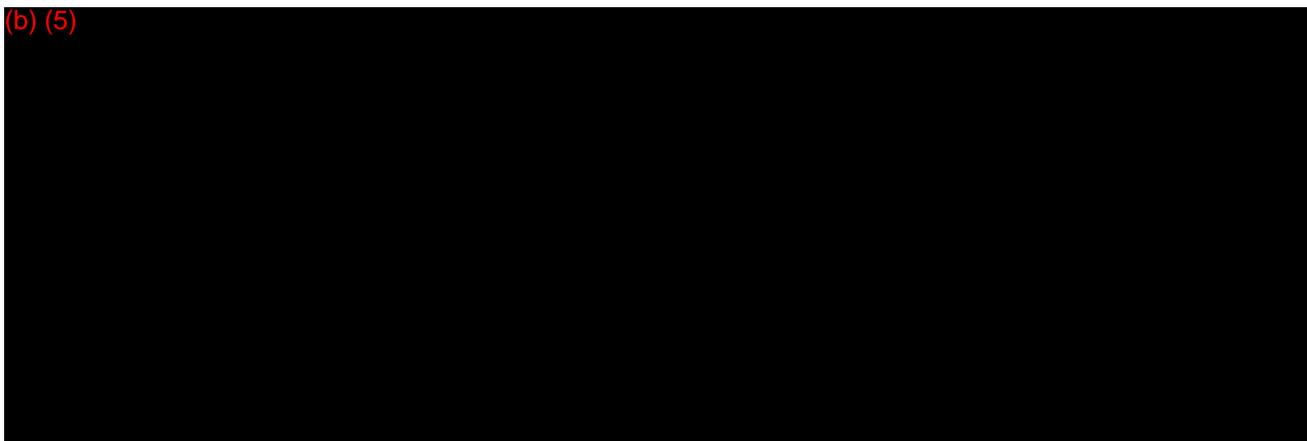


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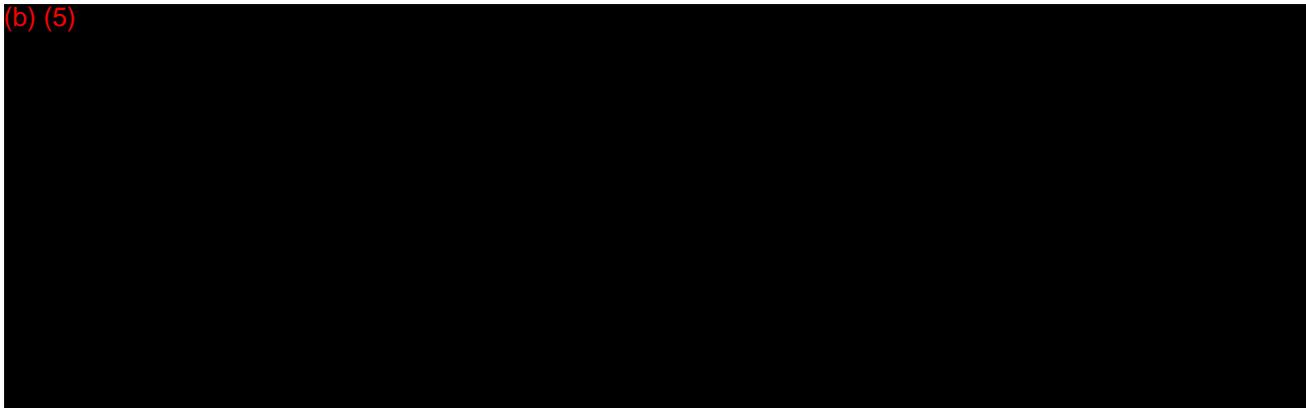
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Commissioner of Food and Drugs

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(b) (5)



Otherwise looks good to me.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: August 28, 2016 at 7:58:54 AM EDT
To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Cc: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: eteplirsen

Friends,

I think I've addressed all the comments and read it thoroughly. I want to make sure we've covered the post-marketing orders. I've also re-read the documents and I don't believe I've left anything unaddressed.

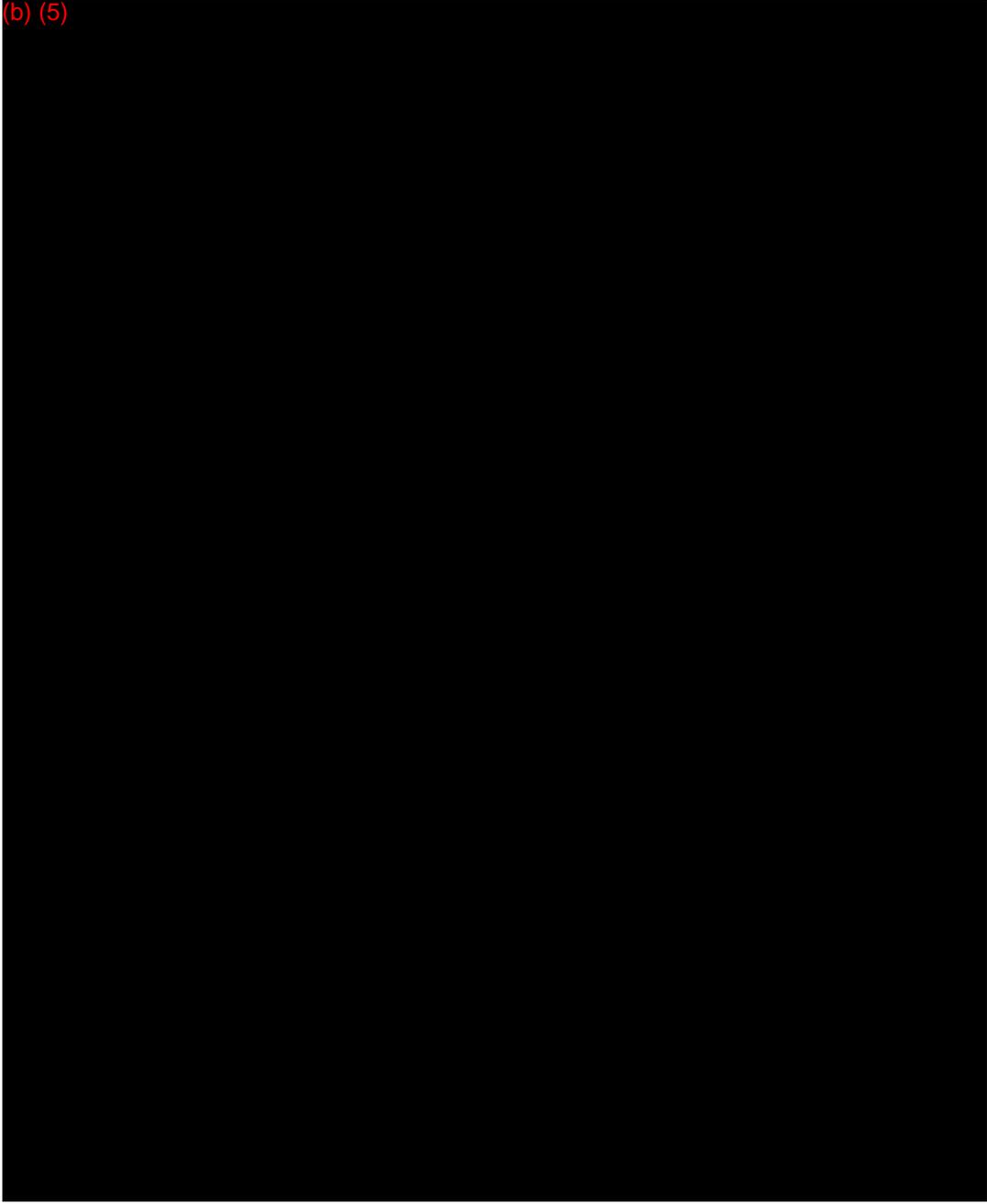
Jonathan, can you produce a clean version?

thx

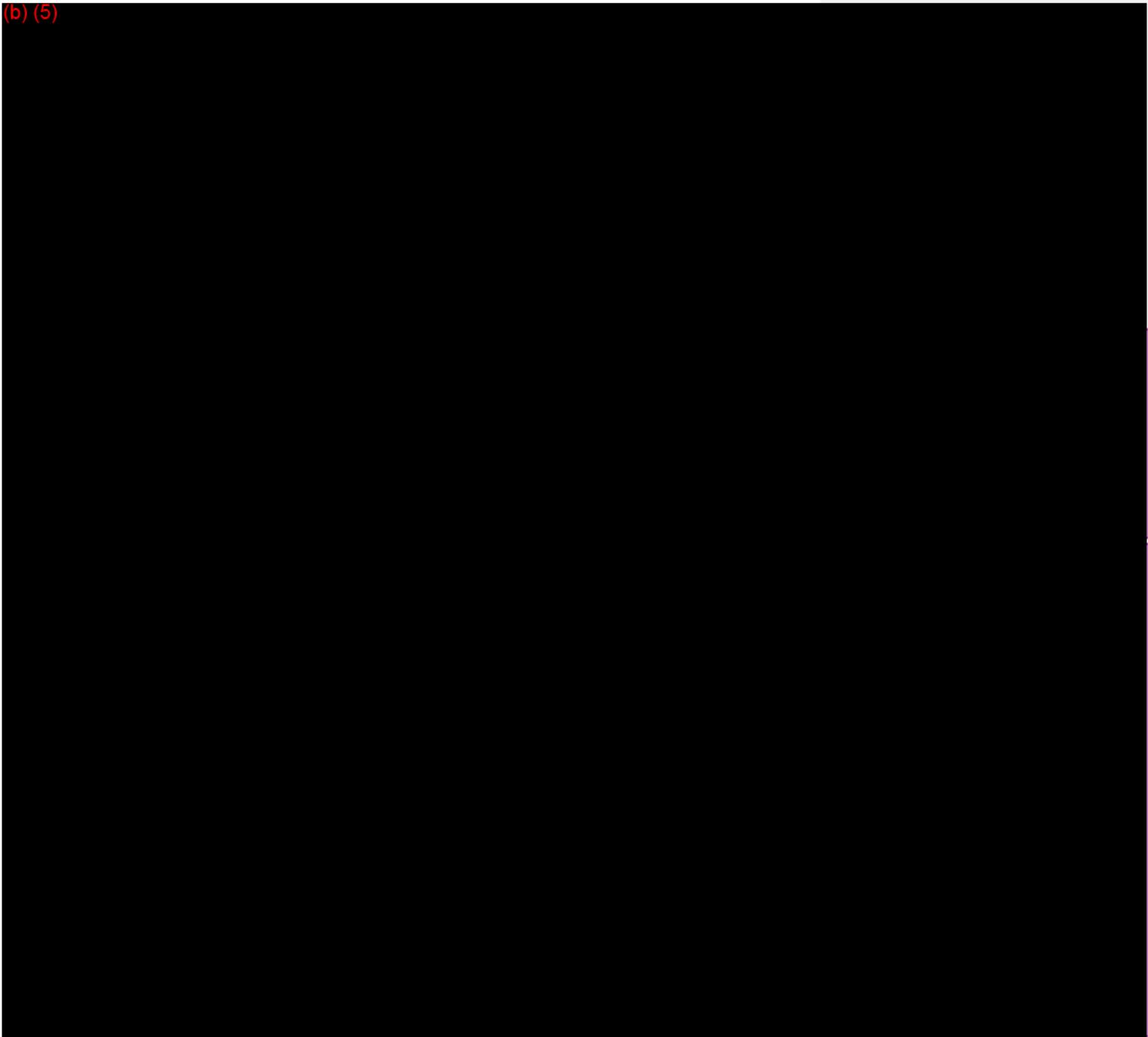
rmc

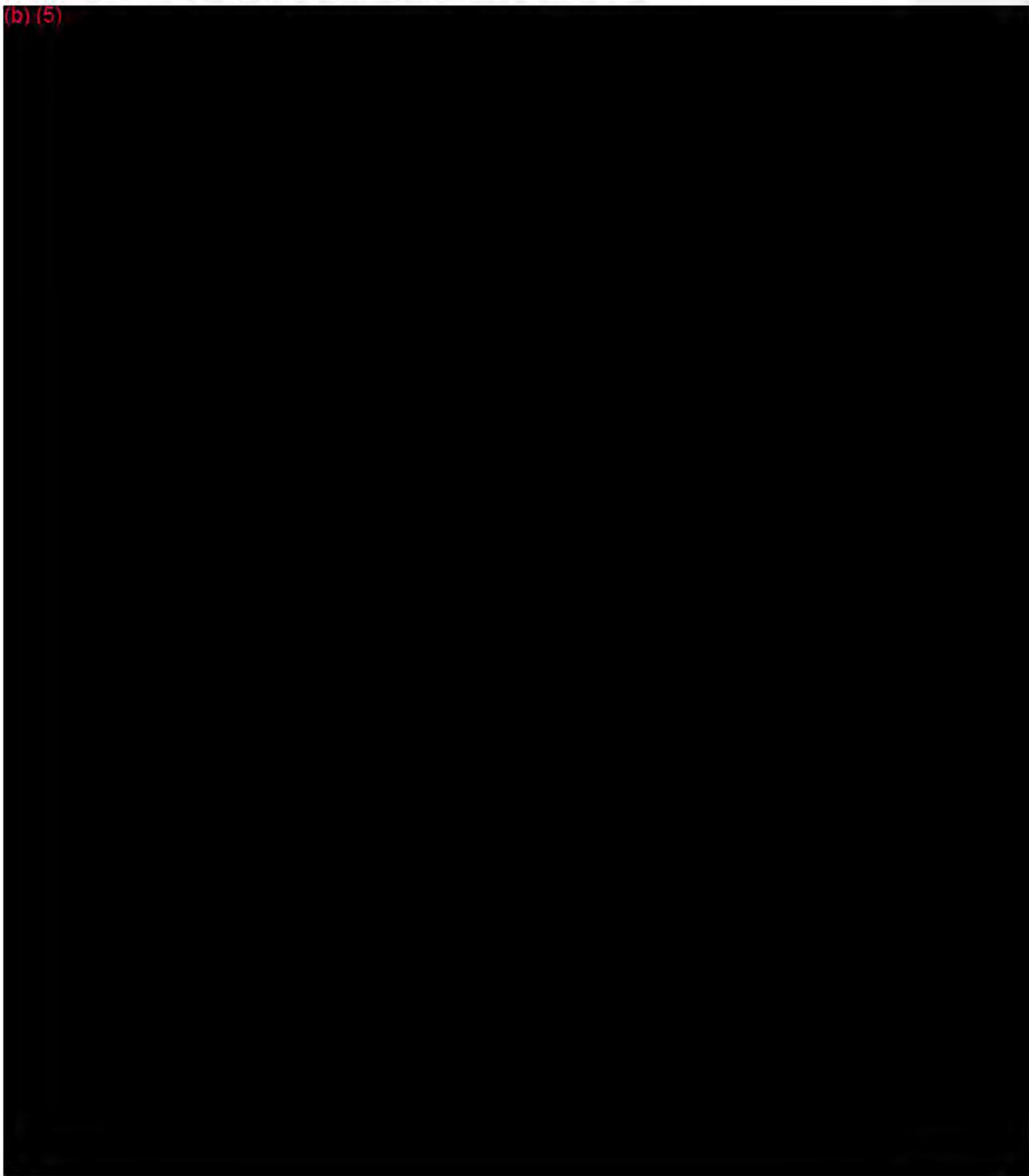
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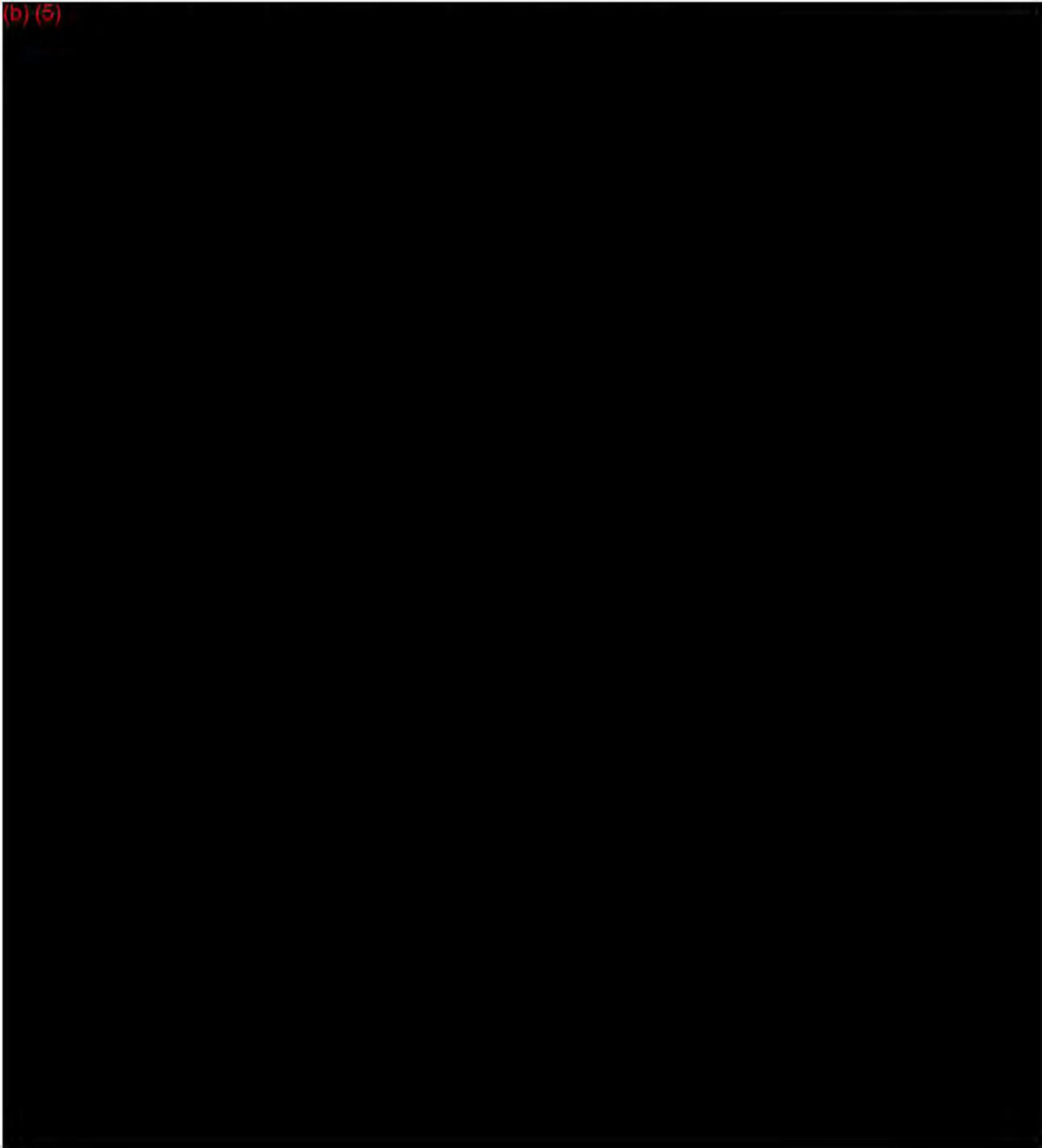
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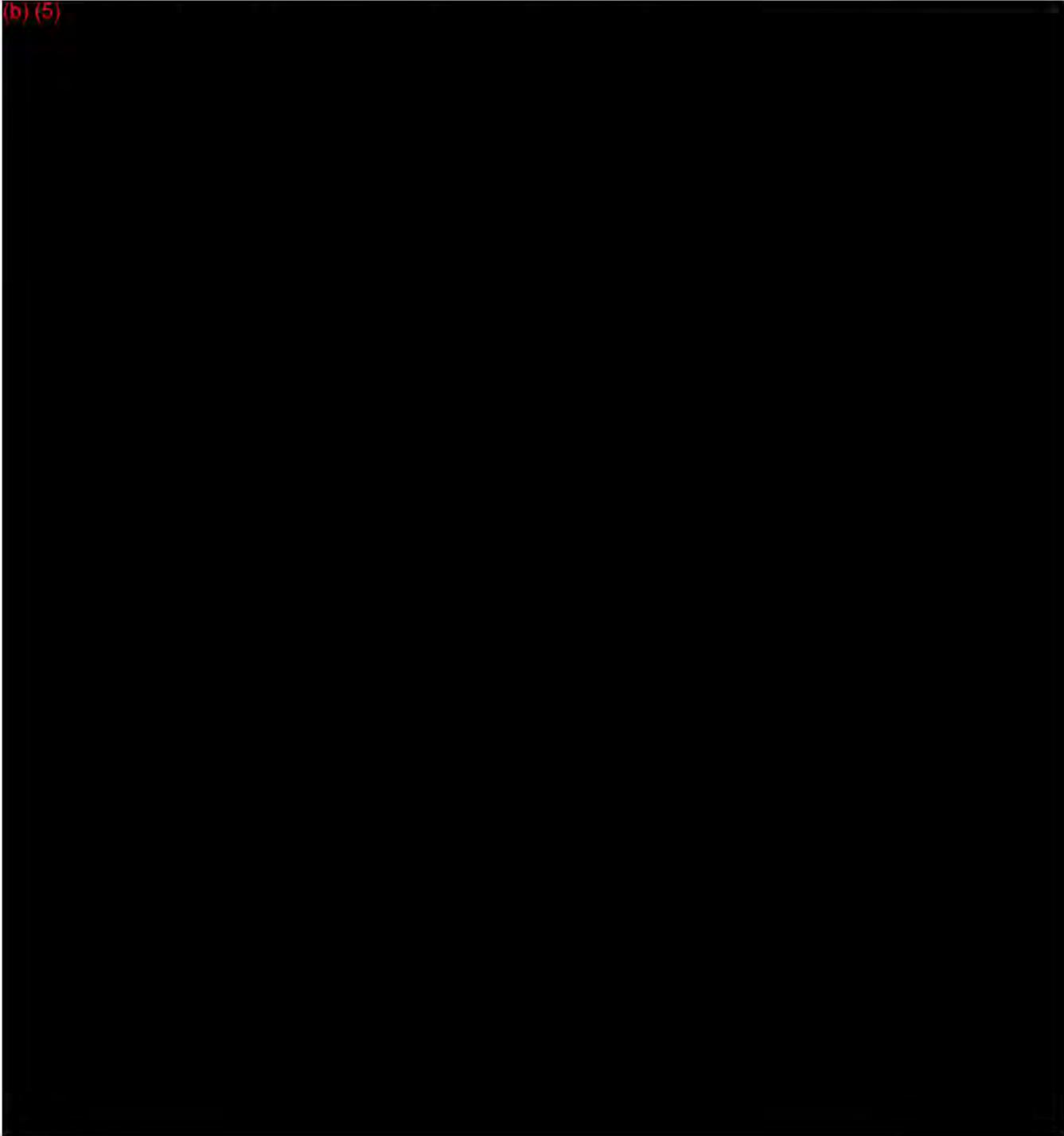


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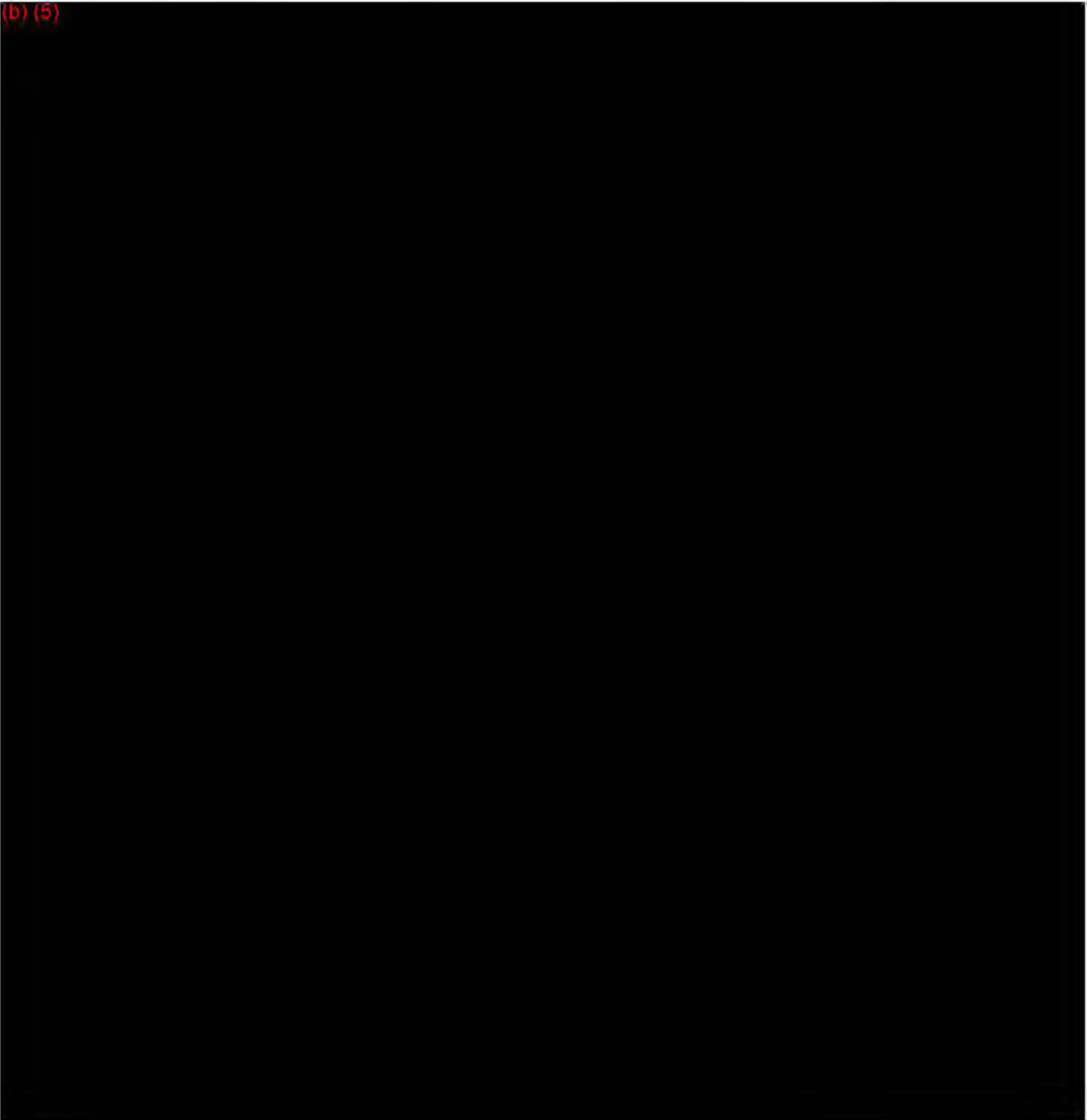
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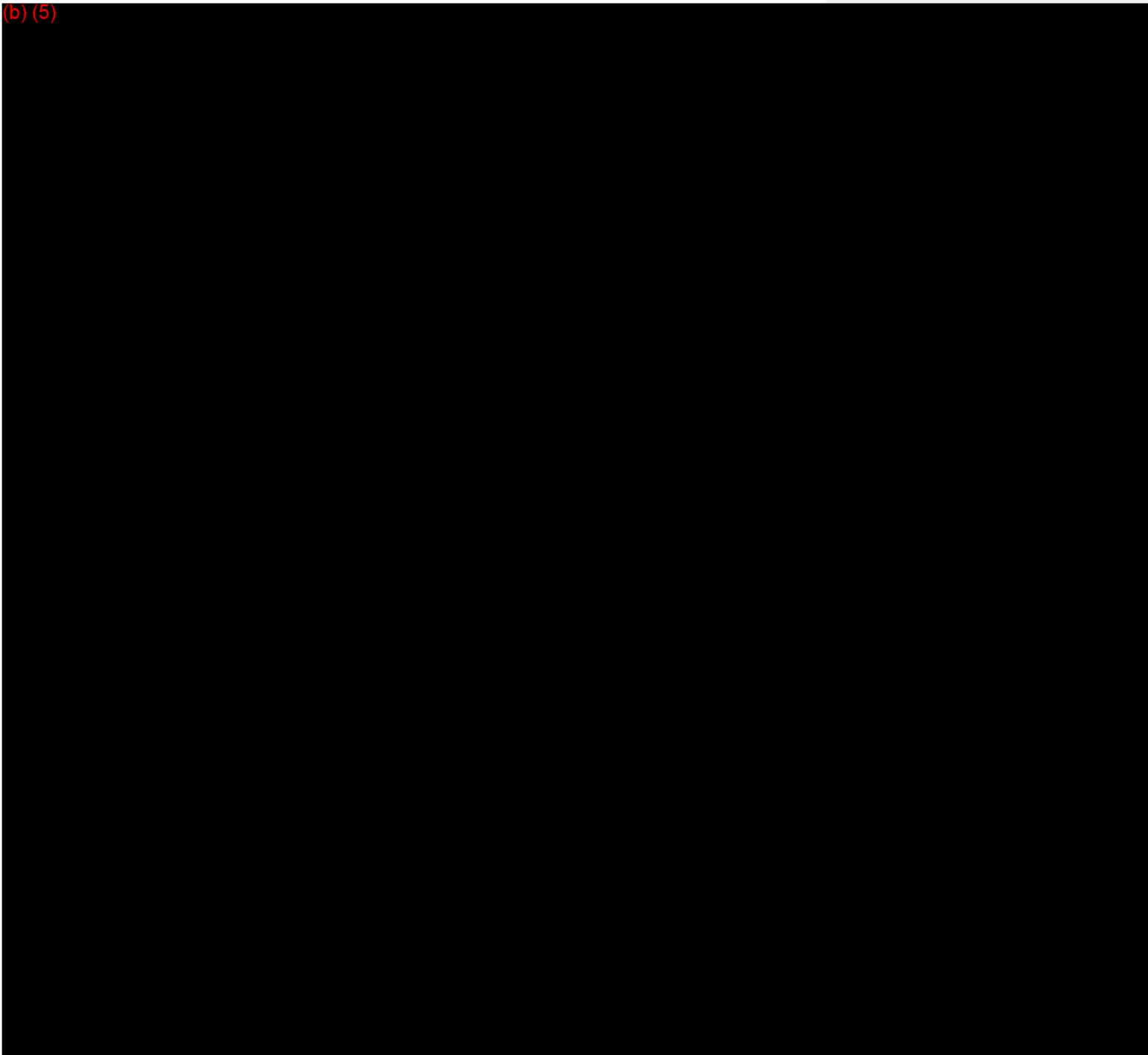
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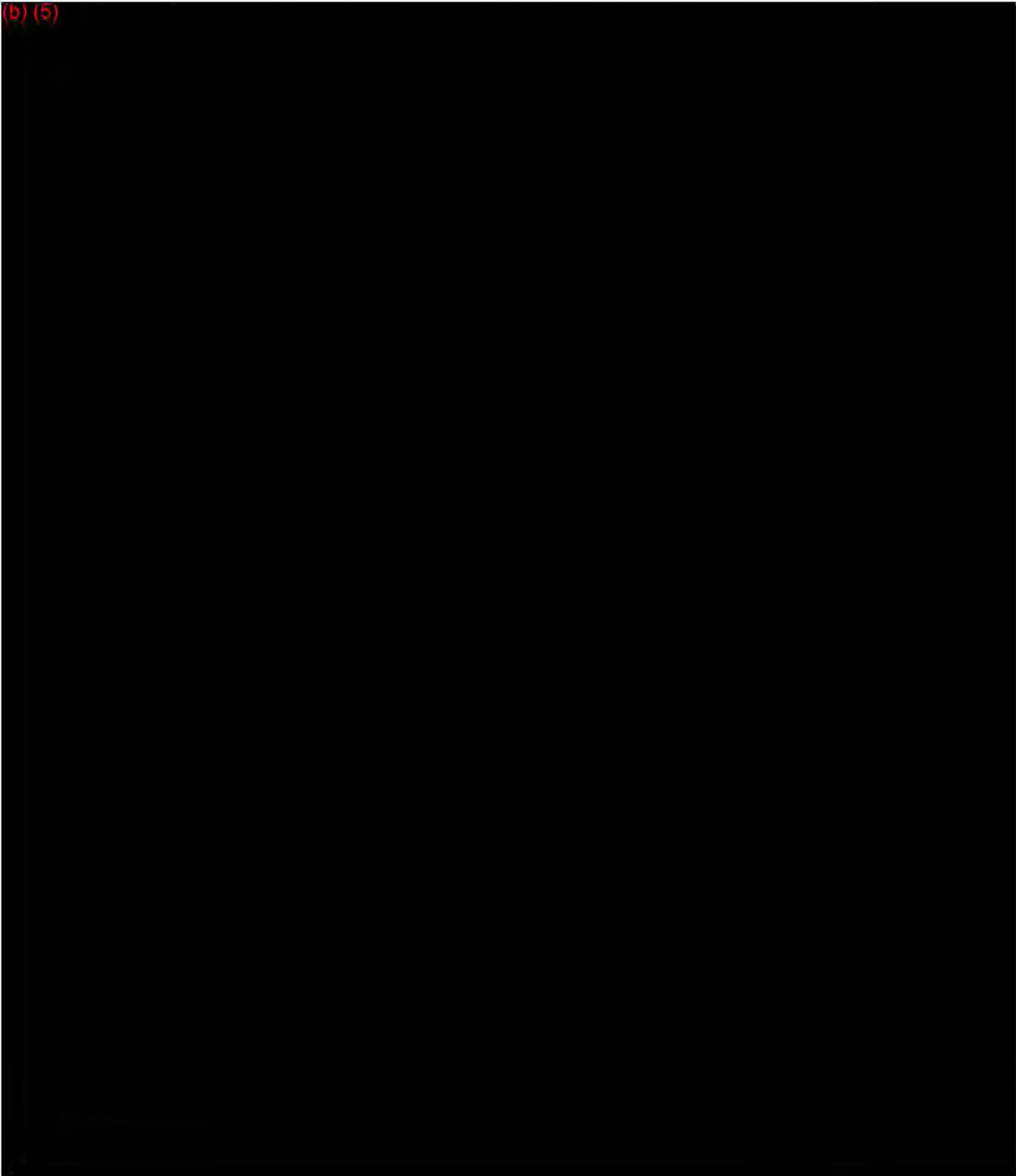
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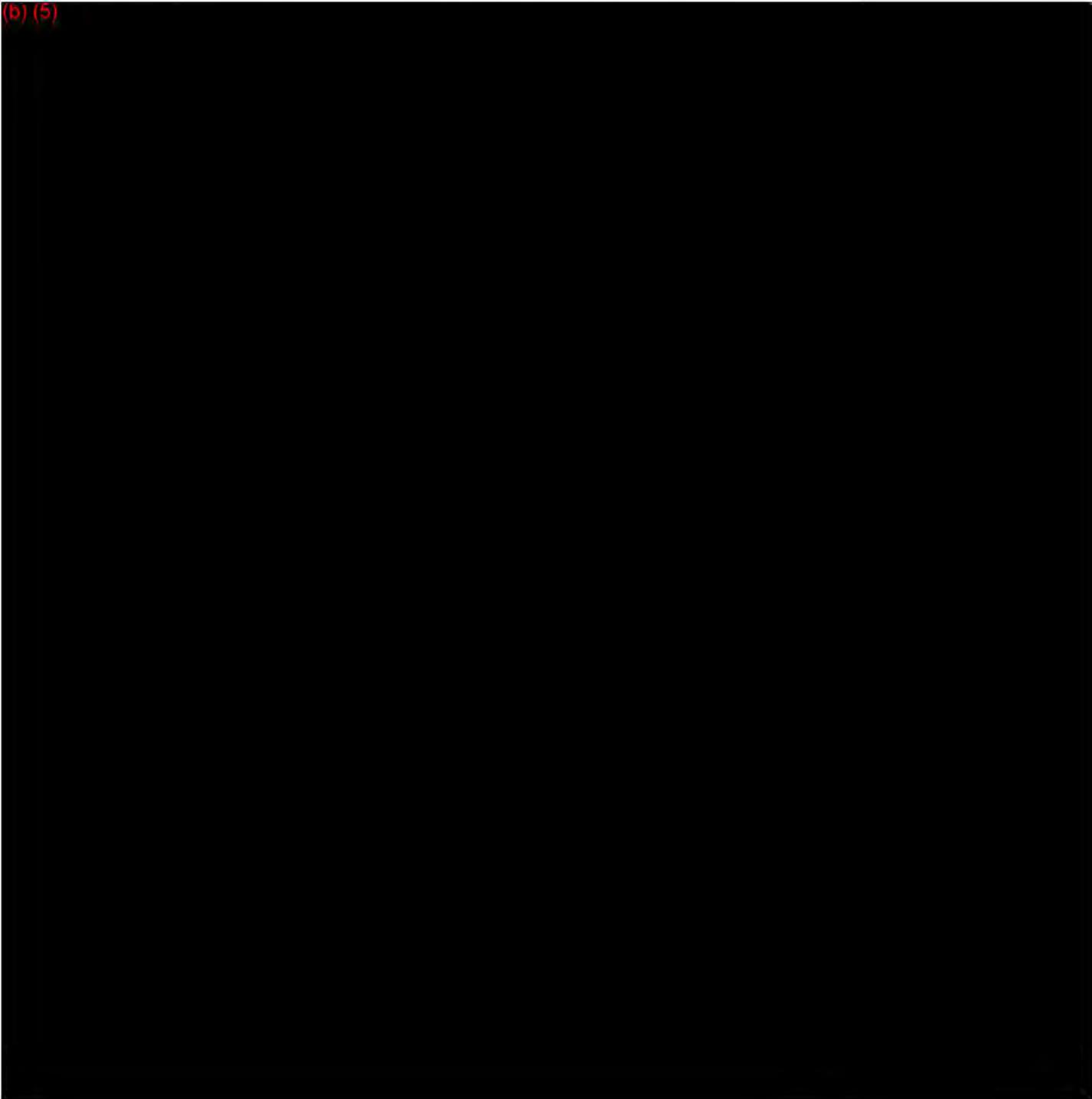
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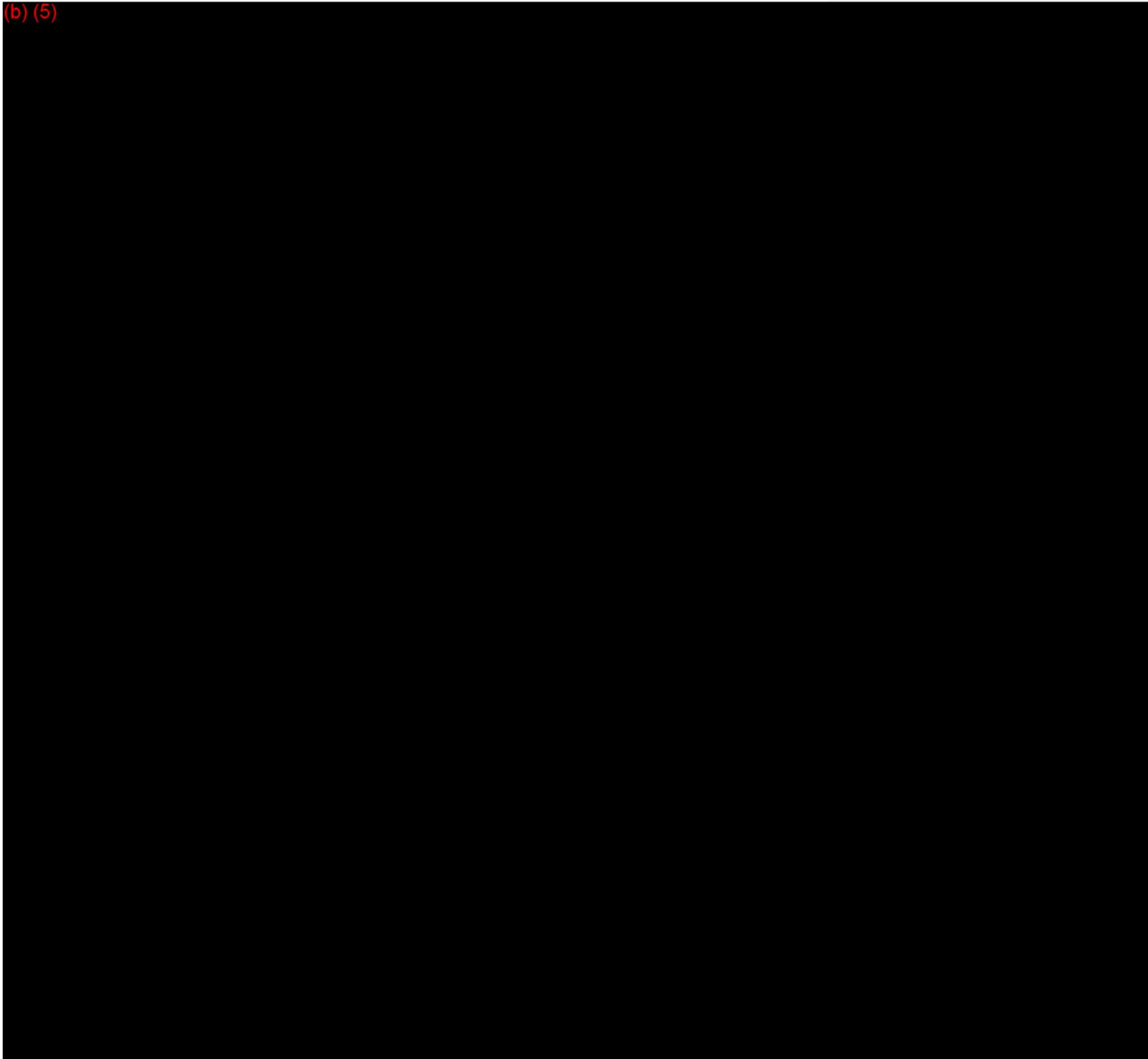
(b) (5)



(b) (5)



(b) (5)



From: [Califf, Robert](#)
To: [Conover, Katie](#); [Rodriguez, Jennifer](#)
Cc: [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#); [McCall, Jonathan *](#)
Subject: FW: Review of materials for drug approval
Date: Sunday, September 04, 2016 10:43:00 AM
Attachments: [eteplirsen KMOA \(occ\) 8.9.16 \(occ 8-15\) oma83016.doc](#)
[eteplirsen PR draft occ reviewed Aug2016.doc](#)
[image013.png](#)
Importance: High

Katie and Jen,

I've copied those working on the appeal documents. A few comments are embedded.

This is a good start. I feel the urge to give more detail from the document, especially on the follow on requirements and some technical issues: (b) (5)

[REDACTED]

rmc

From: Conover, Katie
Sent: Thursday, September 01, 2016 11:33 AM
To: Califf, Robert
Subject: Review of materials for drug approval
Importance: High

Hi Dr. Califf,

In anticipation of our discussion this afternoon, attached please find a draft press release and KMOA to support communications around the approval of the drug. We have not yet sent these materials to Liz – but I am sharing with you now so that you can see what we are envisioning.

I have asked Jen Rodriguez, who has been working on these materials and communications plans, to join me for the call as well. We look forward to speaking with you and providing additional context regarding our communications recommendations.

Best,

Katie

Katie Conover

Acting Associate Commissioner

Office of External Affairs

U.S. Food and Drug Administration

Tel: 240-402-2402 / Cell: 301-512-9120

priscilla.conover@fda.hhs.gov



FDAOC0001659

Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

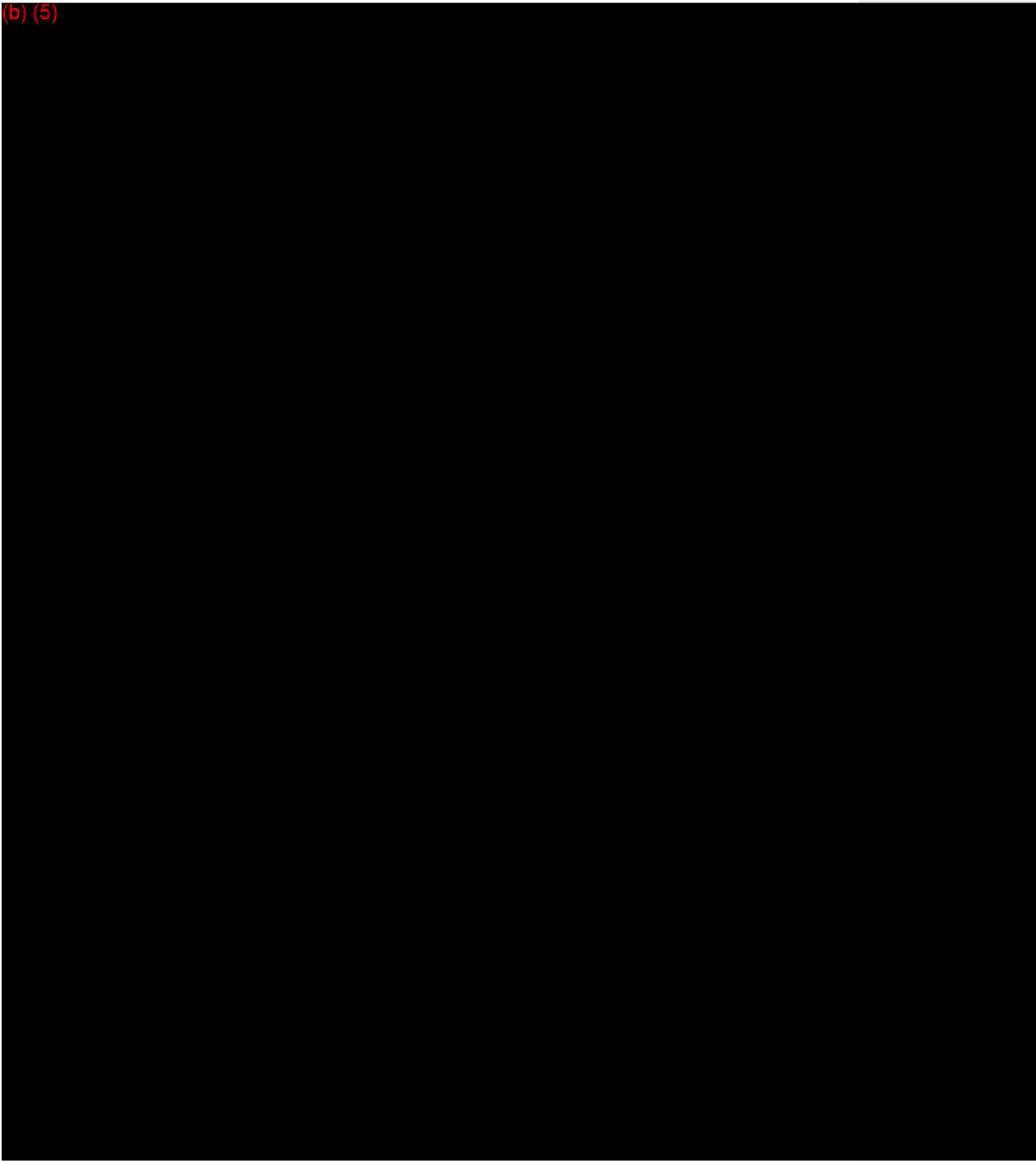
Target date: ~~TBD August~~ early September 2016

Formatted: Space After: 0 pt, Line spacing: single

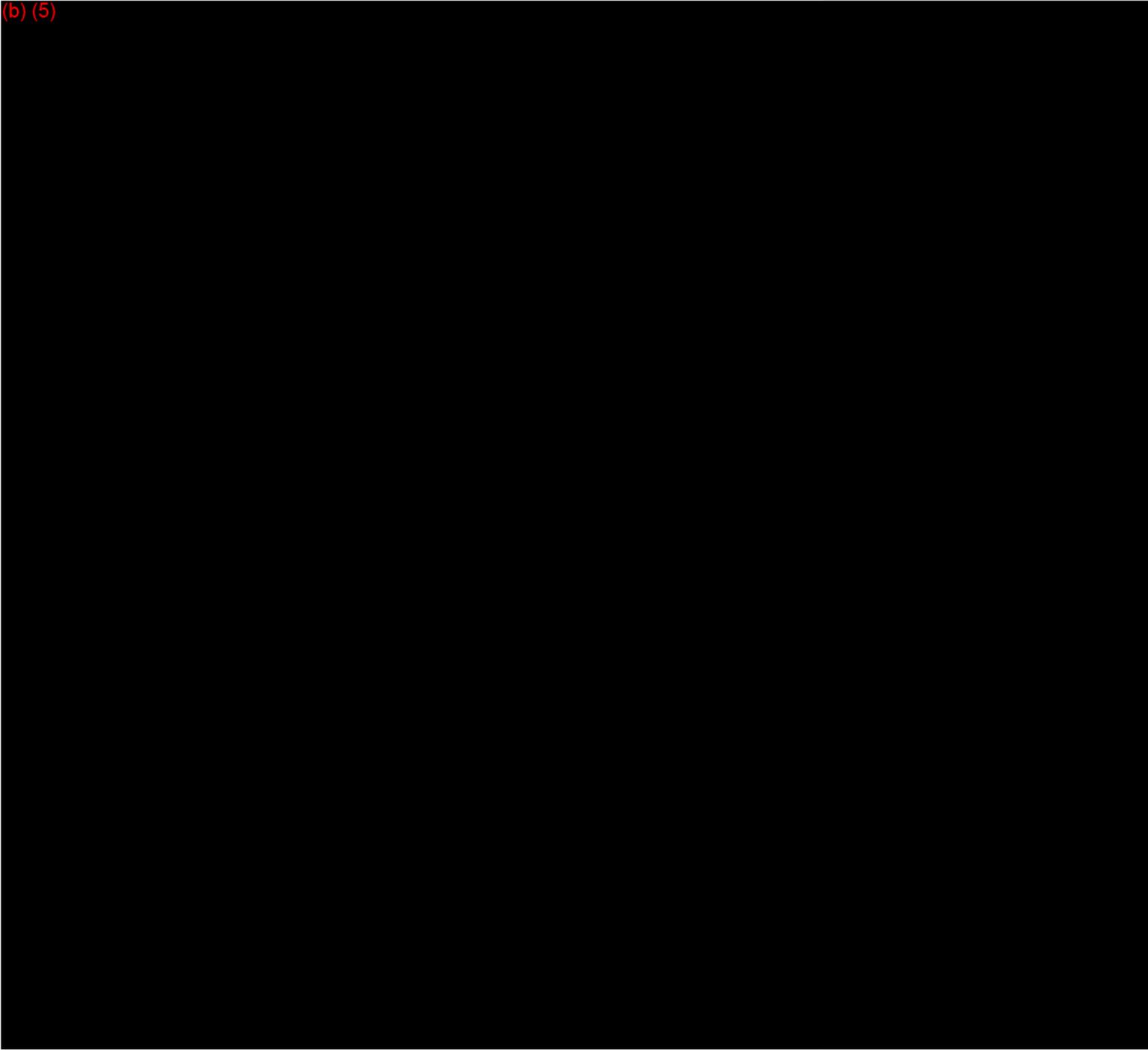
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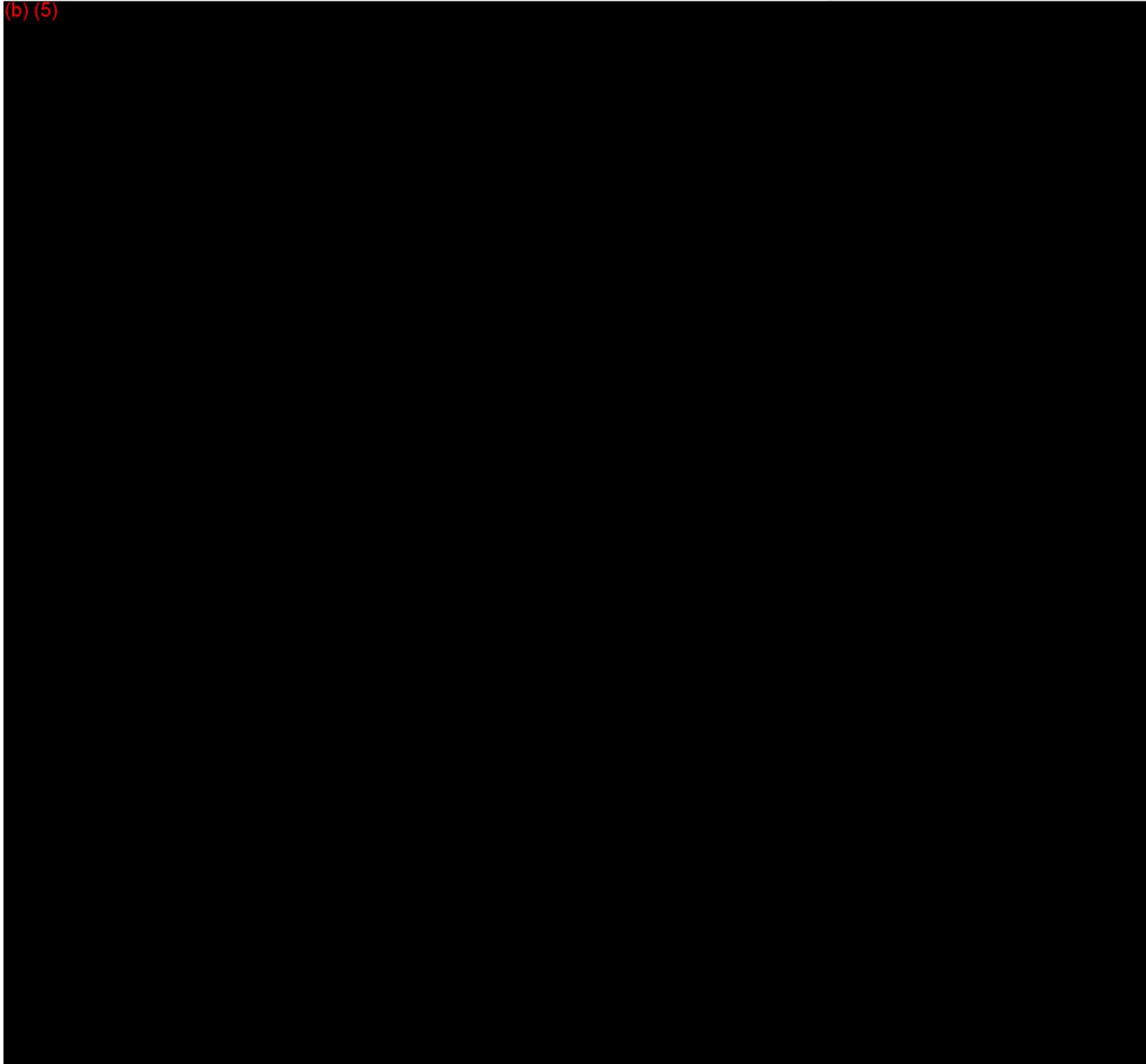


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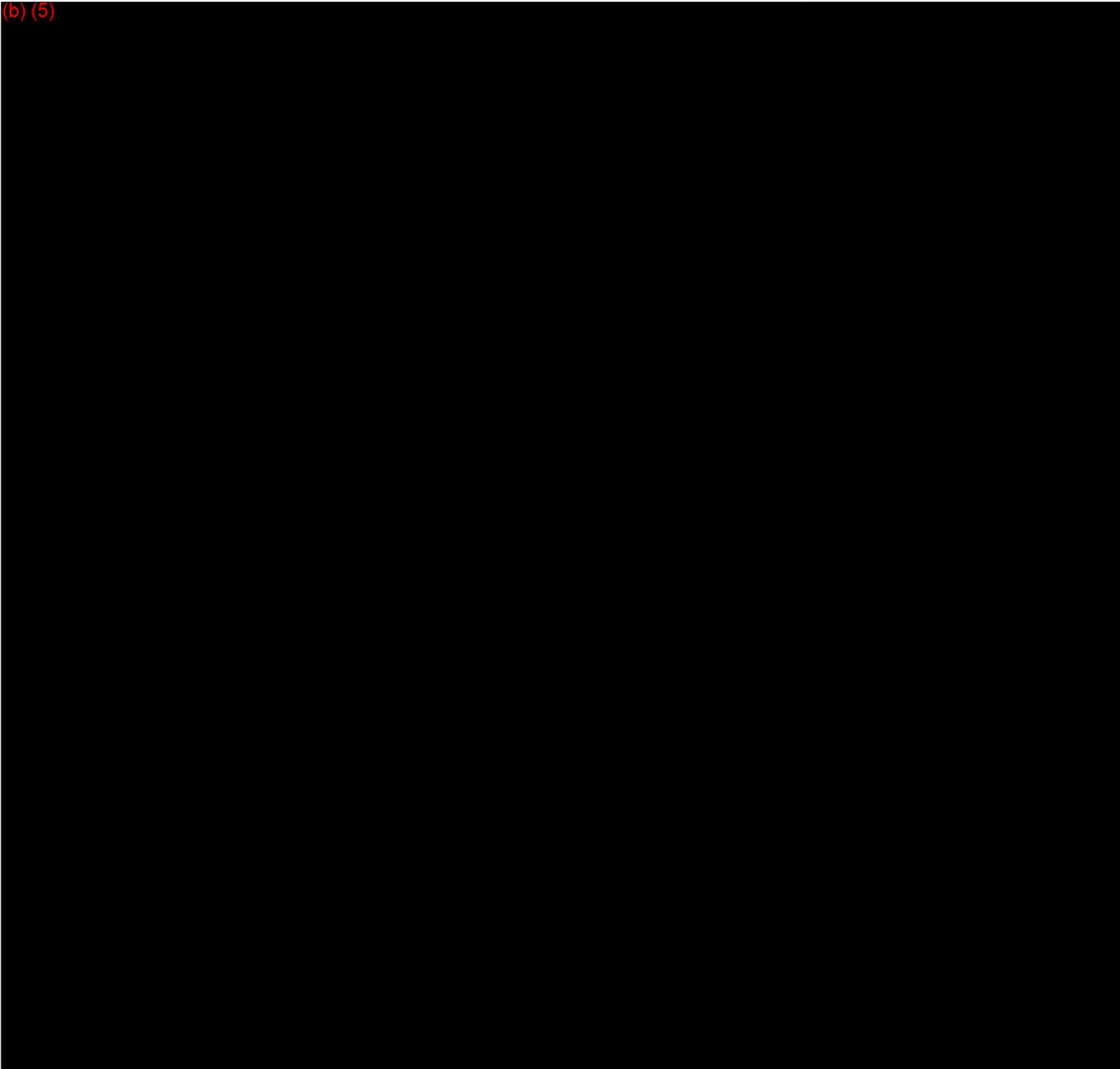
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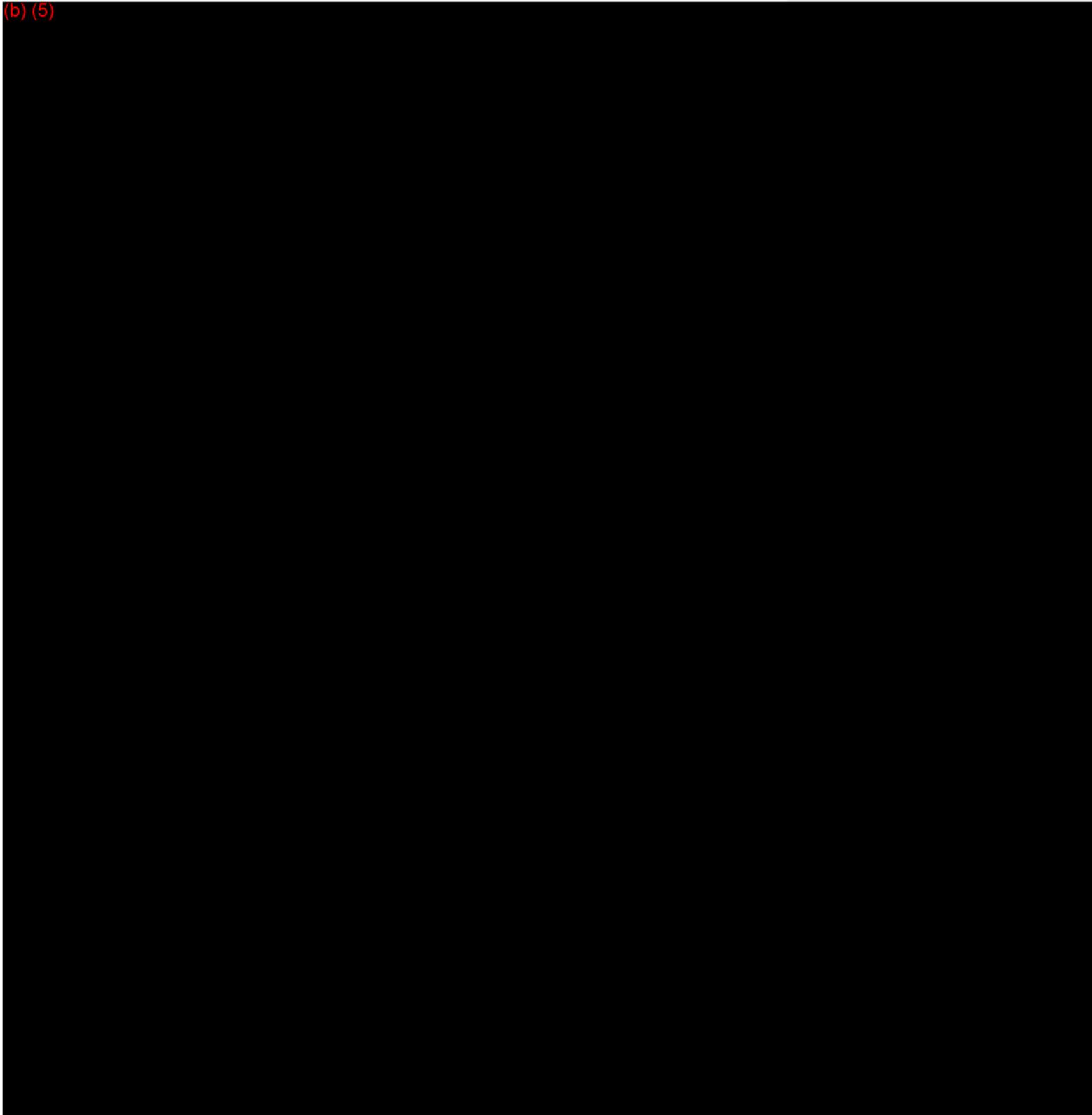
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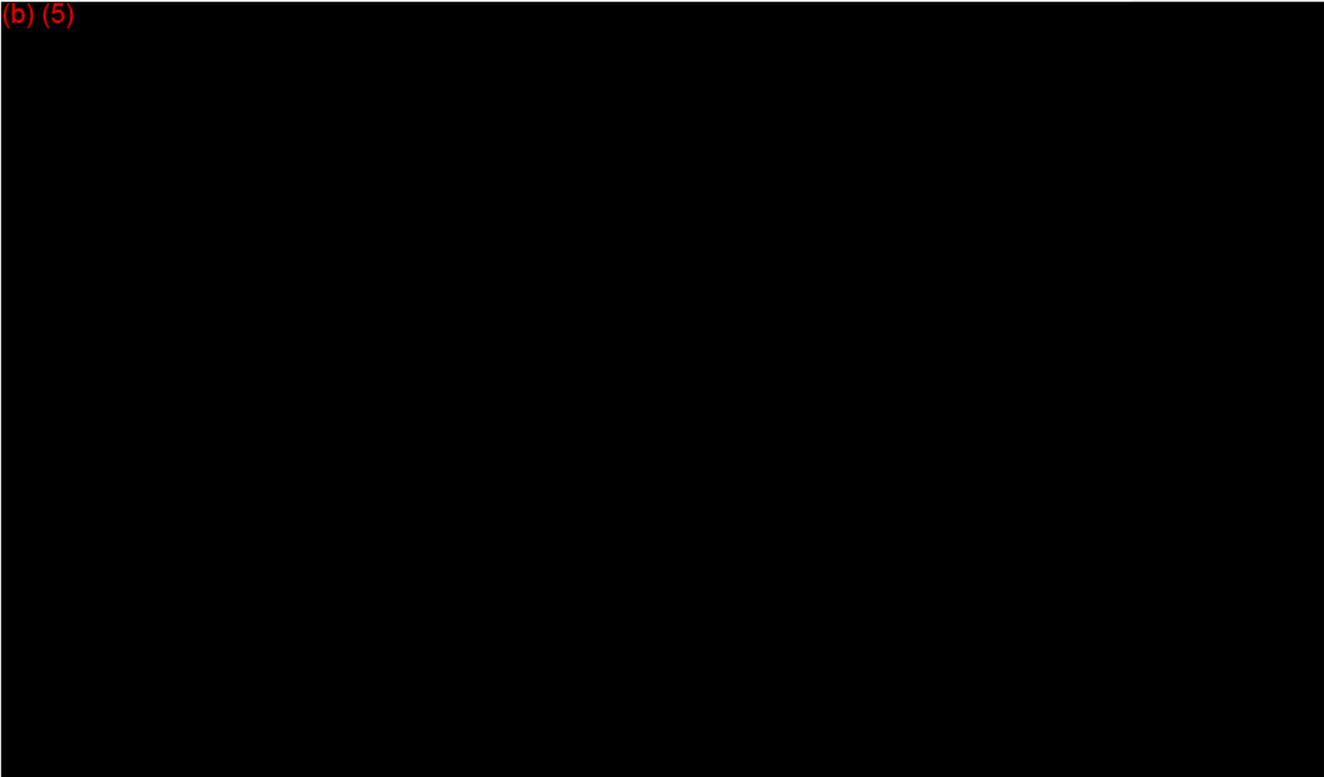


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FDA NEWS RELEASE

For Immediate Release: September xx, 2016

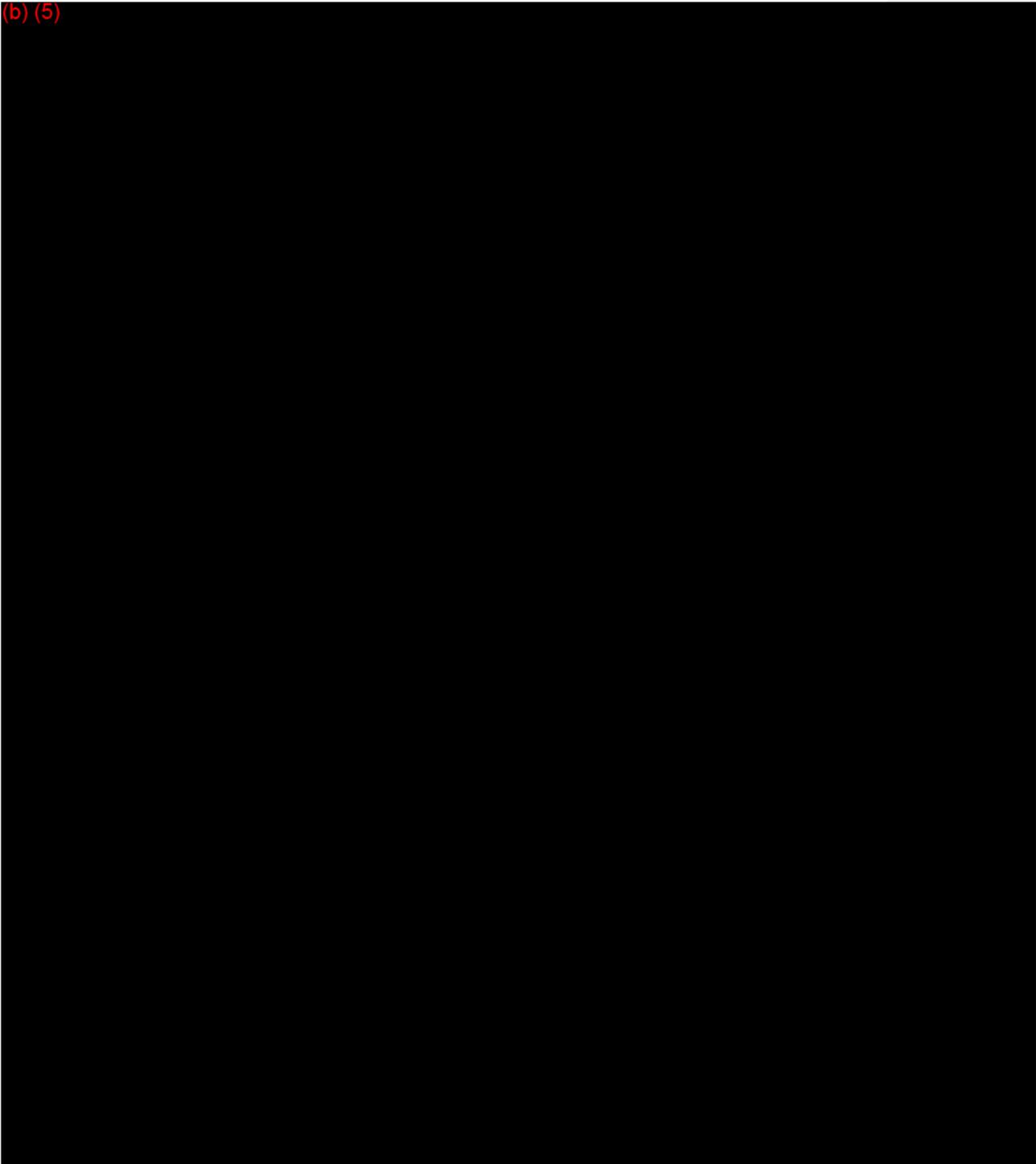
Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

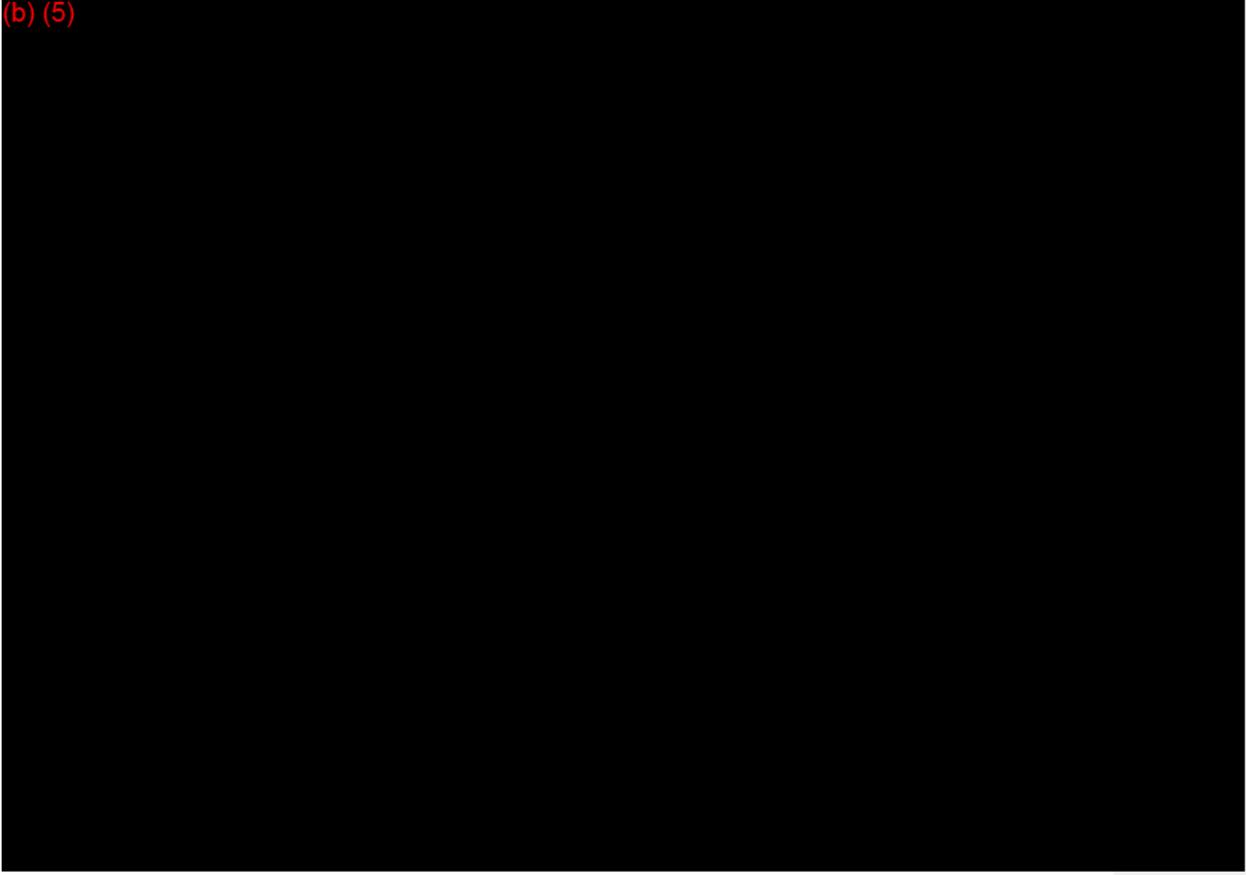
(b) (5)



(b) (5)



(b) (5)



From: [Davies, Kathleen](#)
To: [Sherman, Rachel](#); [Ortwerth, Michael](#); [Soreth, Janice M](#)
Cc: [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Califf, Robert](#)
Subject: RE: Confidential and time sensitive.
Date: Monday, September 05, 2016 1:15:28 PM
Attachments: [DupreeB-502JustificationRequest-22Jan2016-PCNS--OHCA Cleared--CLEAN.DOC](#)

Hi All,

I spoke with Andrea in OHCA earlier this year and she had provided his appearance memo as an example to me for the AC project. I've attached it in case it is useful to the group. My understanding from her is that OHCA handles patient recruitment, not the Centers directly, but confirm with her to be certain as to the process.

Thanks,
Kathleen

From: Sherman, Rachel
Sent: Monday, September 05, 2016 8:15 AM
To: Ortwerth, Michael; Soreth, Janice M
Cc: Davies, Kathleen; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Califf, Robert
Subject: Confidential and time sensitive.

Hi Michael and Janice,

Please see below re the April 25th DMD AC. Can you find out how who nominated Mr. Dupree and how his holdings were handled? Any paper trail would be useful. Our goal is not to make a judgement as to intent but rather discern whether there was (as stated below) anything unusual. I find it odd, because usually the division nominates (the person who wrote the below is a part of the OND chain so they appeared to be concerned that there was interference from an entity outside OND, or at least that is how I read the reference to "CDER" as they are part of CDER).

Please try to involve as few people as possible although I realize you may well have to contact Jayne Peterson and that's fine (unless OCC says otherwise).

If this can be done on Tuesday that would be great. I've copied Kathleen in case you need our help. Deborah and Liz (copied above) are working on this issue for OCC.

Question for Deborah and Liz – (b) (5)

[REDACTED]

Thanks much!
Rachel

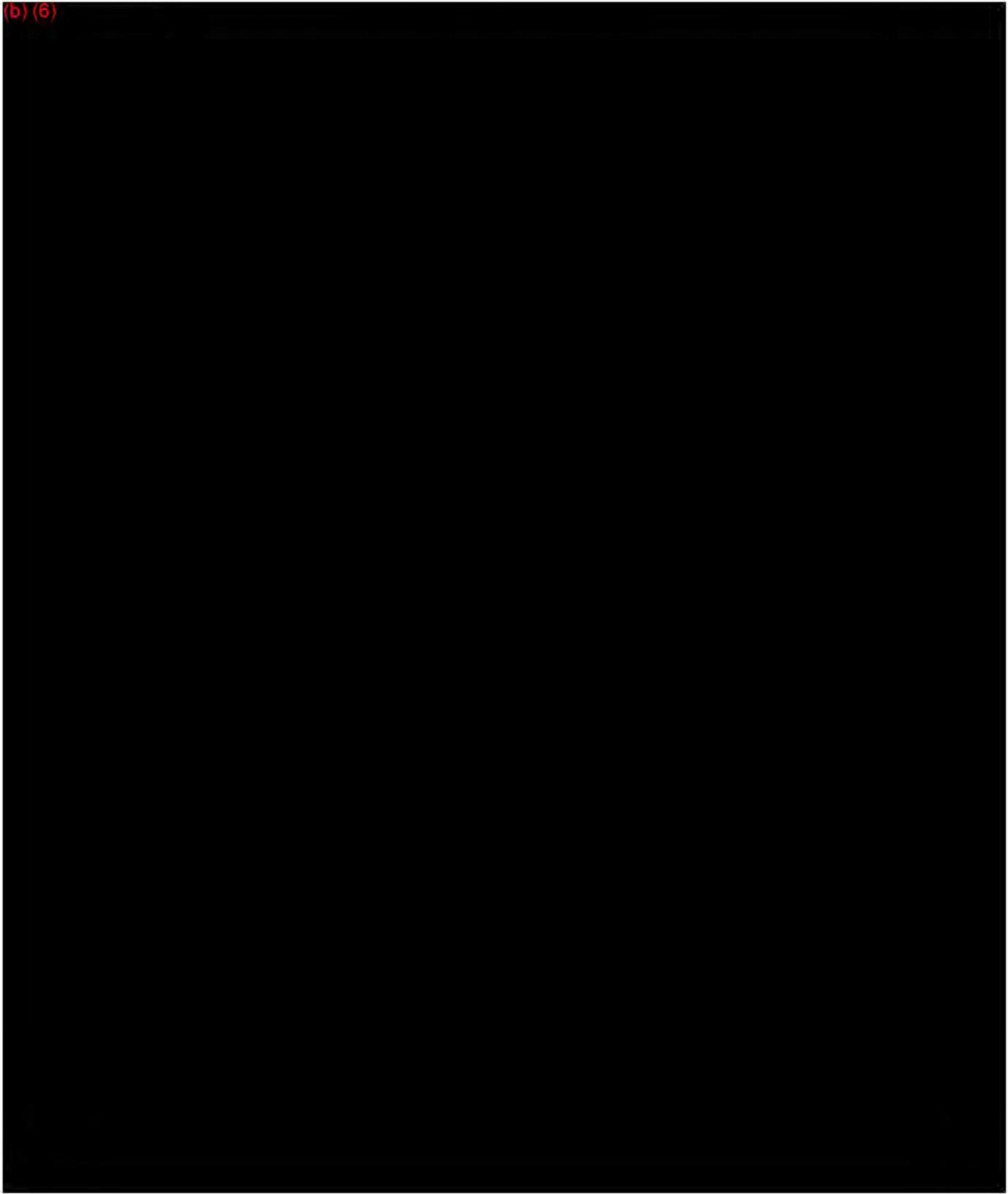
Excerpted in part from an email:

When I received the list of ad hoc members for the AC meeting in late-March, I learned that the

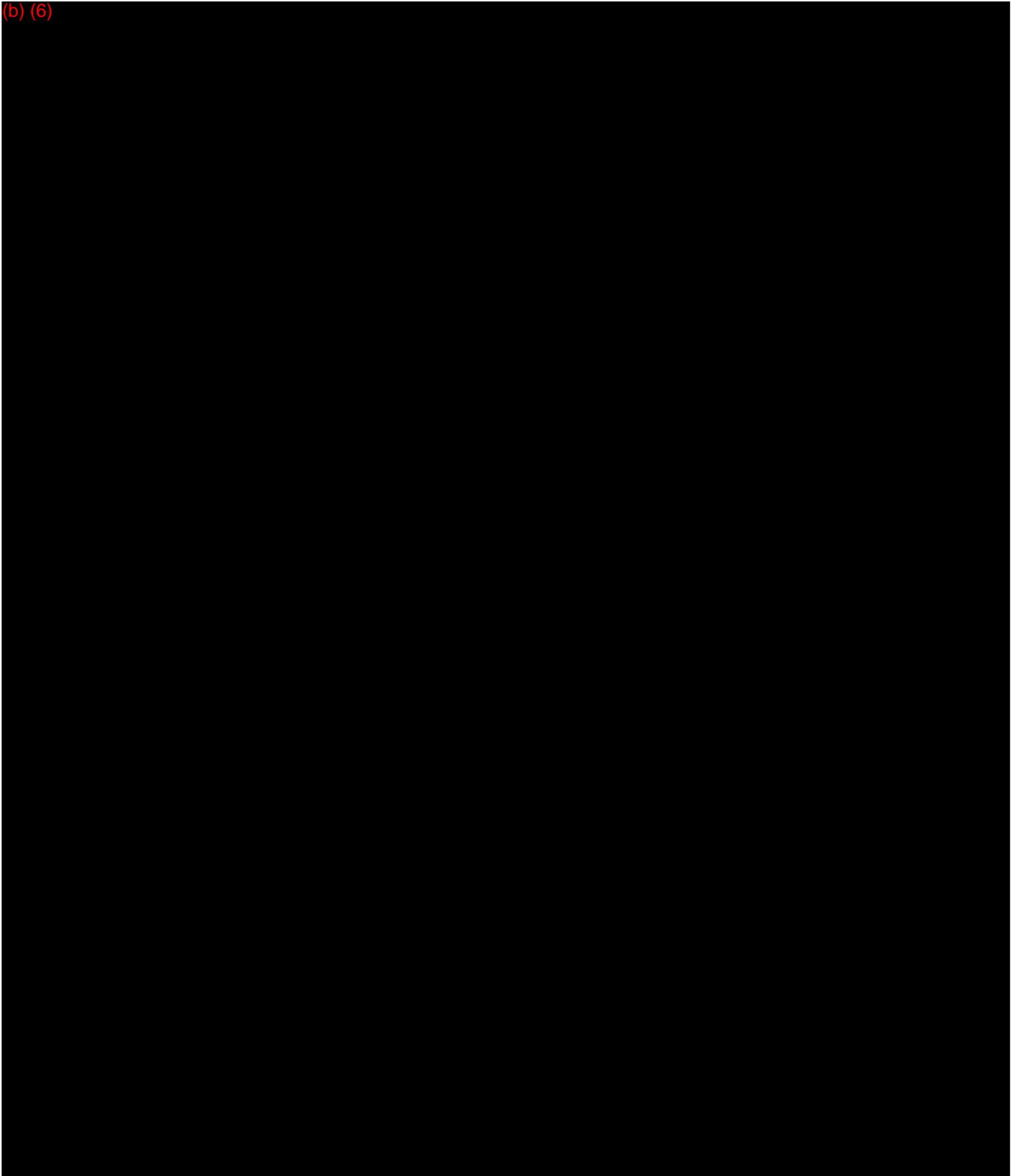
(b) (6) of the DMD patient (Benjamin Dupree) who was to be the voting patient representative on the AC owned shares of Sarepta stock. I viewed this to be an obvious COI, or at least the appearance of a COI. I wanted to avoid the COI, and tried to have him replaced with another DMD patient. I was told by the Division of Advisory Committee and Consultant Management that “the CDER Vote Memo for the April 25th PCNS Advisory Committee will be moving forward as ACOMS and OCHA were consulted regarding Mr. Dupree’s participation for the postponed January 22nd meeting and it was agreed that Mr. Dupree should remain cleared to participate.” They told me that because the (b) (6) investment was not imputed to the boy, it was not a COI. In essence, I was stonewalled by CDER on this issue. I now have to wonder whether my inability to obtain a different patient representative was blocked by CDER management (email chain attached). In my opinion, his selection as an ad hoc voting member of the AC was inappropriate and completely unnecessary.

Benjamin Dupree has reported an interest that requires a 502 Appearance Determination Authorization.

(b) (6)



(b) (6)



From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [Sherman, Rachel](#)
Subject: FW: highly confidential
Date: Monday, September 05, 2016 7:21:00 AM
Attachments: [RE Office Director Signature Needed CDER Vote Memo for Apr 25 PCNS.msg](#)

From: Unger, Ellis
Sent: Wednesday, August 31, 2016 1:39 AM
To: Califf, Robert
Subject: RE: highly confidential

Rob,

Here are my comments on Dr. Borio's memo:

1. (Point of clarification) Page 4 of the memo states:

"The Western blot analysis resulted in Week 180 dystrophin levels that were small, with a mean increase of only 0.93% of normal dystrophin levels in the muscle fibers."

It is important to recognize that the dystrophin levels detected in Study 201/202 represented the *amount* measured at Week 180, and not *increases* from baseline. Dr. Jenkins has repeatedly made the point that the quantities of dystrophin detected at Week 180 could represent baseline levels; the actual baseline levels are unknown. As such, any correlation between dystrophin levels and physical function in Study 201/202 could simply indicate that patients who naturally produce greater levels of dystrophin have better preservation of physical function, i.e., the dystrophin levels detected do not necessarily represent a treatment effect.

2. (Point of clarification) Page 12 of the memo states:

"She stated that she did not interfere with either aspect of the AC meeting because she knew she disagreed with the review team and Dr. Unger had already signaled that he would file an SDR appeal if she decided to grant accelerated approval to eteplirsen."

This may not be important, but in the interest of setting the record straight, I have no recollection of discussing the prospect of an appeal with Dr. Woodcock prior to the April 25th AC meeting. I believe I initially communicated the possibility of an appeal to Dr. Woodcock via my email on July 5, 2016 (quoted on page 14 of the memo).

3. Dr. Borio stated her scientific opinion on page 25 the memo:

"By any meaningful objective standard, however, the overall evidence derived from eteplirsen's limited clinical development program does not support that the levels of dystrophin produced by eteplirsen at the doses studied are reasonably likely to provide clinical benefit"

According to the memo (page 1, bottom), the SDR Board’s written recommendation must reflect the Board’s underlying rationale, along with minority views among the Board members. This led me to wonder whether the Board’s opinions and recommendations were unanimous or whether there were dissenting minority views.

4. There is one additional piece of information I would like to convey to you – something I found very troubling but did not mention to the Board. When I received the list of ad hoc members for the AC meeting in late-March, I learned that the (b) (6) of the DMD patient (Benjamin Dupree) who was to be the voting patient representative on the AC owned shares of Sarepta stock. I viewed this to be an obvious COI, or at least the appearance of a COI. I wanted to avoid the COI, and tried to have him replaced with another DMD patient. I was told by the Division of Advisory Committee and Consultant Management that “the CDER Vote Memo for the April 25th PCNS Advisory Committee will be moving forward as ACOMS and OCHA were consulted regarding Mr. Dupree’s participation for the postponed January 22nd meeting and it was agreed that Mr. Dupree should remain cleared to participate.” They told me that because the (b) (6) investment was not imputed to the boy, it was not a COI. In essence, I was stonewalled by CDER on this issue. (Clearly, a positive outcome at the AC meeting could have doubled the value of his (b) (6) stock.) I now have to wonder whether my inability to obtain a different patient representative was blocked by CDER management (email chain attached). In my opinion, his selection as an ad hoc voting member of the AC was inappropriate and completely unnecessary.

Not surprisingly, Mr. Dupree voted consistently in favor of eteplirsen’s approval, but in the end he cried in front of the Committee with tortured words – that he couldn’t reconcile the eteplirsen patients’ uniformly positive testimonies with the clinical data showing loss of physical function.

Thank you for sharing the report of the SDR Board, and thank you again for your consideration in this matter.

Ellis

From: Califf, Robert
Sent: Tuesday, August 30, 2016 1:46 PM
To: Woodcock, Janet; Unger, Ellis
Cc: Borio, Luciana; Dickinson, Elizabeth (FDA)
Subject: highly confidential

Janet and Ellis,

Enclosed is a copy of the Board’s recommendation and Lu’s reflection in the form of an addendum. Please keep this in strict confidence, but I would like to hear from you by close of business Thursday if you have any major concerns or points of clarification. I have reviewed my reasoning with both of you, pending my conclusion which I will finalize over the weekend.

I do not want to launch a round of “lobbying” and know that you will keep this close and professional.

I appreciate your diligence and attention to procedure.

Regards

rmc

From: [Jenkins, John K](#)
To: [Peterson, Jayne E](#); [Unger, Ellis](#)
Cc: [Jenkins, John K](#)
Subject: RE: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS
Date: Wednesday, April 06, 2016 5:42:55 PM

Thanks. I understand that he has been cleared based on the applicable laws, but some staff in ODE1/DNP, including Ellis, see this as a serious conflict of interest. I understand that we cannot require him to make a statement, and there may be personal privacy issues for him disclosing his parents financial arrangements in a public meeting, but I thought we should ensure the issue has been addressed within FDA and a final determination has been made since a senior member of the review team has voiced objections, including refusing to sign off on the vote memo (I don't recall this having happened before).

From: Peterson, Jayne E
Sent: Wednesday, April 06, 2016 5:34 PM
To: Jenkins, John K; Unger, Ellis
Subject: RE: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

Hi John,

There was discussion back in January of Benjamin Dupree voluntarily disclosing his (b) (6) Sarepta stock interest, the interest for which the appearance authorization was prepared. I'd want to have agreement within CDER that this is what we would want to propose before bringing it up with ACOMS and OHCA. During the January discussions, my recollection is that neither group was in favor of asking Mr. Dupree to disclose but it could certainly be raised again.

Jayne

From: Jenkins, John K
Sent: Tuesday, April 05, 2016 12:15 PM
To: Unger, Ellis
Cc: Peterson, Jayne E; Jenkins, John K
Subject: RE: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

Jayne

In prior discussions about this case there was a suggestion that the patient representative be encouraged to disclose the financial holdings of his (b) (6), which legally do not impute to him. I think it was agreed that he could do this voluntarily, but we could not require it. Thoughts? If we were to go that direction, who would make the contact to suggest he make this disclosure?

John

From: Unger, Ellis
Sent: Tuesday, April 05, 2016 9:34 AM
To: Jenkins, John K
Subject: FW: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

FYI. I think this is misguided.

From: Unger, Ellis
Sent: Tuesday, April 05, 2016 9:32 AM
To: Choi, Moon Hee
Cc: Ngo, Diem-Kieu (CDR,USPHS); Temple, Robert; Dunn, Billy; Bastings, Eric; Choy, Fannie (Yuet); Peterson, Jayne E; Reese, Cicely
Subject: RE: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

I understand that our rules do not provide a basis for disqualifying this person. But we have the latitude not to select him. Selection of this obviously biased person to sit on the Committee would be a travesty – and a huge mistake.

From: Choi, Moon Hee
Sent: Tuesday, April 05, 2016 9:05 AM
To: Unger, Ellis
Cc: Ngo, Diem-Kieu (CDR,USPHS); Temple, Robert; Dunn, Billy; Bastings, Eric; Choy, Fannie (Yuet); Peterson, Jayne E; Reese, Cicely
Subject: RE: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

Dear Dr. Unger,

I want to let you know that the CDER Vote Memo for the April 25th PCNS Advisory Committee will be moving forward as ACOMS and OCHA were consulted regarding Mr. Dupree's participation for the postponed January 22nd meeting and it was agreed that Mr. Dupree should remain cleared to participate.

Thank you.

Moon Hee V. Choi, Pharm.D.
Designated Federal Officer, NDAC & PCNS
Food and Drug Administration (FDA)
Office of Executive Programs (OEP)
Division of Advisory Committee and Consultant Management (DACCM)
White Oak Building 31, Room 2417
10903 New Hampshire Avenue
Silver Spring, MD 20993
Telephone: (301) 796-2894
Fax: (301) 847-8533
Email: Moonhee.Choi@fda.hhs.gov

From: Unger, Ellis
Sent: Friday, April 01, 2016 8:16 AM
To: Choy, Fannie (Yuet)
Cc: Choi, Moon Hee; Ngo, Diem-Kieu (CDR,USPHS); Temple, Robert; Dunn, Billy; Bastings, Eric
Subject: RE: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

Hi Fannie,

I'm not willing to sign this vote memo with Benjamin Dupree as the patient representative, given that we've learned he has a family member who owns stock in Sarepta – the company whose product is being discussed at this AC meeting. His participation as a voting (or non-voting) member of the Committee represents a blatant conflict of interest in my view. (Should the AC vote in favor of approval, Sarepta stock could easily double in value.) I understand that our rules do not prohibit his participation, but that does not mean that we are obliged to select him.

It is important to have patient representation on the Committee. I suggest they quickly find a different patient representative – one who has no known conflicts of interest.

Ellis

From: Choy, Fannie (Yuet)
Sent: Thursday, March 31, 2016 3:45 PM
To: Unger, Ellis
Cc: Choy, Fannie (Yuet)
Subject: FW: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

Dr. Unger

Please review and sign off the Vote memo when you have a moment.

Thank you
Fannie

From: Choi, Moon Hee
Sent: Thursday, March 31, 2016 2:35 PM
To: Choy, Fannie (Yuet)
Cc: Ngo, Diem-Kieu (CDR,USPHS)
Subject: Office Director Signature Needed: CDER Vote Memo for Apr 25 PCNS

Hi Fannie,

Attached you will find the CDER Vote Memo for the Apr 25 PCNS meeting. Can you please have Dr. Unger sign (electronic signature is ok) and get it back to me?

Thank you.

Moon

From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: highly confidential
Date: Monday, September 05, 2016 7:37:00 AM

Not free till around 1030. Is that ok?

rmc

From: Dickinson, Elizabeth (FDA)
Sent: Monday, September 05, 2016 7:36 AM
To: Califf, Robert
Subject: RE: highly confidential

Can you give me a call a (b) (6) ?

From: Califf, Robert
Sent: Monday, September 05, 2016 7:33 AM
To: Dickinson, Elizabeth (FDA)
Subject: RE: highly confidential

No, she said this to Rachel. I'm calling her today (and Ellis) so want to get your opinion.

rmc

From: Dickinson, Elizabeth (FDA)
Sent: Monday, September 05, 2016 7:32 AM
To: Califf, Robert
Subject: RE: highly confidential

(b) (5)

From: Califf, Robert
Sent: Monday, September 05, 2016 7:24 AM
To: Dickinson, Elizabeth (FDA)
Subject: RE: highly confidential

Liz,

(b) (5)

rmc

From: Dickinson, Elizabeth (FDA)
Sent: Monday, September 05, 2016 7:20 AM
To: Califf, Robert
Subject: FW: highly confidential

Rob,

(b) (6), (b) (5)

Liz

From: Woodcock, Janet
Sent: Wednesday, August 31, 2016 7:13 PM
To: Califf, Robert; Unger, Ellis
Cc: Borio, Luciana; Dickinson, Elizabeth (FDA)
Subject: RE: highly confidential

I have several comments.

First, I disagree with the statements by the member of the review team that there was no opportunity to discuss the scientific basis in the literature for what a threshold level of increase in dystrophin production might be, or for that matter why there should be a threshold value. The procedure for evaluating a surrogate EP for accelerated approval involves evaluation of the correlation between some change in the surrogate and some clinical outcome. I believe that the Division, long before I became involved in this case, had relayed to this sponsor that they would be amenable to accelerated approval based on substantial increases in dystrophin. This position presumably was based on the clinical course of Becker MD. Subsequently, when it became clear that much lower levels were being produced, the question of what amount of increase would be sufficient was discussed repeatedly with the team. As I recall, their first position was 20% of normal, but there was no presentation to me about the basis for this threshold. Then 10%, but again with no literature basis presented. There is a review article in the literature presenting this level (10%) as a threshold, but I reviewed it and found the grounds for this assertion very weak indeed. In my opinion, I never received a cogent argument, based on what is known in the scientific literature, on this point, despite many briefings and my asking many questions about it and despite the fact that this is a central tenant of accelerated approval. My own review of the literature showed that the clinical phenotype of "Becker MD" seemed to encompass a wide range of levels of dystrophin expression as evaluated by Western Blot.

It may be "unusual" or unprecedented in the memories of various parties to have a Center Director participate in an AC, but I remember instances of a Commissioner participating actively in a drug AC, and I have certainly actively participated many times, including times, such as the review of thalidomide, where very vigorous opposition to a certain action was voiced by members of CDER.

Finally, I am continuing to point out that mean values, while useful for statistical evaluation, should not always be determinative in assessing response. For example, in oncology, we look at a surrogate (PFS), and may not be impressed by the mean value, but can be very impressed by the long tail of the survival curve, representing only a small fraction of the patients. Not all people respond to a drug.

jw

From: Califf, Robert
Sent: Tuesday, August 30, 2016 1:46 PM
To: Woodcock, Janet; Unger, Ellis
Cc: Borio, Luciana; Dickinson, Elizabeth (FDA)
Subject: highly confidential

Janet and Ellis,

Enclosed is a copy of the Board's recommendation and Lu's reflection in the form of an addendum. Please keep this in strict confidence, but I would like to hear from you by close of business Thursday if you have any major concerns or points of clarification. I have reviewed my reasoning with both of you, pending my conclusion which I will finalize over the weekend.

I do not want to launch a round of "lobbying" and know that you will keep this close and professional.

I appreciate your diligence and attention to procedure.

Regards

rmc

From: [Califf, Robert](#)
To: [Chasan-Sloan, Deborah \(FDA\)](#); [Sherman, Rachel](#); [McCall, Jonathan *](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: eteplirsen
Date: Wednesday, September 07, 2016 6:46:00 AM

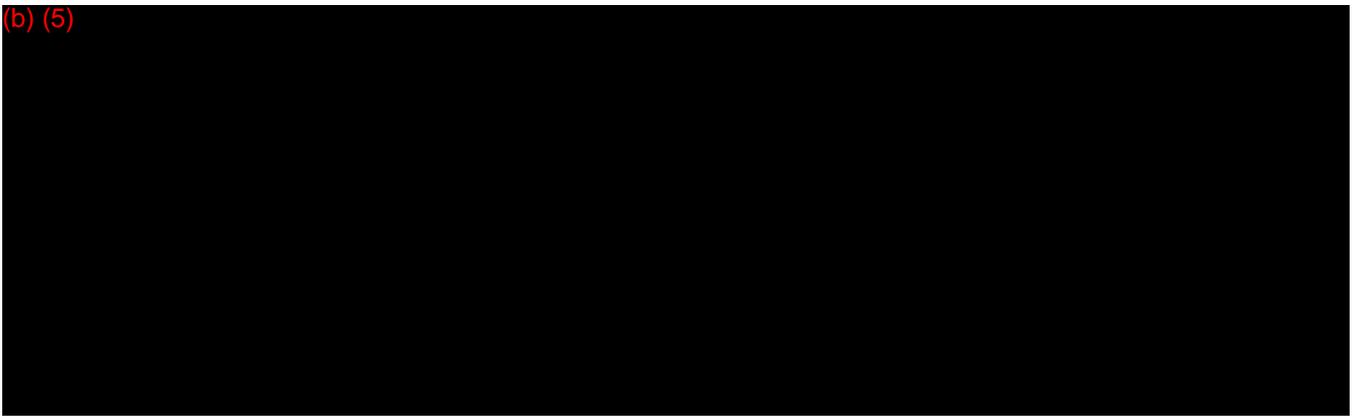
OK, I want to make sure I have the latest version. Is this it?

Thx

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Tuesday, September 06, 2016 6:32 PM
To: Sherman, Rachel; McCall, Jonathan *; Califf, Robert; Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

(b) (5)



From: Sherman, Rachel
Sent: Tuesday, September 06, 2016 6:12 PM
To: McCall, Jonathan *; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: eteplirsen

Clearly I was punished for working on a Saturday, because I can't find the draft...

So, working off the draft Jonathan sent earlier I've edited the (b) (5) text to reflect Liz's and Deborah's comments.

I've added two questions for OCC and one for Rob.

From: McCall, Jonathan *
Sent: Tuesday, September 06, 2016 12:50 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: eteplirsen

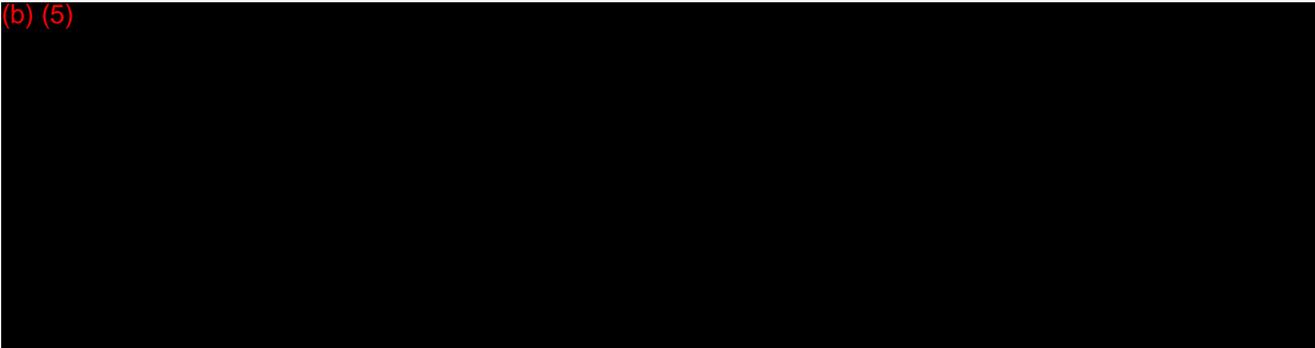
Hello all –

I'm attaching a tracked-changes version, plus a mostly-clean version that includes only a few "live"

comments (settled comments have been removed).

I've inserted some citations; please see comments for details, but a quick summary:

(b) (5)



I'll be standing by if you need any further changes.

Thanks!

--

Jonathan

From: Califf, Robert

Sent: Sunday, September 04, 2016 9:06 AM

To: McCall, Jonathan *; Dickinson, Elizabeth (FDA); Sherman, Rachel

Cc: Chasan-Sloan, Deborah (FDA)

Subject: RE: eteplirsen

Friends,

I have made only a few edits, and it seems like the only unresolved issues are the citations and making sure the "next .steps" squares with CDER. We also have materials from Katie Conover and a preferred strategy of "roll out". Jonathan, can you tidy this up and Liz, Deborah and Rachel, please weigh in on whether I'm wrong in my thinking that I want to frame this in a way that not only is clear about what I've done and why I've done it, but also will shape the discussion in a way that is productive. I truly believe that there is little in this particular decision that is relevant to the future of drug development/FDA, but there is a lot in the generalizable issues.

Thanks again for all your help with this. I hope I'm being open enough to your input as "FDA veterans".

Jonathan, let me know if there are residual issues that you are detecting as you package this up.

rmc

From: McCall, Jonathan *

Sent: Friday, September 02, 2016 2:13 PM

To: Califf, Robert; Dickinson, Elizabeth (FDA); Sherman, Rachel

Cc: Chasan-Sloan, Deborah (FDA)

Subject: RE: eteplirsen

See comments in the attached – I found a citation for (b) (5)

Only changes here are addition of my comments with citation info.

Thanks!

--

J

From: Califf, Robert
Sent: Friday, September 02, 2016 12:51 PM
To: Dickinson, Elizabeth (FDA); McCall, Jonathan *; Sherman, Rachel
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: eteplirsen

This looks good as far as I can tell. Will find cites tonight or tomorrow. Out of action now for Denver lab visit.

Thx
rmc

From: Dickinson, Elizabeth (FDA)
Sent: Thursday, September 01, 2016 6:37 PM
To: McCall, Jonathan *; Califf, Robert; Sherman, Rachel
Cc: Chasan-Sloan, Deborah (FDA)
Subject: RE: eteplirsen

(b) (5)

Liz

From: McCall, Jonathan *
Sent: Monday, August 29, 2016 10:06 AM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel

FDAOC0001690

Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

I wasn't sure if anyone needed a further clean copy of this, but here are tracked and clean versions.
I've made two modifications that I wanted to highlight:

(b) (5)



Please let me know if you have any questions!

Thanks!

--

J

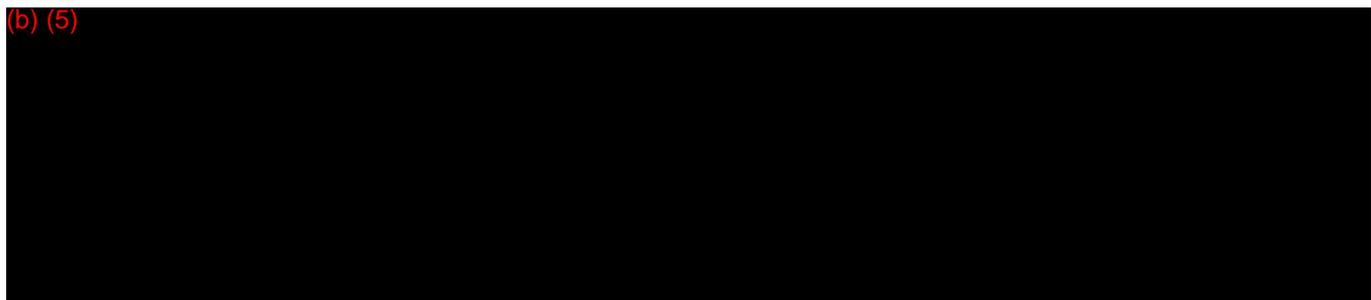
From: Califf, Robert
Sent: Sunday, August 28, 2016 10:28 PM
To: Chasan-Sloan, Deborah (FDA); McCall, Jonathan *; Sherman, Rachel
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

Agreed with all comments and suggestions. I think its looking good.

rmc
Robert M Califf MD
Commissioner of Food and Drugs

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, August 28, 2016 10:16 PM
To: McCall, Jonathan *; Sherman, Rachel; Califf, Robert
Cc: Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

(b) (5)



(b) (5)

Thanks,
Deborah

From: McCall, Jonathan *
Sent: Sunday, August 28, 2016 2:22 PM
To: Sherman, Rachel; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: eteplirsen

Hello all –

I've attached clean and tracked versions that incorporate Rachel's suggestions below.

Please let me know if you need anything else!

Thanks!

--
J

From: Sherman, Rachel
Sent: Sunday, August 28, 2016 8:23 AM
To: McCall, Jonathan *; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: Re: eteplirsen

I'm working off a phone so can't edit, sorry.

(b) (5)

Otherwise looks good to me.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: August 28, 2016 at 7:58:54 AM EDT
To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Cc: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah

FDAOC0001692

(FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Sherman, Rachel
<Rachel.Sherman@fda.hhs.gov>

Subject: eteplirsen

Friends,

I think I've addressed all the comments and read it thoroughly. I want to make sure we've covered the post-marketing orders. I've also re-read the documents and I don't believe I've left anything unaddressed.

Jonathan, can you produce a clean version?

thx

rmc

From: [Califf, Robert](#)
To: [Sherman, Rachel](#); [McCall, Jonathan *](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: discussions tonight
Date: Thursday, September 08, 2016 7:42:00 AM
Attachments: [2016_Sept_06_Eteplirsen_JM_CLEAN-COMMENTEDrscom\(occ\)_rmc.doc](#)

OK, a few more minor changes. My only concern now is that (b) (5) " is clear and firm enough.

rmc

From: Sherman, Rachel
Sent: Thursday, September 08, 2016 7:02 AM
To: McCall, Jonathan *; Conover, Katie; Sharp, Jeremy; Califf, Robert; Dickinson, Elizabeth (FDA); Kraus, Tom
Subject: Re: discussions tonight

Rob

Are you done with the draft?

From: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Date: September 7, 2016 at 10:24:21 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>, Sharp, Jeremy <Jeremy.Sharp@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Kraus, Tom <Tom.Kraus@fda.hhs.gov>
Subject: Re: discussions tonight

Rob,

(b) (5)

Liz

From: Califf, Robert
Sent: Wednesday, September 7, 2016 9:44 PM
To: Conover, Katie; Kraus, Tom; Sharp, Jeremy; Sherman, Rachel; Dickinson, Elizabeth (FDA)
Subject: discussions tonight

I've talked with both John and Ellis. They are disappointed and quite elaborate in expressing their worries, but both acknowledged the importance of non-interference in the individual product decision making process. Next step is a meeting with the 4 of us, which all agree needs to be asap.

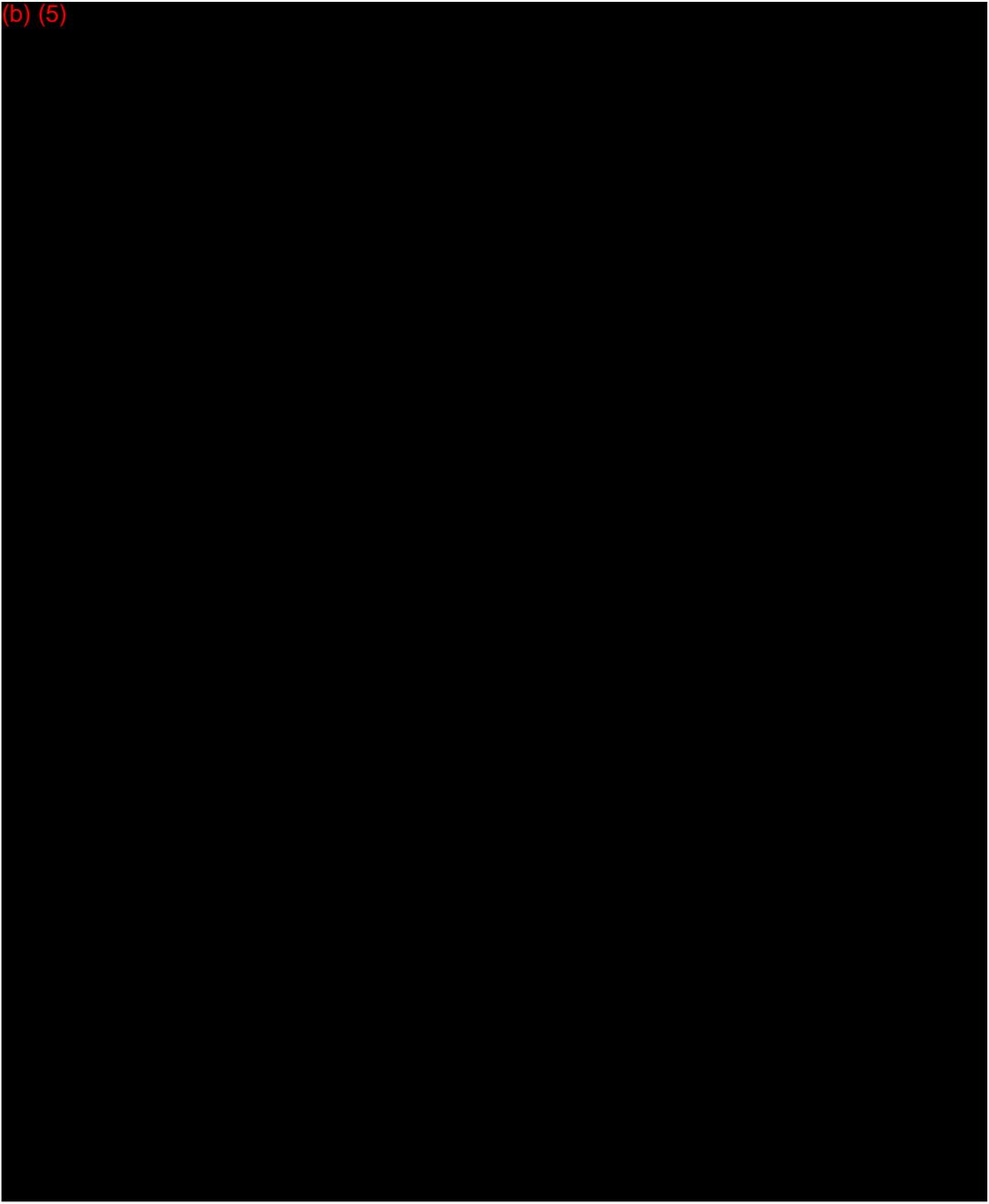
Liz, (b) (5)

Katie, you should go ahead and engage. All agreed to make the best of it.

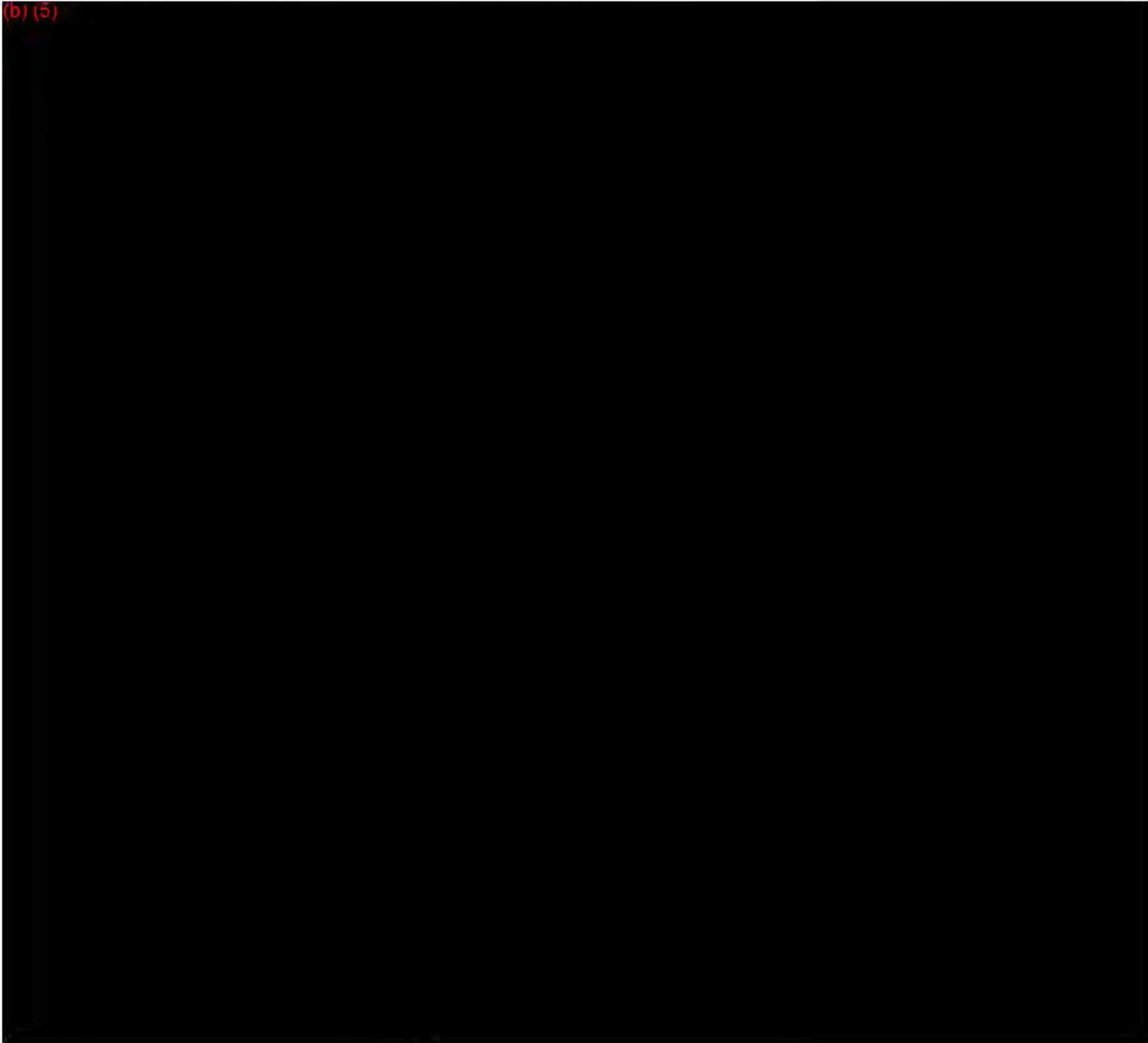
Among this, gene editing and regrow discussions, I am ready for a good night's sleep.

rmc

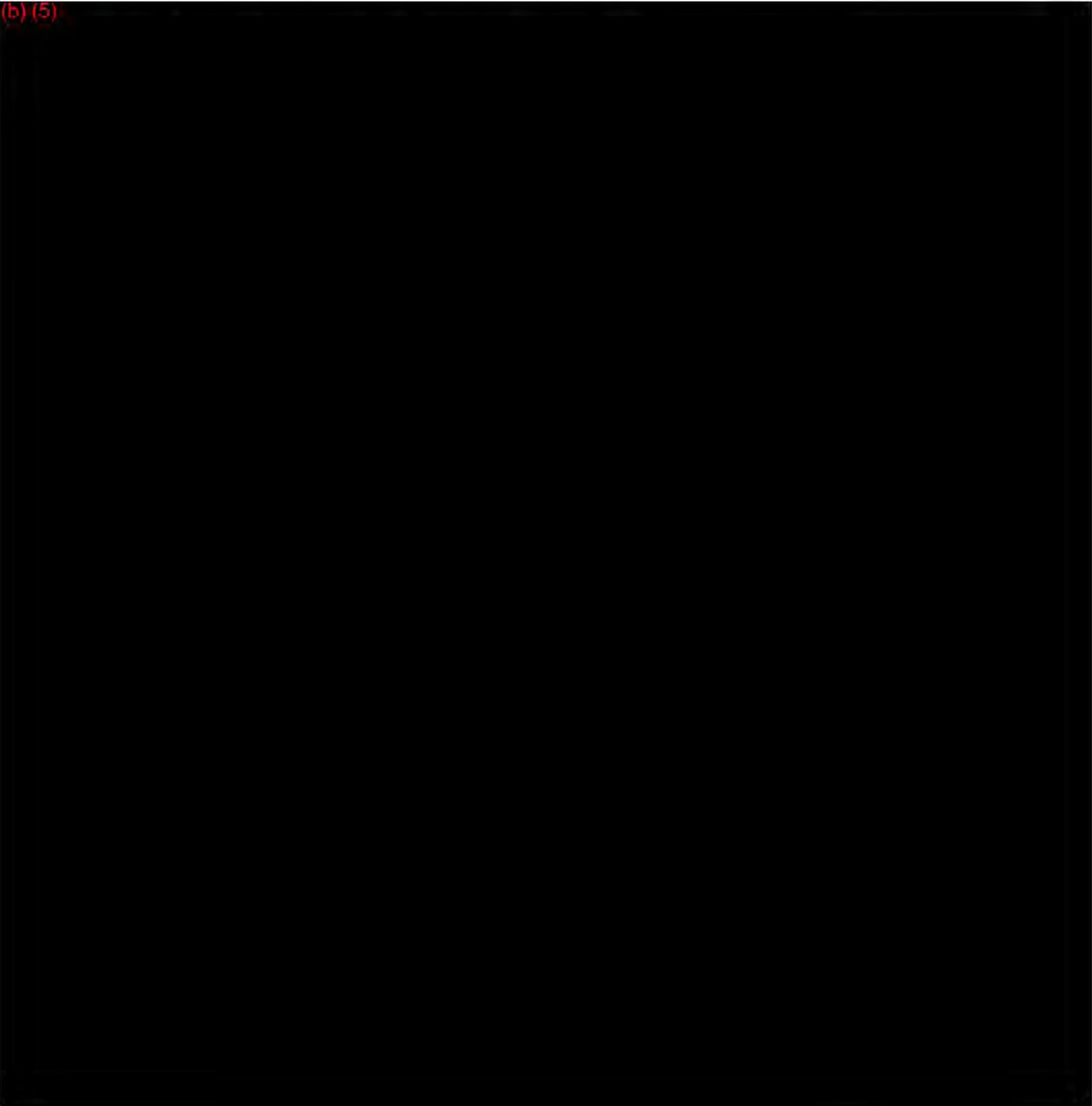
(b) (5)



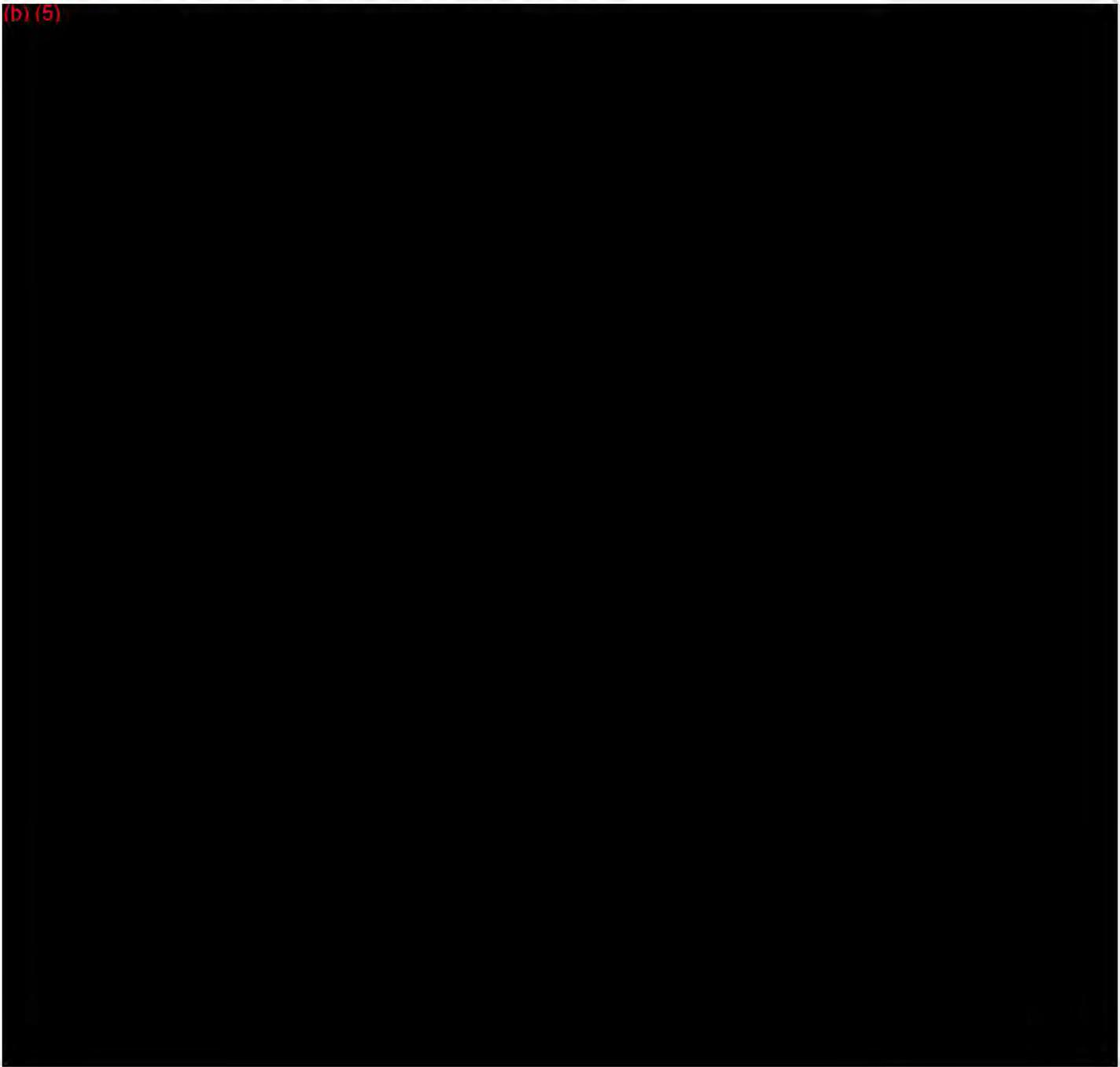
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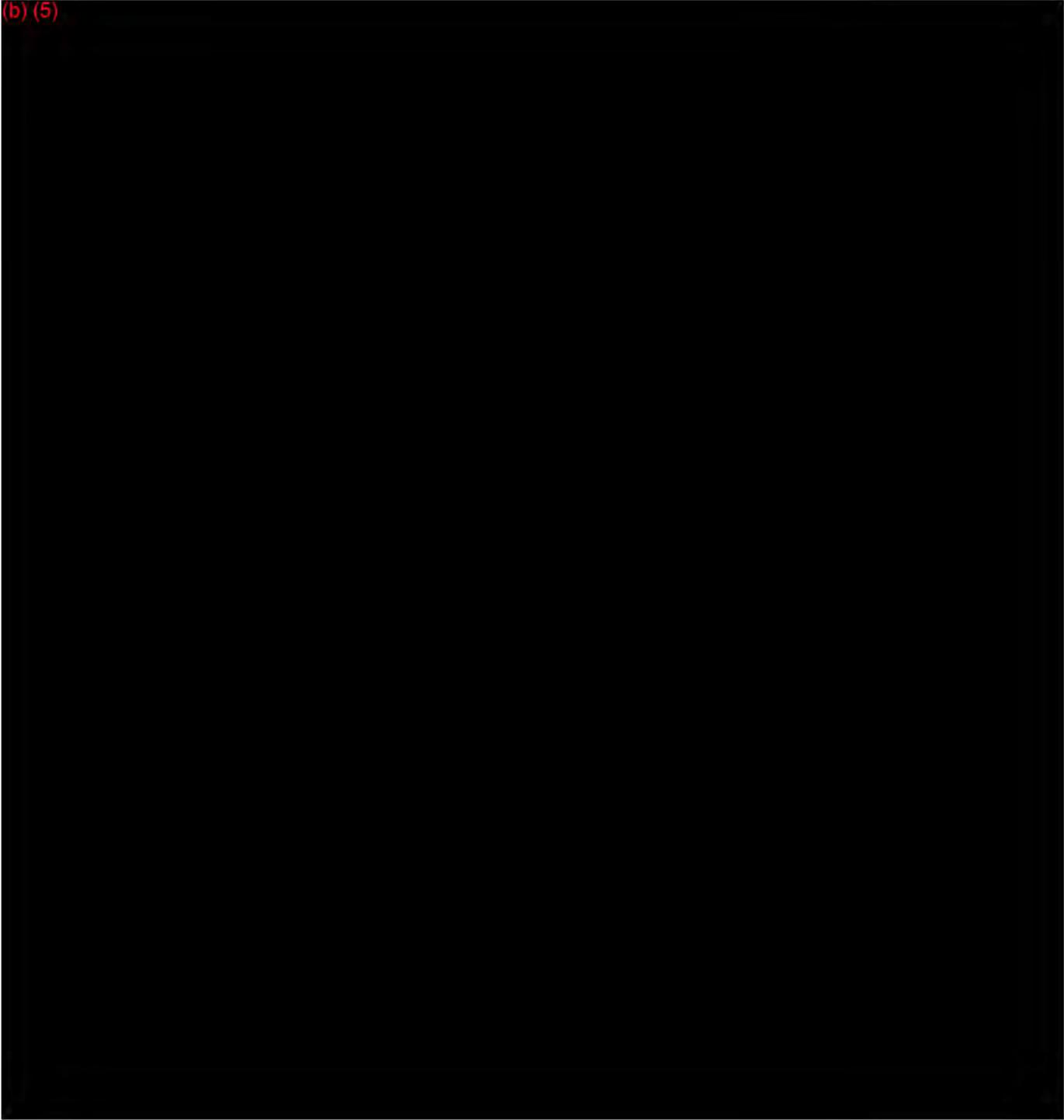
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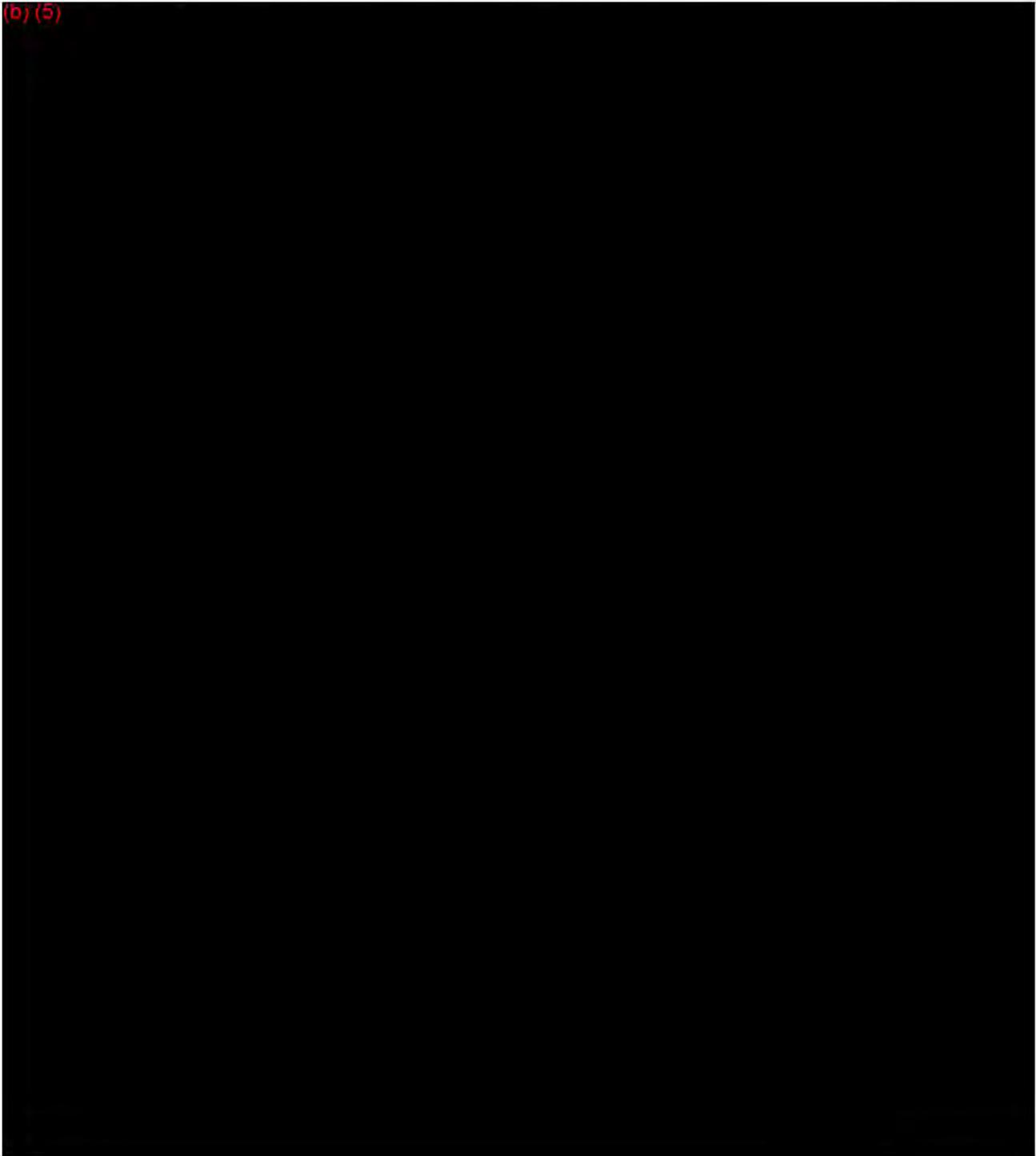
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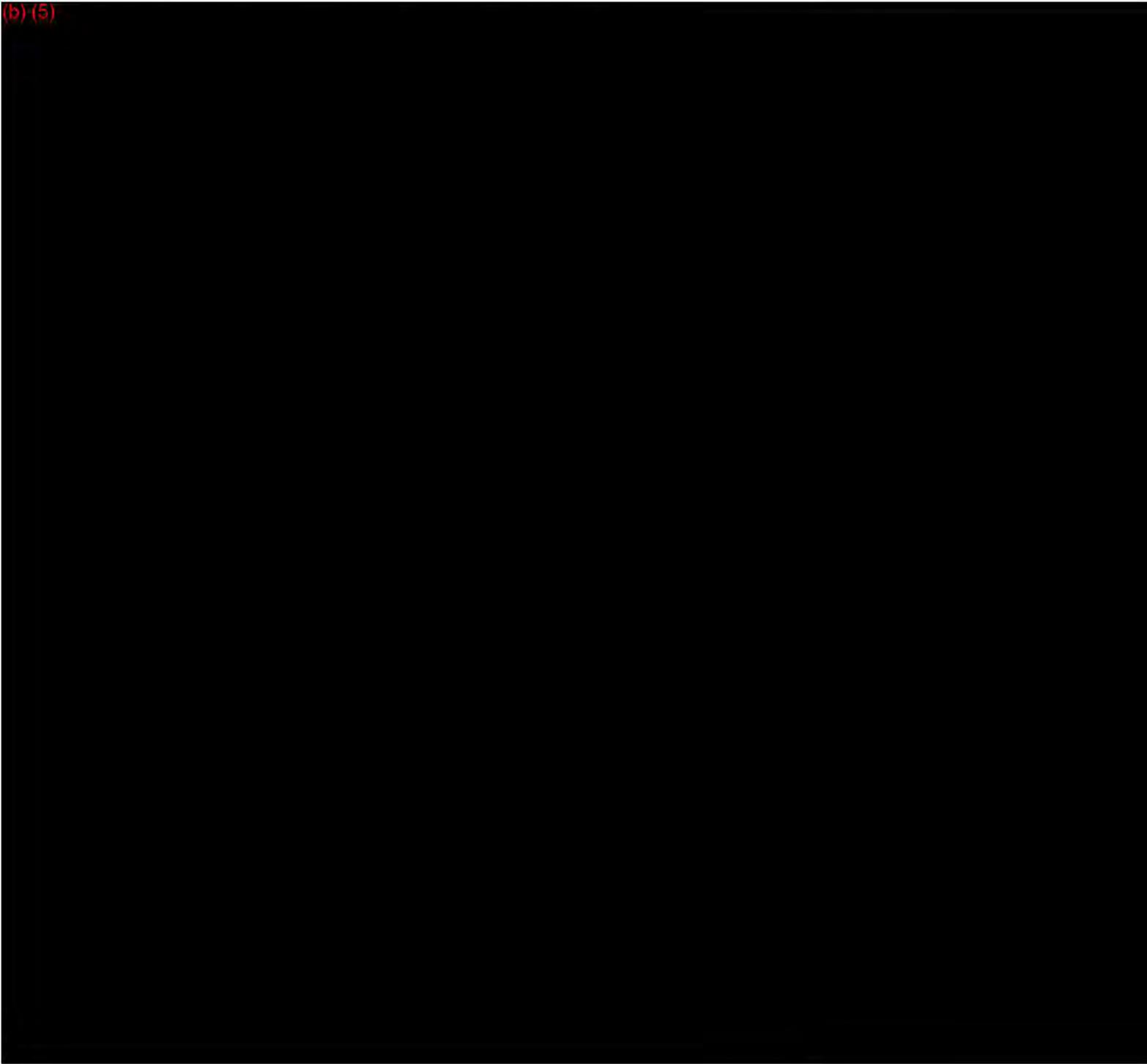
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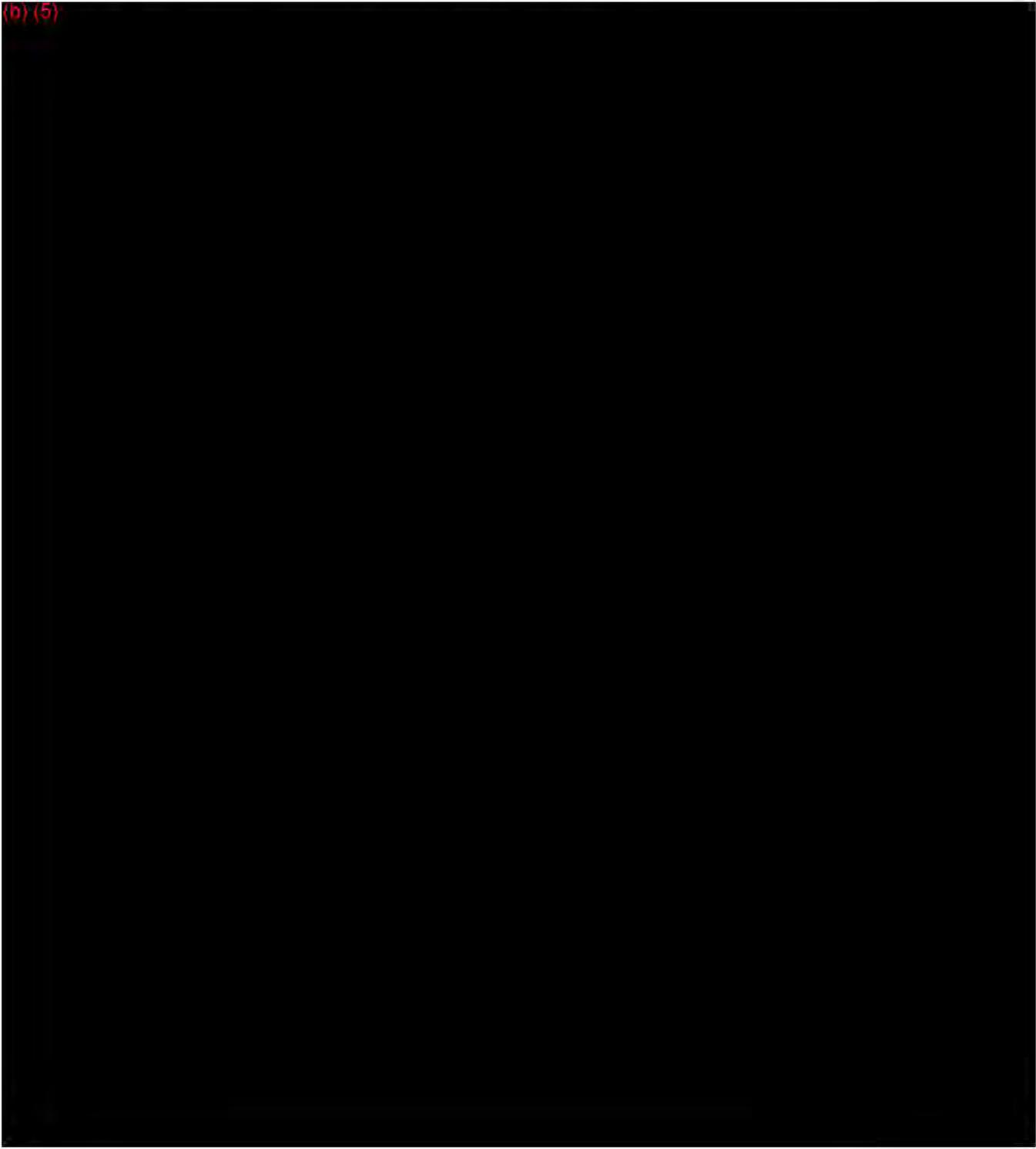
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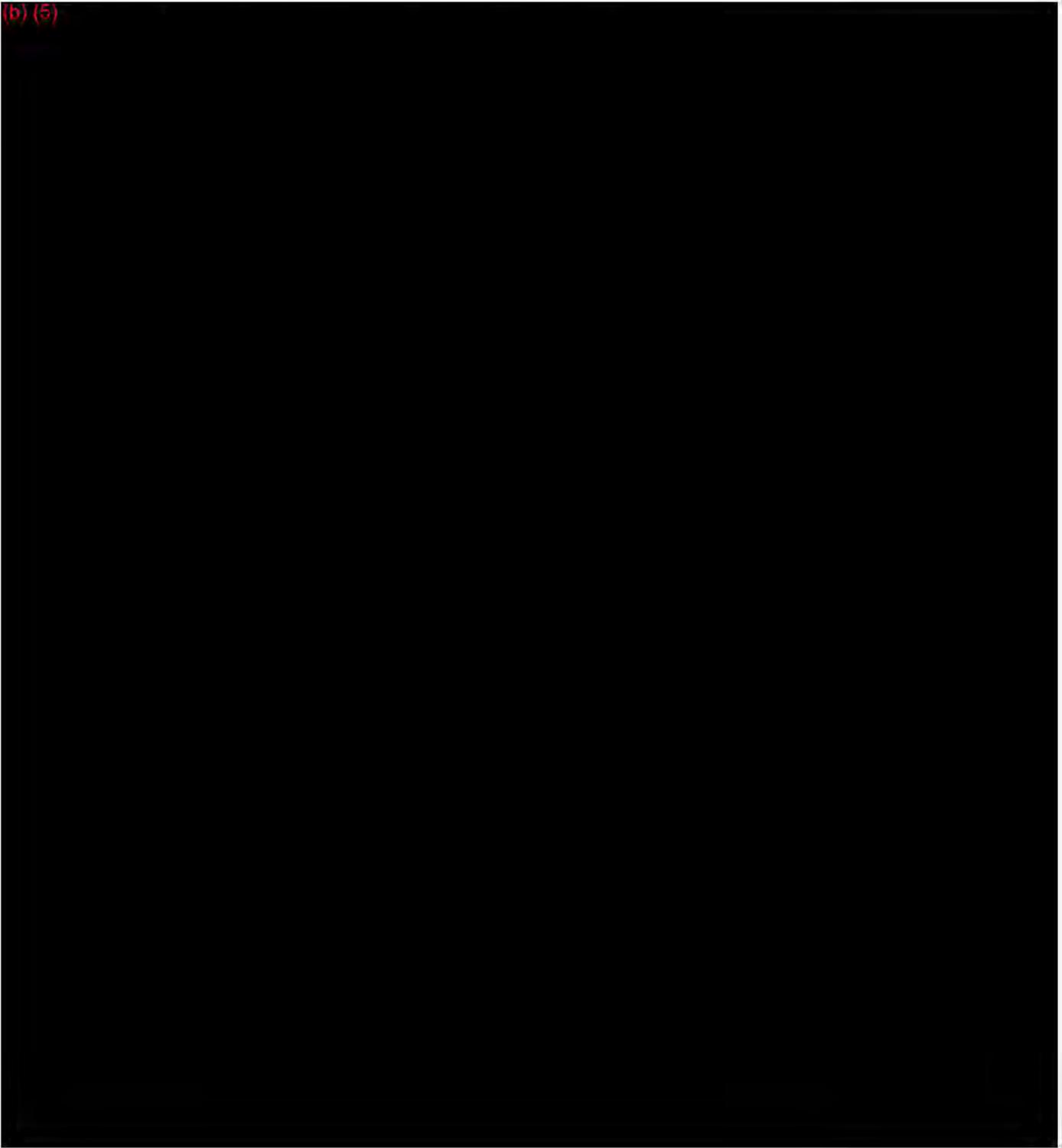
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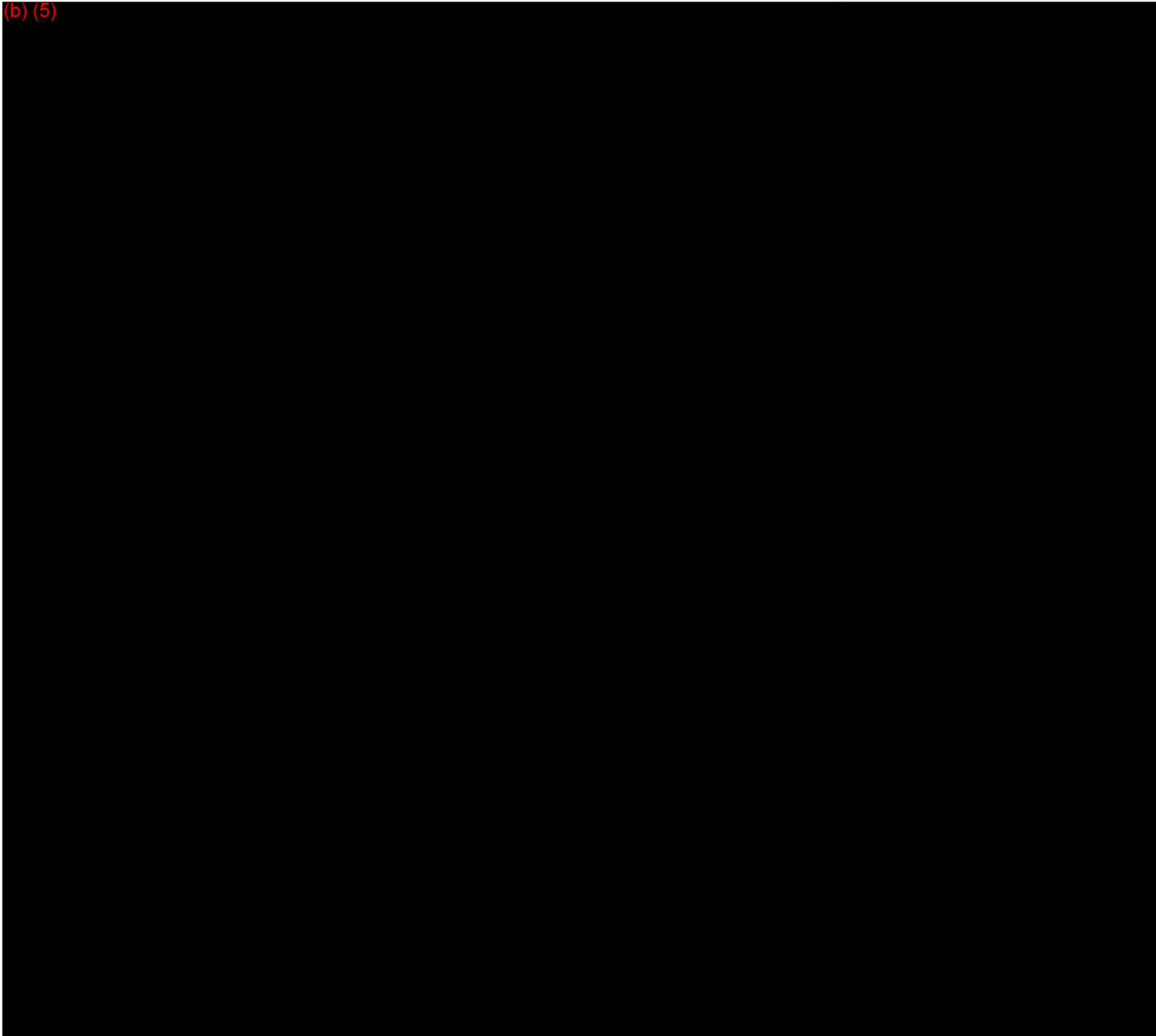
(b) (5)



(b) (5)



(b) (5)



(b) (5)



From: [Califf, Robert](#)
To: [Sherman, Rachel](#)
Subject: FW: I spoke to the firm
Date: Thursday, September 08, 2016 7:43:00 AM

Look at this when you look at (b) (5) " part.

rmc

From: Woodcock, Janet
Sent: Friday, September 02, 2016 11:01 AM
To: Califf, Robert
Subject: I spoke to the firm

And got a much better idea of what is going on. There are a number of studies, but the dose comparison study is not started, they need to reach agreement on the details of the protocol with the division. Of course, they have agreed to do this study.

The ongoing studies with eteplersin on exon 51 amenable:

"PROVMOVI" study: 2yr open label almost at full enrollment. Will use new validated method for dystrophin WB and will use an automated method for ICH that has been validated. Around 70 patients (b) (4).

204: 45 patient. Overenrolled. Open label safety study in non-ambulatory boys. No biopsies.

203: Open label 1 year with extension. MRI studies in age 4-6. Overenrolled already.

Studies on another molecule:

Exon 45/53 amenable Randomized concurrent open label control study. Ethical problems encountered in doing weekly IV therapy in a placebo group of children. Our ethics people in the Peds group said they could do weekly Ivs, probably non-feasible for a 2 year study in children. Apparently Europe was ok w Ports, not sure how this was worked out. Initiated. Patients enrolled, currently in 4-week pre-dosing observation period. 2 sites open. Will also have sites in Europe. This study could shed light on the surrogate. jw

From: [Chasan-Sloan, Deborah \(FDA\)](#)
To: [Sherman, Rachel](#); [Rodriguez, Jennifer](#); [Dickinson, Elizabeth \(FDA\)](#); [Califf, Robert](#)
Cc: [Conover, Katie](#)
Subject: RE: PLEASE SEE: Phase I and II Comms
Date: Thursday, September 08, 2016 4:22:00 PM
Attachments: [Phase II approval reactive QA 090816rscom\(occ\).doc](#)
[image001.png](#)

(b) (5)

Thanks,
Deborah

From: Sherman, Rachel
Sent: Thursday, September 08, 2016 3:47 PM
To: Rodriguez, Jennifer; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Califf, Robert
Cc: Conover, Katie
Subject: RE: PLEASE SEE: Phase I and II Comms

Hi all,

Please see some suggestions on phase II. OCC, please opine on comment 6.

Thanks!
Rachel

From: Rodriguez, Jennifer
Sent: Thursday, September 08, 2016 3:26 PM
To: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Califf, Robert
Cc: Conover, Katie
Subject: PLEASE SEE: Phase I and II Comms

All,

Attached for review, please find the Phase II reactive QA. This document reflects initial edits from OCC. Please review and provide any edits ASAP. Also, you will note that we have one pending response in which we need to work with Lu and her team to address. Can you please let us know if it is OK to reach out to her at this time?

In addition, I am reattaching the Phase II materials – in which, I believe we are awaiting Dr. Califf's final sign off.

Dr. Califf – please let us know when we can expect your review, so that we can frame out the remaining review timeline.

Best,
Jen

Jennifer Rodriguez

Deputy Director of Strategy, OMA

Office of Media Affairs

Office of External Affairs

U.S. Food and Drug Administration

Tel: 301-796-8232 / Cell: 202-763-9073

Jennifer.Rodriguez@fda.hhs.gov



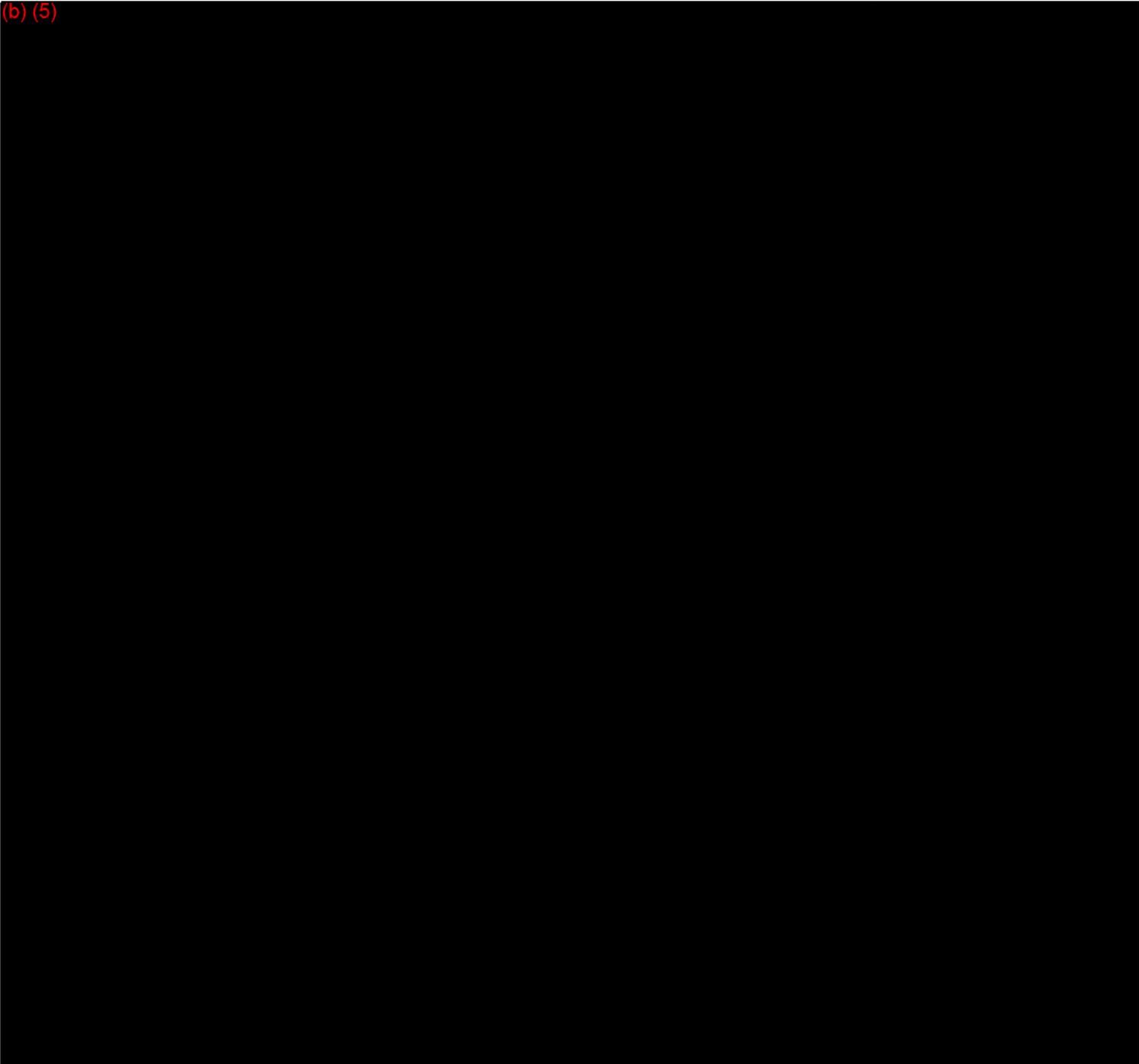
**Reactive Statement and QA: Posting of review documents for approval of
Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy**

Target date: September 2016

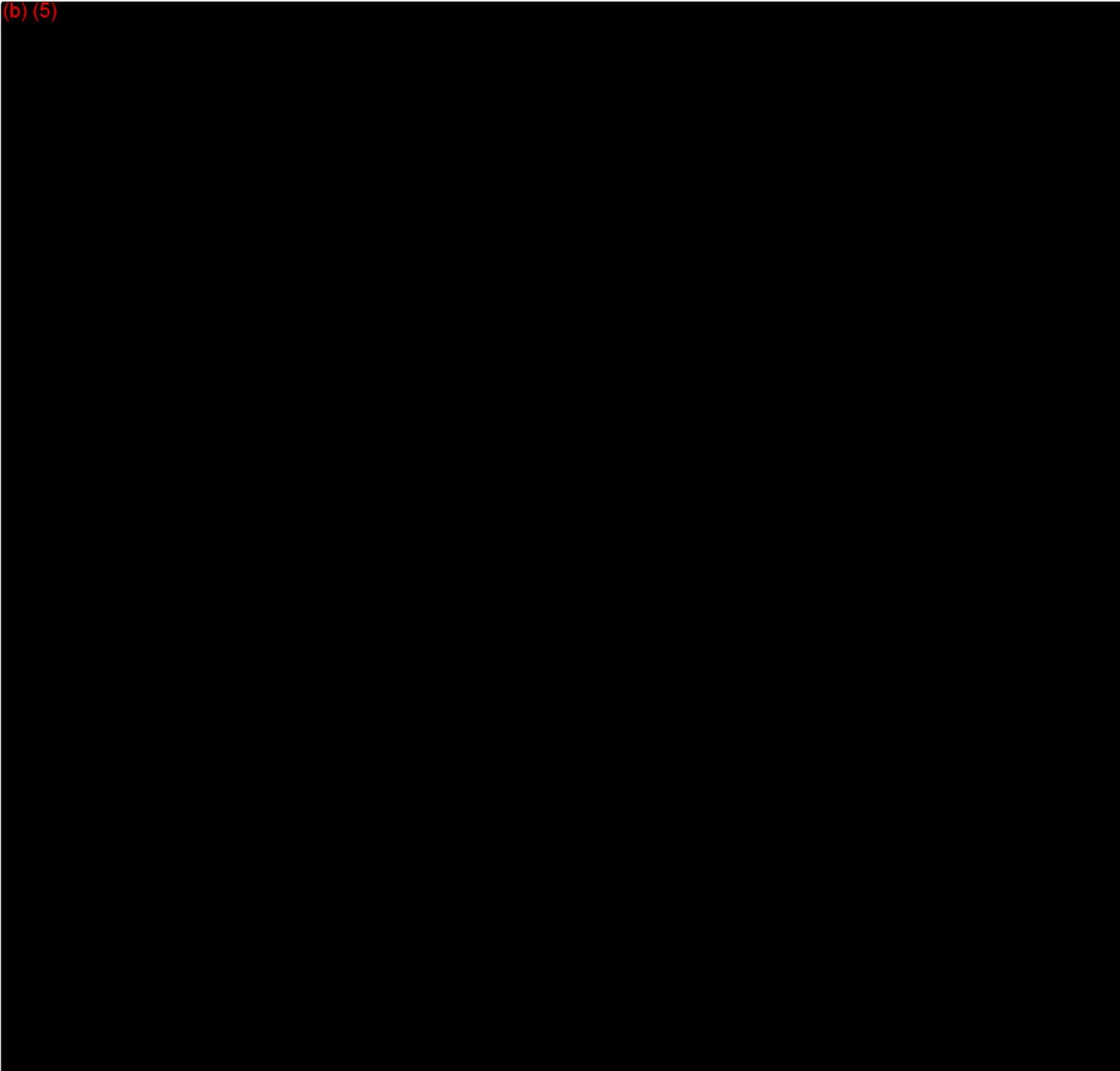
(b) (5)



(b) (5)



(b) (5)



(b) (5)



(b) (5)



From: [Rodriguez, Jennifer](#)
To: [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Califf, Robert](#)
Cc: [Conover, Katie](#)
Subject: PLEASE SEE: Phase I and II Comms
Date: Thursday, September 08, 2016 3:25:46 PM
Attachments: [etelirsen PR draft 9.5.16.doc](#)
[etelirsen KMQA 9.5.16.doc](#)
[Phase II approval reactive OA 090816.doc](#)
[image013.png](#)

All,

Attached for review, please find the Phase II reactive QA. This document reflects initial edits from OCC. Please review and provide any edits ASAP. Also, you will note that we have one pending response in which we need to work with Lu and her team to address. Can you please let us know if it is OK to reach out to her at this time?

In addition, I am reattaching the Phase II materials – in which, I believe we are awaiting Dr. Califf's final sign off.

Dr. Califf – please let us know when we can expect your review, so that we can frame out the remaining review timeline.

Best,
Jen

Jennifer Rodriguez

Deputy Director of Strategy, OMA

Office of Media Affairs

Office of External Affairs

U.S. Food and Drug Administration

Tel: 301-796-8232 / Cell: 202-763-9073

Jennifer.Rodriguez@fda.hhs.gov



From: [Rodriguez, Jennifer](#)
To: [Califf, Robert](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Conover, Katie](#); [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#)
Cc: [McCall, Jonathan *](#)
Subject: RE: Review of materials for drug approval
Date: Monday, September 05, 2016 11:20:43 AM
Attachments: [eteplirsen KMOA 9.5.16.doc](#)
[eteplirsen PR draft 9.5.16.doc](#)
[image001.png](#)

Hi Dr. Califf,

Absolutely, attached please find clean versions (based on the version Deborah shared at 12:28 am) retaining a few comments of items that are still being addressed. All other edits have been accepted.

Thanks for your review over this holiday!

Best,
Jen

From: Califf, Robert
Sent: Monday, September 05, 2016 10:25 AM
To: Rodriguez, Jennifer; Chasan-Sloan, Deborah (FDA); Conover, Katie; Sherman, Rachel; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *
Subject: RE: Review of materials for drug approval

Yes, please clean it up. Perfect day in Carolina, and I have good back yard time to read things.

Thx for your help.

rmc

From: Rodriguez, Jennifer
Sent: Monday, September 05, 2016 10:14 AM
To: Chasan-Sloan, Deborah (FDA); Conover, Katie; Sherman, Rachel; Dickinson, Elizabeth (FDA); Califf, Robert
Cc: McCall, Jonathan *
Subject: RE: Review of materials for drug approval

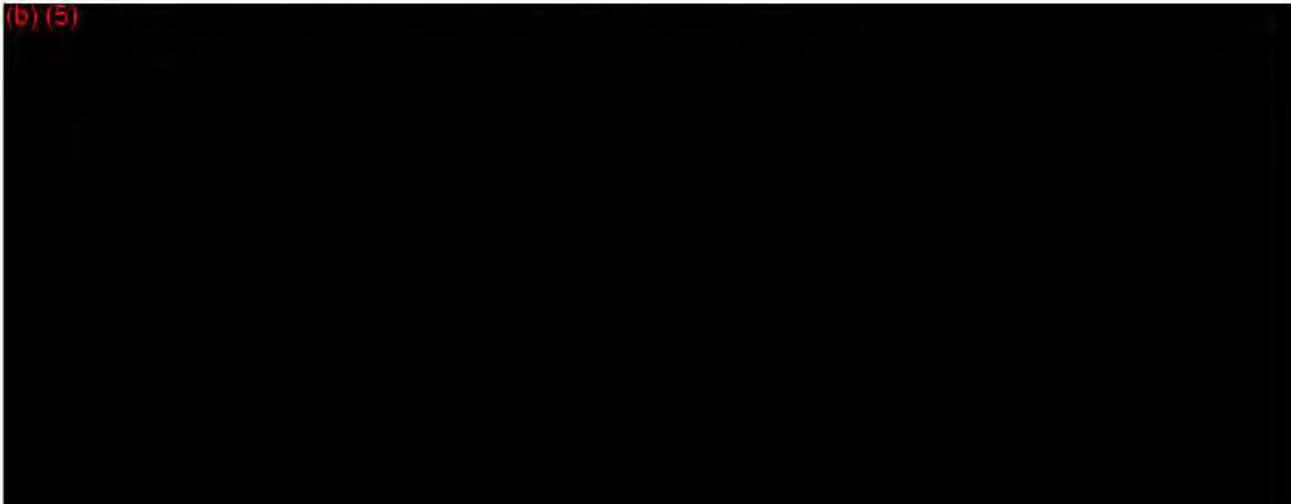
Thanks, Deborah. I have not scrubbed yet as I got the impression from Rachel's last email that we needed Dr. Califf's concurrence -- so thank you for sharing.

Dr. Califf if you prefer a completely scrubbed version I am happy to clean up and resend. Just let me know.

Best,
Jen

From: Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>
Date: September 5, 2016 at 10:08:07 AM EDT
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Califf, Robert <RMC1@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>
Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Subject: RE: Review of materials for drug approval

(b) (5)



Deborah

From: Rodriguez, Jennifer
Sent: Monday, September 05, 2016 9:36 AM
To: Conover, Katie; Sherman, Rachel; Califf, Robert; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *
Subject: RE: Review of materials for drug approval

Once we have De. Califf's concurrence we can clean up and send back to the group. Also, we are simultaneously working on the Phase II comms.

Liz/Deborah - we will likely need a quick chat on those tomorrow to talk through a few of the questions with you.

From: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Date: September 5, 2016 at 7:40:08 AM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>

FDAOC0001717

Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>

Subject: RE: Review of materials for drug approval

Rob,

If you are okay with these Jen can get started.

Thanks,

Rachel

From: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>

Date: September 5, 2016 at 7:19:23 AM EDT

To: Conover, Katie <Priscilla.Conover@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Califf, Robert <RMC1@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>

Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>

Subject: RE: Review of materials for drug approval

(b) (5)



From: Califf, Robert

Sent: Monday, September 05, 2016 6:15 AM

To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Conover, Katie; Rodriguez, Jennifer

Cc: Dickinson, Elizabeth (FDA); McCall, Jonathan *

Subject: RE: Review of materials for drug approval

The tweaks seem fine. Seems like the Q&A could go on forever on this one, but most will have to do with "Phase 2", which I will be glad to move onto and beyond I guess when we hear from Liz, someone will produce a cleaned up version for review? It's a little tough right now with more mark up than text.

rnc

From: Chasan-Sloan, Deborah (FDA)

Sent: Monday, September 05, 2016 12:28 AM

To: Sherman, Rachel; Califf, Robert; Conover, Katie; Rodriguez, Jennifer

Cc: Dickinson, Elizabeth (FDA); McCall, Jonathan *

Subject: RE: Review of materials for drug approval

(b) (5)

From: Sherman, Rachel
Sent: Sunday, September 04, 2016 8:33 PM
To: Califf, Robert; Conover, Katie; Rodriguez, Jennifer
Cc: Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); McCall, Jonathan *
Subject: RE: Review of materials for drug approval

Okay, Rob, could you see if this is what you are hoping for? I don't know what you want about

(b) (5). I tried to address the rest.

Thanks.

From: Califf, Robert
Sent: Sunday, September 04, 2016 10:44 AM
To: Conover, Katie; Rodriguez, Jennifer
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); McCall, Jonathan *
Subject: FW: Review of materials for drug approval
Importance: High

Katie and Jen,

I've copied those working on the appeal documents. A few comments are embedded.

This is a good start. I feel the urge to give more detail from the document, especially on the follow on requirements and some technical issues: (b) (5)

rnc

From: Conover, Katie
Sent: Thursday, September 01, 2016 11:33 AM
To: Califf, Robert
Subject: Review of materials for drug approval
Importance: High

Hi Dr. Califf,

In anticipation of our discussion this afternoon, attached please find a draft press release and KMQA to support communications around the approval of the drug. We have not yet sent these materials to Liz – but I am sharing with you now so that you can see what we are envisioning.

I have asked Jen Rodriguez, who has been working on these materials and communications plans, to join me for the call as well. We look forward to speaking with you and providing additional context regarding our communications recommendations.

FDAOC0001719

Best,

Katie

Katie Conover

Acting Associate Commissioner

Office of External Affairs

U.S. Food and Drug Administration

Tel: 240-402-2402 / Cell: 301-512-9120

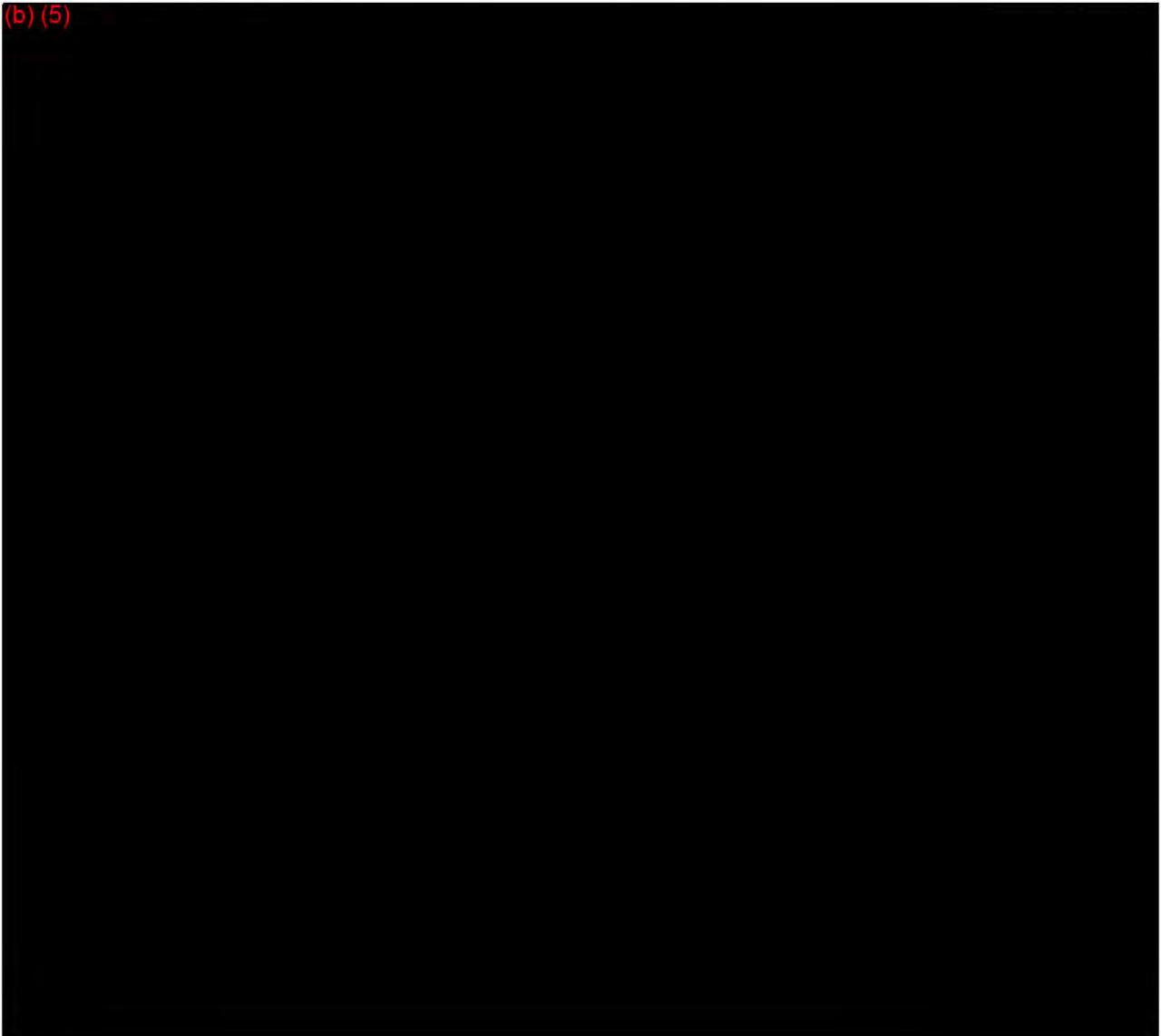
priscilla.conover@fda.hhs.gov



**Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat
Duchenne muscular dystrophy**

Target date: September 2016

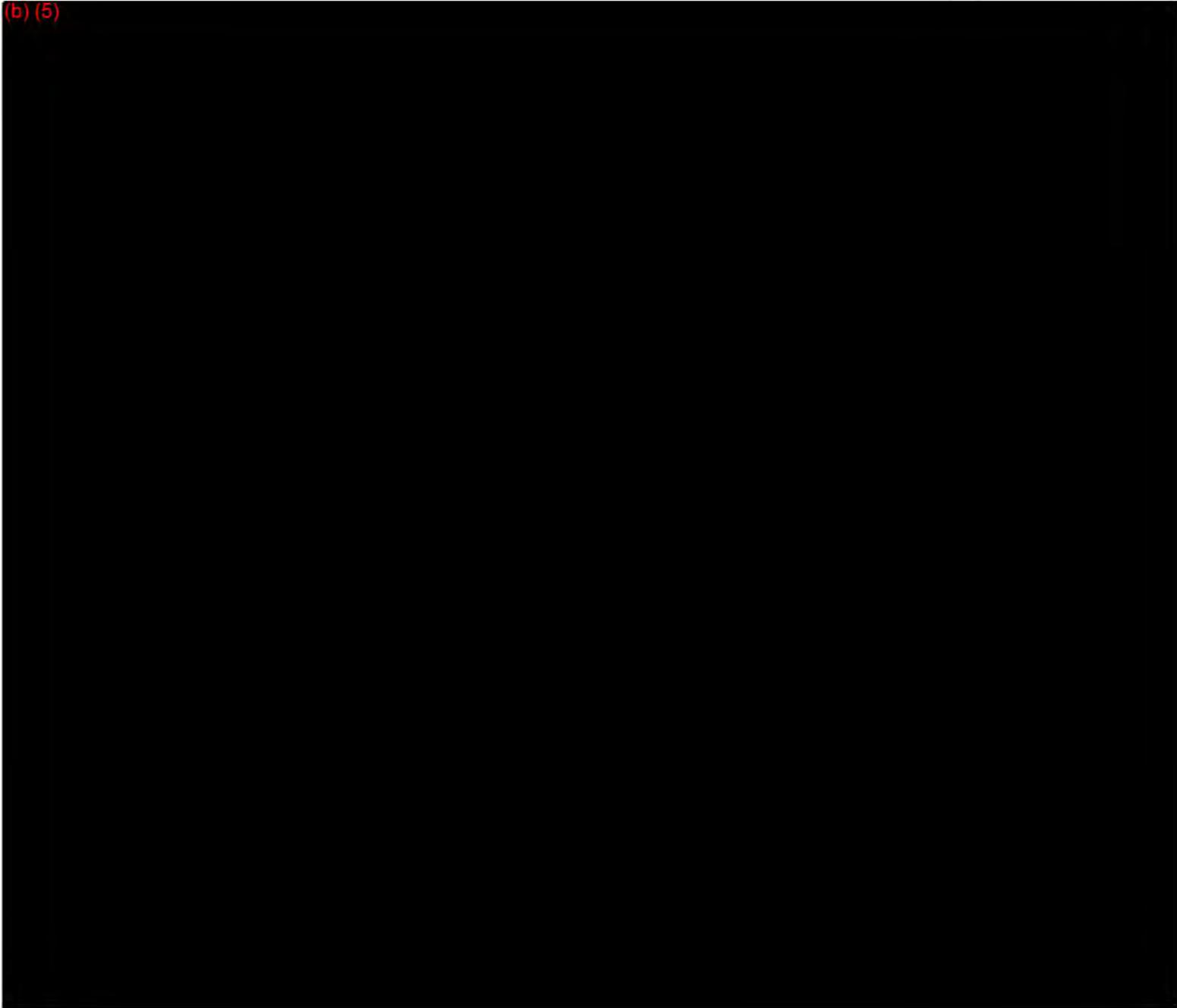
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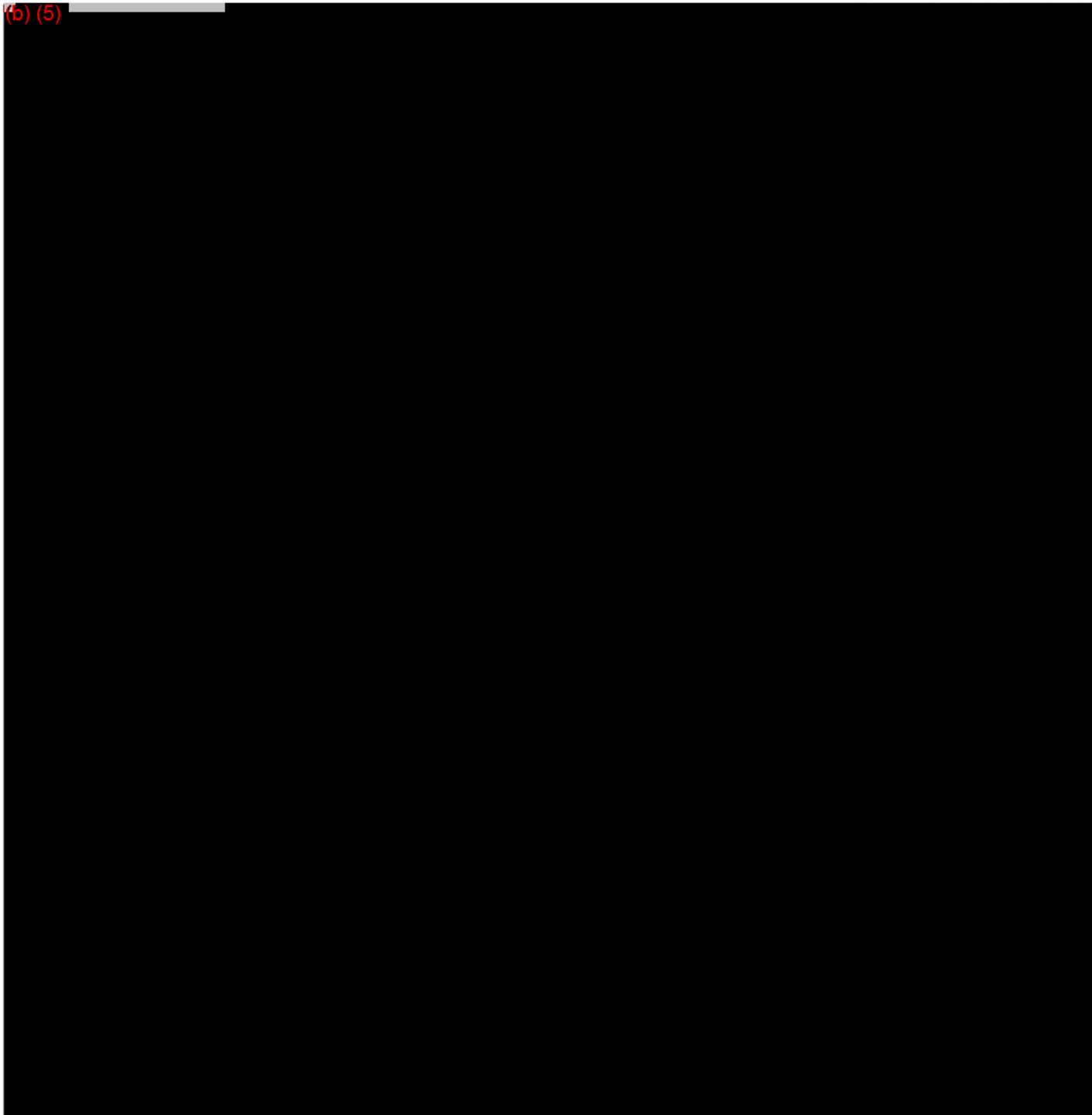
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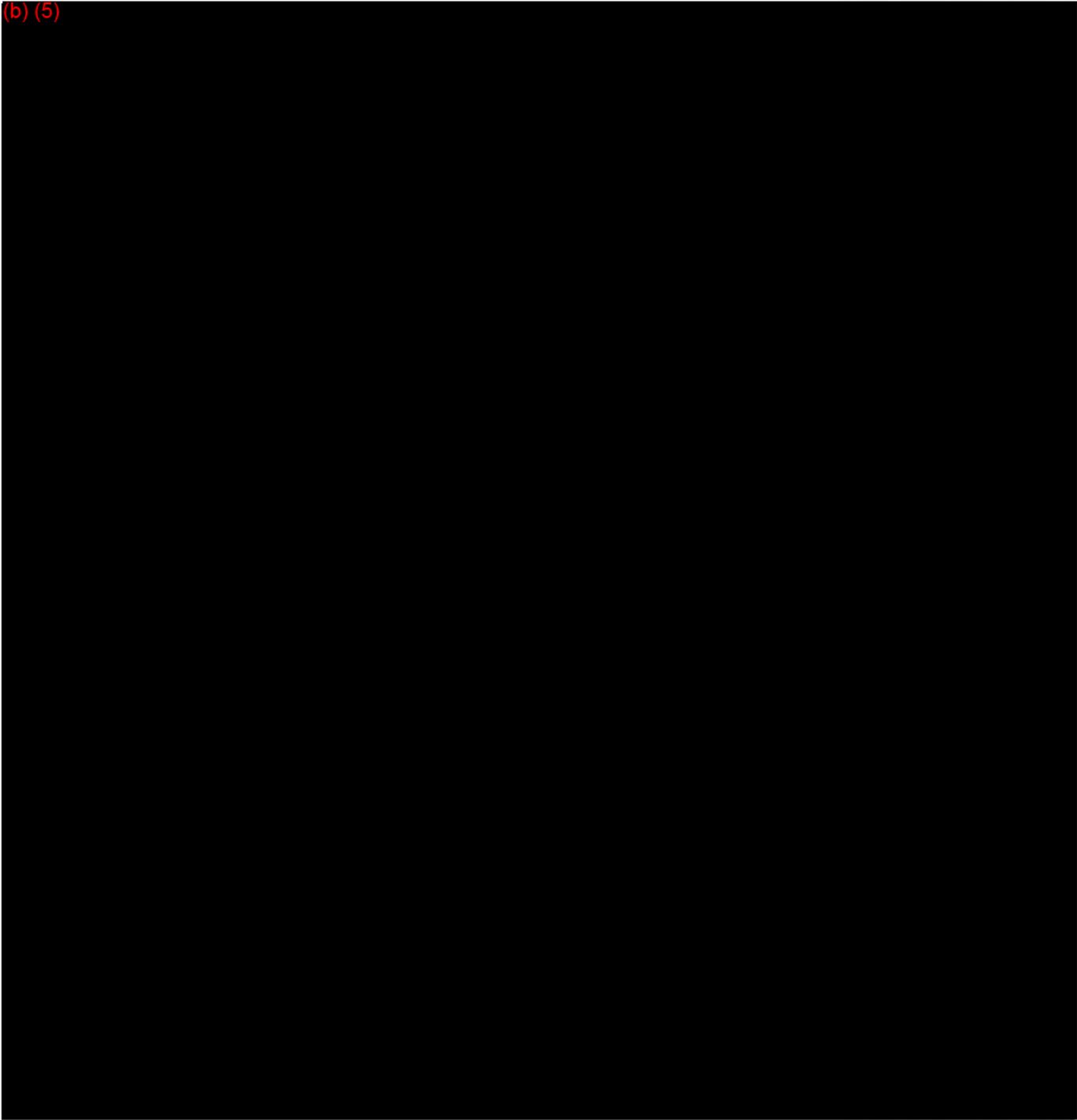
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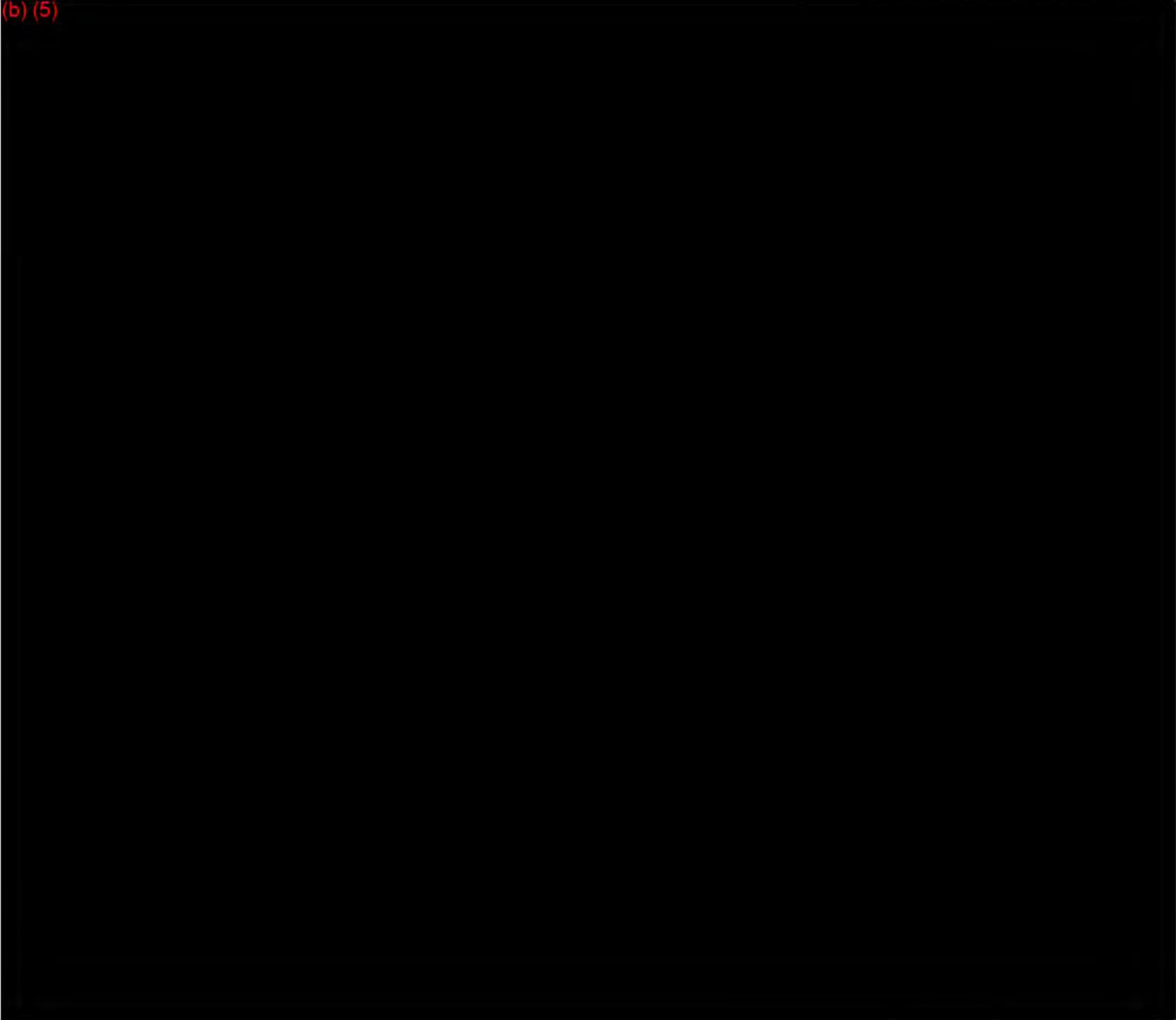
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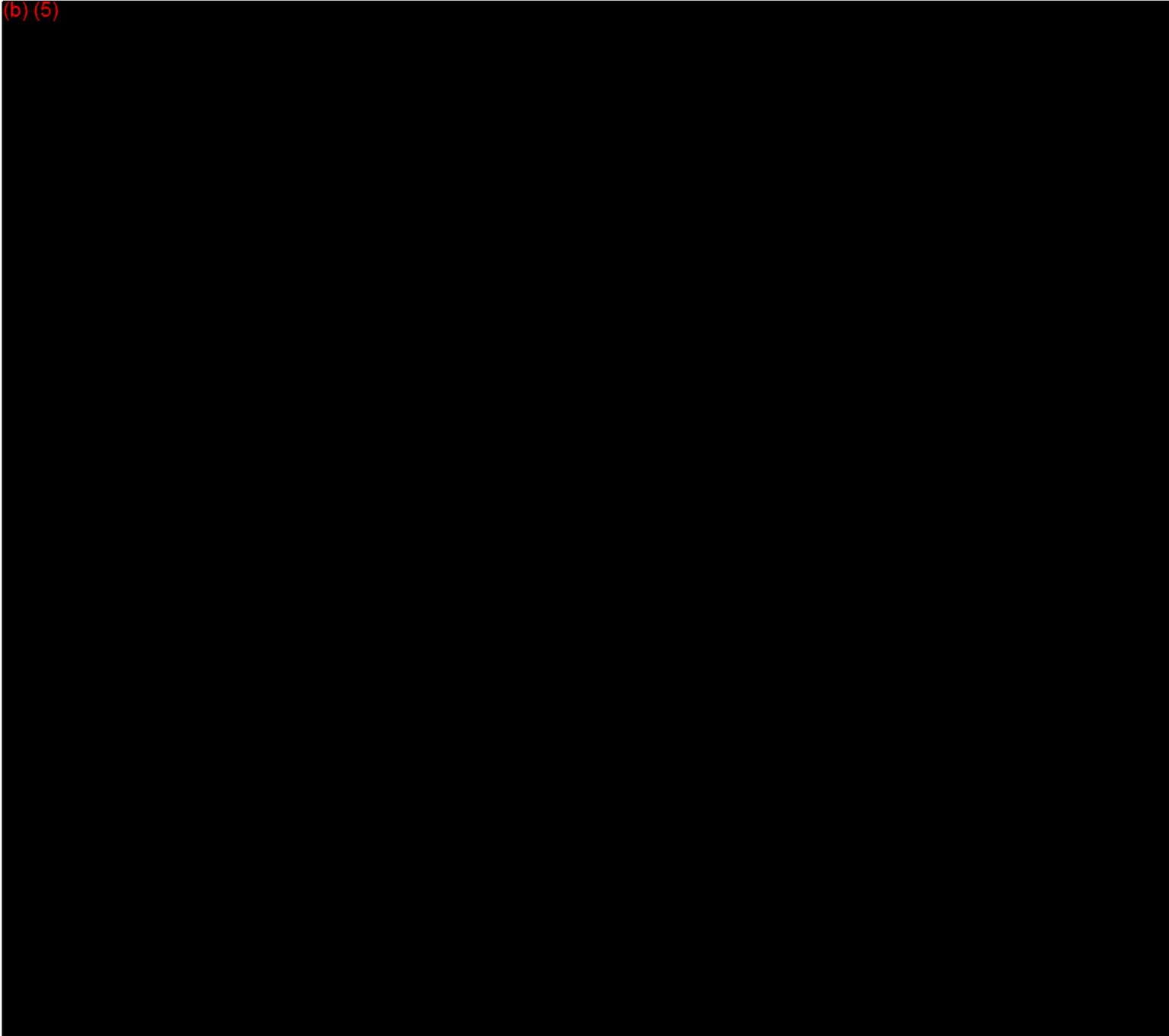
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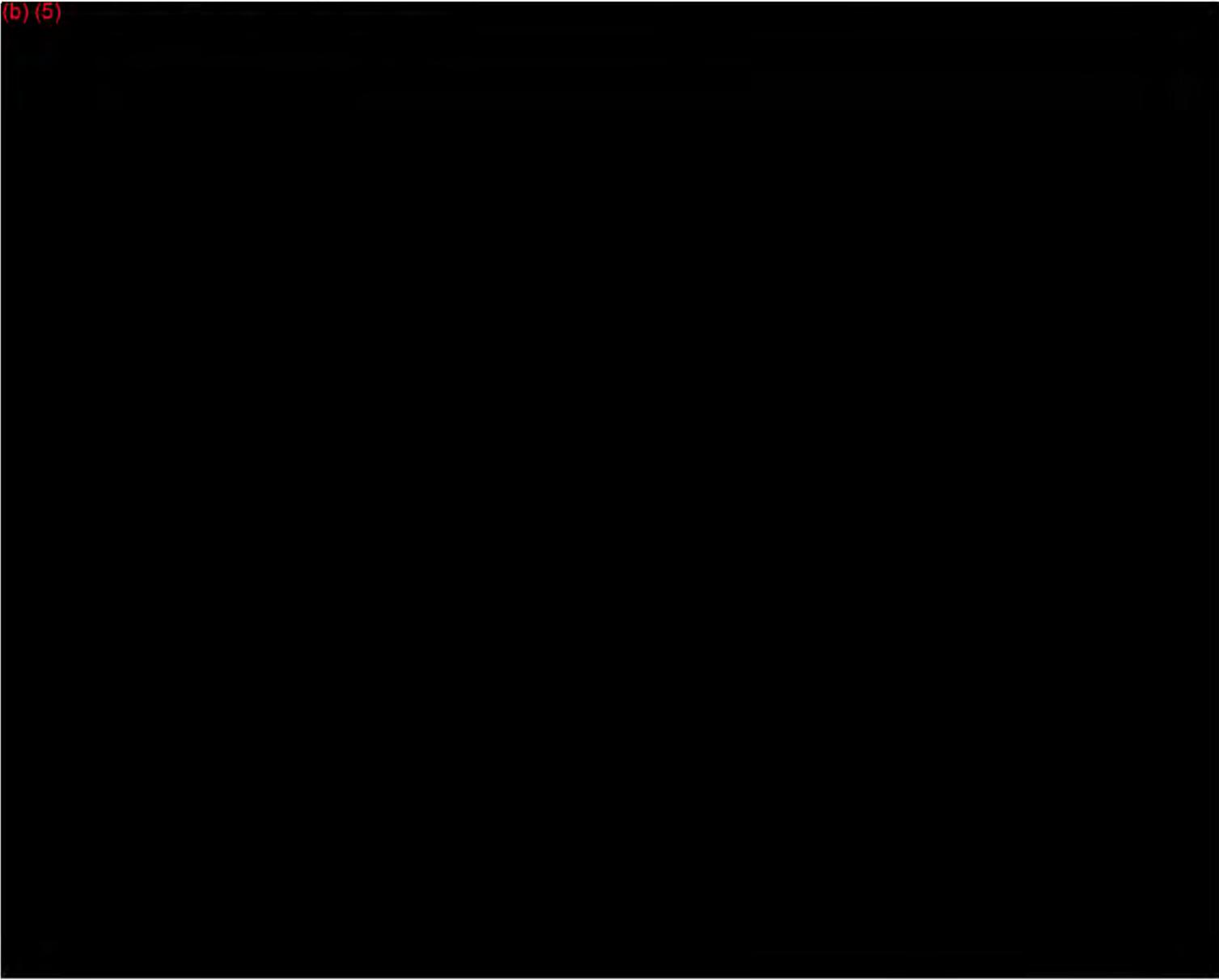
FDA NEWS RELEASE

For Immediate Release: September xx, 2016

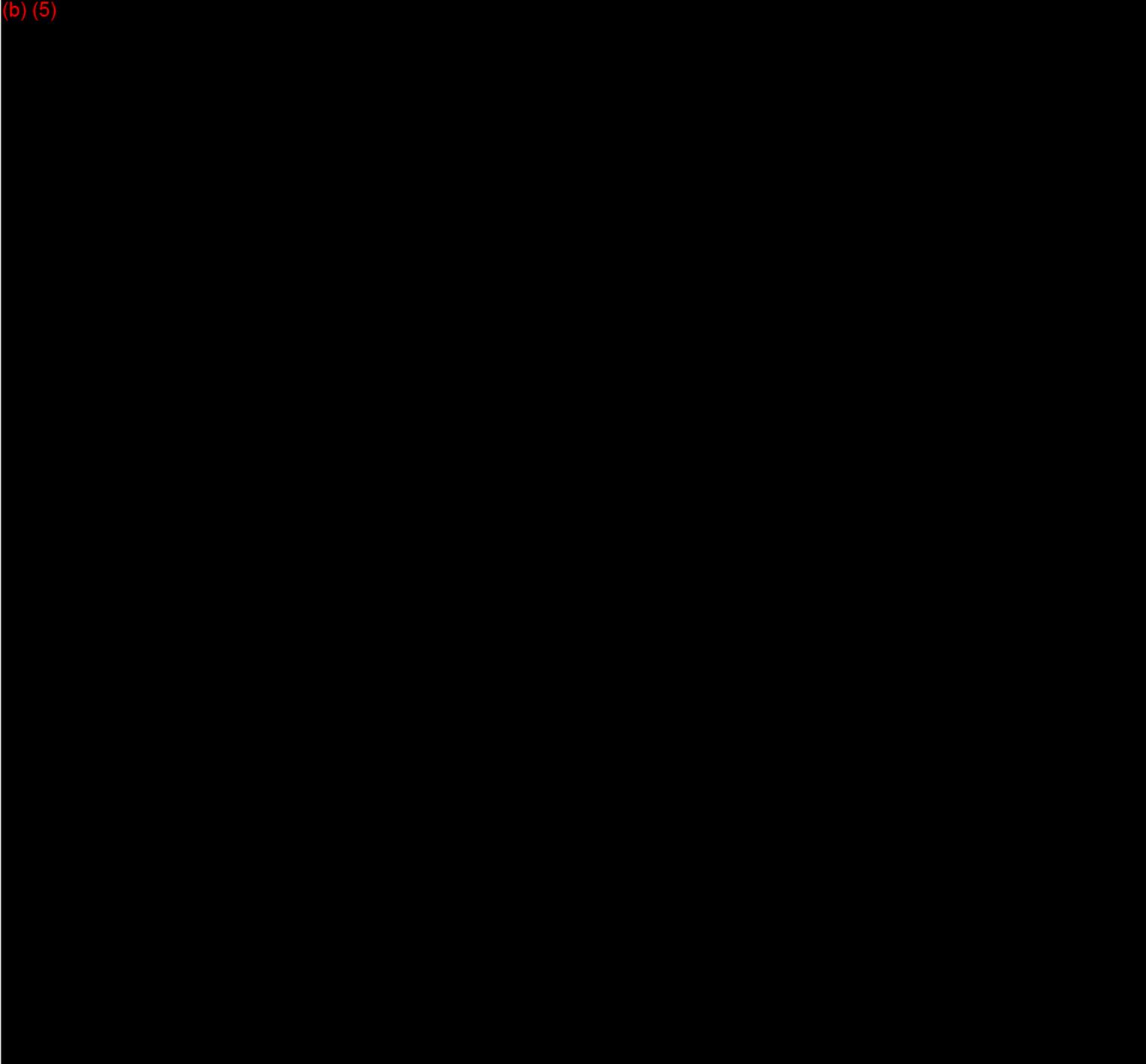
Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

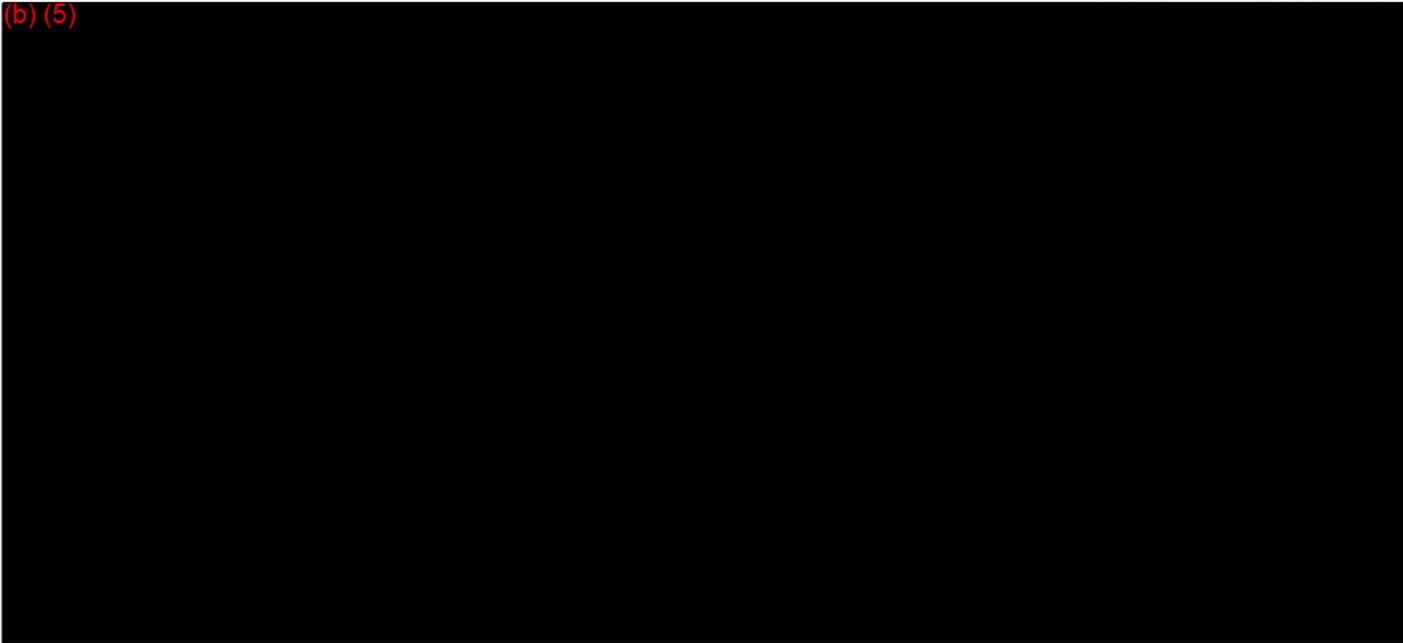
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(b) (5)

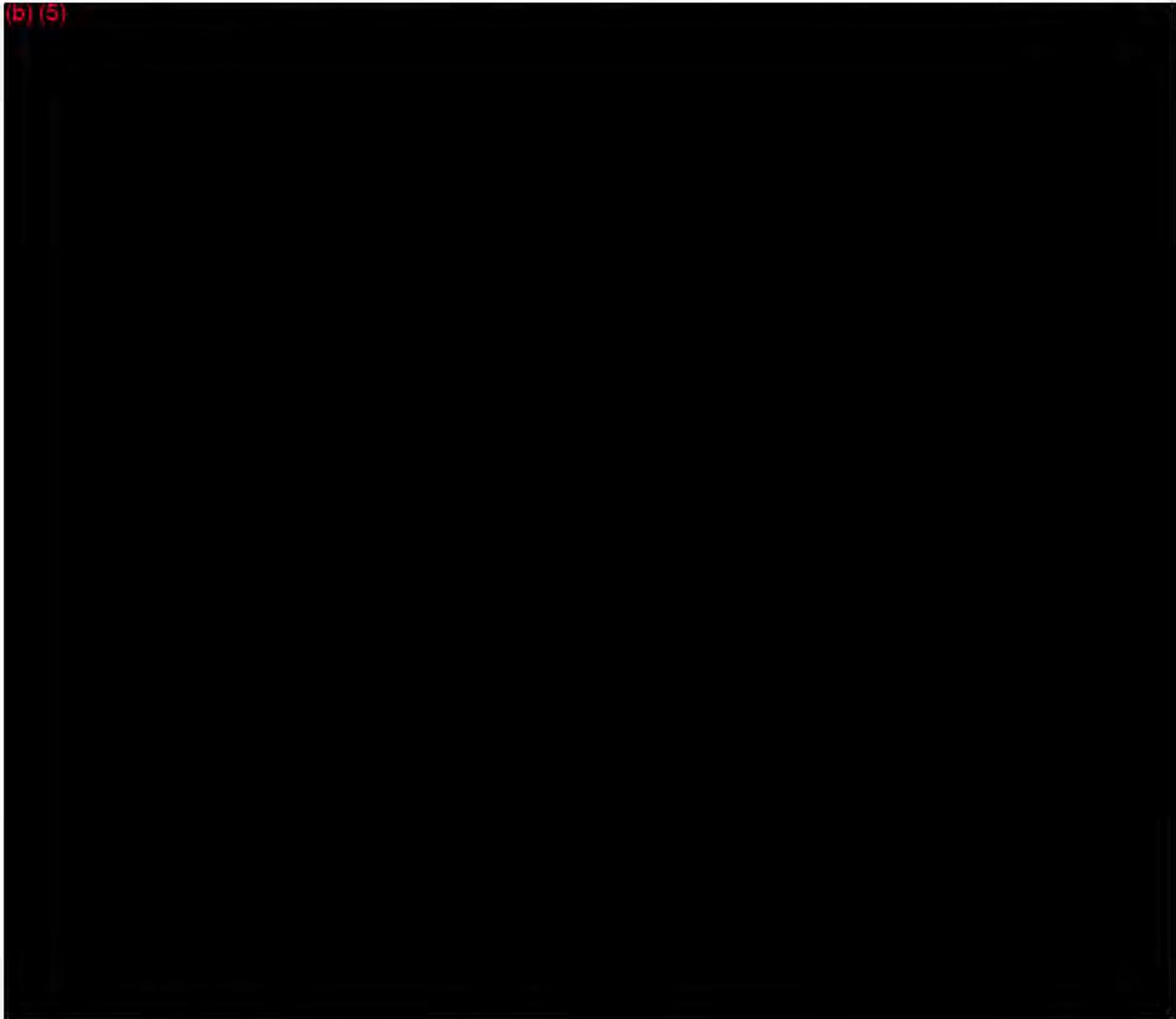


(b) (5)



From: [Chasan-Sloan, Deborah \(FDA\)](#)
To: [Sherman, Rachel](#); [Conover, Katie](#); [Rodriguez, Jennifer](#); [Kraus, Tom](#); [Dickinson, Elizabeth \(FDA\)](#); [Califf, Robert](#); [McCall, Jonathan *](#)
Subject: RE: Draft Action letters: re: NDA 206488 / eteplirsen
Date: Friday, September 09, 2016 12:04:49 AM
Attachments: [eteplirsen KMOA 9.5.16.doc](#)

(b) (5)



From: Sherman, Rachel
Sent: Thursday, September 08, 2016 6:19 PM
To: Conover, Katie; Rodriguez, Jennifer; Kraus, Tom; Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA); McCall, Jonathan *
Subject: FW: Draft Action letters: re: NDA 206488 / eteplirsen
Importance: High

Hi all,

FDAOC0001733

Please note that only a single confirmatory trial is being required.

Also, please note that voucher issue. Do we need a Q and A on that?

Thanks,
Rachel

From: Ligon, Sharnell (CDER)
Sent: Thursday, September 08, 2016 6:05 PM
To: Califf, Robert
Cc: Sherman, Rachel
Subject: FW: Draft Action letters: re: NDA 206488 / eteplirsen
Importance: High

Dear Dr. Califf,

Per your request, attached is the action draft letter with the CR letter being template language. Per Dr. Unger's response below, he was unable to notify the division about your decision. If you require any additional information, please let me know.

Kind Regards,

Sharnell

From: Unger, Ellis
Sent: Thursday, September 08, 2016 5:56 PM
To: Ligon, Sharnell (CDER)
Subject: Fw: Draft Action letters: re: NDA 206488 / eteplirsen

Here it is. I wasn't able to talk with Billy Dunn this evening, and so the Division doesn't know about Dr. Califf's decision.

Sent from my BlackBerry.

From: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Sent: Thursday, September 8, 2016 5:18 PM
To: Unger, Ellis
Cc: Choy, Fannie (Yuet)
Subject: Draft Action letters: re: NDA 206488 / eteplirsen

Dr. Unger

Here're the draft action letters. CR letter is just template language.

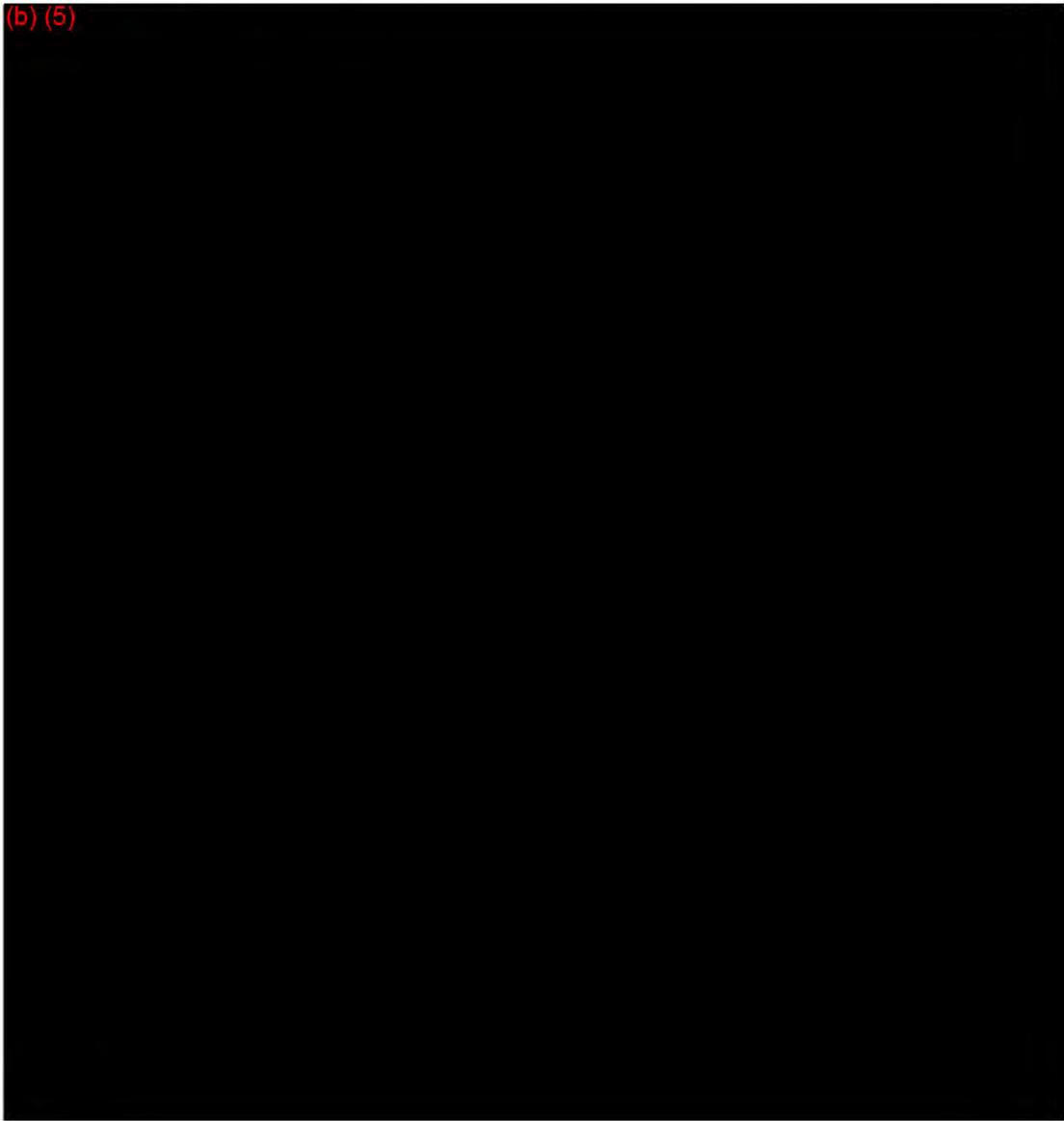
Accelerated approval letter has been cleared by SRT for all the PMCs/PMRs. Eric reviewed it back in 7/1. We added the PMCs/PMRs and Sally reviewed the letter with the revised dates, etc.

Thanks
Fannie

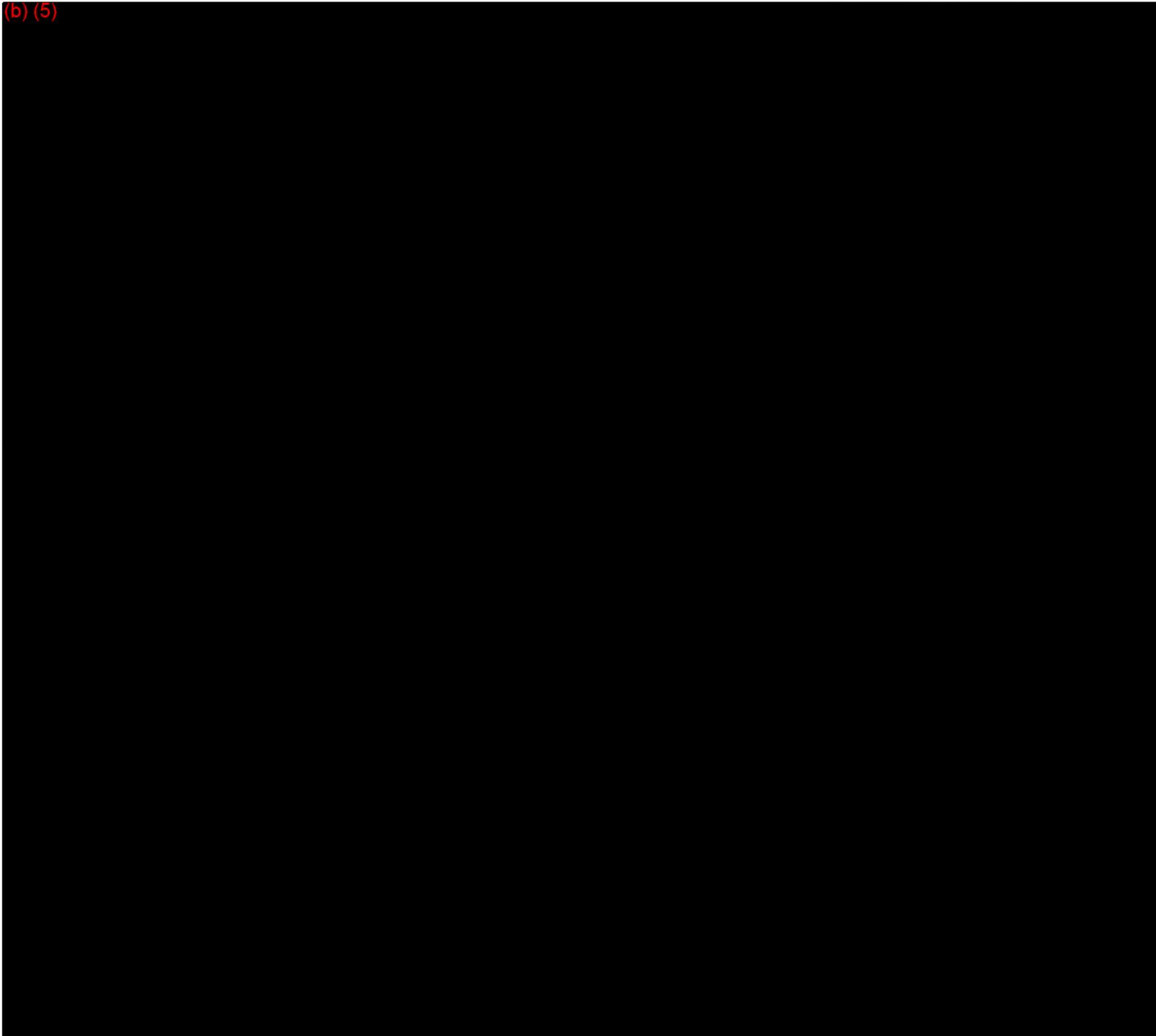
**Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat
Duchenne muscular dystrophy**

Target date: September 2016

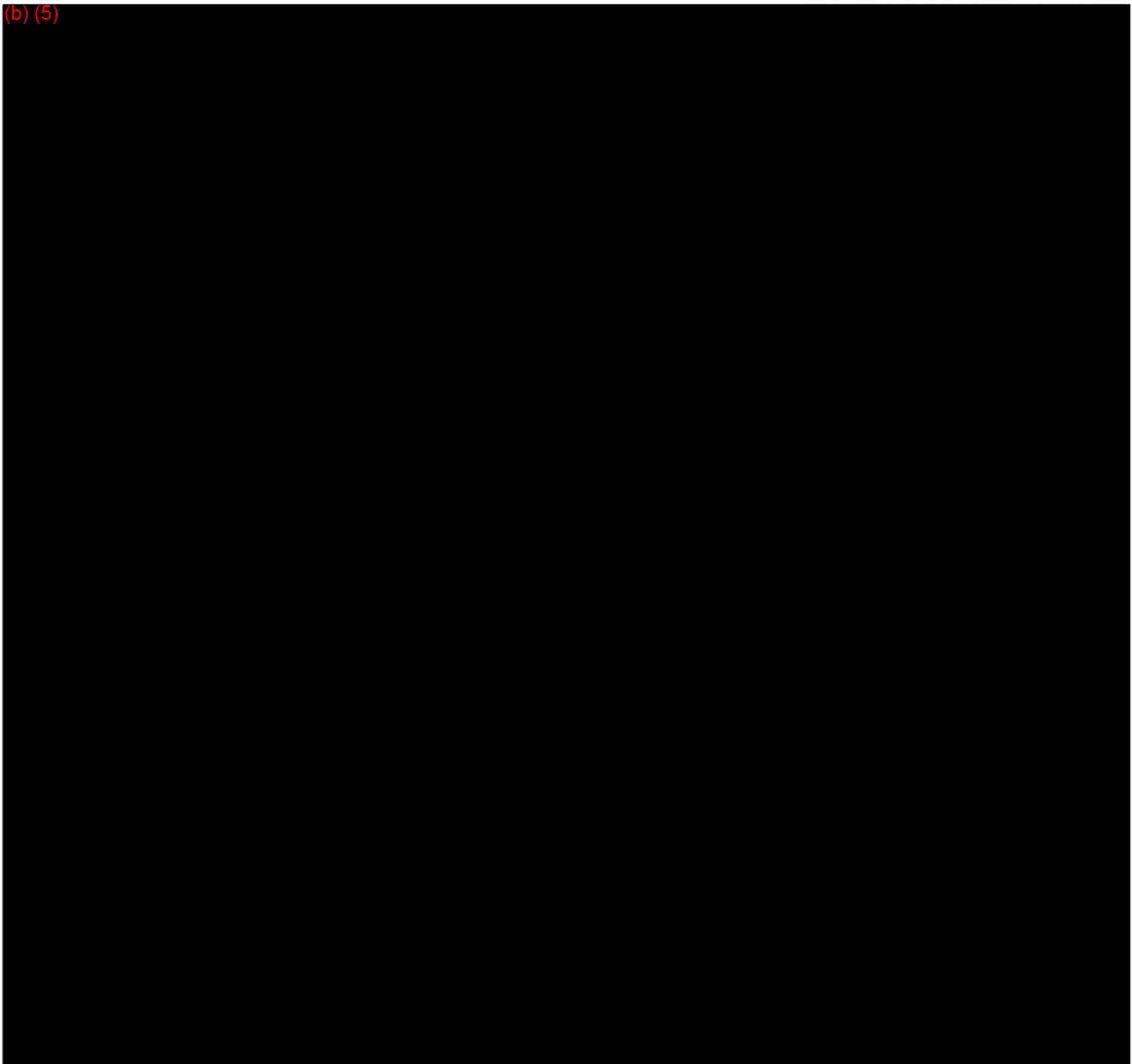
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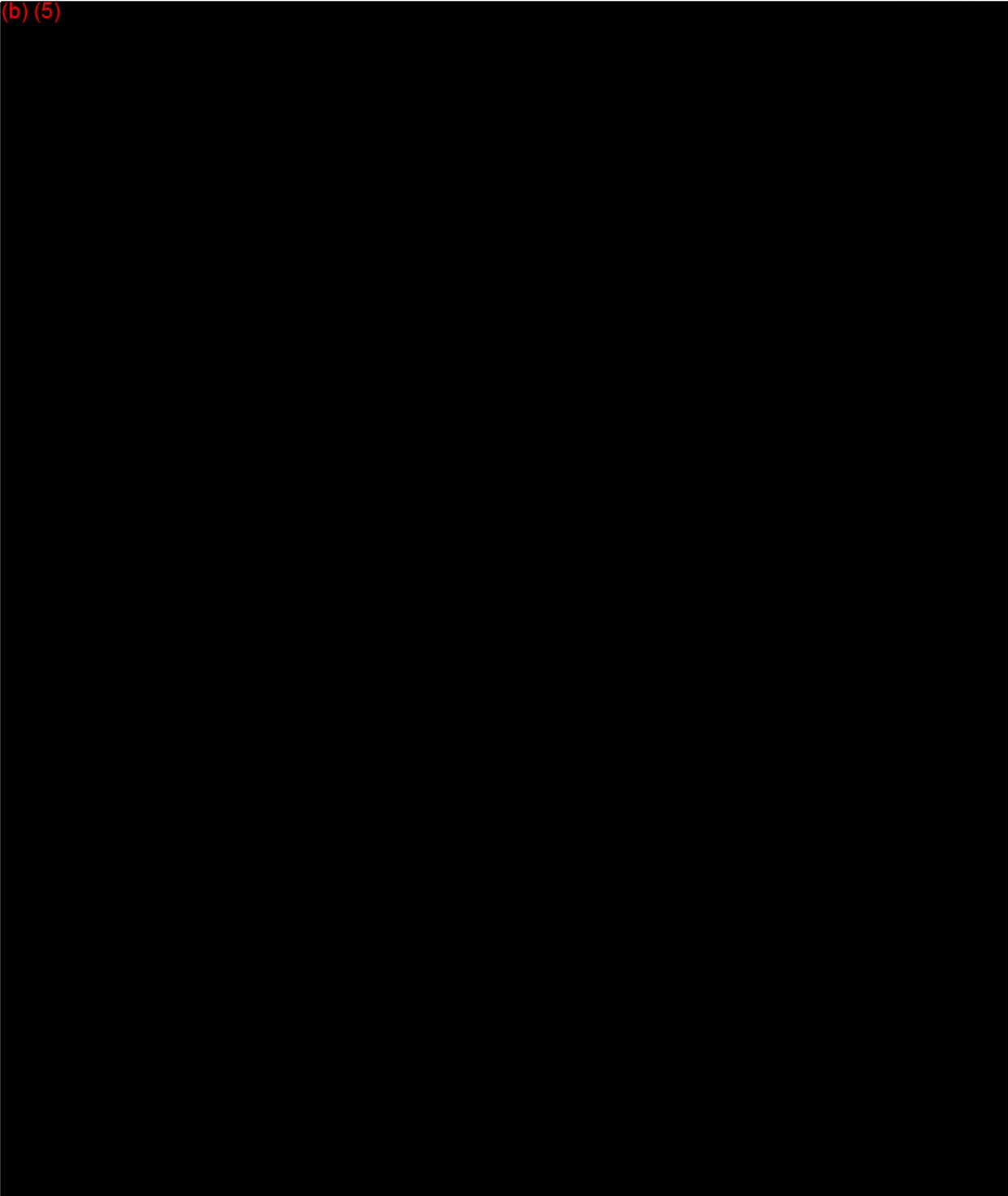
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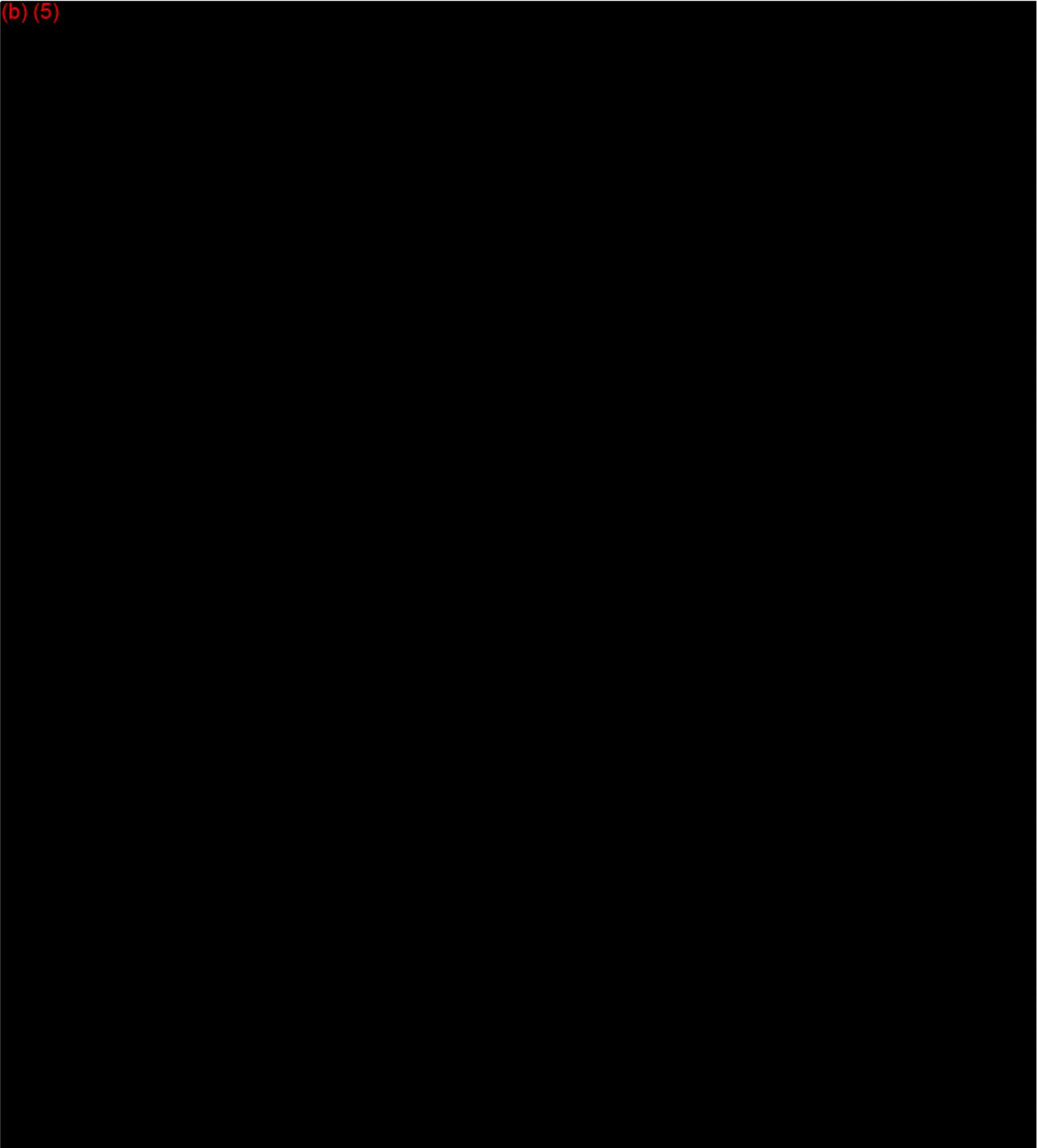
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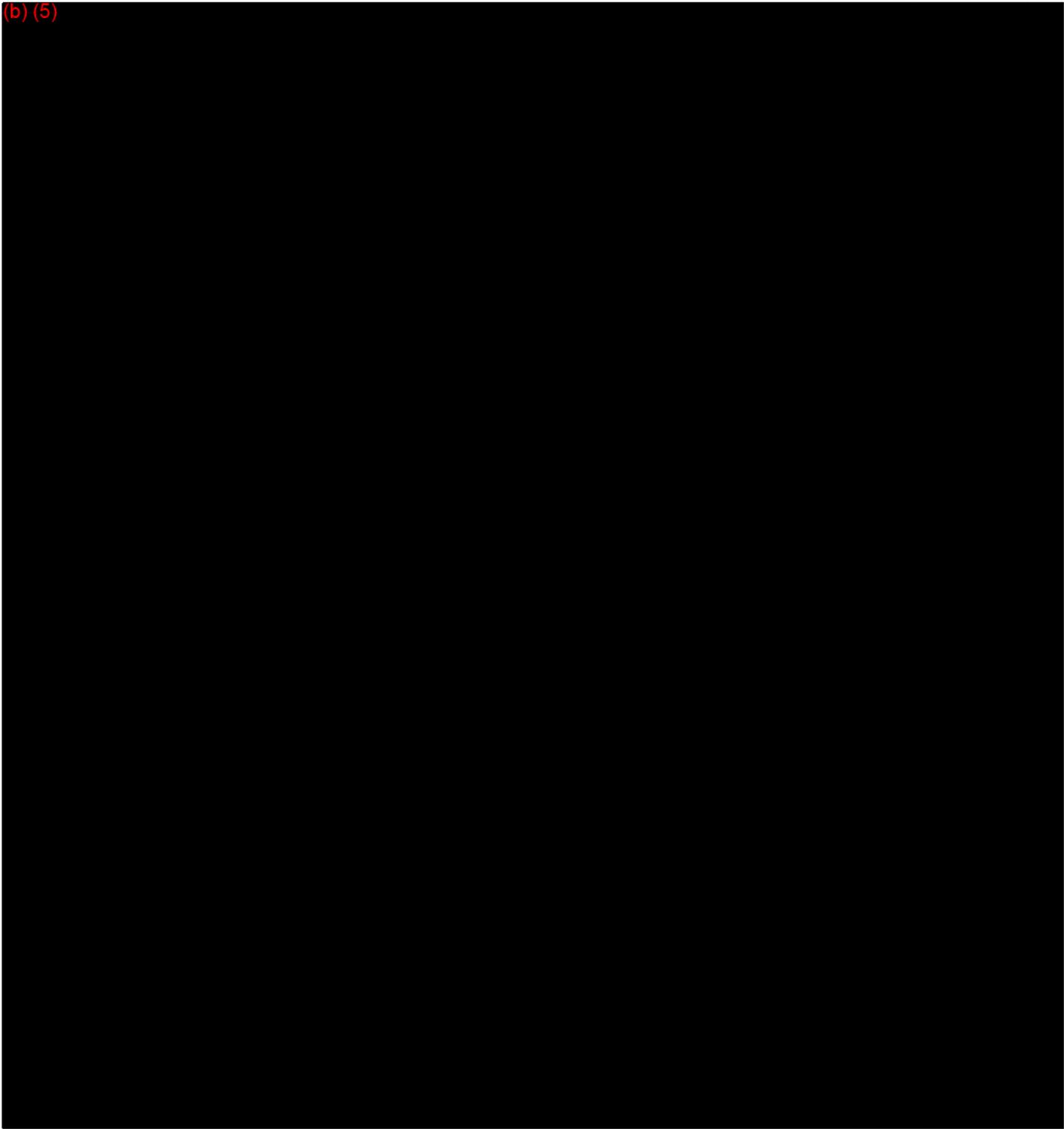
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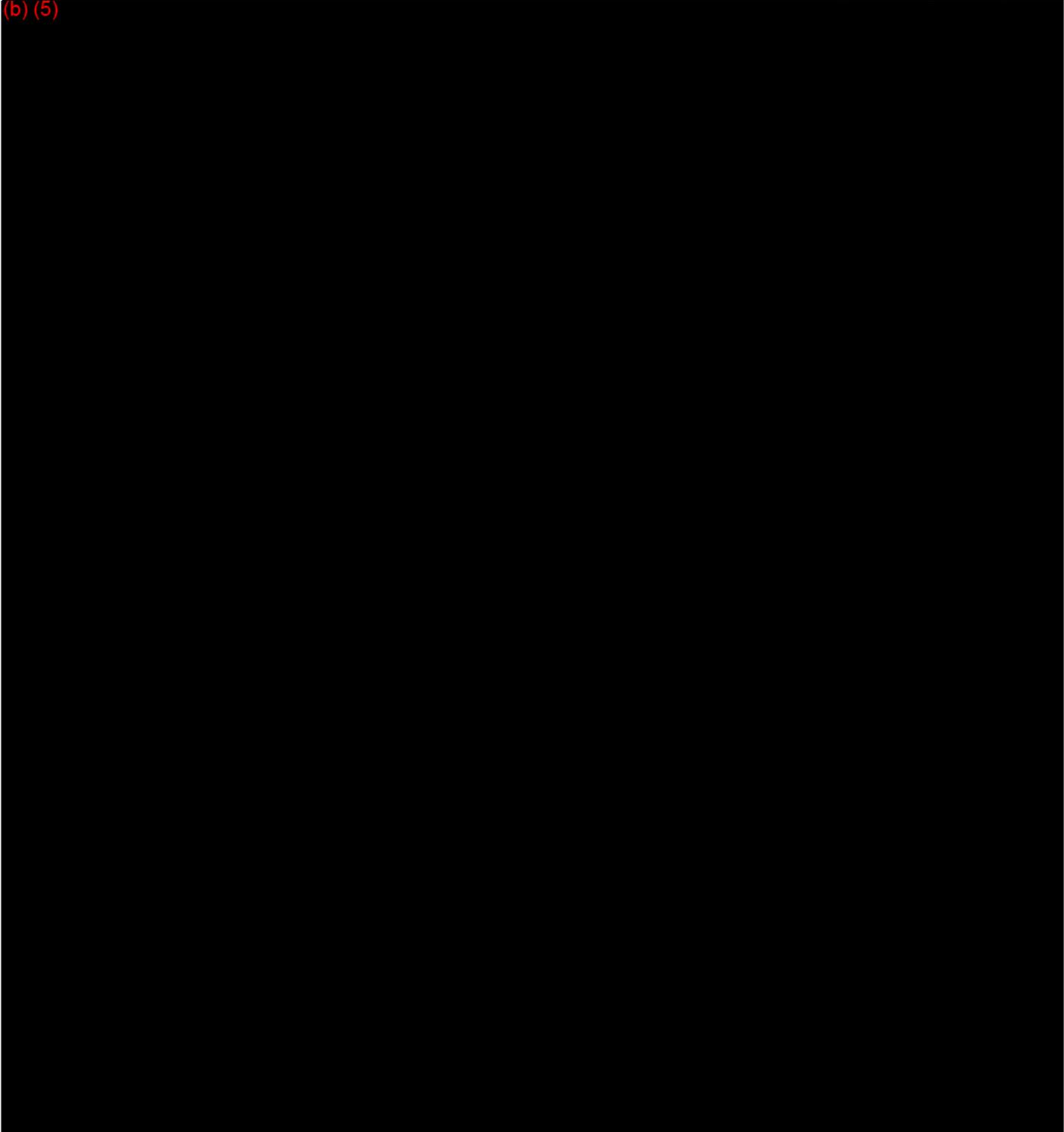
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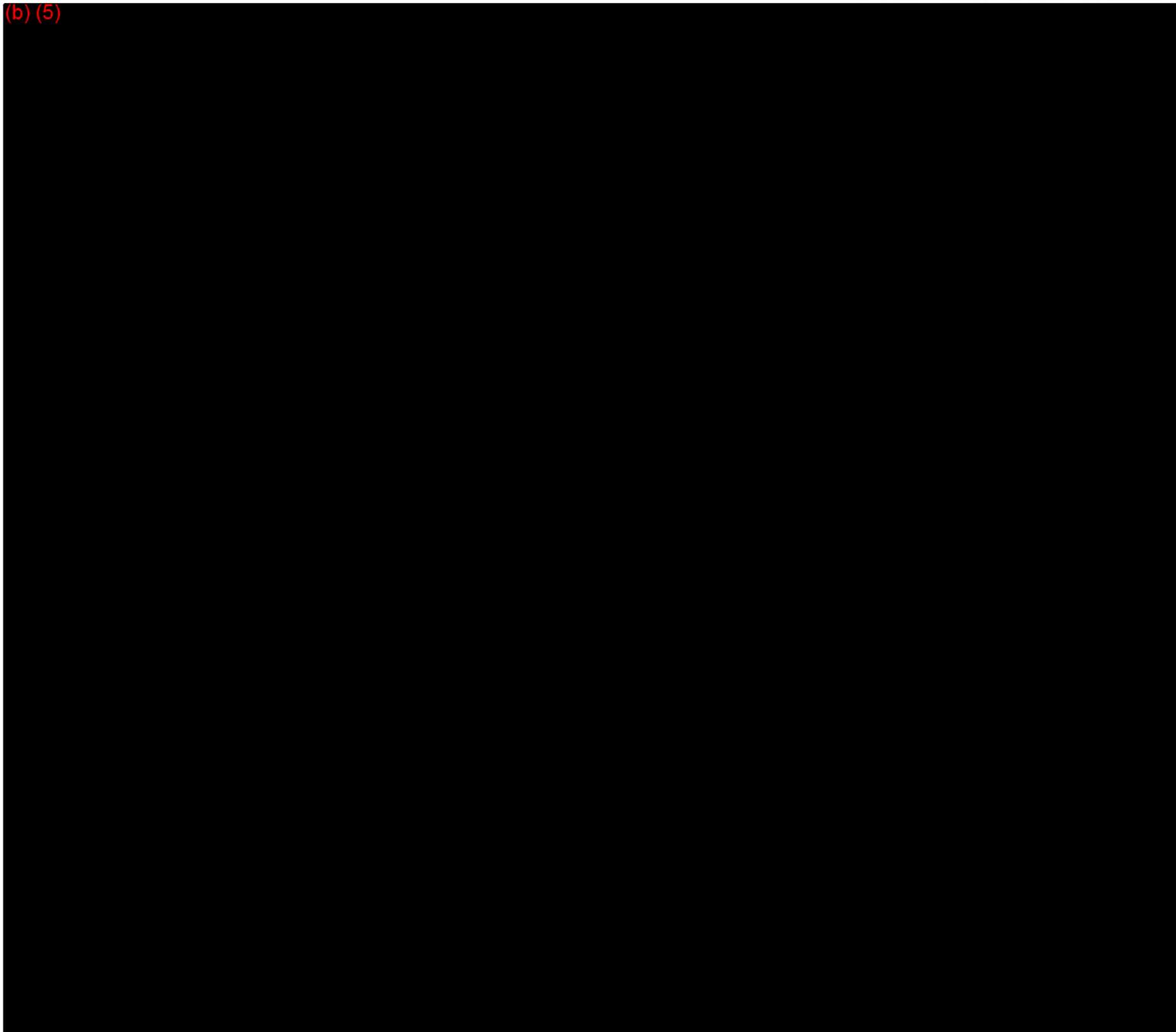
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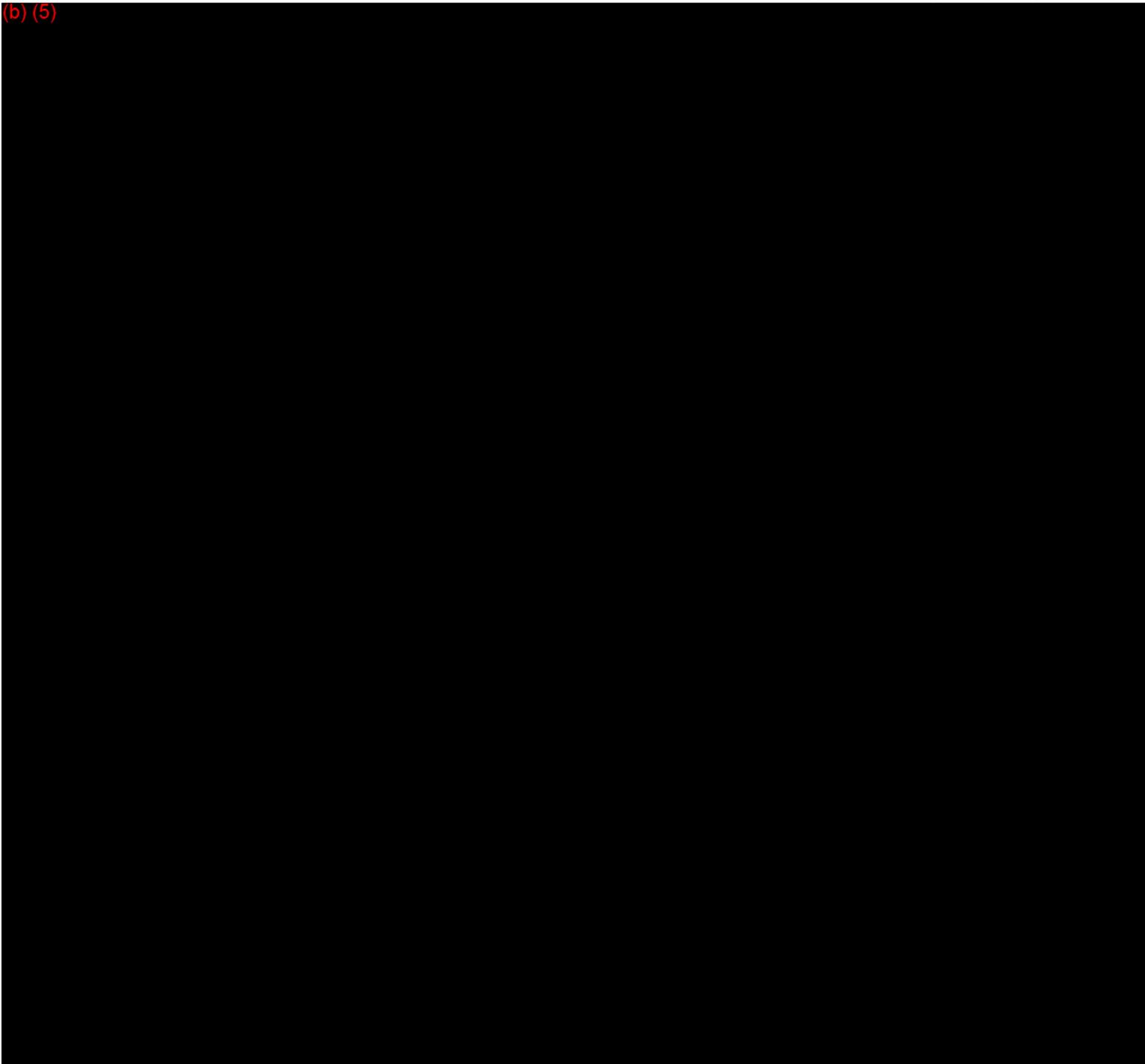
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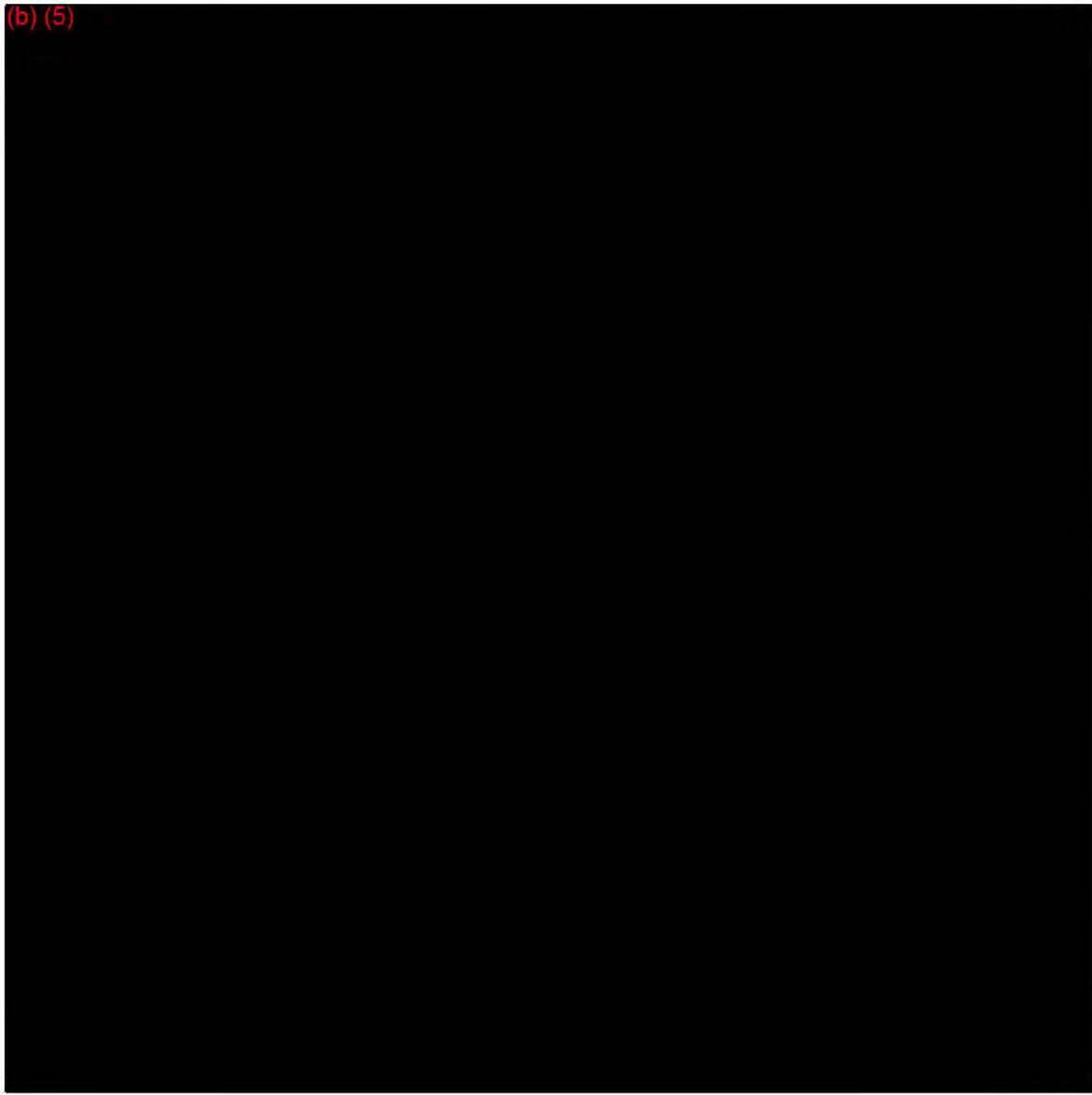
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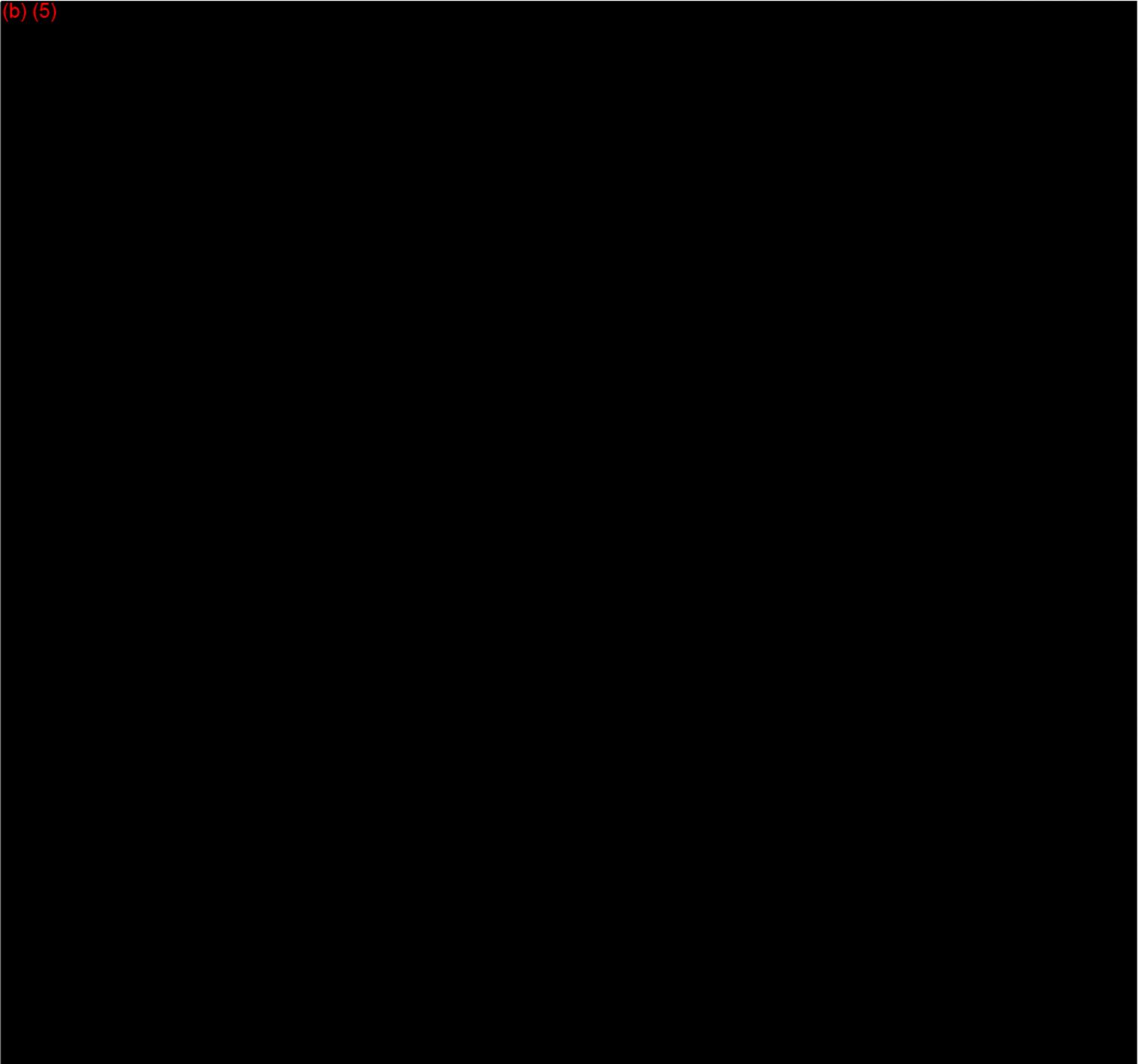
**Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat
Duchenne muscular dystrophy**

Target date: September 2016

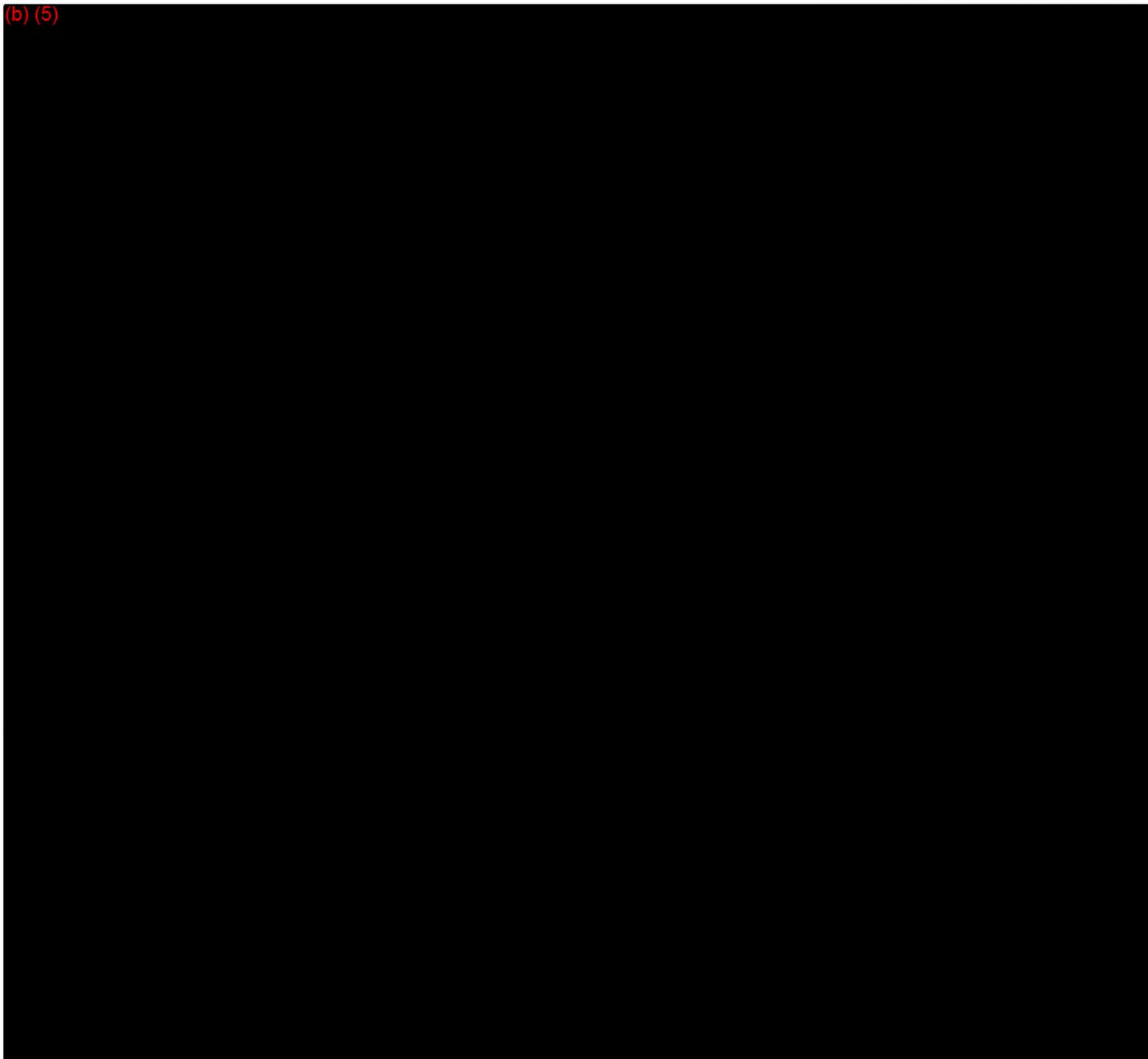
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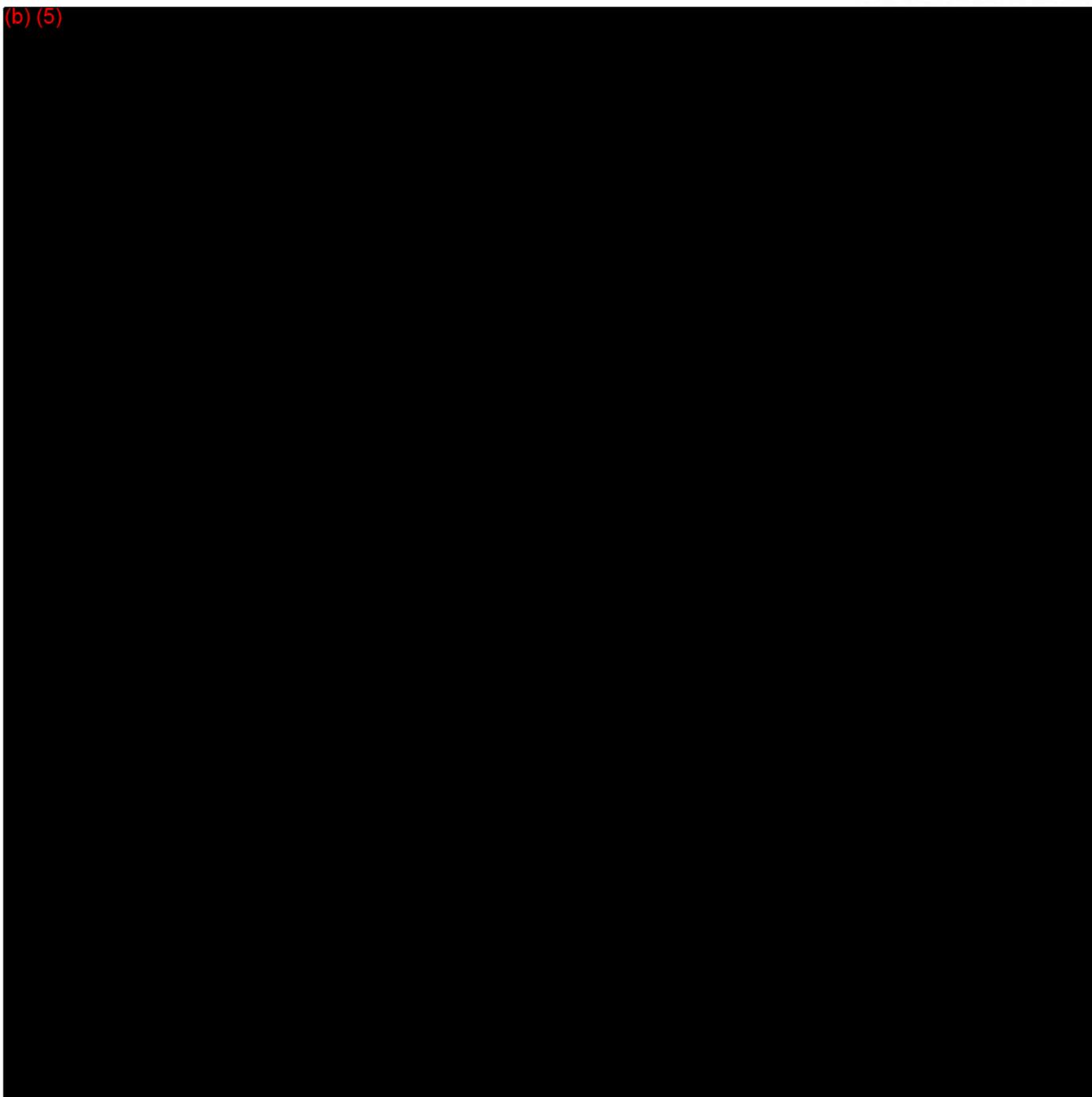
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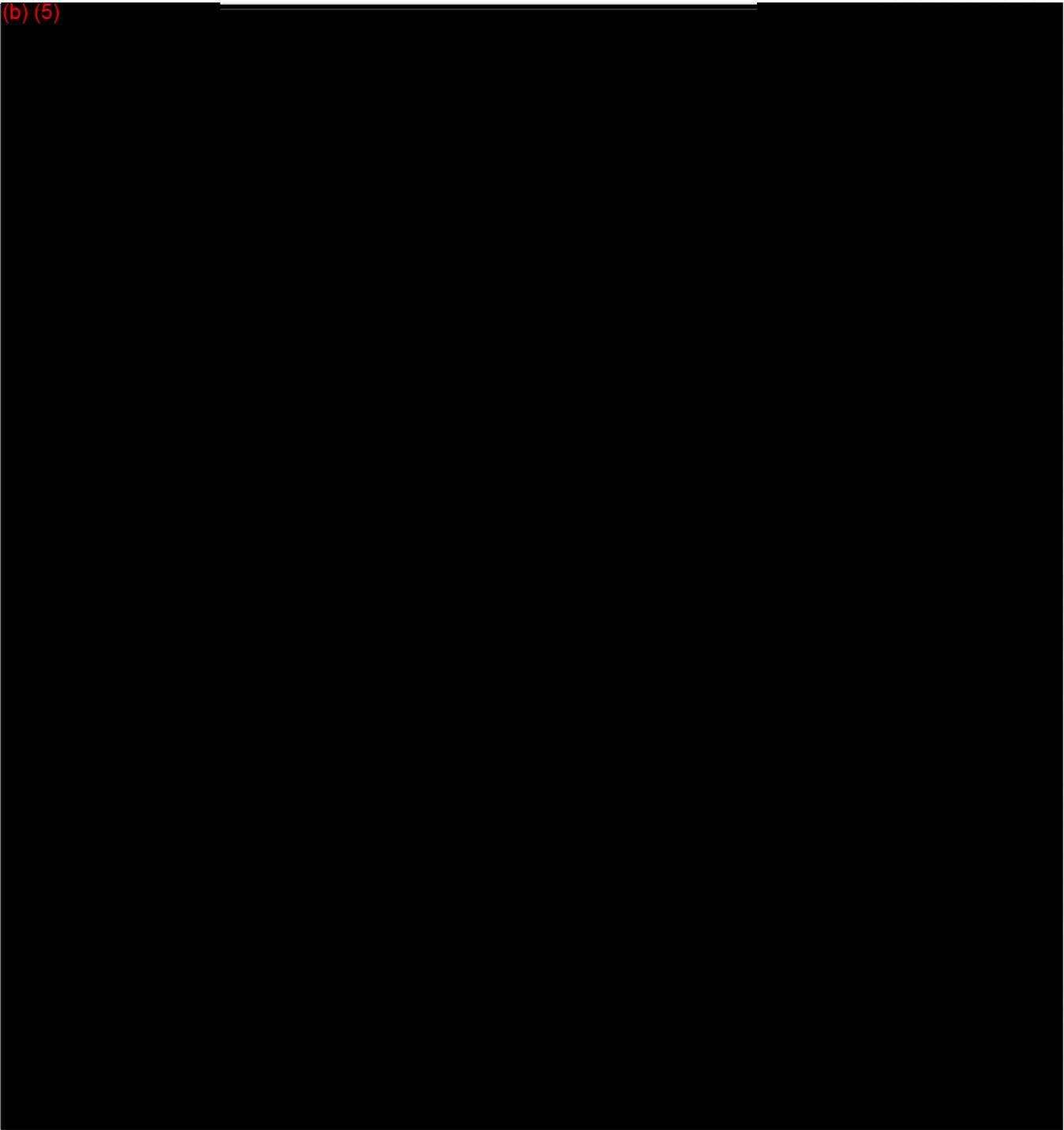
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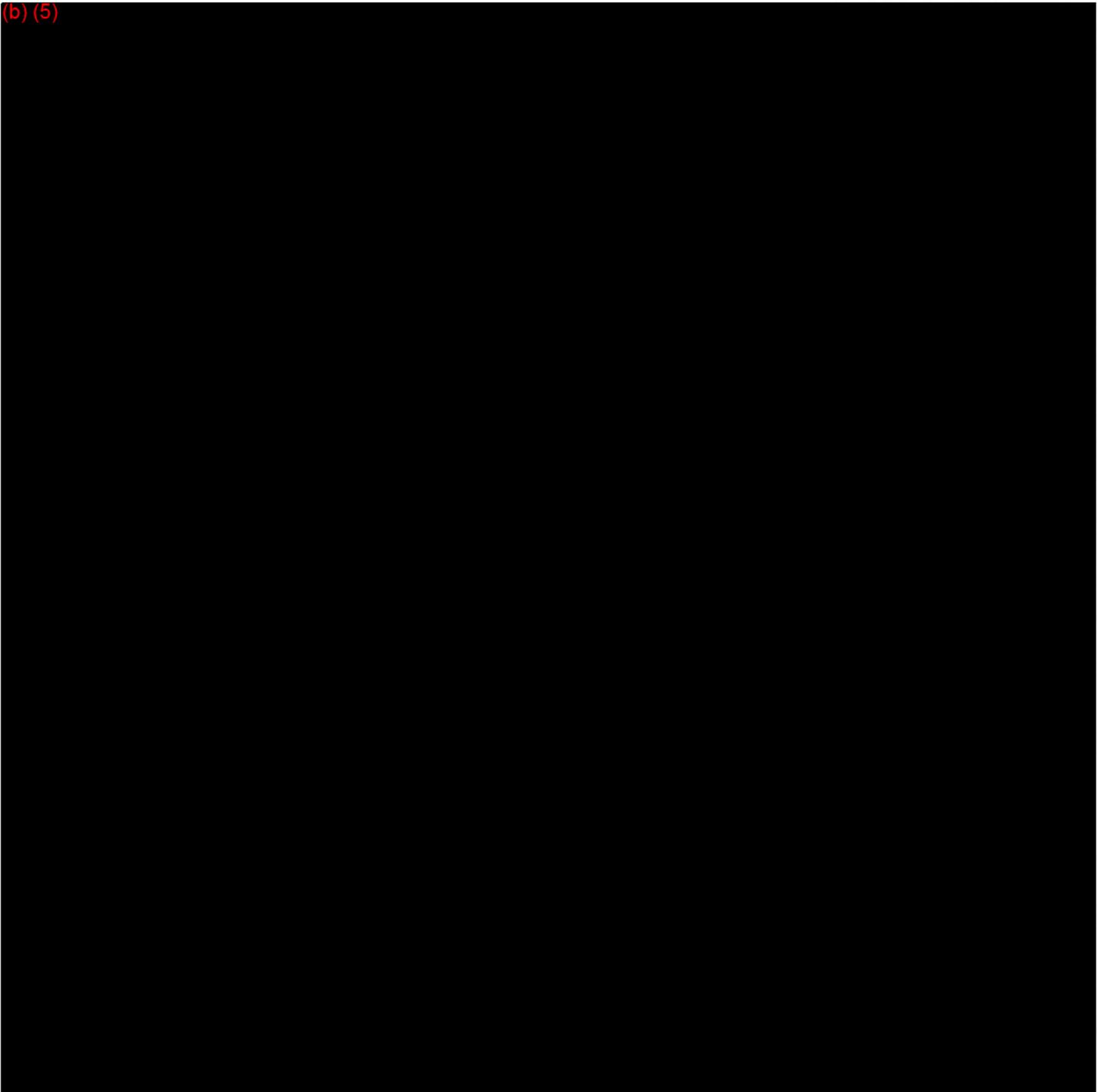
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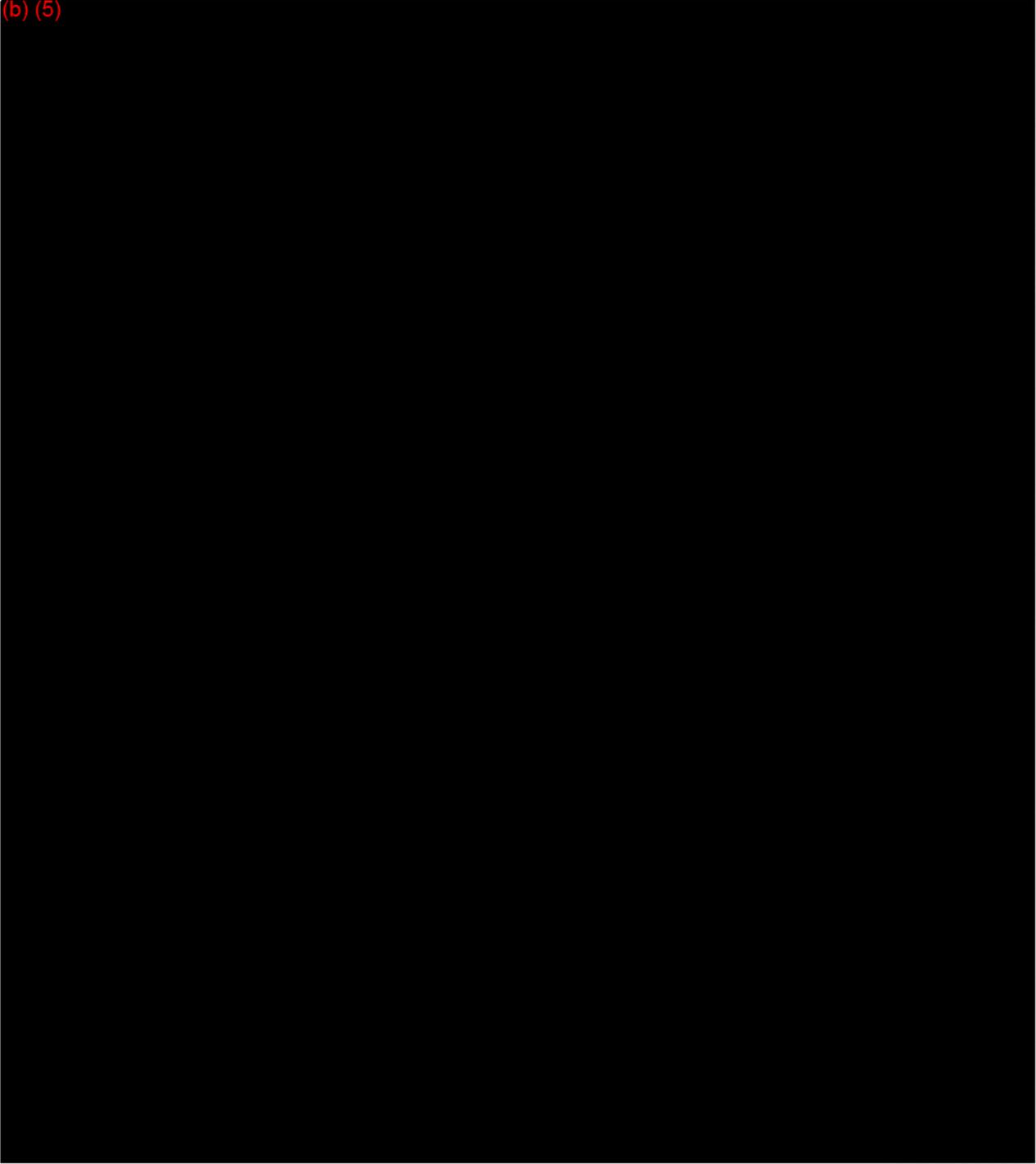
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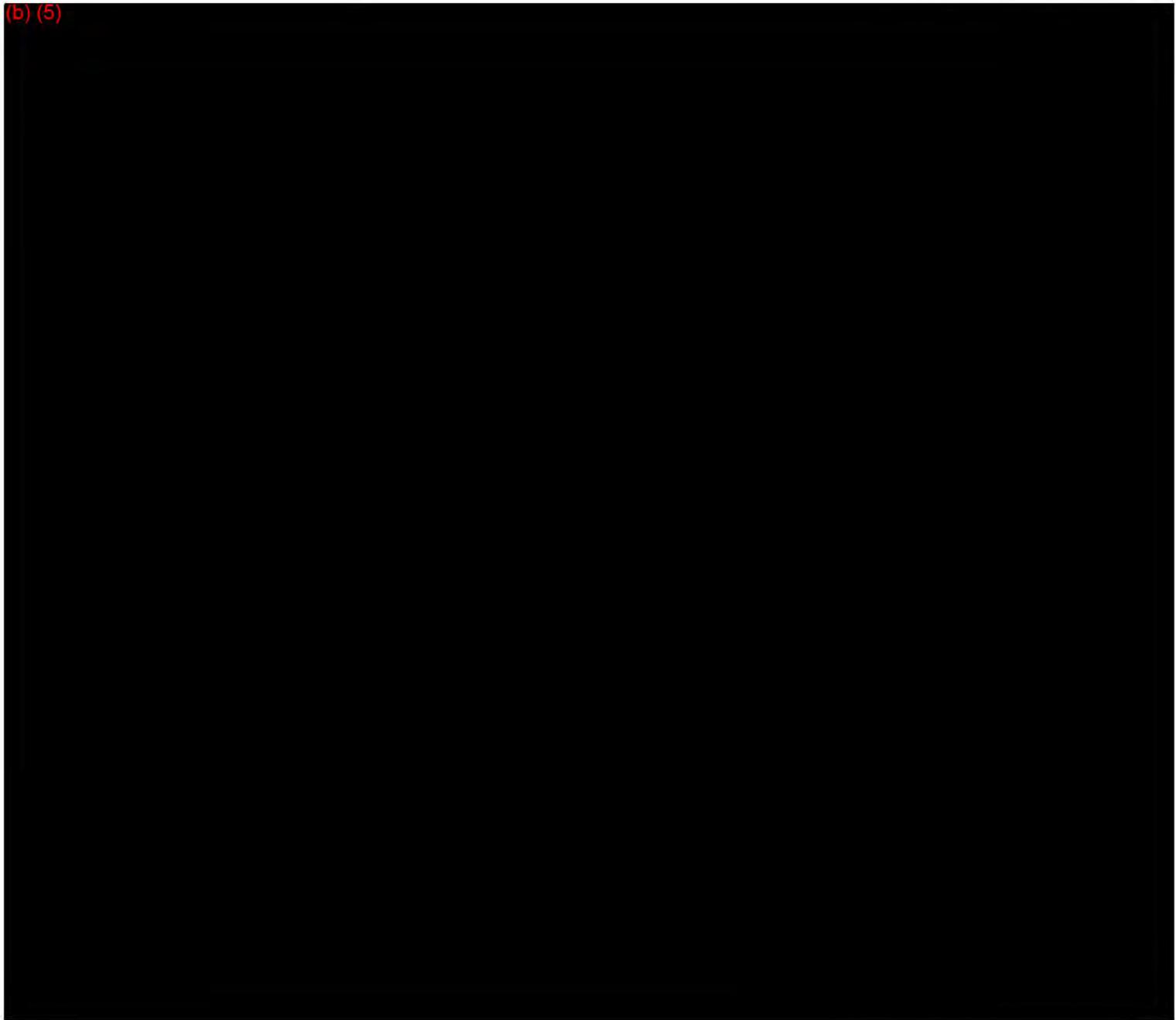
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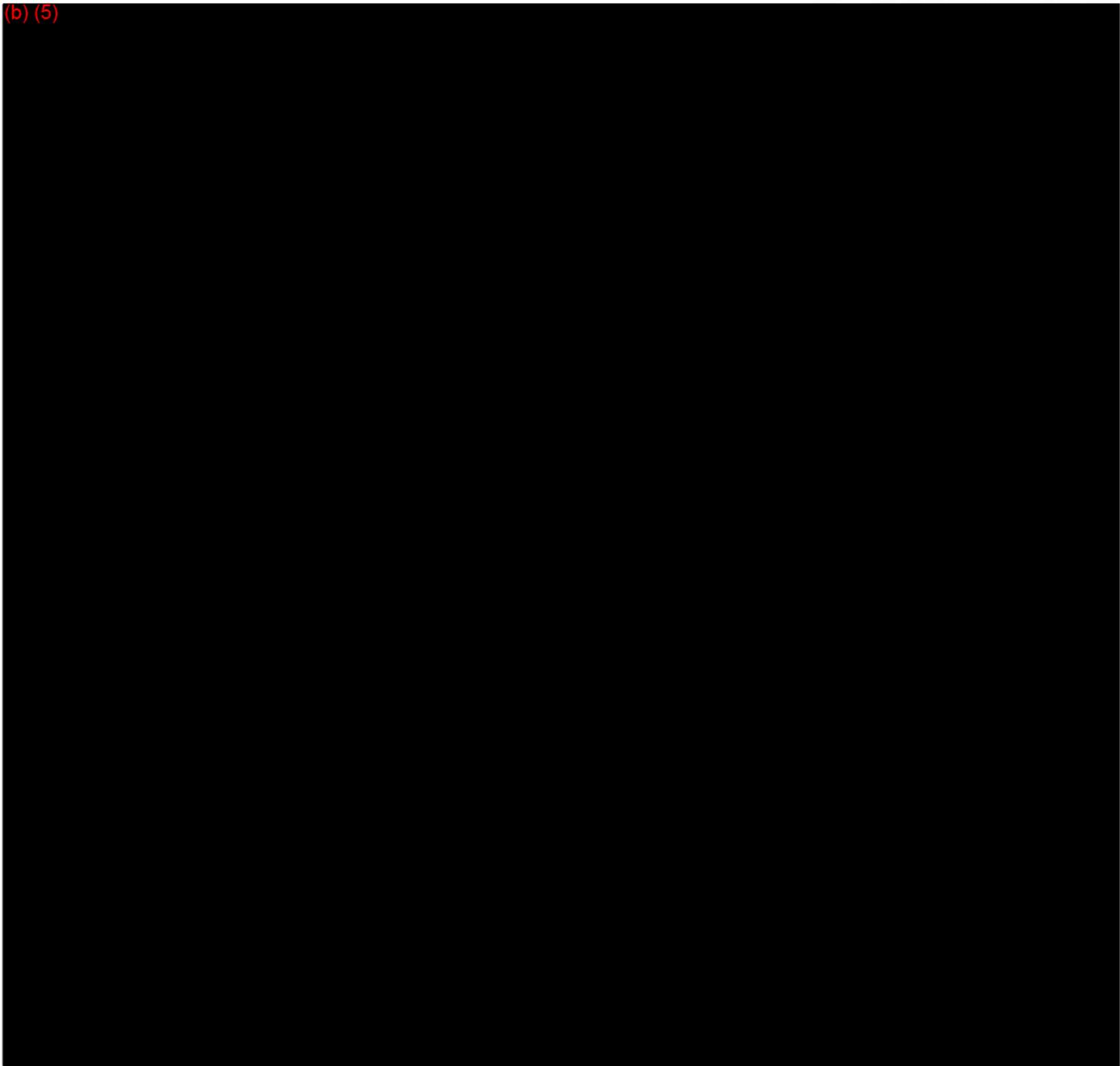
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(b) (5)



(b) (5)



From: [Chasan-Sloan, Deborah \(FDA\)](#)
To: [Rodriguez, Jennifer](#); [Califf, Robert](#); [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#)
Cc: [Conover, Katie](#)
Subject: RE: DR. CALIFF PLEASE SEE: Phase I and II Comms--timing
Date: Friday, September 09, 2016 5:20:53 PM
Attachments: [Phase II approval reactive QA 090916\(occ\).doc](#)
[image001.png](#)

(b) (5)



Thanks,
Deborah

From: Rodriguez, Jennifer
Sent: Friday, September 09, 2016 12:52 PM
To: Califf, Robert; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Cc: Conover, Katie
Subject: RE: DR. CALIFF PLEASE SEE: Phase I and II Comms--timing

Dr. Califf (and team)-

Attached please find an updated version of the Phase II comms. We have addressed your comment and added two QAs, including one to your question about whether (b) (5)





On the remaining questions you noted, we believe they are addressed in the Phase I QA, as noted below. However, if there are any you feel we need to address more specifically – please let us know.

(b) (5)



Thanks for your review. I have reattached the Phase I comms for your convenience.

Best,

Jen

From: Califf, Robert
Sent: Friday, September 09, 2016 7:01 AM
To: Rodriguez, Jennifer; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Cc: Conover, Katie
Subject: RE: DR. CALIFF PLEASE SEE: Phase I and II Comms--timing

Jen and team,

I've gotten caught in a time squeeze as I was booked through 9 pm yesterday and have several events today that I just got reading materials for last night. I've read the documents and I think we're close, but will need to review more carefully tomorrow when nothing is on my calendar. These are obviously tight answers, and I agree we need to be tight on the specifics of this case, but there are general questions that deserve discussion for the future.

(b) (5)



I'm downtown all AM and at WH in afternoon, but will be available all weekend.

rmc

From: Rodriguez, Jennifer
Sent: Thursday, September 08, 2016 4:44 PM
To: Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert
Cc: Conover, Katie
Subject: DR. CALIFF PLEASE SEE: Phase I and II Comms

FDAOC0001755

Dr. Califf,

Attached please find the current version of the Phase I and II documents for your review.

Best,

Jen

From: Sherman, Rachel

Sent: Thursday, September 08, 2016 4:34 PM

To: Chasan-Sloan, Deborah (FDA); Rodriguez, Jennifer; Dickinson, Elizabeth (FDA); Califf, Robert

Cc: Conover, Katie

Subject: RE: PLEASE SEE: Phase I and II Comms

Great, thanks!

This version should go into a consolidated email to Rob.

From: Chasan-Sloan, Deborah (FDA)

Sent: Thursday, September 08, 2016 4:22 PM

To: Sherman, Rachel; Rodriguez, Jennifer; Dickinson, Elizabeth (FDA); Califf, Robert

Cc: Conover, Katie

Subject: RE: PLEASE SEE: Phase I and II Comms

(b) (5)

A large black rectangular redaction box covers the content of the email body between the second and third email headers.

Thanks,

Deborah

From: Sherman, Rachel

Sent: Thursday, September 08, 2016 3:47 PM

To: Rodriguez, Jennifer; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Califf, Robert

Cc: Conover, Katie

Subject: RE: PLEASE SEE: Phase I and II Comms

Hi all,

Please see some suggestions on phase II. OCC, please opine on comment 6.

Thanks!

Rachel

From: Rodriguez, Jennifer

Sent: Thursday, September 08, 2016 3:26 PM

To: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Califf, Robert

Cc: Conover, Katie

Subject: PLEASE SEE: Phase I and II Comms

All,

Attached for review, please find the Phase II reactive QA. This document reflects initial edits from OCC. Please review and provide any edits ASAP. Also, you will note that we have one pending response in which we need to work with Lu and her team to address. Can you please let us know if it is OK to reach out to her at this time?

In addition, I am reattaching the Phase II materials – in which, I believe we are awaiting Dr. Califf’s final sign off.

Dr. Califf – please let us know when we can expect your review, so that we can frame out the remaining review timeline.

Best,
Jen

Jennifer Rodriguez

Deputy Director of Strategy, OMA

Office of Media Affairs

Office of External Affairs

U.S. Food and Drug Administration

Tel: 301-796-8232 / Cell: 202-763-9073

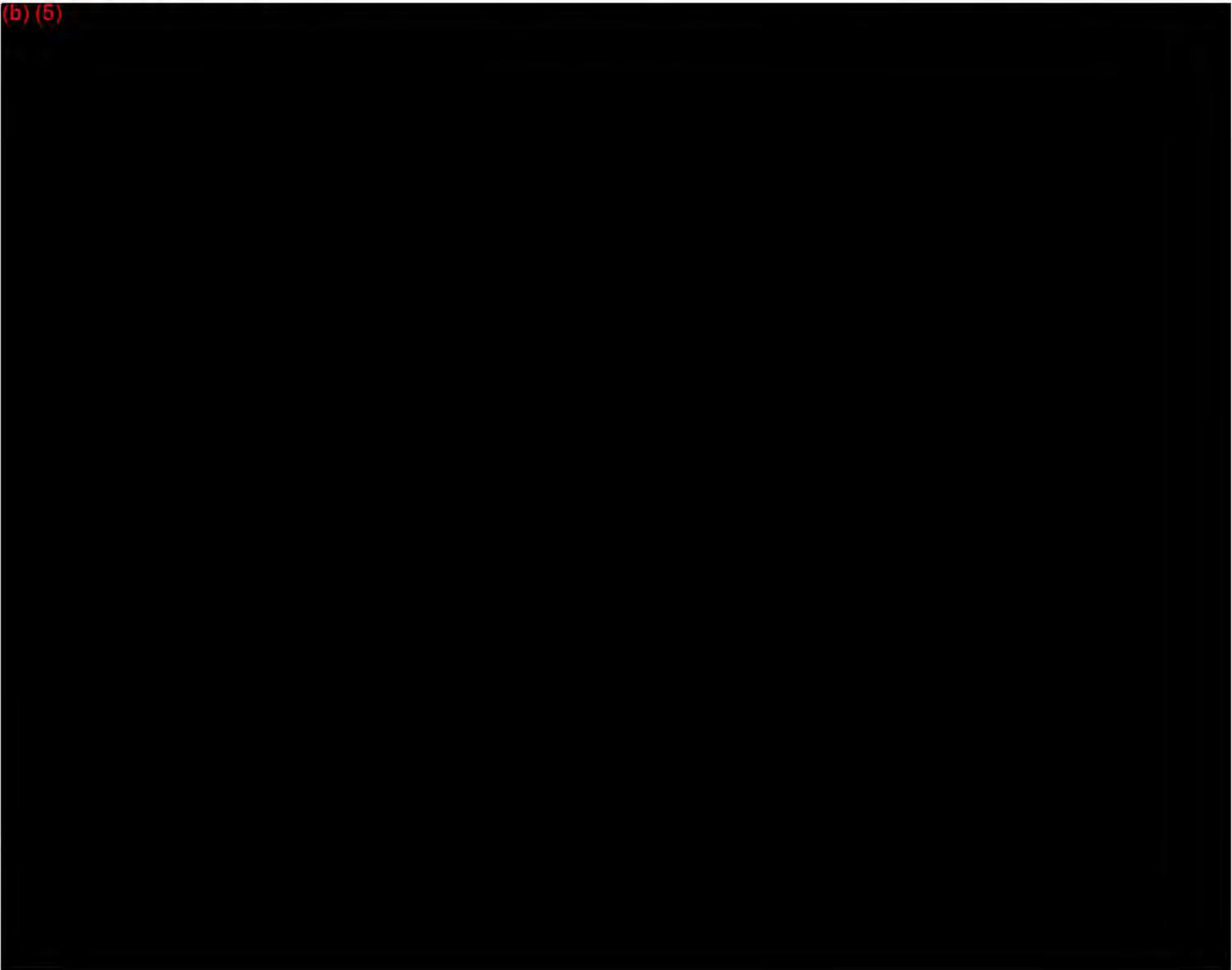
Jennifer.Rodriguez@fda.hhs.gov



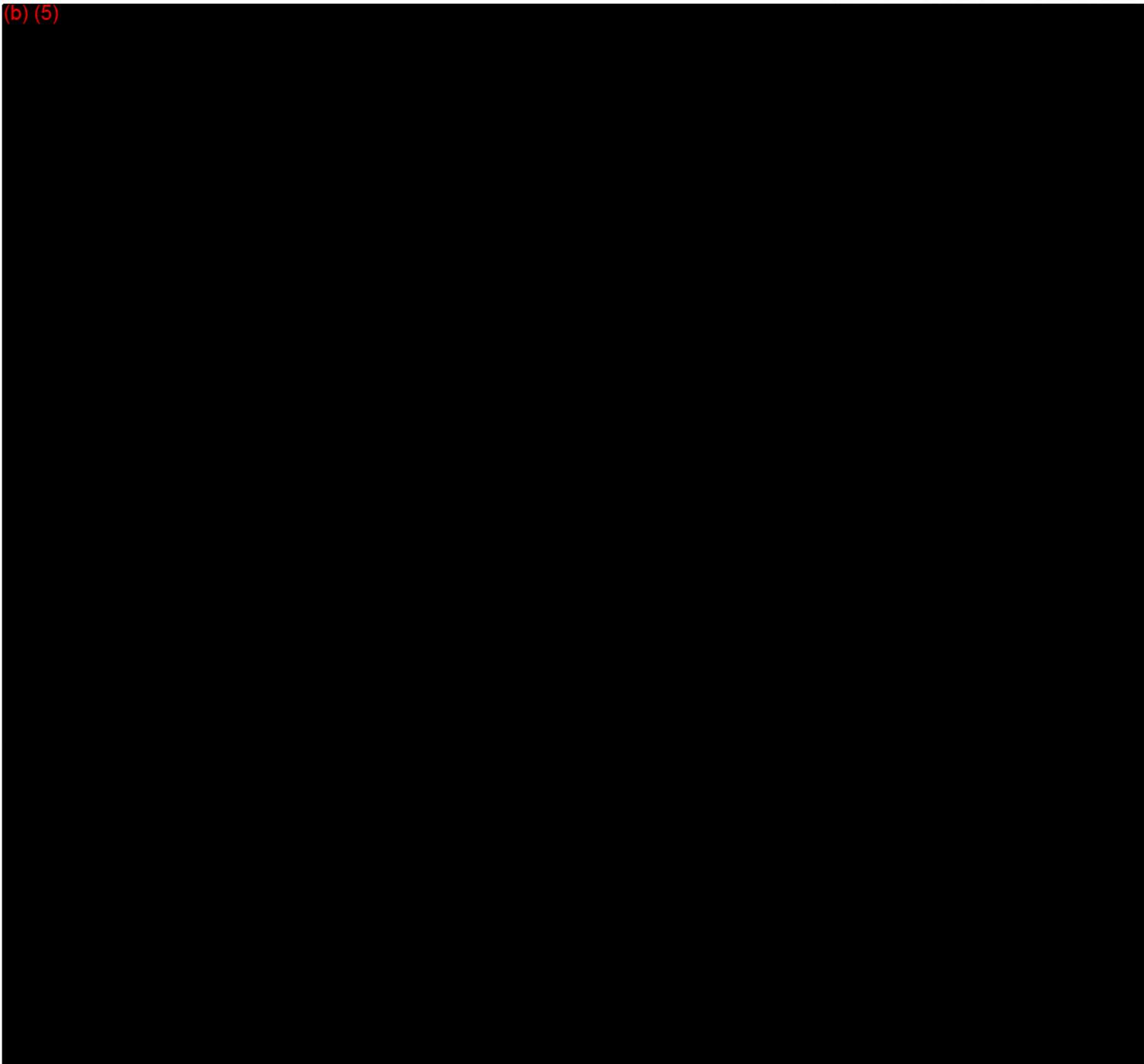
**Reactive Statement and QA: Posting of review documents for approval of
Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy**

Target date: September 2016

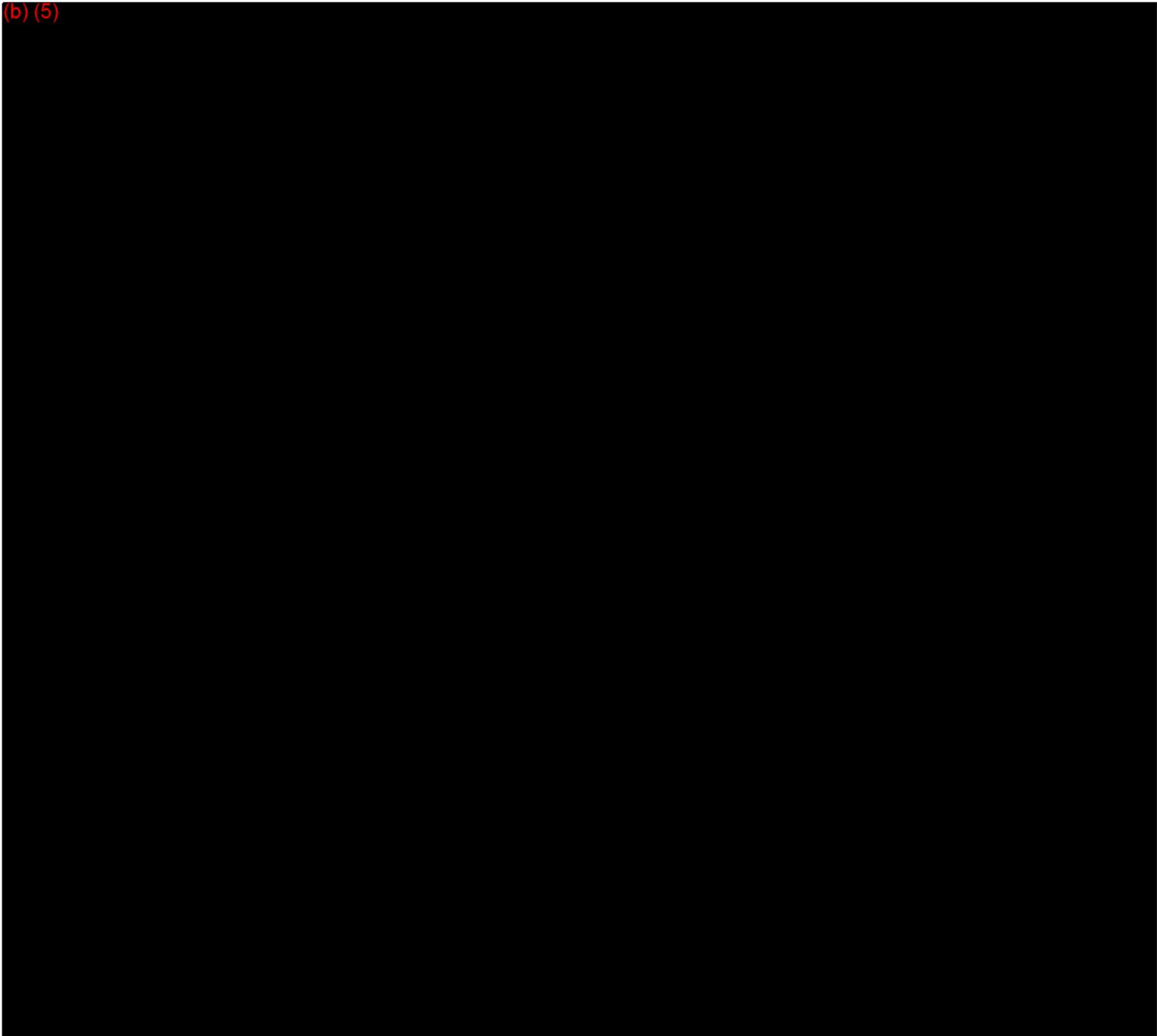
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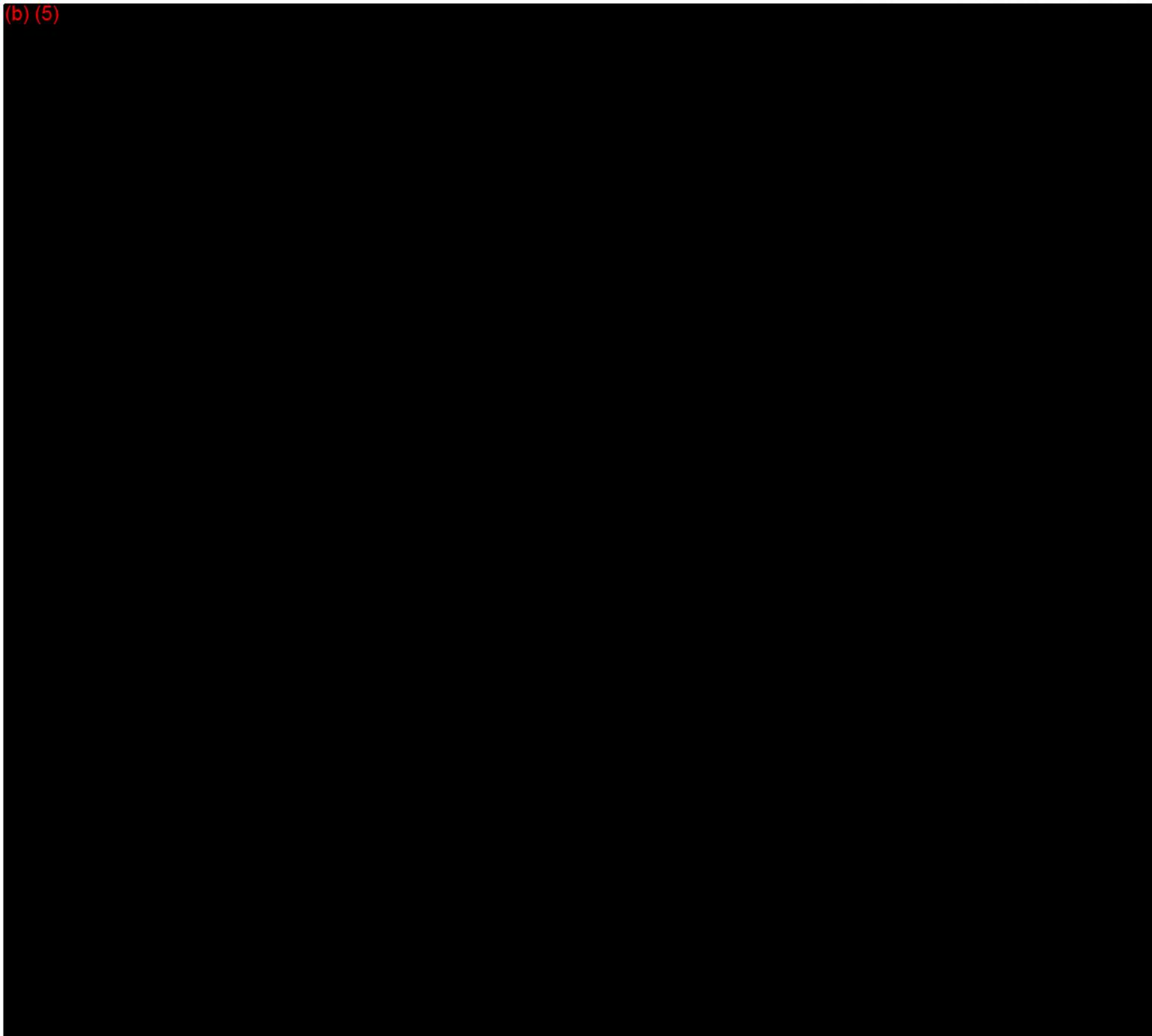
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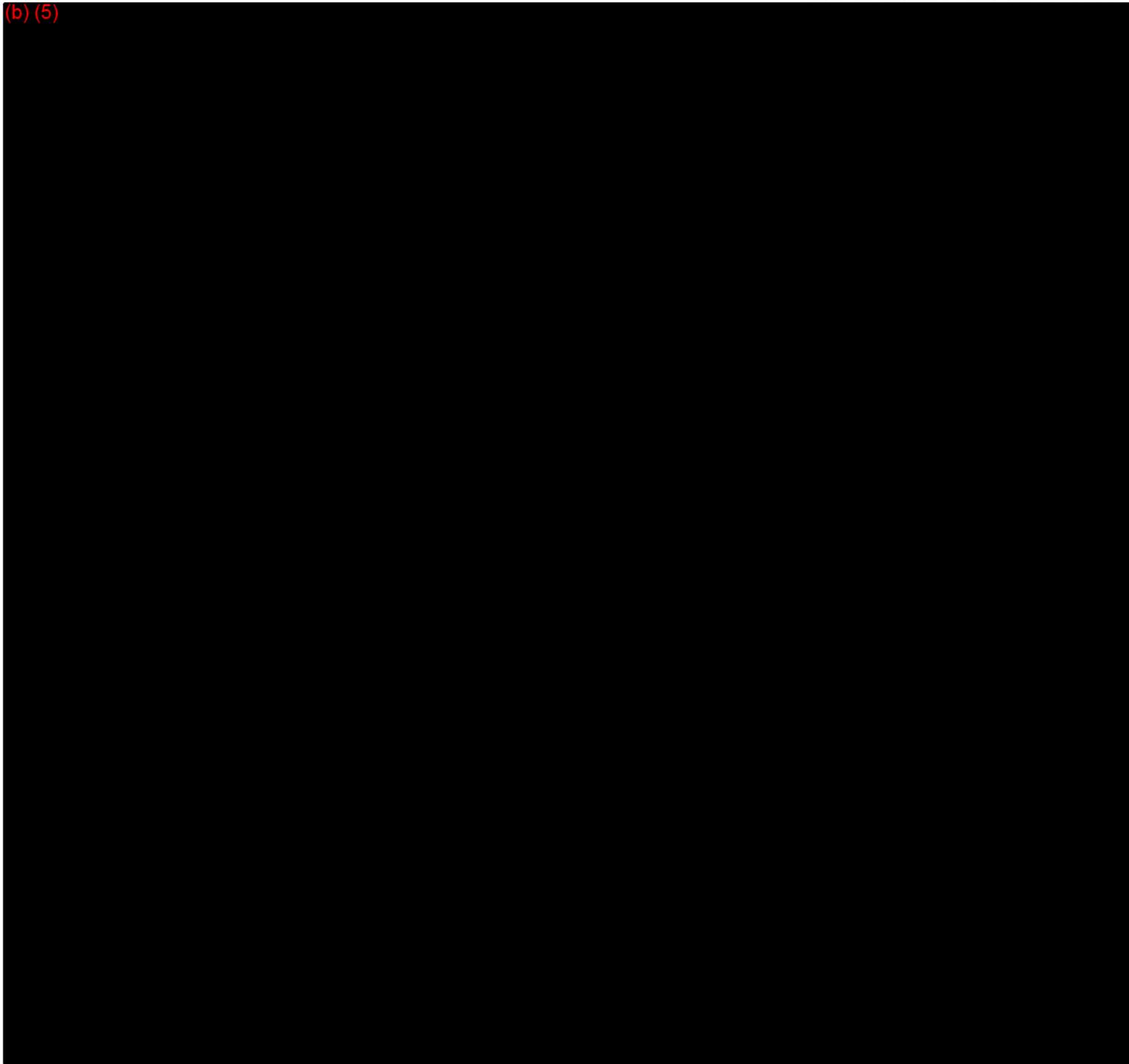
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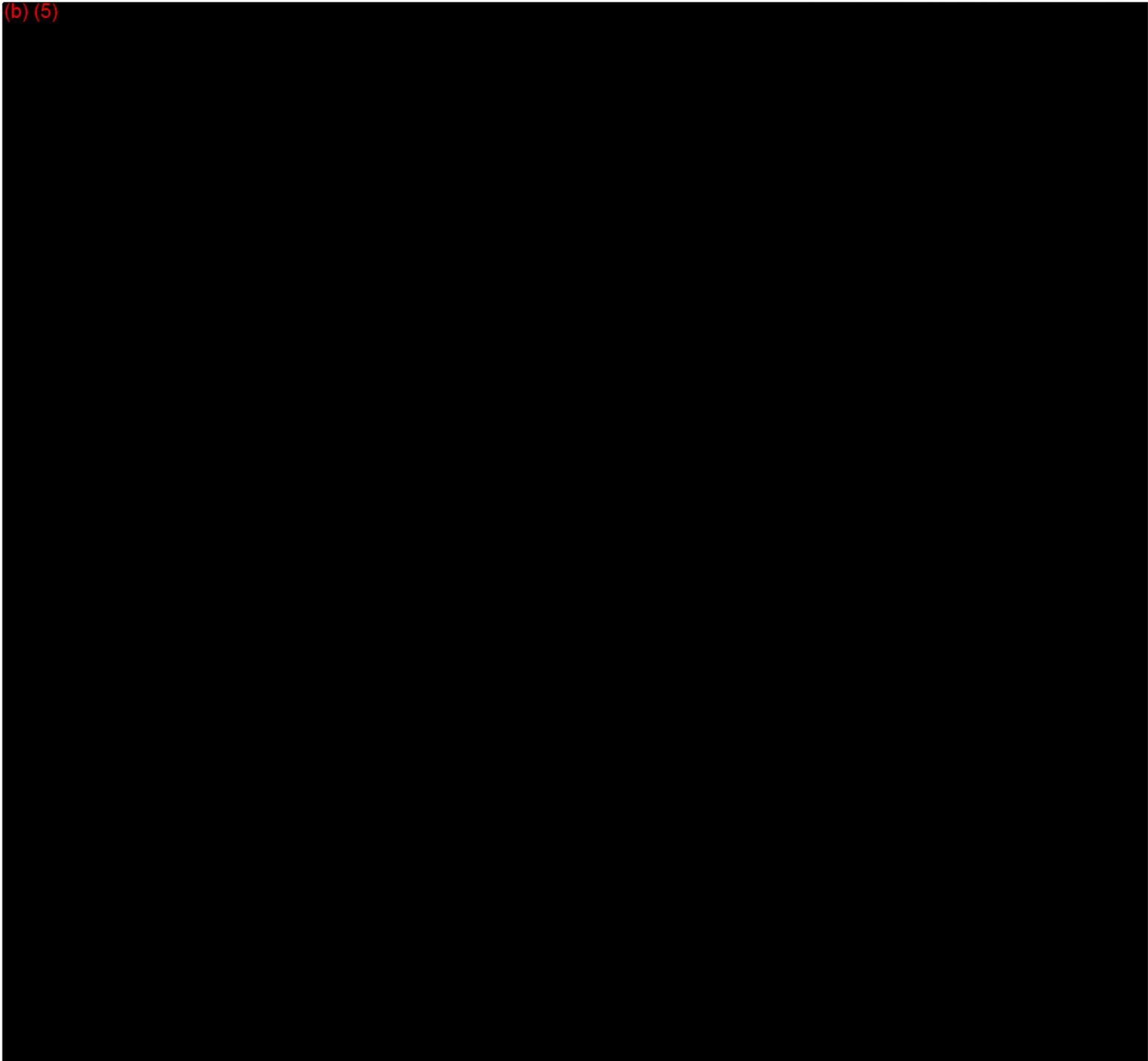
(b) (5)



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(b) (5)



From: [Rodriguez, Jennifer](#)
To: [Califf, Robert](#); [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Dickinson, Elizabeth \(FDA\)](#)
Cc: [Conover, Katie](#)
Subject: RE: DR. CALIFF PLEASE SEE: Phase I and II Comms--timing
Date: Friday, September 09, 2016 12:51:52 PM
Attachments: [image001.png](#)
[Phase II approval reactive QA 090916.doc](#)
[etepilrsen KMOA 9.5.16.doc](#)
[etepilrsen PR draft 9.5.16.doc](#)

Dr. Califf (and team)-

Attached please find an updated version of the Phase II comms. We have addressed your comment and added two QAs, including one to your question about (b) (5)

(b) (5)

(b) (5)

On the remaining questions you noted, we believe they are addressed in the Phase I QA, as noted below. However, if there are any you feel we need to address more specifically – please let us know:

(b) (5)

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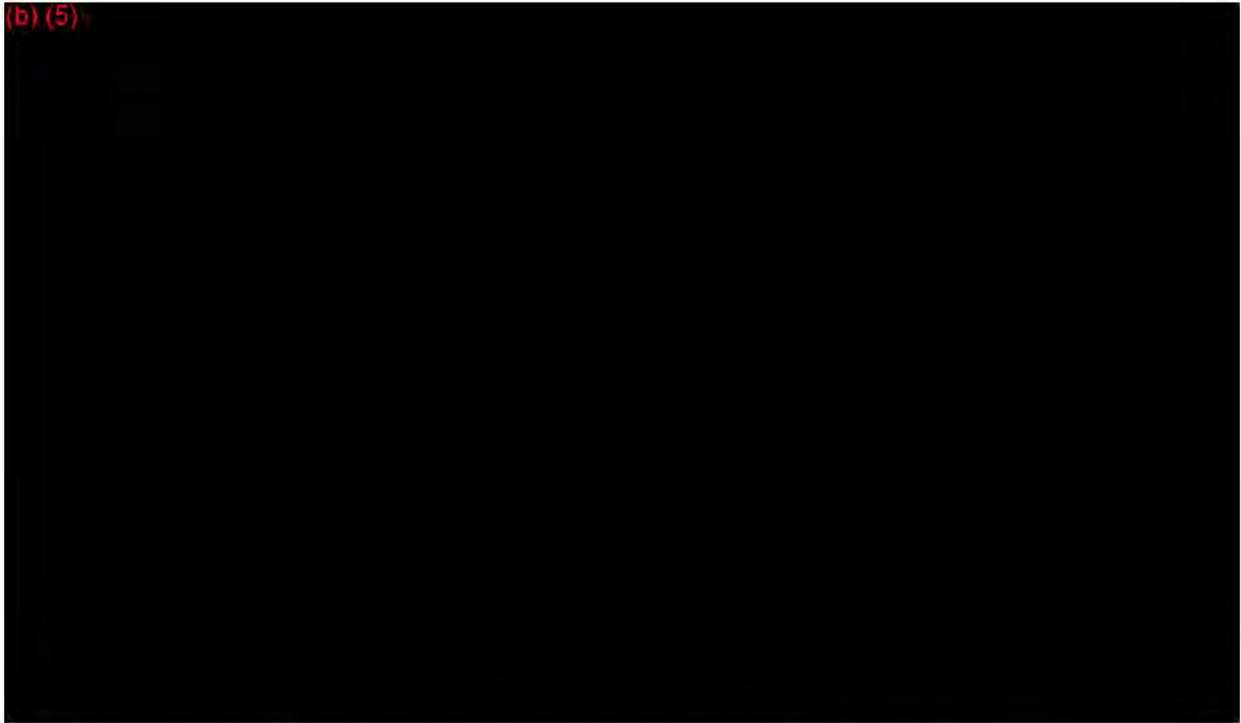
Best,
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Sent: Friday, September 09, 2016 7:01 AM
To: Rodriguez, Jennifer; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Cc: Conover, Katie
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(b) (5)



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rmc

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Cc: Conover, Katie
Subject: RE: PLEASE SEE: Phase I and II Comms

Great, thanks!

FDAOC0001765

This version should go into a consolidated email to Rob.

From: Chasan-Sloan, Deborah (FDA)
Sent: Thursday, September 08, 2016 4:22 PM
To: Sherman, Rachel; Rodriguez, Jennifer; Dickinson, Elizabeth (FDA); Califf, Robert
Cc: Conover, Katie
Subject: RE: PLEASE SEE: Phase I and II Comms

(b) (5)



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Deborah

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Subject: PLEASE SEE: Phase I and II Comms

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Jennifer Rodriguez

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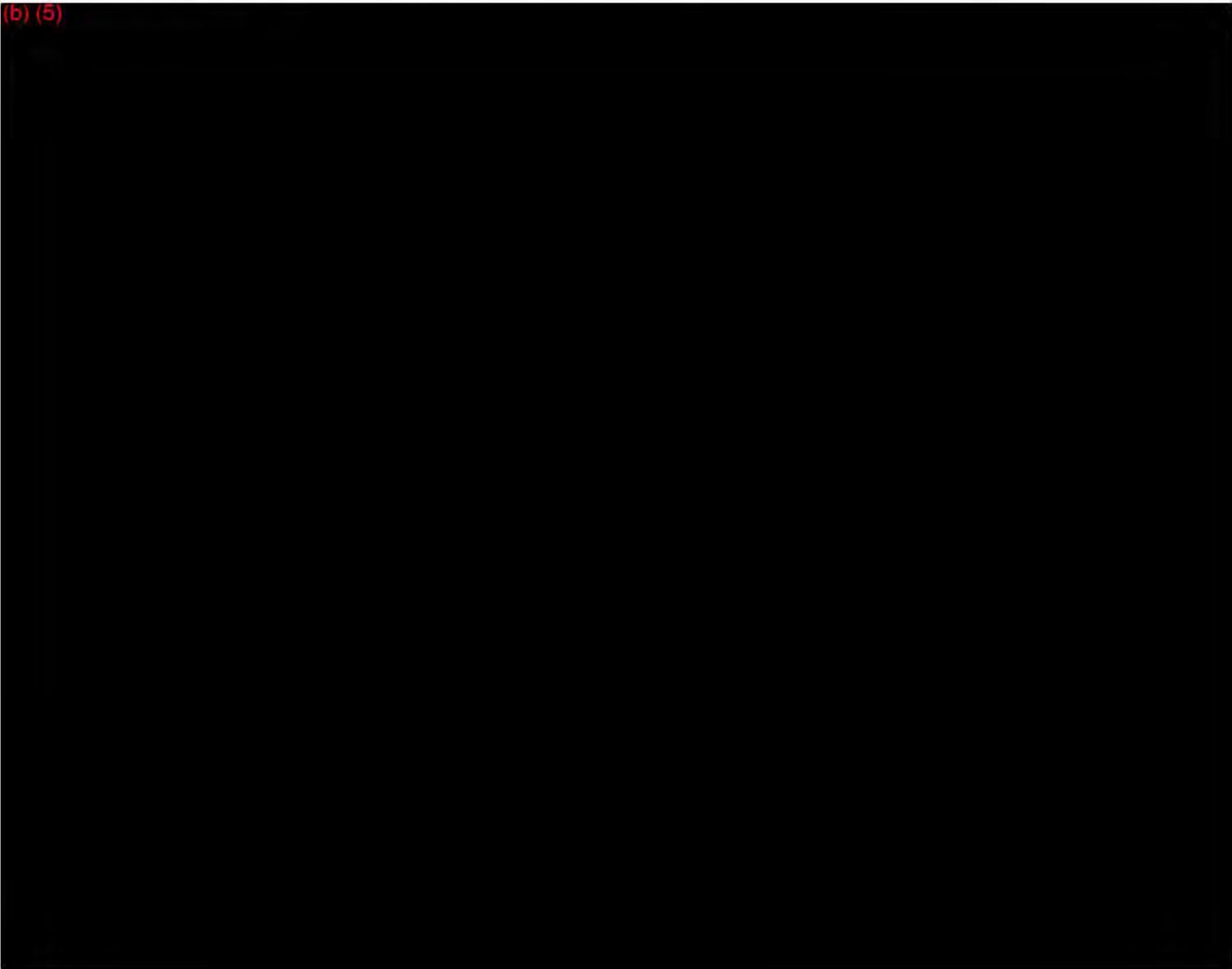
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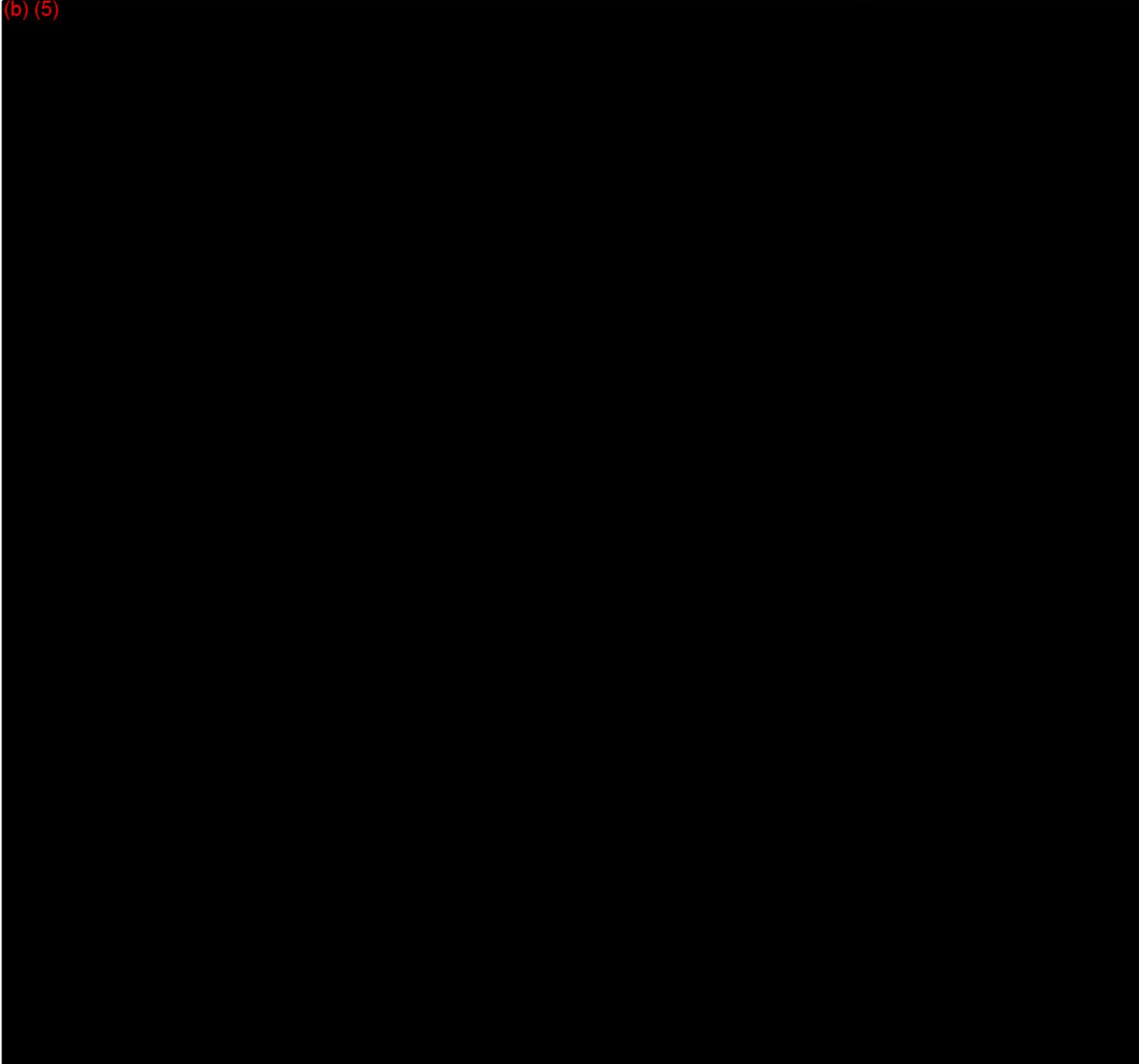
**Reactive Statement and QA: Posting of review documents for approval of
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Target date: September 2016

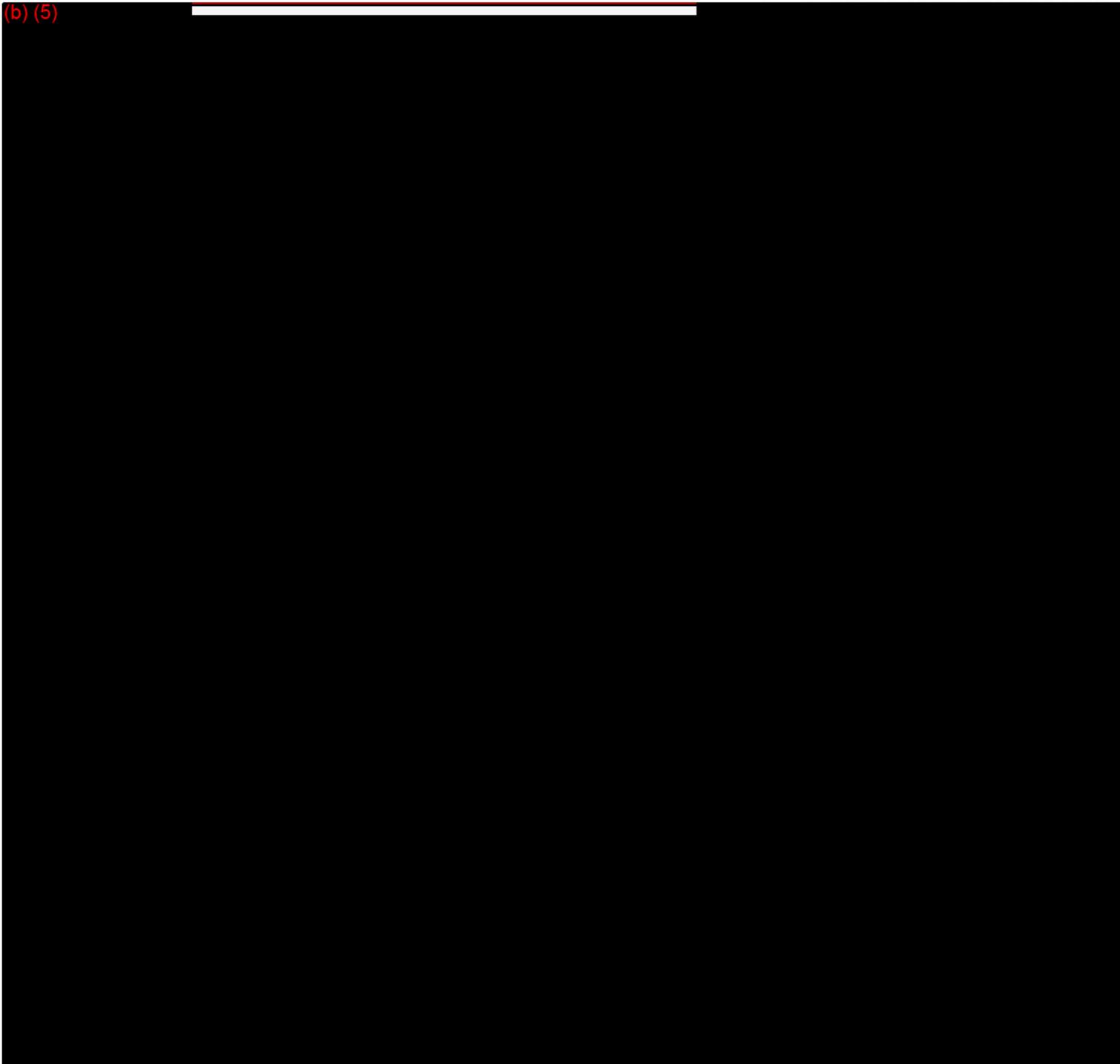
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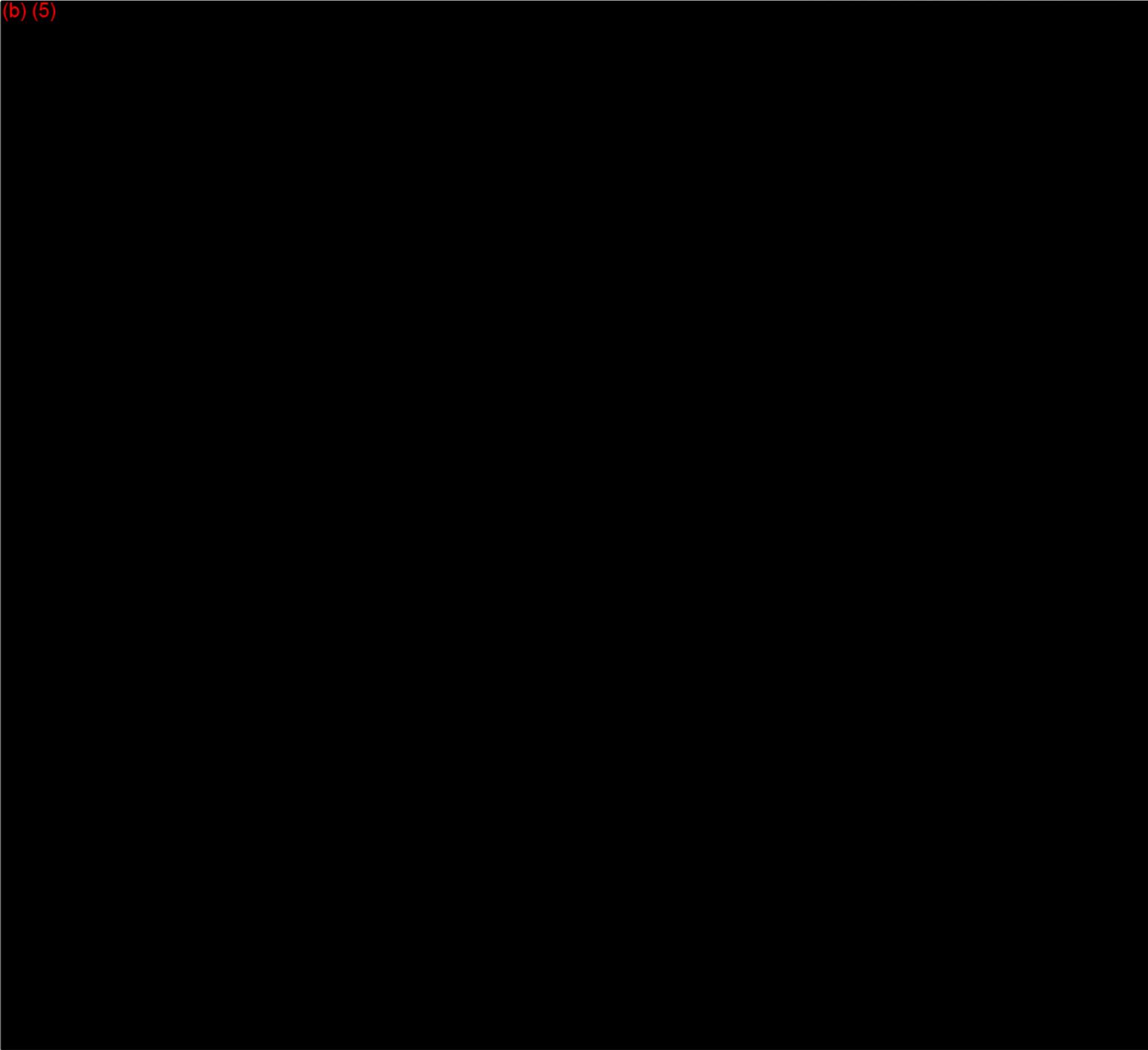
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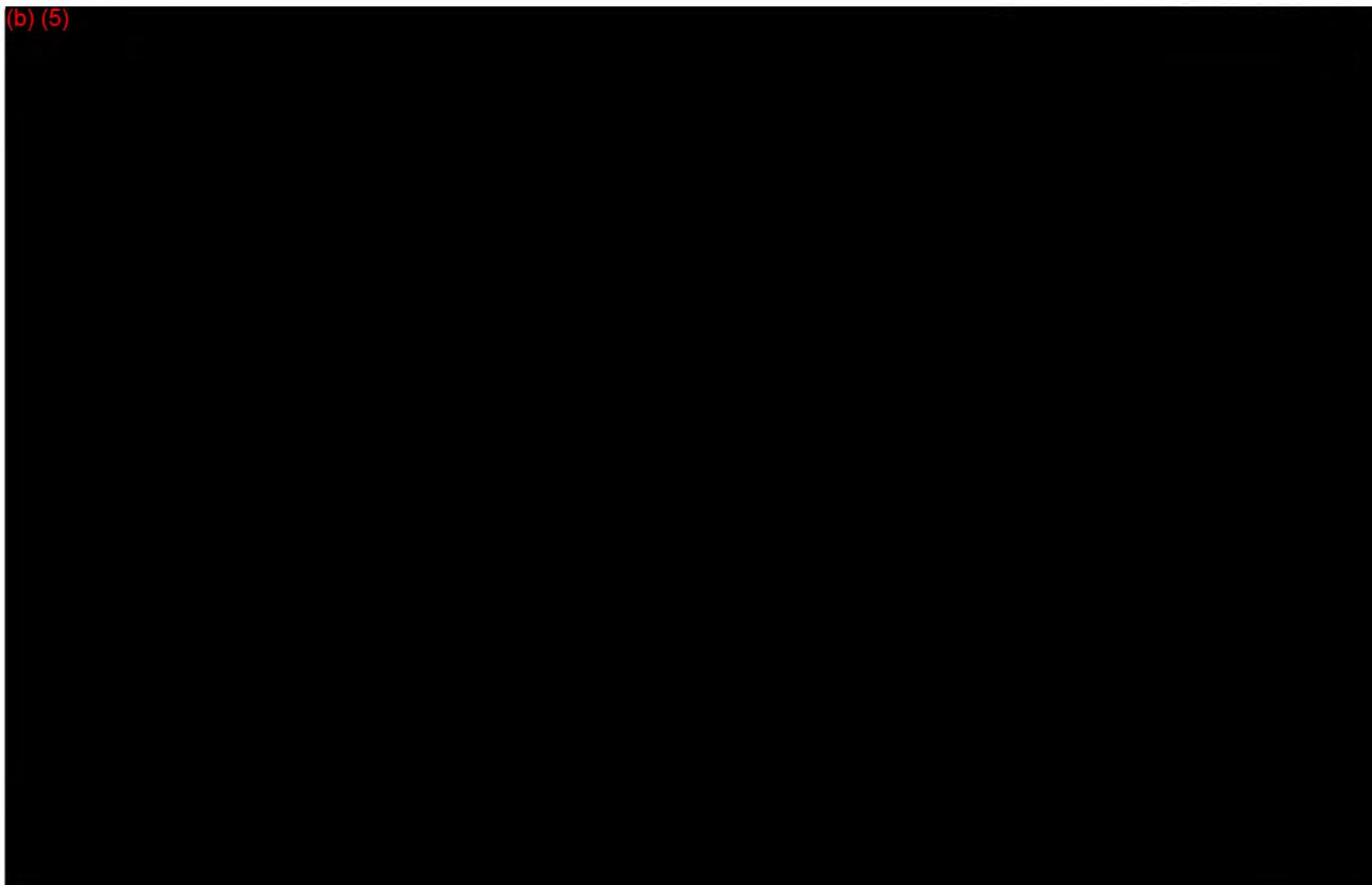
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**Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat
Duchenne muscular dystrophy**

Target date: September 2016

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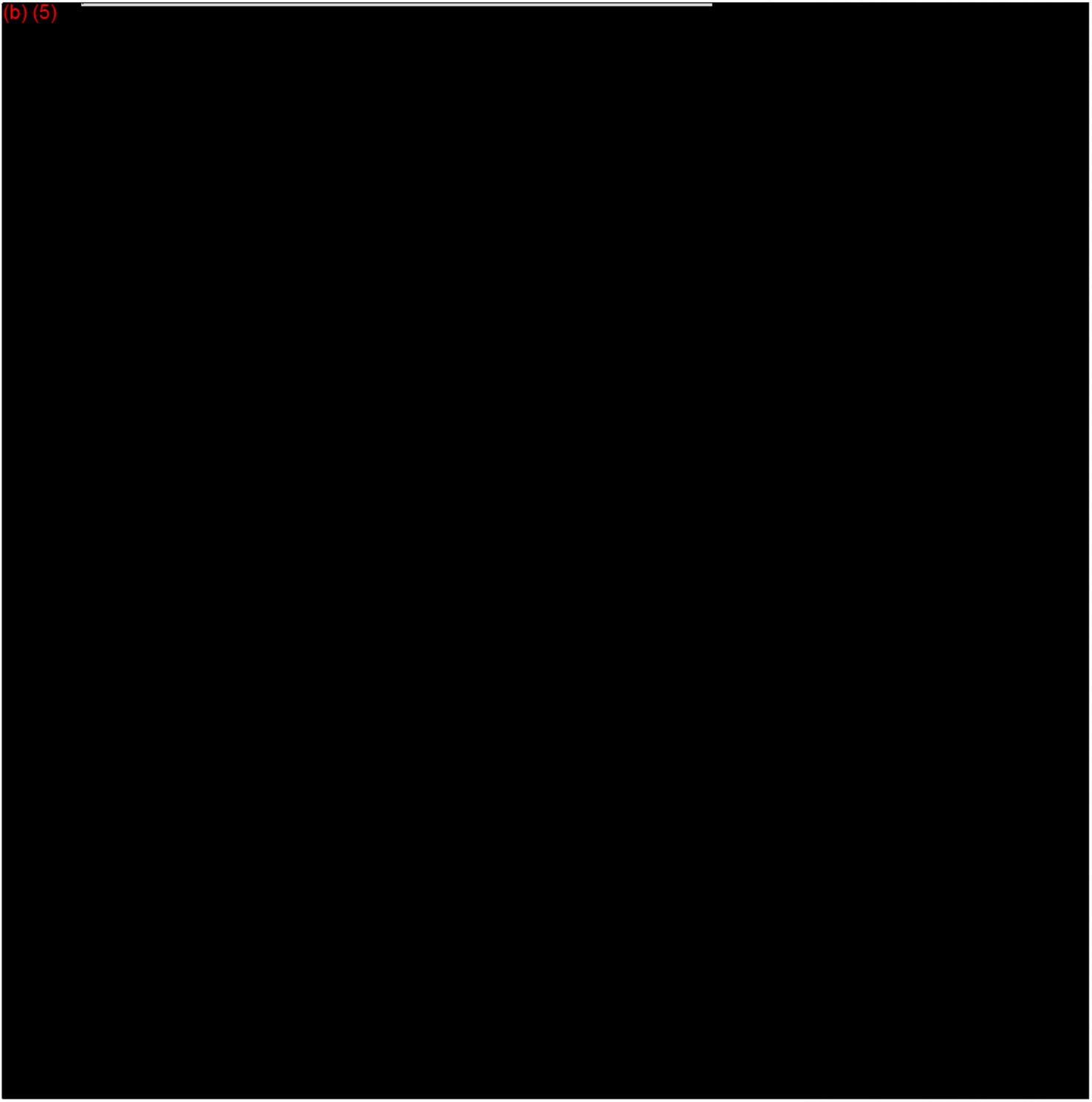


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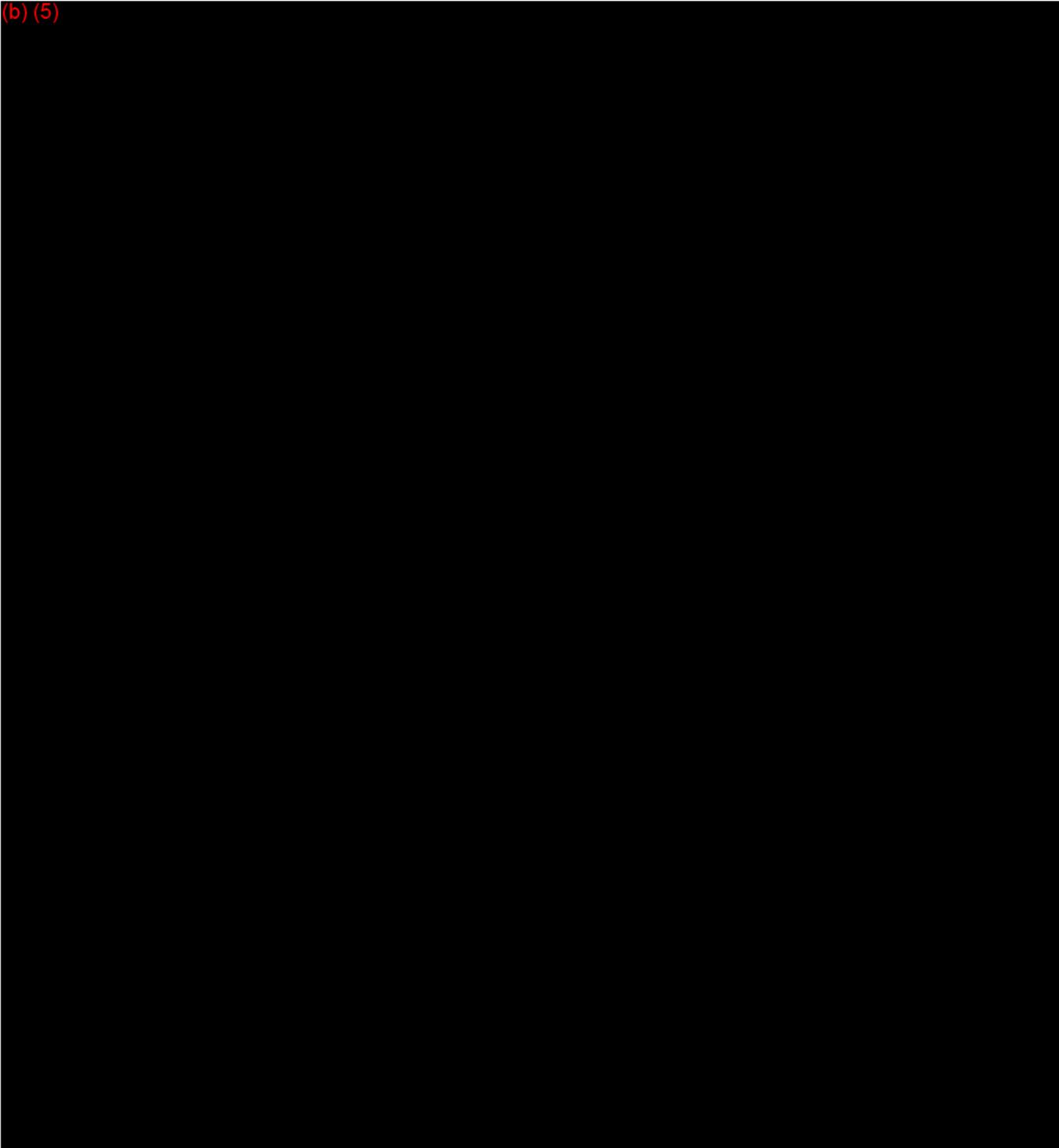
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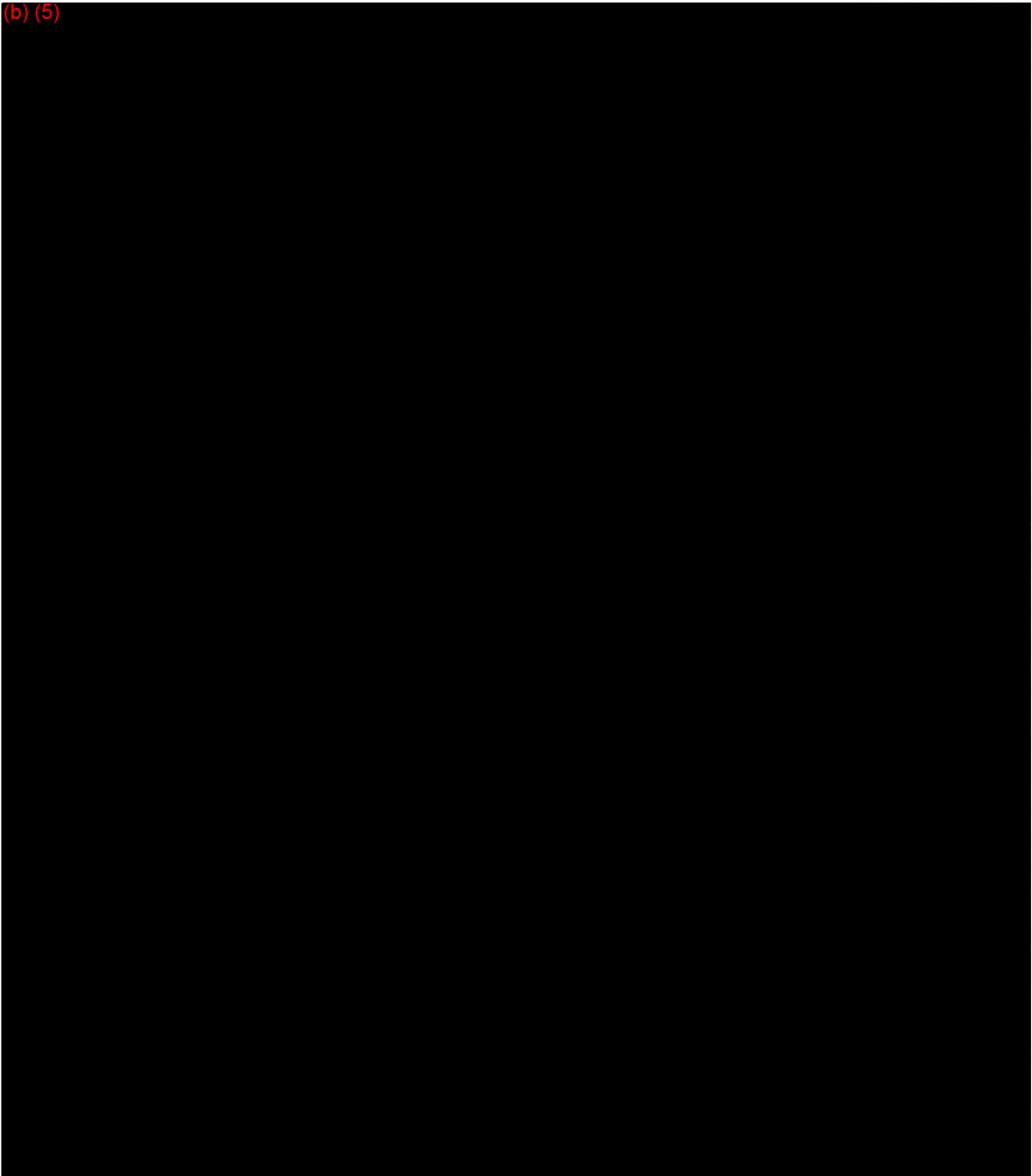
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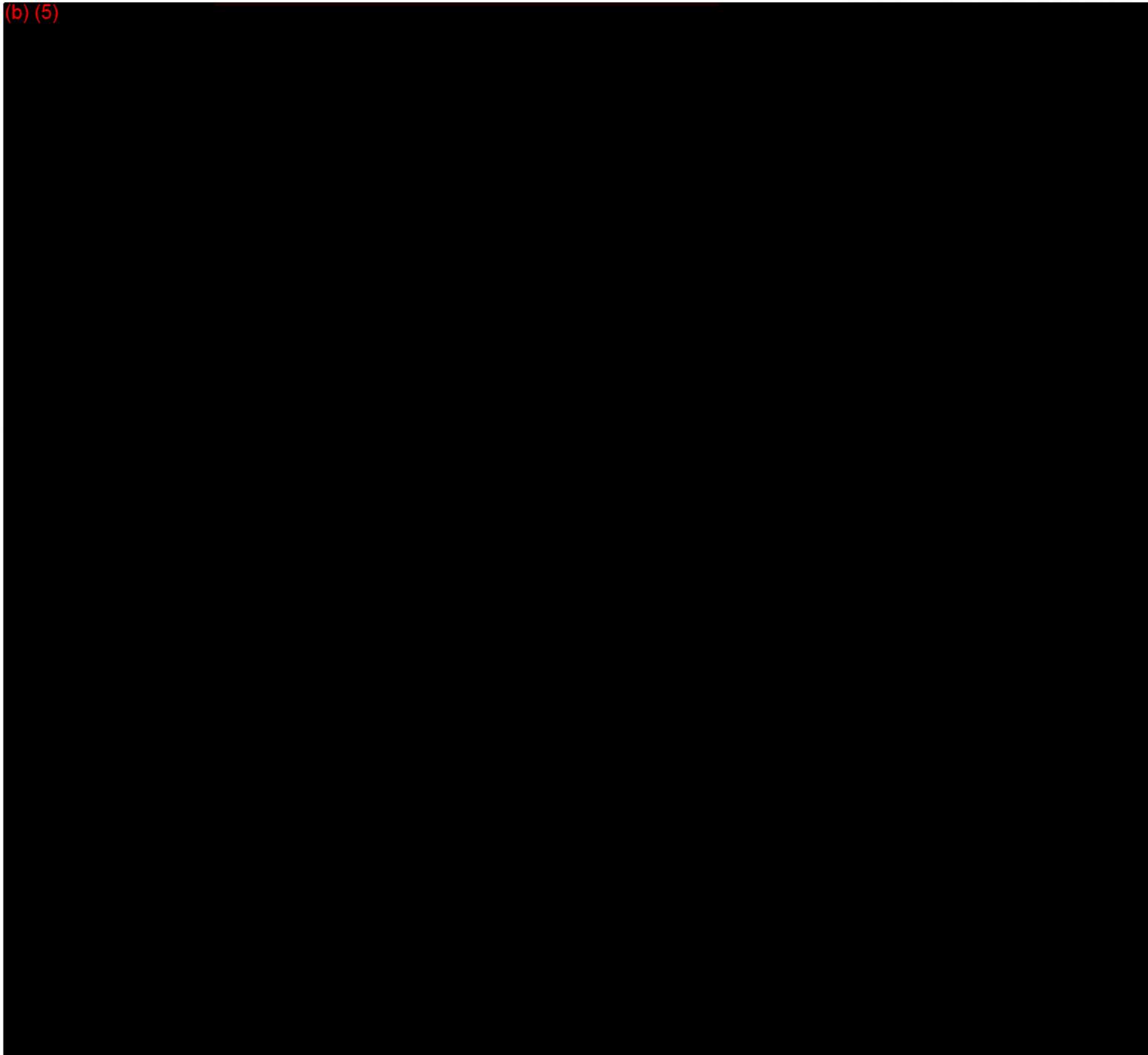
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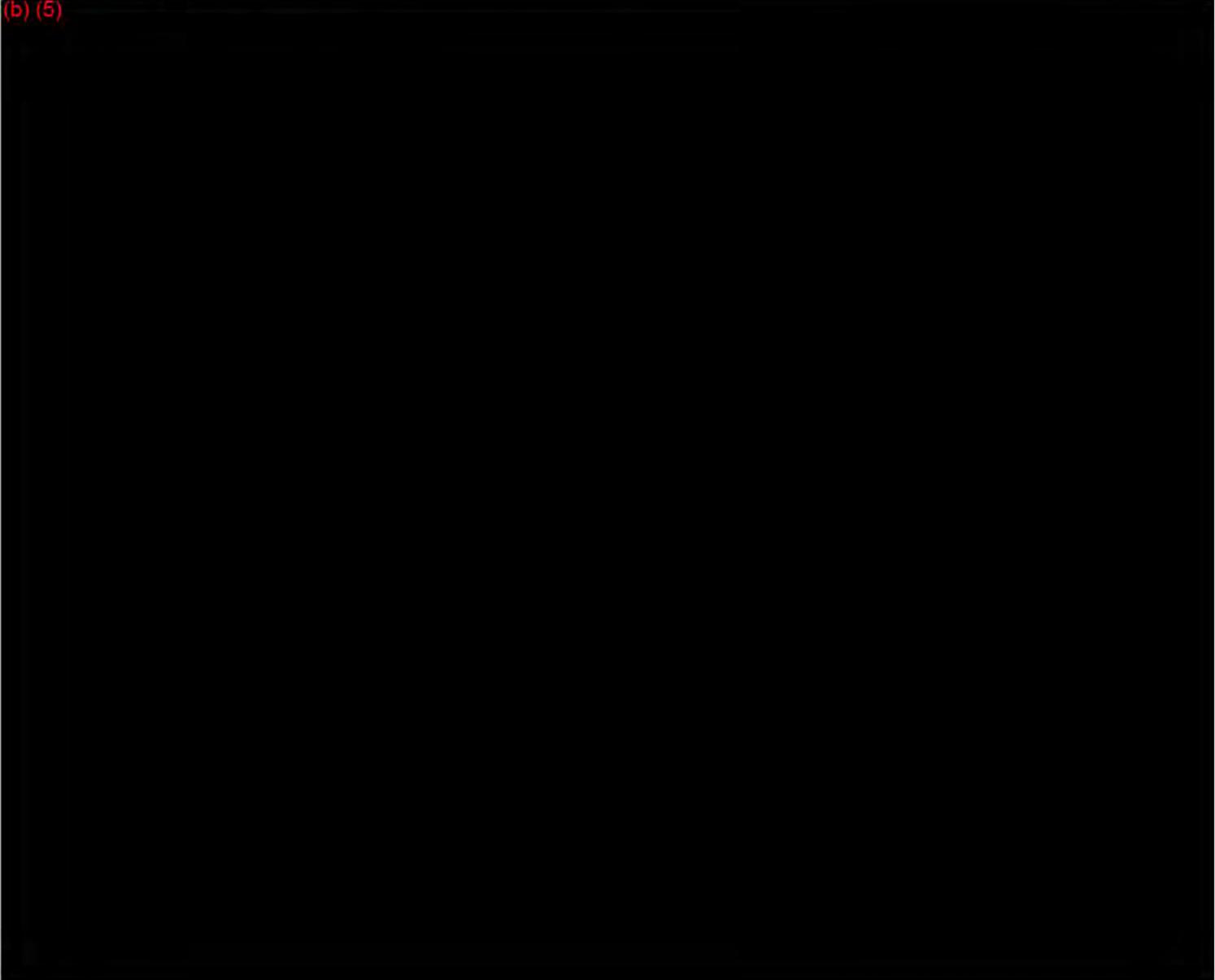
FDA NEWS RELEASE

For Immediate Release: September xx, 2016

Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

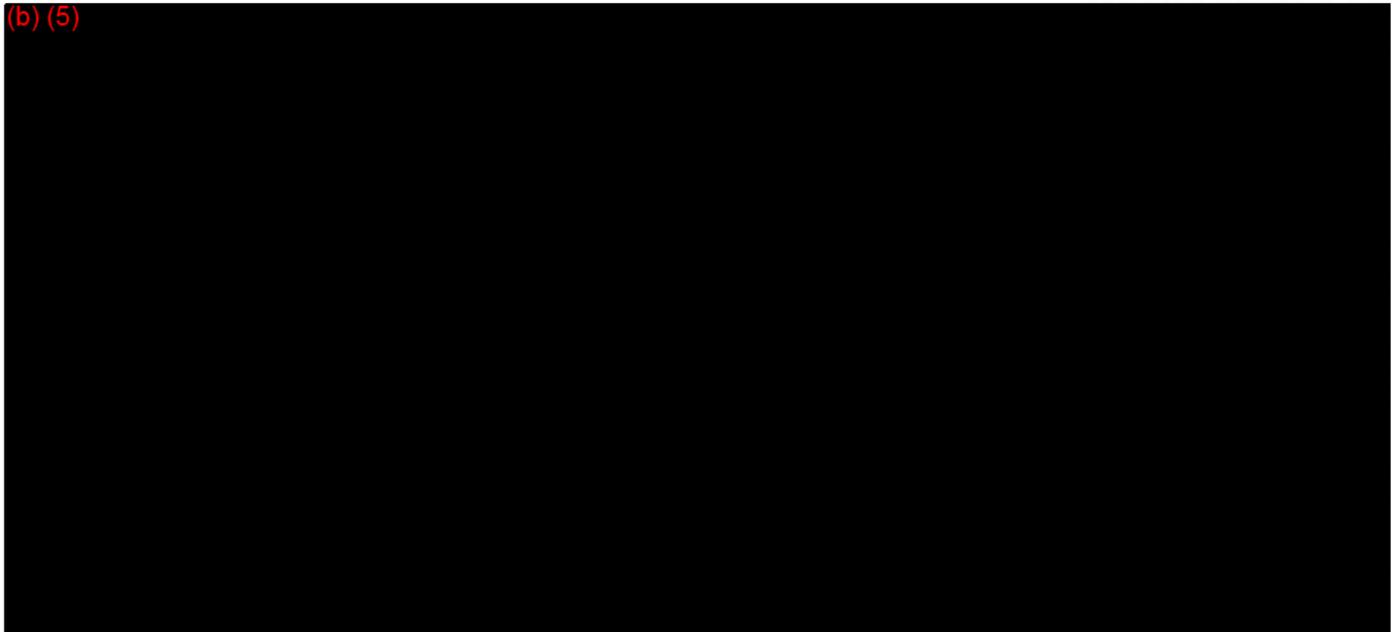
(b) (5)



(b) (5)



(b) (5)



From: [Califf, Robert](#)
To: [Conover, Katie](#); [Rodriguez, Jennifer](#)
Cc: [Kraus, Tom](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: FW: Follow up on Eteplirsen
Date: Sunday, September 11, 2016 7:14:00 AM

Friends,

Please see exchange below related to rollout. Seems like we agree on the transparency issue, but not on the timing of releasing the documents and the method of dealing with the press.

rmc

From: Califf, Robert
Sent: Sunday, September 11, 2016 7:13 AM
To: Jenkins, John K; Woodcock, Janet; Unger, Ellis
Subject: RE: Follow up on Eteplirsen

John,

Thanks for putting this list together. Much of this is in CDER's baileywick, but I want to be sure I do what I need to do. See below:

From: Jenkins, John K
Sent: Friday, September 09, 2016 4:09 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: Follow up on Eteplirsen

Rob

Do we have any follow up on the items we discussed yesterday and timelines? I just had my regular meeting with Ellis and we discussed the planned action. Some issues that need to be sorted out:

1. Timeline for approval action.

My understanding is that we're aiming for a week from tomorrow. Please let me know if that is not feasible.

2. Verification that we have reached final agreement on the labeling/PMRs with the sponsor. Ellis was not sure that there was final agreement on the labeling. Our usual practice/policy is to ensure that the sponsor has agreed to the labeling before approval, which is usually accomplished by the division sending the final draft of the label to the sponsor and the sponsor formally returning that to us indicating their concurrence. We can check to see if we have documentation of that agreement, or if there is a need to ask Sarepta to submit as

final the most recent version of the labeling we sent them. Ellis can follow up and confirm the status. If there are to be any changes to the most recent version of the final draft label that the division sent to the sponsor, we would ask that we be included in reviewing those edits. Same for the PMR.

Will follow with interest.

3. Timeline for Rob to meet with review team. Since the review team will have to be involved in some of the work to finalize action on the application, we recommend this meeting occur soon.

OK with me-I want to meet with them. It's a rough couple of weeks coming up so we'll have to do some rearranging. I'm out of town Wed and Thursday of this week and in town all week next week, but have a total of 12 "events" at which I have to make remarks. But I'm sure we can work it out on the schedule.

4. Timeline for sharing Rob's review memo with Ellis and me. Ideally this should occur in advance of the meeting with the review team so we can understand the context of Rob's decision.

Will get back with you later today.

5. Plans for the press release and release of documents that support the approval. Our normal process is to release the approval letter and the labeling on the day of approval, followed some time later (I think we have 30 days) by the redacted action package. In this case, we would strongly advocate for releasing the most important memoranda at the time of approval to ensure transparency for the action. The more complete action package could then be released on the usual timeline (e.g., the CMC review, the pharm/tox review). In our view, the redacted documents that should be released at the time of approval would include the Cross Disciplinary Team Leader (CDTL) memo (Farkas), the deputy division director memo (Bastings), the ODE director decisional memo (Ellis), the Center Director decisional memo, Ellis' appeal memo, the acting Chief Scientist memo, and Rob's decisional memo. We strongly advocate for transparency in this case and if you agree these documents will need to be redacted on an expedited timeline.

Our plan has been as you say but to release all the memos at the time of all the other documents rather than with the approval letter and labeling. I have no particular reason to hold information back other than to give people all the information at one time. Glad to continue to discuss.

6. The draft press release. Again, we strongly advocate for transparency in the press release about the differing opinions, the appeal, and how the appeal was decided.

We will be transparent. The question is timing as above.

7. Any plans for press availability to discuss the approval. In the past for controversial/high profile actions we have scheduled a media call where we describe the basis for the action and take questions from reporters. We have also often scheduled a separate briefing for stakeholders.

OEA had not planned a media call to my knowledge. For sure there will be a lot of media interest and questions.

I spent yesterday cleaning up a lot of other things and am available today if we need to talk.

John

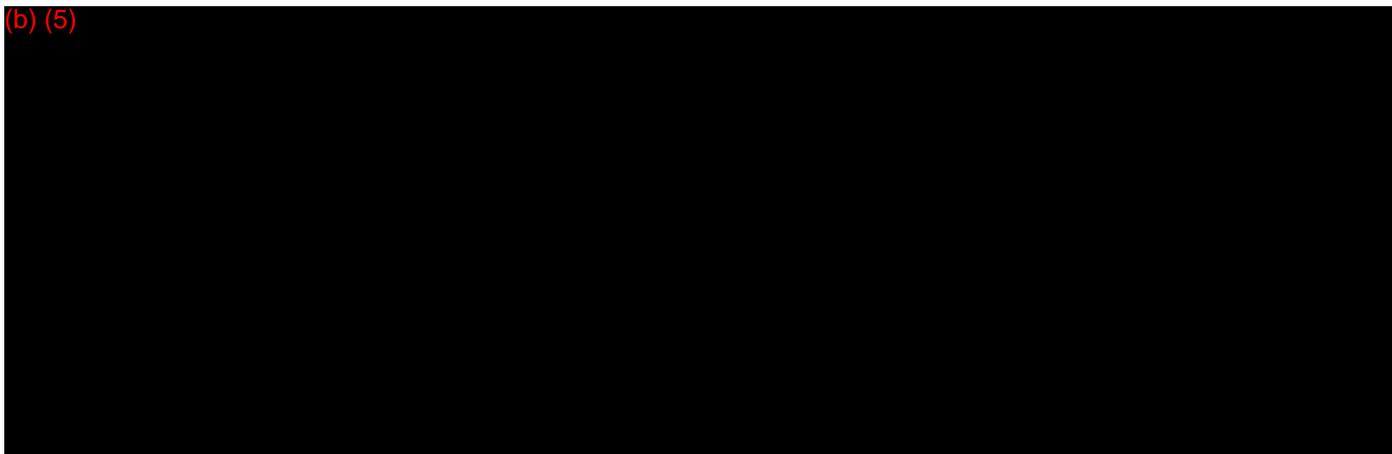
From: [Califf, Robert](#)
To: [Chasan-Sloan, Deborah \(FDA\)](#); [Sherman, Rachel](#); [Rodriguez, Jennifer](#); [Conover, Katie](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: Q&A
Date: Sunday, September 11, 2016 7:49:00 PM

Nice job. These changes improve what I was trying to get across. Thanks.

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

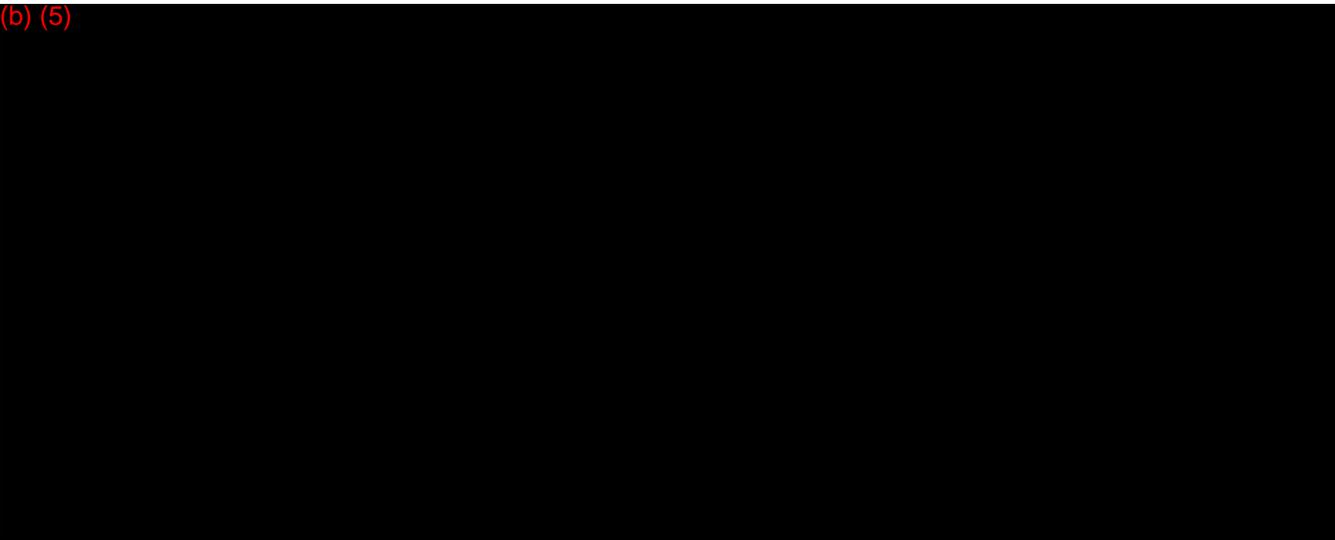
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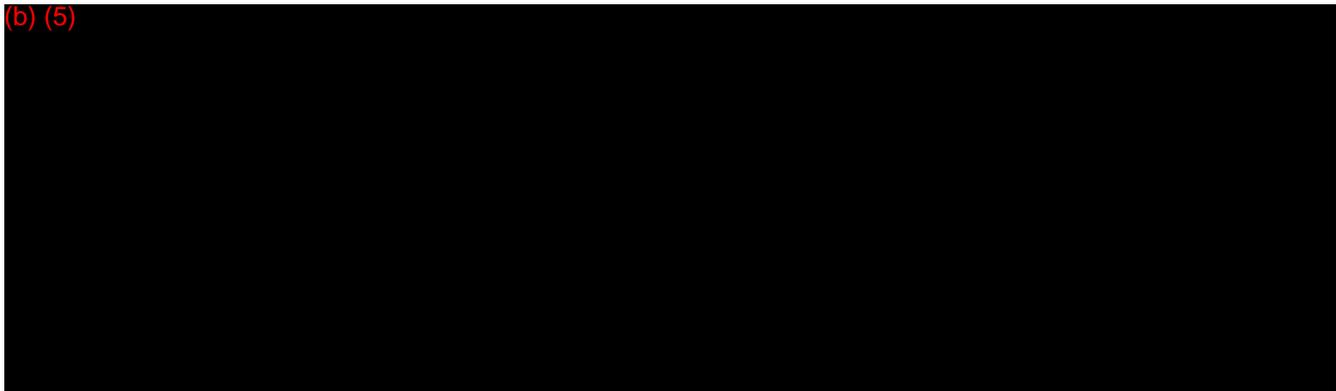
From: Sherman, Rachel
Sent: Sunday, September 11, 2016 8:45 AM
To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.

(b) (5)



(b) (5)



Hope this helps

Rachel

Why do you equivocate and say I'm right on most things? I thought we agreed I was always right.....

From: Califf, Robert

Sent: Sunday, September 11, 2016 8:23 AM

To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

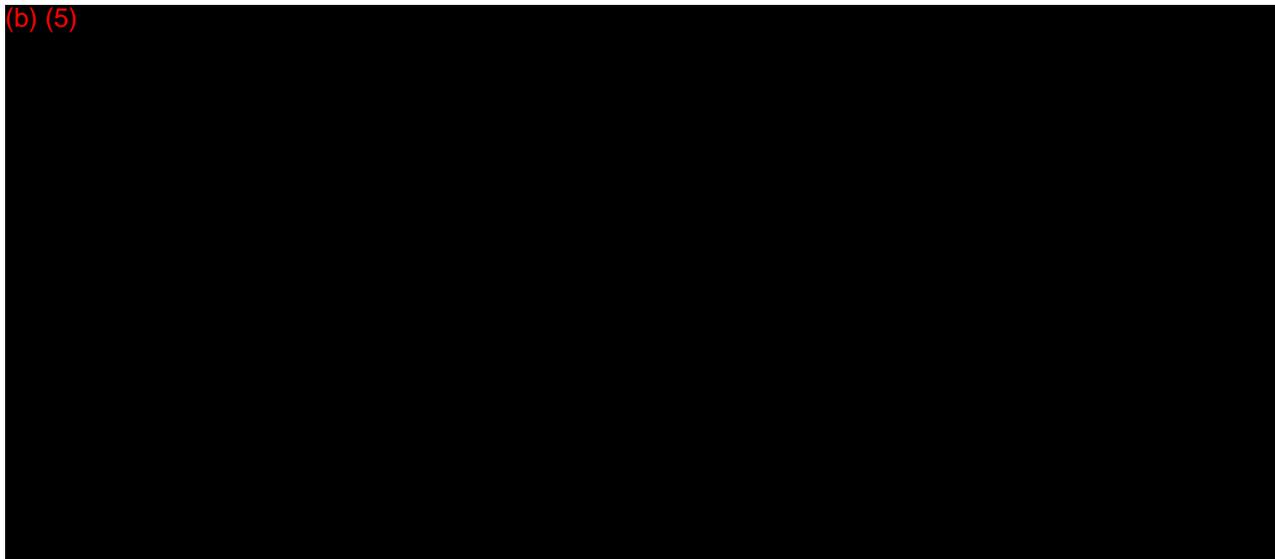
Subject: Q&A

Friends,

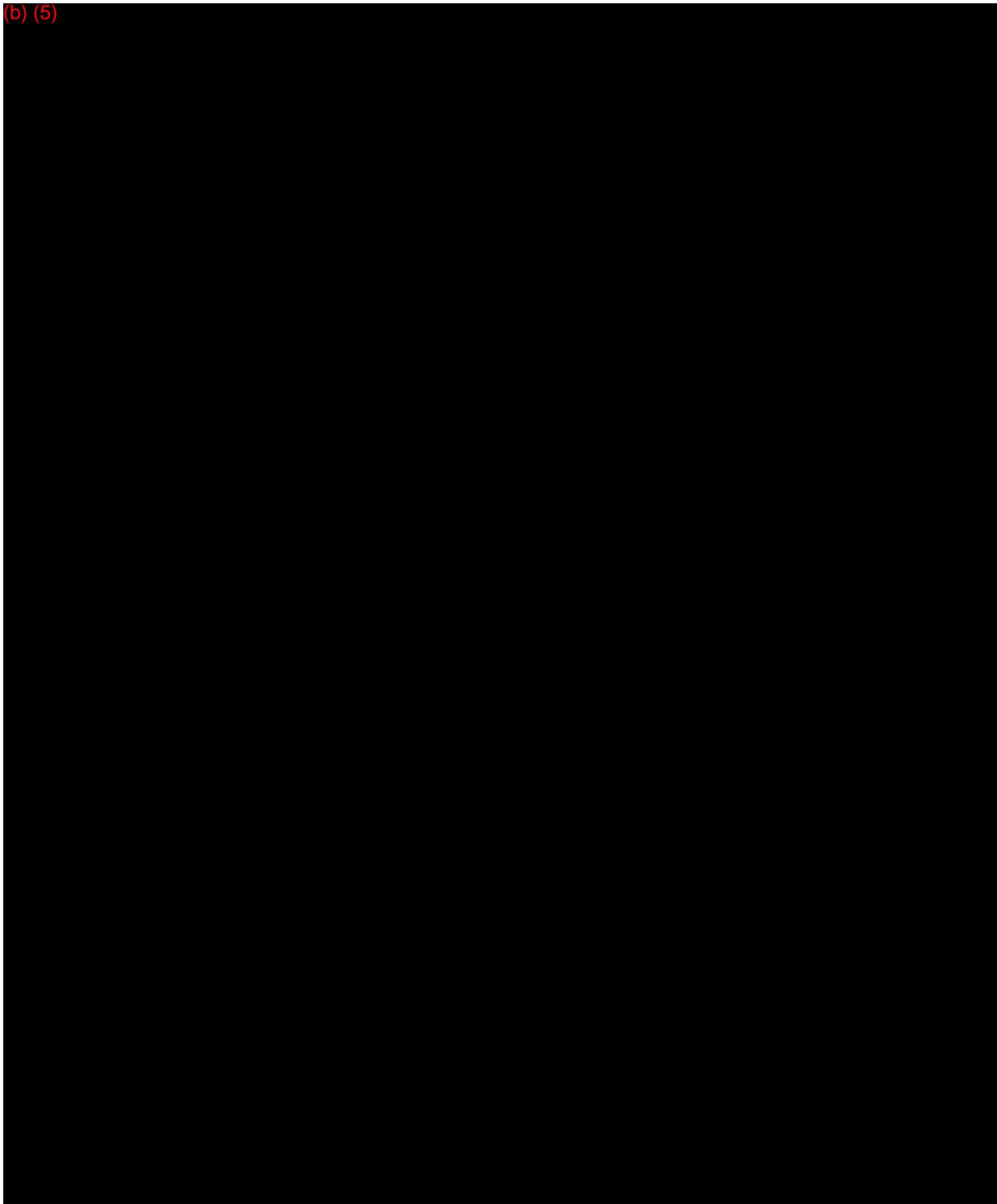
I have done a little editing, but not much as I think its good. There are still several loose ends. Are we still ok on the timeline?

3 issues strike me as needing more work:

(b) (5)



(b) (5)



From: [Chasan-Sloan, Deborah \(FDA\)](#)
To: [Sherman, Rachel](#); [Califf, Robert](#); [Rodriguez, Jennifer](#); [Conover, Katie](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: Q&A
Date: Sunday, September 11, 2016 7:44:09 PM
Attachments: [eteplirsen KMQA 9.5.16_rmc\(occ\).doc](#)

(b) (5)



From: Sherman, Rachel
Sent: Sunday, September 11, 2016 8:45 AM
To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises:

(b) (5)



(b) (5)

Hope this helps

Rachel

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To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

Subject: Q&A

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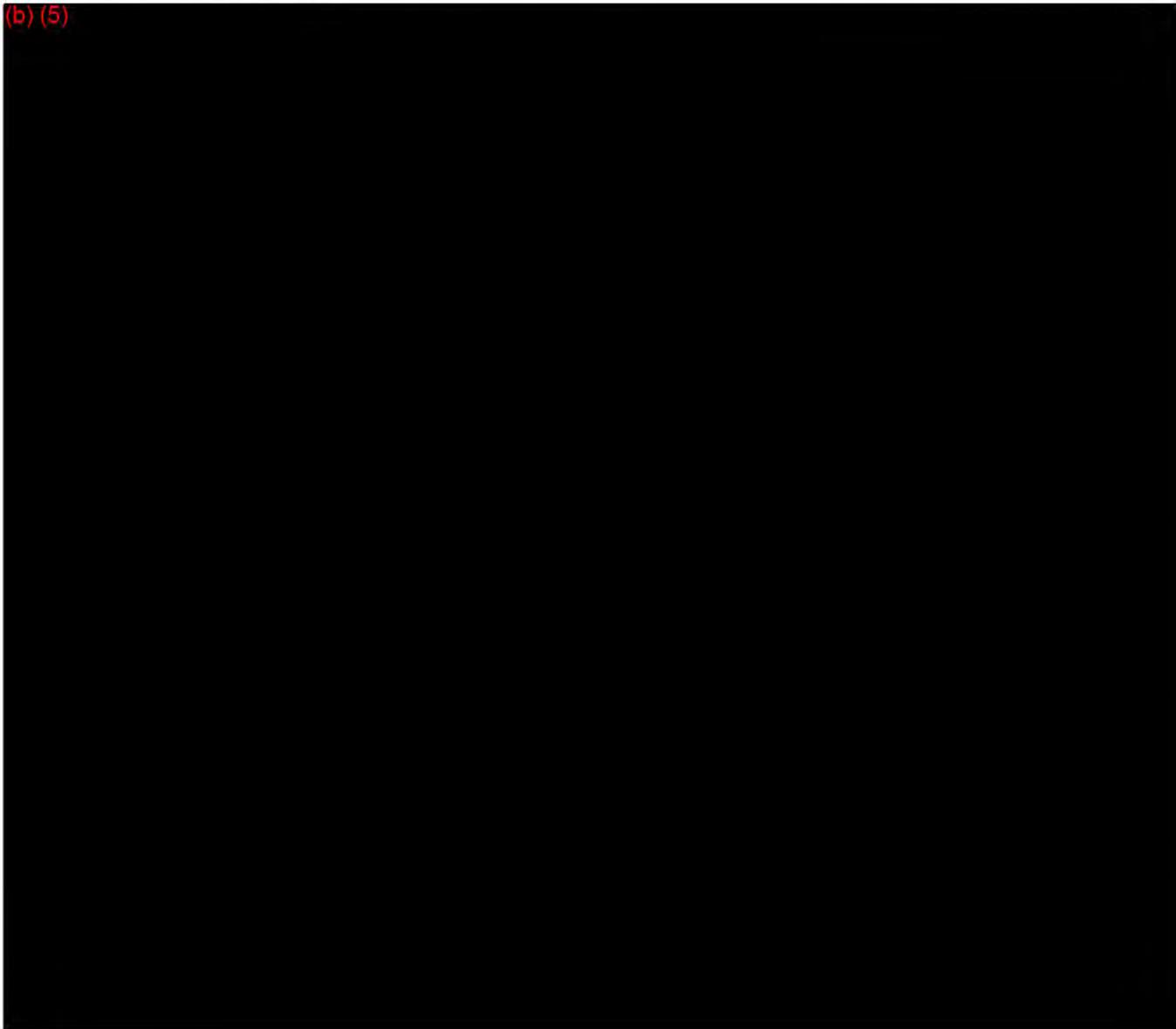
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Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

Target date: September 2016

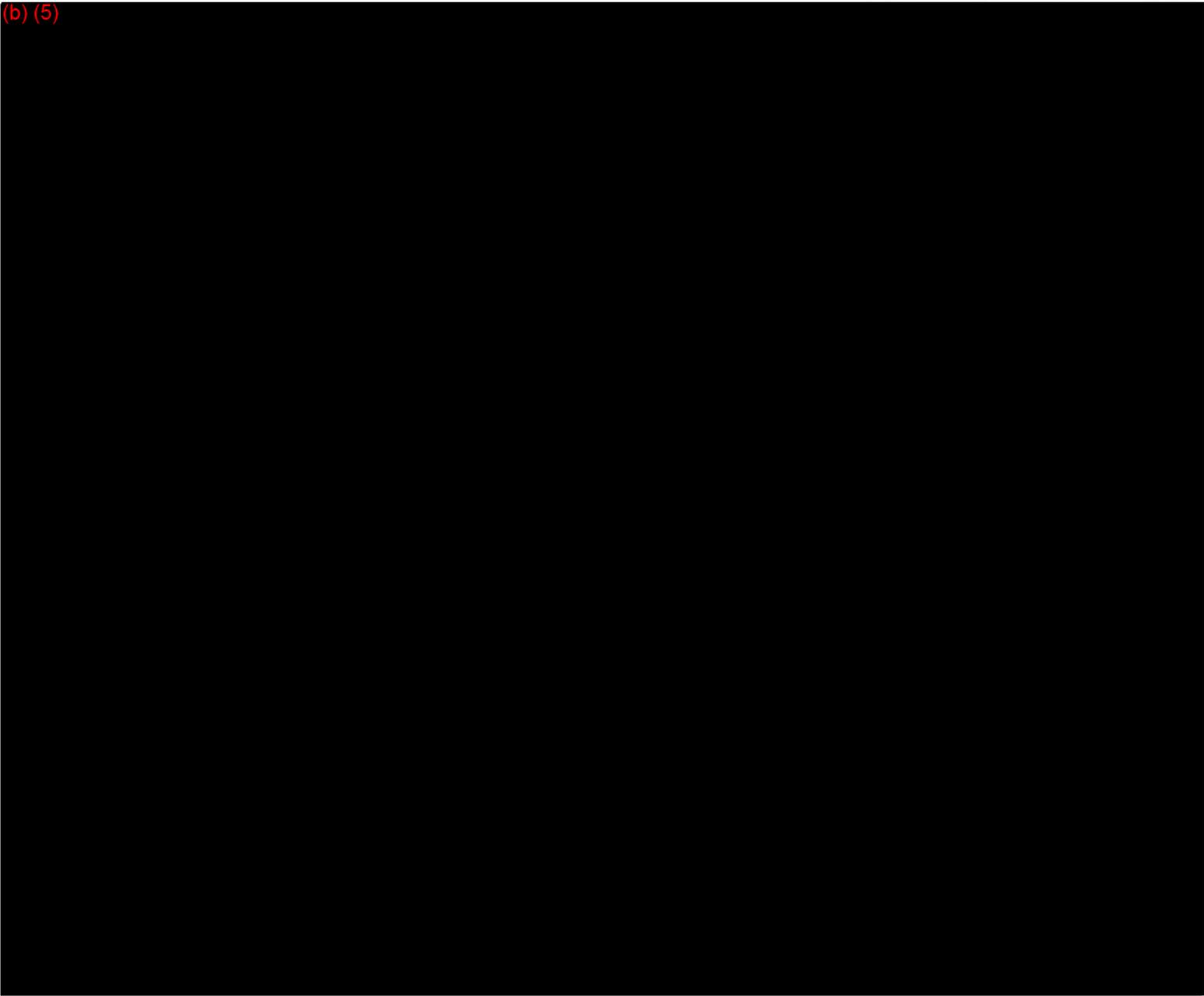
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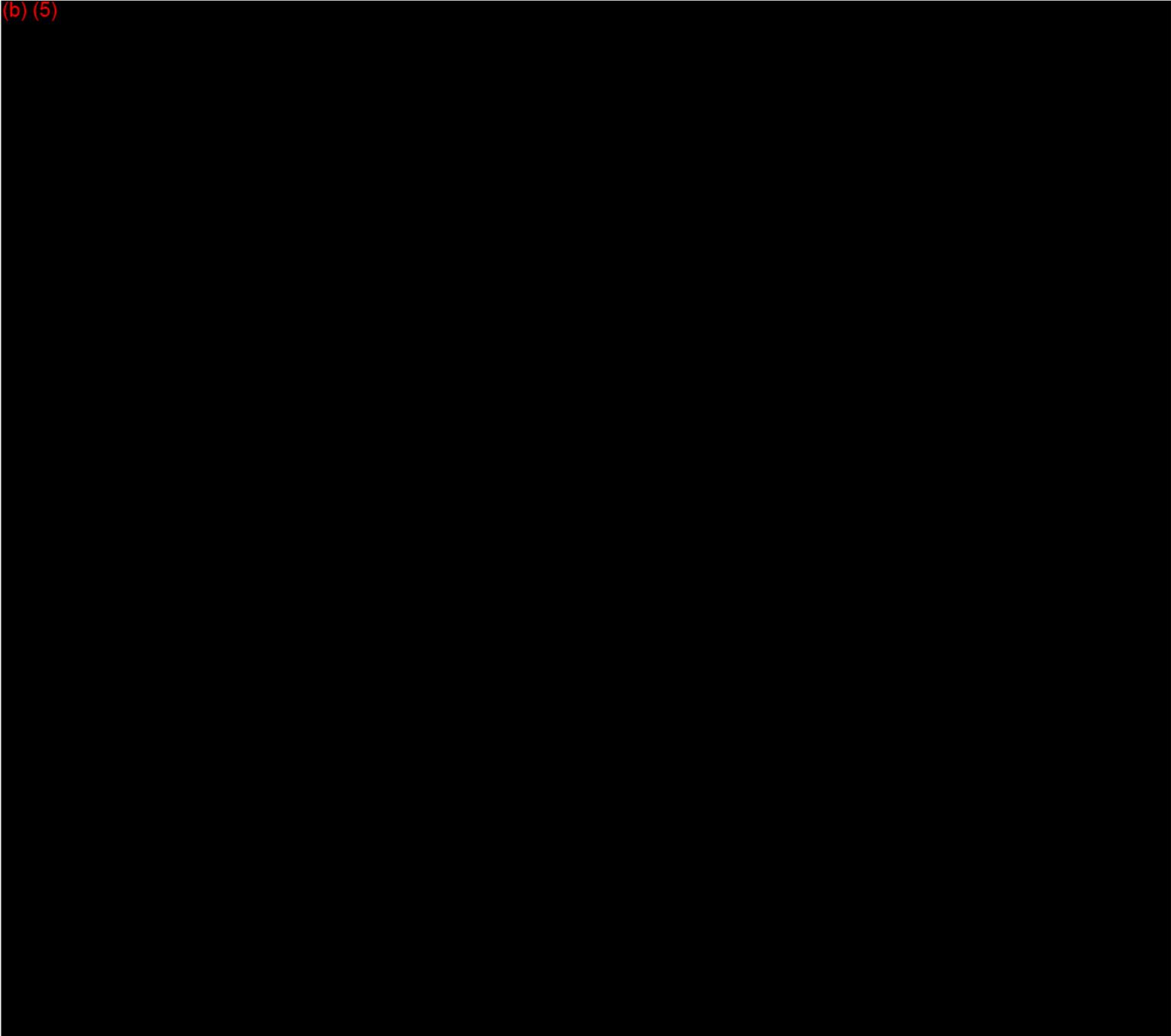
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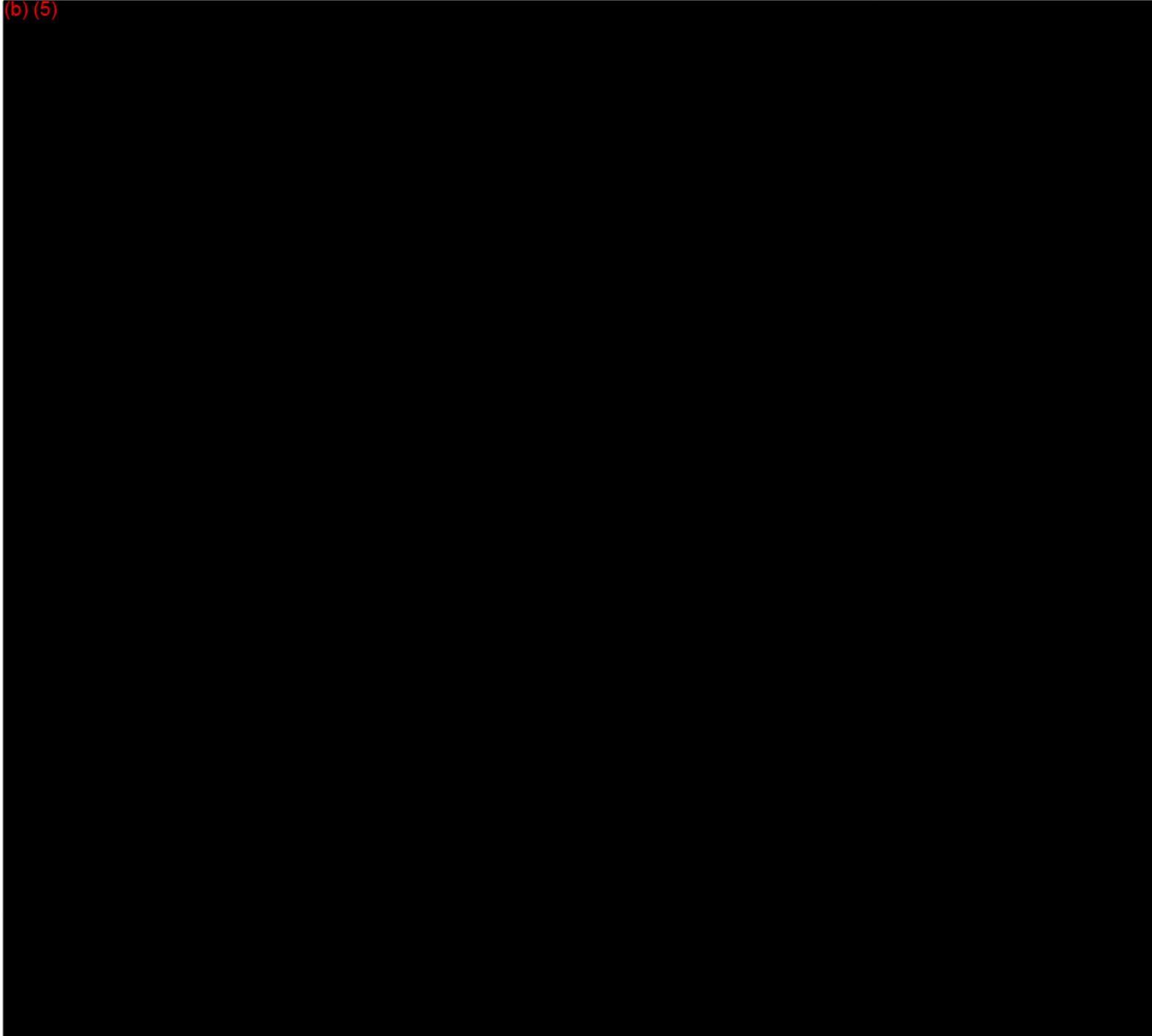
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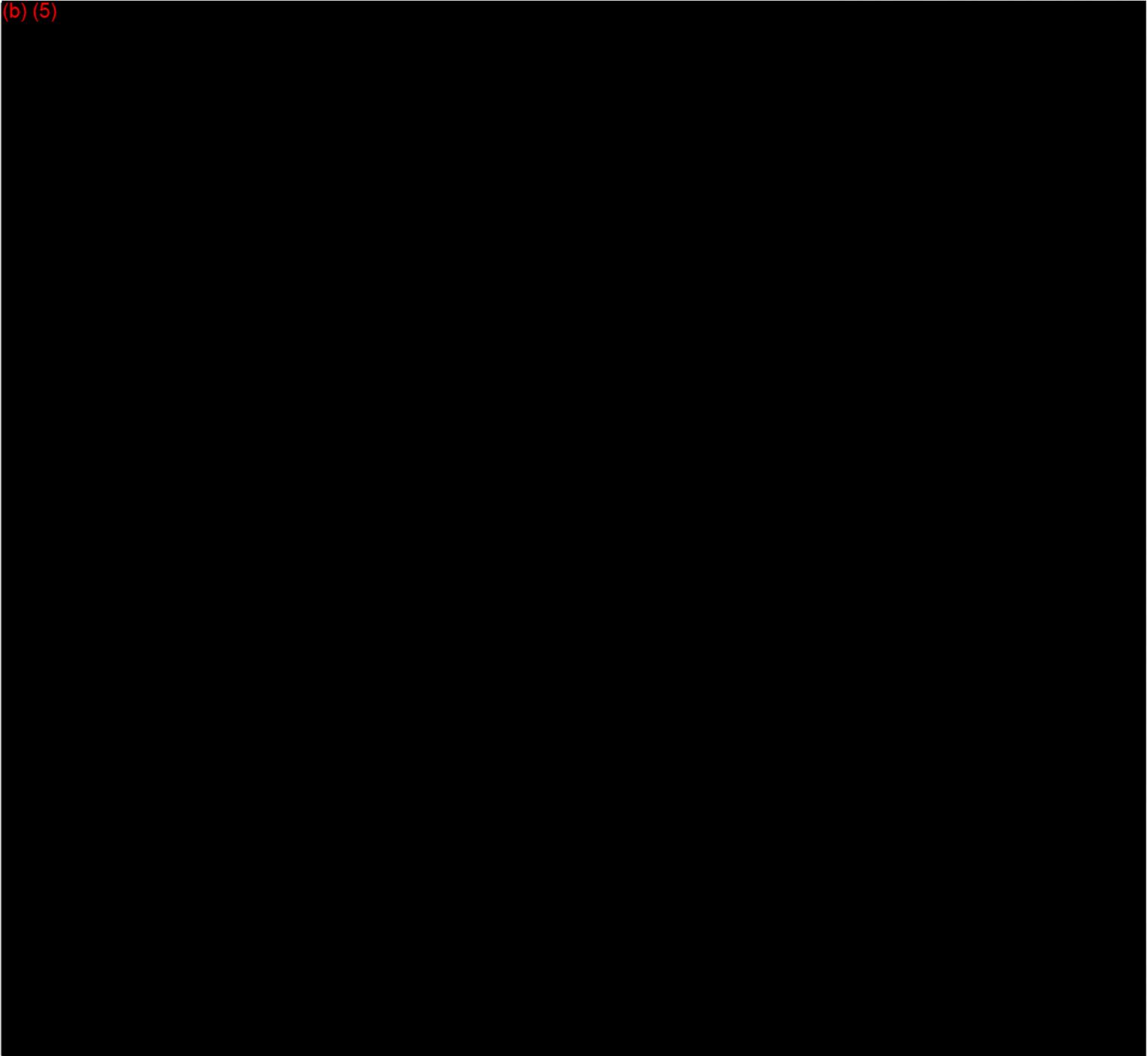
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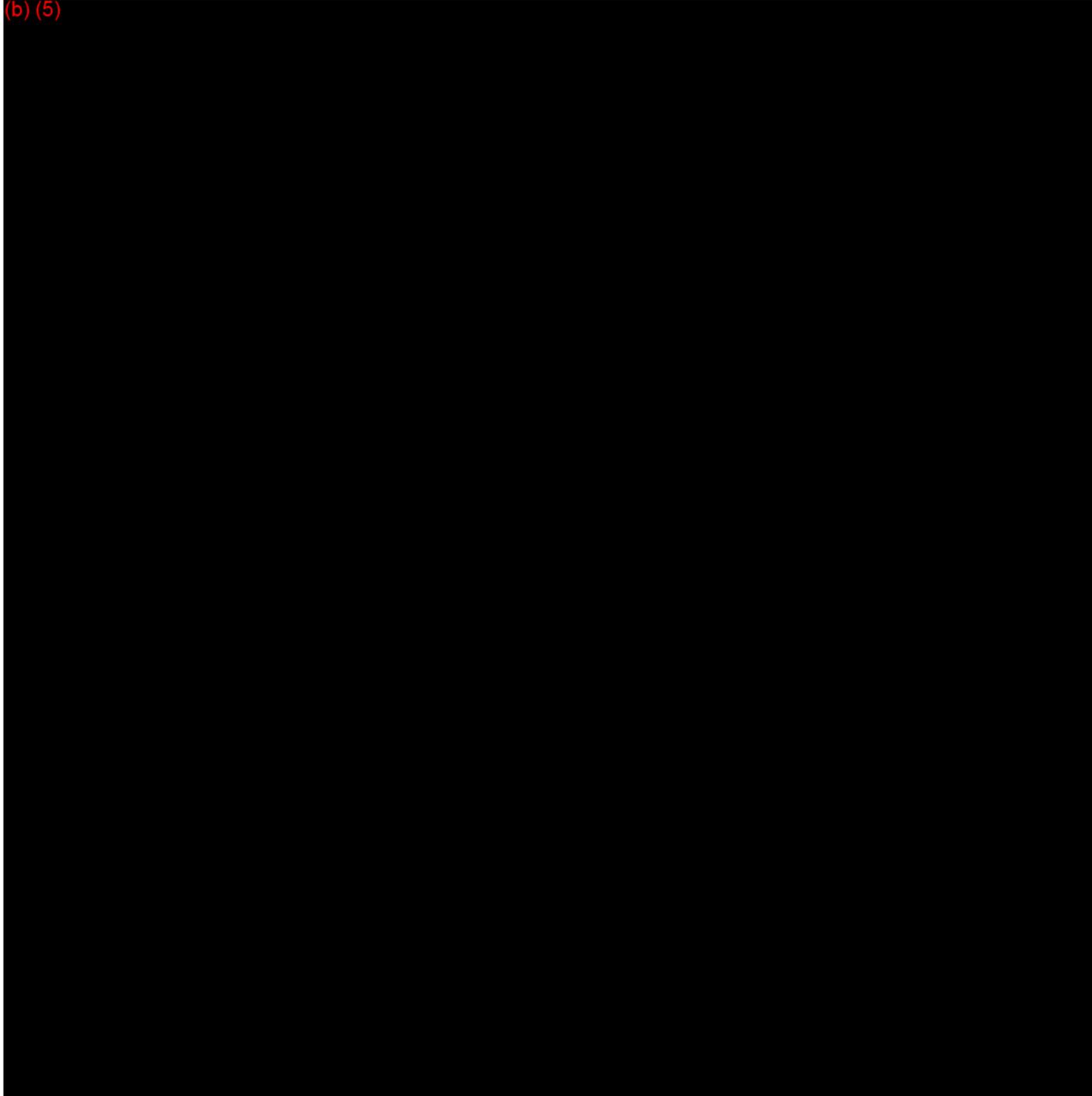
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(b) (5)



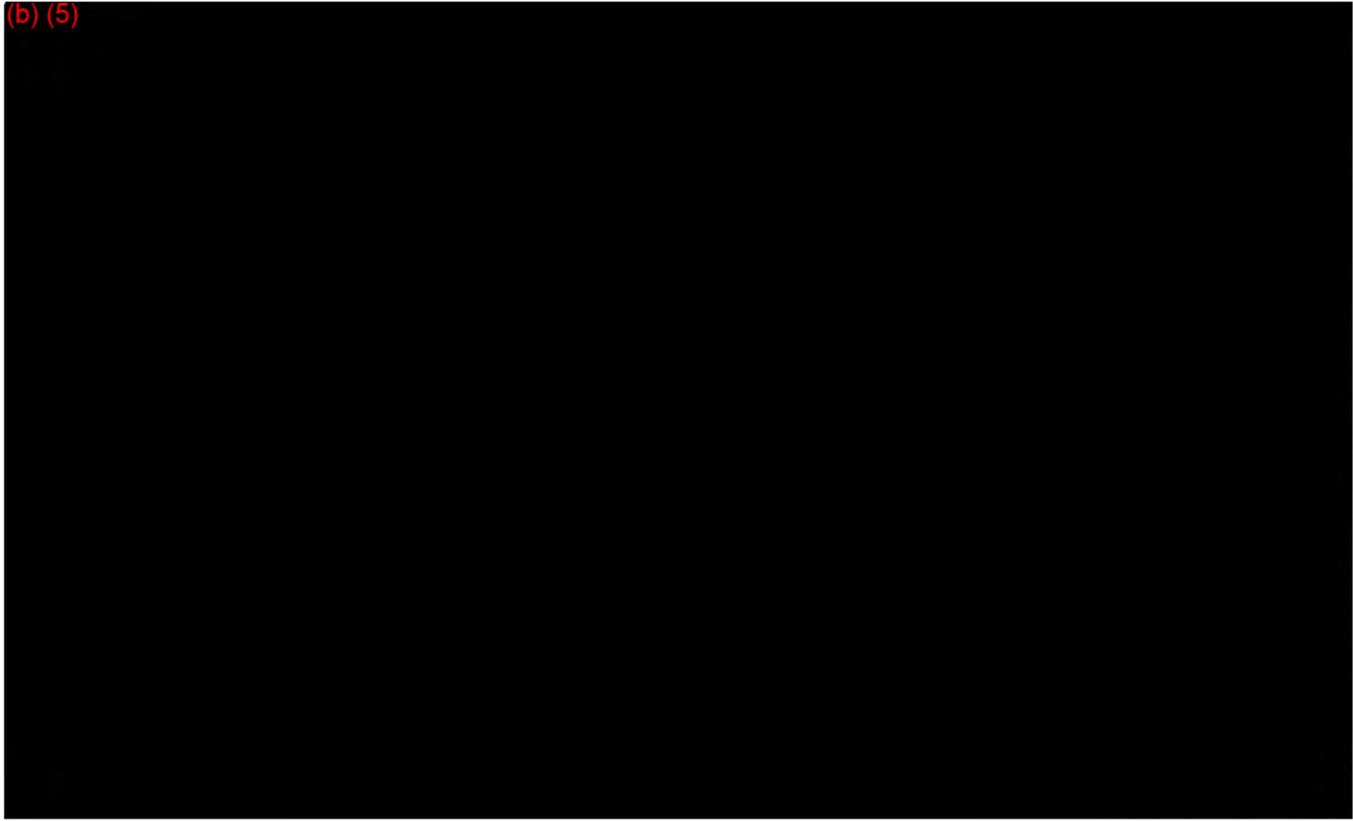
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(b) (5)



(b) (5)



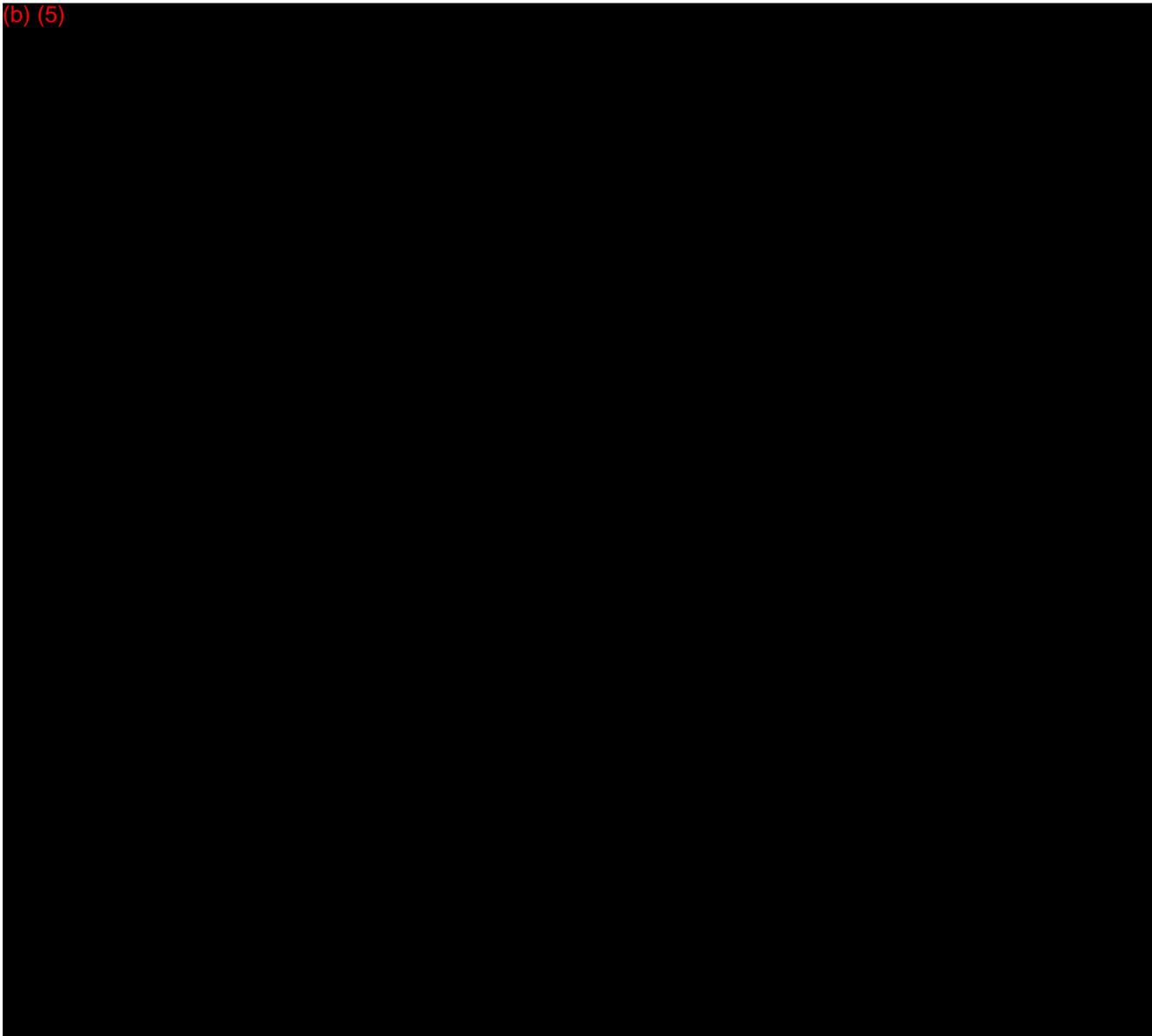
From: [Califf, Robert](#)
To: [Rodriguez, Jennifer](#); [Conover, Katie](#); [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: Q&A
Date: Sunday, September 11, 2016 8:22:00 AM
Attachments: [eteplirsen KMOA 9.5.16_rmc.doc](#)
[Phase II approval reactive QA 090916\(occ\)_rmc.doc](#)

Friends,

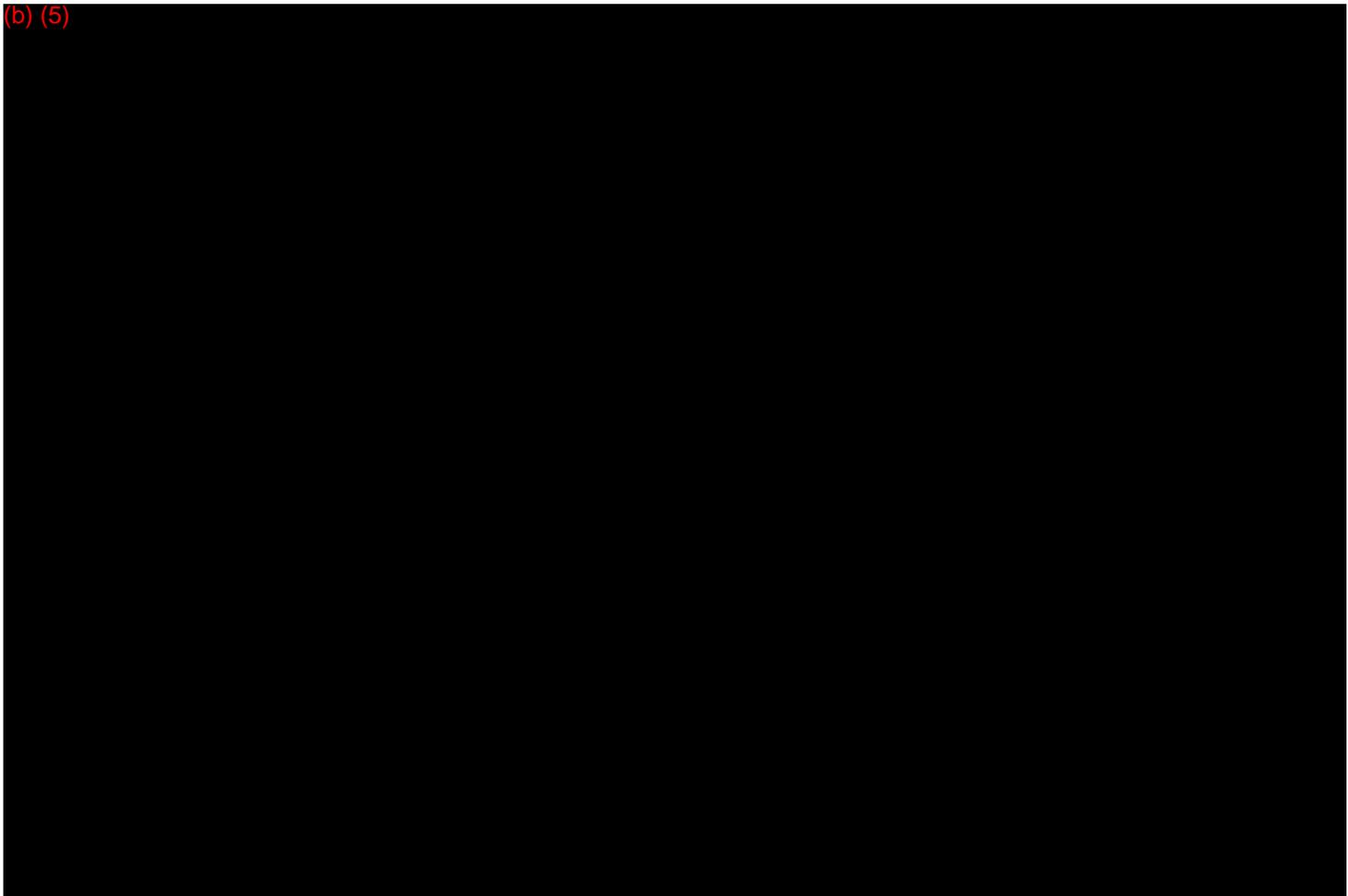
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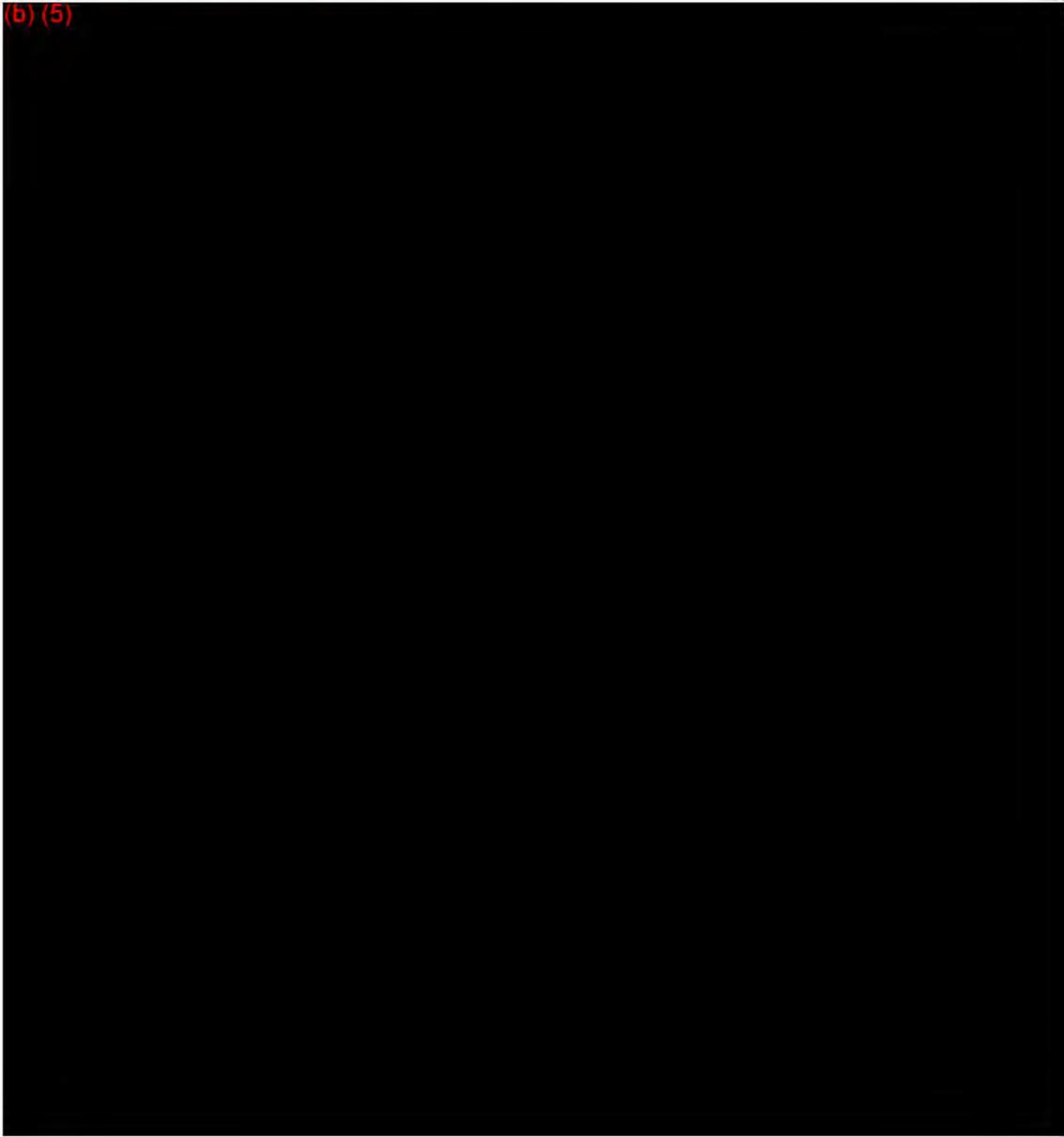
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Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

Target date: September 2016

(b) (5)

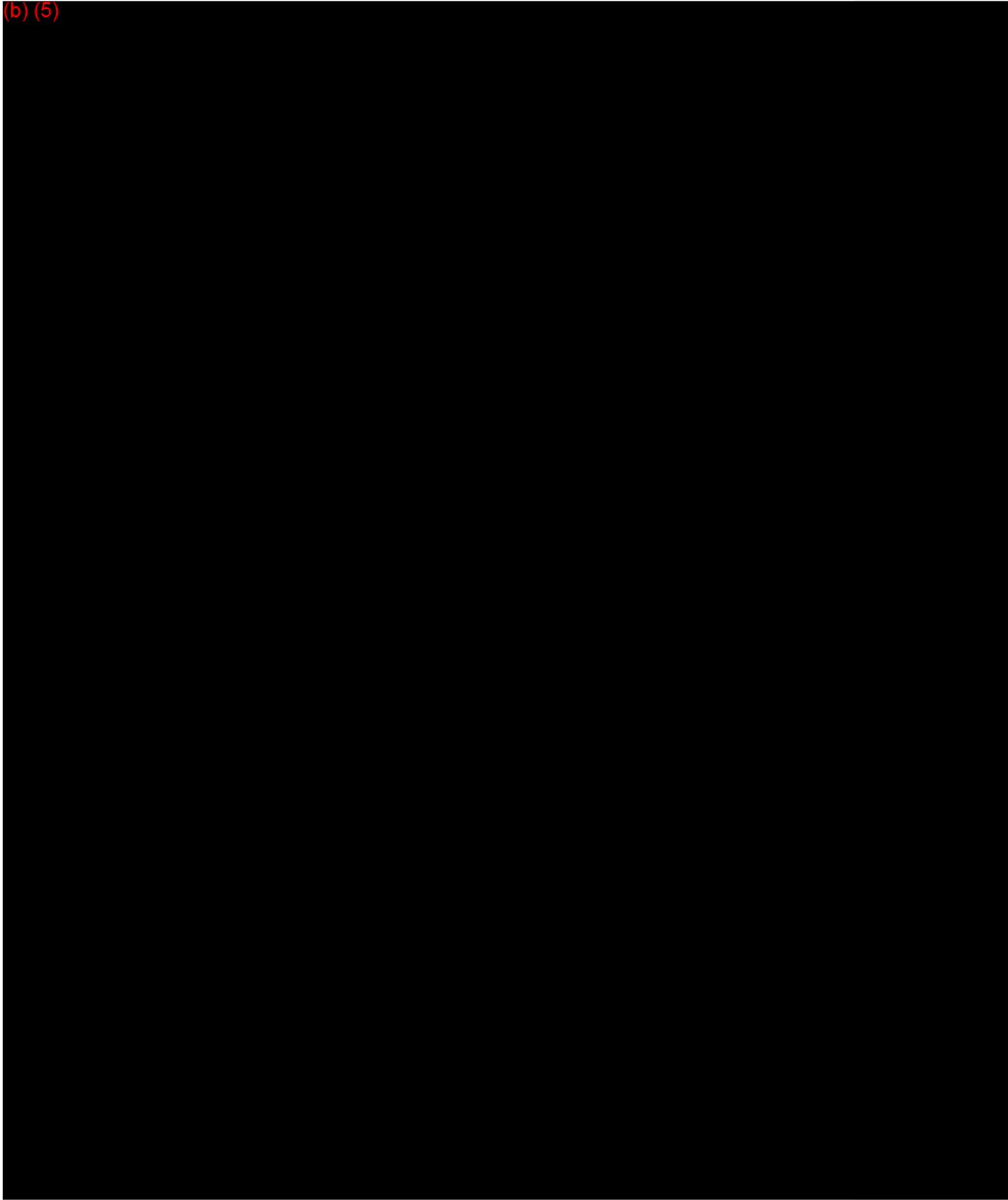


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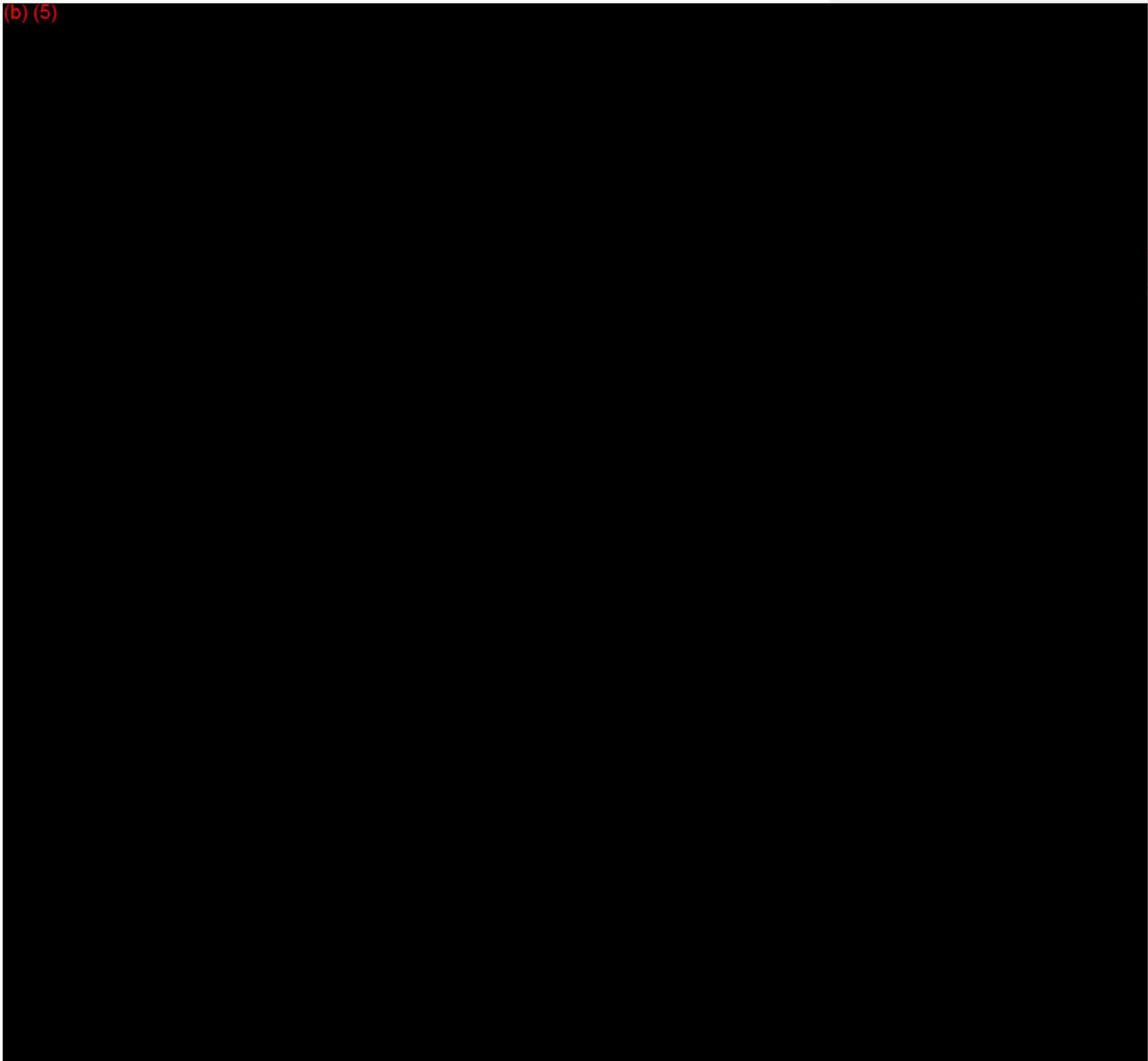
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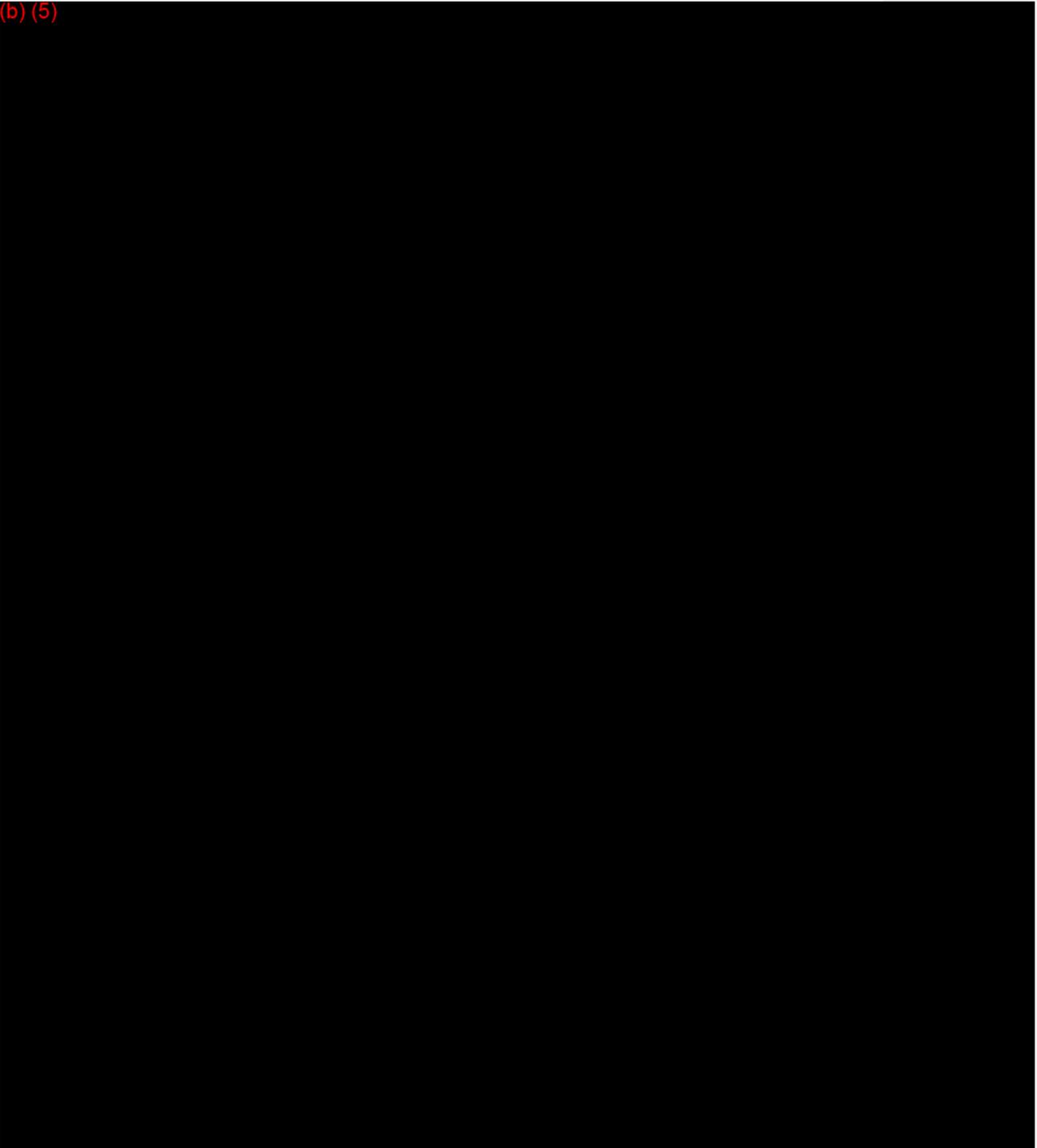


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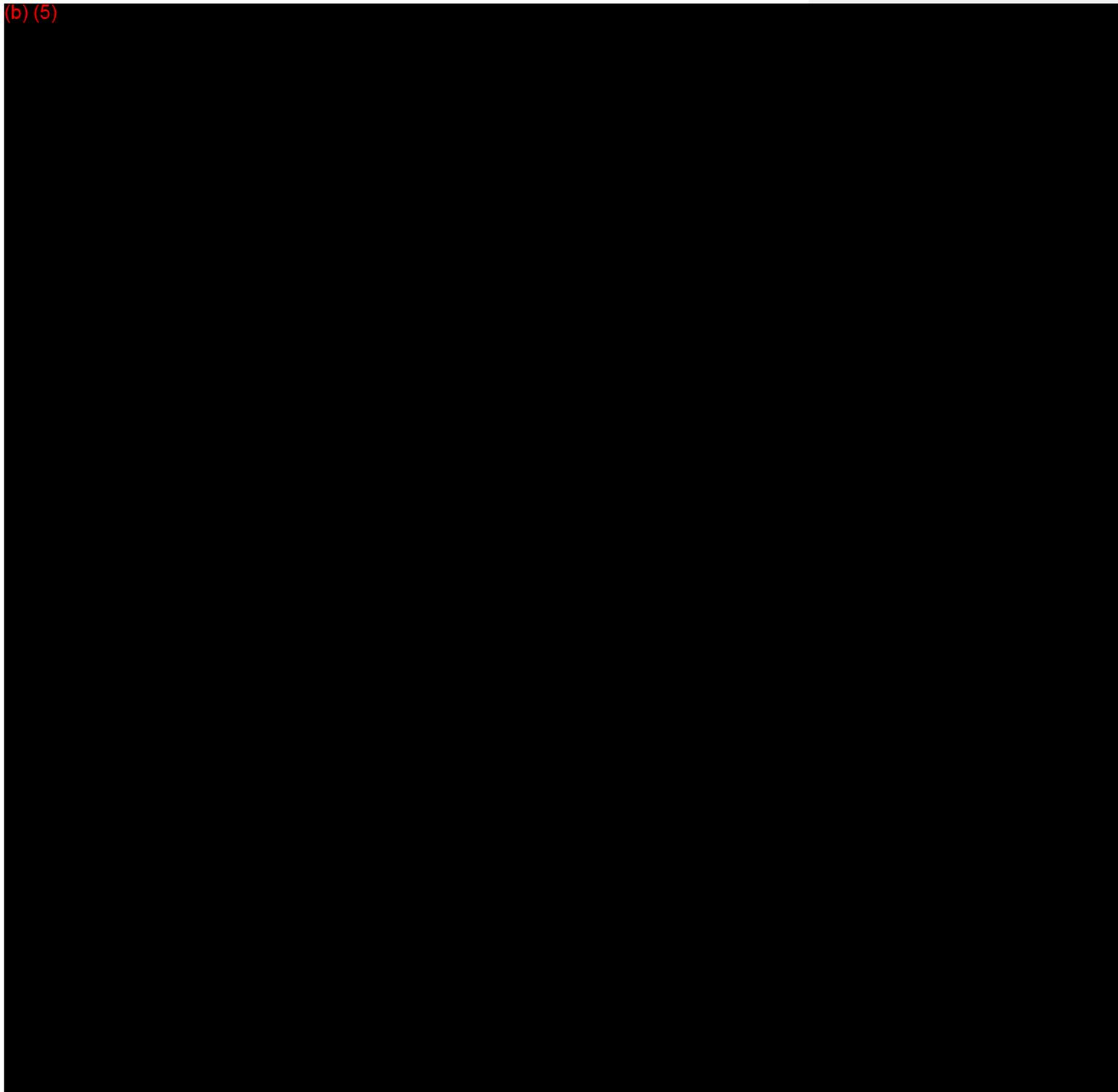
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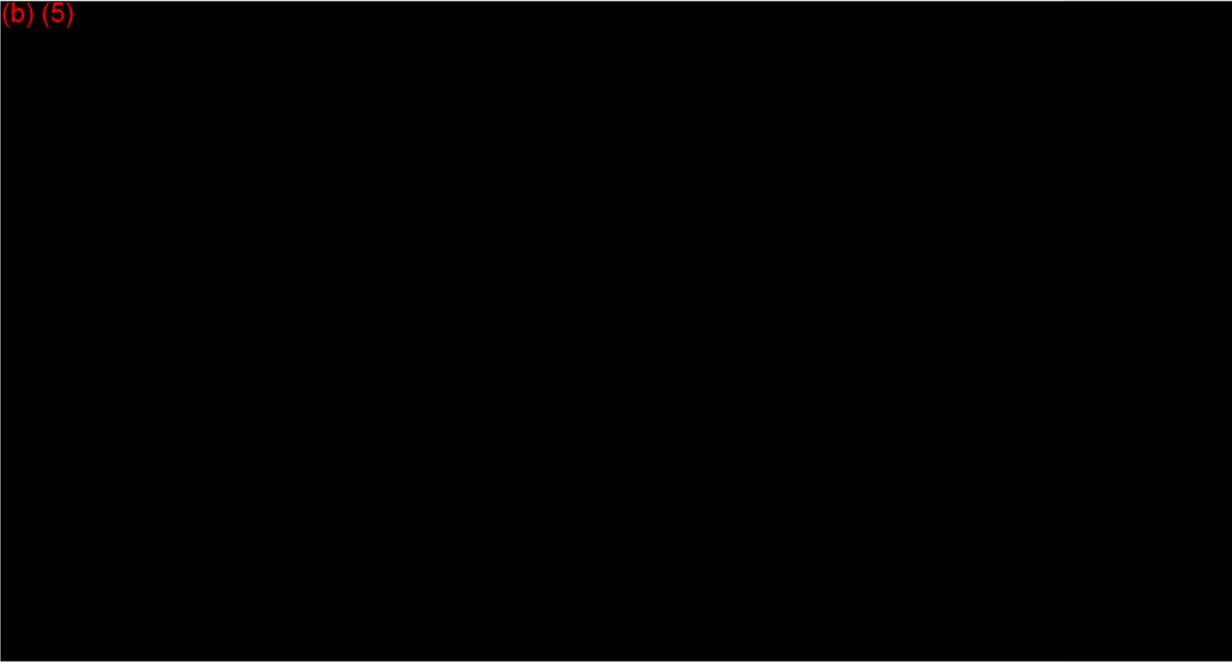


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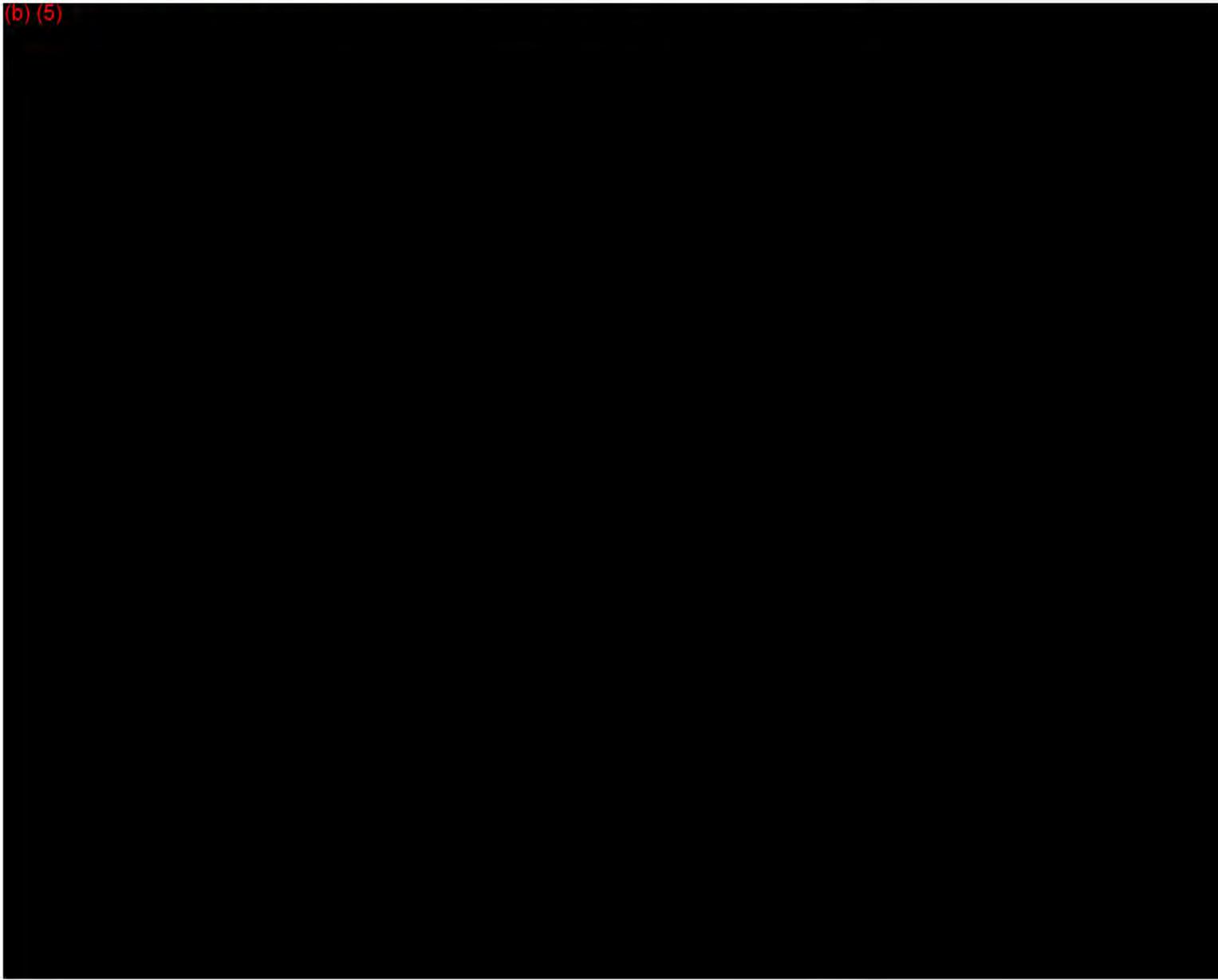
(b) (5)



Reactive Statement and QA: Posting of review documents for approval of
Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

Target date: September 2016

(b) (5)



(b) (5)

(b) (5)

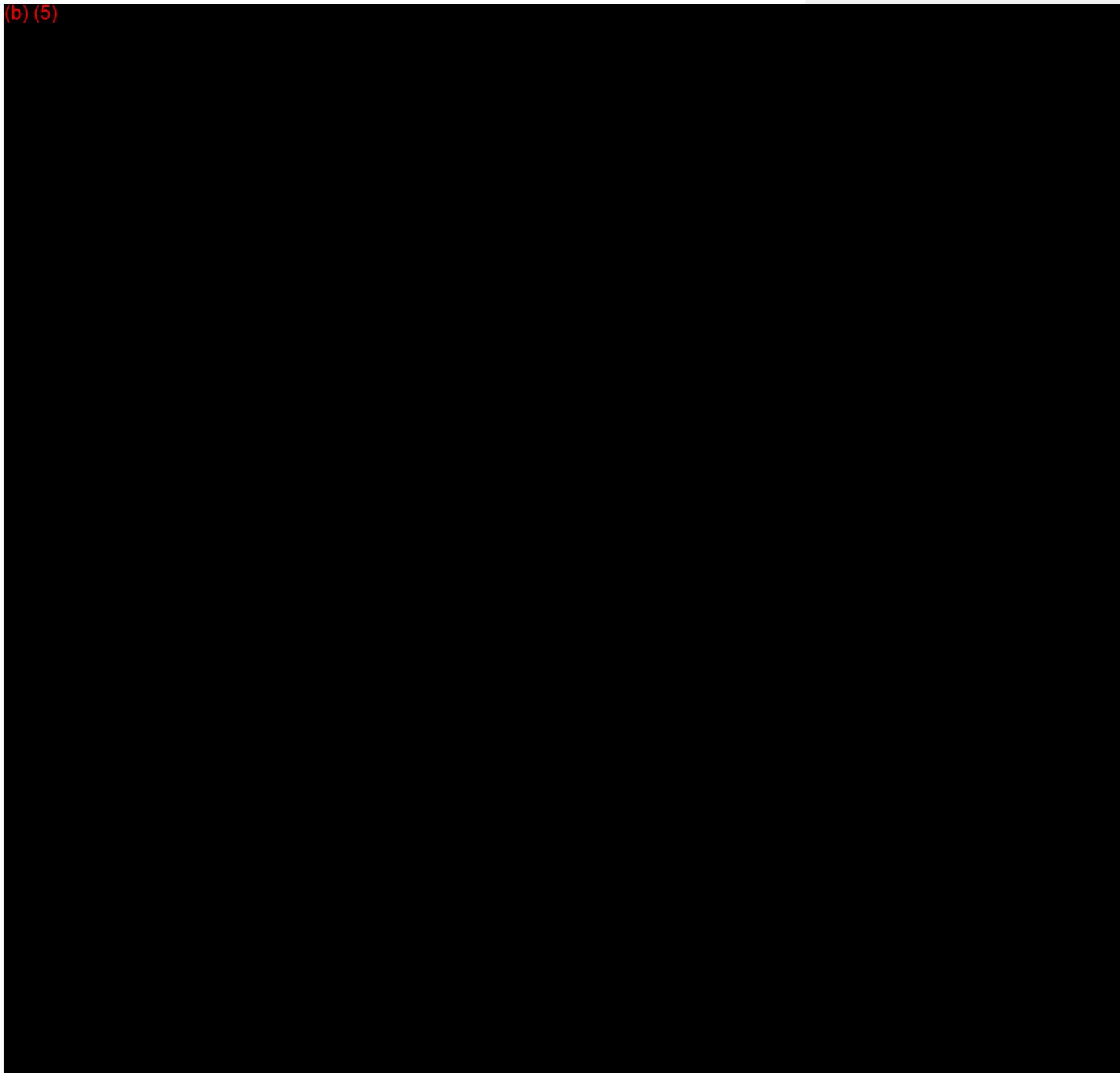
(b) (5)



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(b) (5)



From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Sherman, Rachel](#); [Rodriguez, Jennifer](#); [Conover, Katie](#)
Subject: RE: Q&A
Date: Sunday, September 11, 2016 8:48:00 PM

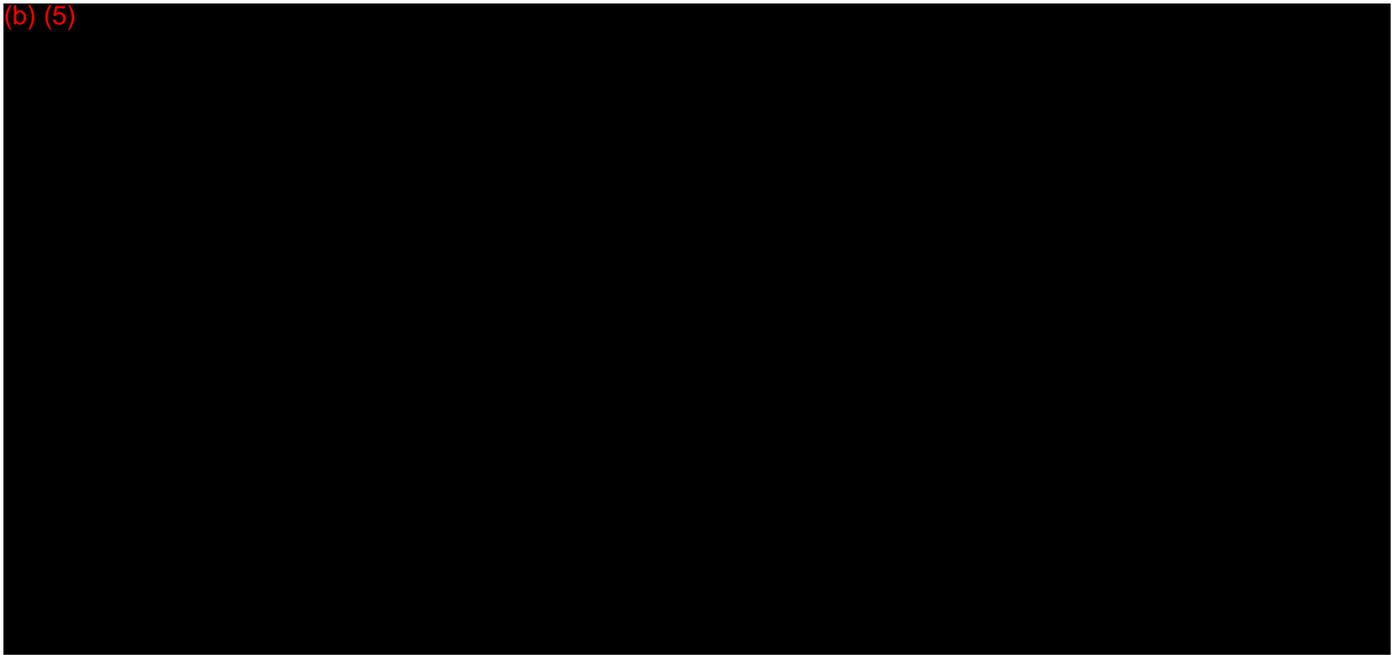
Good point

Thx

rmc

From: Dickinson, Elizabeth (FDA)
Sent: Sunday, September 11, 2016 8:32 PM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie
Subject: RE: Q&A

(b) (5)



From: Califf, Robert
Sent: Sunday, September 11, 2016 7:49 PM
To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

Nice job. These changes improve what I was trying to get across. Thanks.

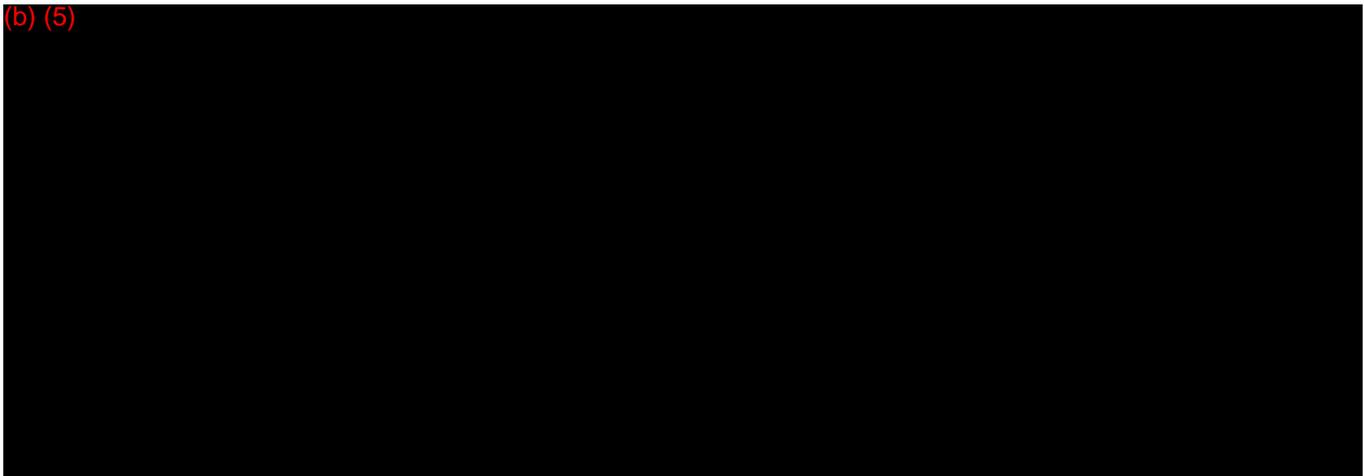
rmc

From: Chasan-Sloan, Deborah (FDA)

FDAOC0001824

Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

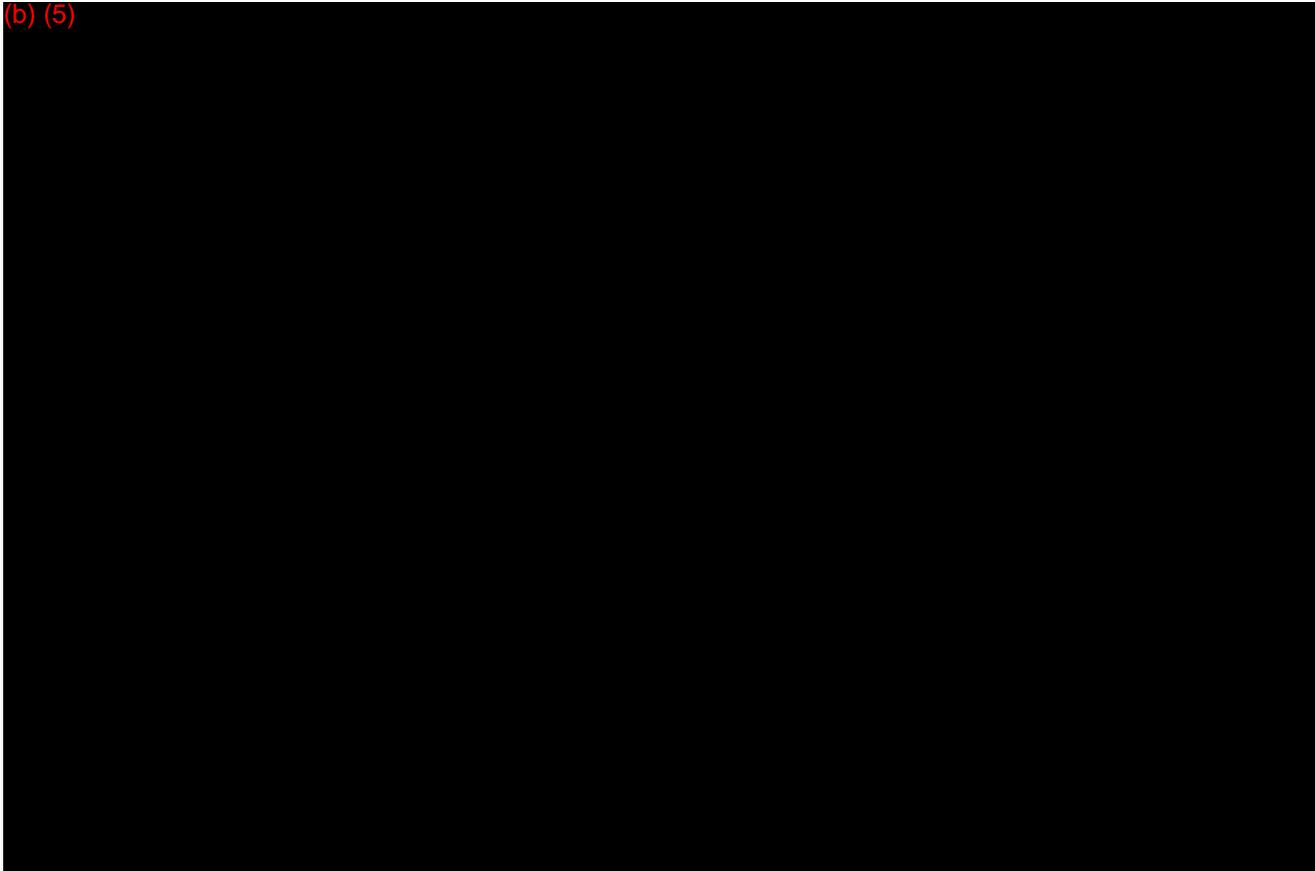
(b) (5)



From: Sherman, Rachel
Sent: Sunday, September 11, 2016 8:45 AM
To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.

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Hope this helps

Rachel

Why do you equivocate and say I'm right on most things? I thought we agreed I was always right.....

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To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

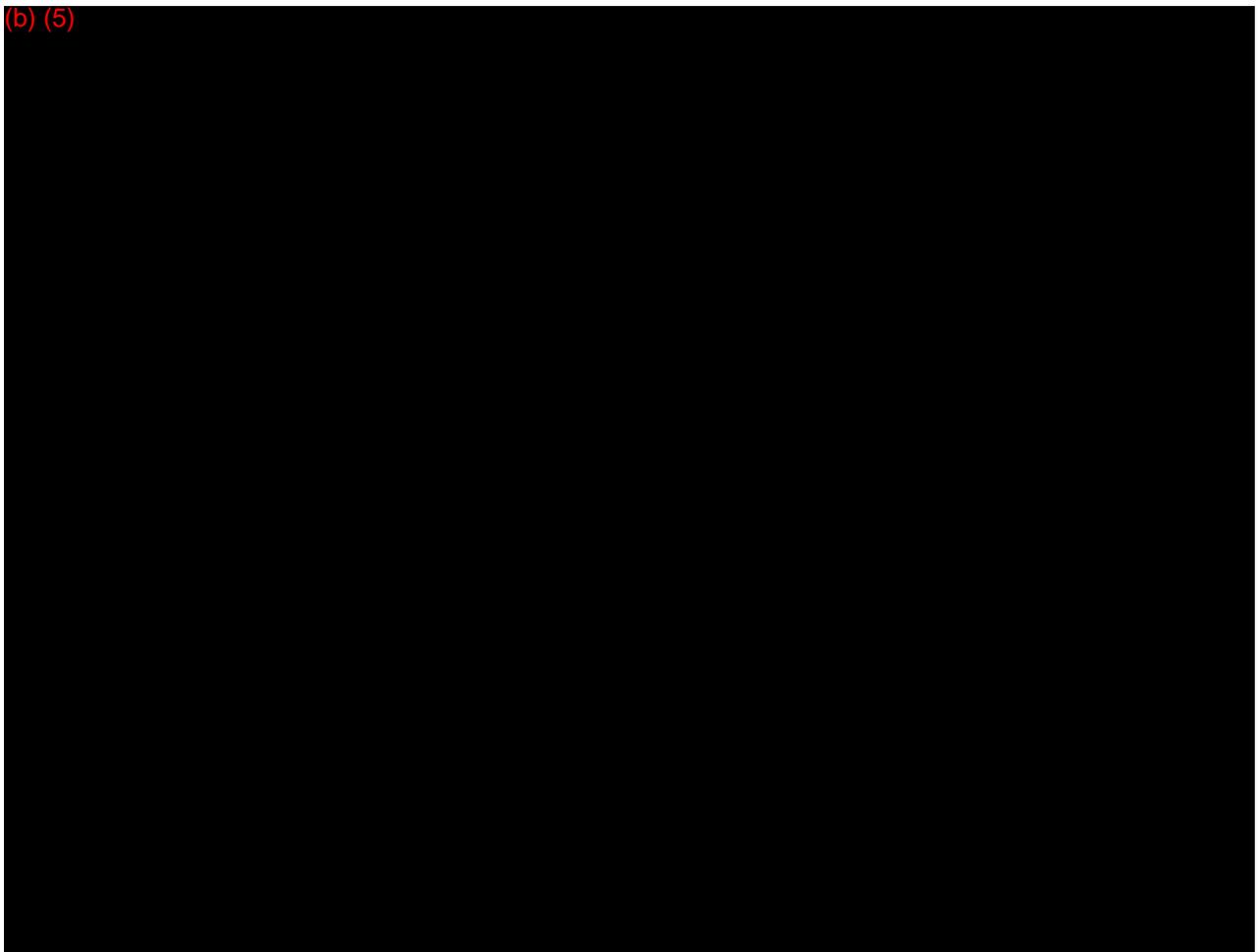
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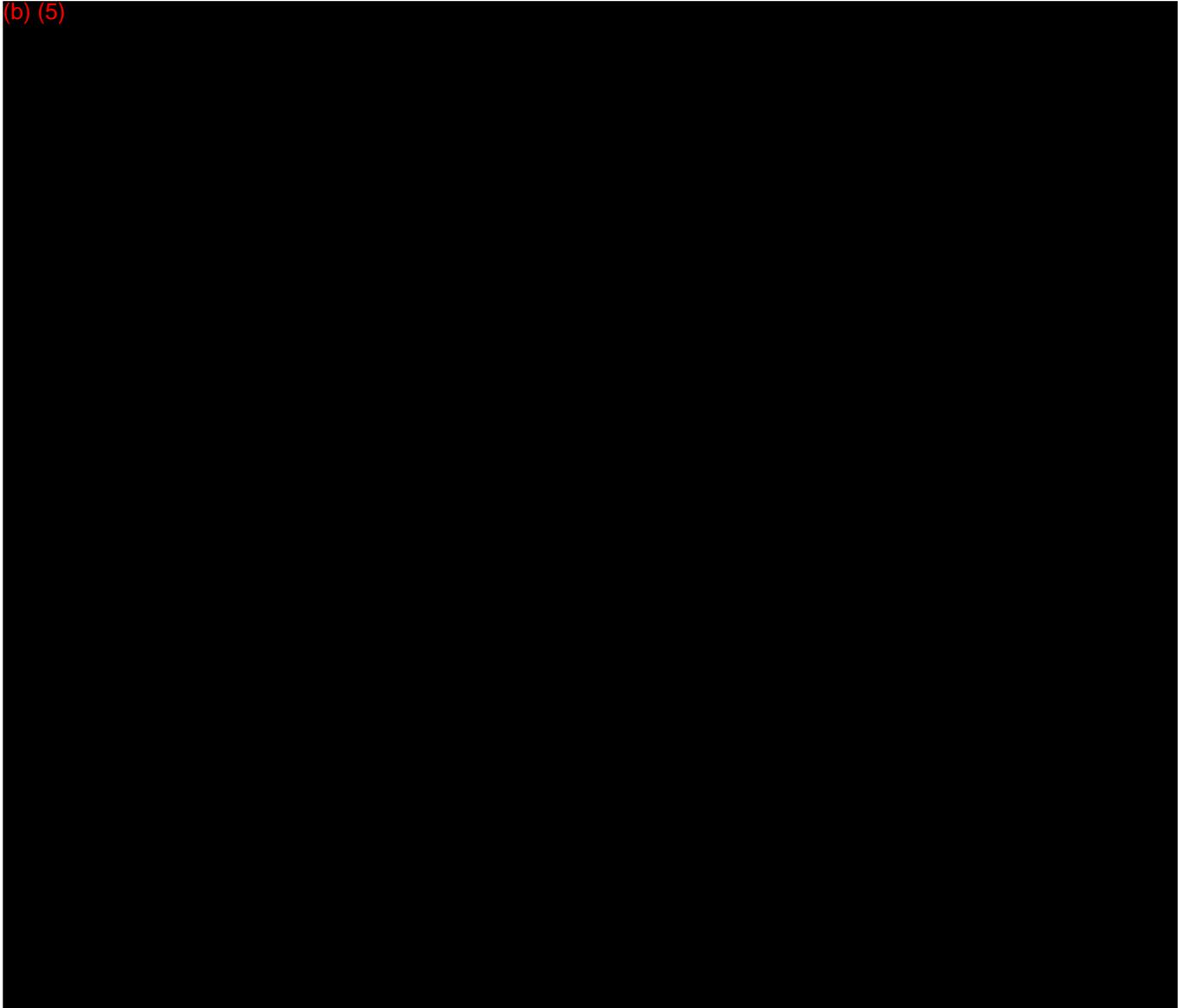
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From: [Califf, Robert](#)
To: [Rodriguez, Jennifer](#)
Subject: RE: Q&A
Date: Sunday, September 11, 2016 8:48:00 AM

How are we looking on the timeline? Is there a good time to talk today if need be? The next 2 weeks are unbelievable and I don't want to drop the ball!

rnc

Robert M Califf MD
Commissioner of Food and Drugs

From: Rodriguez, Jennifer
Sent: Sunday, September 11, 2016 8:46 AM
To: Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Conover, Katie
Subject: Re: Q&A

Thank you, Dr. Califf. I'll hold off on addressing to give Rachel and Liz/Deborah a chance to weigh in - then happy to work on addressing your points in the document.

Best,
Jen

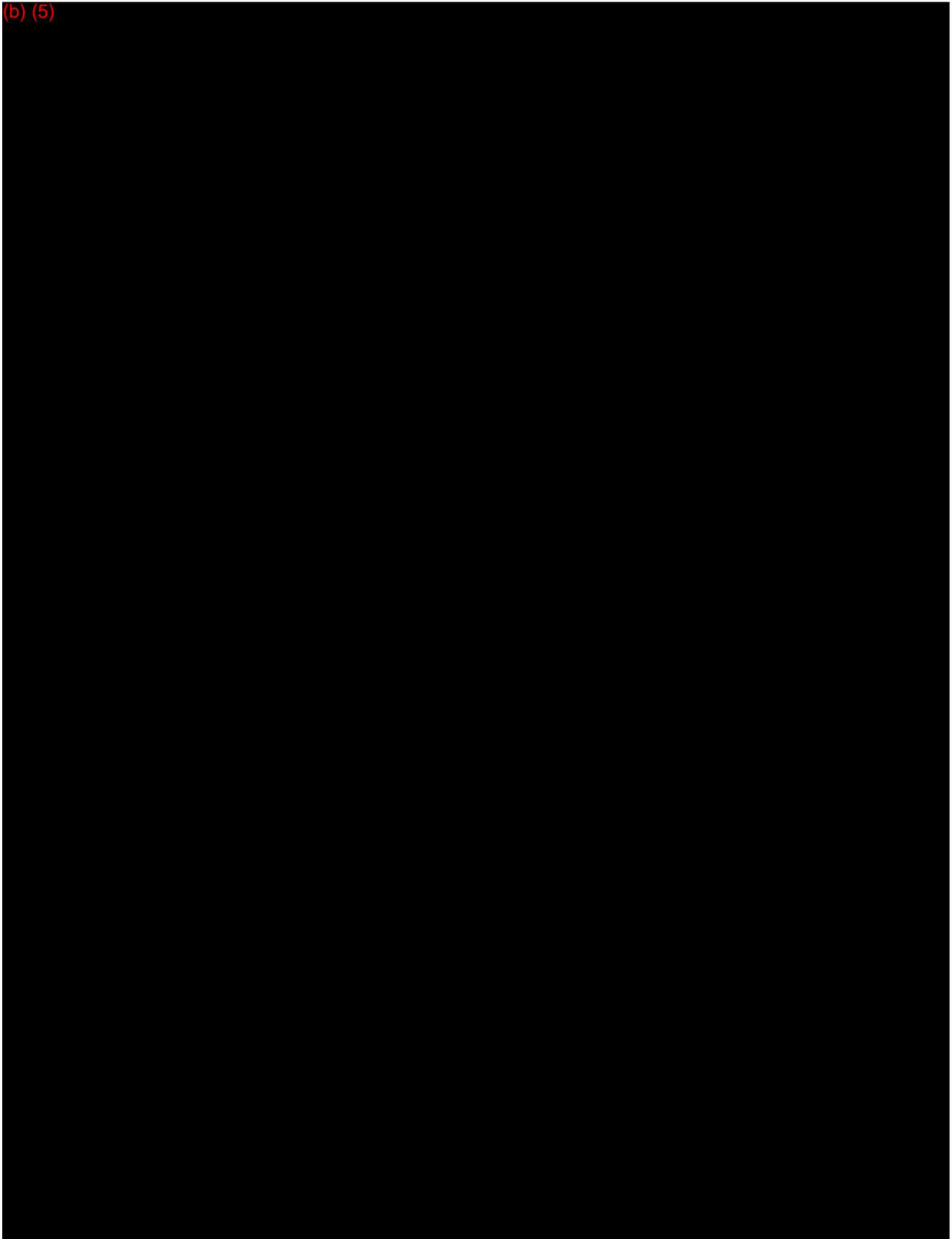
From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 11, 2016 at 8:22:33 AM EDT
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>
Subject: Q&A

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(b) (5)



From: [Califf, Robert](#)
To: [Sherman, Rachel](#)
Subject: FW: Follow up on Eteplirsen
Date: Sunday, September 11, 2016 8:50:00 AM

fyi

[Robert M Califf MD](#)

[Commissioner of Food and Drugs](#)

From: Califf, Robert
Sent: Sunday, September 11, 2016 7:13 AM
To: Jenkins, John K; Woodcock, Janet; Unger, Ellis
Subject: RE: Follow up on Eteplirsen

John,

Thanks for putting this list together. Much of this is in CDER's baileywick, but I want to be sure I do what I need to do. See below:

From: Jenkins, John K
Sent: Friday, September 09, 2016 4:09 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: Follow up on Eteplirsen

Rob

Do we have any follow up on the items we discussed yesterday and timelines? I just had my regular meeting with Ellis and we discussed the planned action. Some issues that need to be sorted out:

1. Timeline for approval action.

My understanding is that we're aiming for a week from tomorrow. Please let me know if that is not feasible.

2. Verification that we have reached final agreement on the labeling/PMRs with the sponsor. Ellis was not sure that there was final agreement on the labeling. Our usual practice/policy is to ensure that the sponsor has agreed to the labeling before approval, which is usually accomplished by the division sending the final draft of the label to the sponsor and the sponsor formally returning that to us indicating their concurrence. We can check to see if we have documentation of that agreement, or if there is a need to ask Sarepta to submit as final the most recent version of the labeling we sent them. Ellis can follow up and confirm the status. If there are to be any changes to the most recent version of the final draft label that

the division sent to the sponsor, we would ask that we be included in reviewing those edits. Same for the PMR.

Will follow with interest.

3. Timeline for Rob to meet with review team. Since the review team will have to be involved in some of the work to finalize action on the application, we recommend this meeting occur soon.

OK with me-I want to meet with them. It's a rough couple of weeks coming up so we'll have to do some rearranging. I'm out of town Wed and Thursday of this week and in town all week next week, but have a total of 12 "events" at which I have to make remarks. But I'm sure we can work it out on the schedule.

4. Timeline for sharing Rob's review memo with Ellis and me. Ideally this should occur in advance of the meeting with the review team so we can understand the context of Rob's decision.

Will get back with you later today.

5. Plans for the press release and release of documents that support the approval. Our normal process is to release the approval letter and the labeling on the day of approval, followed some time later (I think we have 30 days) by the redacted action package. In this case, we would strongly advocate for releasing the most important memoranda at the time of approval to ensure transparency for the action. The more complete action package could then be released on the usual timeline (e.g., the CMC review, the pharm/tox review). In our view, the redacted documents that should be released at the time of approval would include the Cross Disciplinary Team Leader (CDTL) memo (Farkas), the deputy division director memo (Bastings), the ODE director decisional memo (Ellis), the Center Director decisional memo, Ellis' appeal memo, the acting Chief Scientist memo, and Rob's decisional memo. We strongly advocate for transparency in this case and if you agree these documents will need to be redacted on an expedited timeline.

Our plan has been as you say but to release all the memos at the time of all the other documents rather than with the approval letter and labeling. I have no particular reason to hold information back other than to give people all the information at one time. Glad to continue to discuss.

6. The draft press release. Again, we strongly advocate for transparency in the press release about the differing opinions, the appeal, and how the appeal was decided.

We will be transparent. The question is timing as above.

7. Any plans for press availability to discuss the approval. In the past for controversial/high

profile actions we have scheduled a media call where we describe the basis for the action and take questions from reporters. We have also often scheduled a separate briefing for stakeholders.

OEA had not planned a media call to my knowledge. For sure there will be a lot of media interest and questions.

I spent yesterday cleaning up a lot of other things and am available today if we need to talk.

John

From: [Califf, Robert](#)
To: [Rodriguez, Jennifer](#)
Subject: RE: Q&A
Date: Sunday, September 11, 2016 9:09:00 AM

I'd say anytime after dark. 9 pm would be best.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Rodriguez, Jennifer
Sent: Sunday, September 11, 2016 8:56 AM
To: Califf, Robert
Subject: RE: Q&A

This evening works best for me as well as my Dad is in town. Is there a good time for you and I can send a calendar invite?

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 11, 2016 at 8:55:03 AM EDT
To: Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>
Subject: RE: Q&A

Given that its going to be the first decent day in a while, should we aim for this evening? I admit I think we're going to the Nats!

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Rodriguez, Jennifer
Sent: Sunday, September 11, 2016 8:54 AM
To: Califf, Robert
Subject: RE: Q&A

We are tracking well on the revised timeline to have this out on Monday, Sept. 19. I've given HHS a heads up that we will need their expedited review.

I just wrote and suggested we try to speak about the media/timing approach today if you are available. Would also be great to work out your three points below if Rachel can join us.

Best,
Jen

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 11, 2016 at 8:48:05 AM EDT
To: Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>
Subject: RE: Q&A

How are we looking on the timeline? Is there a good time to talk today if need be? The next 2 weeks are unbelievable and I don't want to drop the ball!

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Robert M Califf MD
Commissioner of Food and Drugs

From: Rodriguez, Jennifer
Sent: Sunday, September 11, 2016 8:46 AM
To: Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Conover, Katie
Subject: Re: Q&A

Thank you, Dr. Califf. I'll hold off on addressing to give Rachel and Liz/Deborah a chance to weigh in - then happy to work on addressing your points in the document.

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Jen

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 11, 2016 at 8:22:33 AM EDT
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>

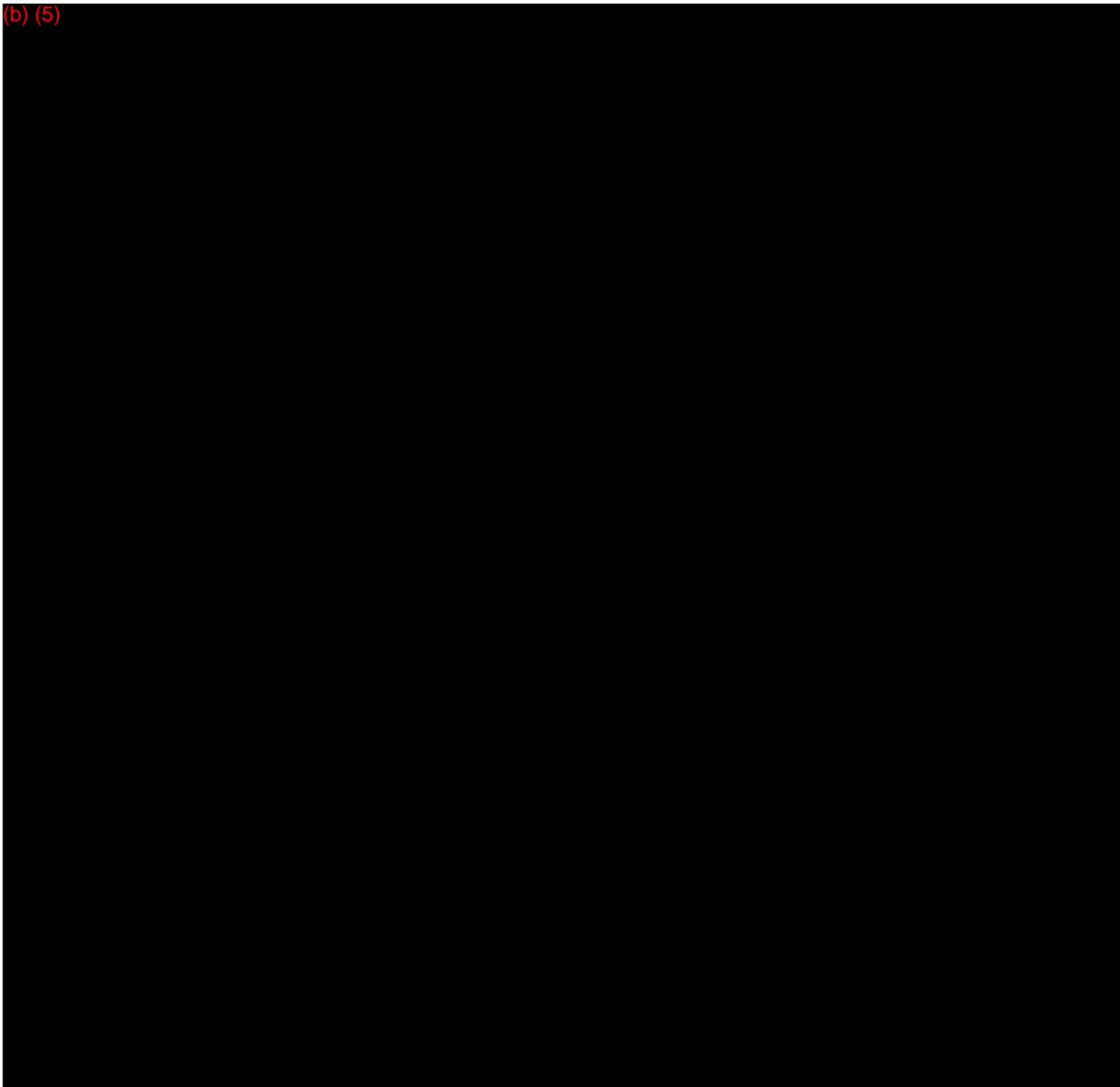
Subject: Q&A

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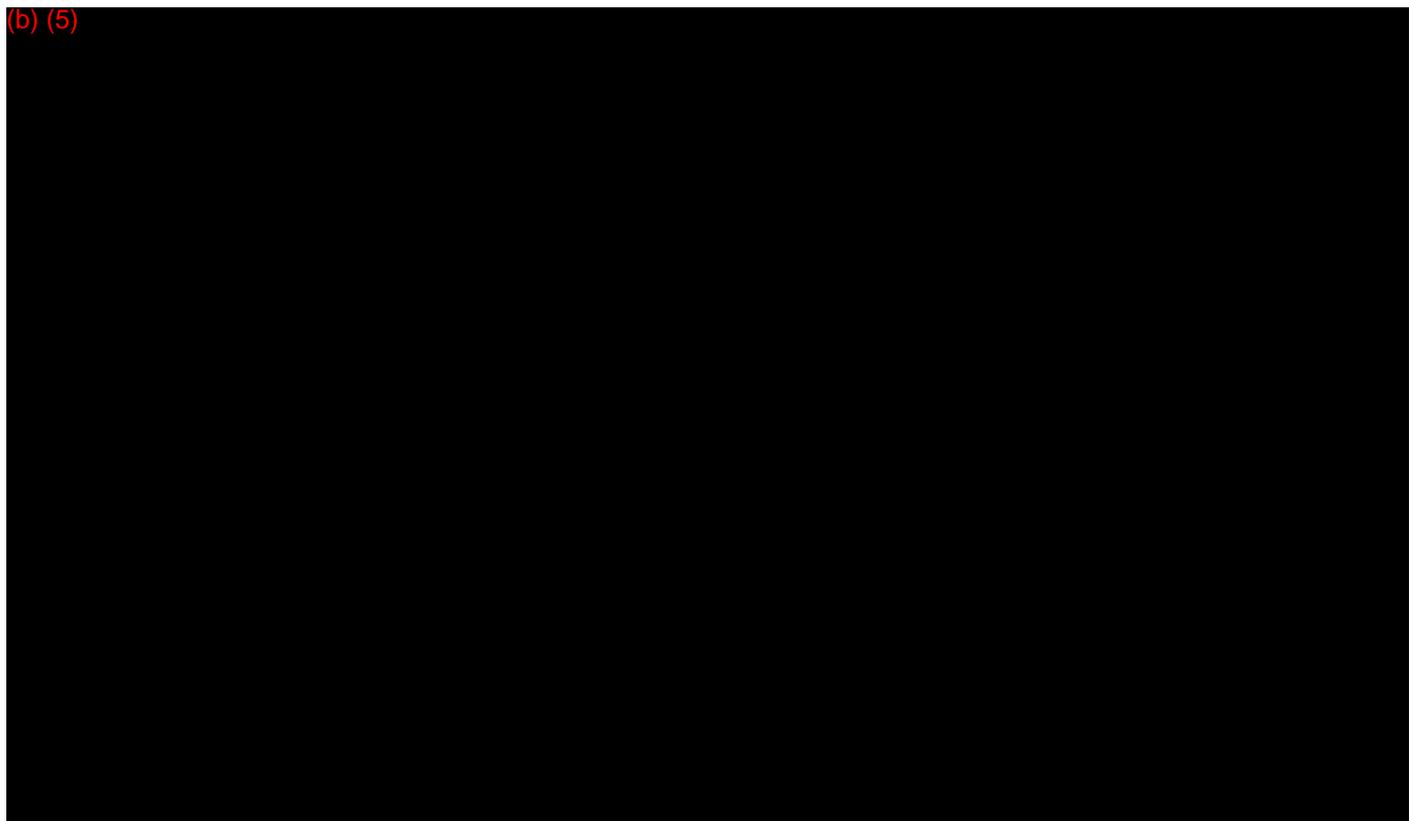
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(b) (5)



From: [Califf, Robert](#)
To: [Rodriguez, Jennifer](#)
Subject: FW: Q&A
Date: Sunday, September 11, 2016 9:45:00 PM
Attachments: [eteplirsen KMOA 9.5.16_rmc\(occ\).doc](#)

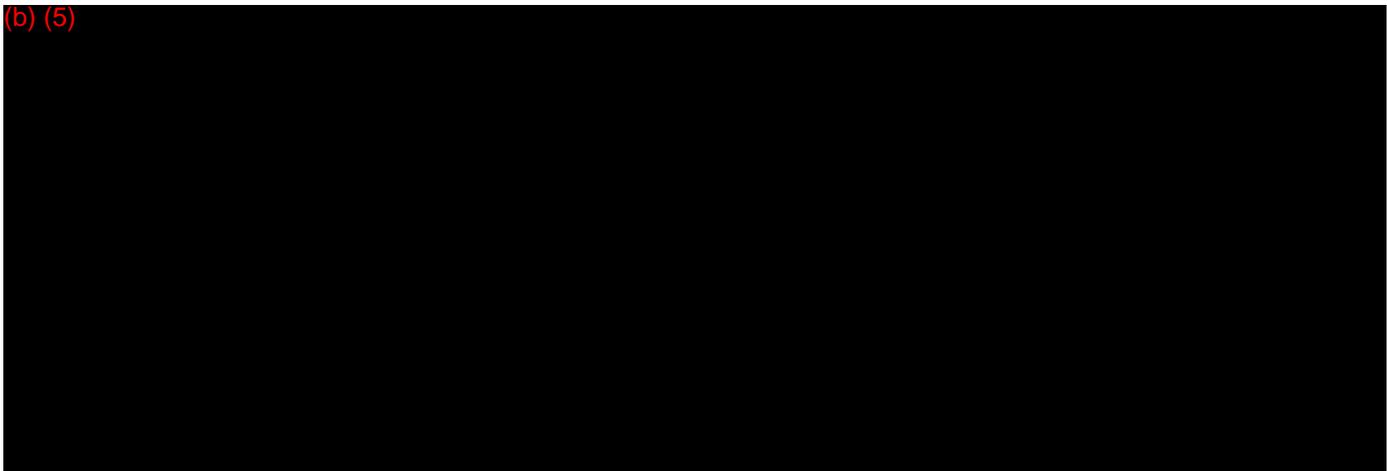
Can you circulate new drafts tomorrow? This is very close.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

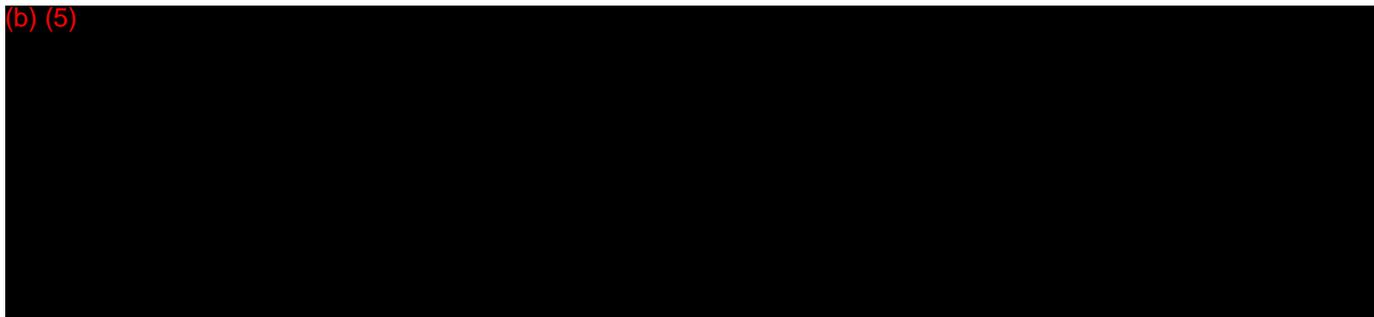
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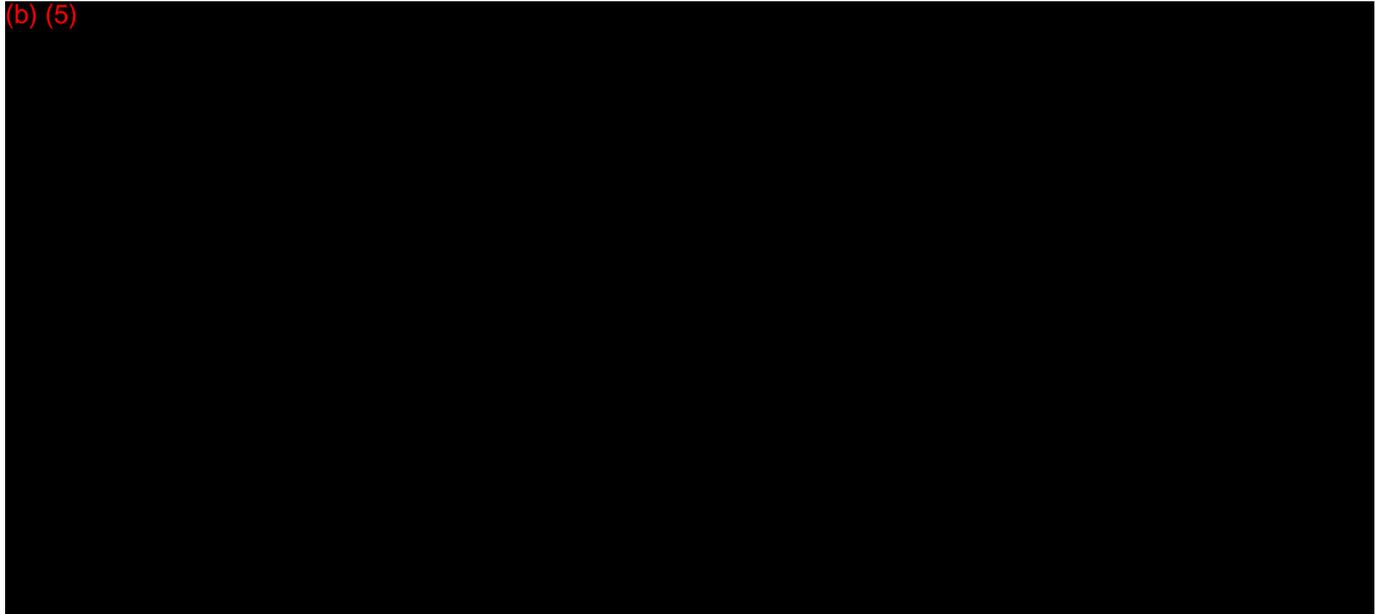
From: Sherman, Rachel
Sent: Sunday, September 11, 2016 8:45 AM
To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.

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Hope this helps

Rachel

Why do you equivocate and say I'm right on most things? I thought we agreed I was always right.....

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Sent: Sunday, September 11, 2016 8:23 AM

To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

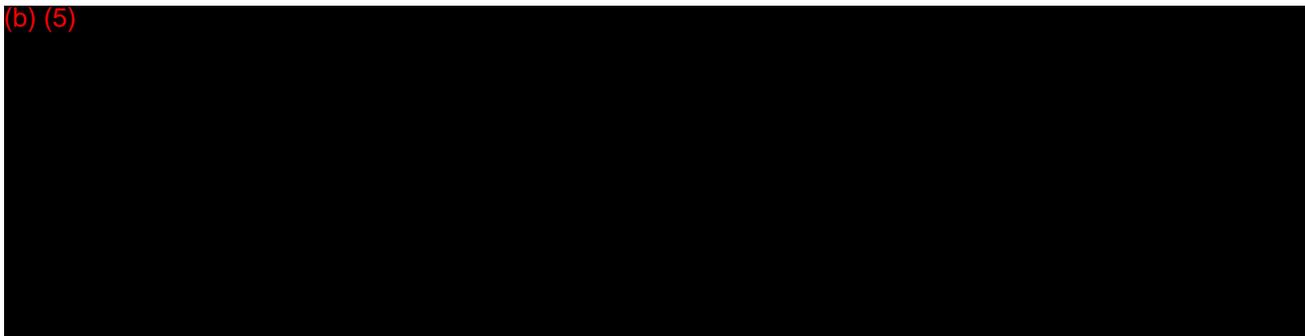
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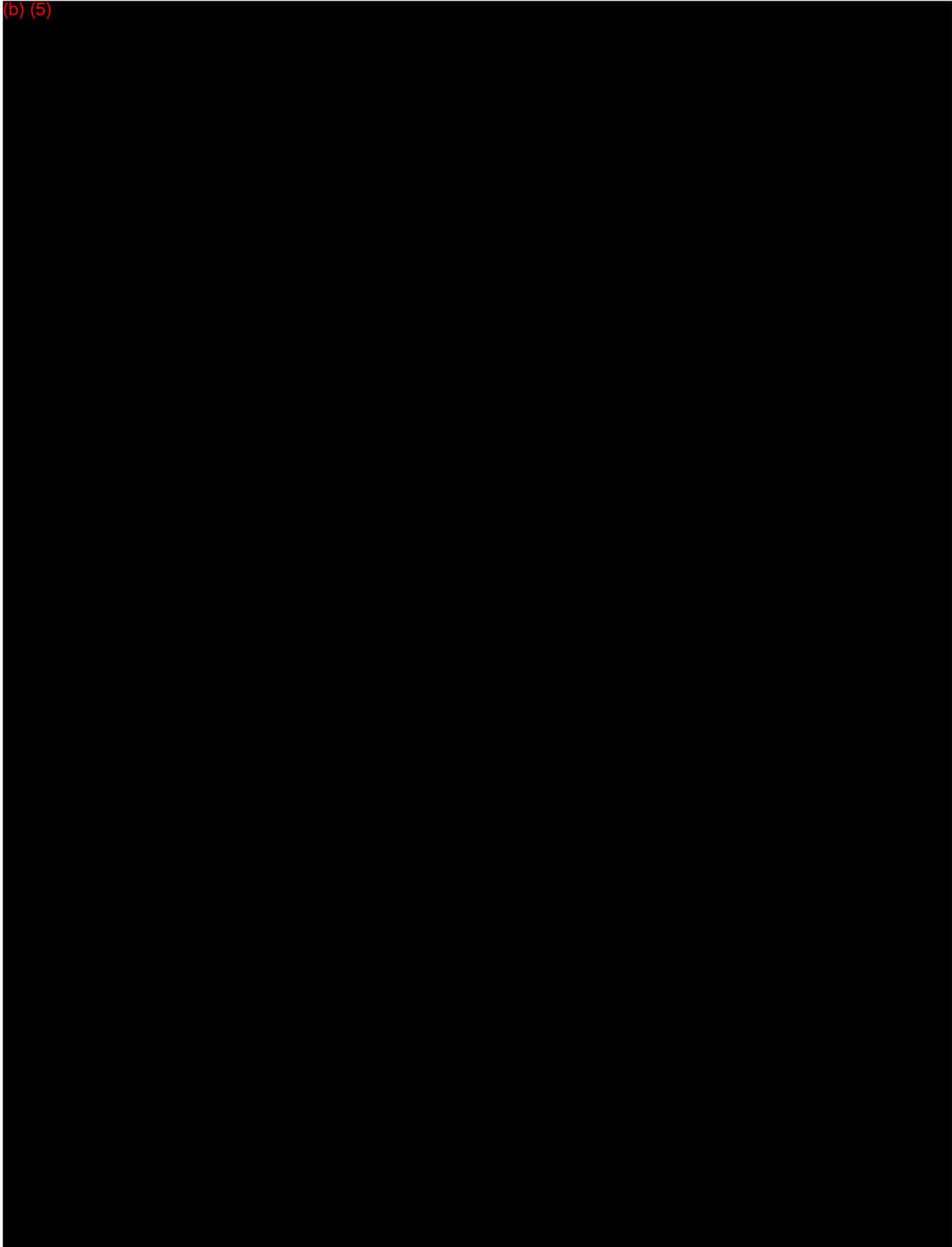
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From: [Califf, Robert](#)
To: [Chasan-Sloan, Deborah \(FDA\)](#); [Sherman, Rachel](#); [Rodriguez, Jennifer](#); [Conover, Katie](#); [Dickinson, Elizabeth \(FDA\)](#); [Kraus, Tom](#)
Cc: [McCall, Jonathan *](#)
Subject: RE: Q&A
Date: Monday, September 12, 2016 6:54:00 AM
Attachments: [2016_Sept_09_Eteplirsen_CLEAN-COMMENTED\(occ\)_rmc.doc](#)

Here is what I hope is the penultimate version of my memo. I'm assuming:

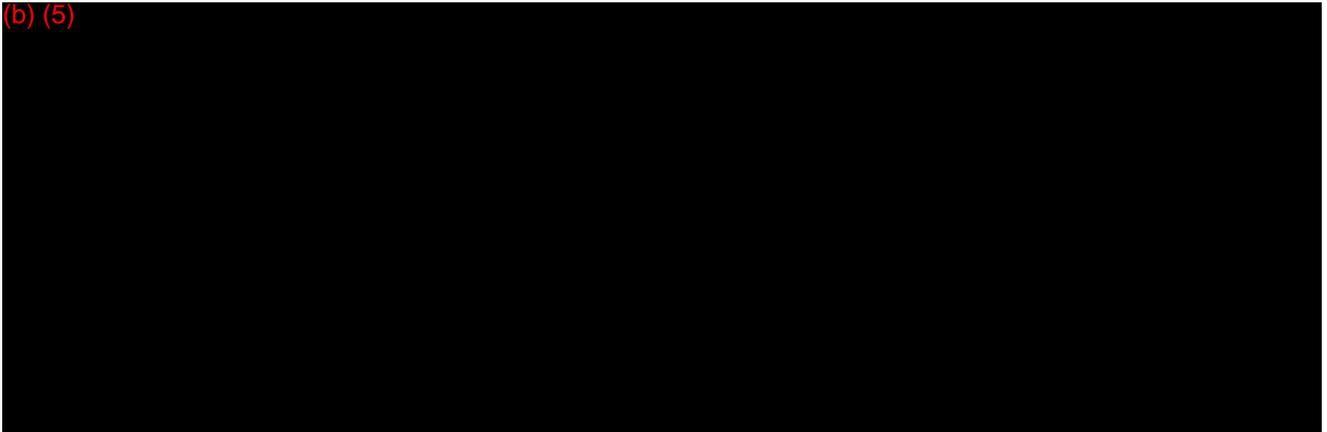
1. Jonathan will edit and recirculate.
2. People will have their final say today.
3. I will send to Ellis, John and Janet this afternoon with 24 hours to review.

Is this ok?

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

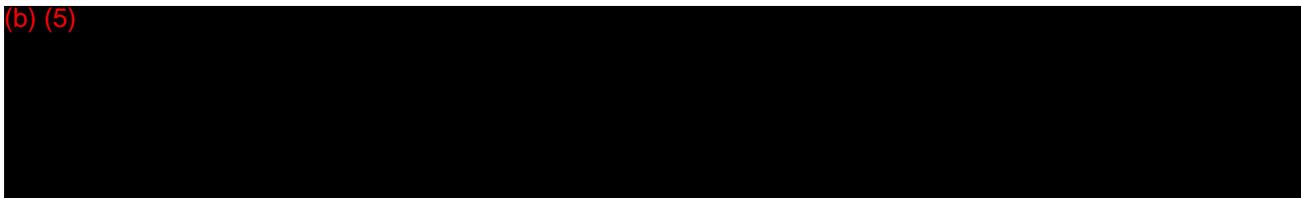
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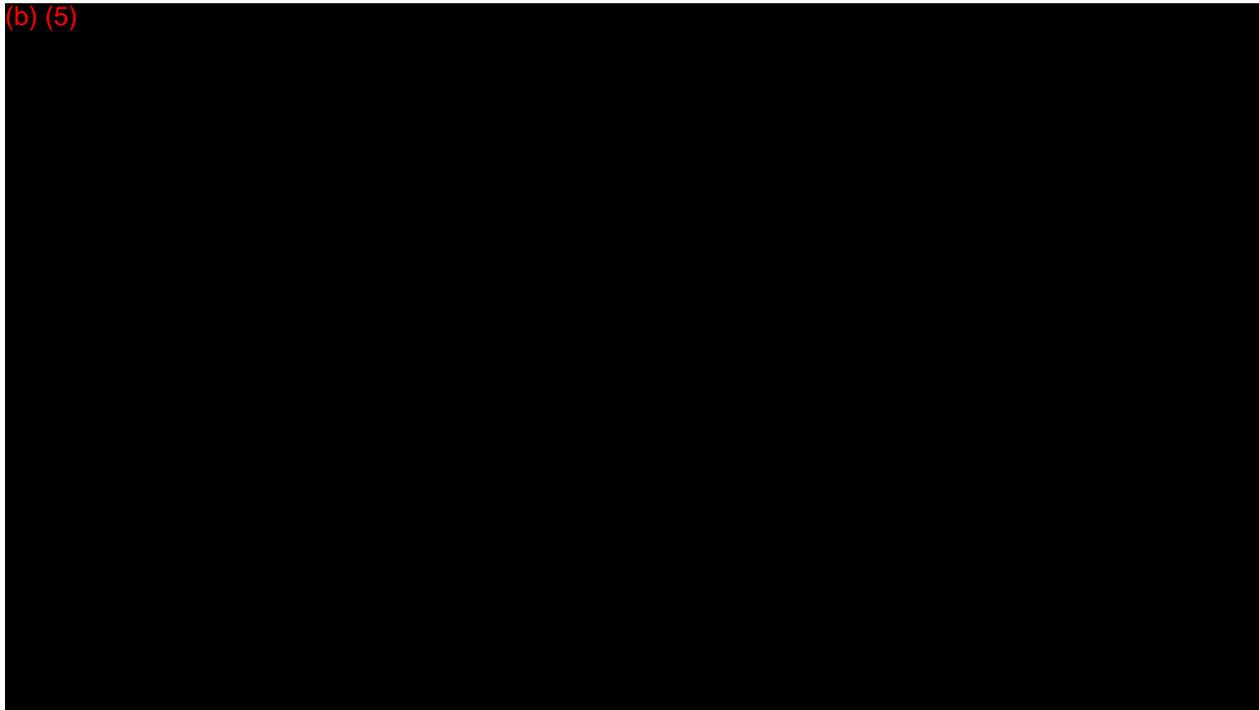
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Hope this helps

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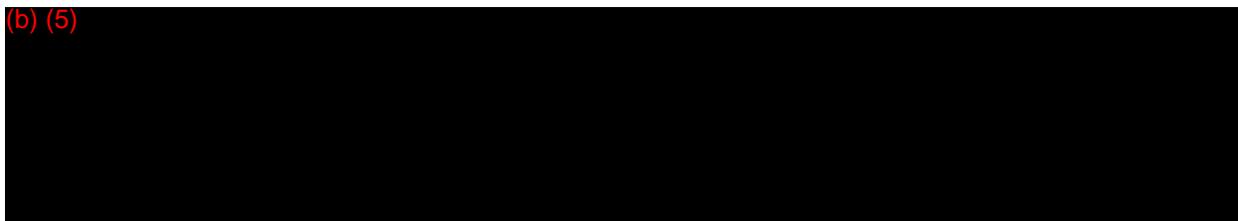
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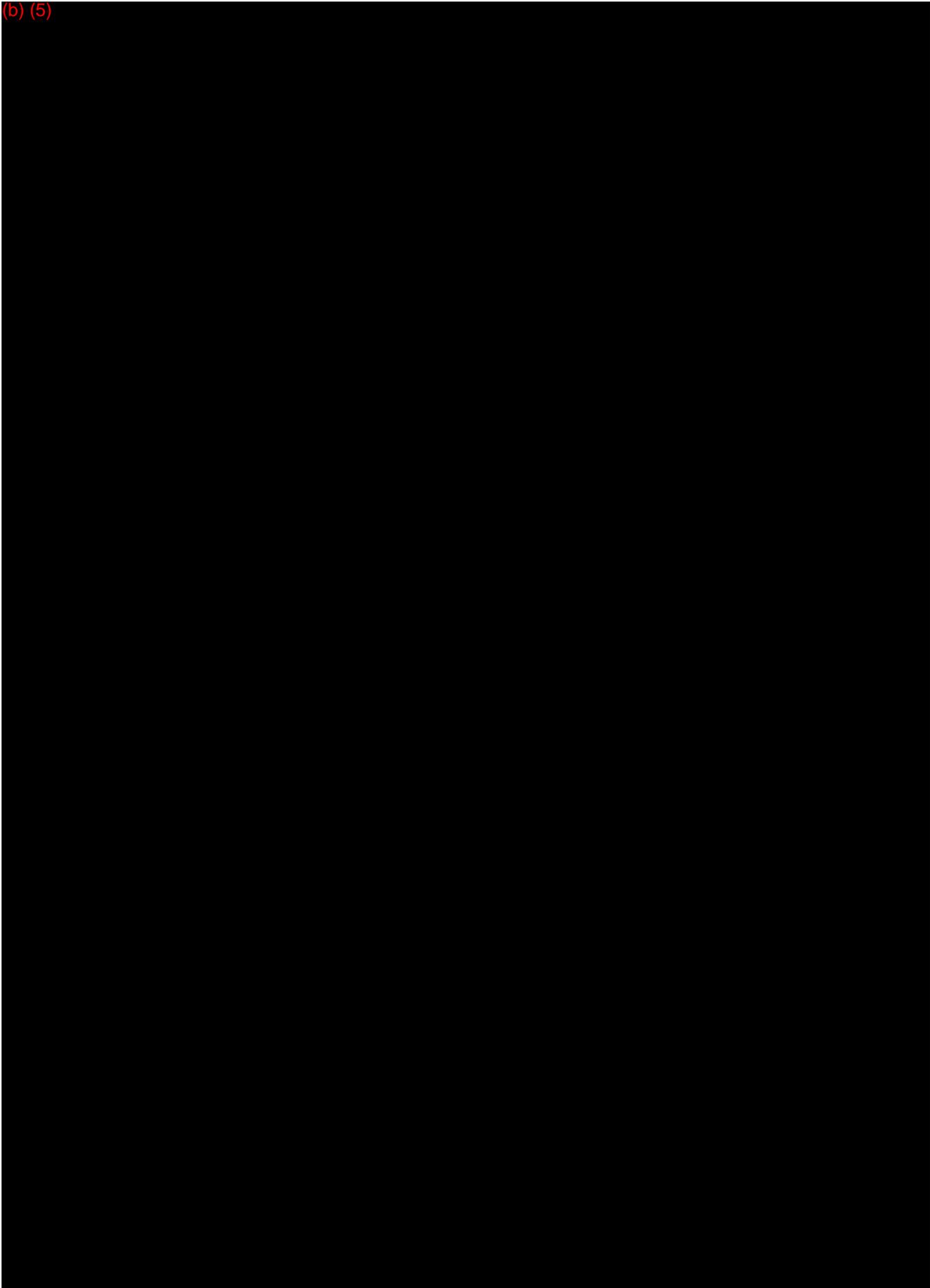
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(b) (5)



(b) (5)



(b) (5)



From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [McCall, Jonathan *](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Sherman, Rachel](#); [Rodriguez, Jennifer](#); [Conover, Katie](#); [Kraus, Tom](#)
Subject: RE: Q&A
Date: Monday, September 12, 2016 7:49:00 PM

I am happy with the couple of changes, but I am not an expert on the stylistic, font , spacing and footnote changes. Can someone clean this up so I can send to Ellis, John, Lu and Janet tomorrow AM? I hate to send them something with a bunch of comments.

Sorry to be a pain.

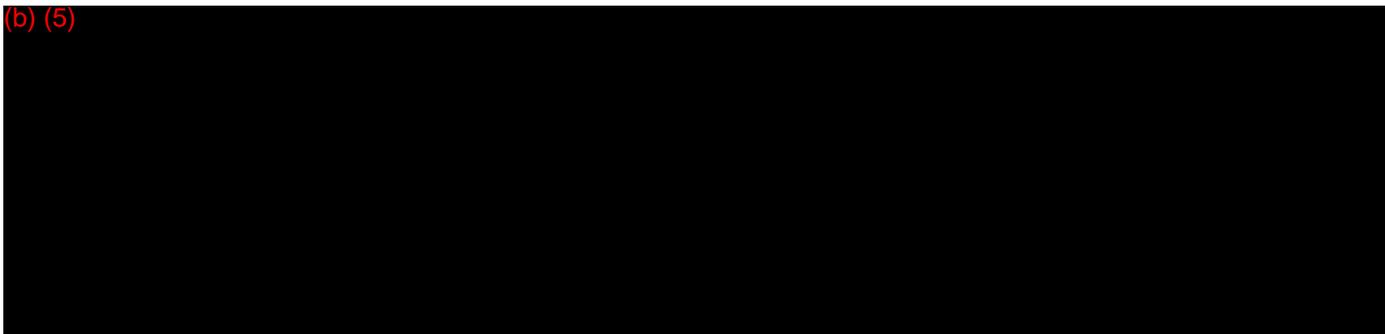
rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Dickinson, Elizabeth (FDA)
Sent: Monday, September 12, 2016 5:21 PM
To: McCall, Jonathan *; Chasan-Sloan, Deborah (FDA); Califf, Robert; Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Kraus, Tom
Subject: RE: Q&A

All,

(b) (5)



Liz

From: McCall, Jonathan *
Sent: Monday, September 12, 2016 3:25 PM
To: Chasan-Sloan, Deborah (FDA); Califf, Robert; Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom
Subject: RE: Q&A

Hello all –

I'm recirculating the memo draft (R1) with Deborah's suggested edit included. In addition to the tracked-changes and clean-commented versions, I'm also including a clean version without any comments.

Please let me know if you have any questions!

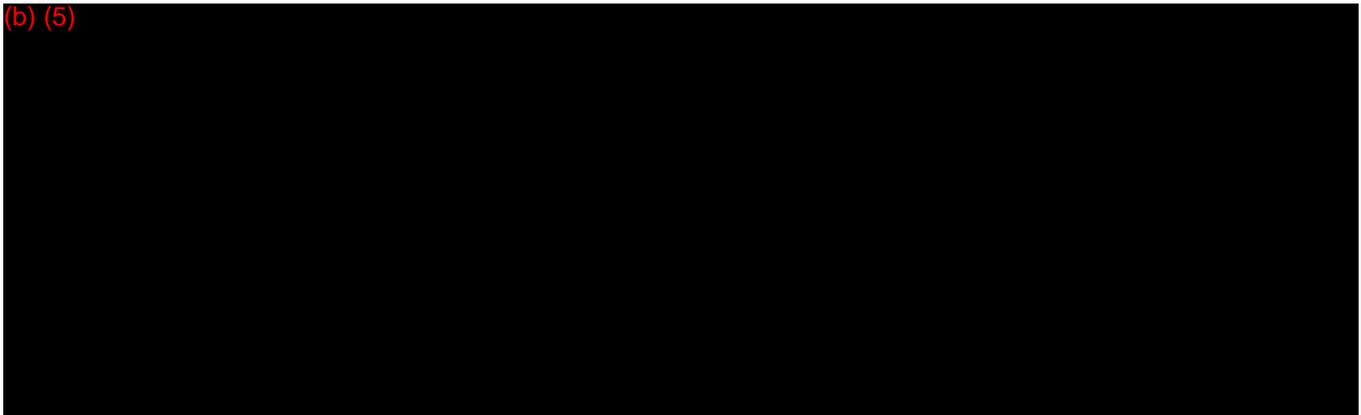
FDAOC0001845

Best,

Jonathan

From: Chasan-Sloan, Deborah (FDA)
Sent: Monday, September 12, 2016 11:58 AM
To: McCall, Jonathan *; Califf, Robert; Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom
Subject: Re: Q&A

(b) (5)



Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: McCall, Jonathan *†
Sent: Monday, September 12, 2016 10:34 AM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom
Subject: RE: Q&A

Hello all –

I'm attaching a tracked-changes version with a few additional edits from me. The clean-commented version accepts all changes and removes all comments that have already been resolved. There are a few additional comments from me, mostly to verify acceptability of some wording changes.

Please let me know if you have any questions!

Best,

Jonathan

From: Califf, Robert

FDAOC0001846

Sent: Monday, September 12, 2016 6:54 AM

To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom

Cc: McCall, Jonathan *

Subject: RE: Q&A

Here is what I hope is the penultimate version of my memo. I'm assuming:

1. Jonathan will edit and recirculate.
2. People will have their final say today.
3. I will send to Ellis, John and Janet this afternoon with 24 hours to review.

Is this ok?

rmc

From: Chasan-Sloan, Deborah (FDA)

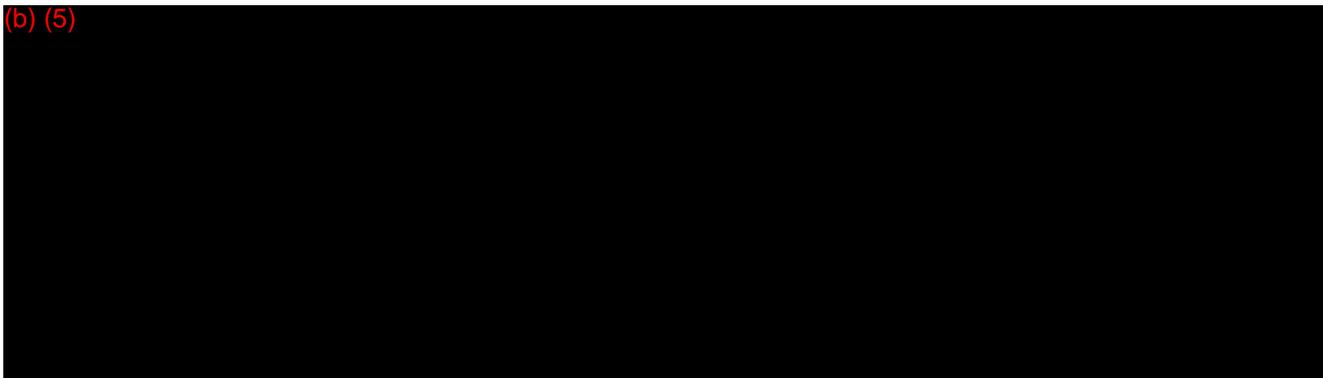
Sent: Sunday, September 11, 2016 7:44 PM

To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)

Subject: RE: Q&A

Adding my thoughts here – Liz may add some of her own separately:

(b) (5)



From: Sherman, Rachel

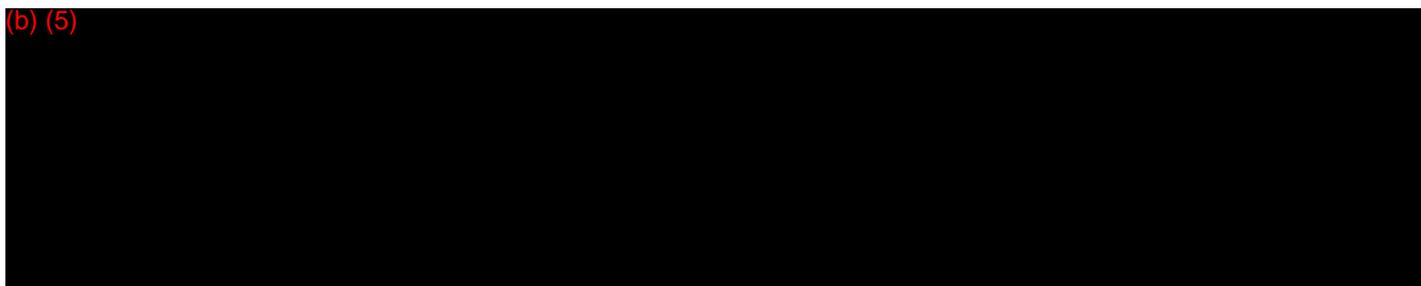
Sent: Sunday, September 11, 2016 8:45 AM

To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

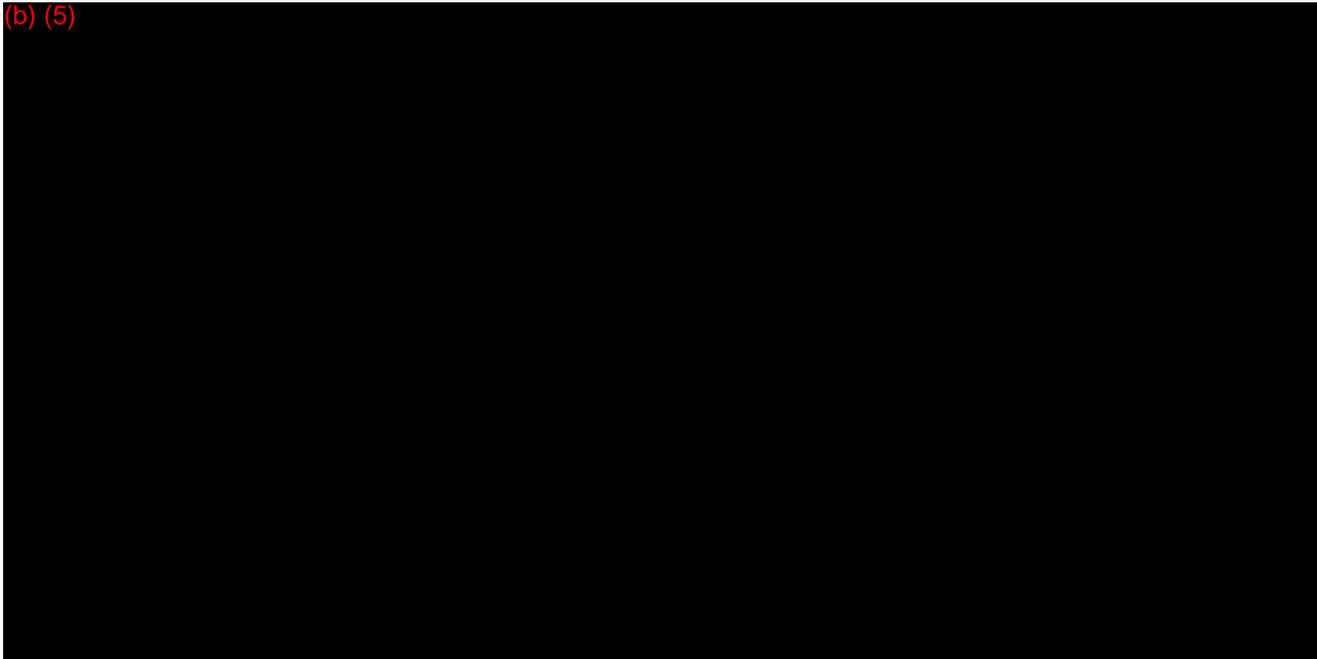
Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.

(b) (5)



(b) (5)



Hope this helps

Rachel

Why do you equivocate and say I'm right on most things? I thought we agreed I was always right.....

From: Califf, Robert

Sent: Sunday, September 11, 2016 8:23 AM

To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

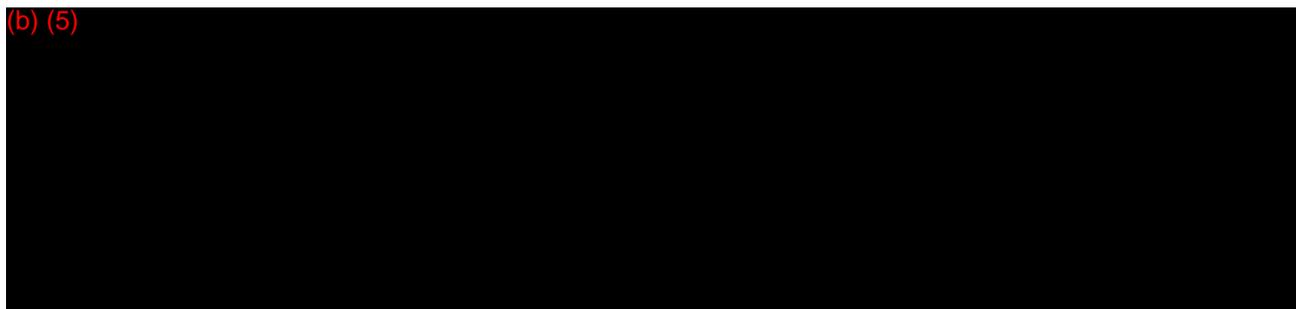
Subject: Q&A

Friends,

I have done a little editing, but not much as I think its good. There are still several loose ends. Are we still ok on the timeline?

3 issues strike me as needing more work:

(b) (5)



(b) (5)

From: [Califf, Robert](#)
To: [Sherman, Rachel](#)
Subject: RE: Q&A
Date: Monday, September 12, 2016 9:50:00 AM

You are the only person I've talked to who doesn't believe Janet got more involved with this one than with other cases.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Monday, September 12, 2016 9:11 AM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom
Cc: McCall, Jonathan *
Subject: RE: Q&A

One comment on your addition about (b) (5)

[REDACTED] (b) (5)

[REDACTED]

From: Califf, Robert
Sent: Monday, September 12, 2016 6:54 AM
To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom
Cc: McCall, Jonathan *
Subject: RE: Q&A

Here is what I hope is the penultimate version of my memo. I'm assuming:

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2. People will have their final say today.
3. I will send to Ellis, John and Janet this afternoon with 24 hours to review.

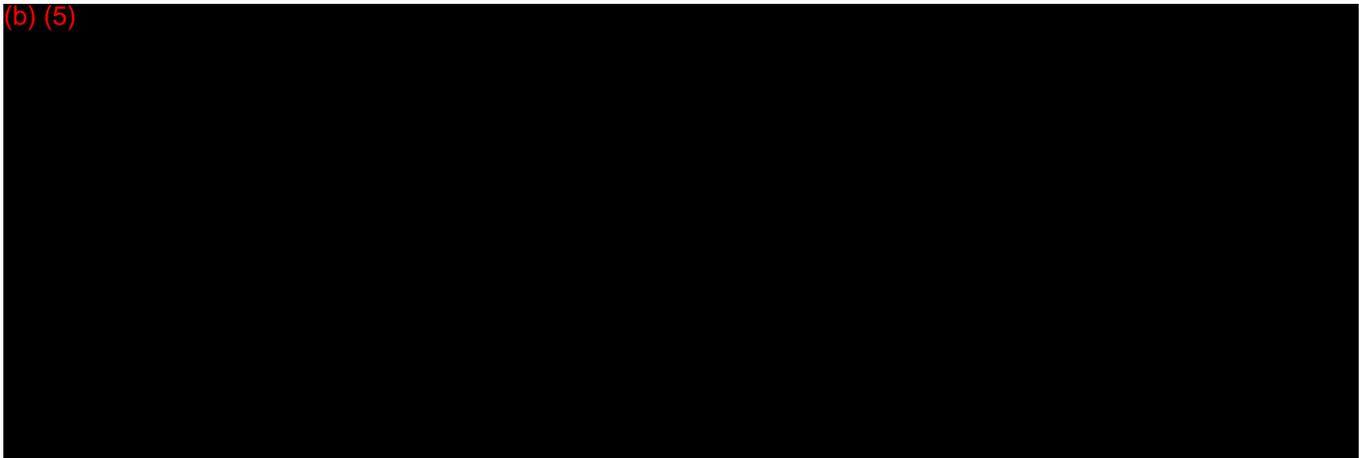
Is this ok?

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)

Subject: RE: Q&A

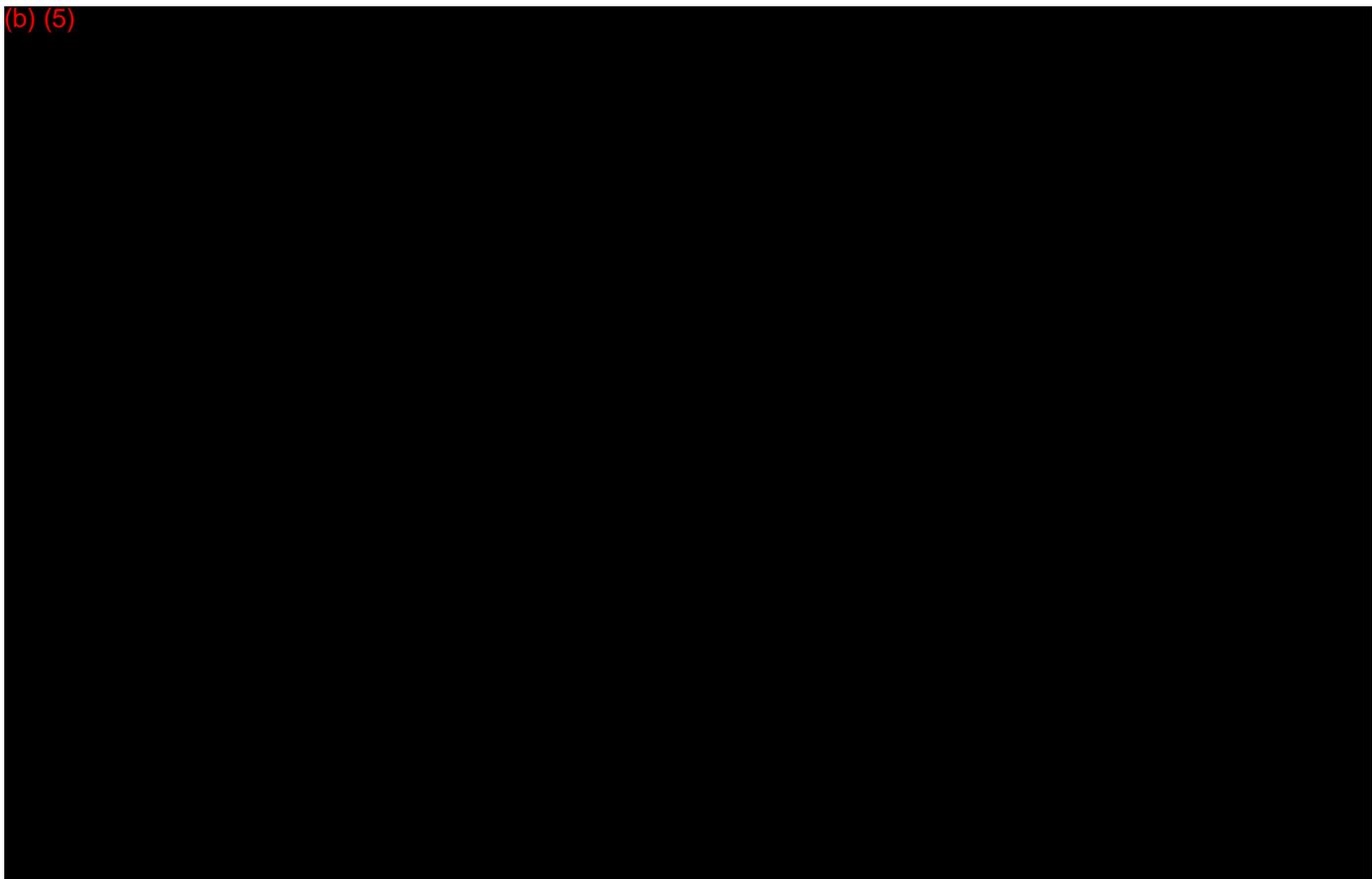
(b) (5)



From: Sherman, Rachel
Sent: Sunday, September 11, 2016 8:45 AM
To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.

(b) (5)



Hope this helps

FDAOC0001851

Rachel

Why do you equivocate and say I'm right on most things? I thought we agreed I was always right....

From: Califf, Robert

Sent: Sunday, September 11, 2016 8:23 AM

To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

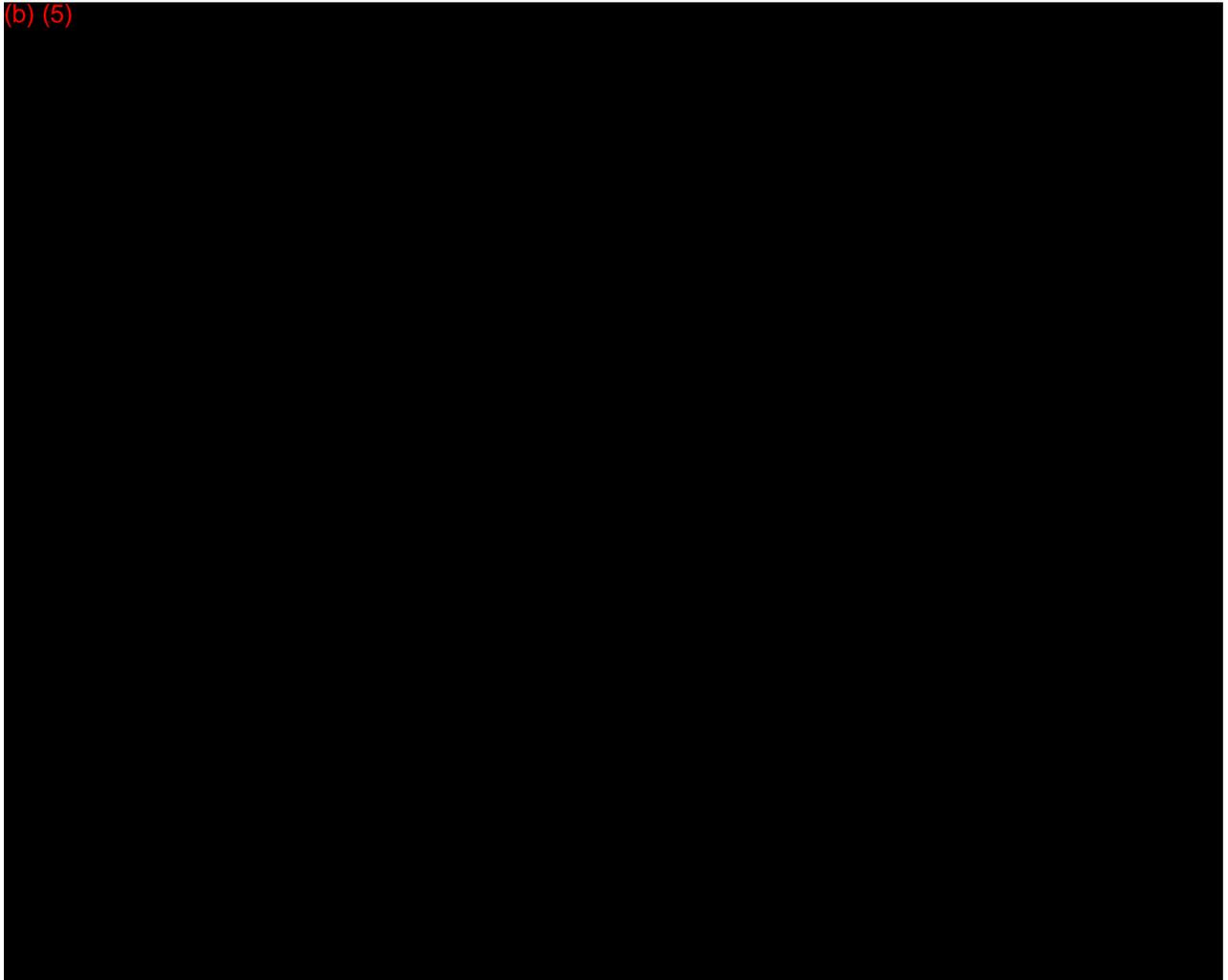
Subject: Q&A

Friends,

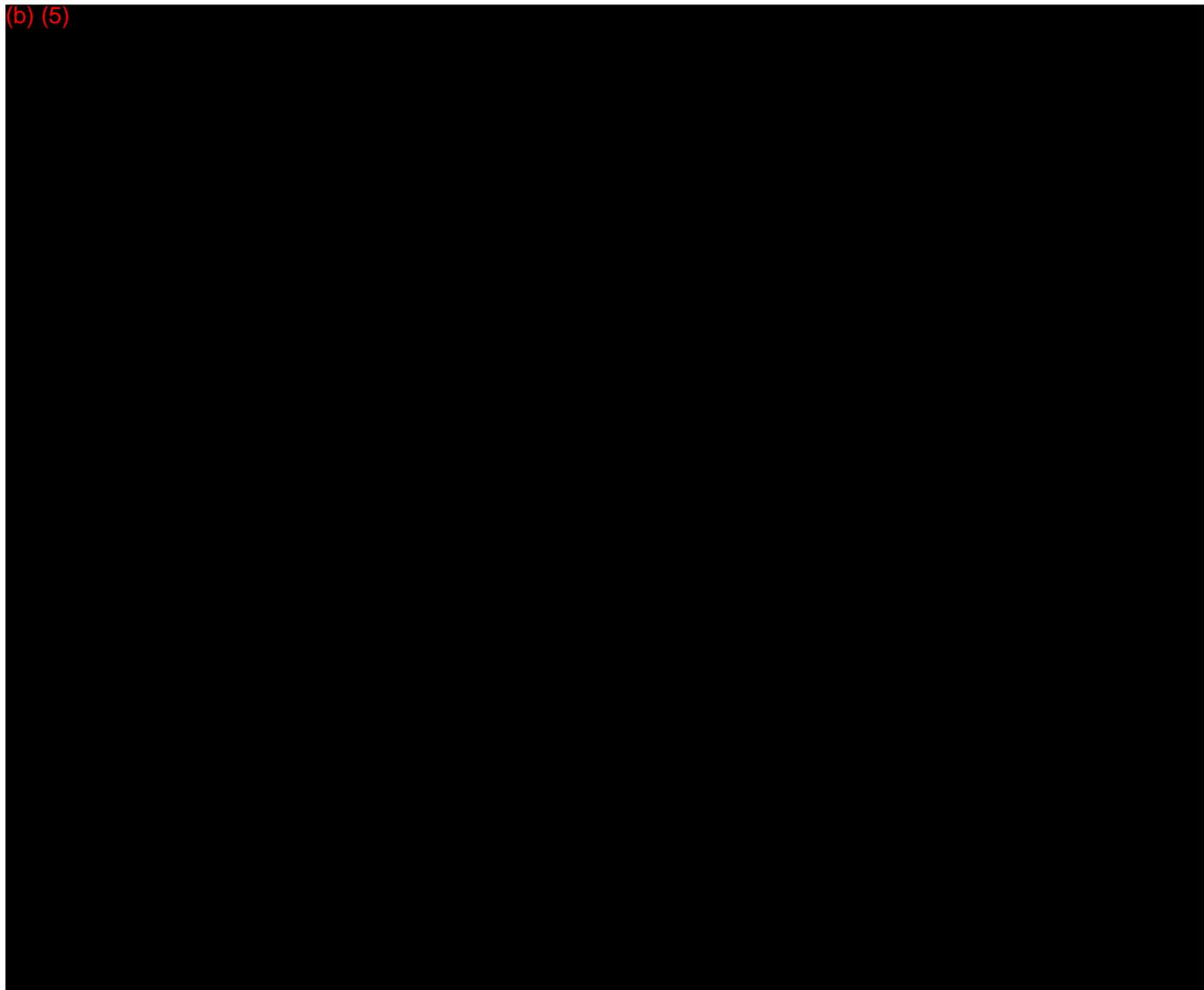
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3 issues strike me as needing more work:

(b) (5)

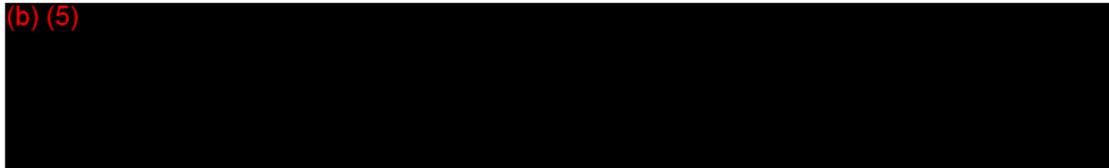


(b) (5)



From: [Califf, Robert](#)
To: [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Rodriguez, Jennifer](#); [Conover, Katie](#); [Dickinson, Elizabeth \(FDA\)](#); [Kraus, Tom](#)
Cc: [McCall, Jonathan *](#)
Subject: RE: Q&A
Date: Monday, September 12, 2016 9:52:00 AM

(b) (5)



rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Monday, September 12, 2016 9:11 AM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom
Cc: McCall, Jonathan *
Subject: RE: Q&A

One comment on your addition (b) (5)



(b) (5)



From: Califf, Robert
Sent: Monday, September 12, 2016 6:54 AM
To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom
Cc: McCall, Jonathan *
Subject: RE: Q&A

Here is what I hope is the penultimate version of my memo. I'm assuming:

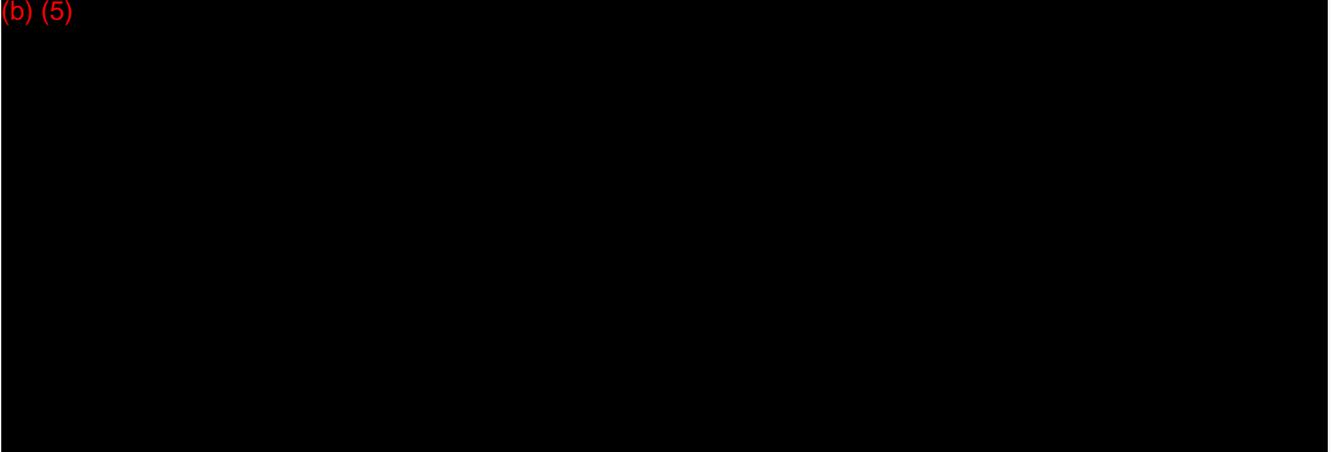
1. Jonathan will edit and recirculate.
2. People will have their final say today.
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Is this ok?

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

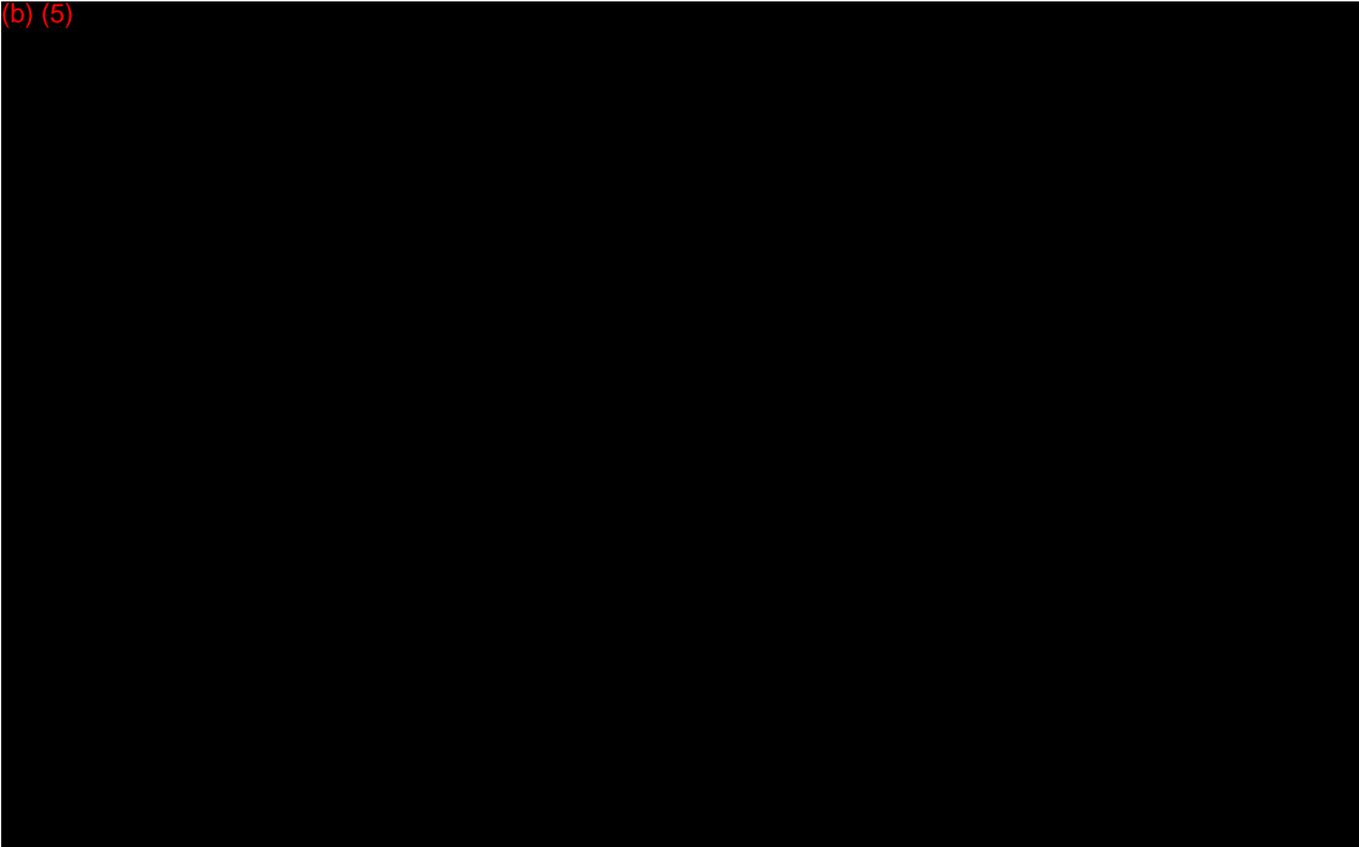
(b) (5)



From: Sherman, Rachel
Sent: Sunday, September 11, 2016 8:45 AM
To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.

(b) (5)



(b) (5)

Hope this helps

Rachel

Why do you equivocate and say I'm right on most things? I thought we agreed I was always right.....

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Sent: Sunday, September 11, 2016 8:23 AM

To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

Subject: Q&A

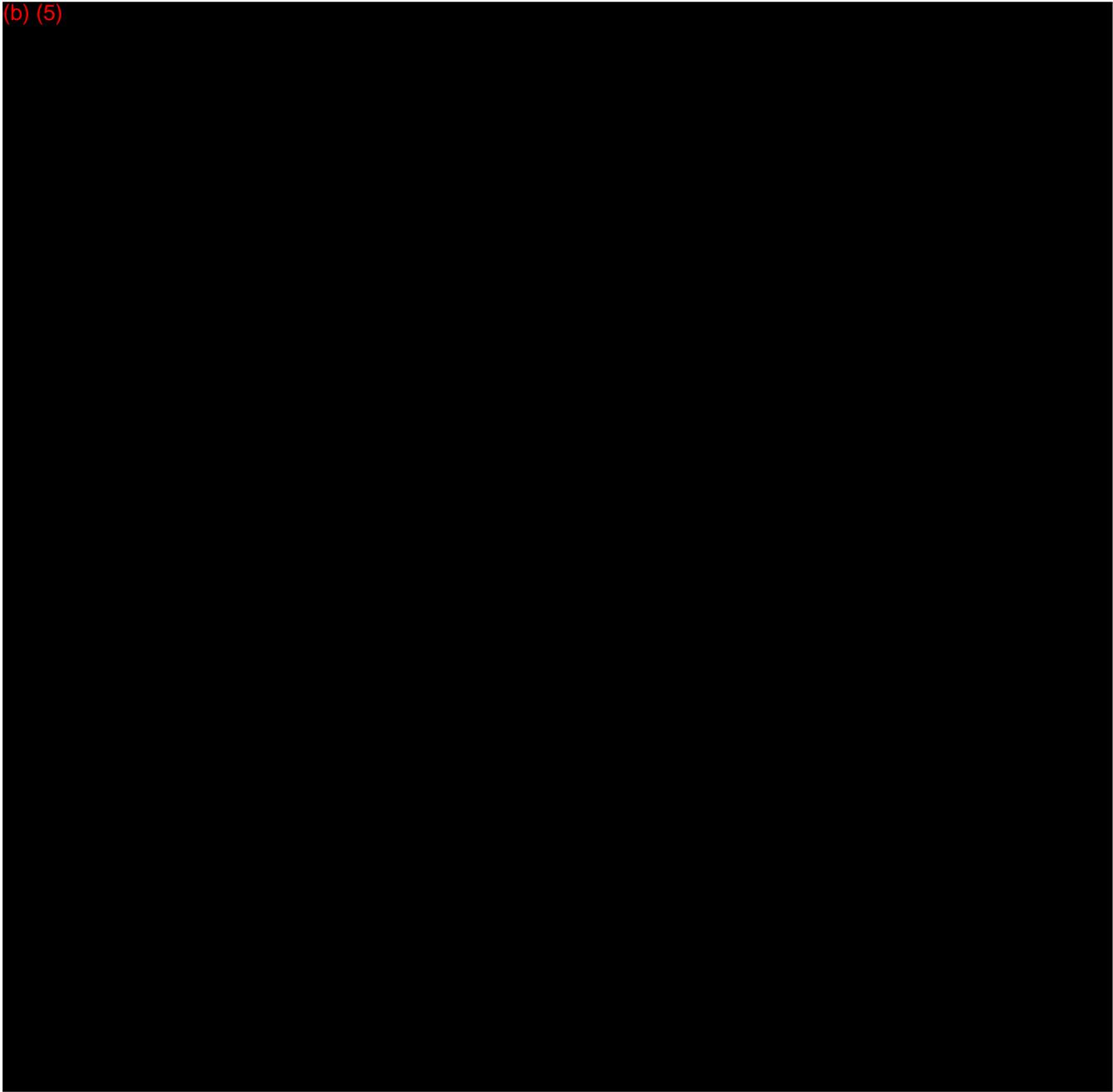
Friends,

I have done a little editing, but not much as I think its good. There are still several loose ends. Are we still ok on the timeline?

3 issues strike me as needing more work:

(b) (5)

(b) (5)



From: [Califf, Robert](#)
To: [Evans, Dana](#)
Subject: FW: PLEASE SEE -- Updated Comms
Date: Monday, September 12, 2016 10:51:00 AM
Attachments: [Phase II approval reactive QA 09.12.16.doc](#)
[eteplirsen KMOA 9.12.16.doc](#)
[eteplirsen PR draft 9.12.16.doc](#)
Importance: High

Please print this out.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Rodriguez, Jennifer
Sent: Monday, September 12, 2016 10:17 AM
To: Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Conover, Katie; Kraus, Tom
Subject: PLEASE SEE -- Updated Comms
Importance: High

Hi All,

Attached please find the updated QAs, as well as the PR, reflecting the edits to date. In addition, below please find a slightly revised response to the question about the review team. Please let me know if you would like us to go further.

Also, is it OK for us to reach out to Lu Borio's team to get the information for (b) (5)

Once we have your OK, we will share the comms package with Chris Shreeve for CDER review – asking them to flag anything that is inaccurate or provides significant heart burn. We would like to be able to share with CDER by noon to keep on schedule.

Thanks for all your feedback.

Jen

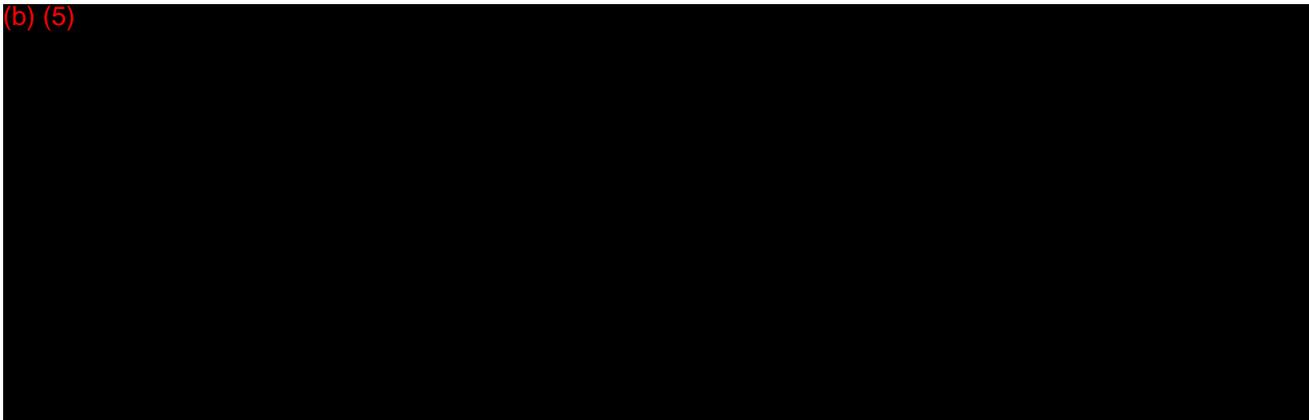
(b) (5)

(b) (5)



From: Dickinson, Elizabeth (FDA)
Sent: Sunday, September 11, 2016 8:32 PM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie
Subject: RE: Q&A

(b) (5)



From: Califf, Robert
Sent: Sunday, September 11, 2016 7:49 PM

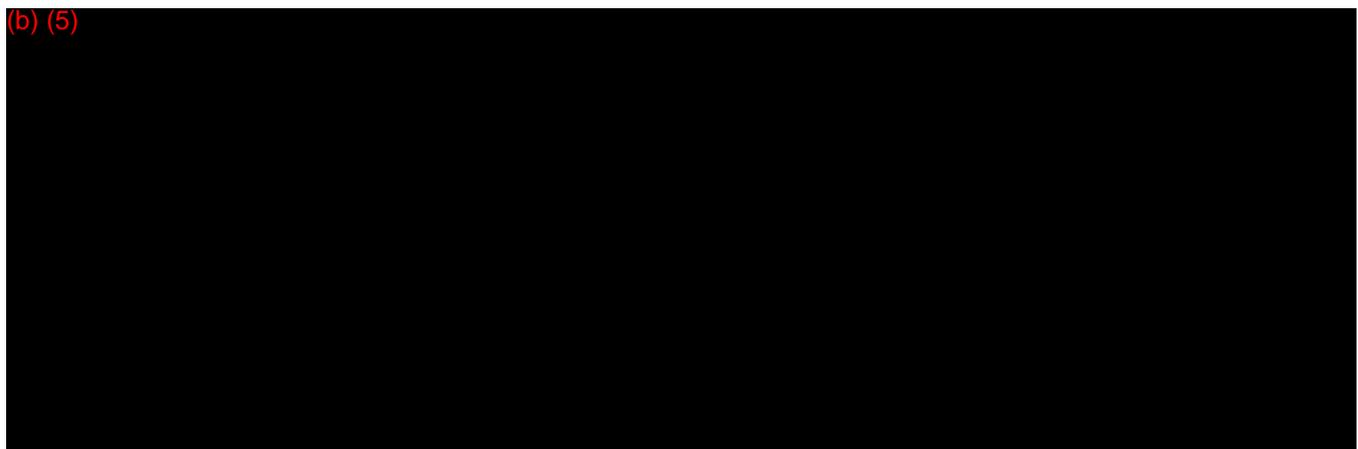
To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

Nice job. These changes improve what I was trying to get across. Thanks.

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

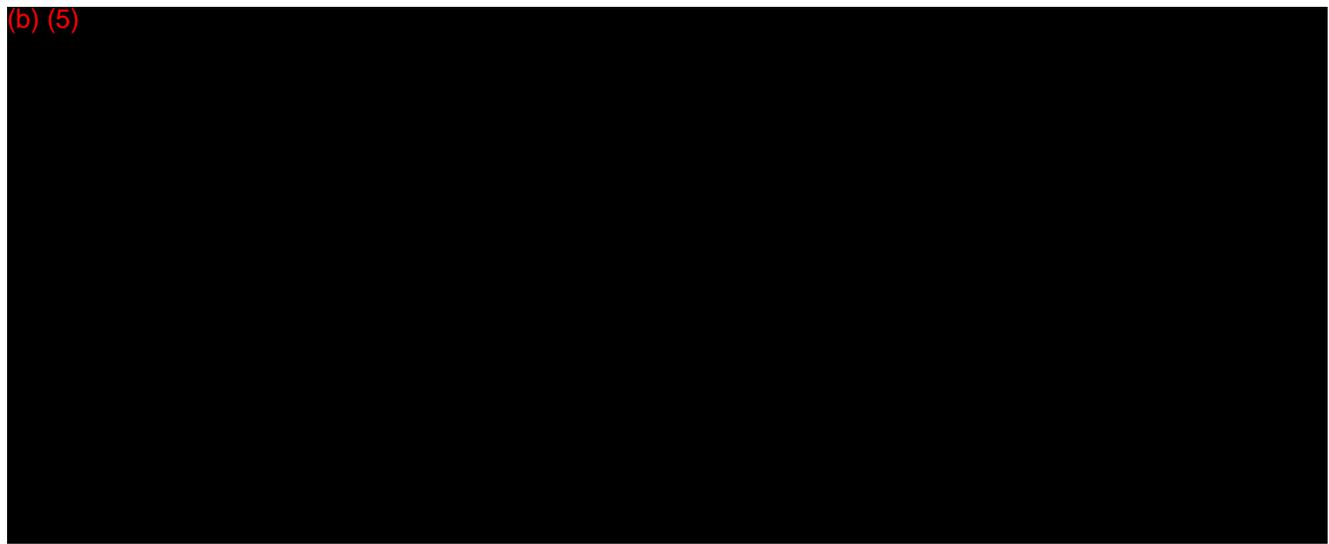
(b) (5)



From: Sherman, Rachel
Sent: Sunday, September 11, 2016 8:45 AM
To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.

(b) (5)



(b) (5)



Hope this helps

Rachel

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Sent: Sunday, September 11, 2016 8:23 AM

To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

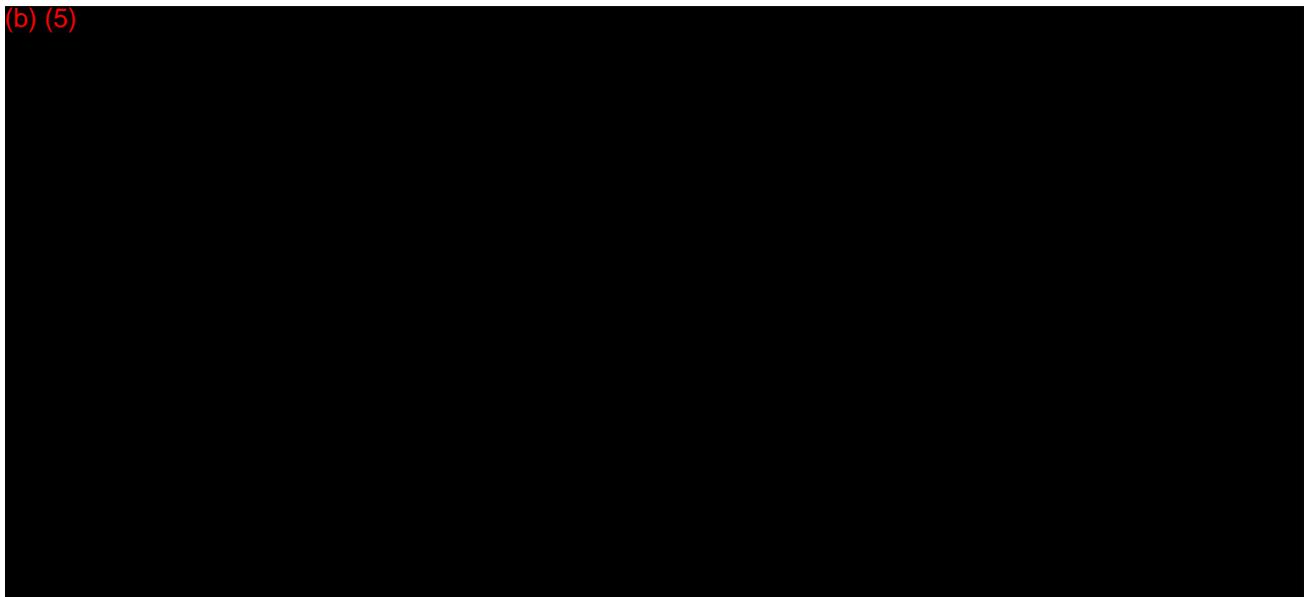
Subject: Q&A

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(b) (5)

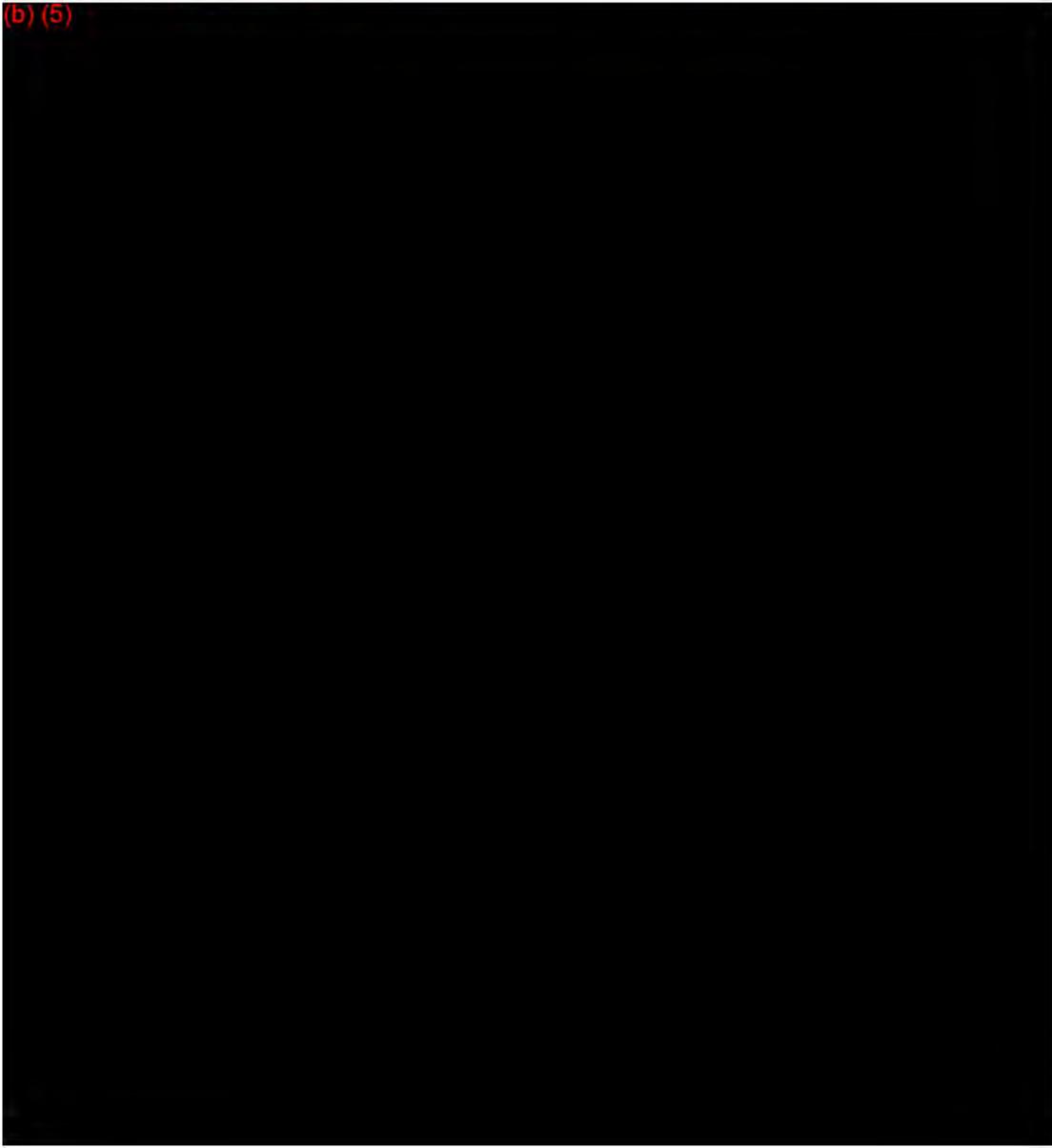


(b) (5)

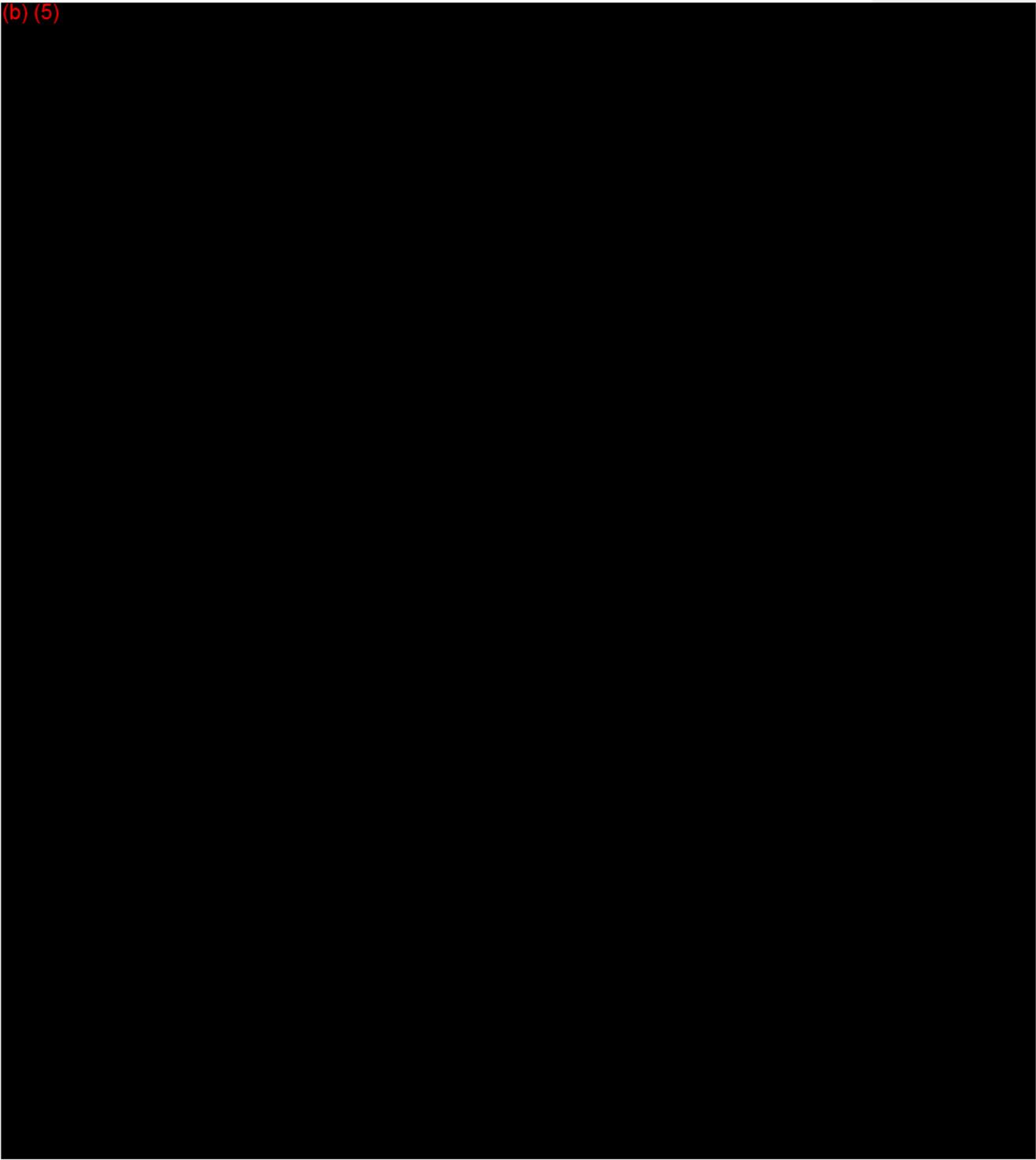
Reactive Statement and QA: Posting of review documents for approval of
Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

Target date: September 2016

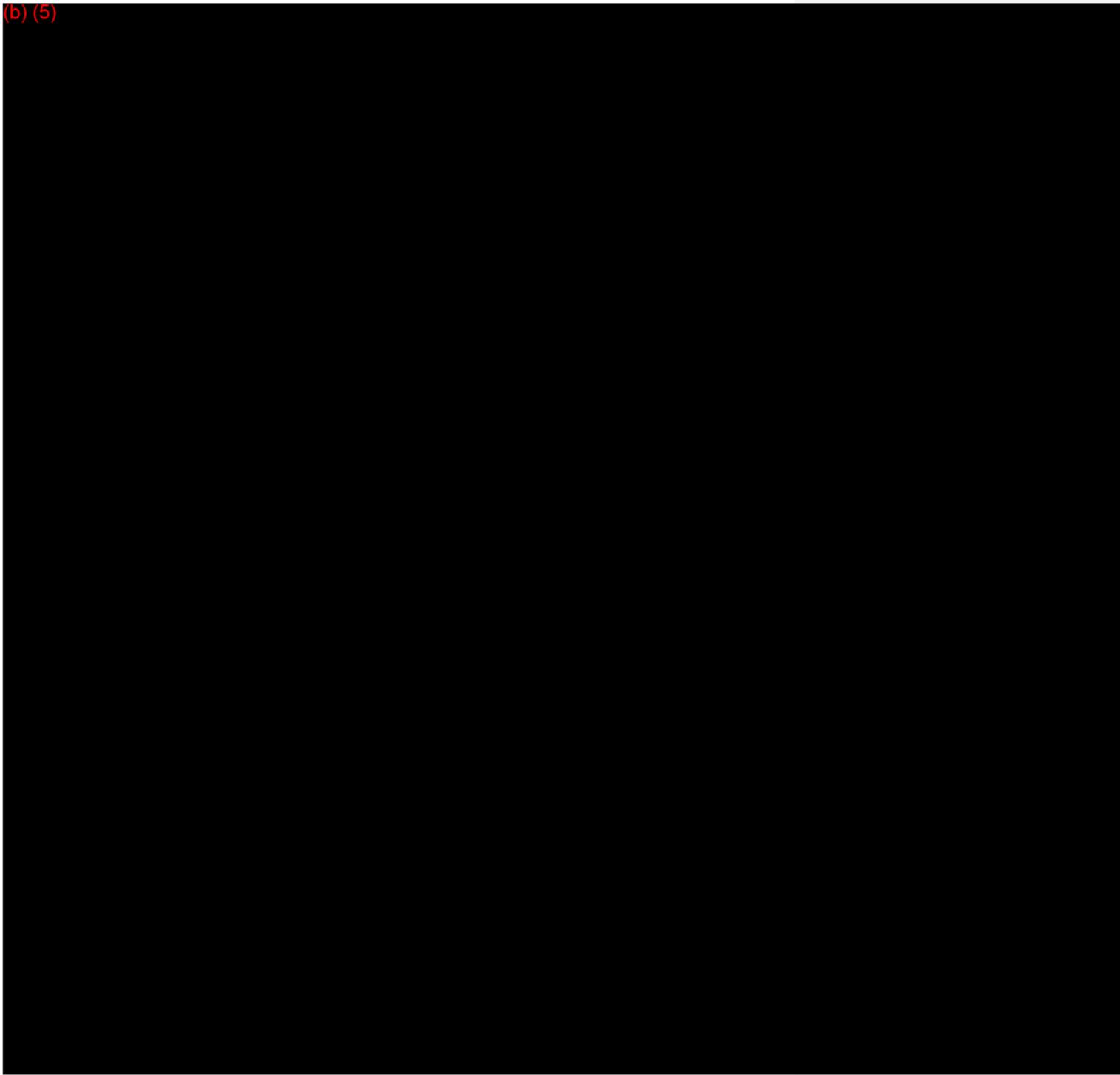
(b) (5)



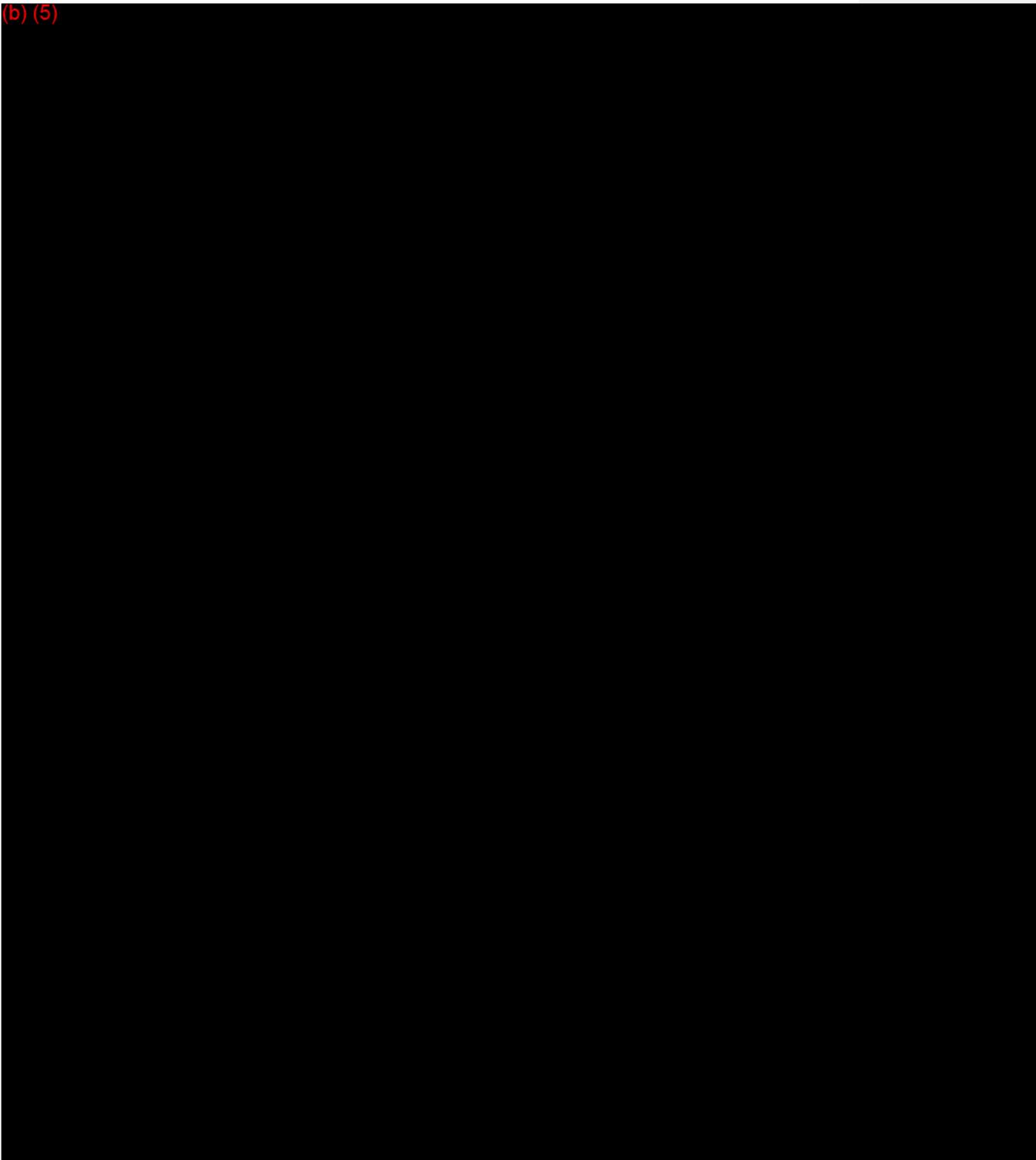
(b) (5)



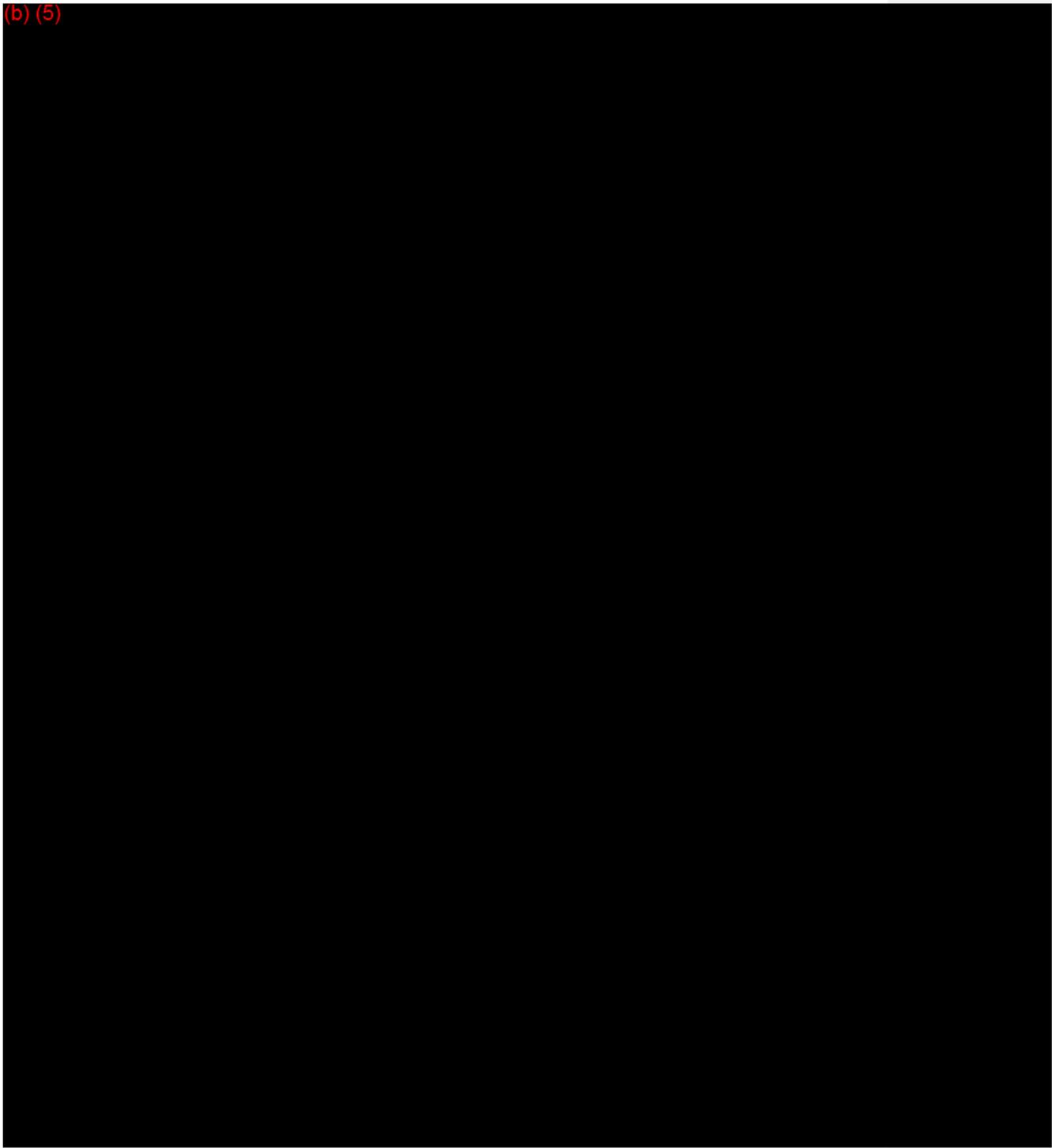
(b) (5)



(b) (5)



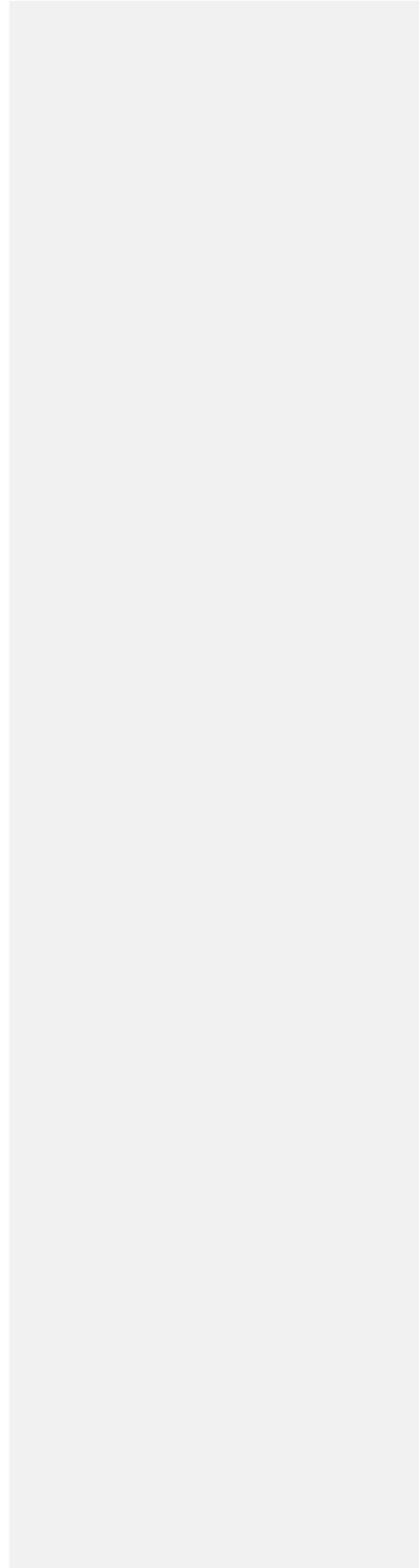
(b) (5)



(b) (5)



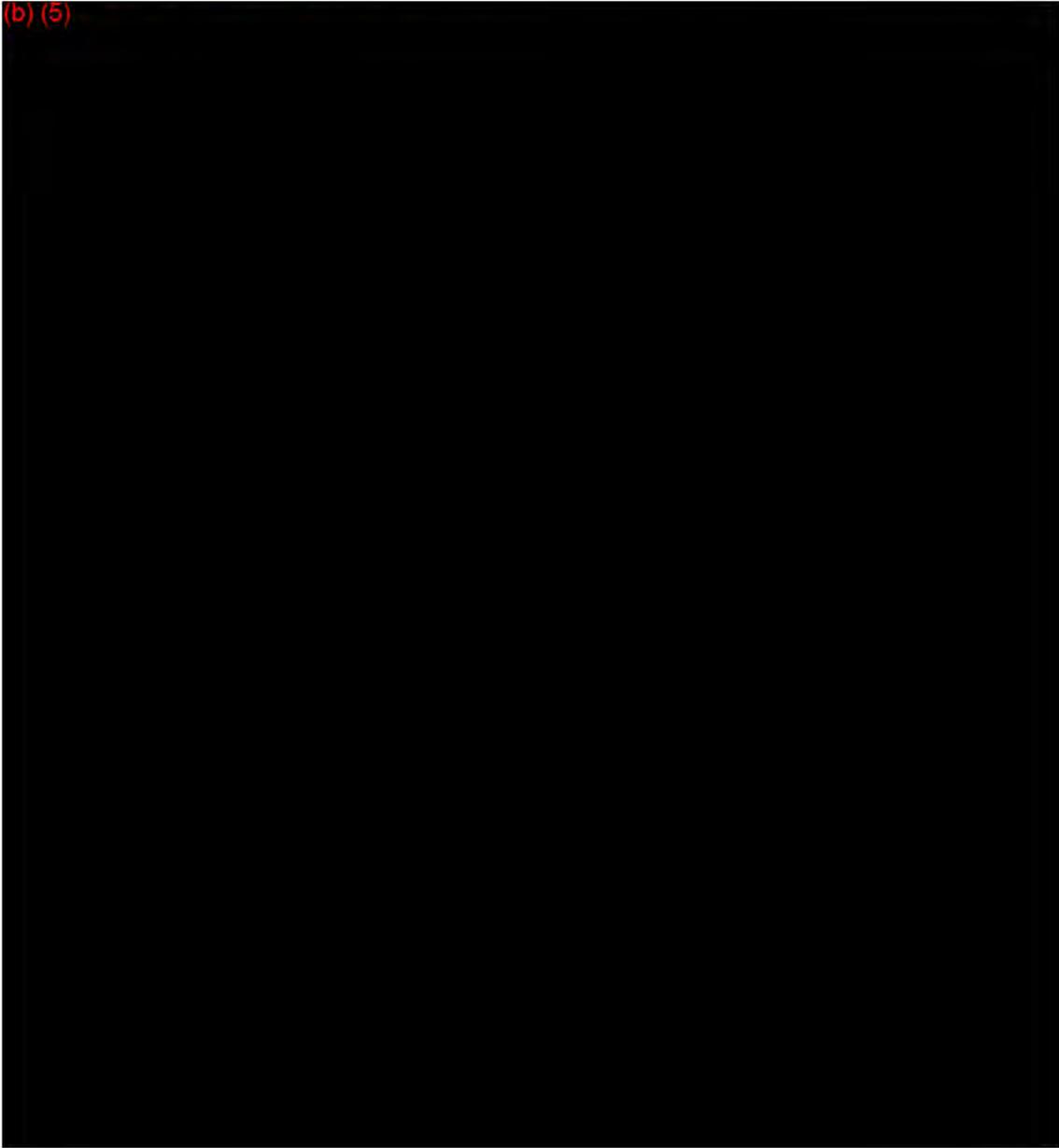
(b) (5)



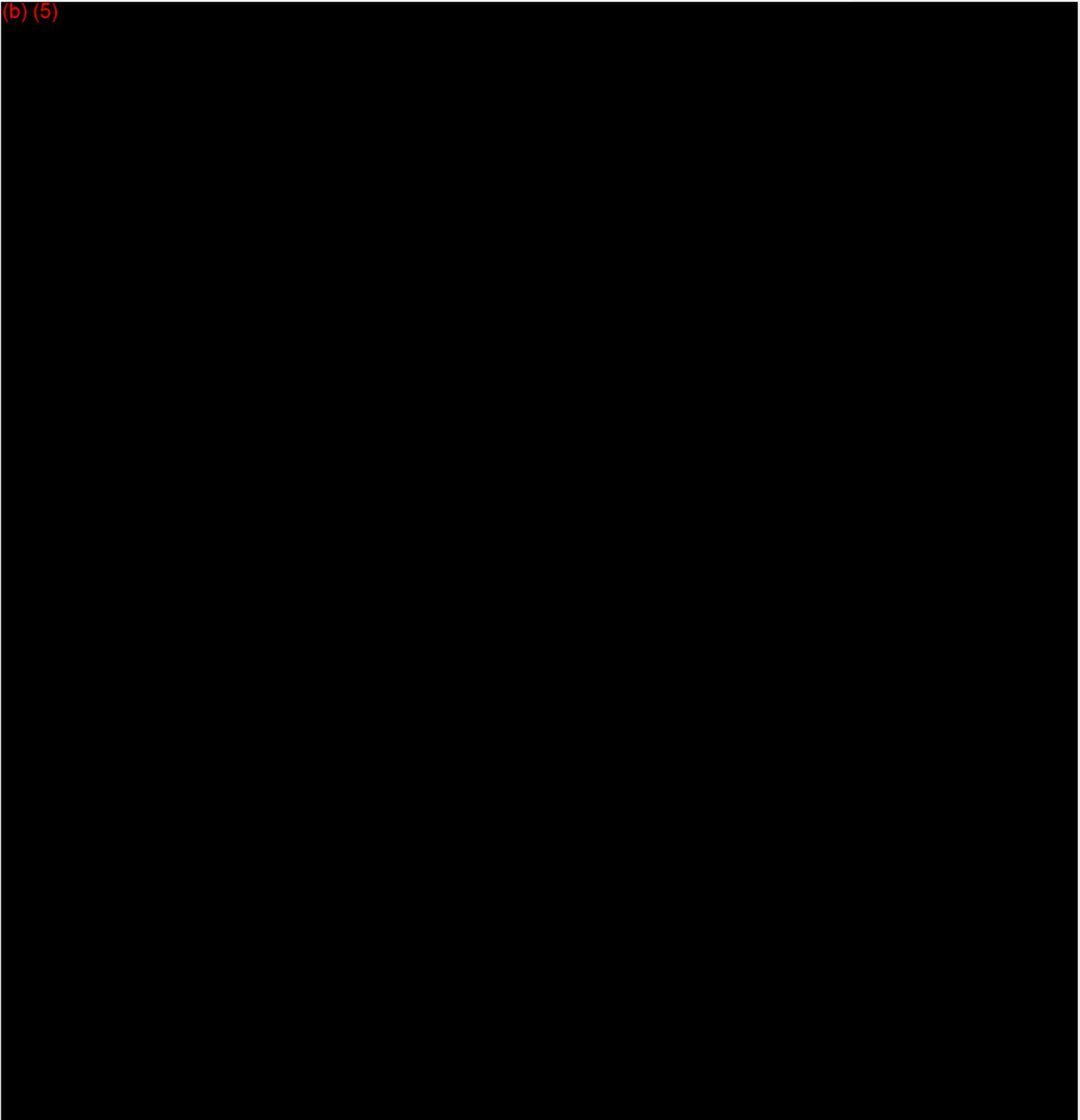
Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

Target date: September 2016

(b) (5)

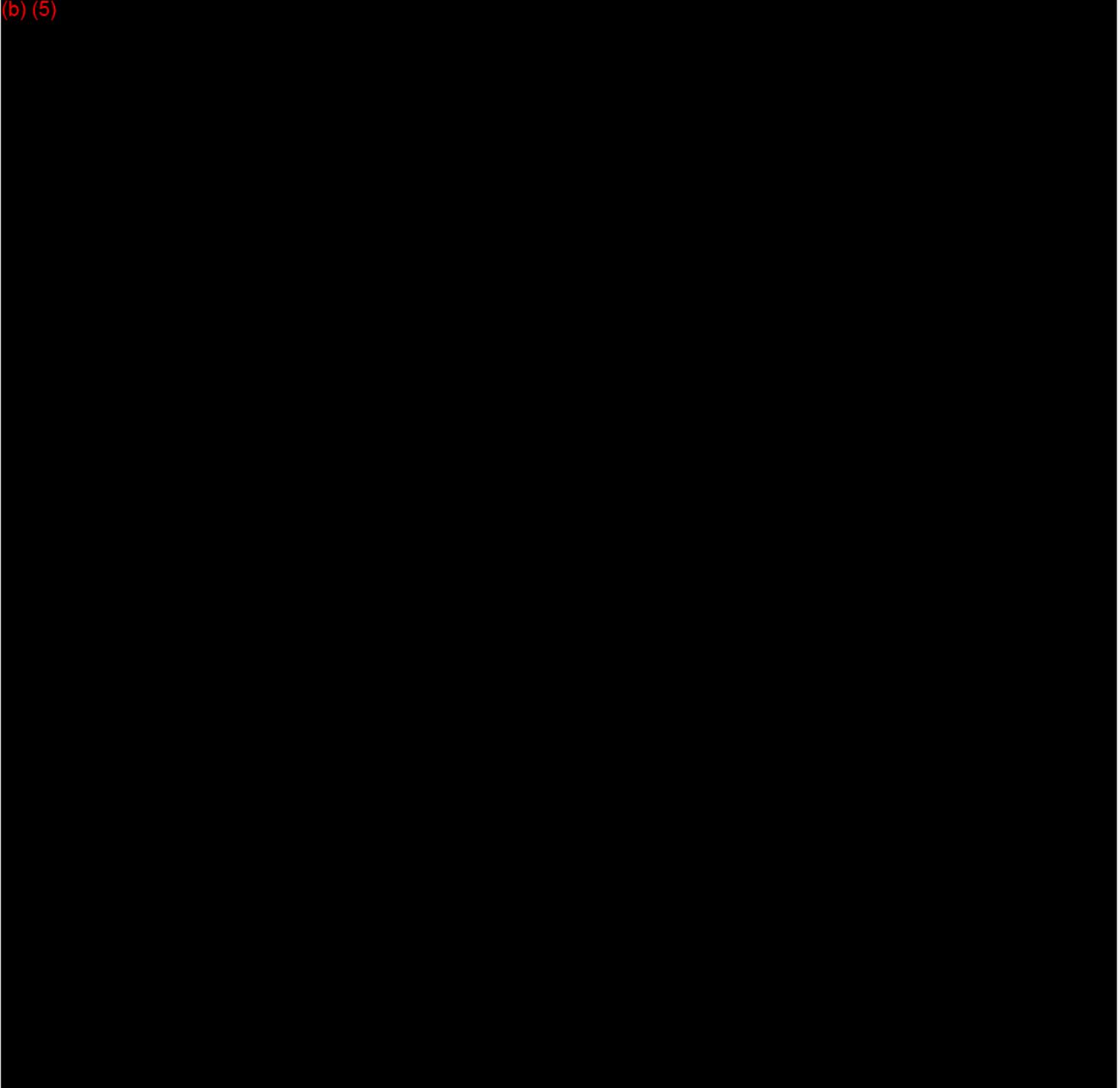


(b) (5)

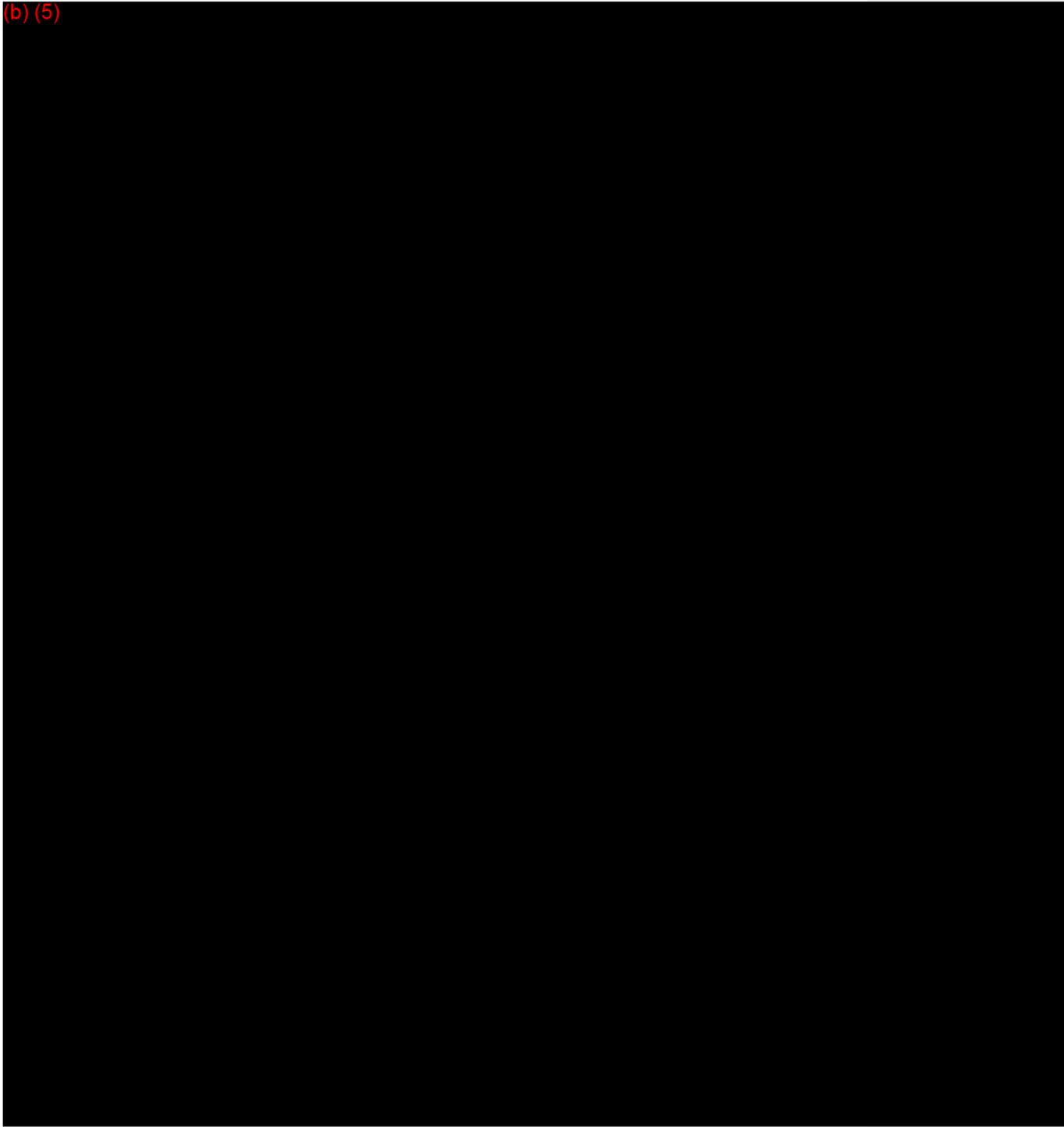


(b) (5)

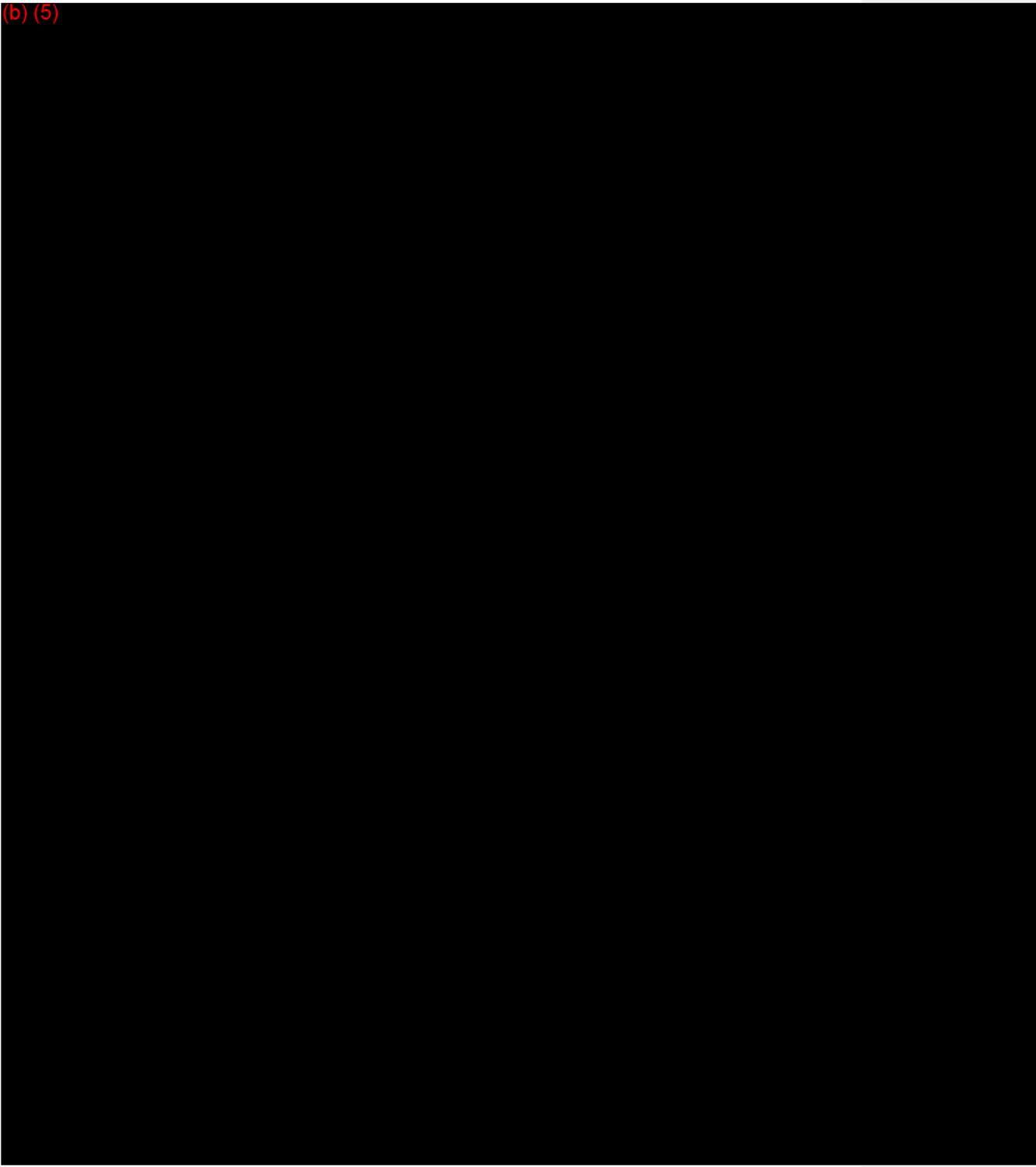
(b) (5)



(b) (5)



(b) (5)

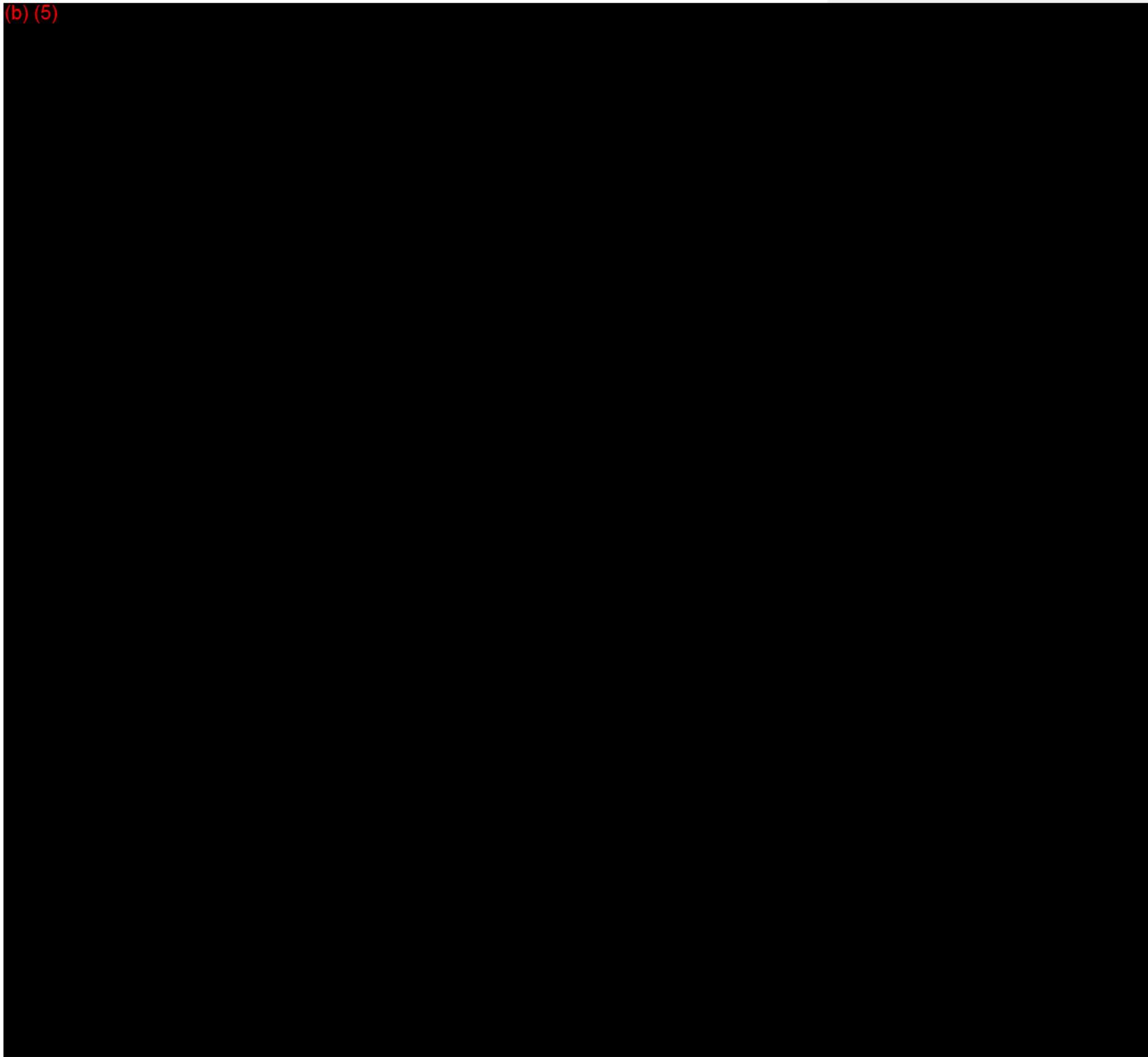


(b) (5)

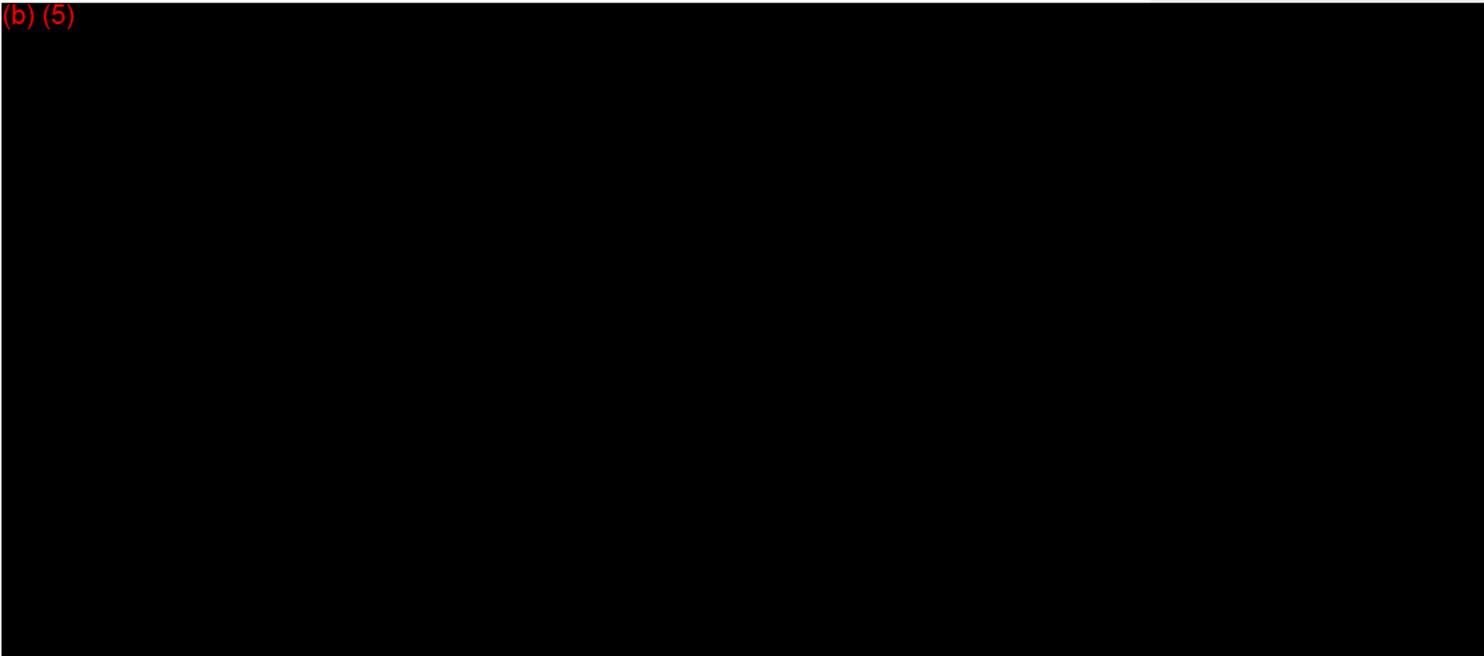


(b) (5)

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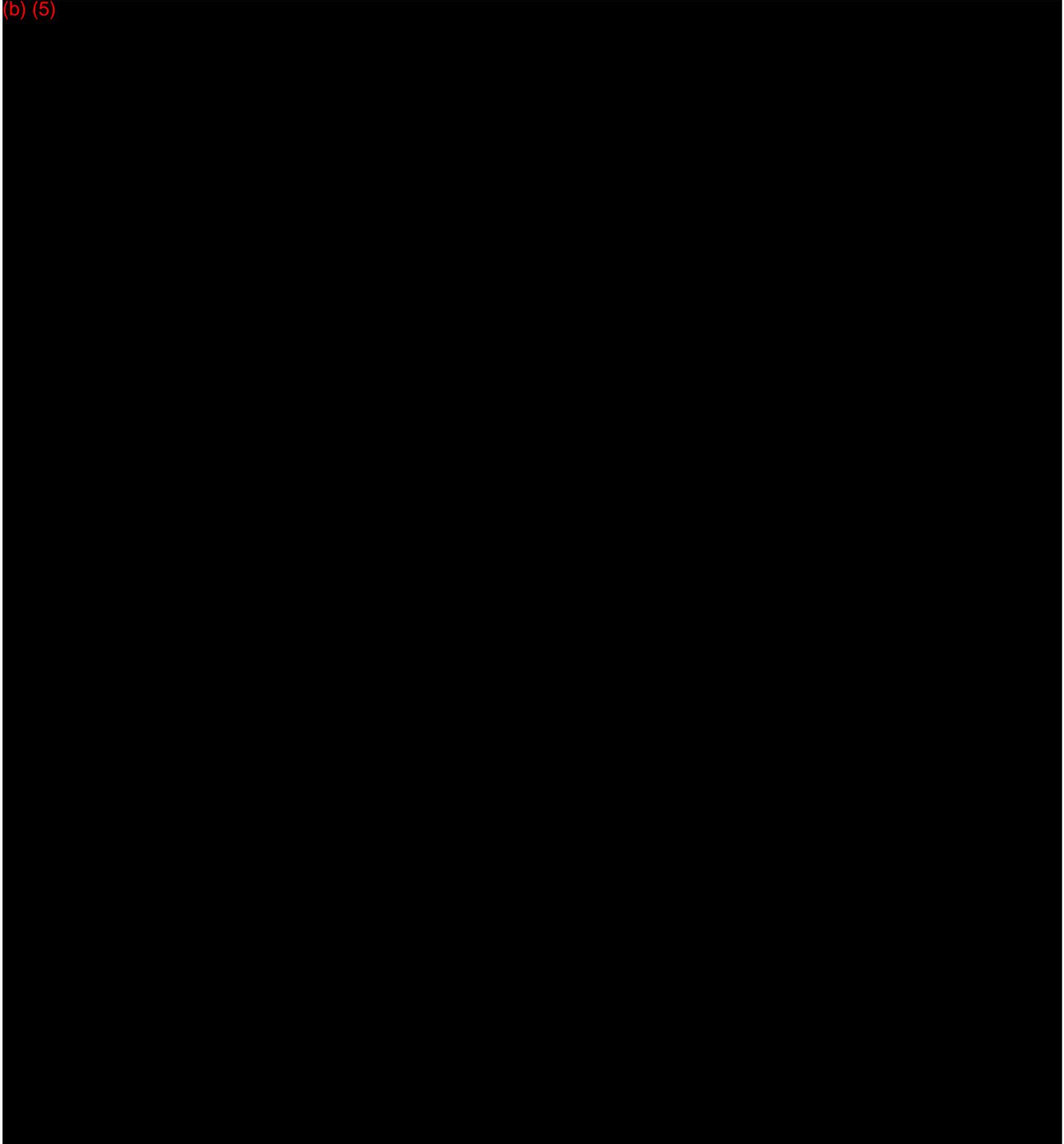
FDA NEWS RELEASE

For Immediate Release: September xx, 2016

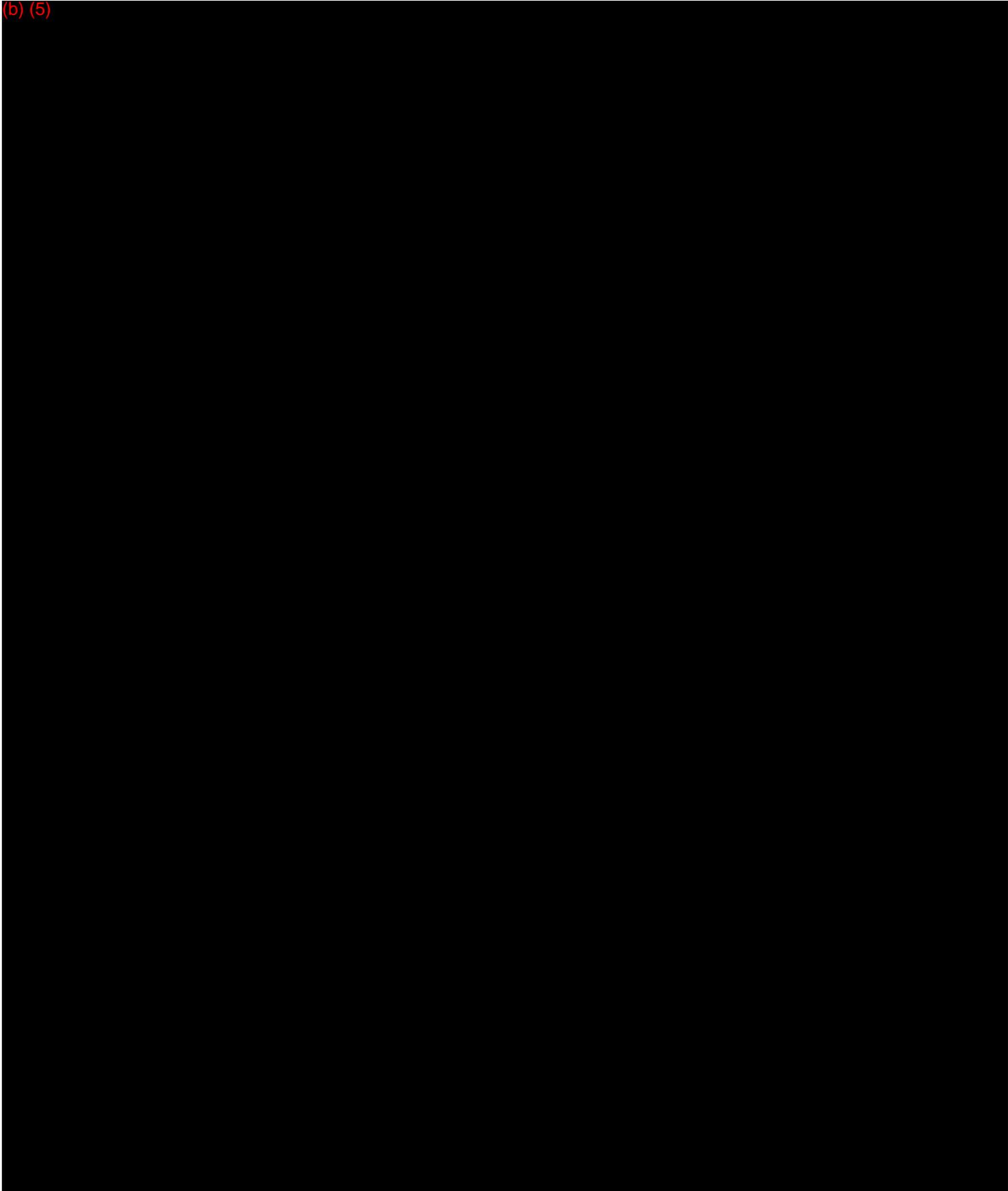
Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

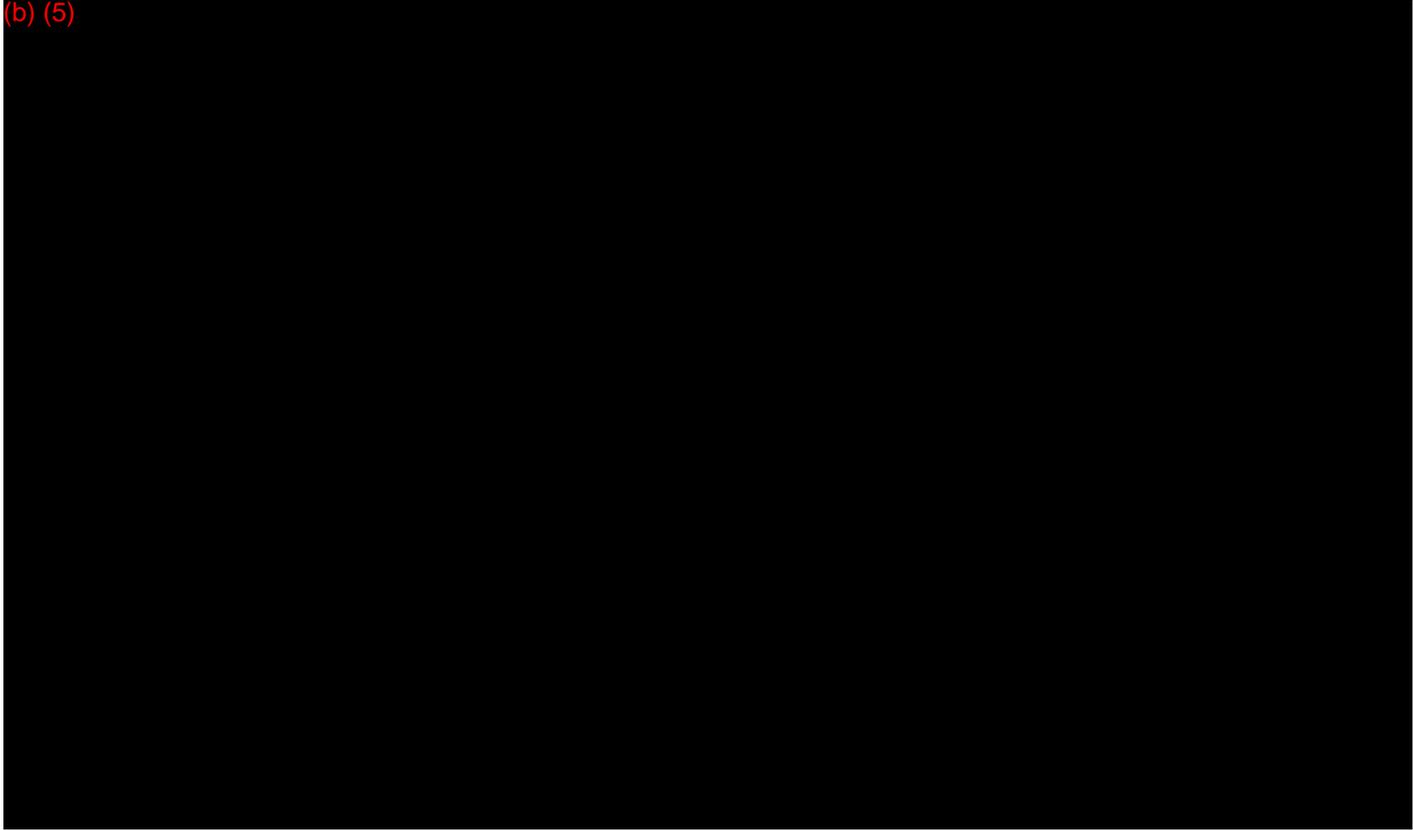
(b) (5)



(b) (5)



(b) (5)



From: [Rodriguez, Jennifer](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [Califf, Robert](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Sherman, Rachel](#); [Conover, Katie](#); [Kraus, Tom](#)
Subject: PLEASE SEE — Updated Comms
Date: Monday, September 12, 2016 10:17:10 AM
Attachments: [Phase II approval reactive OA 09.12.16.doc](#)
[eteplirsen KMOA 9.12.16.doc](#)
[eteplirsen PR draft 9.12.16.doc](#)
Importance: High

Hi All,

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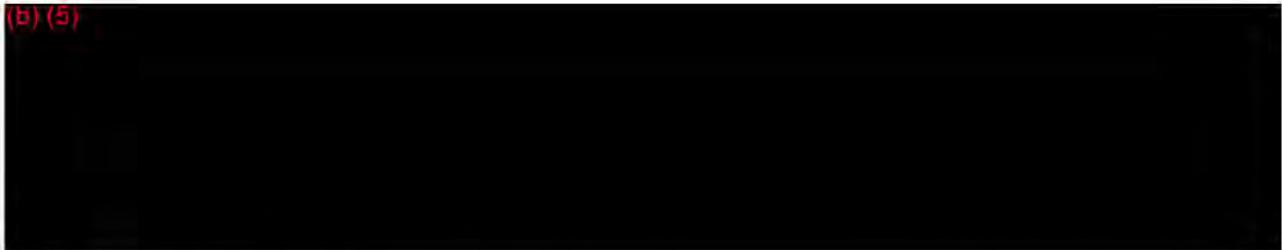
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Jen

(b) (5)

(b) (5)



From: Dickinson, Elizabeth (FDA)
Sent: Sunday, September 11, 2016 8:32 PM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie
Subject: RE: Q&A

(b) (5)



From: Califf, Robert
Sent: Sunday, September 11, 2016 7:49 PM
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Nice job. These changes improve what I was trying to get across. Thanks.

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

(b) (5)



(b) (5)



From: Sherman, Rachel

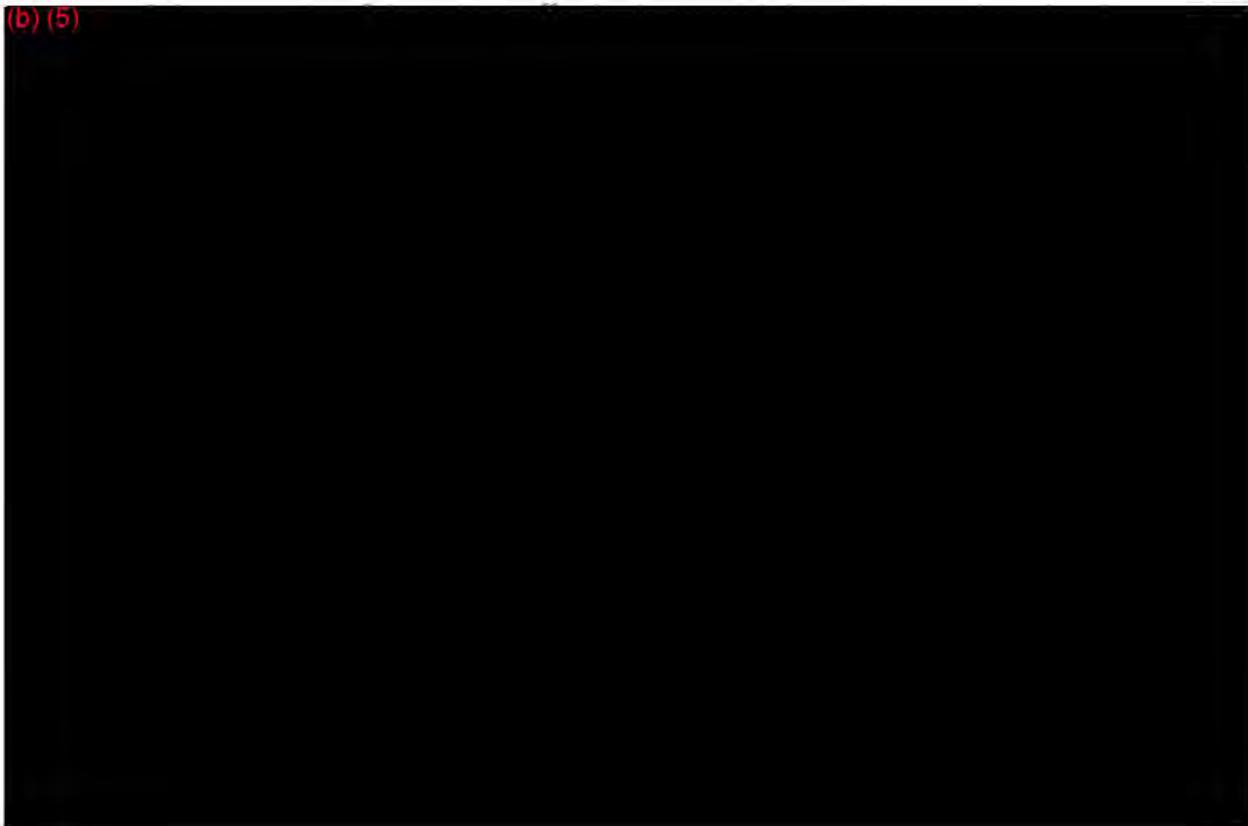
Sent: Sunday, September 11, 2016 8:45 AM

To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

Subject: RE: Q&A

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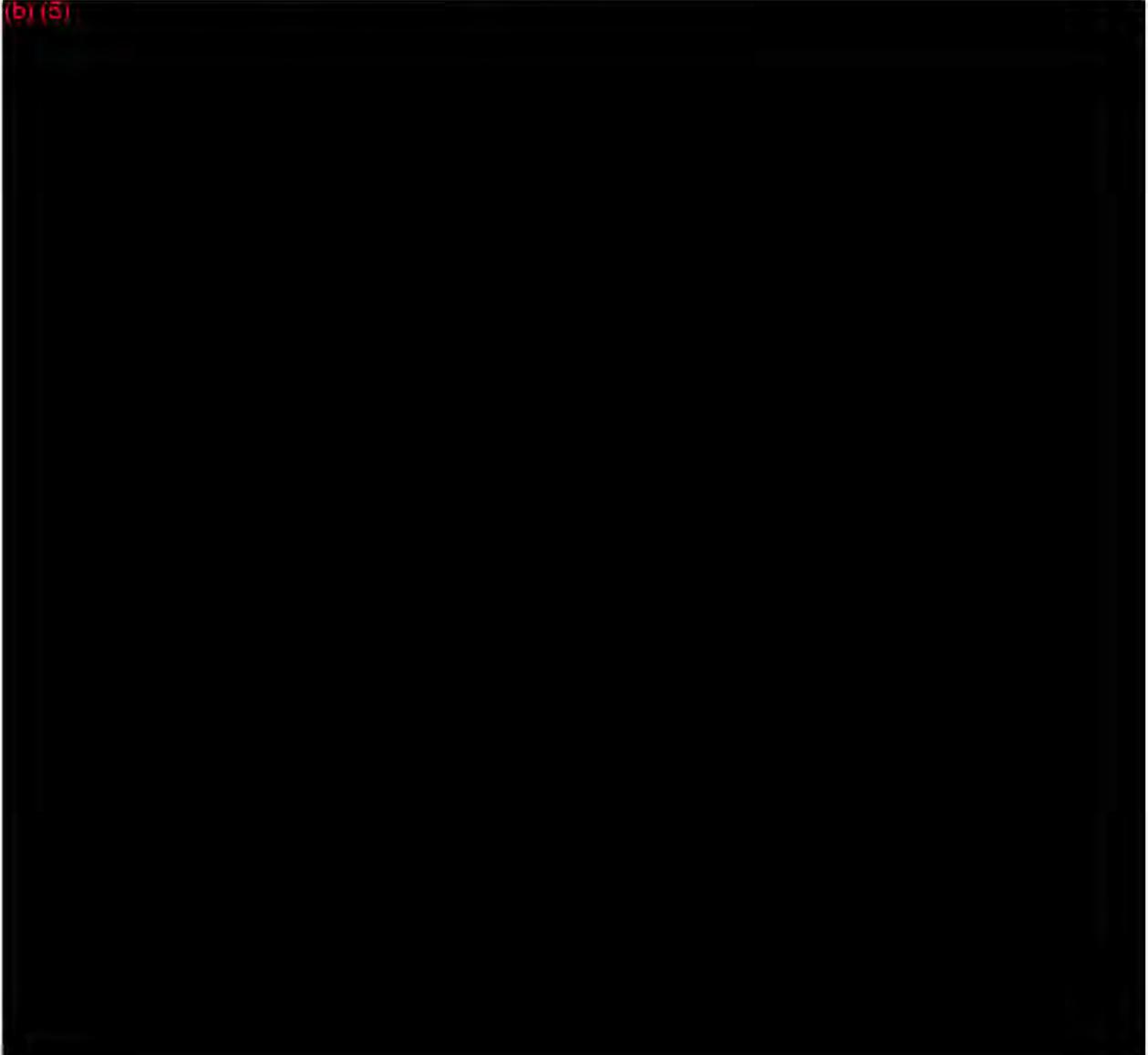
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(b) (5)



(b) (5)



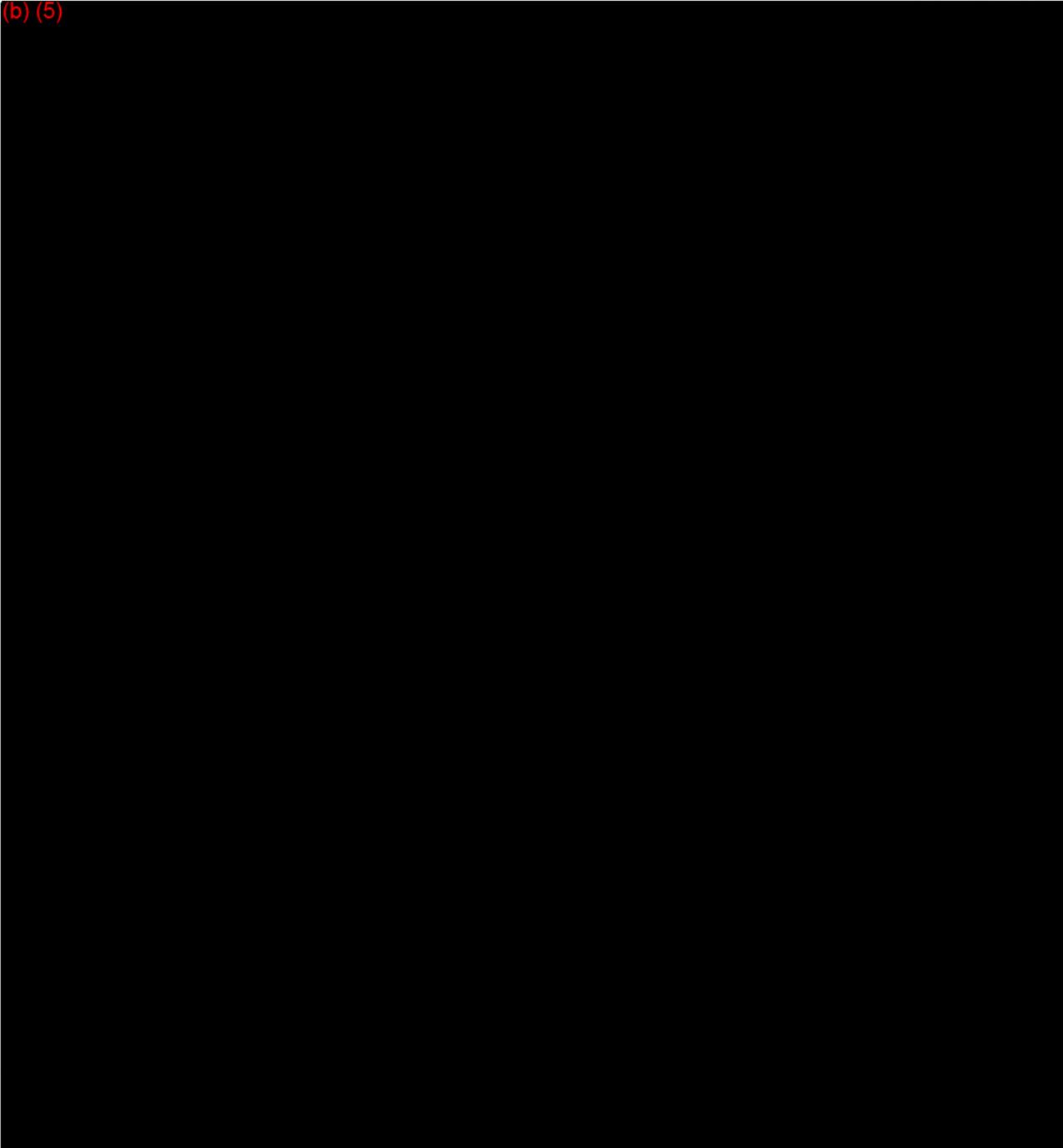
**Reactive Statement and QA: Posting of review documents for approval of
Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy**

Target date: September 2016

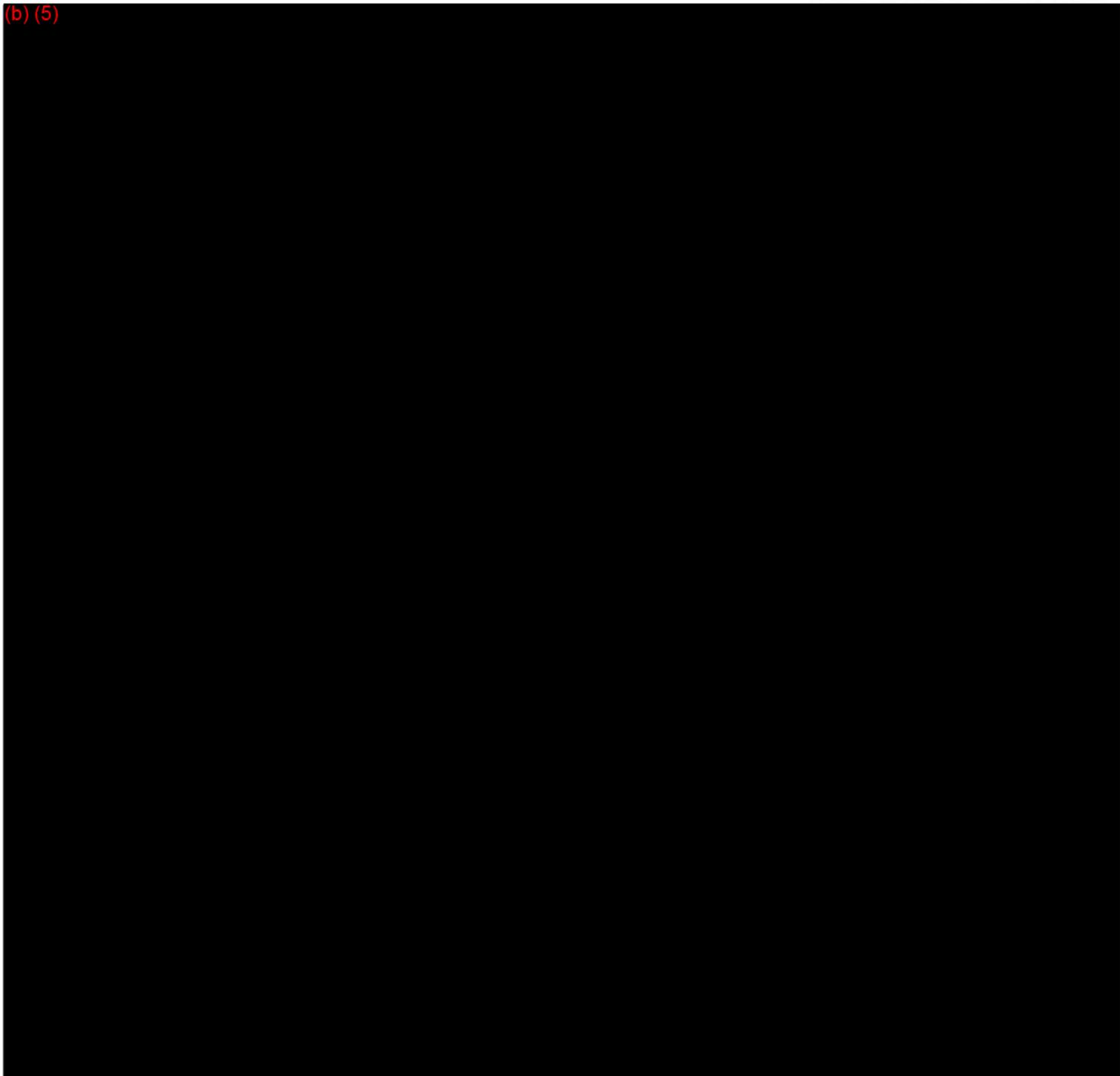
(b) (5)



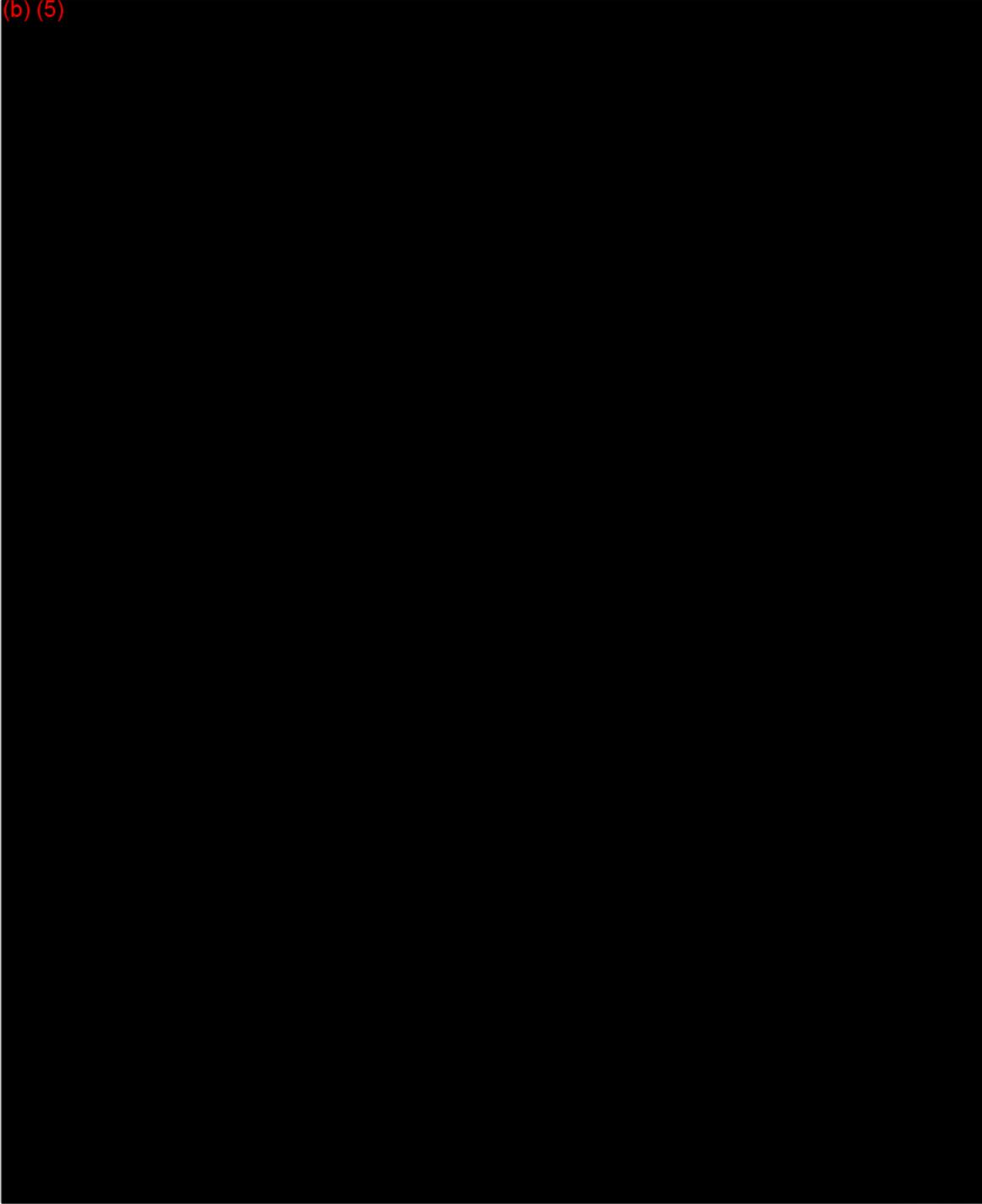
(b) (5)



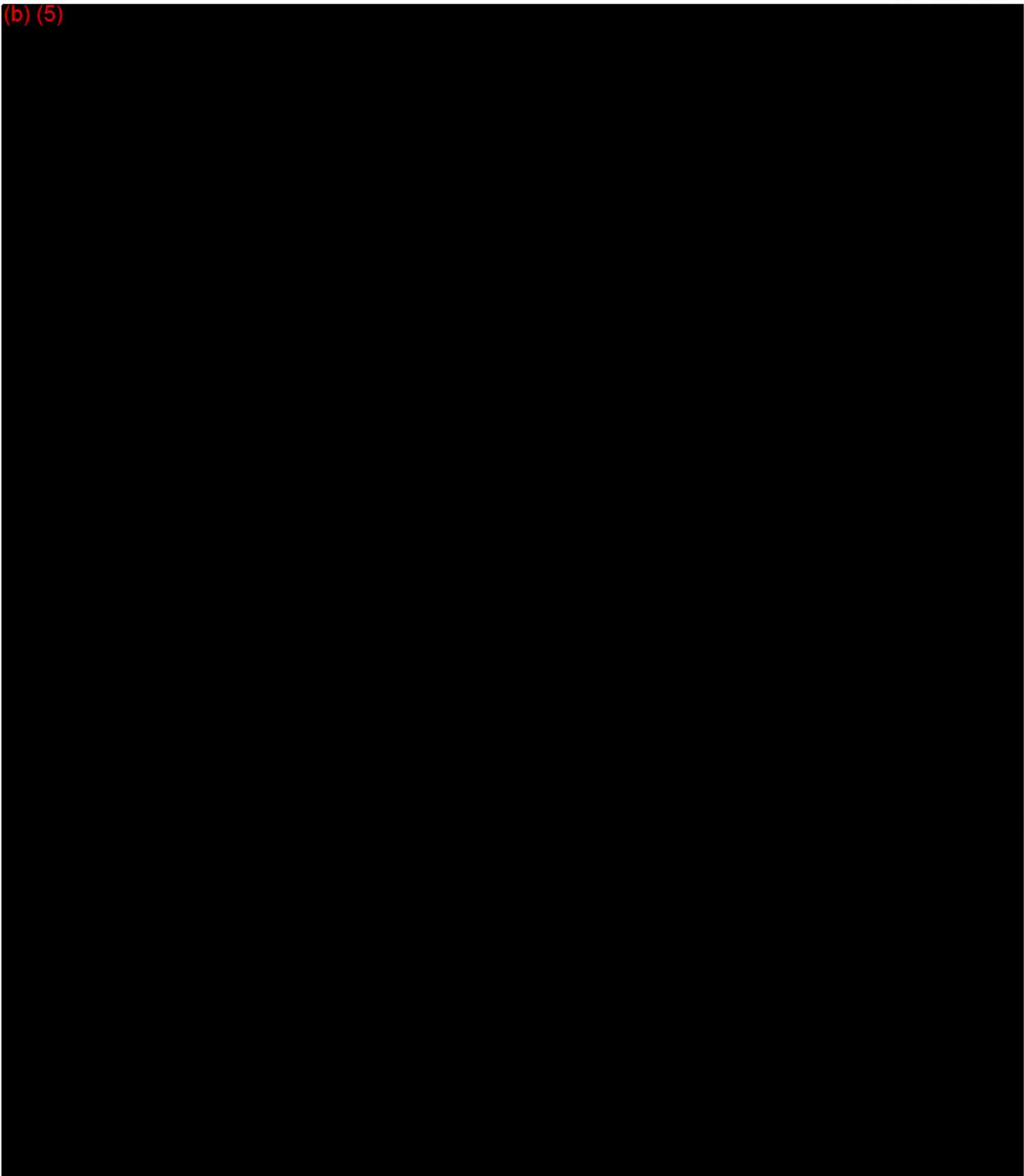
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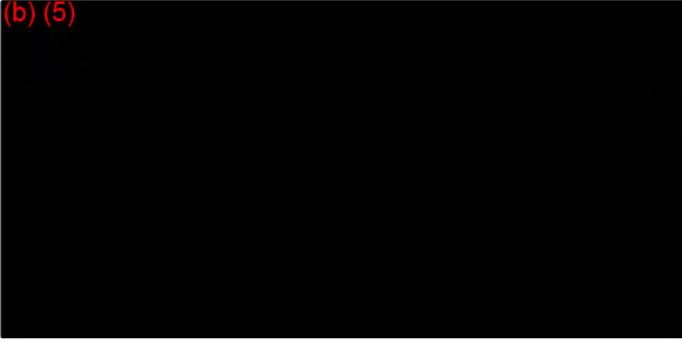
(b) (5)



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**Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat
Duchenne muscular dystrophy**

Target date: September 2016

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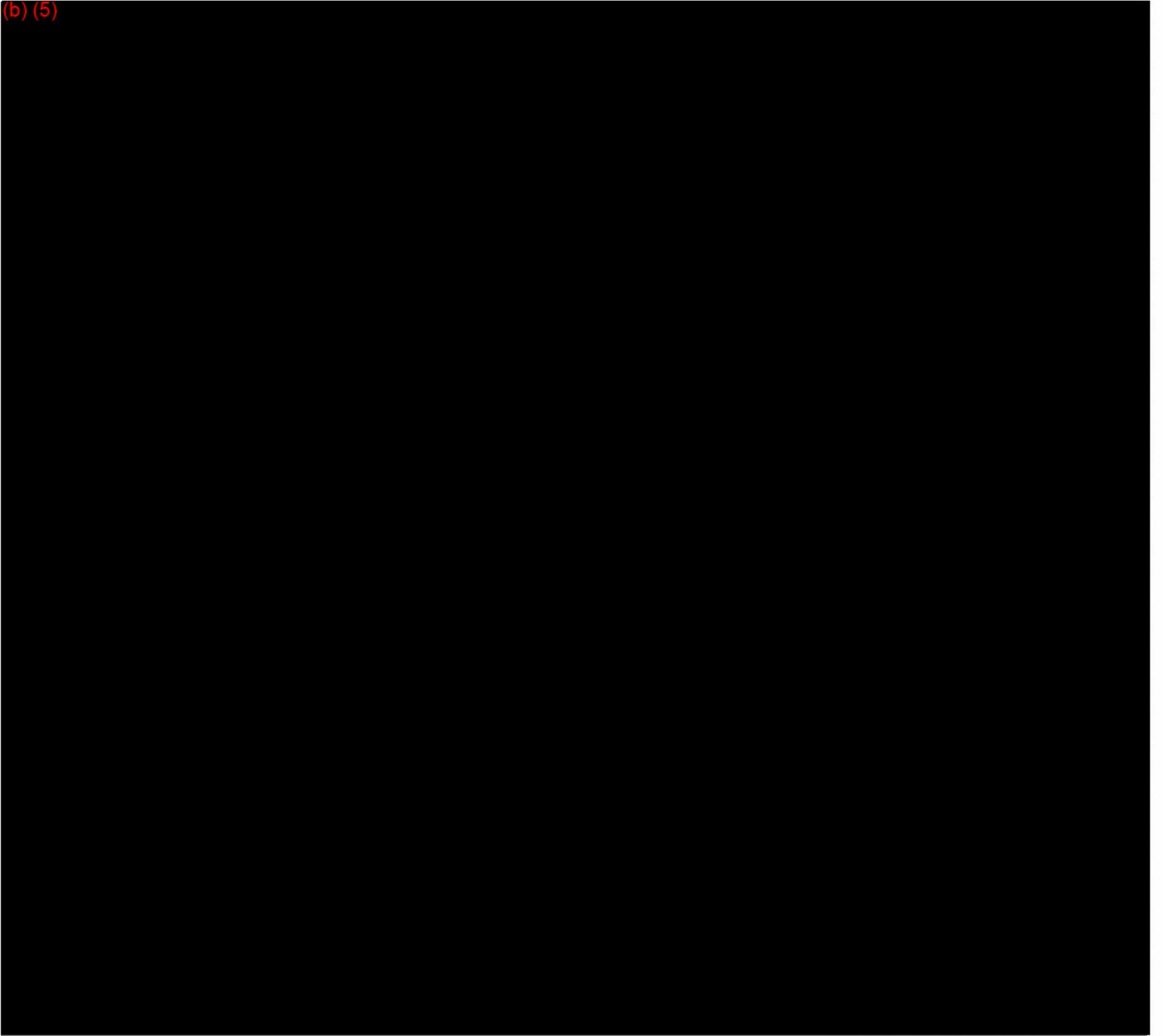
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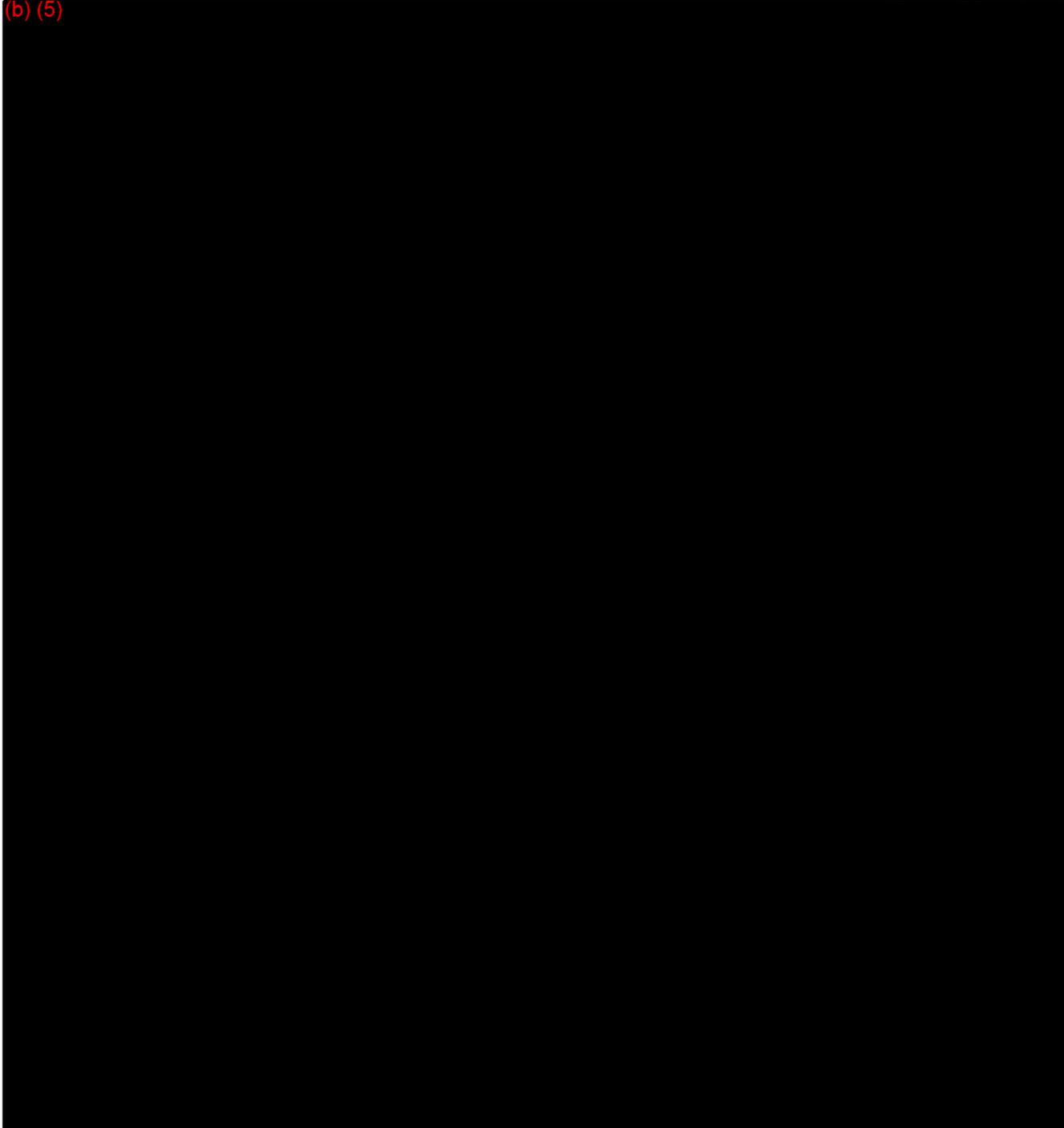
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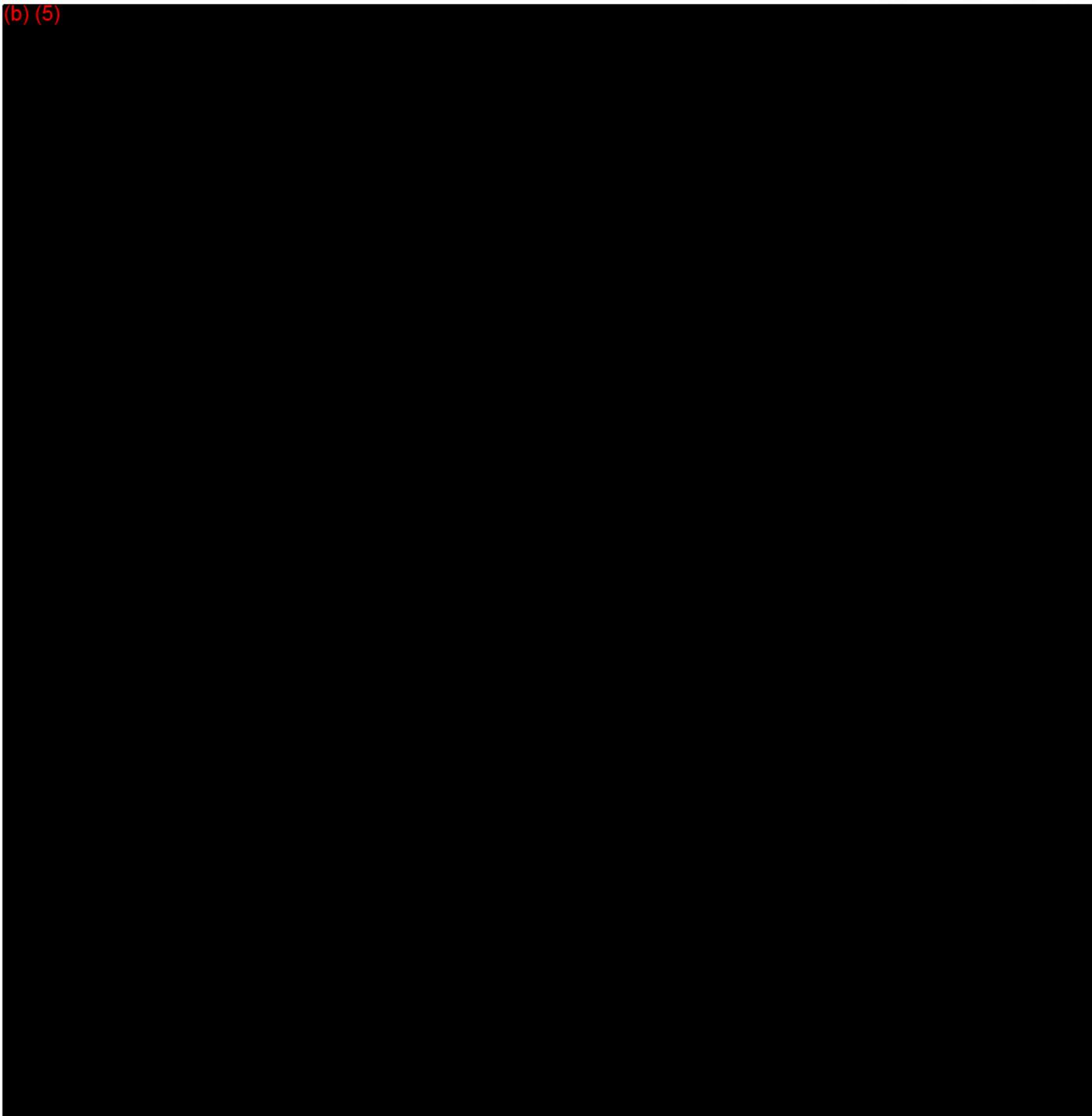
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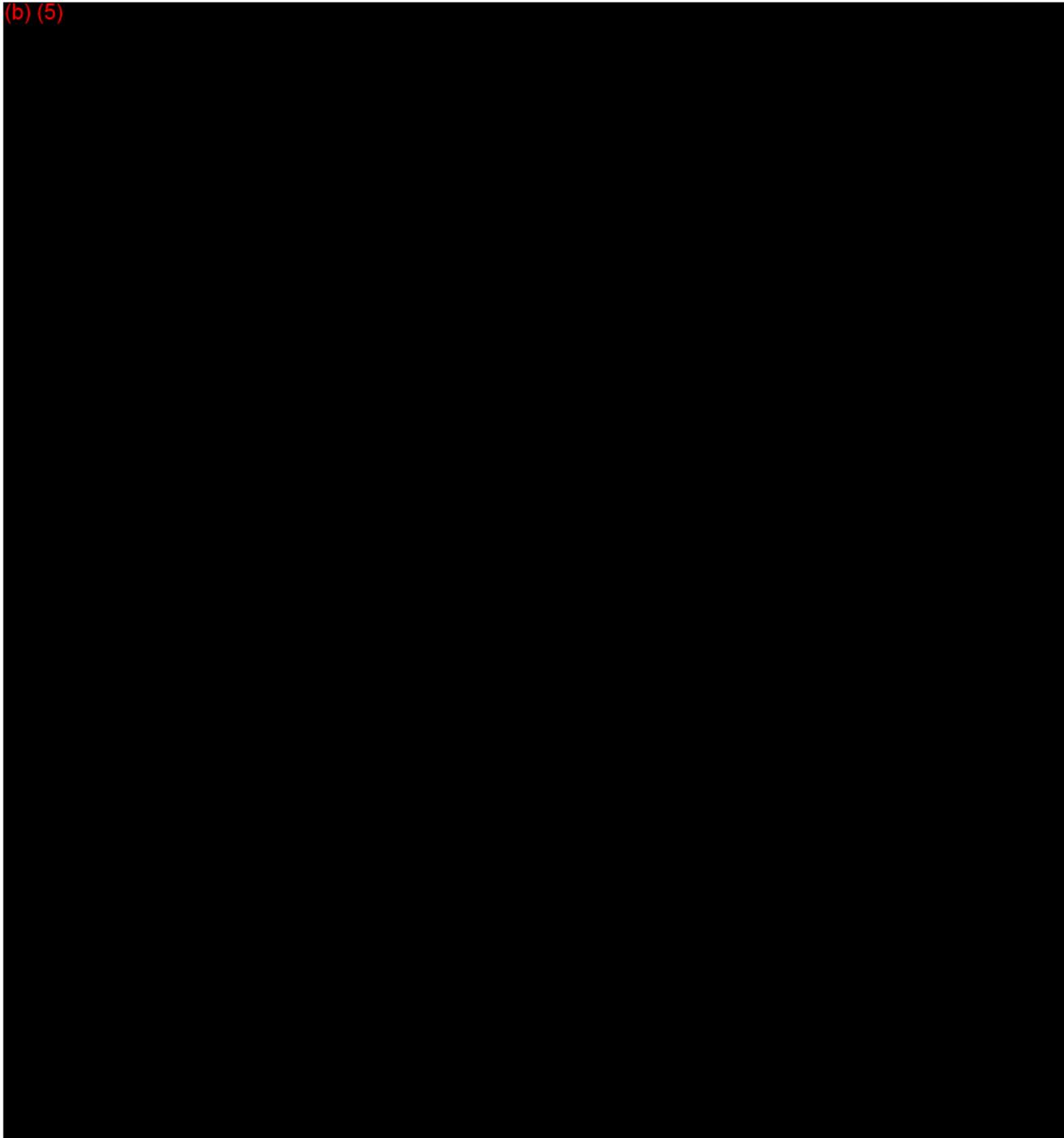
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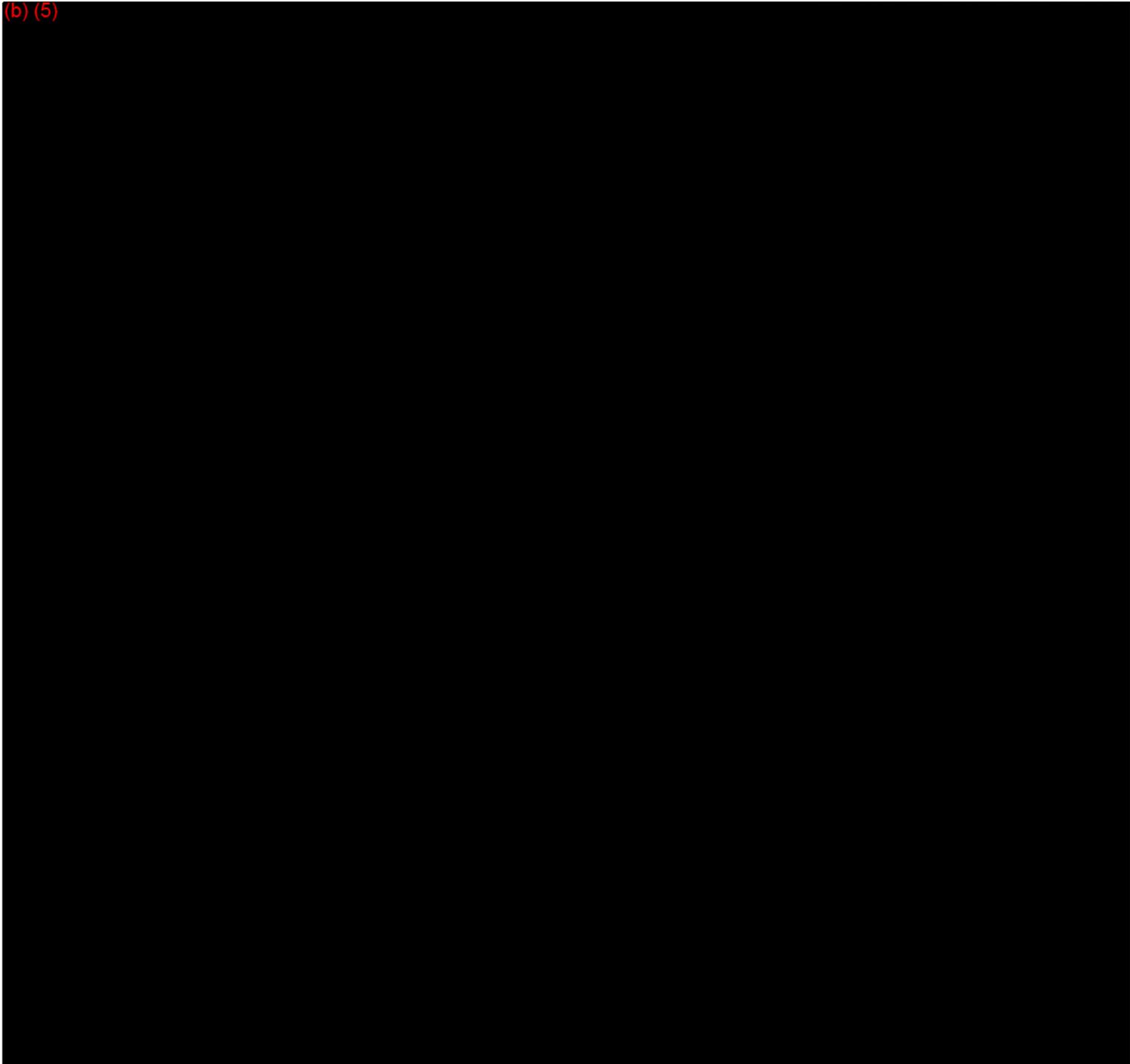
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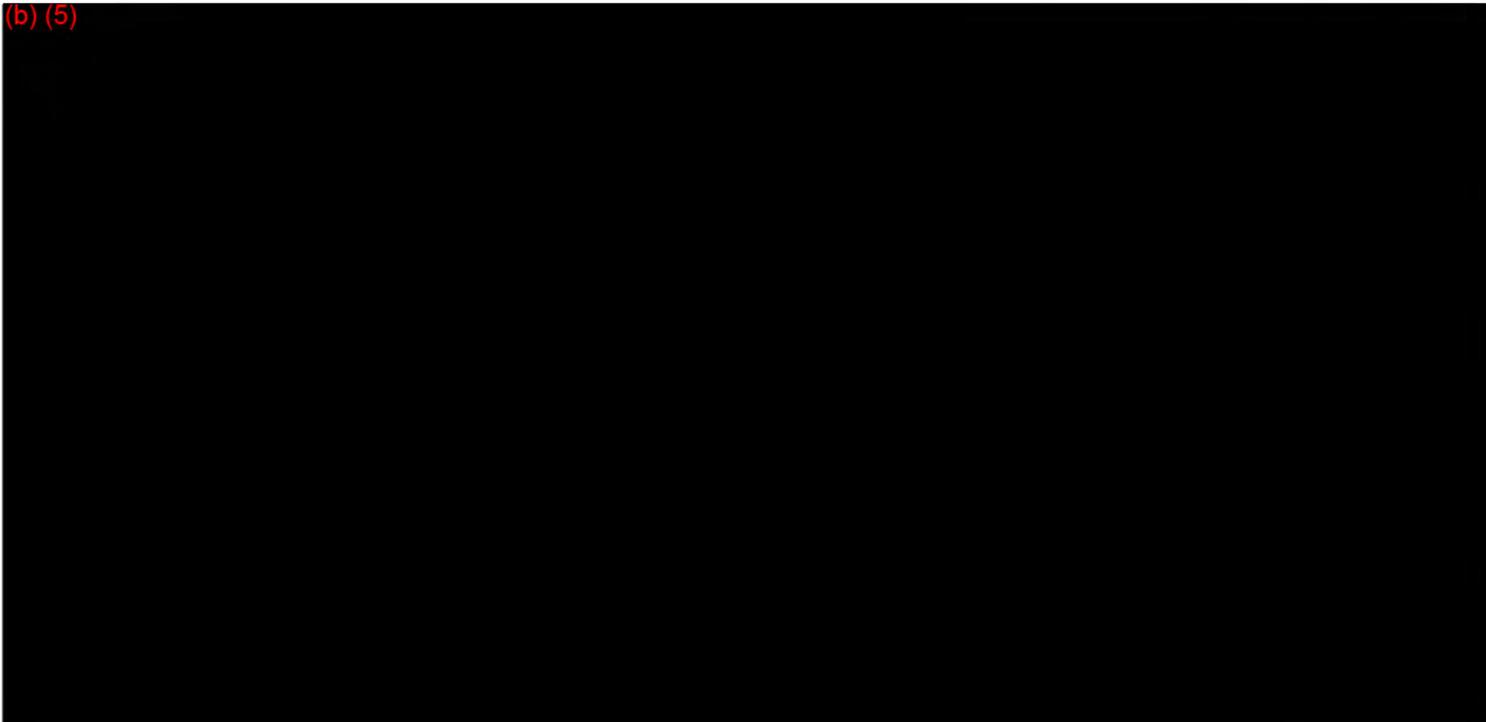
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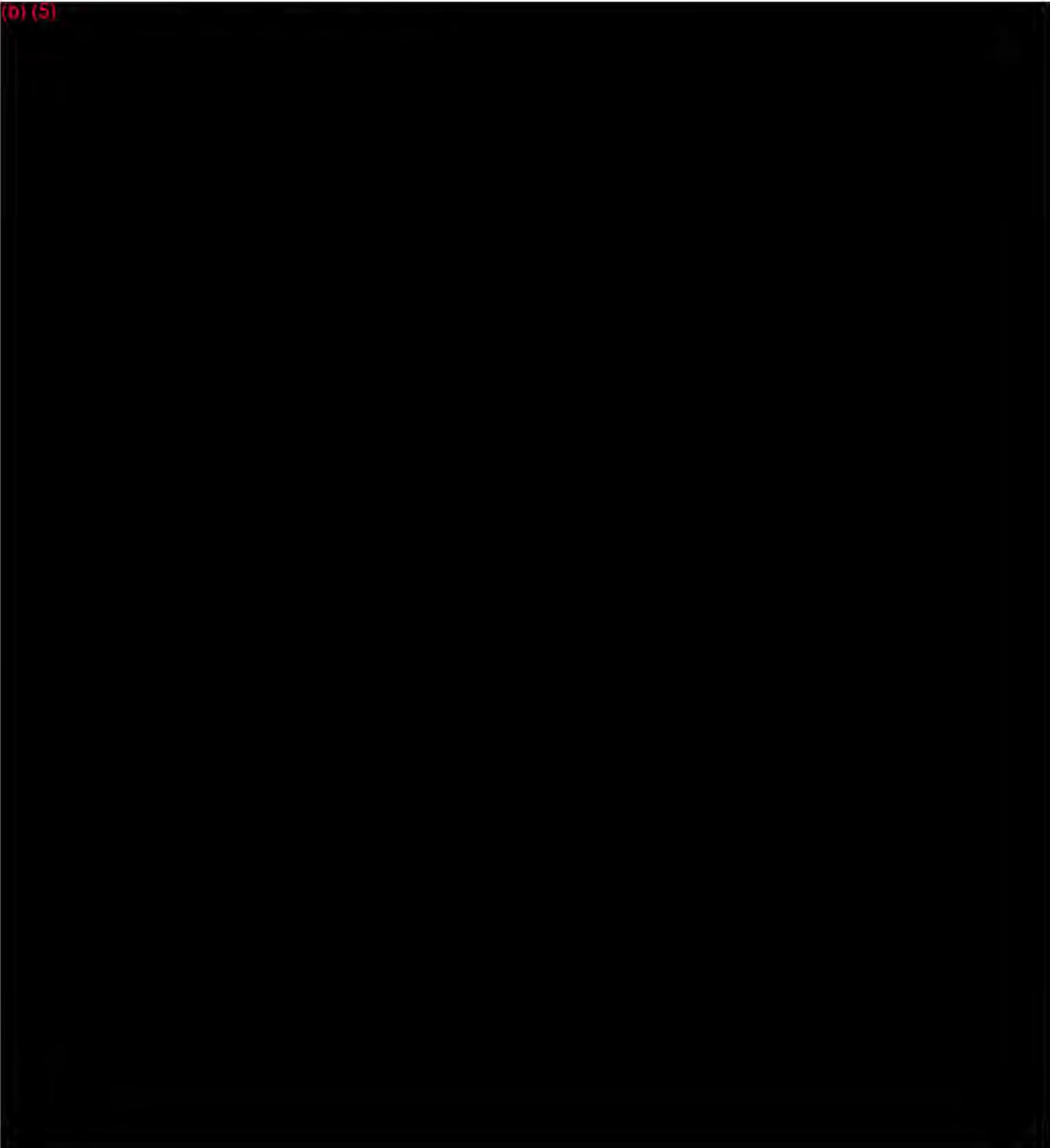
FDA NEWS RELEASE

For Immediate Release: September xx, 2016

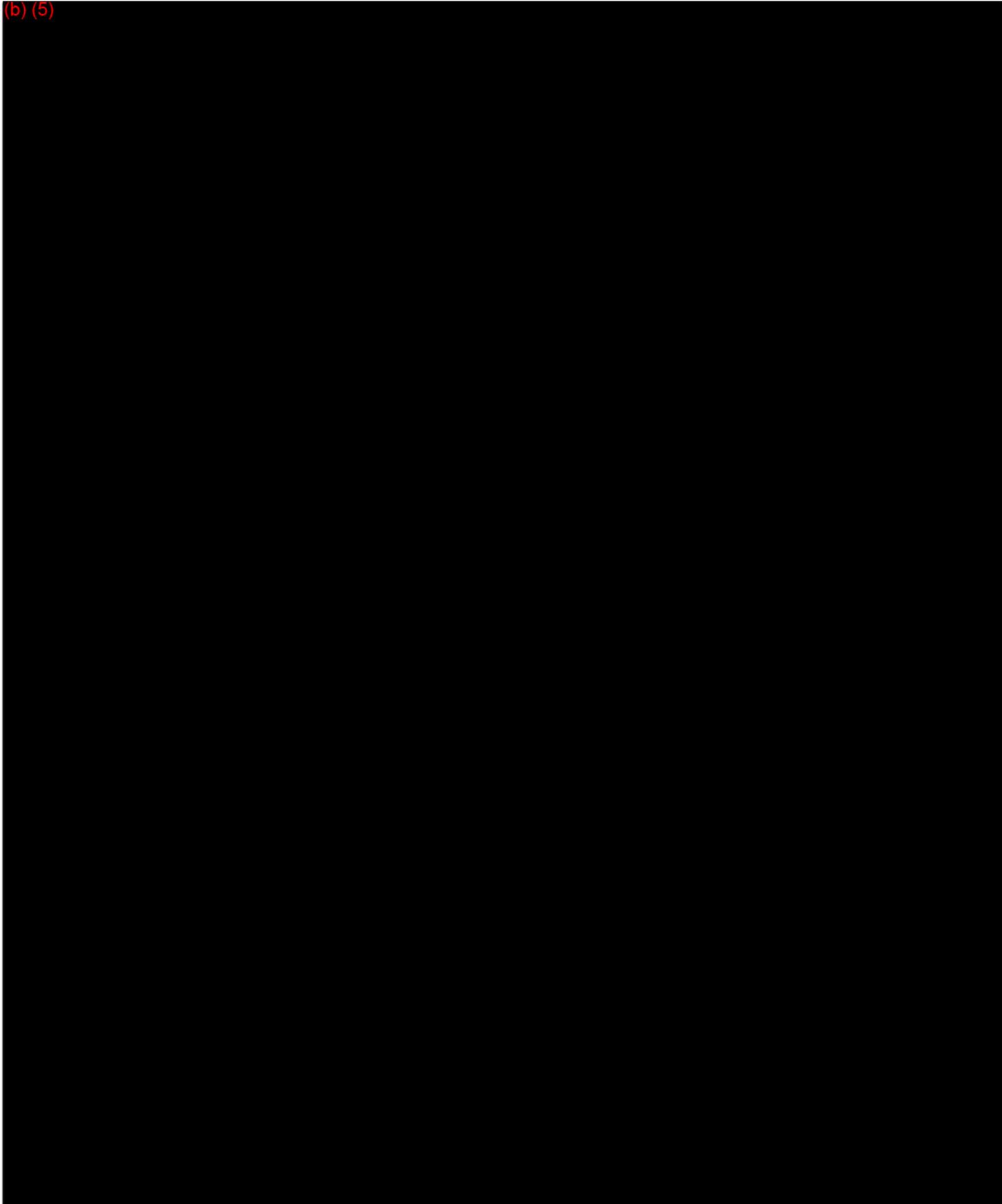
Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

(b) (5)



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(b) (5)



From: [Califf, Robert](#)
To: [Sherman, Rachel](#)
Subject: FW: Q&A
Date: Tuesday, September 13, 2016 5:51:00 AM
Attachments: [2016 Sept 012 R2 Eteplirsen CLEAN.doc](#)

Is this a good version to share?

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: McCall, Jonathan *
Sent: Monday, September 12, 2016 9:28 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Kraus, Tom
Subject: RE: Q&A

Here's a clean version.

Thanks!

--

J

From: Califf, Robert
Sent: Monday, September 12, 2016 7:49 PM
To: Dickinson, Elizabeth (FDA); McCall, Jonathan *; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Kraus, Tom
Subject: RE: Q&A

I am happy with the couple of changes, but I am not an expert on the stylistic, font , spacing and footnote changes. Can someone clean this up so I can send to Ellis, John, Lu and Janet tomorrow AM? I hate to send them something with a bunch of comments.

Sorry to be a pain.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

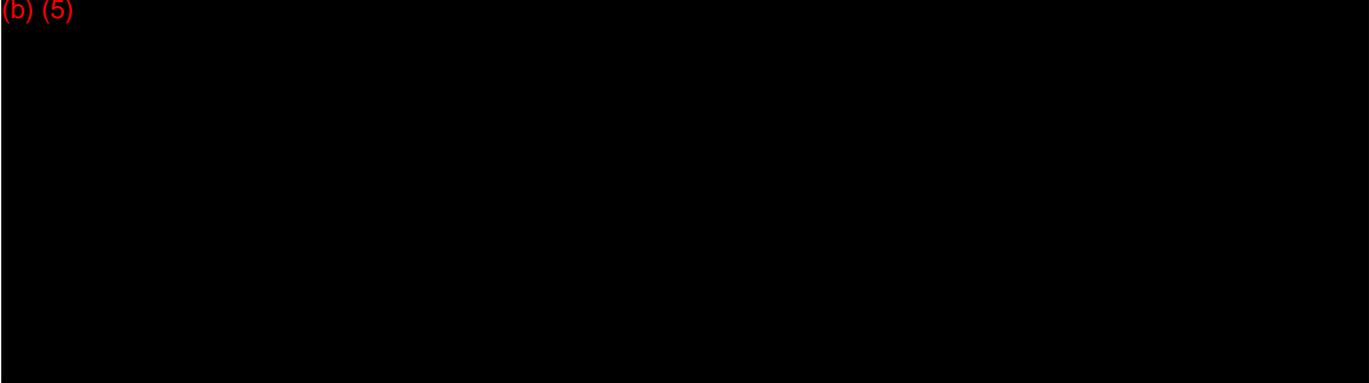
From: Dickinson, Elizabeth (FDA)

Sent: Monday, September 12, 2016 5:21 PM

To: McCall, Jonathan *; Chasan-Sloan, Deborah (FDA); Califf, Robert; Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Kraus, Tom

Subject: RE: Q&A

(b) (5)



Liz

From: McCall, Jonathan *

Sent: Monday, September 12, 2016 3:25 PM

To: Chasan-Sloan, Deborah (FDA); Califf, Robert; Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom

Subject: RE: Q&A

Hello all –

I'm recirculating the memo draft (R1) with Deborah's suggested edit included. In addition to the tracked-changes and clean-commented versions, I'm also including a clean version without any comments.

Please let me know if you have any questions!

Best,

Jonathan

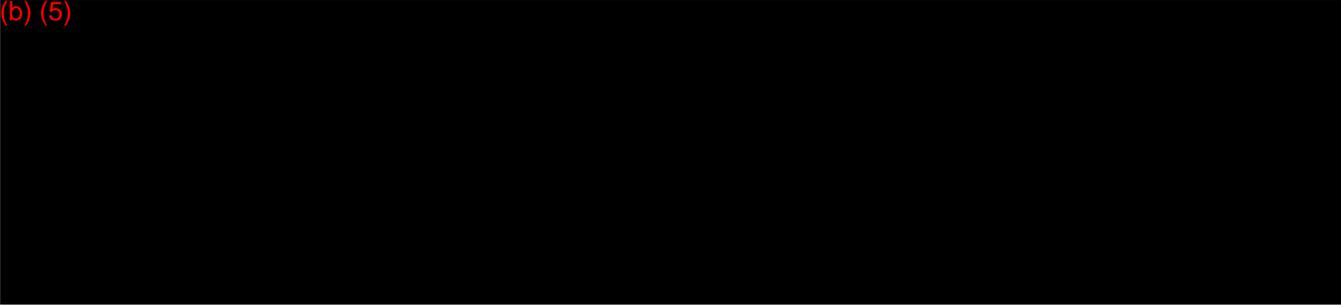
From: Chasan-Sloan, Deborah (FDA)

Sent: Monday, September 12, 2016 11:58 AM

To: McCall, Jonathan *; Califf, Robert; Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom

Subject: Re: Q&A

(b) (5)



(b) (5)

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: McCall, Jonathan *†

Sent: Monday, September 12, 2016 10:34 AM

To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom

Subject: RE: Q&A

Hello all –

I'm attaching a tracked-changes version with a few additional edits from me. The clean-commented version accepts all changes and removes all comments that have already been resolved. There are a few additional comments from me, mostly to verify acceptability of some wording changes.

Please let me know if you have any questions!

Best,

Jonathan

From: Califf, Robert

Sent: Monday, September 12, 2016 6:54 AM

To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA); Kraus, Tom

Cc: McCall, Jonathan *

Subject: RE: Q&A

Here is what I hope is the penultimate version of my memo. I'm assuming:

1. Jonathan will edit and recirculate.
2. People will have their final say today.
3. I will send to Ellis, John and Janet this afternoon with 24 hours to review.

Is this ok?

rmc

From: Chasan-Sloan, Deborah (FDA)

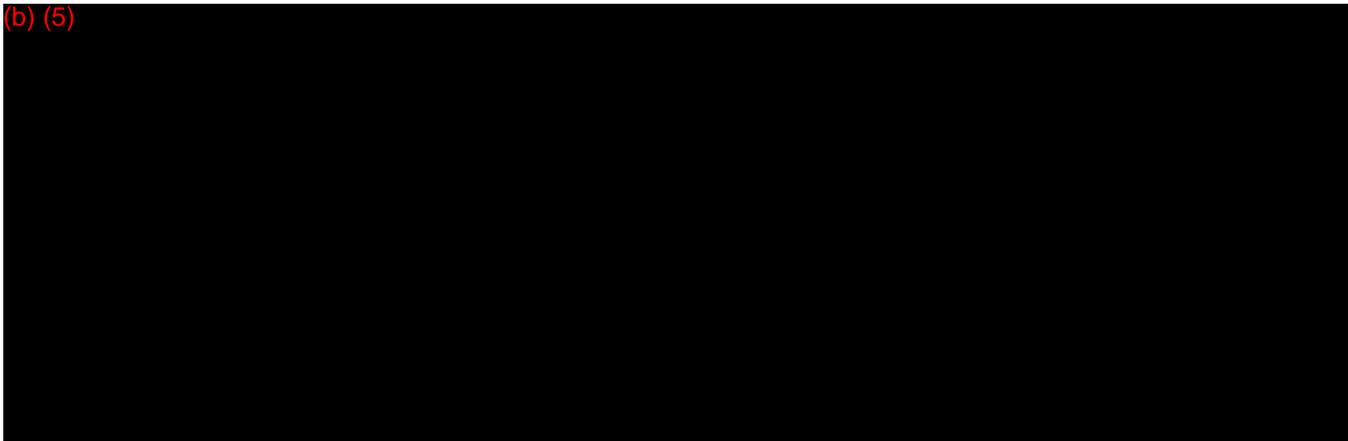
Sent: Sunday, September 11, 2016 7:44 PM

To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)

FDAOC0001910

Subject: RE: Q&A

(b) (5)



From: Sherman, Rachel
Sent: Sunday, September 11, 2016 8:45 AM
To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.

(b) (5)



Hope this helps

FDAOC0001911

Rachel

Why do you equivocate and say I'm right on most things? I thought we agreed I was always right....

From: Califf, Robert

Sent: Sunday, September 11, 2016 8:23 AM

To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

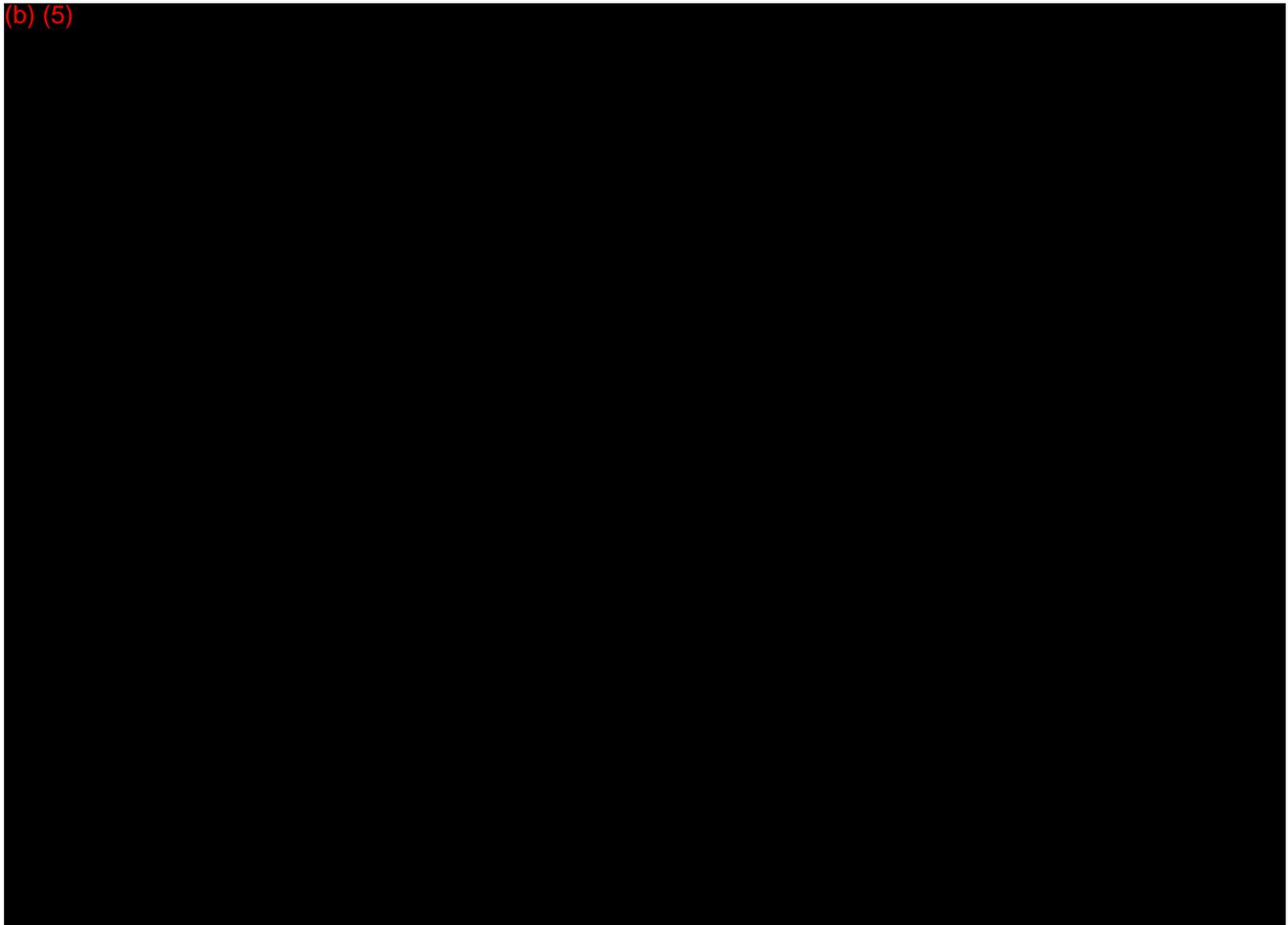
Subject: Q&A

Friends,

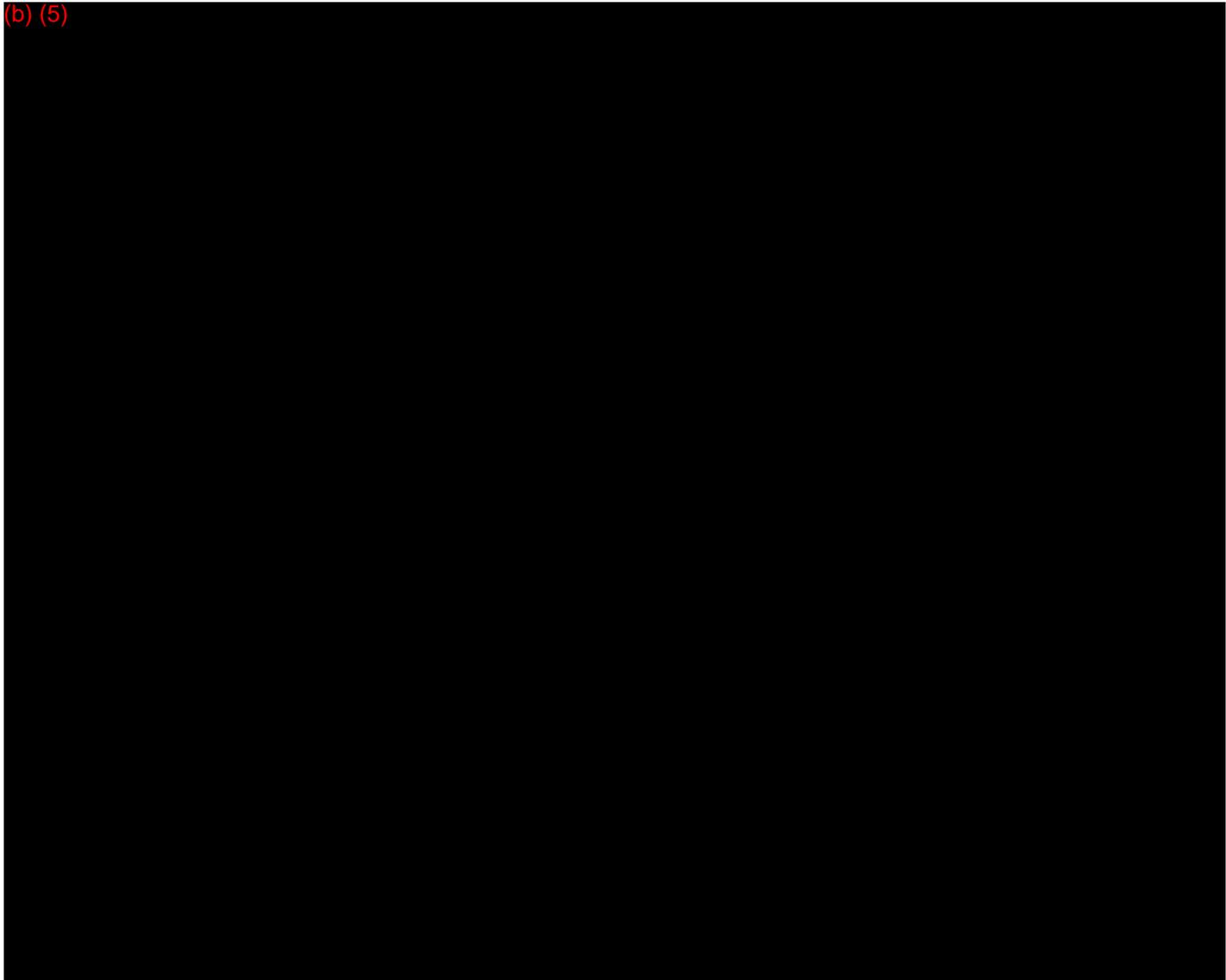
I have done a little editing, but not much as I think its good. There are still several loose ends. Are we still ok on the timeline?

3 issues strike me as needing more work:

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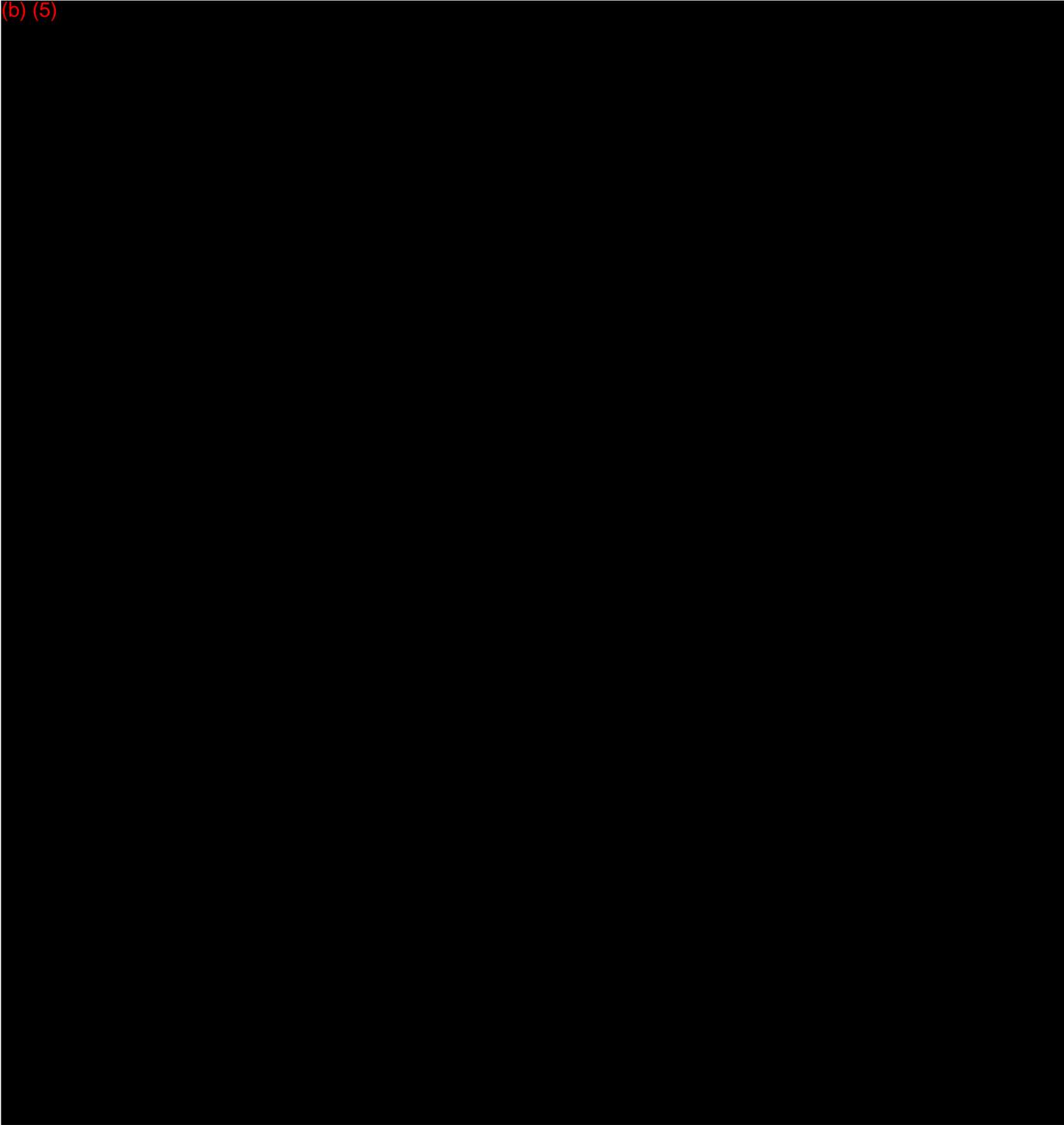


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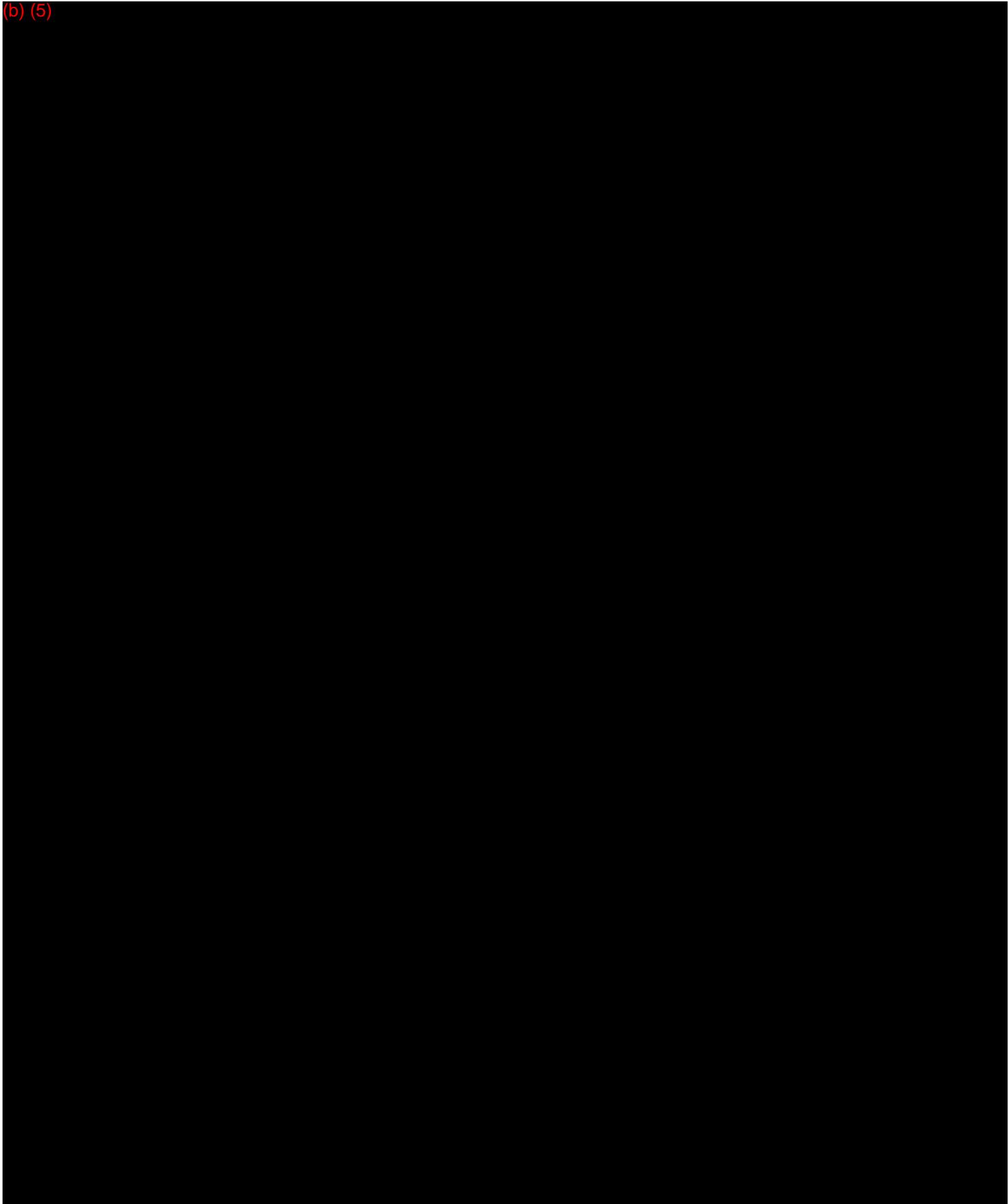


Scientific Dispute Regarding Approval of Sarepta Therapeutics’ Eteplirsen – Commissioner’s Decision

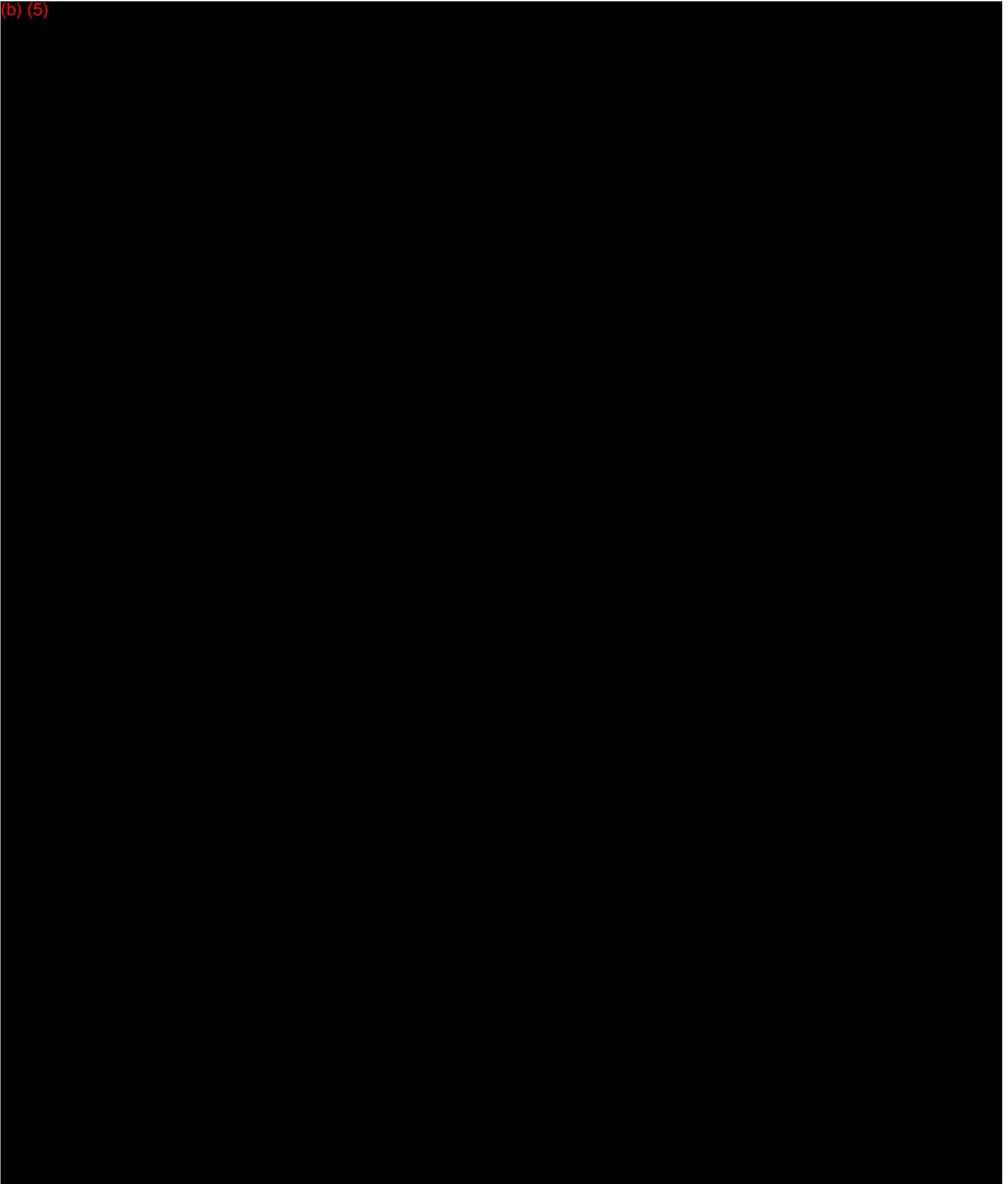
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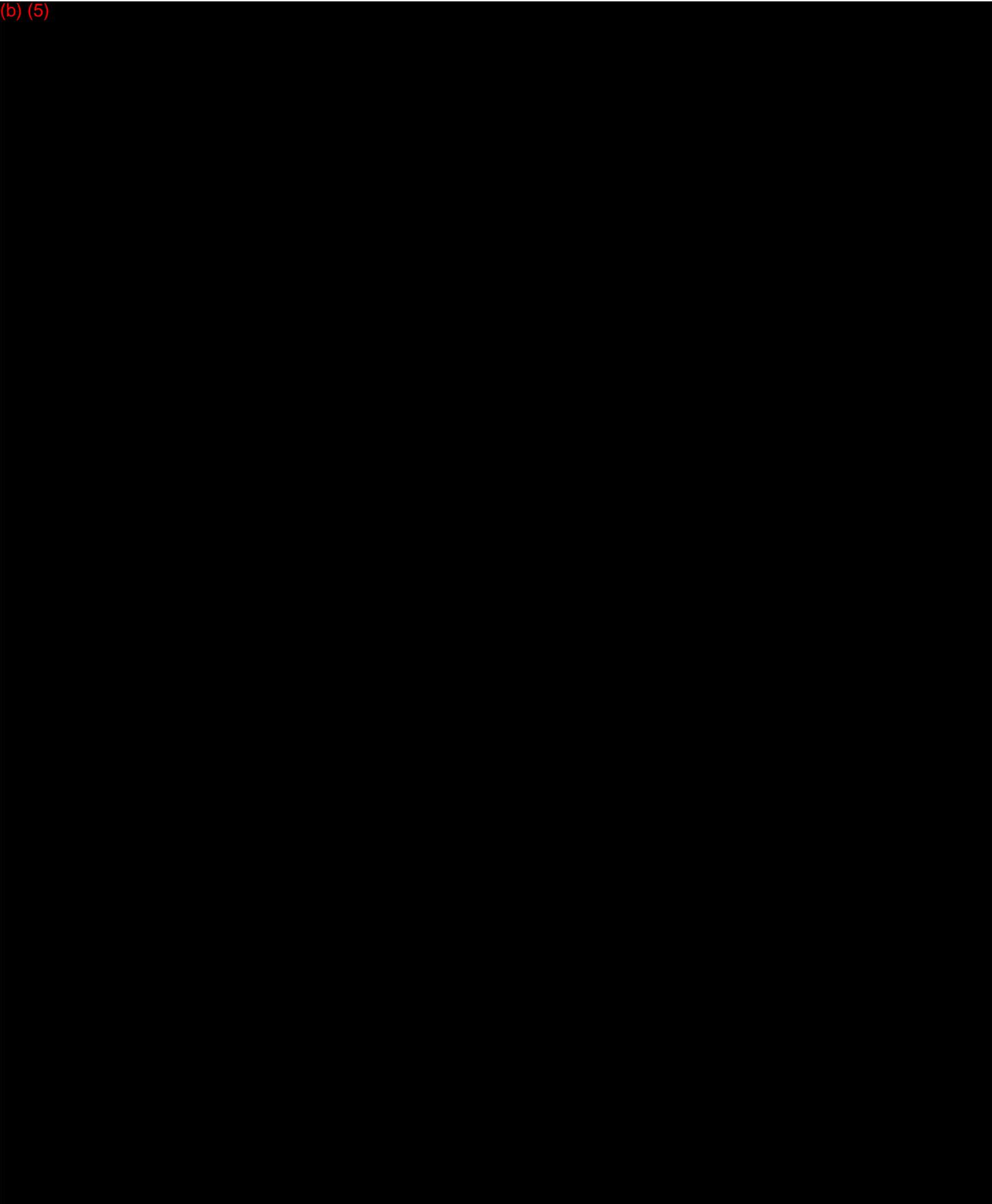
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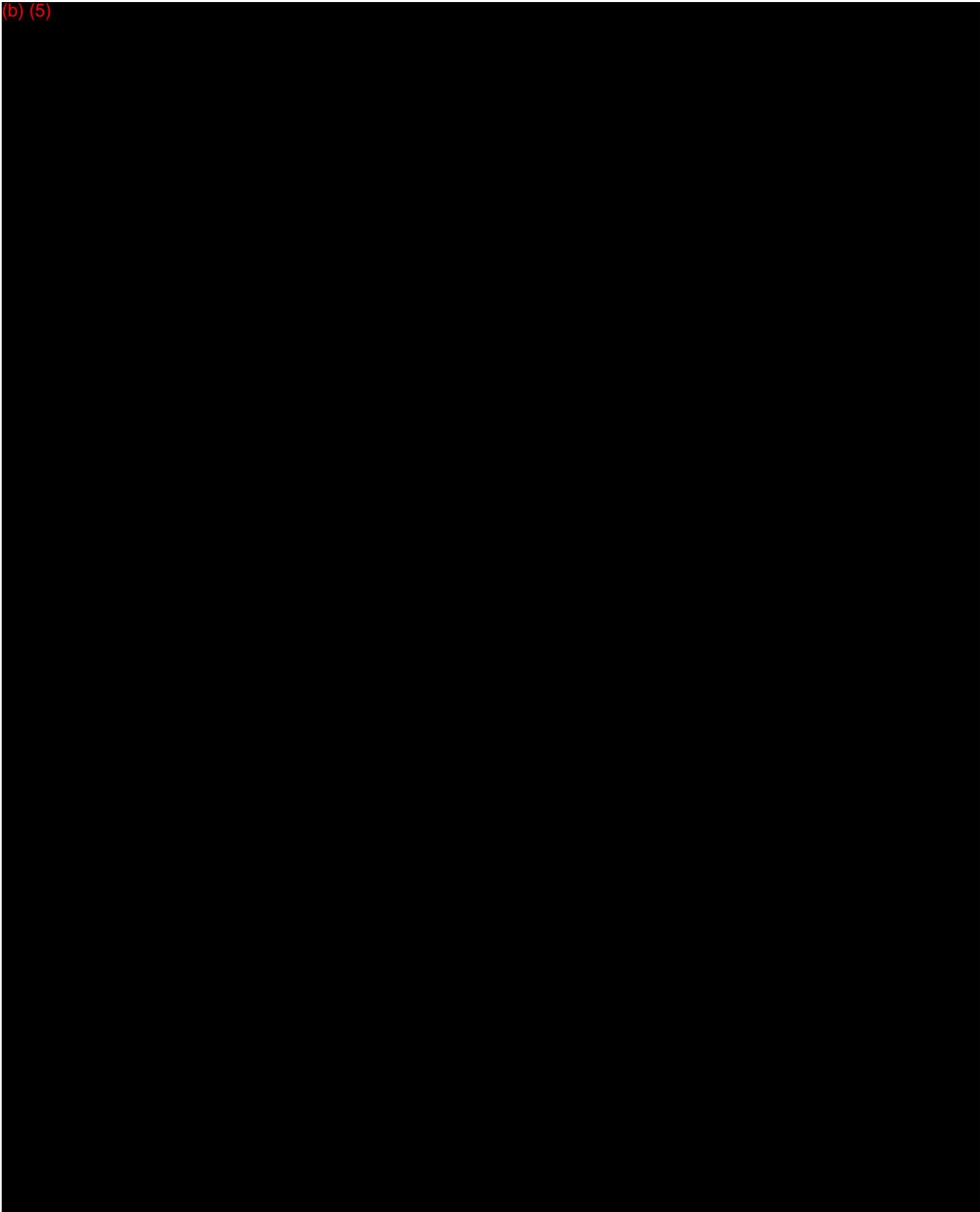
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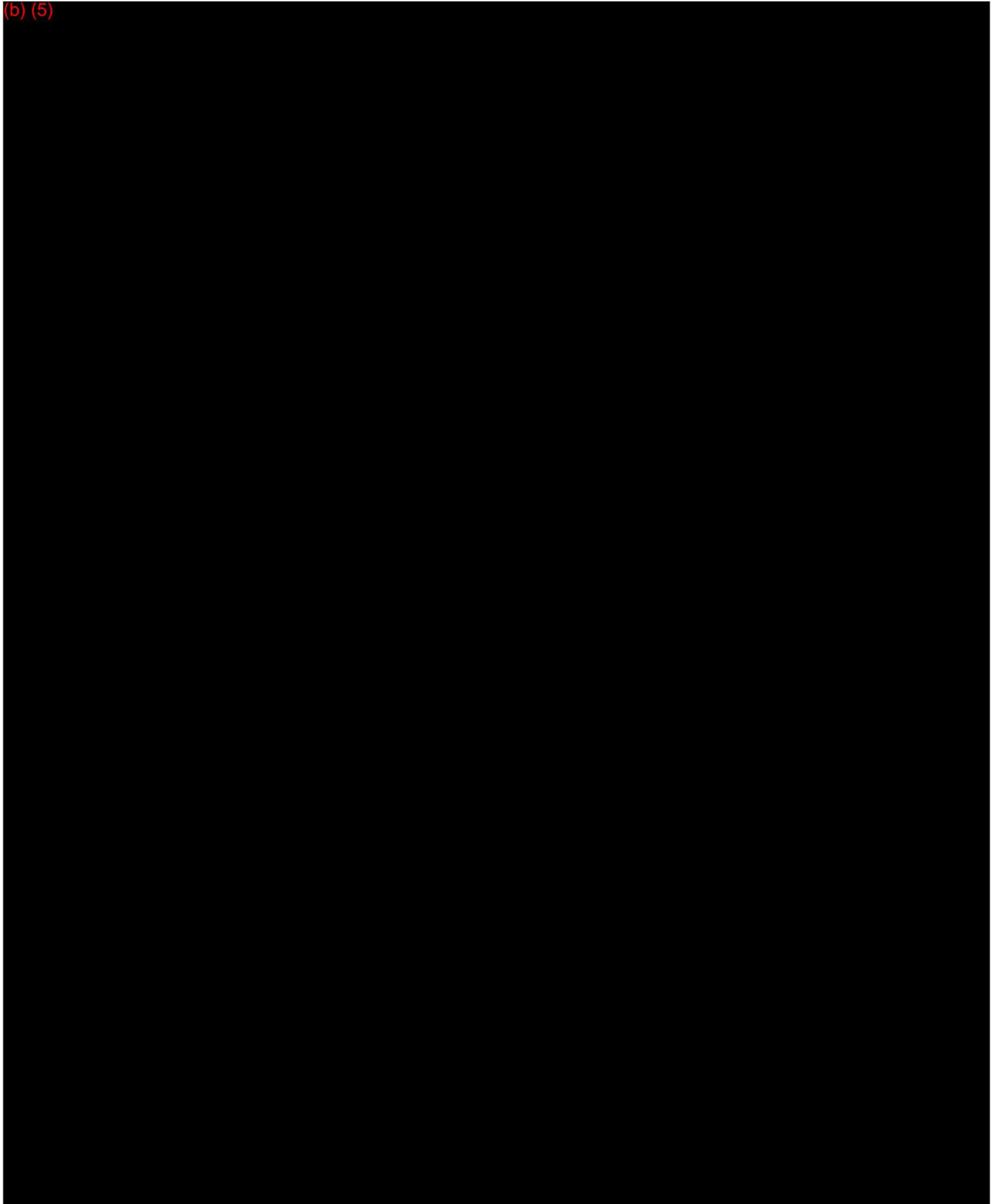
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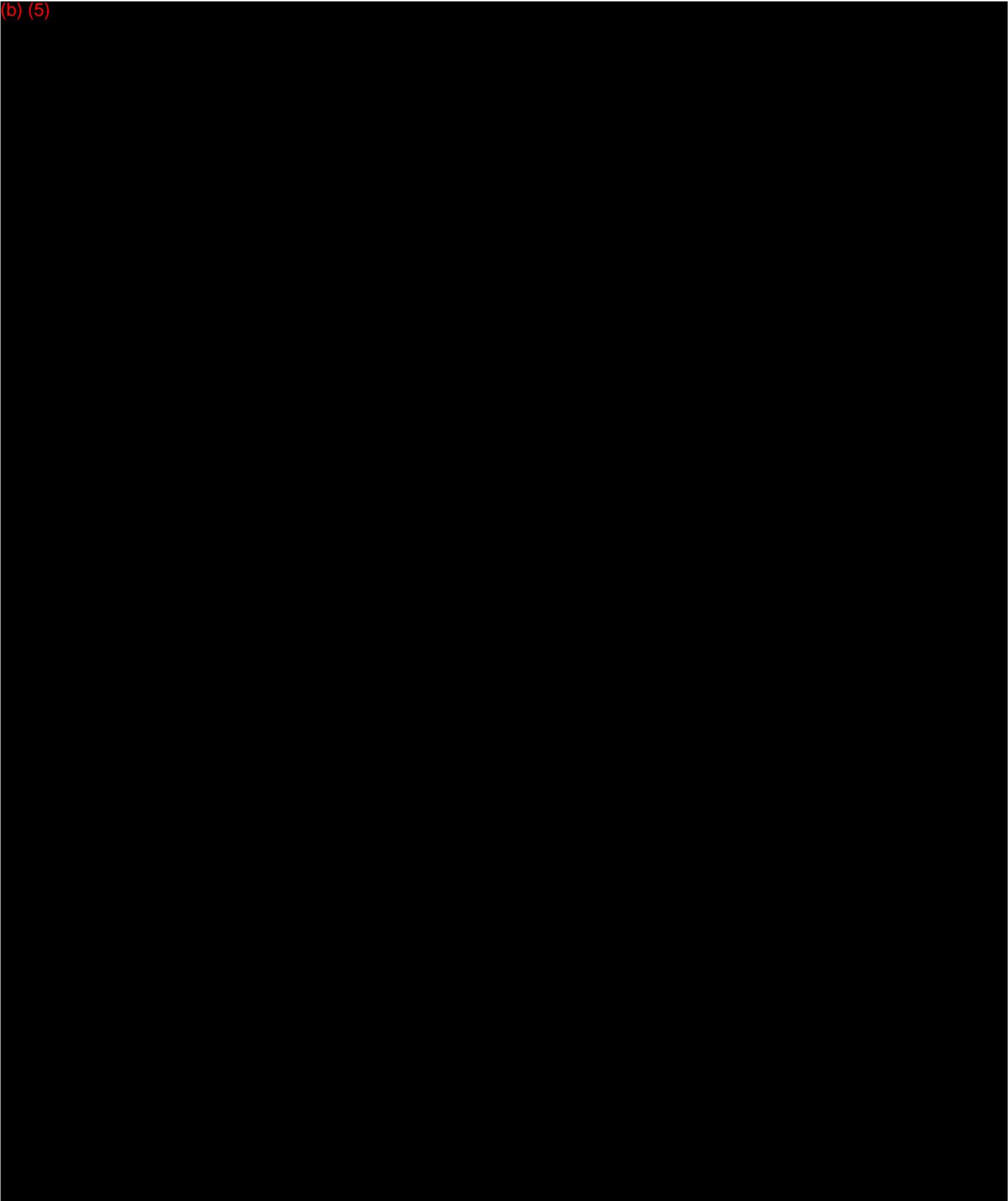
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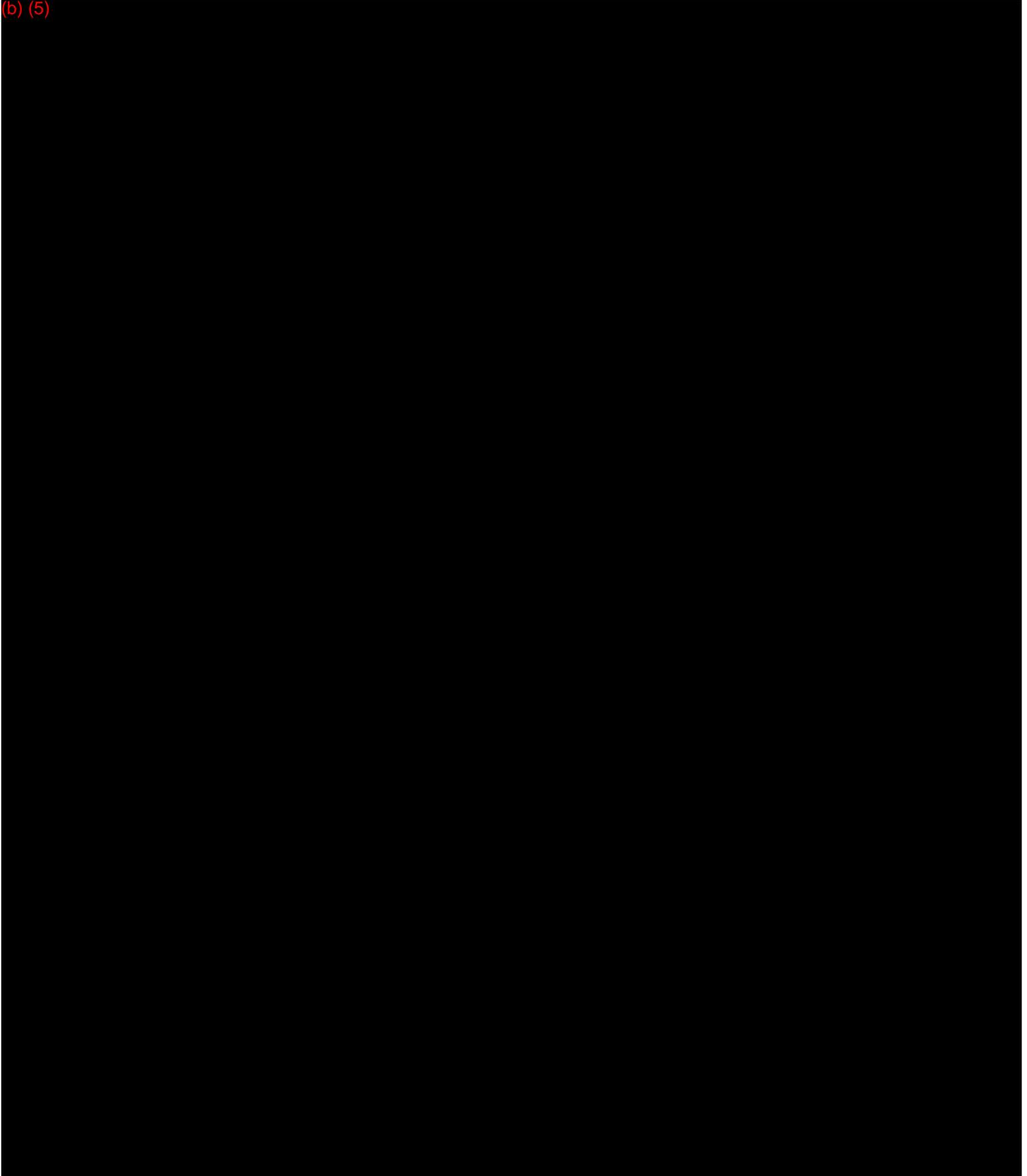
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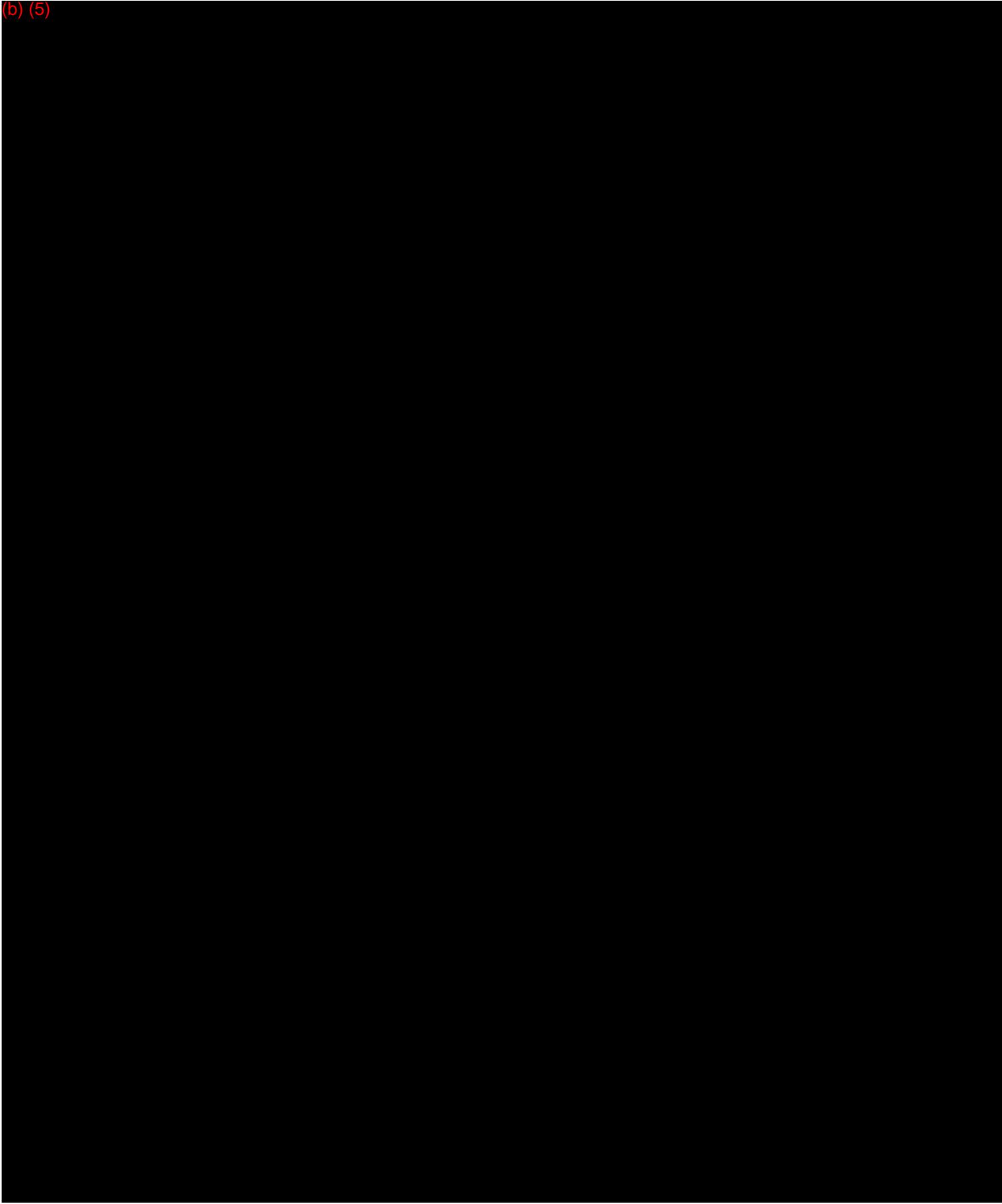
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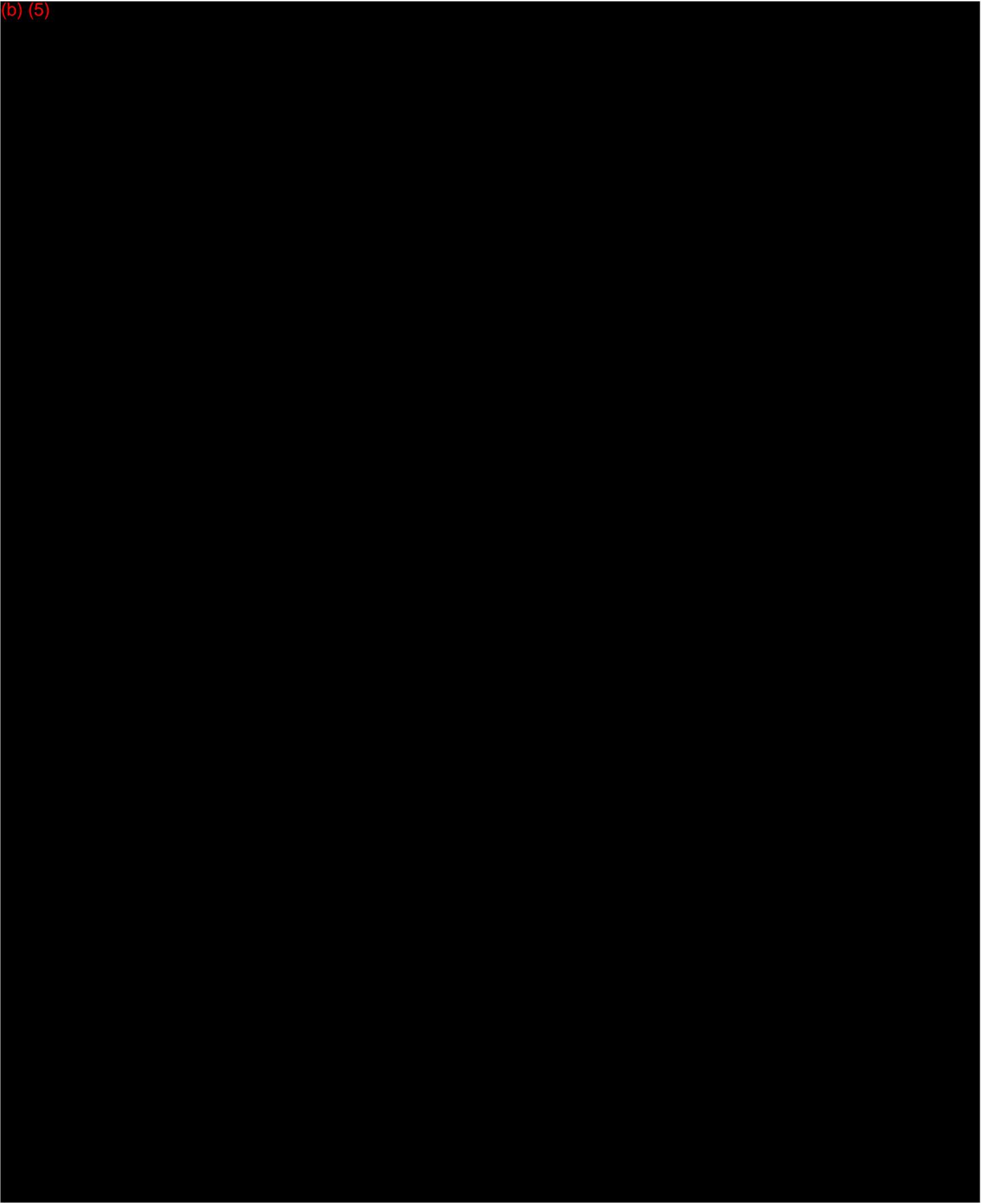
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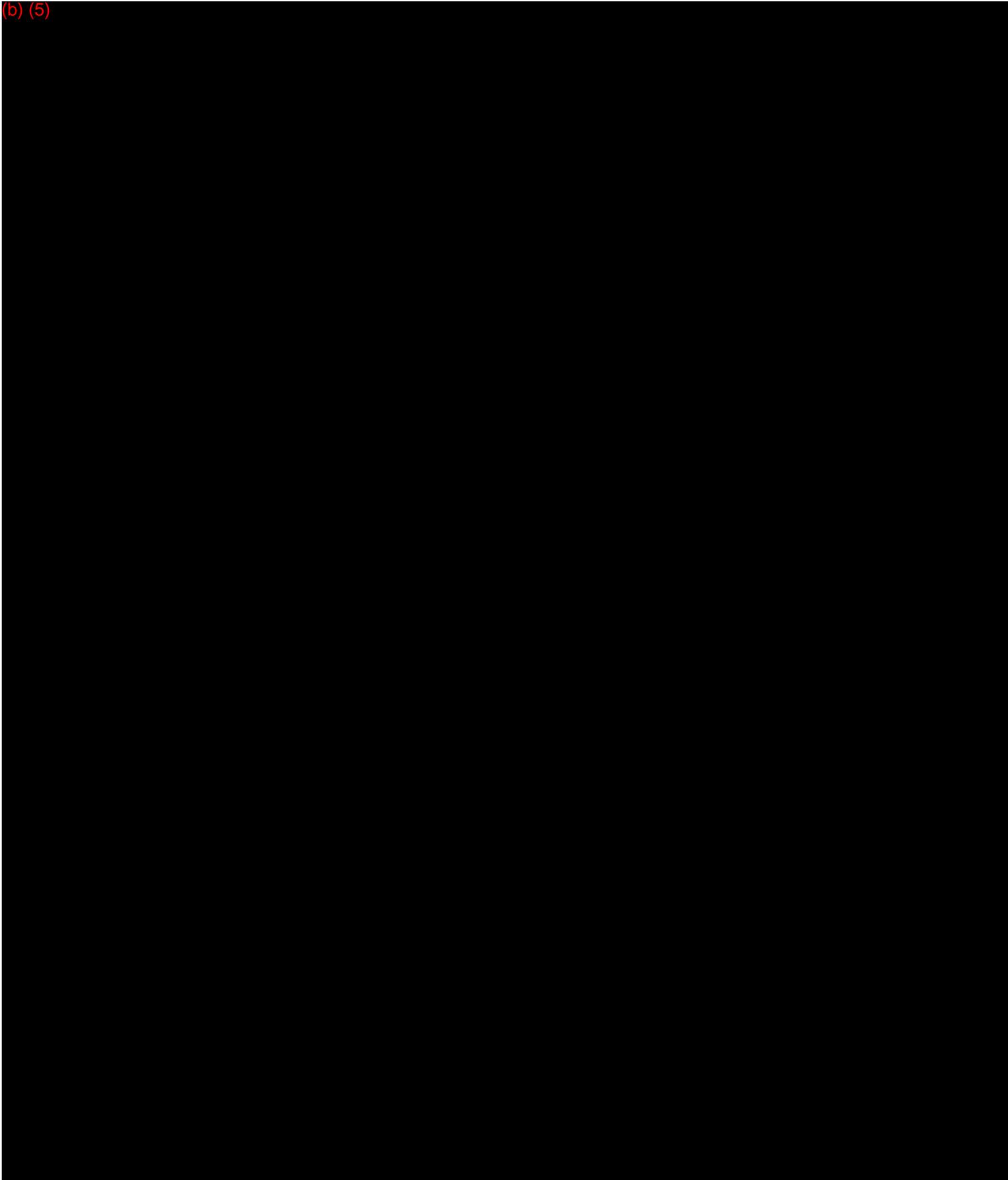
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From: [Califf, Robert](#)
To: [Woodcock, Janet](#); [Jenkins, John K \(John.Jenkins@fda.hhs.gov\)](#); [Unger, Ellis](#); [Borio, Luciana](#)
Subject: memo
Date: Tuesday, September 13, 2016 6:39:00 PM
Attachments: [2016_Sept_012_R2_Eteplirsen_CLEAN.doc](#)

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

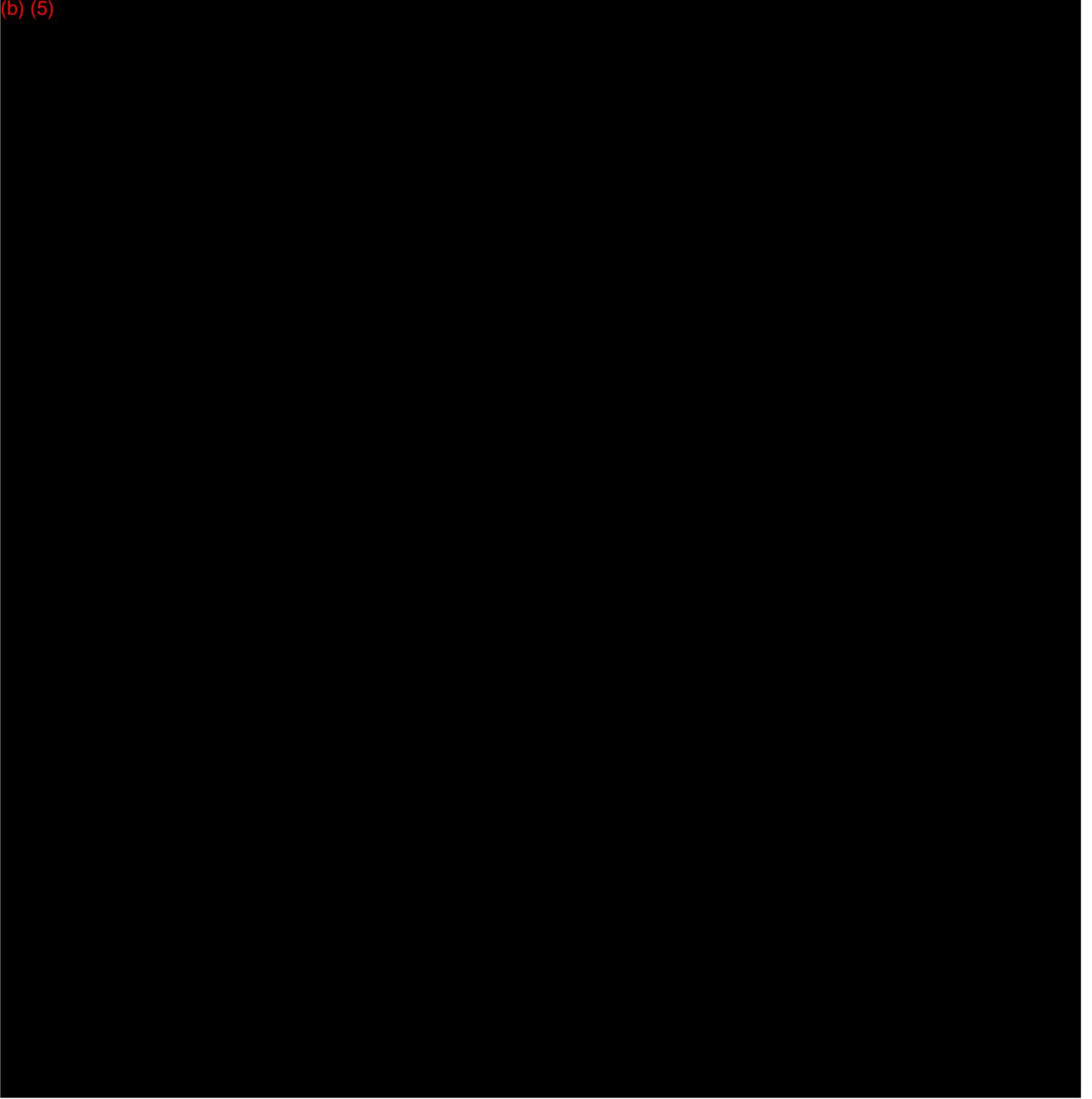
I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD

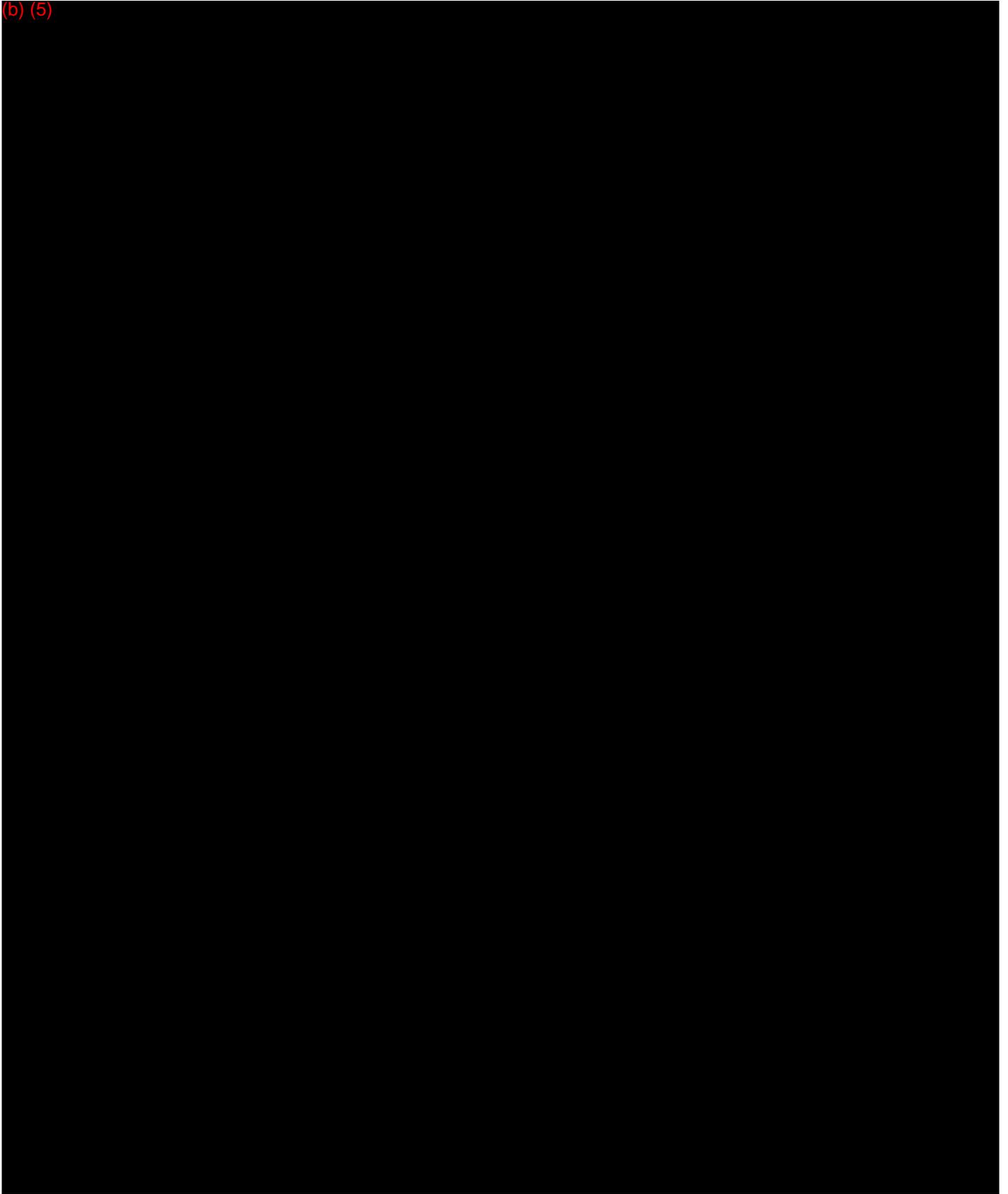
Commissioner, Food and Drugs

Scientific Dispute Regarding Approval of Sarepta Therapeutics’ Eteplirsen – Commissioner’s Decision

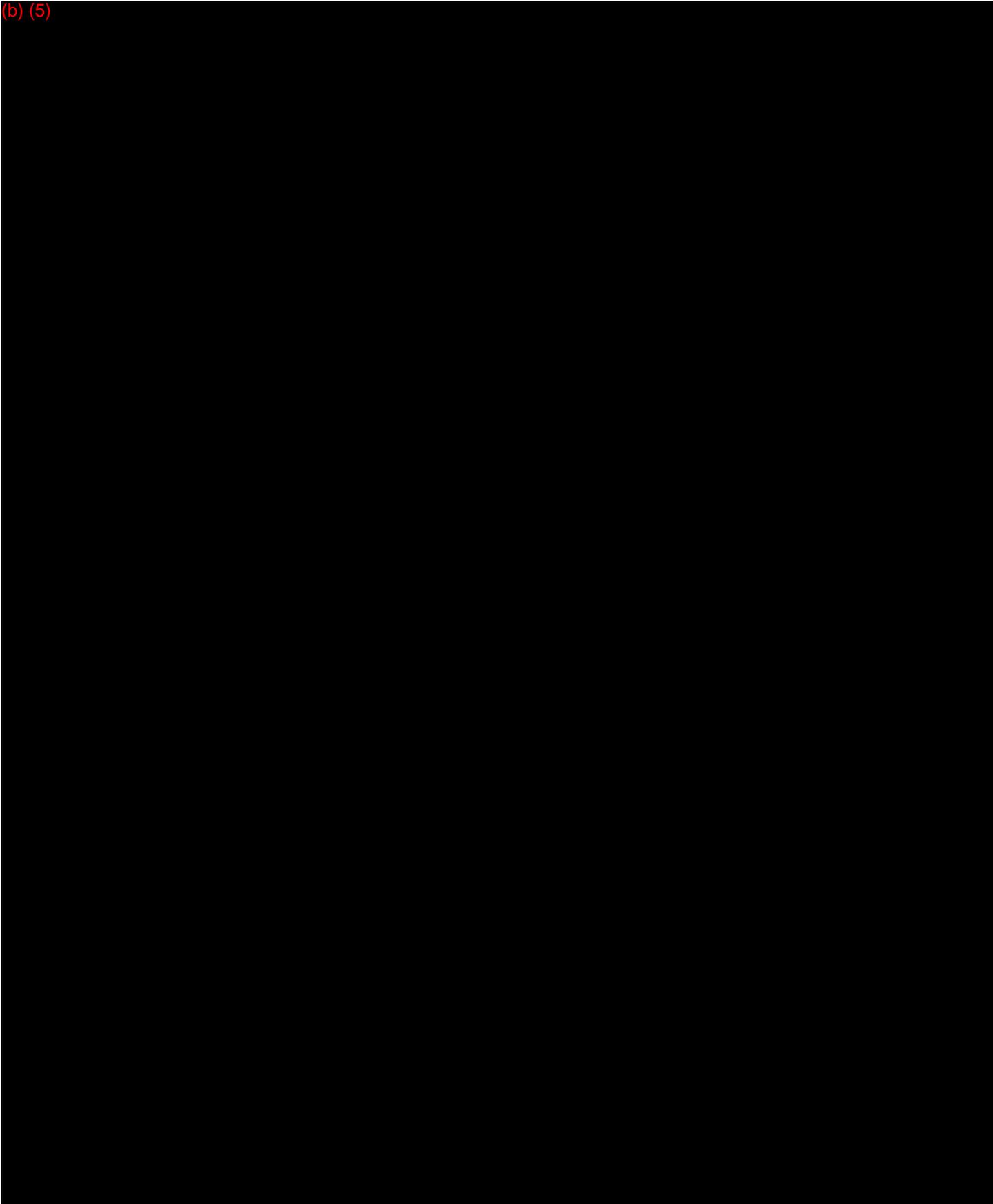
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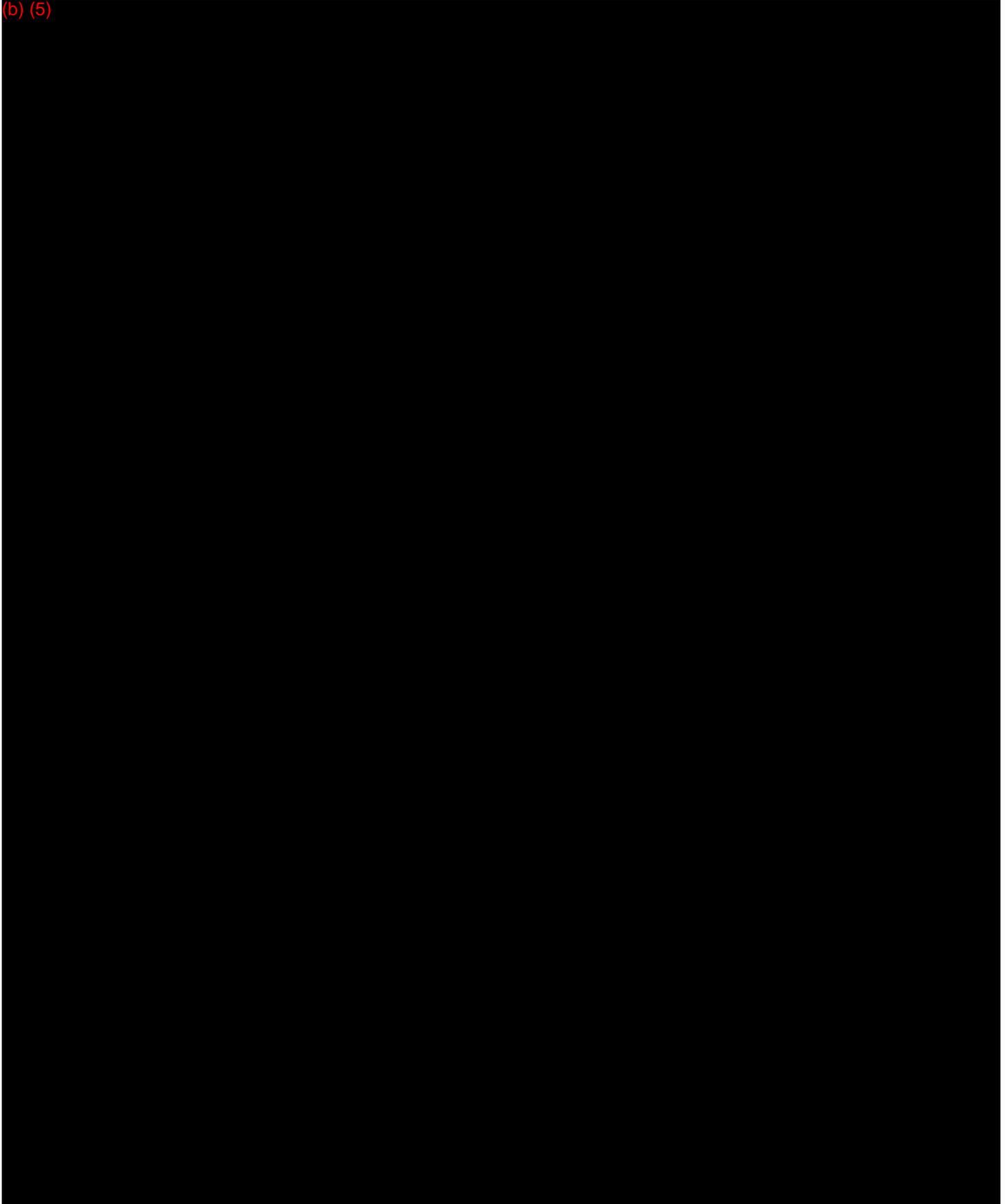
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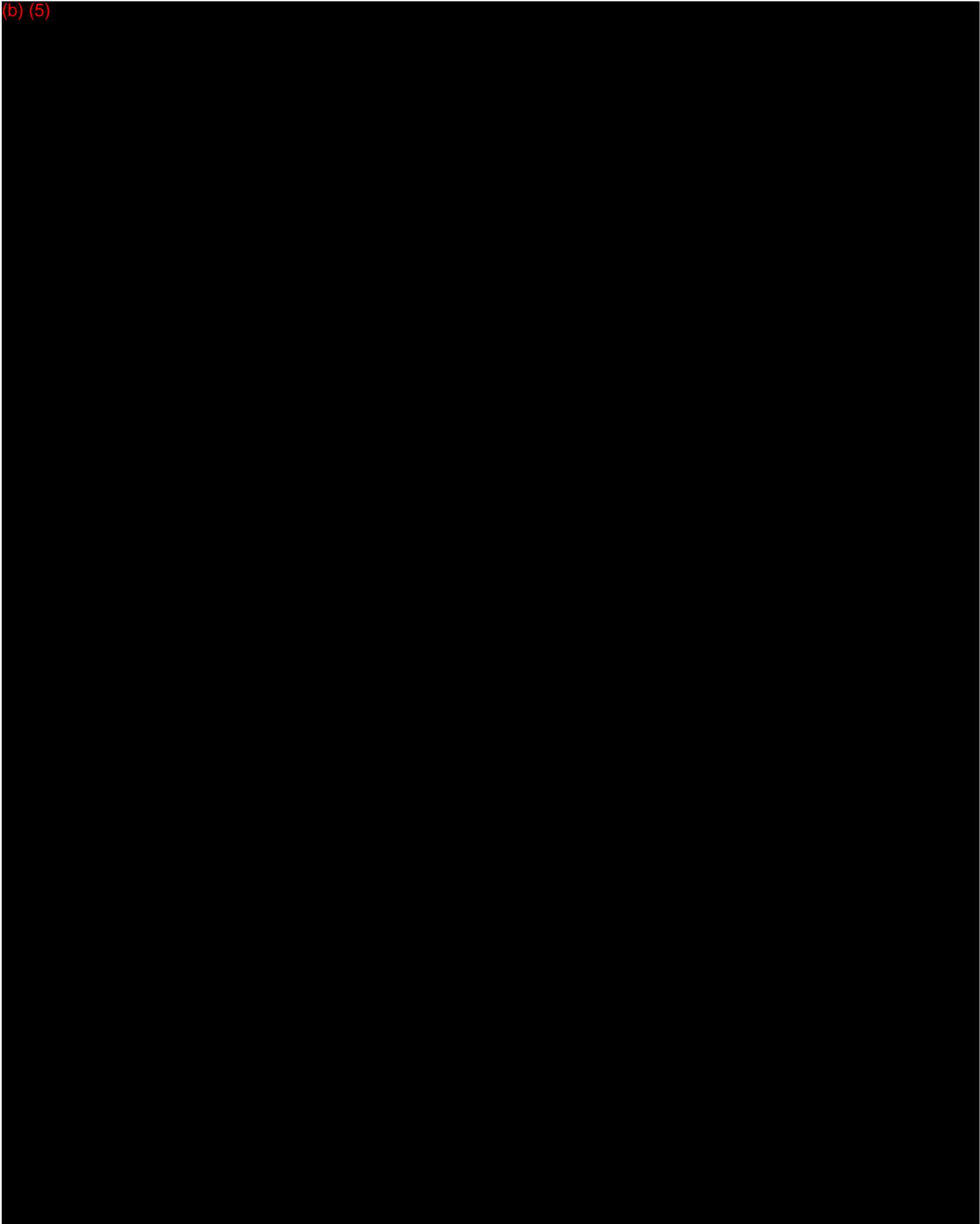
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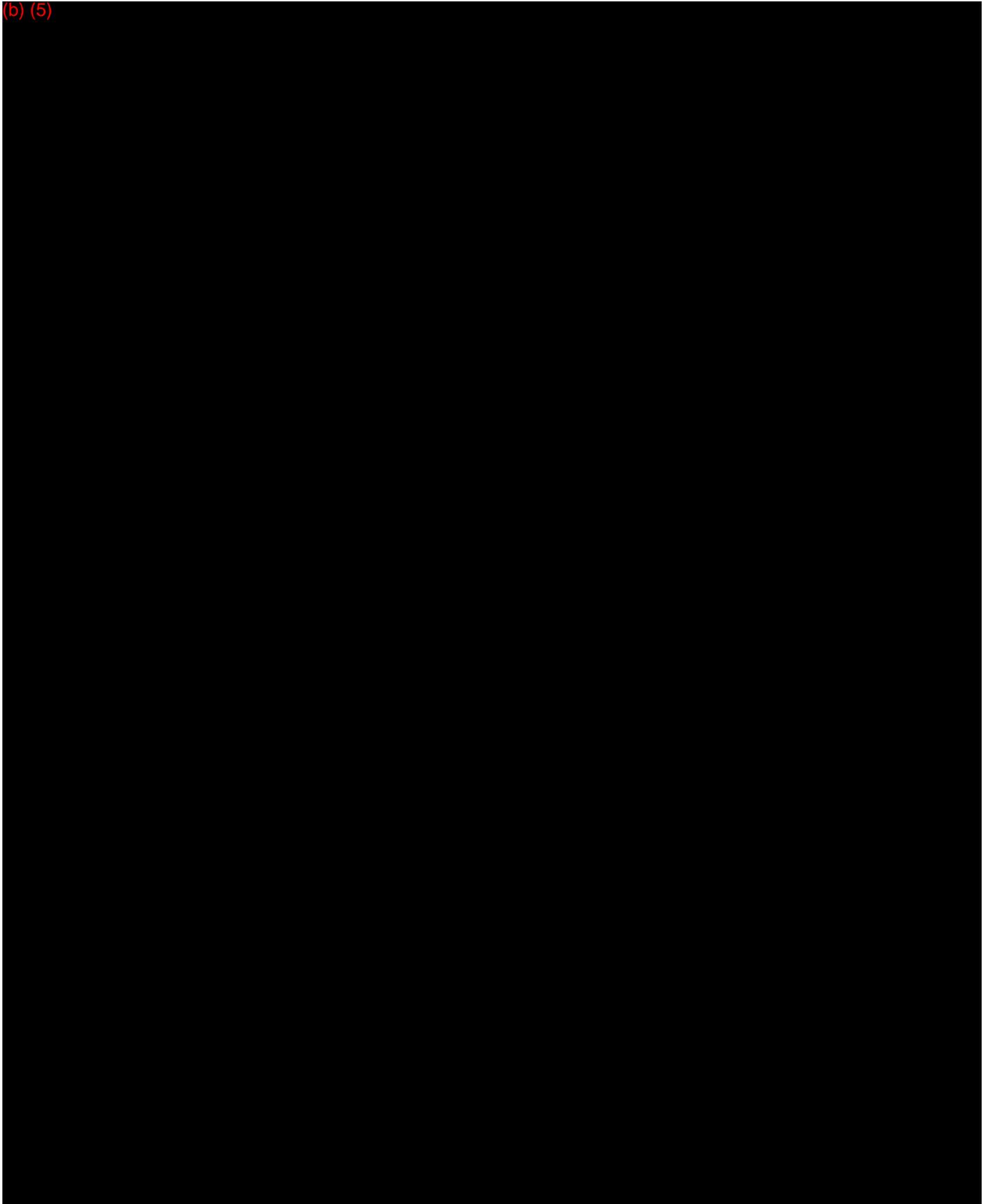
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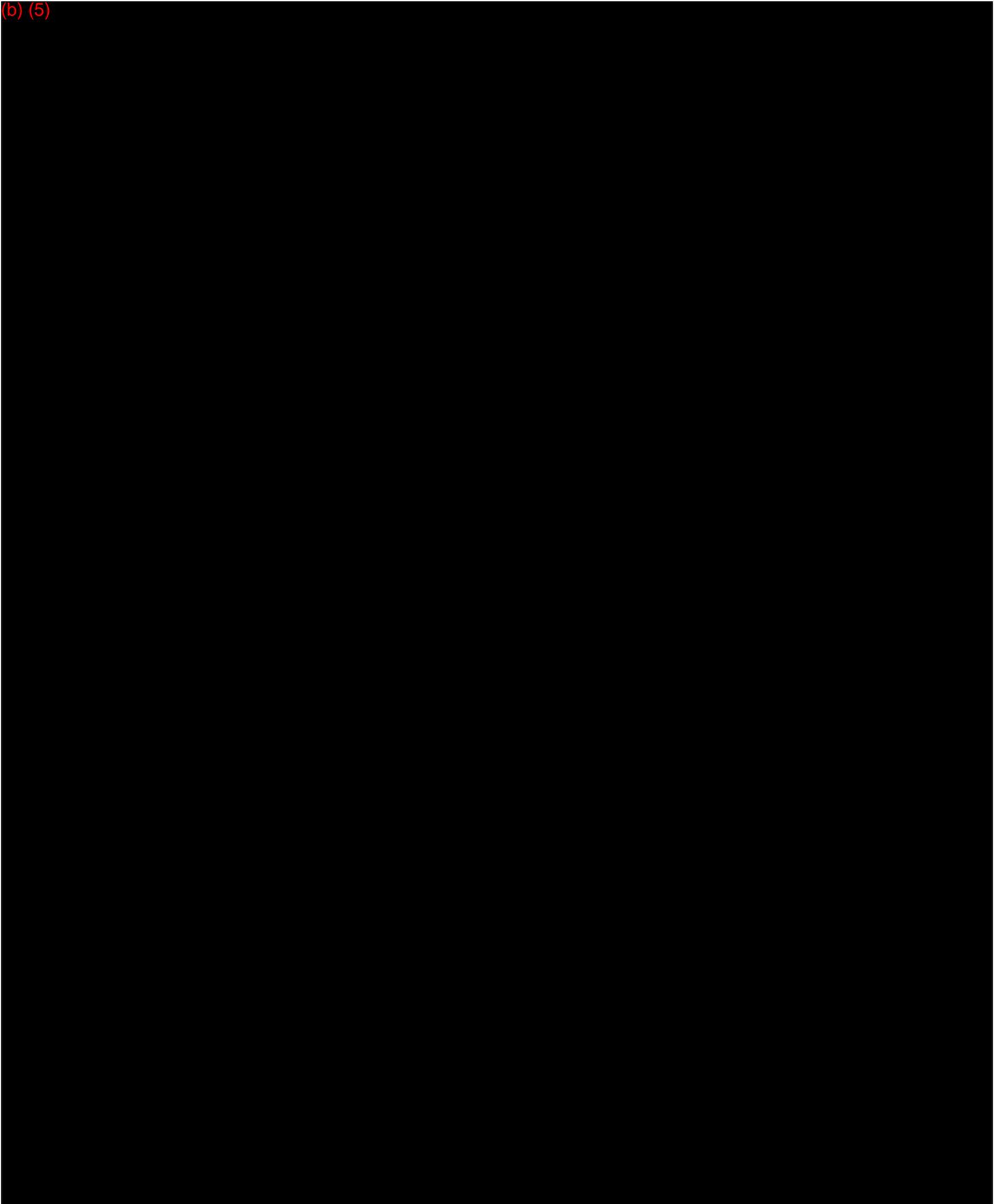
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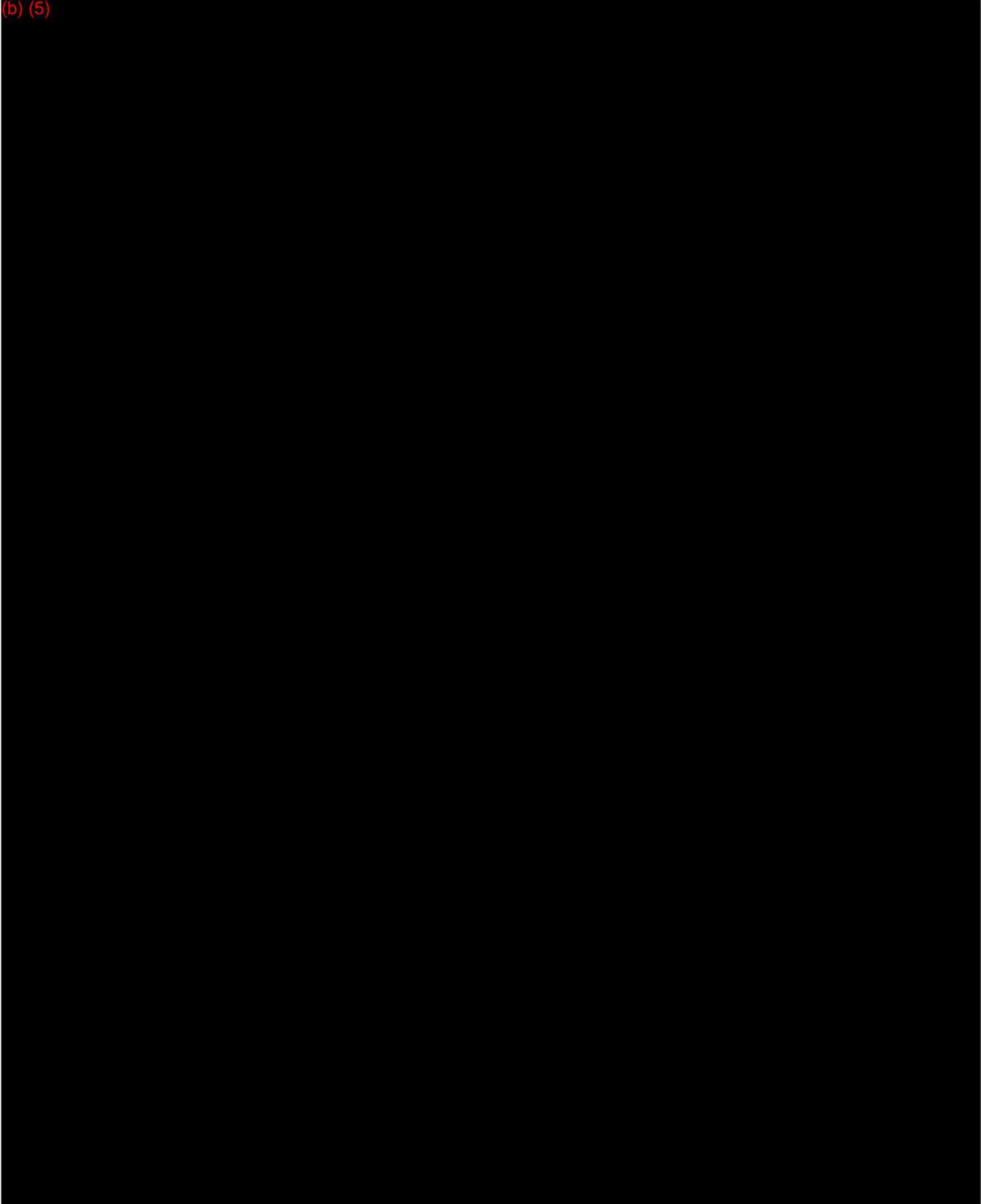
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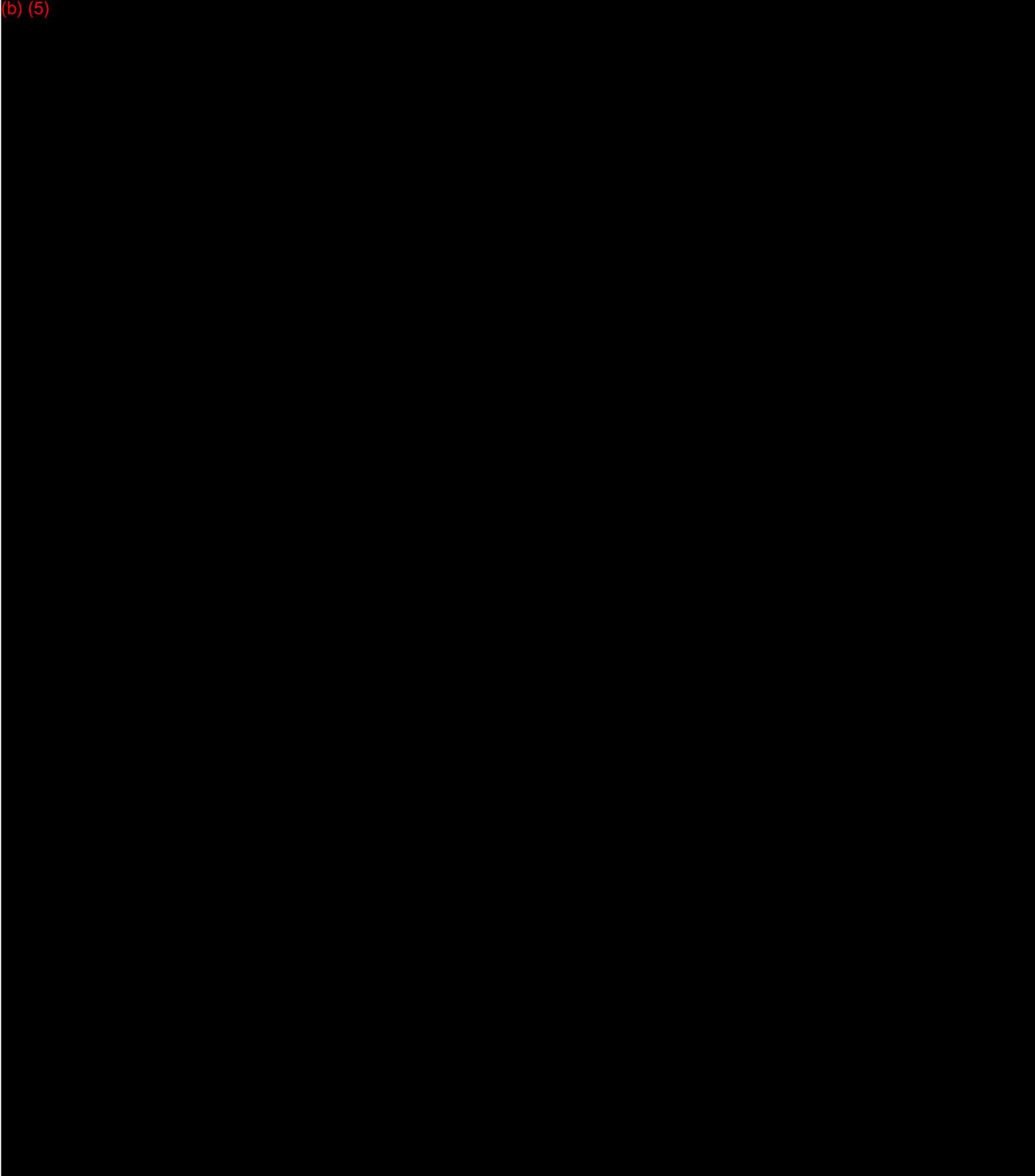
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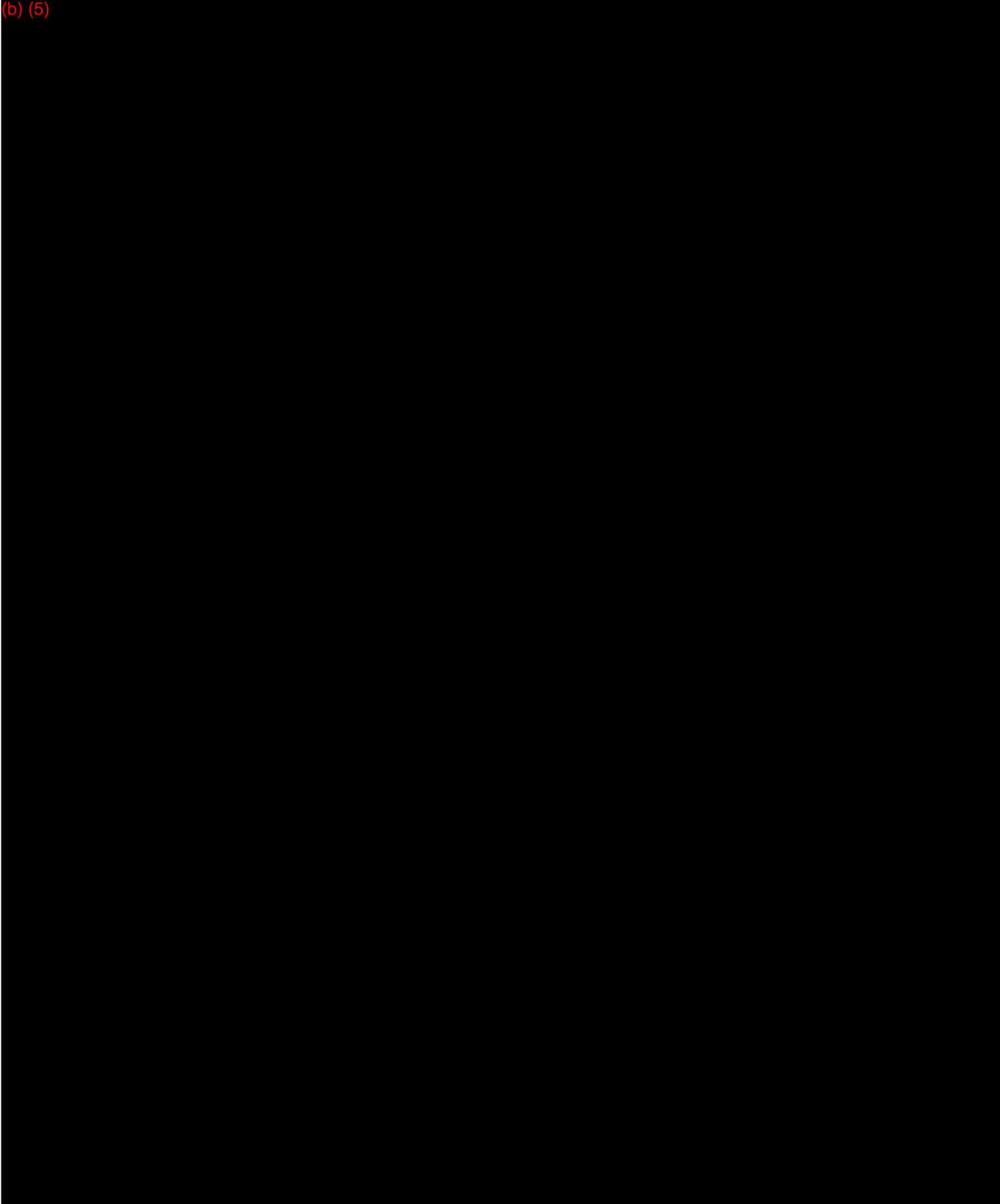
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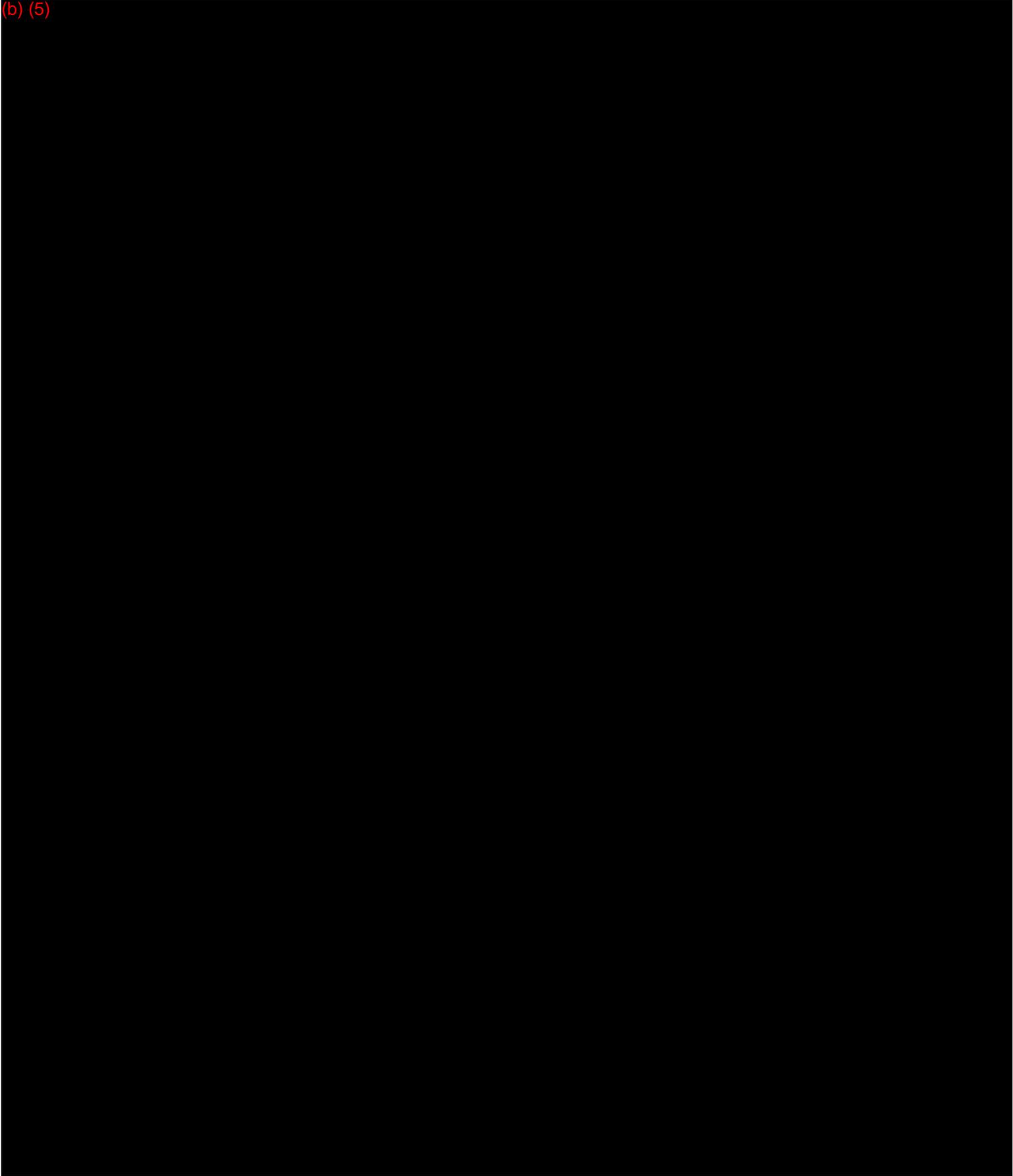
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From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [Sherman, Rachel](#); [Conover, Katie](#); [Kraus, Tom](#); [Rodriguez, Jennifer](#)
Subject: fyi
Date: Tuesday, September 13, 2016 6:44:00 PM
Attachments: [2016_Sept_012_R2_Eteplirsen_CLEAN.doc](#)

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K (John.Jenkins@fda.hhs.gov); Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

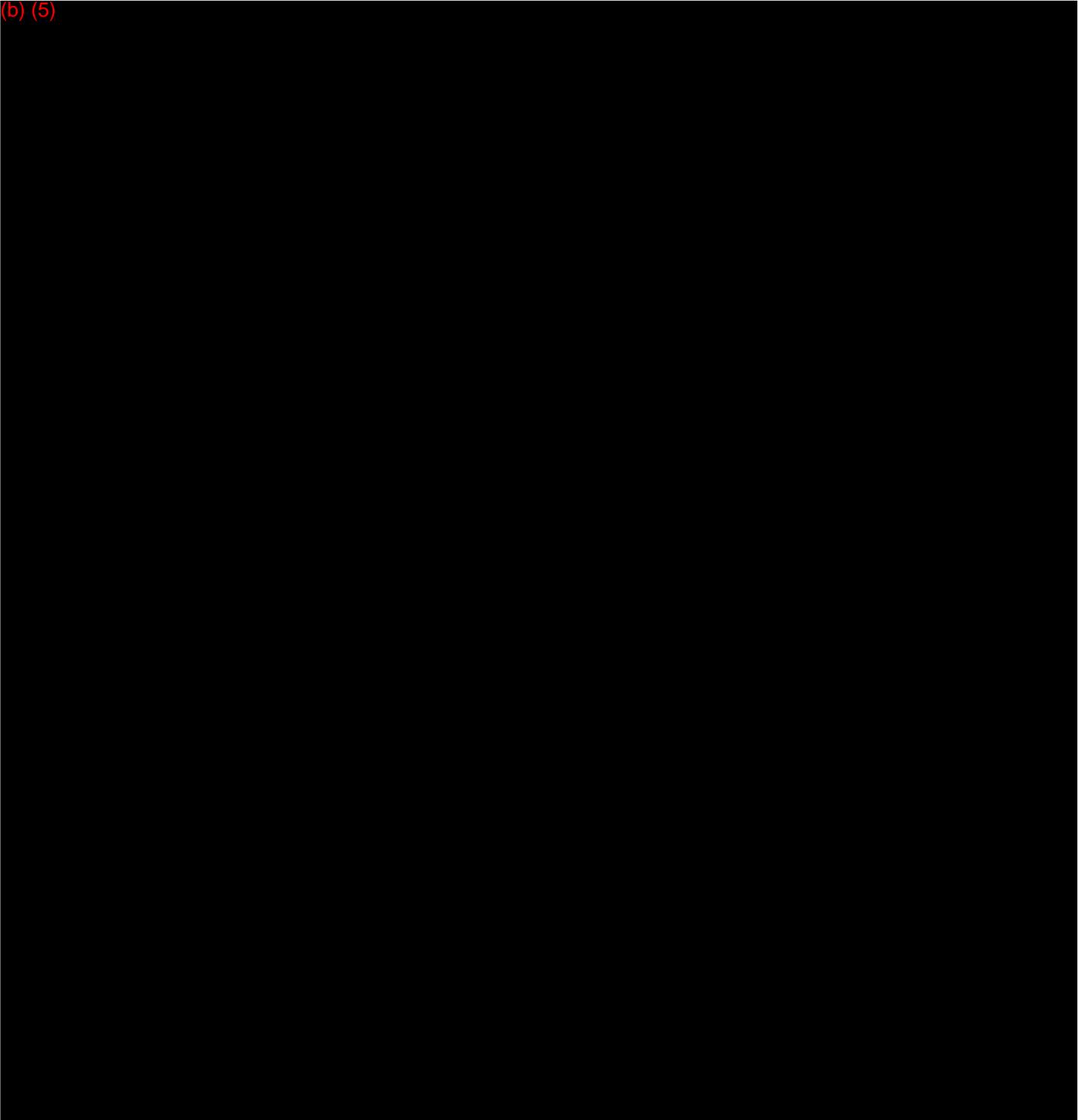
I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

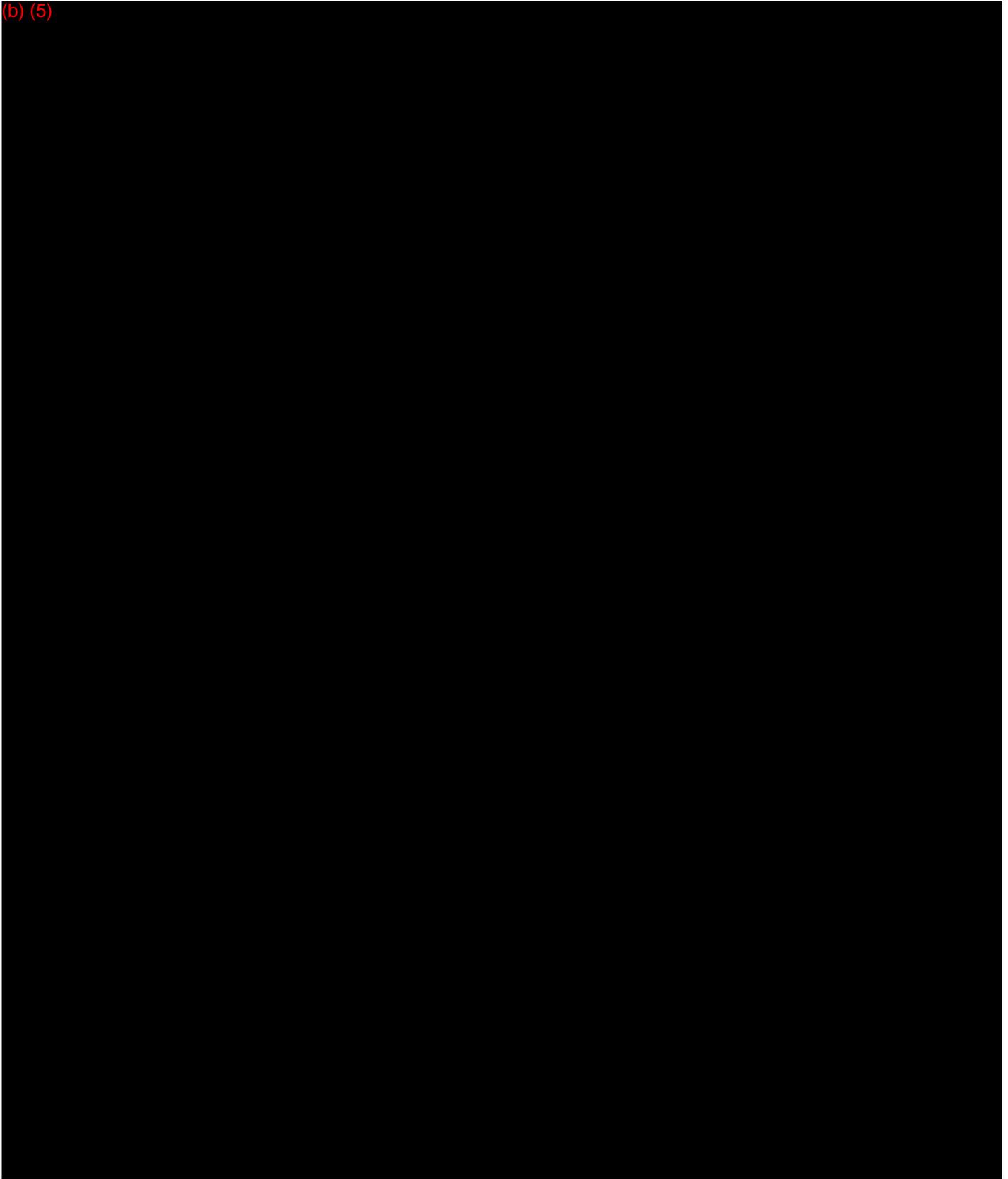
I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant

Scientific Dispute Regarding Approval of Sarepta Therapeutics’ Eteplirsen – Commissioner’s Decision

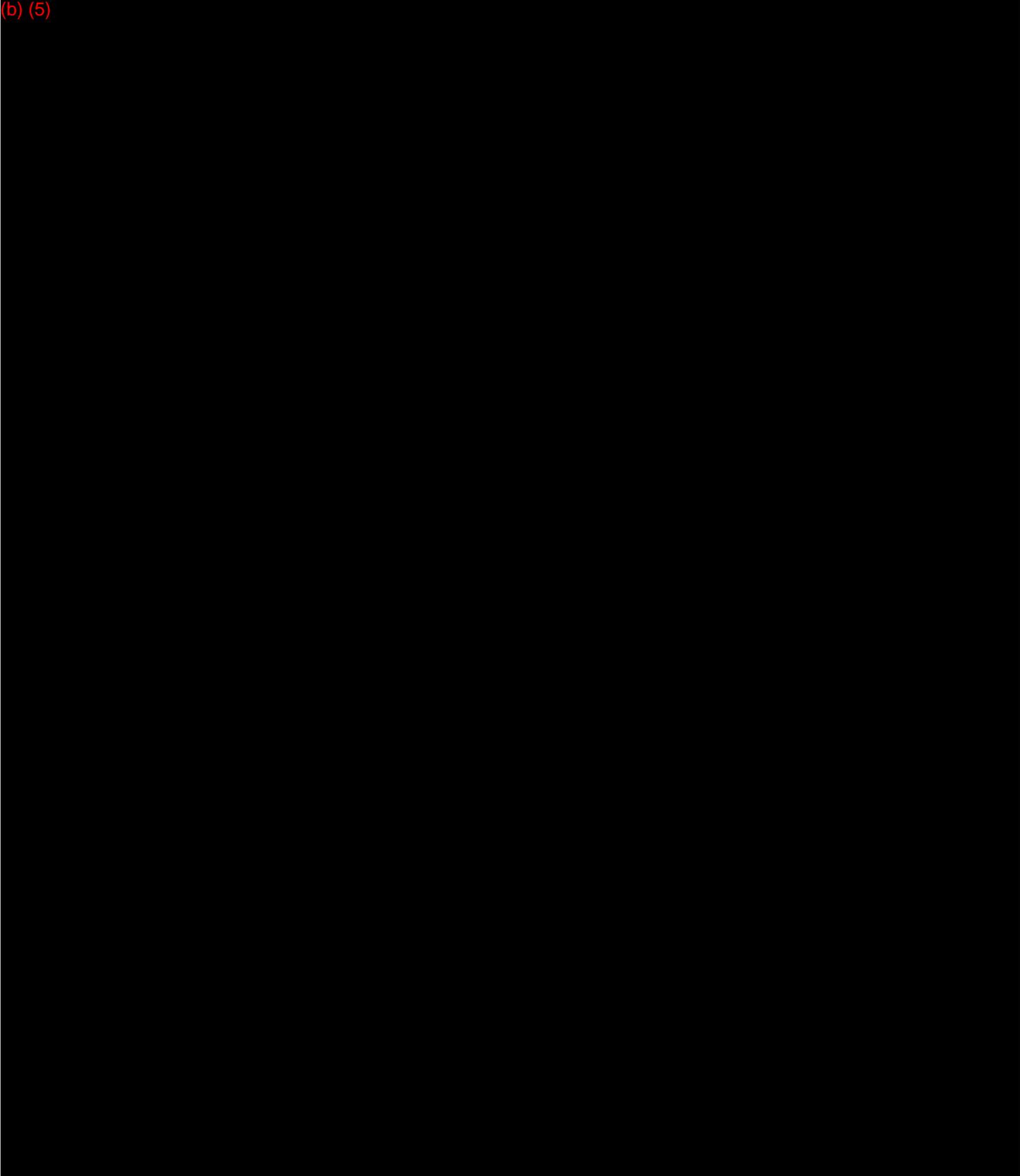
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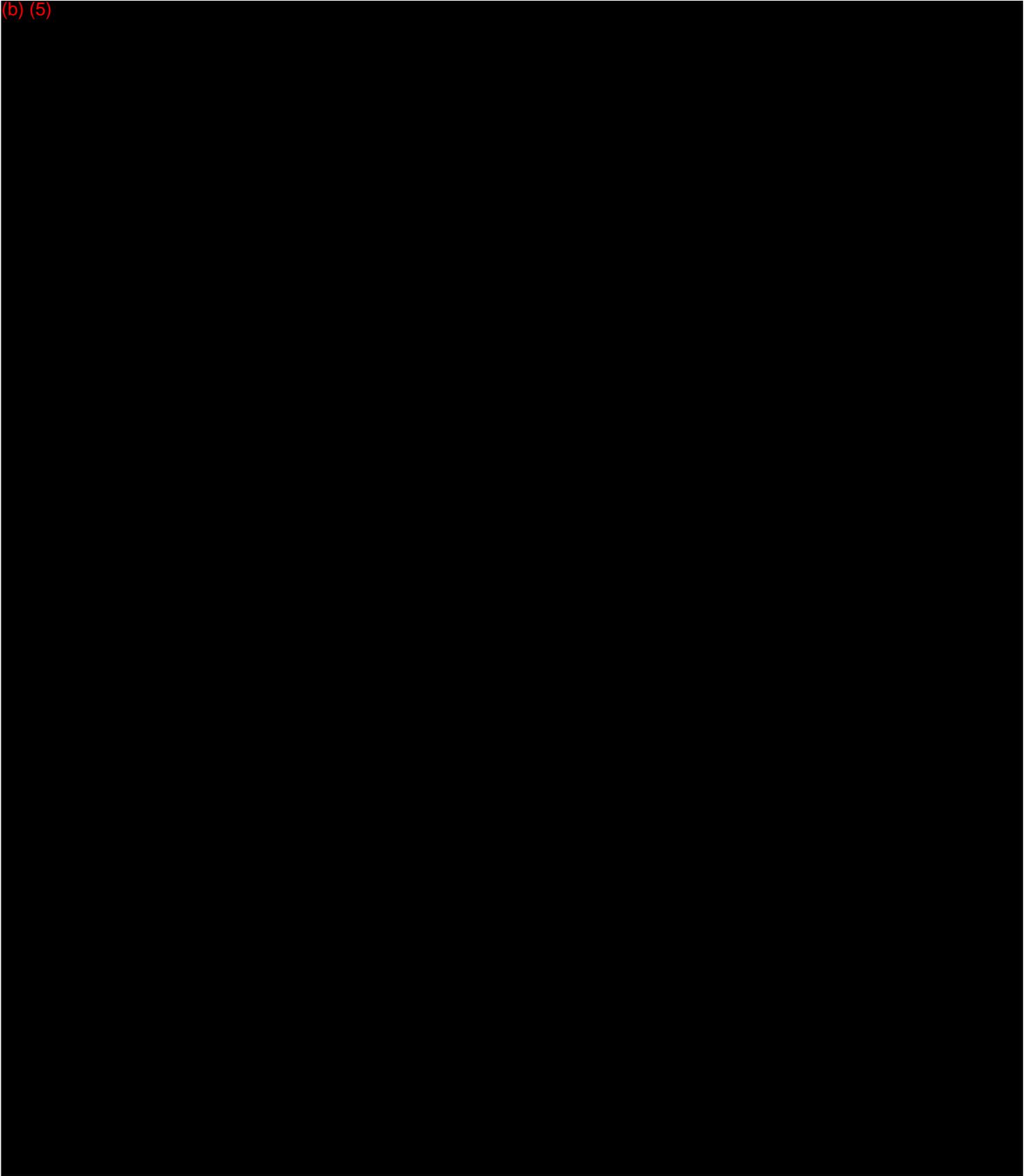
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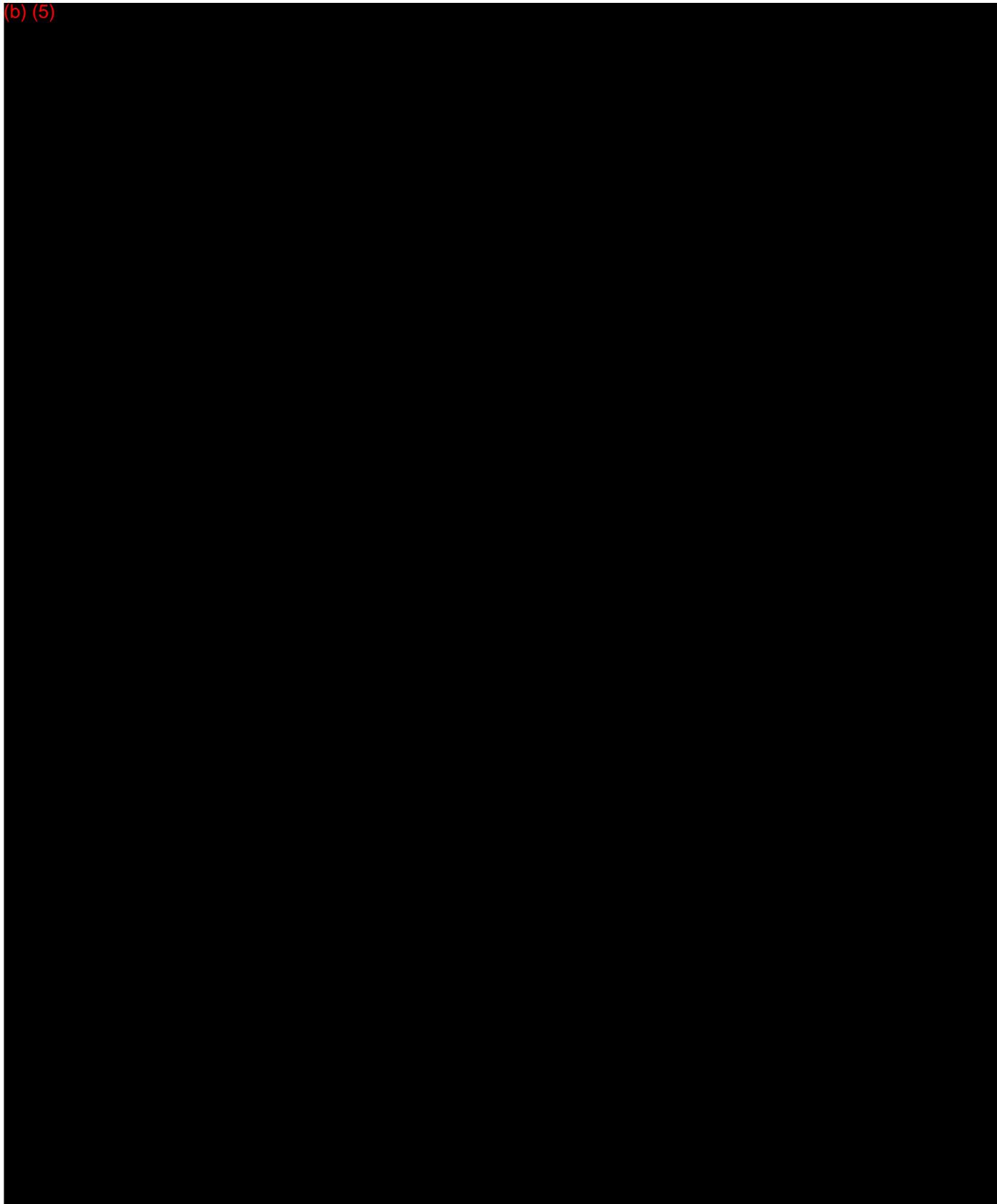
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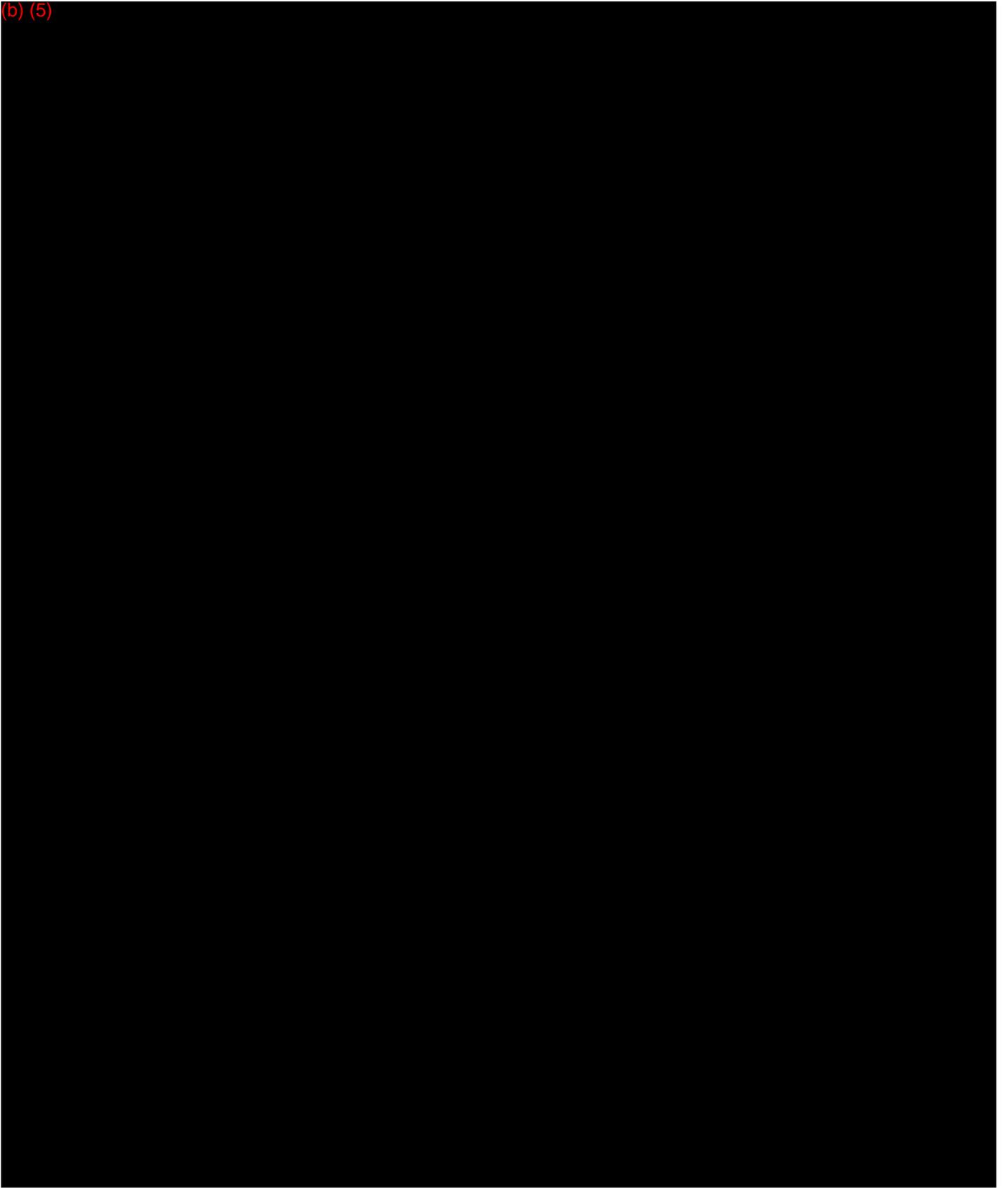
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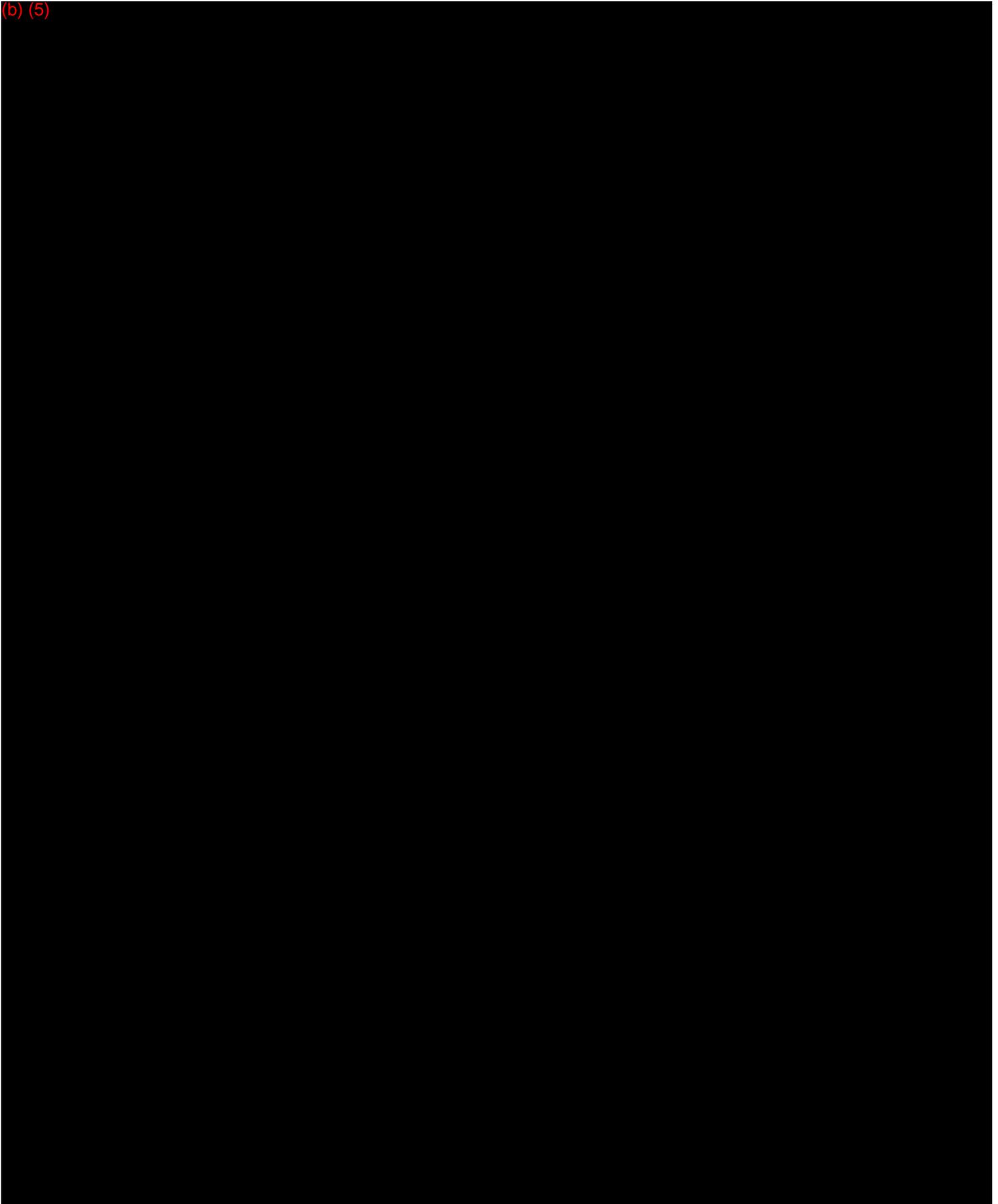
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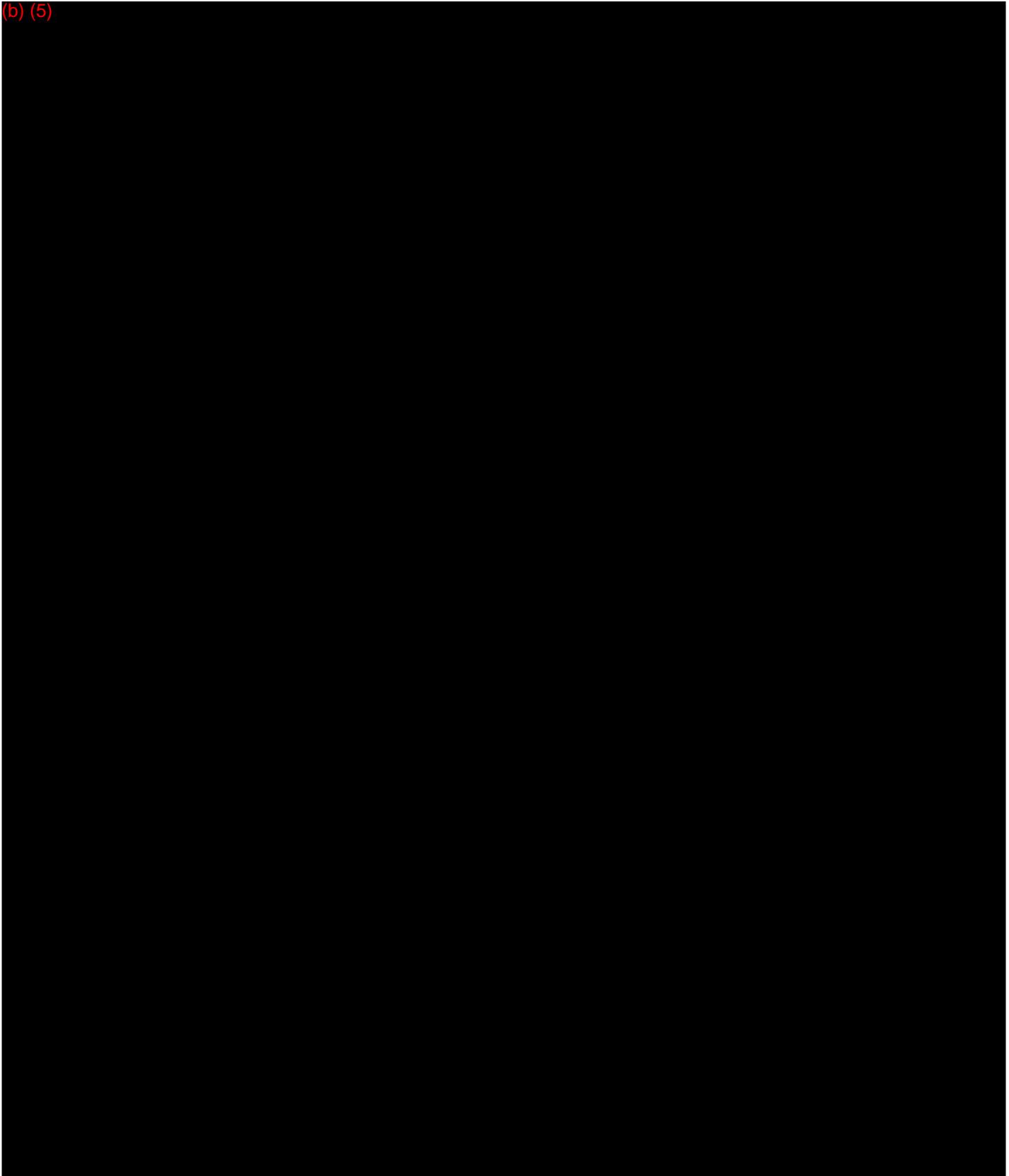
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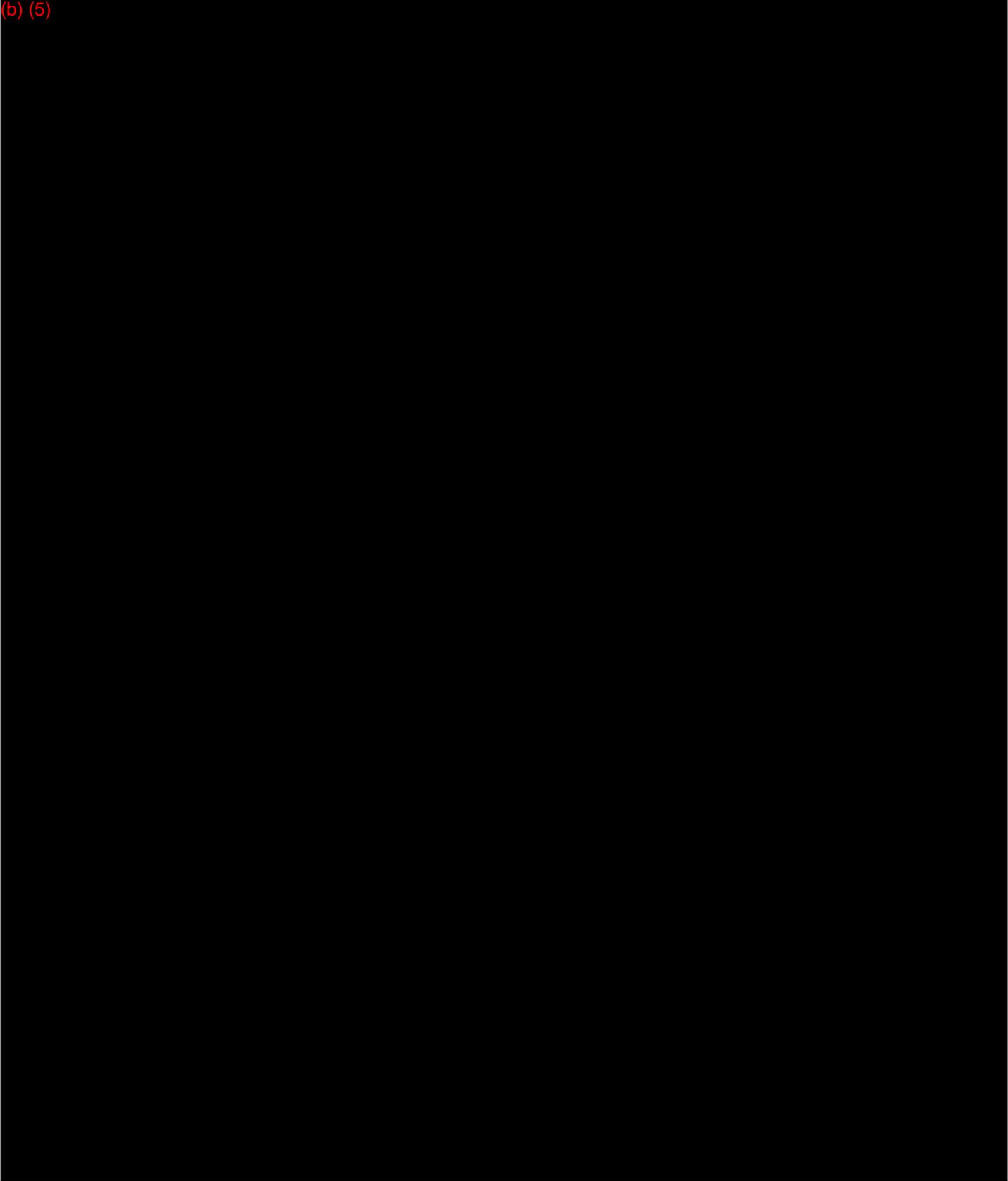
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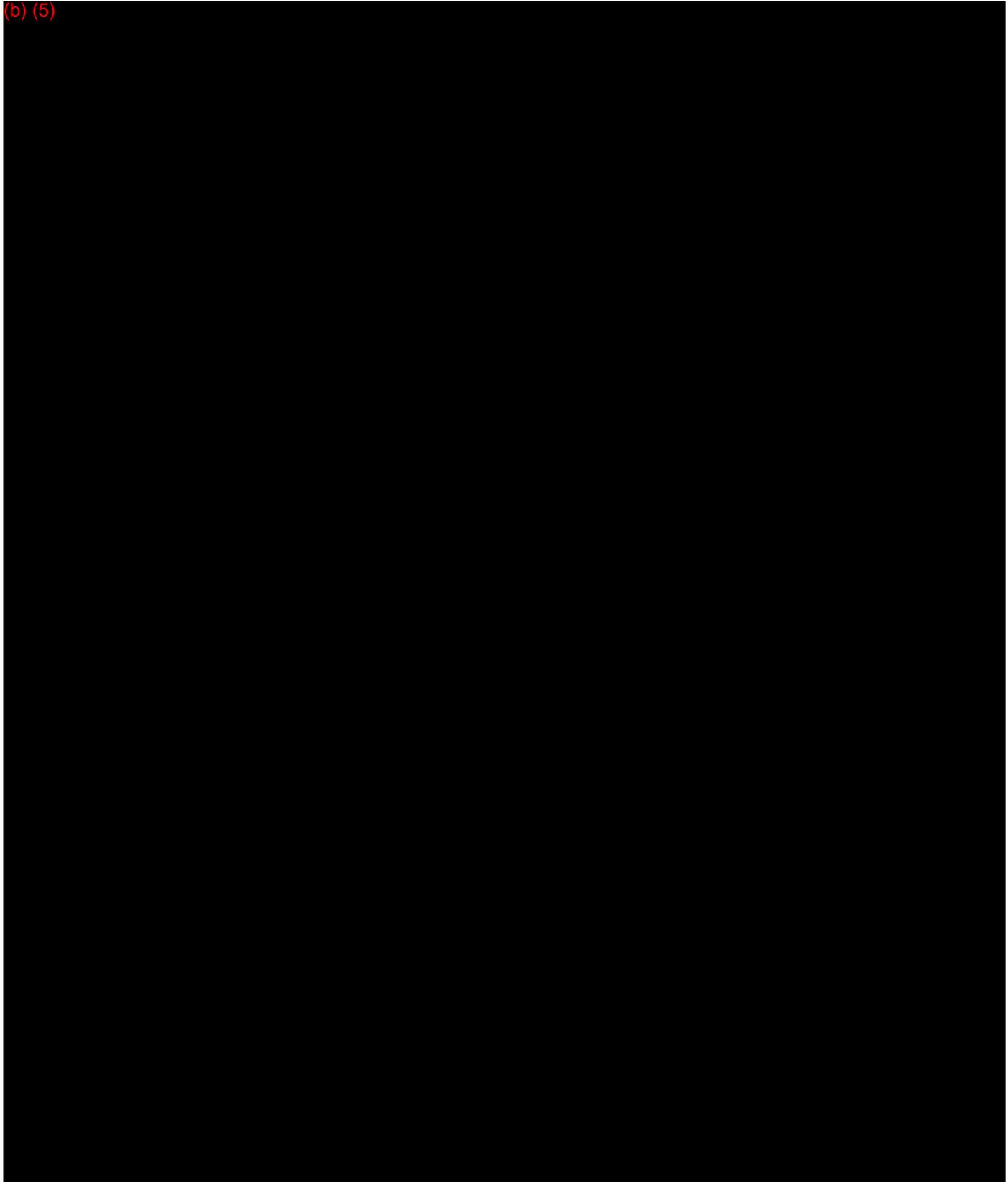
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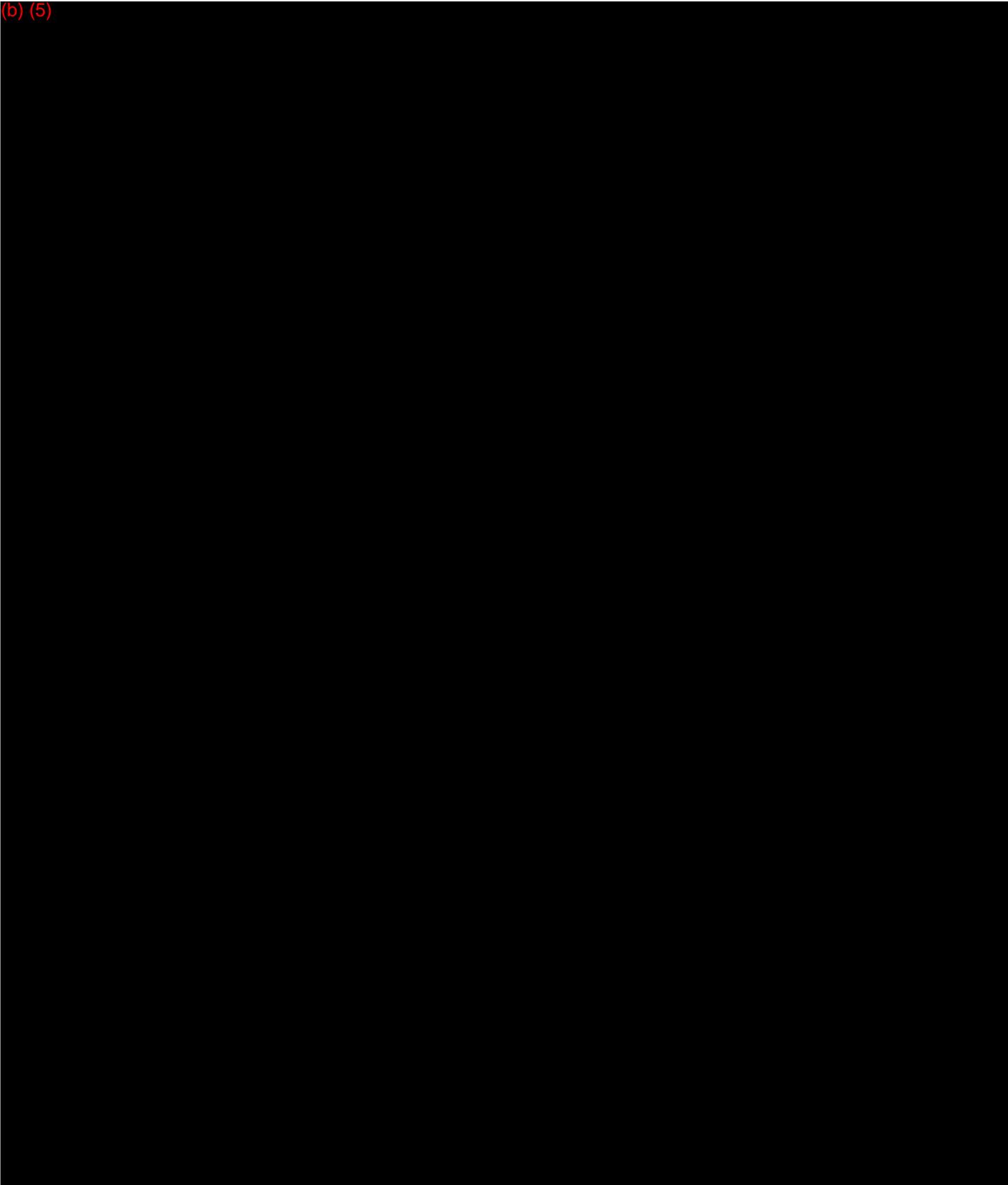
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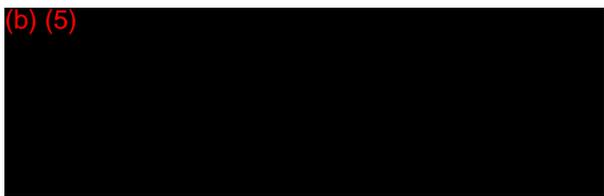


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factual errors in this document, please advise me by COB Wednesday, September 14.

(b) (5)



From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [Sherman, Rachel](#); [Kraus, Tom](#); [Conover, Katie](#); [Rodriguez, Jennifer](#)
Subject: FW: Follow up on Eteplirsen
Date: Tuesday, September 13, 2016 8:52:00 PM

See below. Open for ideas here.

rmc

From: Unger, Ellis
Sent: Tuesday, September 13, 2016 4:28 PM
To: Califf, Robert
Cc: Jenkins, John K
Subject: RE: Follow up on Eteplirsen

I will add that I would like to know when it would be OK to share Dr. Borio's memorandum with the review team. They would really appreciate being able to see it.

From: Jenkins, John K
Sent: Tuesday, September 13, 2016 3:58 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: RE: Follow up on Eteplirsen

Rob

As to the issue of when to release documents, I was just reminded that there is a statutory requirement that we release a "high level summary" review within 48 hours of NME approvals. Usually we meet this by releasing the division director review. In this case that would not make sense given that the division level review (Eric Bastings) argues against approval. I guess we could release Dr. Woodcock's memo to meet this obligation, but her memo does not really address the entire range of issues for the application that would typically be included in the division director memo. Again, my preference would be to release the documents I listed in item 5 below at the time of approval. Such an approach provides the most transparency and will avoid a "rebound" of media coverage a month or so later about the details of the internal dispute.

John

From: Califf, Robert
Sent: Sunday, September 11, 2016 7:13 AM
To: Jenkins, John K; Woodcock, Janet; Unger, Ellis
Subject: RE: Follow up on Eteplirsen

John,

Thanks for putting this list together. Much of this is in CDER's baileywick, but I want to be

sure I do what I need to do. See below:

From: Jenkins, John K
Sent: Friday, September 09, 2016 4:09 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: Follow up on Eteplirsen

Rob

Do we have any follow up on the items we discussed yesterday and timelines? I just had my regular meeting with Ellis and we discussed the planned action. Some issues that need to be sorted out:

1. Timeline for approval action.

My understanding is that we're aiming for a week from tomorrow. Please let me know if that is not feasible.

2. Verification that we have reached final agreement on the labeling/PMRs with the sponsor. Ellis was not sure that there was final agreement on the labeling. Our usual practice/policy is to ensure that the sponsor has agreed to the labeling before approval, which is usually accomplished by the division sending the final draft of the label to the sponsor and the sponsor formally returning that to us indicating their concurrence. We can check to see if we have documentation of that agreement, or if there is a need to ask Sarepta to submit as final the most recent version of the labeling we sent them. Ellis can follow up and confirm the status. If there are to be any changes to the most recent version of the final draft label that the division sent to the sponsor, we would ask that we be included in reviewing those edits. Same for the PMR.

Will follow with interest.

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OEA had not planned a media call to my knowledge. For sure there will be a lot of media interest and questions.

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John

From: [Califf, Robert](#)
To: [Jenkins, John K](#); [Woodcock, Janet](#); [Unger, Ellis](#)
Subject: RE: Follow up on Eteplirsen
Date: Tuesday, September 13, 2016 8:54:00 PM

Thx John. This is new to me so I'll seek advice and we'll discuss.

Regards

rmc

From: Jenkins, John K
Sent: Tuesday, September 13, 2016 3:58 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: RE: Follow up on Eteplirsen

Rob

As to the issue of when to release documents, I was just reminded that there is a statutory requirement that we release a "high level summary" review within 48 hours of NME approvals. Usually we meet this by releasing the division director review. In this case that would not make sense given that the division level review (Eric Bastings) argues against approval. I guess we could release Dr. Woodcock's memo to meet this obligation, but her memo does not really address the entire range of issues for the application that would typically be included in the division director memo. Again, my preference would be to release the documents I listed in item 5 below at the time of approval. Such an approach provides the most transparency and will avoid a "rebound" of media coverage a month or so later about the details of the internal dispute.

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Subject: RE: Follow up on Eteplirsen

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To: Califf, Robert; Woodcock, Janet; Unger, Ellis
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To: [Rodriguez, Jennifer](#); [Kraus, Tom](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Conover, Katie](#)
Subject: Re: Follow up on Eteplirsen
Date: Tuesday, September 13, 2016 10:35:01 PM

Based on what he said, I would suggest releasing Ellis' on up.

I agree the review team should see first. Can we a matter of hours.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 13, 2016 at 8:52:21 PM EDT
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Kraus, Tom <Tom.Kraus@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>
Subject: FW: Follow up on Eteplirsen

See below. Open for ideas here.

rmc

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and questions.

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John

From: [Chasan-Sloan, Deborah \(FDA\)](#)
To: [Sherman, Rachel](#); [Califf, Robert](#); [Conover, Katie](#); [Kraus, Tom](#); [Dickinson, Elizabeth \(FDA\)](#); [Rodriguez, Jennifer](#)
Cc: [Woodcock, Janet](#)
Subject: RE: PLEASE SEE -- CDER Cleared Comms
Date: Tuesday, September 13, 2016 4:51:01 PM
Attachments: [Phase II approval reactive OA 09.13.16 CDER OMA dcs.doc](#)

Jen,

(b) (5)

Thanks,

Deborah

From: Sherman, Rachel
Sent: Tuesday, September 13, 2016 4:41 PM
To: Califf, Robert; Conover, Katie; Kraus, Tom; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Rodriguez, Jennifer
Cc: Woodcock, Janet
Subject: RE: PLEASE SEE -- CDER Cleared Comms

No additional comments from me.

Thanks!

From: Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>
Date: September 13, 2016 at 4:39:20 PM EDT
To: Kraus, Tom <Tom.Kraus@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Califf, Robert <RMC1@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>
Cc: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: RE: PLEASE SEE -- CDER Cleared Comms
Importance: High

Hi All,

I've heard back from CDER/Janet with the all clear, but wanted to ensure we also hear if others have any concerns.

Please let me know if you have any edits **ASAP but no later than 6pm** at which time I will share with HHS to ensure we keep to our review schedule.

Thank you,

Jen

From: Rodriguez, Jennifer
Sent: Tuesday, September 13, 2016 3:48 PM
To: Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Conover, Katie; Kraus, Tom
Cc: Woodcock, Janet
Subject: RE: PLEASE SEE -- CDER Cleared Comms
Importance: High

All-

In looking at the most recent changes to the to Dr. Califf's memo, we made a few edits to the Phase II QA. Please let us know ASAP if you would like us to continue with these edits or keep what was originally in the QA.

Thanks!

Jen

From: Sherman, Rachel
Sent: Tuesday, September 13, 2016 2:10 PM
To: Rodriguez, Jennifer; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Conover, Katie; Kraus, Tom
Cc: Woodcock, Janet
Subject: RE: PLEASE SEE -- CDER Cleared Comms

Welcome!

From: Rodriguez, Jennifer
Sent: Tuesday, September 13, 2016 2:03 PM
To: Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Conover, Katie; Kraus, Tom
Cc: Woodcock, Janet
Subject: RE: PLEASE SEE -- CDER Cleared Comms

Thanks, Rachel! We will take a quick review of the comms against the most current version of RMC's memo to ensure there are no glaring contradictions or differences before sending it to HHS for review.

Thanks!

Jen

From: Sherman, Rachel

Sent: Tuesday, September 13, 2016 1:55 PM
To: Rodriguez, Jennifer; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Conover, Katie; Kraus, Tom
Cc: Woodcock, Janet
Subject: RE: PLEASE SEE -- CDER Cleared Comms

Hi all,

I just poked me head into their meeting and have attached an edit on page as per Drs. Califf and Woodcock. So, this issue is resolved.

Rachel

From: Rodriguez, Jennifer
Sent: Tuesday, September 13, 2016 1:41 PM
To: Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); Califf, Robert; Sherman, Rachel; Conover, Katie; Kraus, Tom
Subject: PLEASE SEE -- CDER Cleared Comms
Importance: High

All,

Janet has reviewed the comms and had no edits on the press release or phase II QA. She has one comment and minor edits attached in the phase I KMQA (attached). I was told that Janet would be reaching out to talk to Califf directly about his comment on page 3. In the interest of time, we will proceed with sending up the comms to HHS by 2:30pm. If there are any edits (new QA) resulting from Janet and Dr. Califf's conversation we can make those at that time.

Please let me know by 2:30pm if you have any questions or concerns.

Best,
Jen

From: Chasan-Sloan, Deborah (FDA)
Sent: Monday, September 12, 2016 11:37 AM
To: Rodriguez, Jennifer; Dickinson, Elizabeth (FDA); Califf, Robert; Sherman, Rachel; Conover, Katie; Kraus, Tom
Subject: Re: PLEASE SEE -- Updated Comms

(b) (5)



Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Rodriguez, Jennifer
Sent: Monday, September 12, 2016 10:17 AM
To: Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Conover,

Katie; Kraus, Tom

Subject: PLEASE SEE -- Updated Comms

Hi All,

Attached please find the updated QAs, as well as the PR, reflecting the edits to date. In addition, below please find a slightly revised response to the question about the review team. Please let me know if you would like us to go further.

Also, is it OK for us to reach out to Lu Borjo's team to get the information for (b) (5) [REDACTED]

Once we have your OK, we will share the comms package with Chris Shreeve for CDER review – asking them to flag anything that is inaccurate or provides significant heart burn. We would like to be able to share with CDER by noon to keep on schedule.

Thanks for all your feedback.

Jen

(b) (5)



From: Dickinson, Elizabeth (FDA)
Sent: Sunday, September 11, 2016 8:32 PM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie
Subject: RE: Q&A

(b) (5)



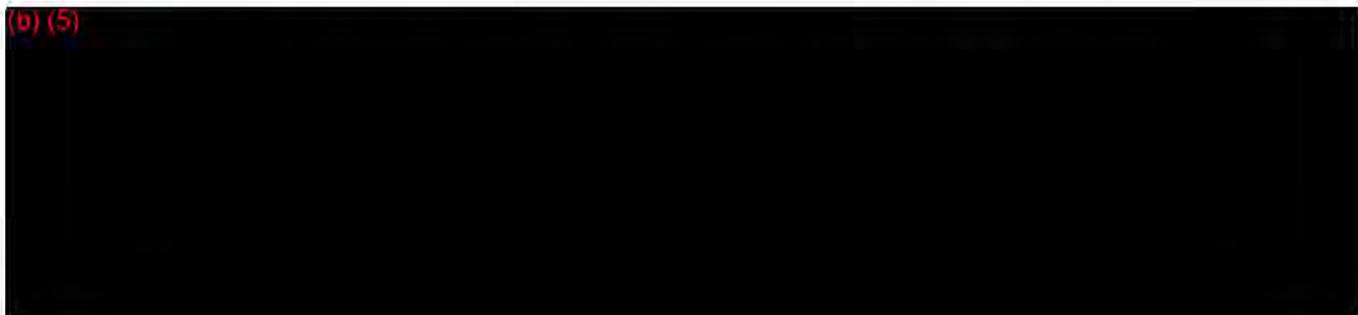
From: Califf, Robert
Sent: Sunday, September 11, 2016 7:49 PM
To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

Nice job. These changes improve what I was trying to get across. Thanks.

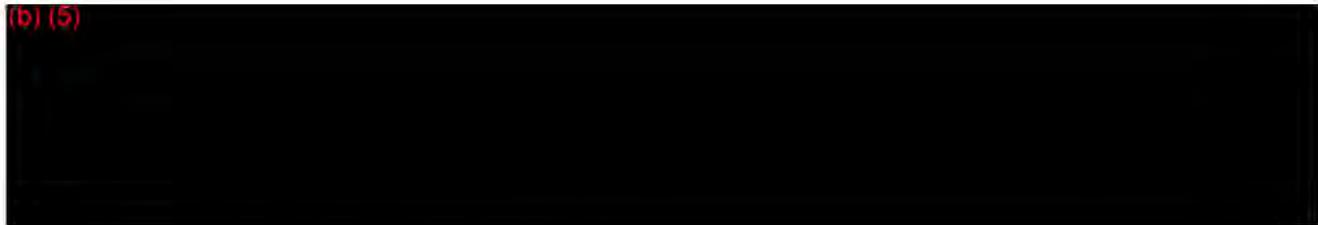
mmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

(b) (5)



(b) (5)



From: Sherman, Rachel

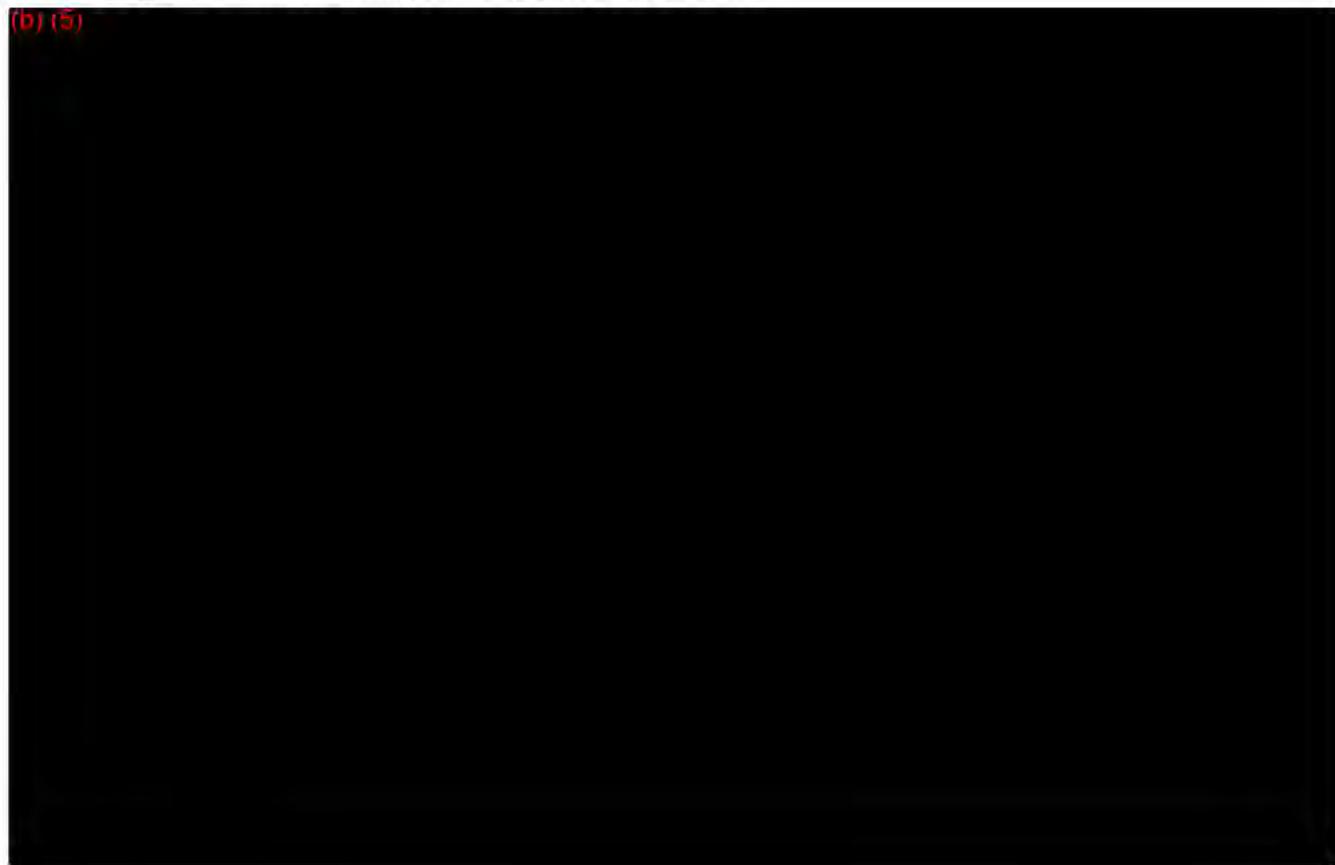
Sent: Sunday, September 11, 2016 8:45 AM

To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.

(b) (5)



Hope this helps

Rachel

Why do you equivocate and say I'm right on most things? I thought we agreed I was always right.....

From: Califf, Robert

Sent: Sunday, September 11, 2016 8:23 AM

To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

FDAOC0001965

Subject: Q&A

Friends,

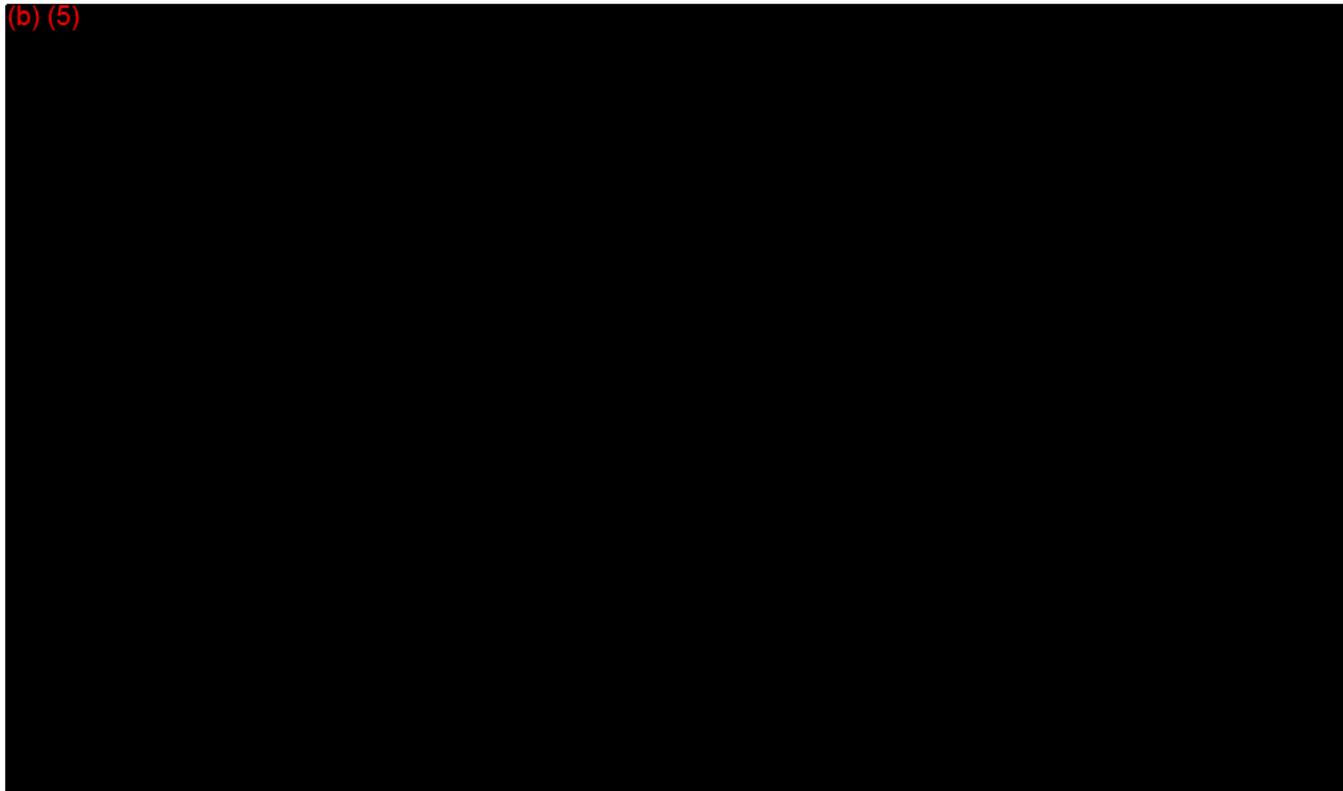
I have done a little editing, but not much as I think its good. There are still several loose ends. Are we still ok on the timeline?

3 issues strike me as needing more work:

(b) (5)



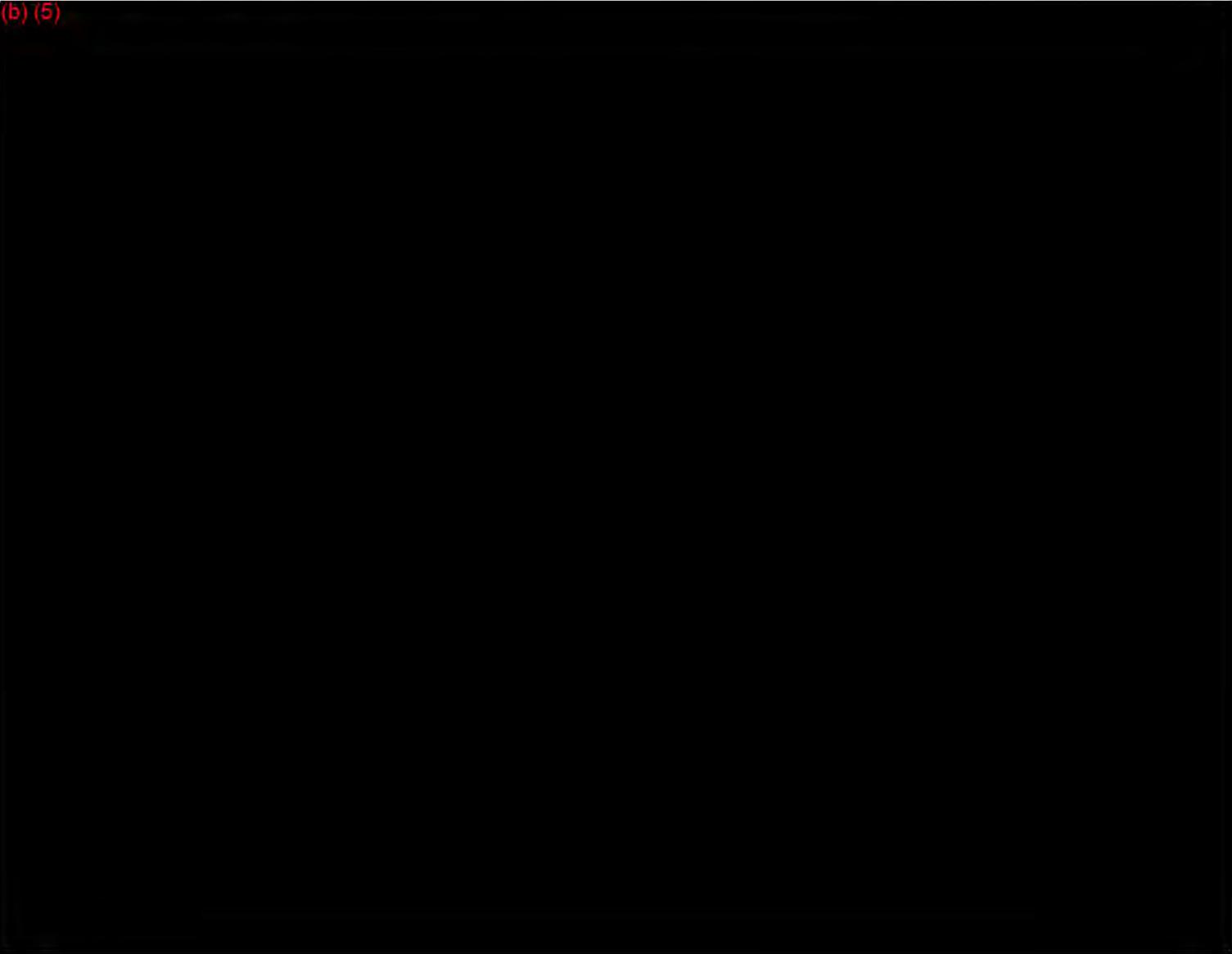
(b) (5)



**Reactive Statement and QA: Posting of review documents for approval of
Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy**

Target date: September 2016

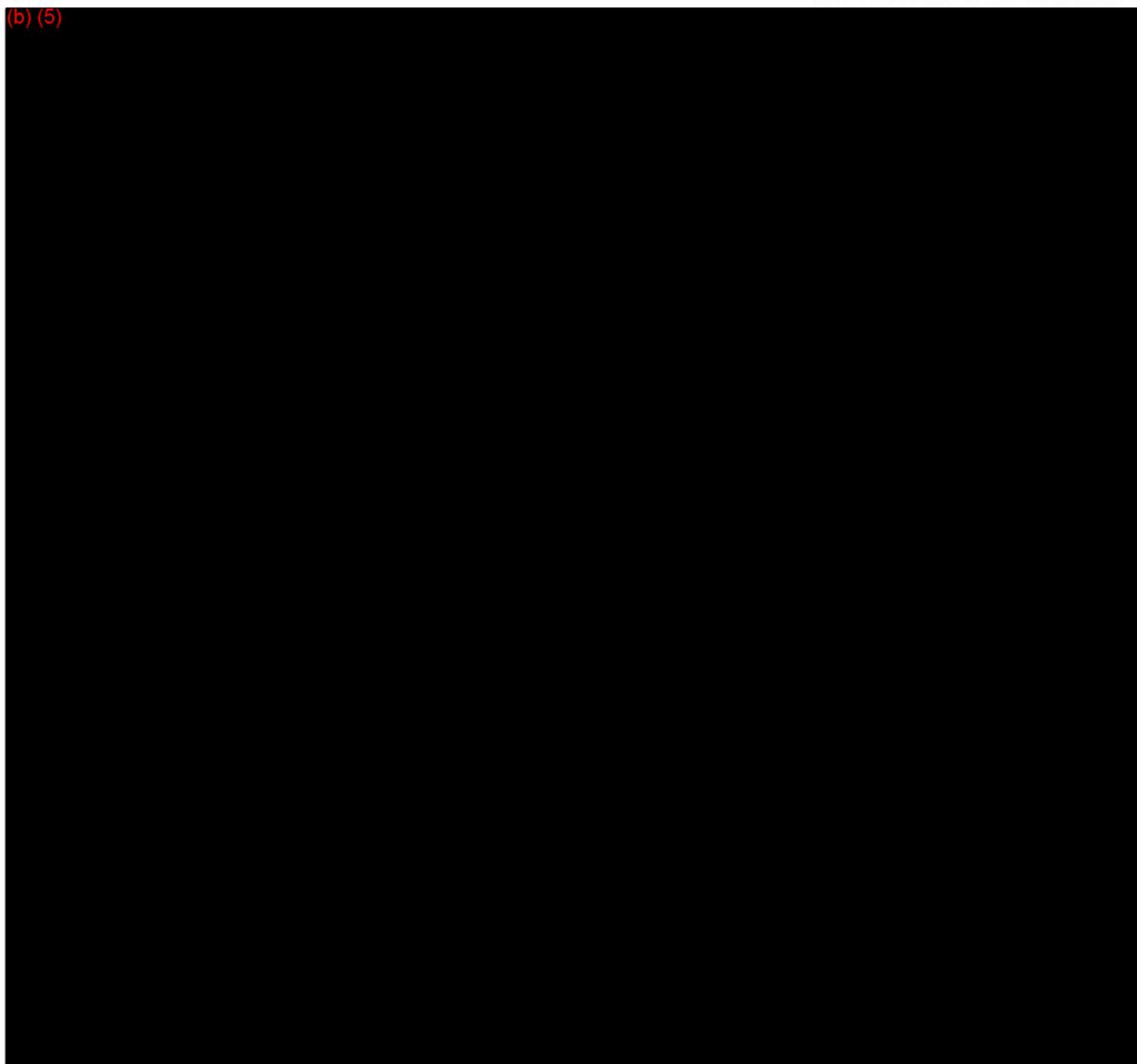
(b) (5)



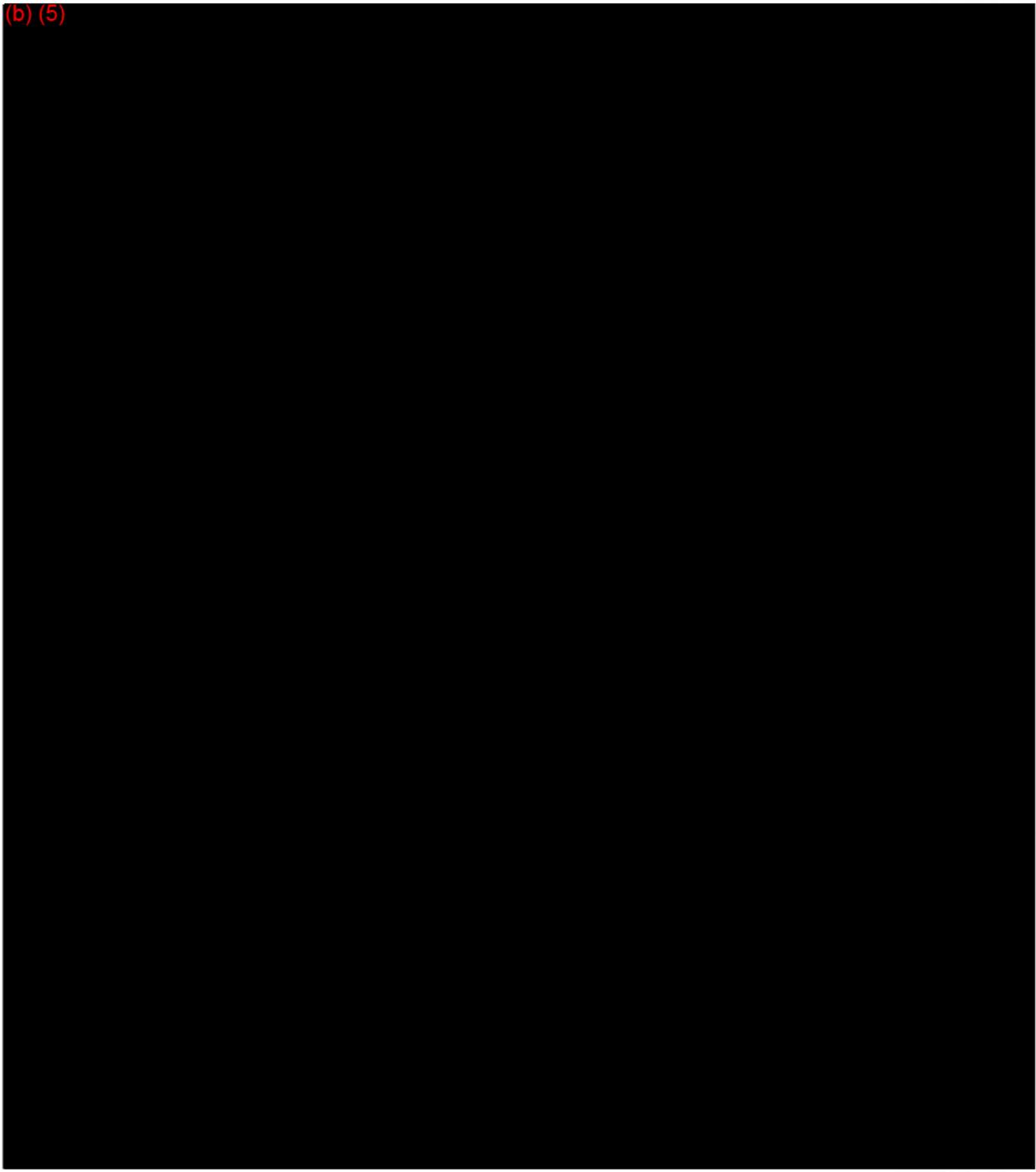
(b) (5)



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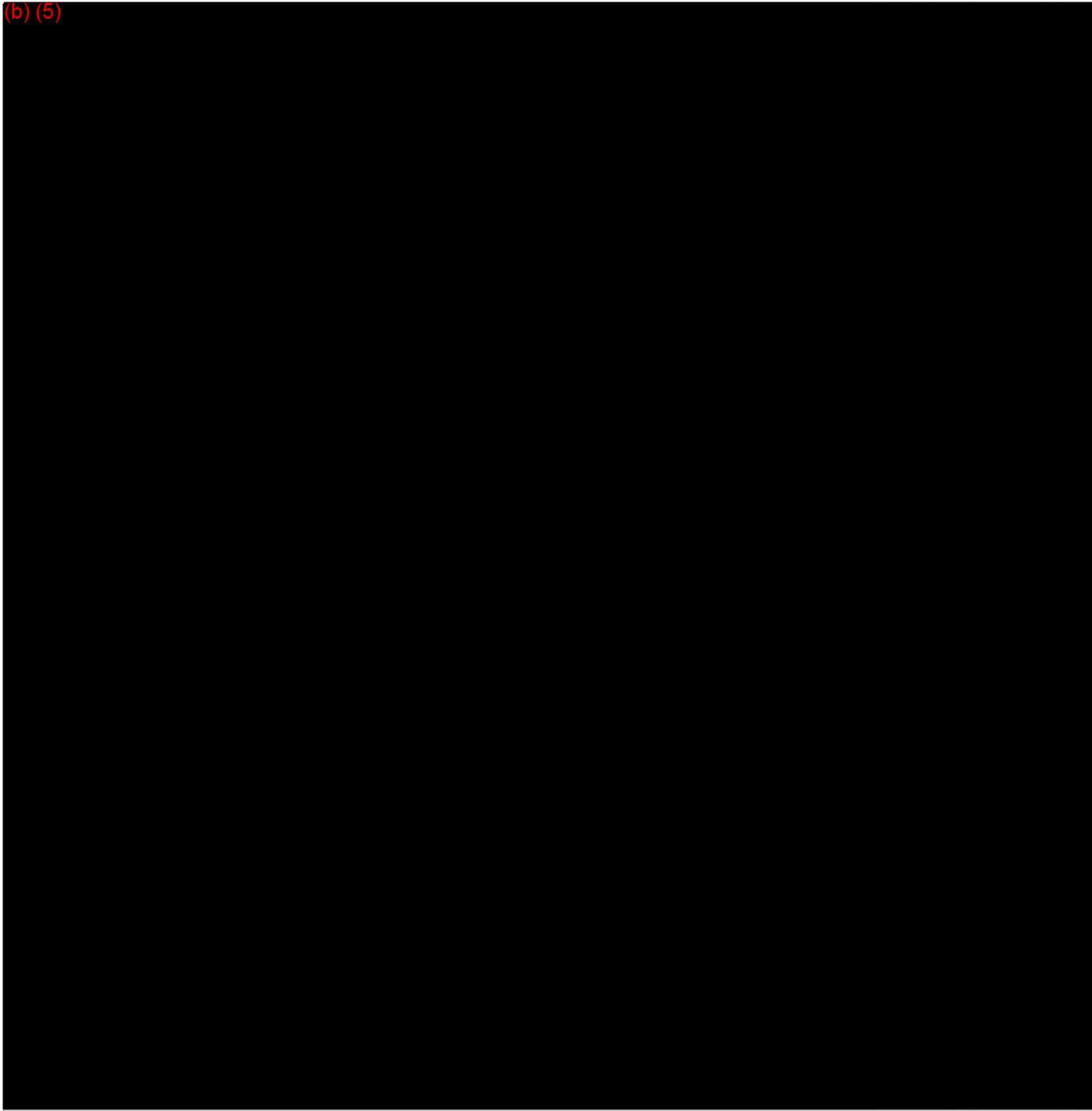
(b) (5)



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(b) (5)



From: [Rodriguez, Jennifer](#)
To: [Kraus, Tom](#); [Sherman, Rachel](#); [Califf, Robert](#); [Conover, Katie](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: Re: Follow up on Eteplirsen
Date: Tuesday, September 13, 2016 9:01:51 PM

I wonder how this was handled for Addyi?

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 13, 2016 at 8:52:21 PM EDT
To: Conover, Katie <Priscilla.Conover@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Kraus, Tom <Tom.Kraus@fda.hhs.gov>
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Will get back with you later today.

5. Plans for the press release and release of documents that support the approval. Our normal process is to release the approval letter and the labeling on the day of approval, followed some time later (I think we have 30 days) by the redacted action package. In this case, we would strongly advocate for releasing the most important memoranda at the time of approval to ensure transparency for the action. The more complete action package could then be released on the usual timeline (e.g., the CMC review, the pharm/tox review). In our view, the redacted documents that should be released at the time of approval would include the Cross Disciplinary Team Leader (CDTL) memo (Farkas), the deputy division director memo (Bastings), the ODE director decisional memo (Ellis), the Center Director decisional memo, Ellis' appeal memo, the acting Chief Scientist memo, and Rob's decisional memo. We strongly advocate for transparency in this case and if you agree these documents will need to be redacted on an expedited timeline.

Our plan has been as you say but to release all the memos at the time of all the other documents rather than with the approval letter and labeling. I have no particular reason to hold information back other than to give people all the information at one time. Glad to continue to discuss.

6. The draft press release. Again, we strongly advocate for transparency in the press release about the differing opinions, the appeal, and how the appeal was decided.

We will be transparent. The question is timing as above.

7. Any plans for press availability to discuss the approval. In the past for controversial/high profile actions we have scheduled a media call where we describe the basis for the action and take questions from reporters. We have also often scheduled a separate briefing for stakeholders.

OEA had not planned a media call to my knowledge. For sure there will be a lot of media interest and questions.

I spent yesterday cleaning up a lot of other things and am available today if we need to talk.

John

From: [Rodriguez, Jennifer](#)
To: [Chasan-Sloan, Deborah \(FDA\)](#); [Dickinson, Elizabeth \(FDA\)](#); [Califf, Robert](#); [Sherman, Rachel](#); [Conover, Katie](#); [Kraus, Tom](#)
Subject: PLEASE SEE -- CDER Cleared Comms
Date: Tuesday, September 13, 2016 1:41:24 PM
Attachments: [etepilrsen KMOA 9.13.16 JW.DOC](#)
Importance: High

All,

Janet has reviewed the comms and had no edits on the press release or phase II QA. She has one comment and minor edits attached in the phase I KMOA (attached). I was told that Janet would be reaching out to talk to Califf directly about his comment on page 3. In the interest of time, we will proceed with sending up the comms to HHS by 2:30pm. If there are any edits (new QA) resulting from Janet and Dr. Califf's conversation we can make those at that time.

Please let me know by 2:30pm if you have any questions or concerns.

Best,
Jen

From: Chasan-Sloan, Deborah (FDA)
Sent: Monday, September 12, 2016 11:37 AM
To: Rodriguez, Jennifer; Dickinson, Elizabeth (FDA); Califf, Robert; Sherman, Rachel; Conover, Katie; Kraus, Tom
Subject: Re: PLEASE SEE -- Updated Comms

(b) (5)



Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Rodriguez, Jennifer
Sent: Monday, September 12, 2016 10:17 AM
To: Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Conover, Katie; Kraus, Tom
Subject: PLEASE SEE -- Updated Comms

Hi All,

Attached please find the updated QAs, as well as the PR, reflecting the edits to date. In addition, below please find a slightly revised response to the question about the review team. Please let me know if you would like us to go further.

Also, is it OK for us to reach out to Lu Borio's team to get the information for (b) (5)



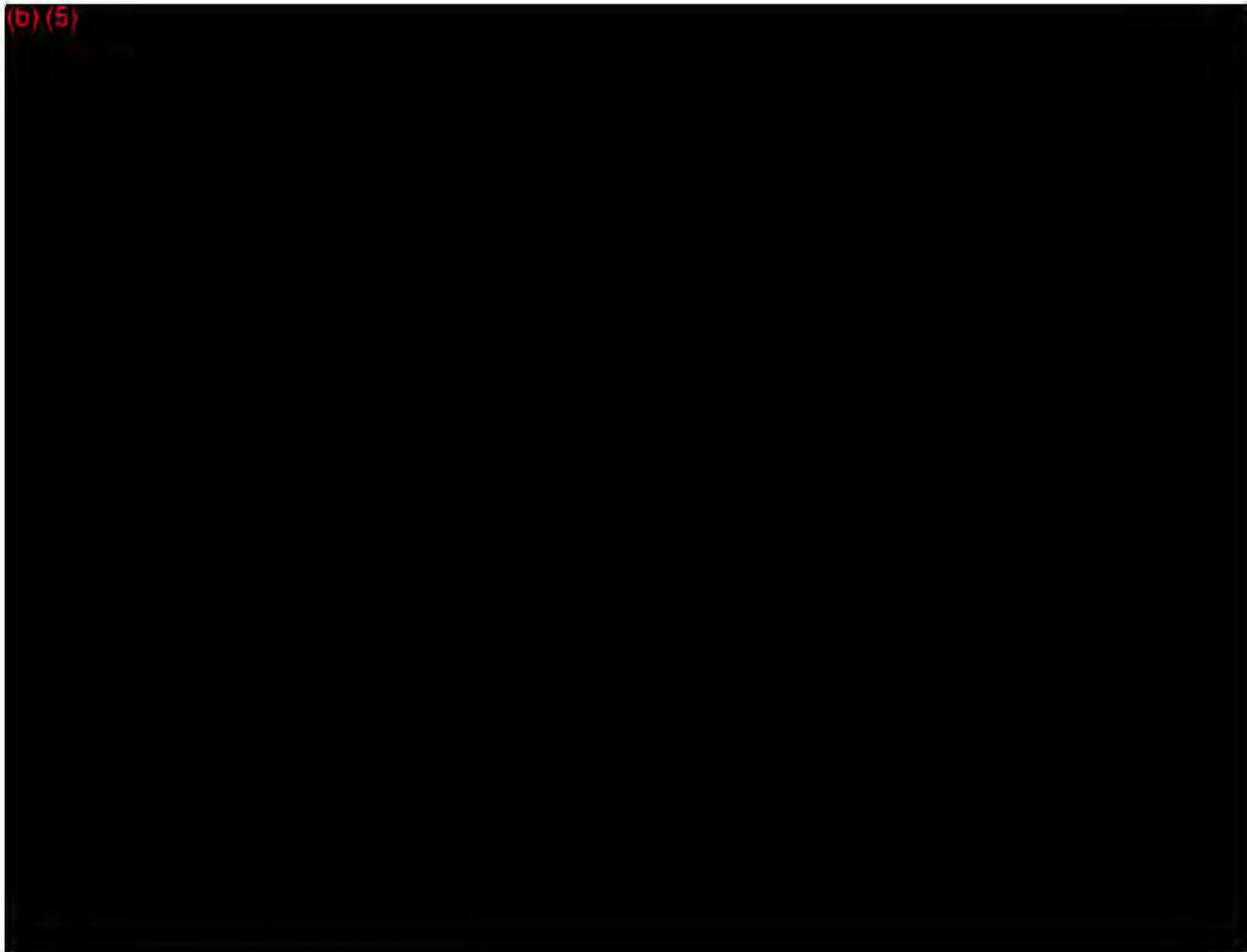

Once we have your OK, we will share the comms package with Chris Shreeve for CDER review – asking them to flag anything that is inaccurate or provides significant heart burn. We would like to

be able to share with CDER by noon to keep on schedule.

Thanks for all your feedback.

Jen

(b) (5)



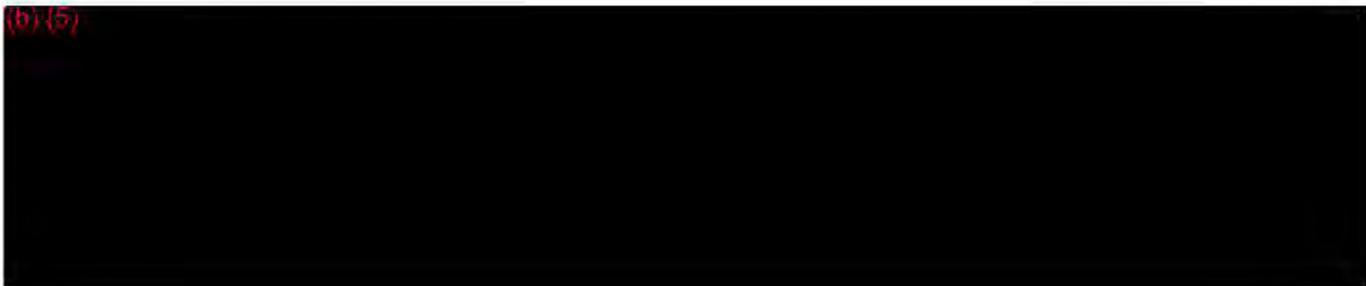
From: Dickinson, Elizabeth (FDA)

Sent: Sunday, September 11, 2016 8:32 PM

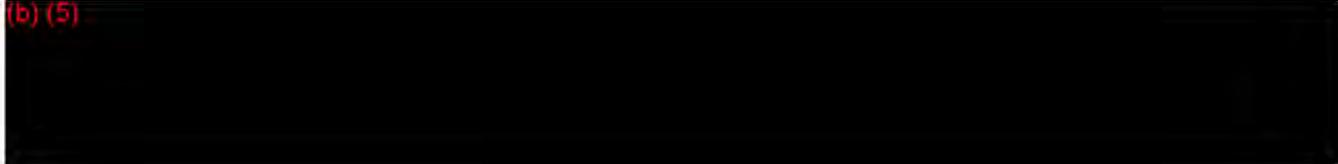
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie

Subject: RE: Q&A

(b) (5)



(b) (5)



From: Califf, Robert
Sent: Sunday, September 11, 2016 7:49 PM
To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

Nice job. These changes improve what I was trying to get across. Thanks.

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Sunday, September 11, 2016 7:44 PM
To: Sherman, Rachel; Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

(b) (5)



From: Sherman, Rachel
Sent: Sunday, September 11, 2016 8:45 AM
To: Califf, Robert; Rodriguez, Jennifer; Conover, Katie; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)
Subject: RE: Q&A

I will try to explain my thinking on the two topics Rob raises.

(b) (5)



Hope this helps.

Rachel

Why do you equivocate and say I'm right on most things? I thought we agreed I was always right...

From: Califf, Robert

Sent: Sunday, September 11, 2016 8:23 AM

To: Rodriguez, Jennifer; Conover, Katie; Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA)

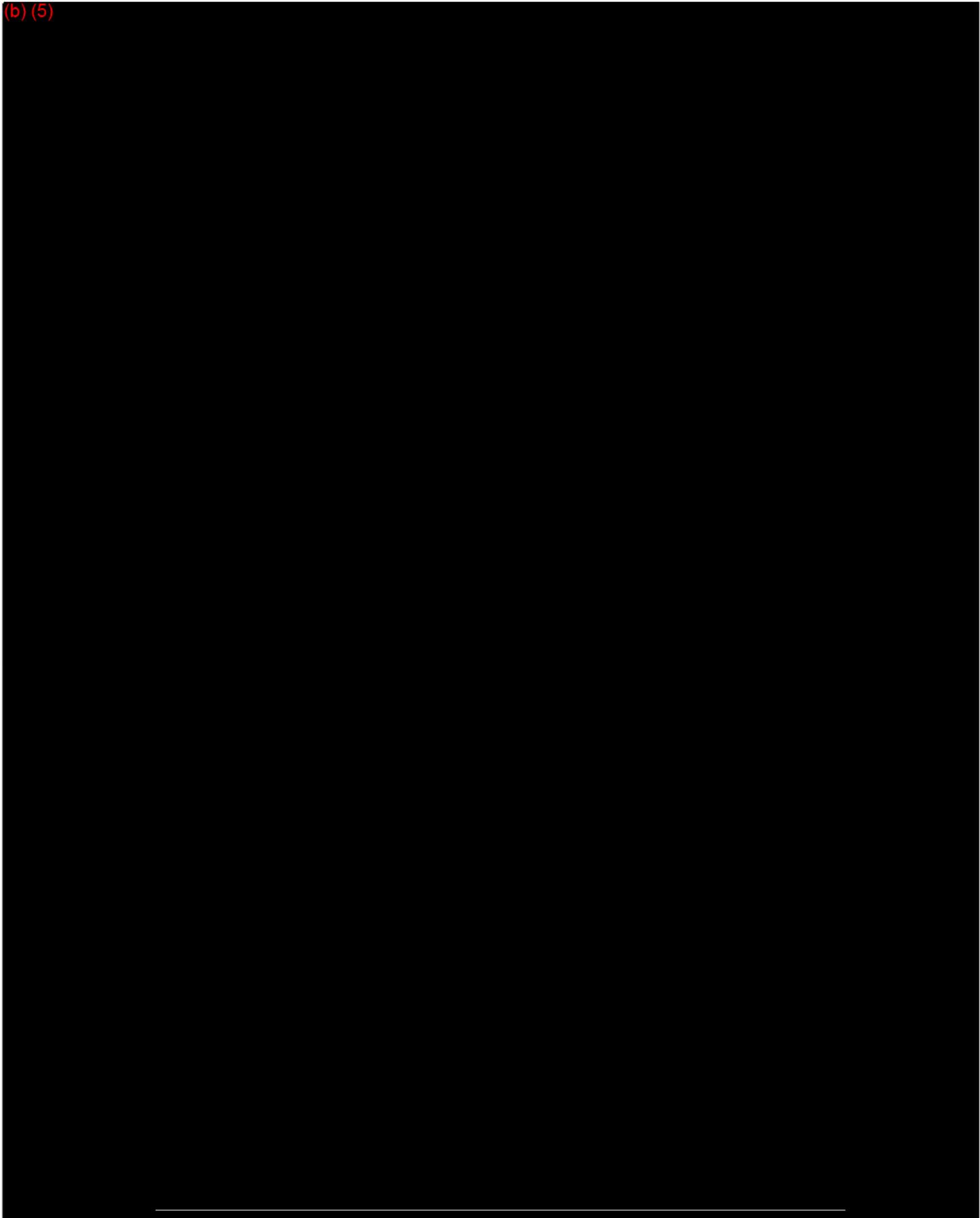
Subject: Q&A

Friends,

I have done a little editing, but not much as I think its good. There are still several loose ends. Are we still ok on the timeline?

3 issues strike me as needing more work:

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(b) (5)



Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

Target date: September 2016

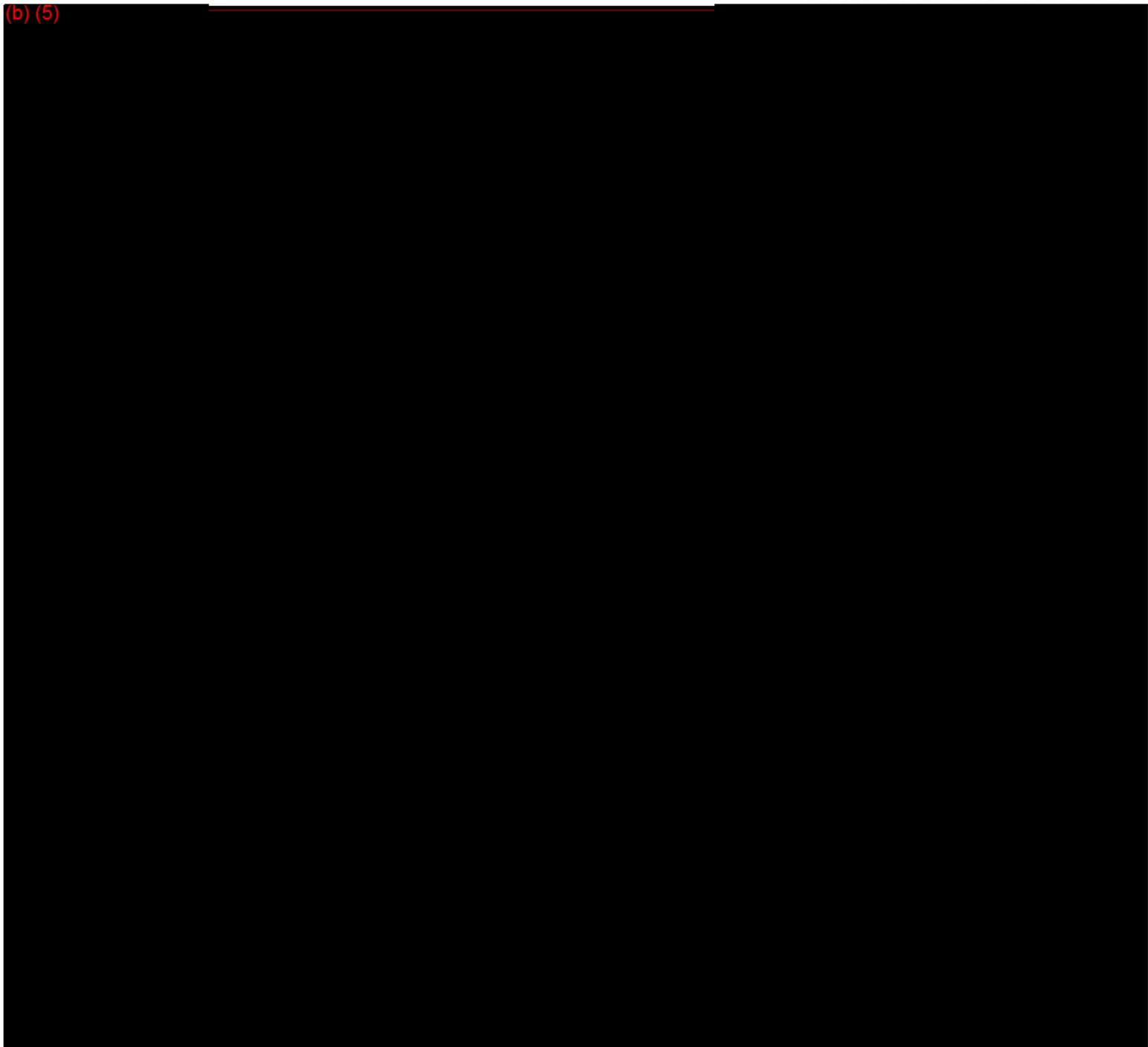
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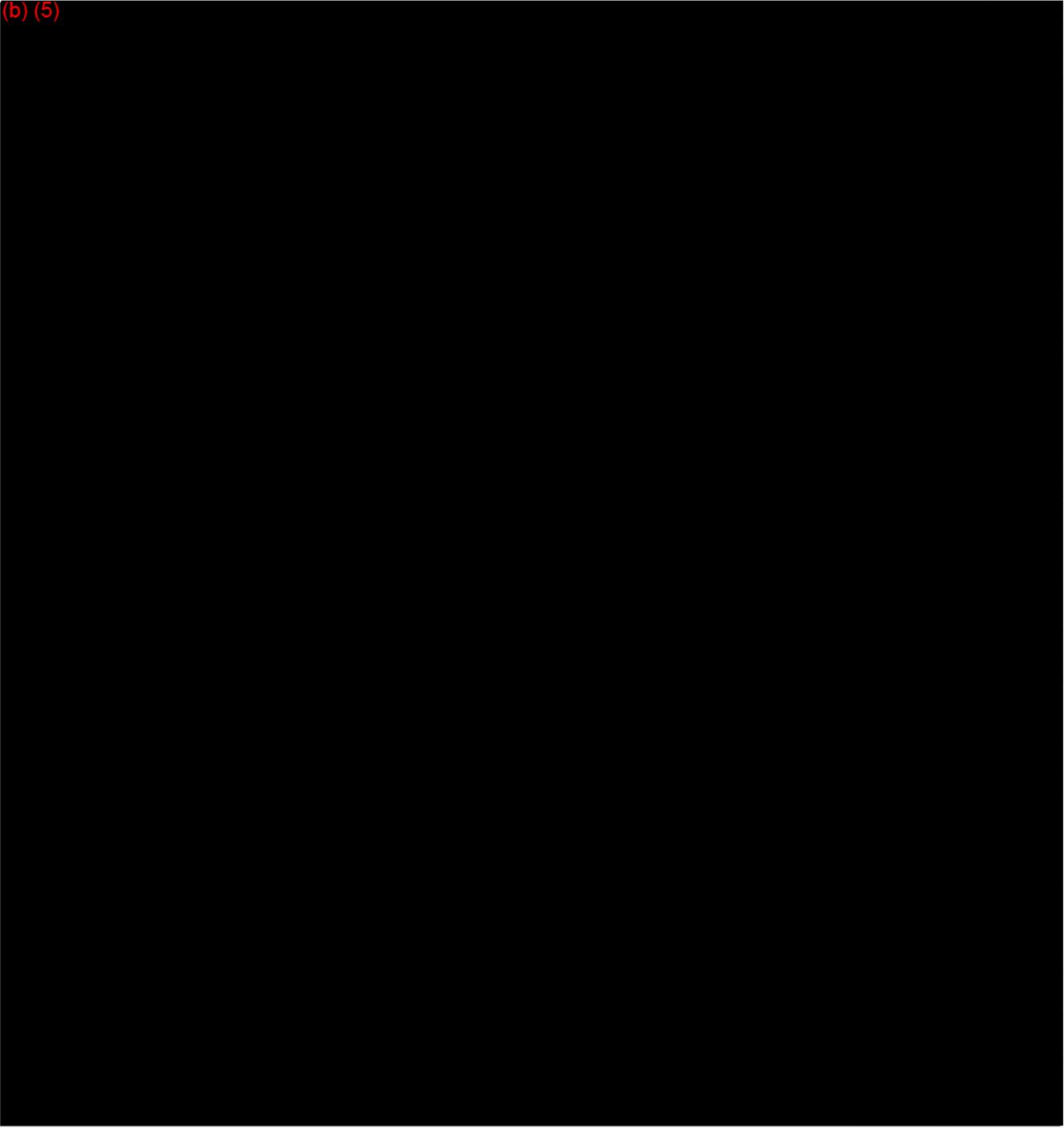
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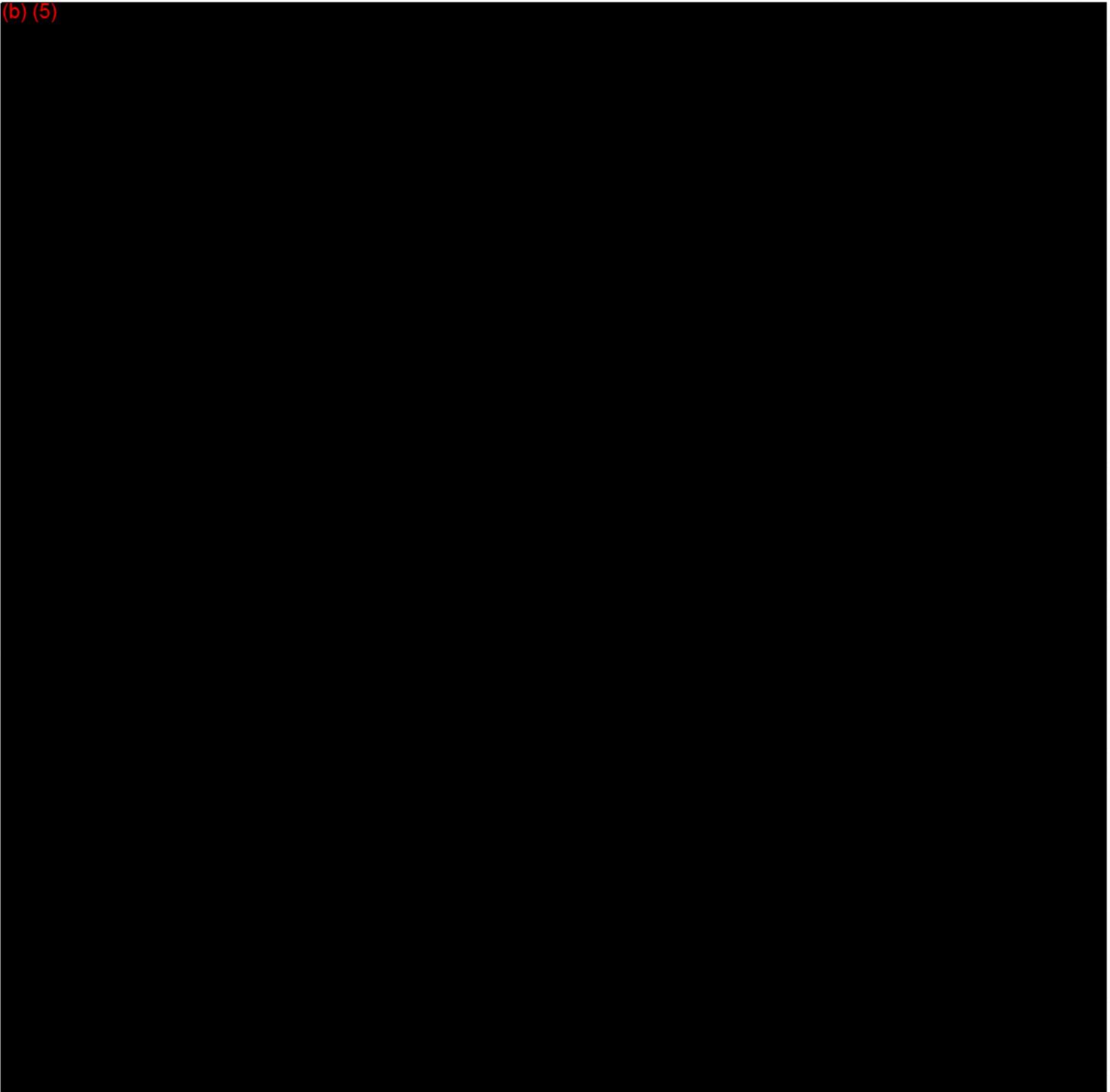
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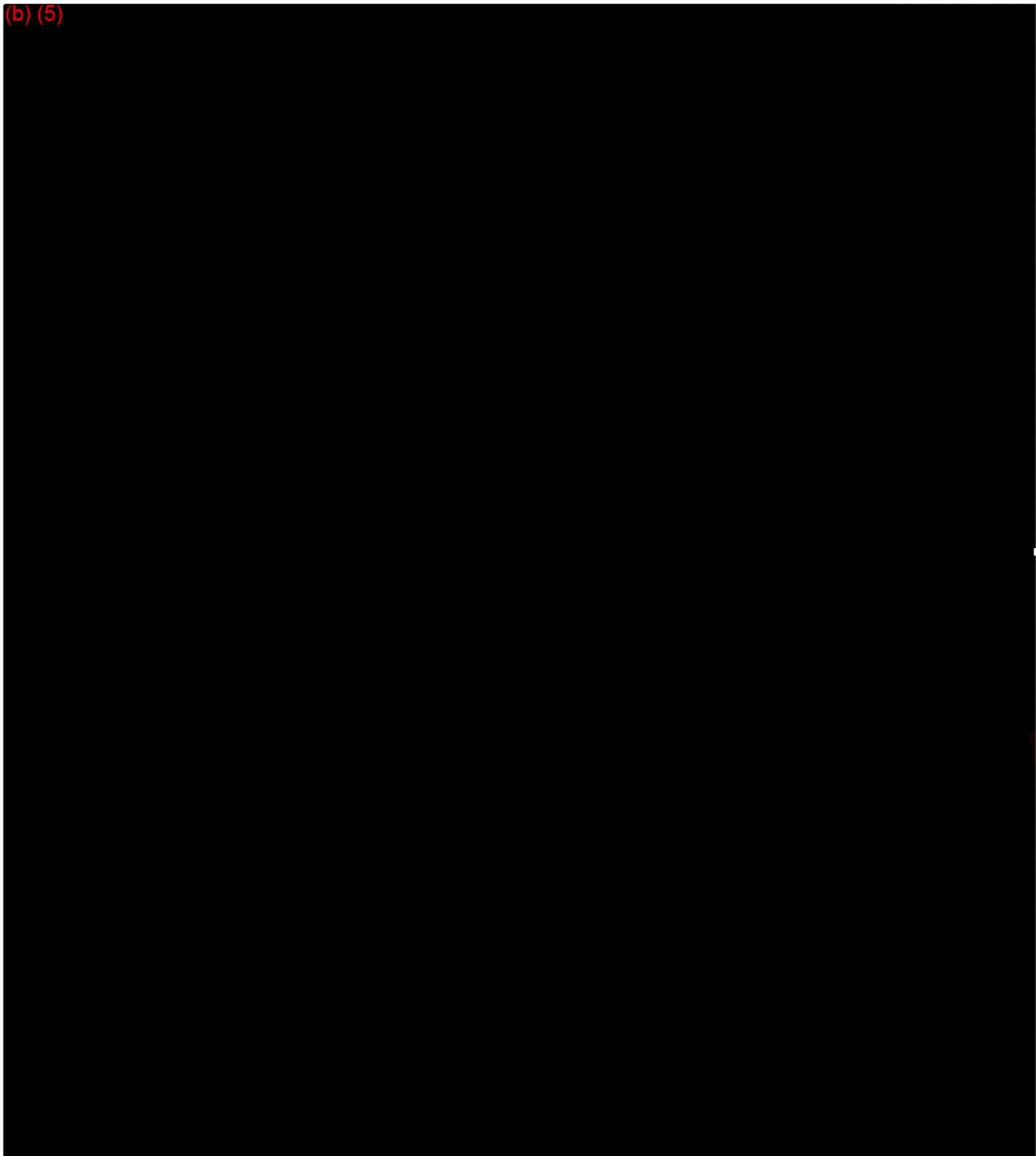
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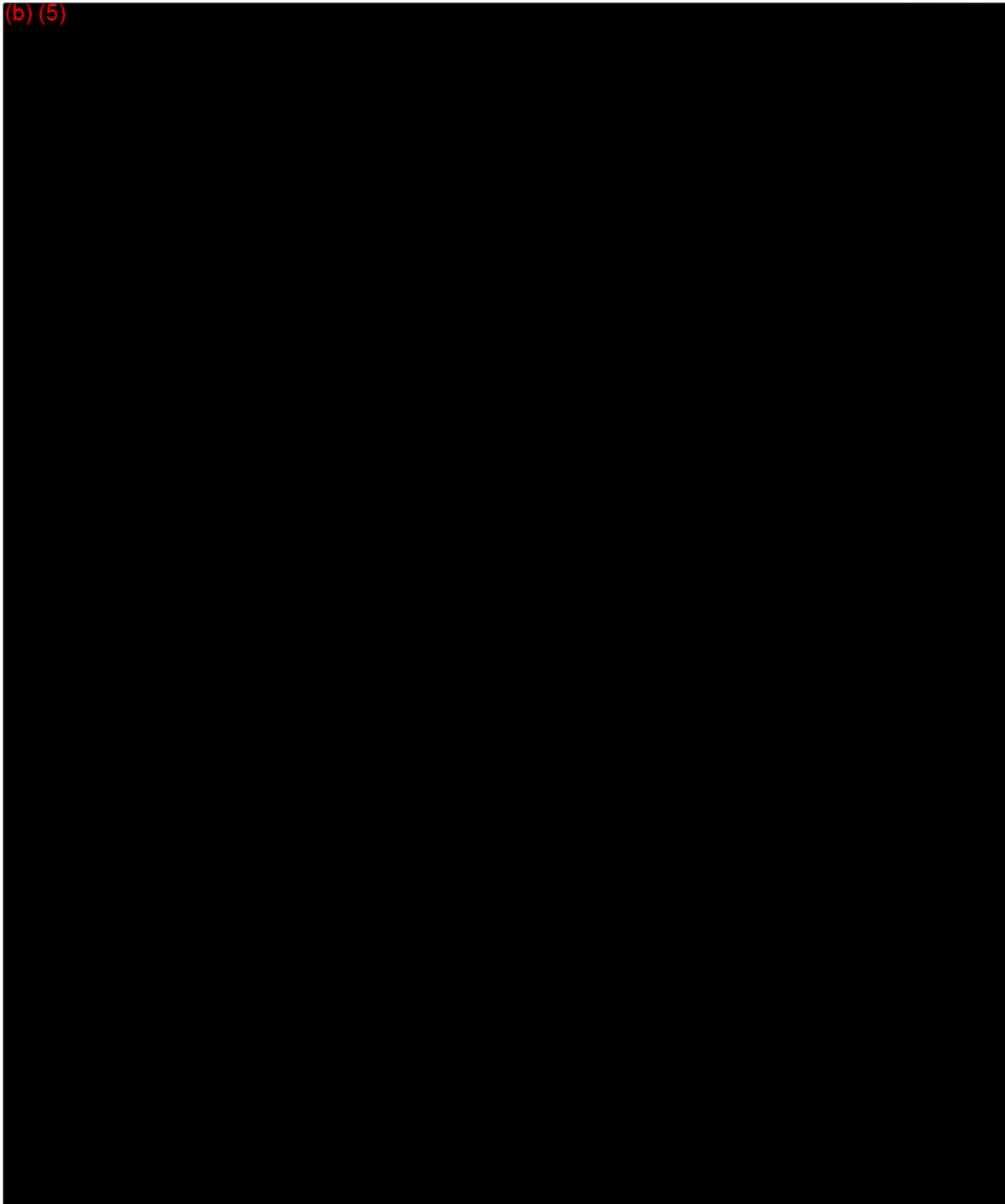
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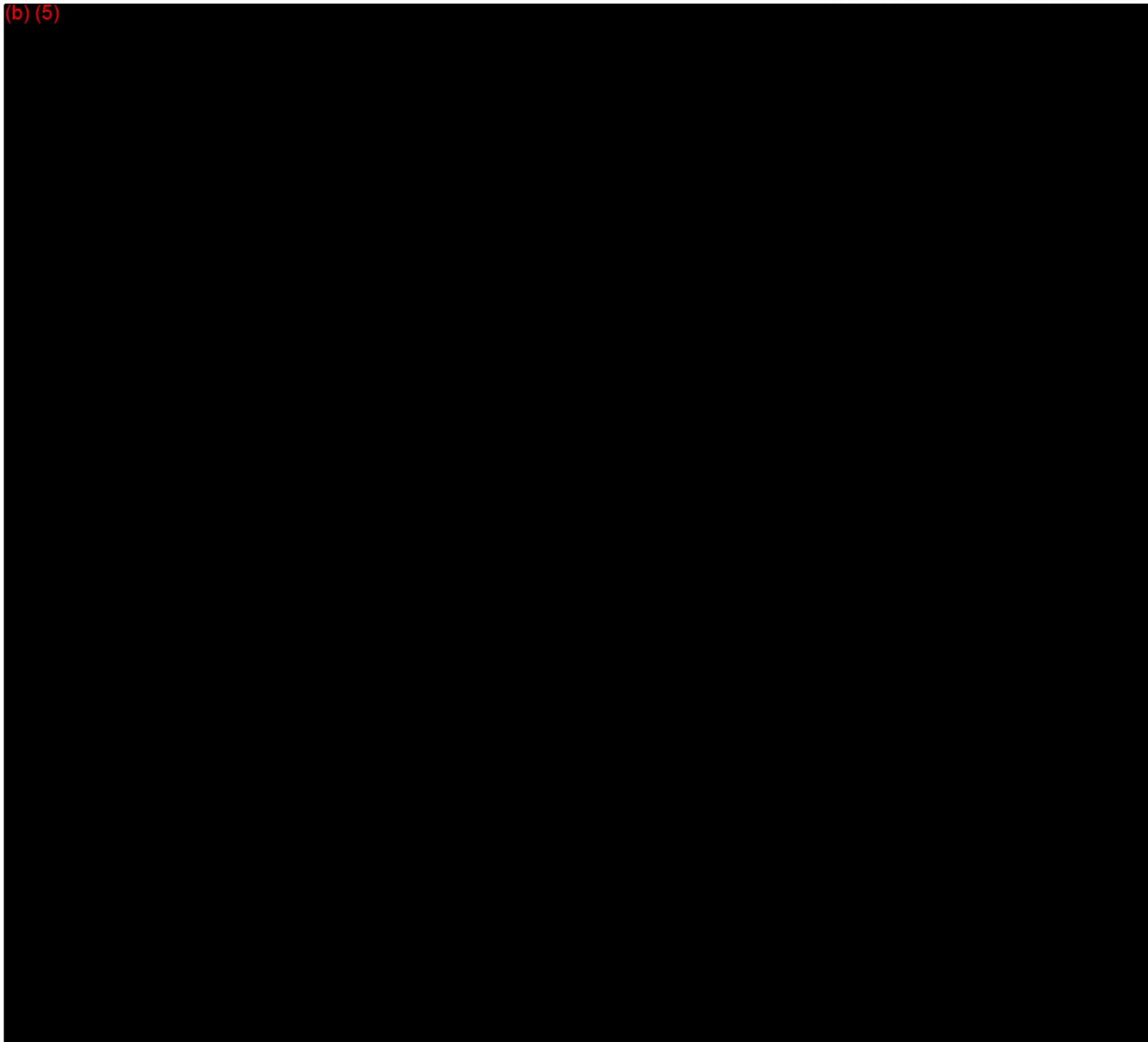
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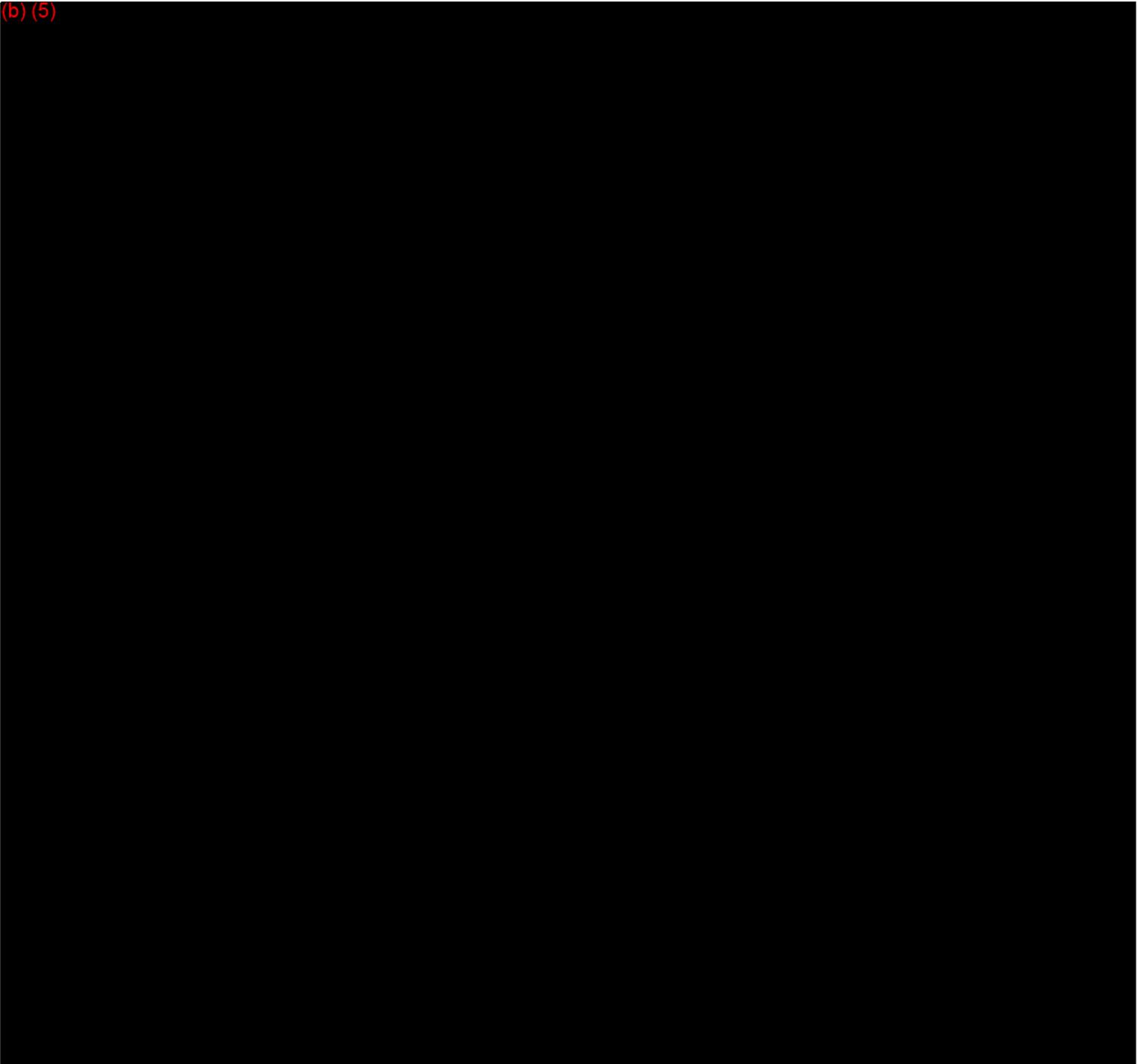
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(b) (5)



(b) (5)



From: [Jenkins, John K](#)
To: [Califf, Robert](#)
Cc: [Jenkins, John K](#)
Subject: RE: memo
Date: Wednesday, September 14, 2016 5:35:44 PM

Rob

Thanks for providing an opportunity to review your draft memo regarding the eteplirsen dispute. I am responding just to you since some of the issues I raise below are sensitive. I would be happy to speak with you privately to discuss my concerns in greater detail if you would be open to that.

1. I ask that you remove reference to quoting me from the July 12, 2016, e-mail that "reasonable people can disagree." I think as used it is mischaracterized and used out of context. I strongly disagree with Janet's decision and do not want my words in a single e-mail to suggest that is not the case.
2. As to footnote 7, I think the review team needs to weigh in, but it was my impression that use of corticosteroids has been interpreted based on data to have changed the course of the disease in DMD. We currently have a pending NDA for use of a corticosteroid in DMD.
3. You note on page 3 that due to the serious defects in the development program, "it is impossible to use much of the resulting trial evidence in regulatory decision-making, including reasonable extrapolation to clinical care." Yet you later support Janet's conclusion that the sponsor has provided data from "two adequate and well-controlled trials." I can find no effort to reconcile these very different statements.
4. On page 4, you state "there is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence..." This implies she took these actions BEFORE reaching a decision on the application, which is clearly not correct given her statement to the review team of her intention to overrule them and approve the drug BEFORE they had completed their reviews. Keep in mind this occurred after an AC meeting at which the majority of the panel voted against both AA and full approval. It is also clear that she was prepared to approve the drug over the team's objections by the original PDUFA goal date and only reluctantly agreed to press the sponsor for additional data on dystrophin production from the ongoing open-label trial. While I am glad she agreed to go along with that request, convincing her to take what seemed like a very logical action was not easy. So, I find it hard to reconcile your statements about the process with the actions taken. Keep in mind that the usual course of action would be for the Office to issue a CR letter and then the sponsor could submit a FDRR that would first come to me and only if I supported the Office would an FDRR go to the Center Director. In this case that process was bypassed.
5. On page 4 you state that Dr. Woodcock "finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is "reasonably likely" to predict clinical benefit." This statement defies any sense of scientific reason (would one molecule of dystrophin be enough) and goes directly to Dr. Unger's concern that "any" level of protein seems to be enough for Janet to support approval. You then go on to reference Janet's regression analyses from her memo

suggesting a correlation between dystrophin production and clinical outcomes. As I have noted to you on several occasions, I find this to be a scientifically invalid analysis that compares the endpoint value for dystrophin to a delta in a clinical endpoint. This analysis simply shows a correlation between higher levels of dystrophin, without regard to drug effect (there is no delta for dystrophin change that is due to drug), and cannot support the conclusion she reached. Your citation of this analysis is troubling.

6. You make reference in several places to a “totality of evidence” standard. That is not the statutory standard for demonstration of effectiveness and FDA has always stated that the statutory standard for demonstration of an effect on a surrogate endpoint for AA is the same as for regular approval (i.e., substantial evidence). Perhaps you are using “totality of evidence” to support the decision that the data provided on the surrogate are reasonably likely to predict clinical benefit, but there must be substantial evidence of the drug’s effect on the surrogate and the data are very weak to meet that standard.
7. You dismiss the concerns about Janet’s level of involvement in this review and her role at the AC by suggesting this is simply part of her leadership style. I have worked with Janet for over 20 years and I can say without a doubt that her involvement in this case far exceeds her usual “hands on” approach. You note that there were 14 Center director briefings related to this case, that is clearly not the “norm” for how CDER operates. You also suggest that because CDER has been successful under her leadership that suggests that her intense involvement in this case does not raise concern. I see that as true, true, and unrelated. The question in this case is not whether she has overall been an effective leader of CDER, but whether she acted appropriately and without bias in the current case, something I don’t think you effectively address given the evidence and the seriousness of the allegations and concerns expressed.
8. As to your footnote 23, there are direct statements that Janet made to the team that contradict the statements you reference from your interview with her. I am happy to discuss these statements with you further. In addition, Janet has had frequent private conversations with the sponsor and the stakeholder community. To my knowledge, she has not documented the substance of those conversations to the record, as is required under FDA regulations. That leaves a gap of knowledge to evaluate the concerns raised by the review team and Dr. Borio.
9. I do not find your statements about how this case does not lower the bar for future drug approvals convincing. I share the concerns voiced by Drs. Unger and Borio about the potential adverse impact on FDA’s ability to reach science-based conclusions on future applications.
10. On page 9 it would be nice to see you call explicitly for retraction of the publications that have now been discredited.
11. Also on page 9 it is ironic that you attribute to Janet the idea of randomizing early in order to generate good evidence. That is exactly what the review team planned to require of Sarepta after the results of the 12-patient study became available, but it was Janet that pressed that a new randomized trial not be required. So, if Janet had followed the normal CDER process

in this case the review team would have required placebo-controlled trials, as they did for drisapersen (b) (4), and we would have better data on which to make a decision. I would note that Janet did not and has not involved herself in the drisapersen (b) (4) cases to the same degree as eteplirsen. Drisapersen arguably (b) (4) they had a positive phase 2 trial and a second trial that leaned favorably on a clinical endpoint. Janet did not object to the division asking for a large phase 3 trial and did not object to ODE1's decision to issue a CR letter based on (b) (4). I think it is reasonable to question why she devoted so much attention to eteplirsen and not the other (b) (4) drugs. One could speculate that she too was misled by the early reports on dystrophin production that were later discredited.

12. The overall tone of your memo seems to say that you conclude that Janet behaved and conducted herself appropriately in this case. That is at odds with the experience of the review team and is counter to the team-based, collegial working environment that we hope to create at FDA so we can accomplish our important public health mission. This validation from your level of her actions and behavior is worrisome. While I understand your desire not to undercut her role as Center Director, her actions have at best created a serious appearance of bias among the review team members and that has created distrust and a sense of undue pressure to "come around" to her way of thinking. Even if you uphold her decision I would think you should counsel her about how her behavior and actions have undermined her credibility among the review staff and should be avoided in future similar cases. Effective leaders must have the trust and respect of their staff. As I noted in our call last week, there are frequent disagreements about data and actions in CDER, and that is healthy and encouraged so we can ensure we hear all voices as we make decision, what is not healthy is a situation where the actions of a leader creates the appearance of bias since this undermines the trust necessary for the review team to conclude that the action was fair and move on.

I understand this appeal has placed you in a very difficult position. I also understand that you have made your decision. I hope, that my comments can help you to structure your decisional memo to avoid similar situations in the future. As you know, I had planned to retire from FDA last spring. I have delayed my departure for a variety of reasons, but one of the most important reasons is that Janet has told me she plans to serve as acting in my place as head of OND once I leave. I am very concerned about the impact of that decision on the future of the new drugs review program and would be happy to discuss those concerns further.

John

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD

Commissioner, Food and Drugs

From: [Unger, Ellis](#)
To: [Califf, Robert](#)
Cc: [Woodcock, Janet](#); [Jenkins, John K](#); [Borio, Luciana](#)
Subject: RE: memo
Date: Wednesday, September 14, 2016 6:51:47 PM
Attachments: [2016_Sept_012_R2_Eteplirsen_CLEAN_unger.doc](#)

Rob,

I have concerns with respect to two areas of your memo, first, whether proper procedures were followed such that all evidence and analyses were reviewed by the Center Director before a decision was rendered, and second, whether this decision will set a general precedent – where accelerated approval could be provided for a rare disease based solely only on the medical and scientific judgment/opinion of the Center Director, as was clearly the case here. I've also returned your memo with just a few tracked comments and text.

1. Whether proper procedures were followed; whether all evidence was considered

Having read your draft memo and the August 8, 2016, memorandum of the Scientific Dispute Process Review Board (SDR Board), I do not agree with your conclusions that:

- all applicable processes and procedures were followed;
- the appealing parties had ample opportunity to present their views; and
- the decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

As Director of Office of Drug Evaluation-I, I provide a final level of review and sign-off for various New Drug Applications. Not infrequently, as I write these memoranda, I recognize areas where there is lack of clarity, or I may have concerns about the data or the reviews. In these situations, I find myself doing some last minute "digging" on my own.

Such was the case here. As I was writing my Complete Response memorandum for eteplirsen, I began to recognize the very confusing nature of the immunohistochemistry results from Study 201/202. As stated in the SDR Board's memo (page 12), Dr. Woodcock "...thought that the review team's presentation of the IHC data, in particular, was confusing."

In trying to understand the ambiguities and discrepancies myself, I realized that the original analysis for Study 201/202 showed 13% positive muscle fibers at baseline, whereas a subsequent analysis found only 1.1% positive fibers. (All slides had been analyzed by the same panel of pathologists.) As noted in Figure 2 of my appeal, for the 3 patients whose baseline tissue blocks were analyzed on two occasions, the immunohistochemistry results differed by an order of magnitude. Unfortunately, this disparity had not been addressed adequately by the review team, and had not been described at the April 25, 2016, Advisory Committee meeting.

Because of this lack of reliability, there is simply no way to relate or compare the applicant's immunohistochemistry results to results from other laboratories reported in the literature.

Importantly, this discrepancy, raising important doubts about all of the immunohistochemistry data,

was not known to Dr. Woodcock at the time she filed her approval memo on 7/14/16. (I had not performed these analyses until the evening of 7/15/16.) Her issuance of a decisional memorandum prior to careful consideration of my final review represents a critical deviation from protocol. As pointed out in the SDR memo (page 10): “Dr. Woodcock conceded to the SDR Board that she was leaning toward granting approval in light of the available data as early as 2014,” and page 20: “...at the conclusion of the review, Dr. Unger will not have received a substantive review of his scientific concerns under any formal process at any level.”

It follows, therefore, that:

- All applicable processes and procedures were not followed;
- I did not have the opportunity to present this highly relevant scientific evidence to Dr. Woodcock; and
- Dr. Woodcock’s decision to grant accelerated approval was made prior to consideration of all relevant scientific evidence.

The information showing the applicant’s lack of ability to reproduce its own dystrophin results is critically important because any attempt to identify a quantity of truncated dystrophin that is “reasonably likely to predict clinical benefit” would hinge on the demonstration of a relationship between skeletal muscle dystrophin content and physical function, presumably as accepted by the scientific/medical community. With respect to the immunohistochemistry analyses in Study 201/202, the applicant’s inability to reproduce its own findings raises considerable doubt about any ability to relate and compare the dystrophin values obtained by the applicant to those reported in the literature.

With respect to the Western blot analyses, the applicant stated at the Advisory Committee meeting that their data should not be compared to data from other laboratories (page 14 of my appeal):

“Our validated Western blot method, optimized to detect low levels of dystrophin, is arguably the first dystrophin Western blot to be truly quantitative. This was achieved by use of a 5 point calibration curve on each gel and prespecified loading and exposure limits to avoid signal saturation....Given these significant methodological differences, it is inappropriate to compare our data to literature approximations.” (Source: Official transcript of the meeting; underlining for emphasis.)

In conclusion therefore, there is no way to reach a rational conclusion that the dystrophin detected by the applicant, by either immunohistochemistry or Western blot, is “reasonably likely to predict clinical benefit.” There is no way to correlate a mean increase of 0.3% (median increase = 0.1%) to an effect on physical function, based on clinical experience external to the development program.

Unaware of my final conclusions on this matter, Dr. Woodcock did not rebut the above reasoning. As I noted (and the SDR Board appeared to agree), she provided no cogent rationale for her decision that the barely detectable amount of dystrophin produced is “reasonably likely to predict clinical benefit.” Dr. Woodcock told the SDR Board that her decision was based on her 30 years of experience at FDA and her own “medical/scientific judgment.” (SDR Board Memo, page 16).

I think it will be important for the regulatory record to reflect that there was no scientific basis

underlying the conclusion of “reasonably likely” in this case. This was simply a judgment call by Dr. Woodcock. (Dr. Woodcock might have also taken the position that, in this desperate patient population, *any* dystrophin production would suffice as a basis for accelerated approval, but she didn’t state this.)

2. Whether this decision will set a general precedent and degrade the evidence standard for accelerated approval

In your draft Commissioner’s Decisional Memorandum, I fail to see any explicit basis for considering how DMD differs from many other rare diseases, i.e., why DMD/eteplirsen represents a “unique situation that will not set a general precedent for the standard of evidence supporting drug approvals under the accelerated approval pathway.” You note that “...the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of data and information.”

We all agree that each situation must be evaluated on its own merits; however, I fail to see how DMD differs intrinsically from other rare neurological diseases, e.g., Alexander disease, Canavan disease, Early infantile GM1 gangliosidosis, Krabbe disease, Metachromatic leukodystrophy, Niemann–Pick disease, Pelizaeus–Merzbacher disease, Pompe disease, Sandhoff disease, and X-linked adrenoleukodystrophy. Based on what you have written in your draft memo, it is not clear to me why a standard of any increase in the surrogate endpoint wouldn’t apply for these diseases.

Perhaps granting accelerated approval to drugs that show a mere scintilla of an effect on a surrogate endpoint represents a stroke of brilliance – one that will stimulate investment in the development of drugs for these disorders. But in my opinion, this approach should receive broader public (and FDA) input before being implemented.

Your decision seems to say that the “reasonably likely” standard for accelerated approval need have no quantitative component at all. We all agree that making a reasonable amount of dystrophin would provide a sound basis for accelerated approval. But the amount here – a median value of one part in a thousand that is not perceptibly greater than none – fails to meet the “reasonably likely” test.

I thank you for your consideration in all of this.

Ellis

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

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Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

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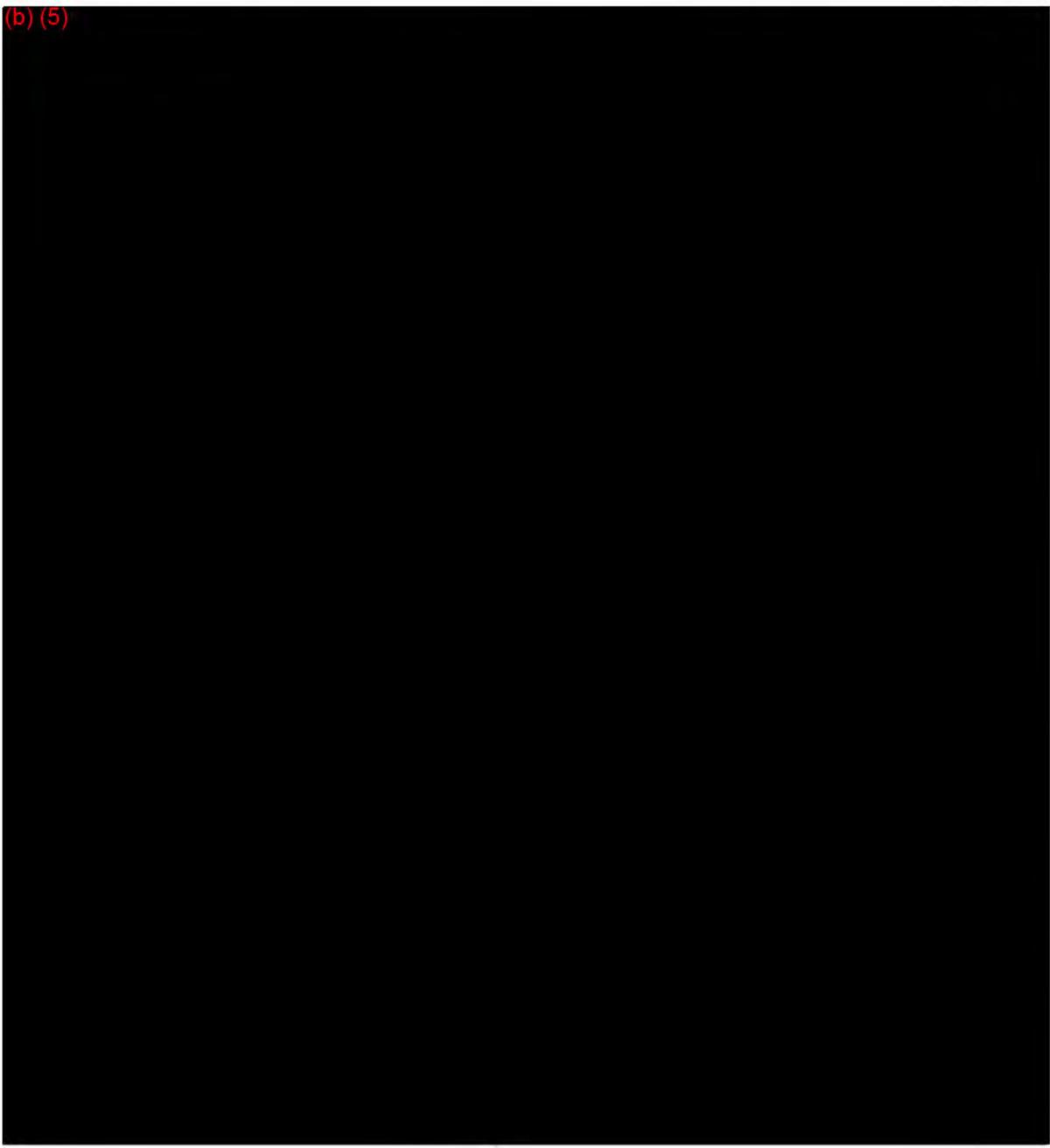
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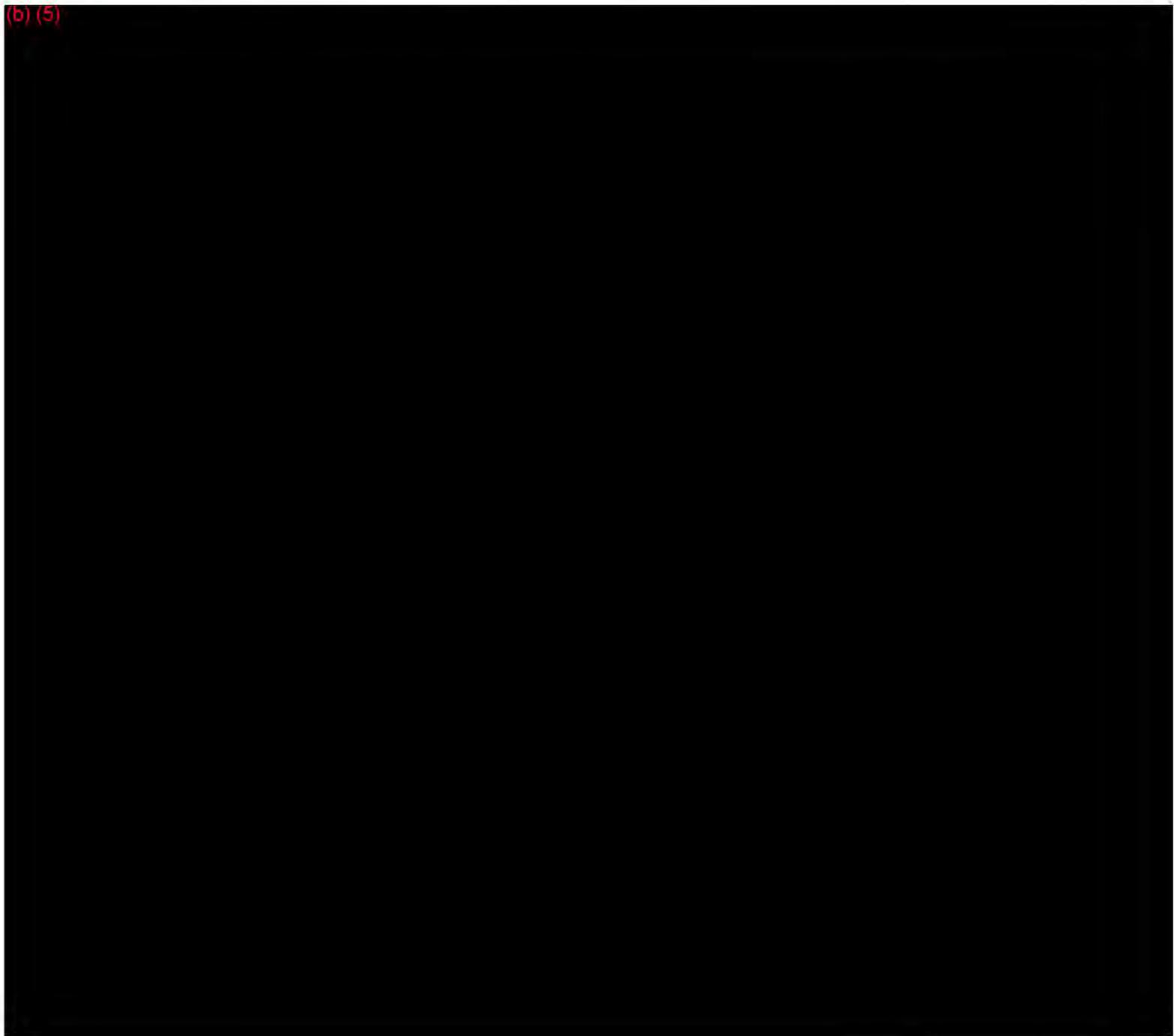
Robert M. Califf, MD

Commissioner, Food and Drugs

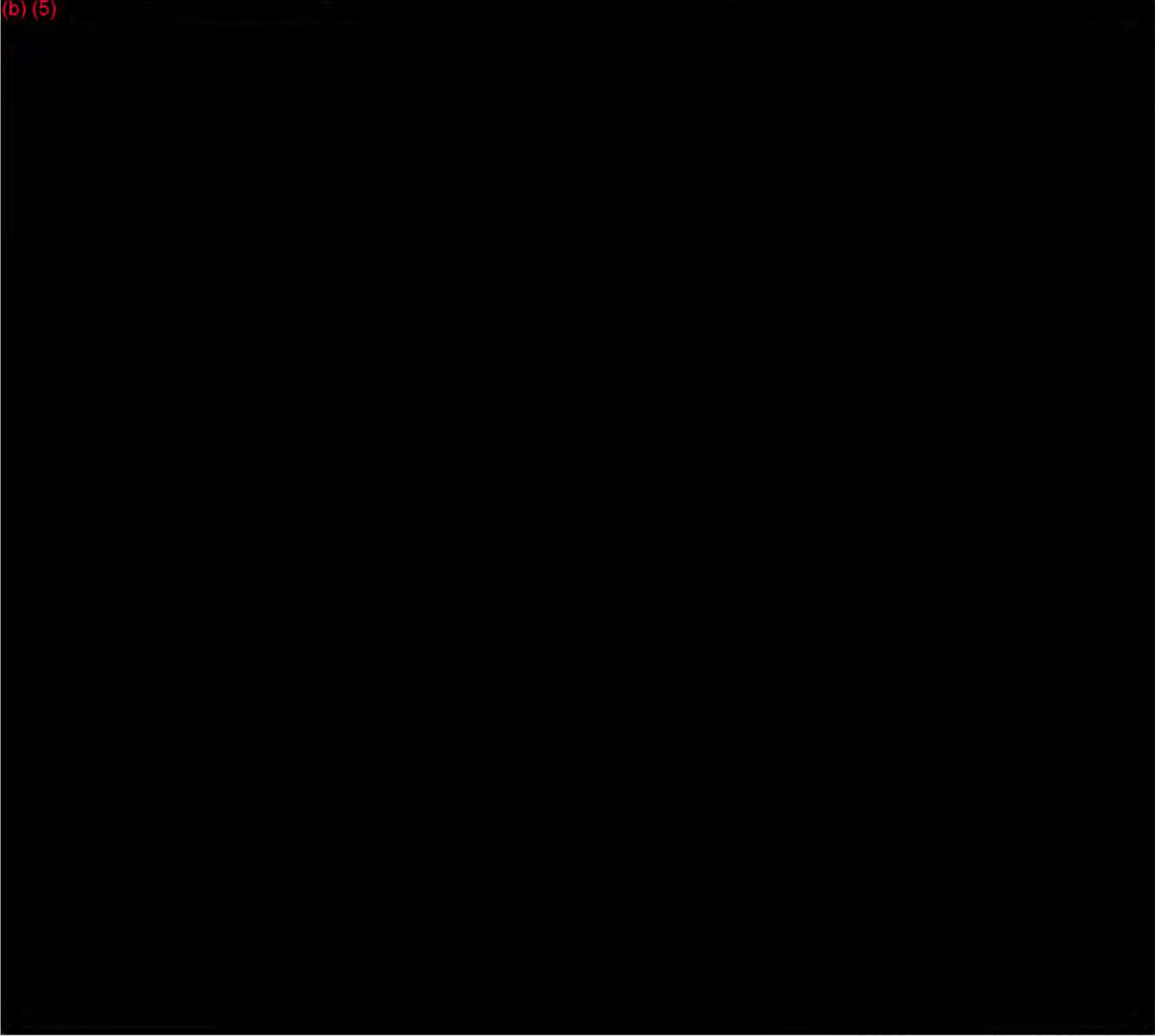
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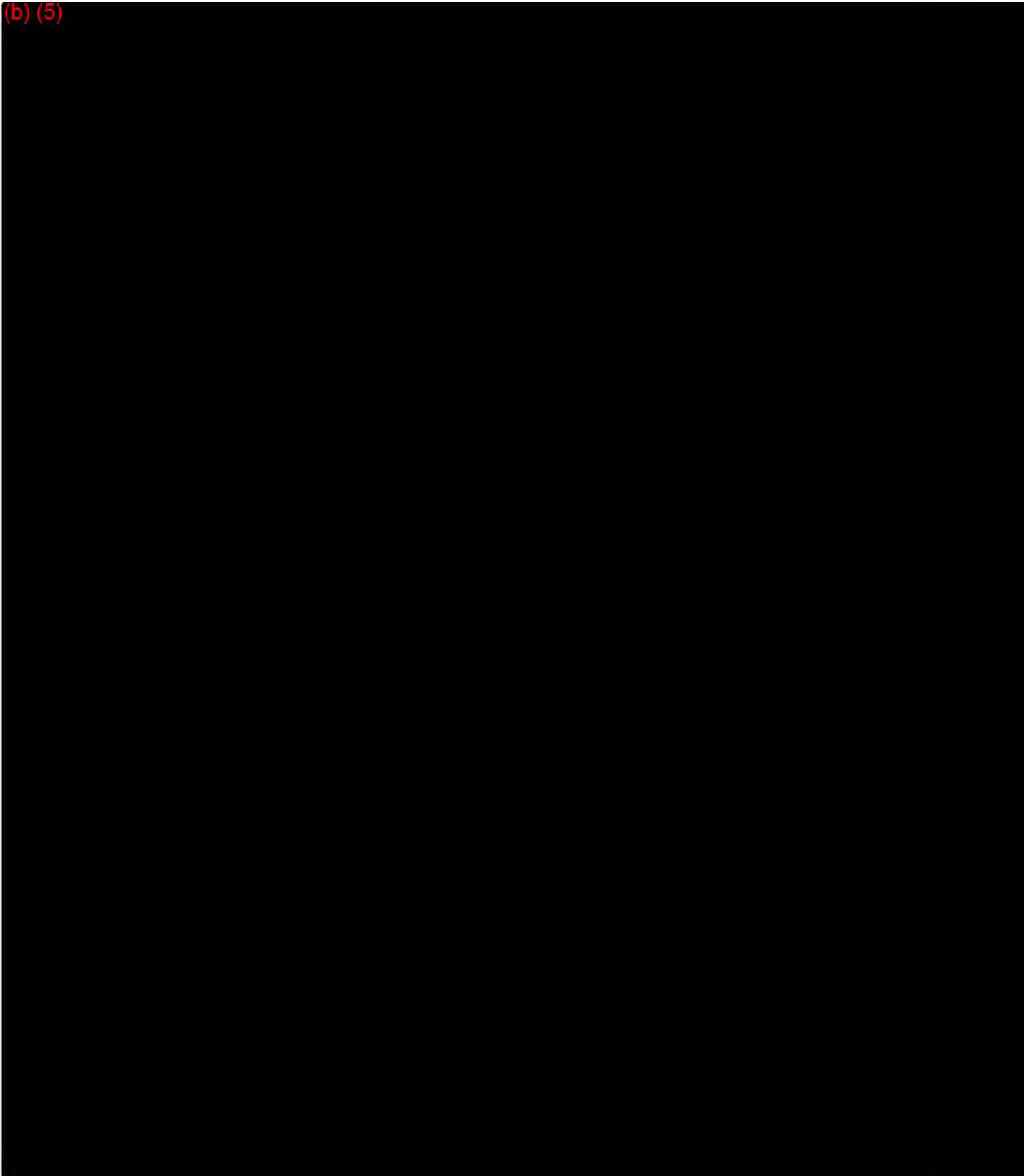
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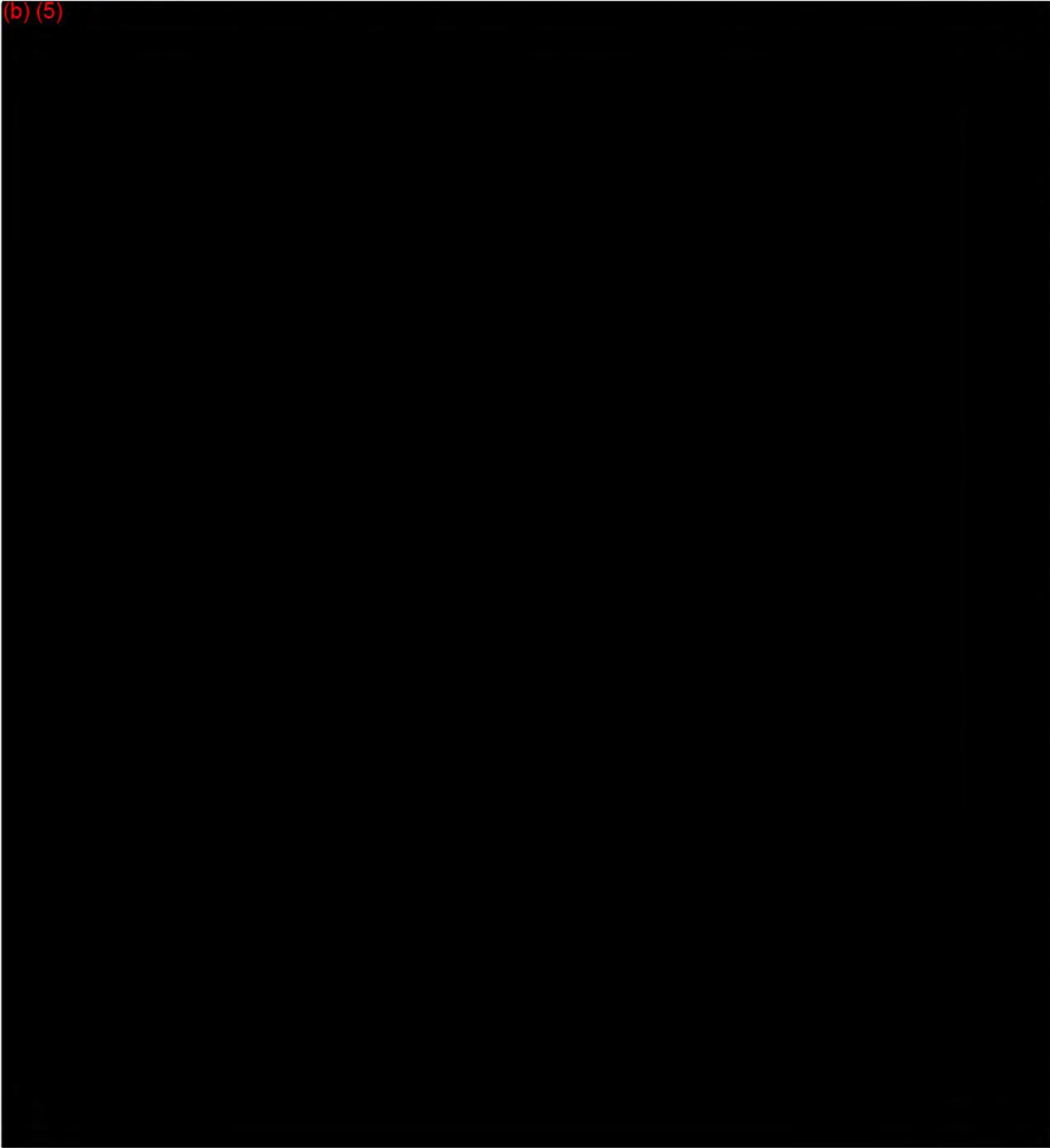
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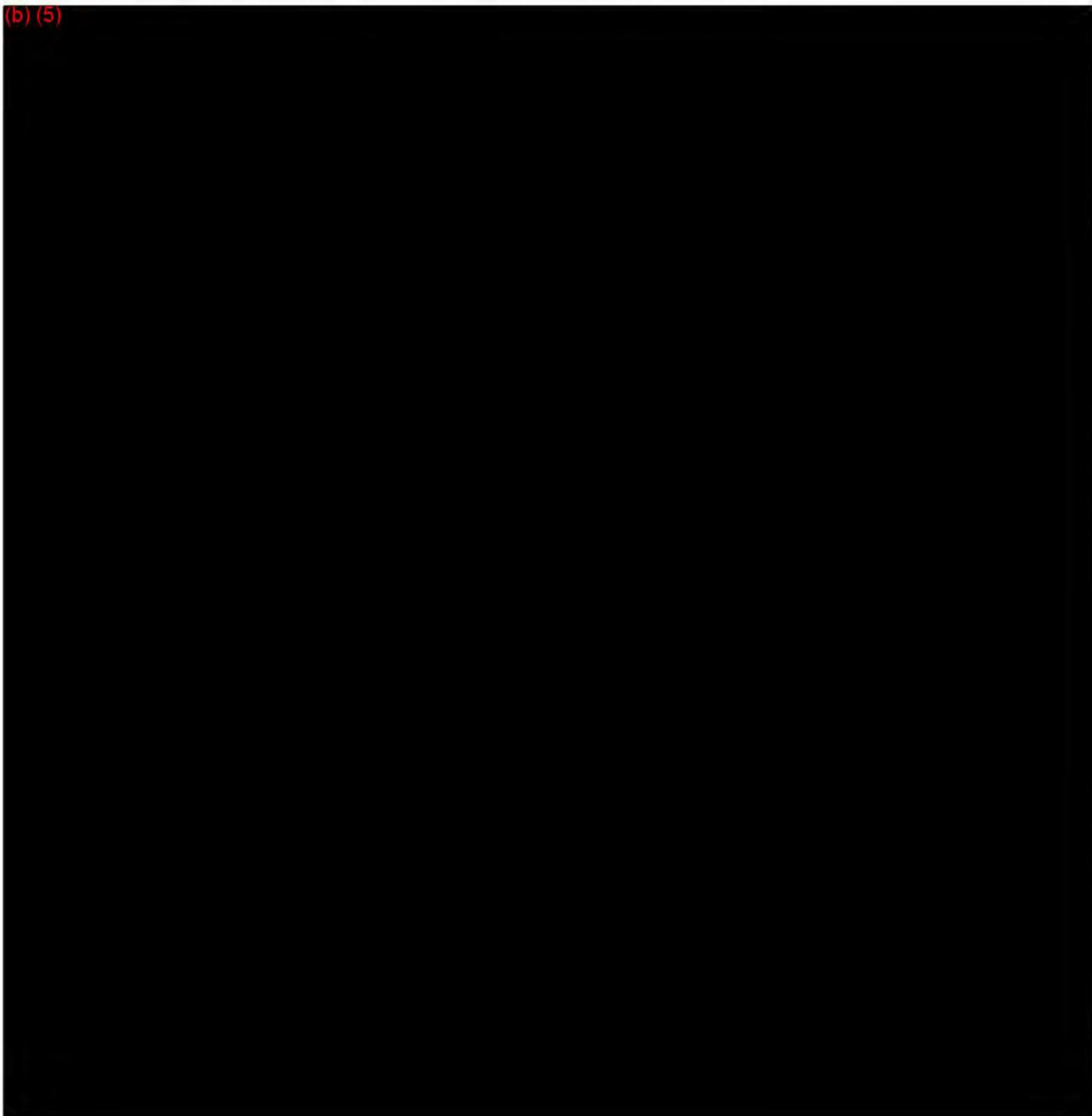
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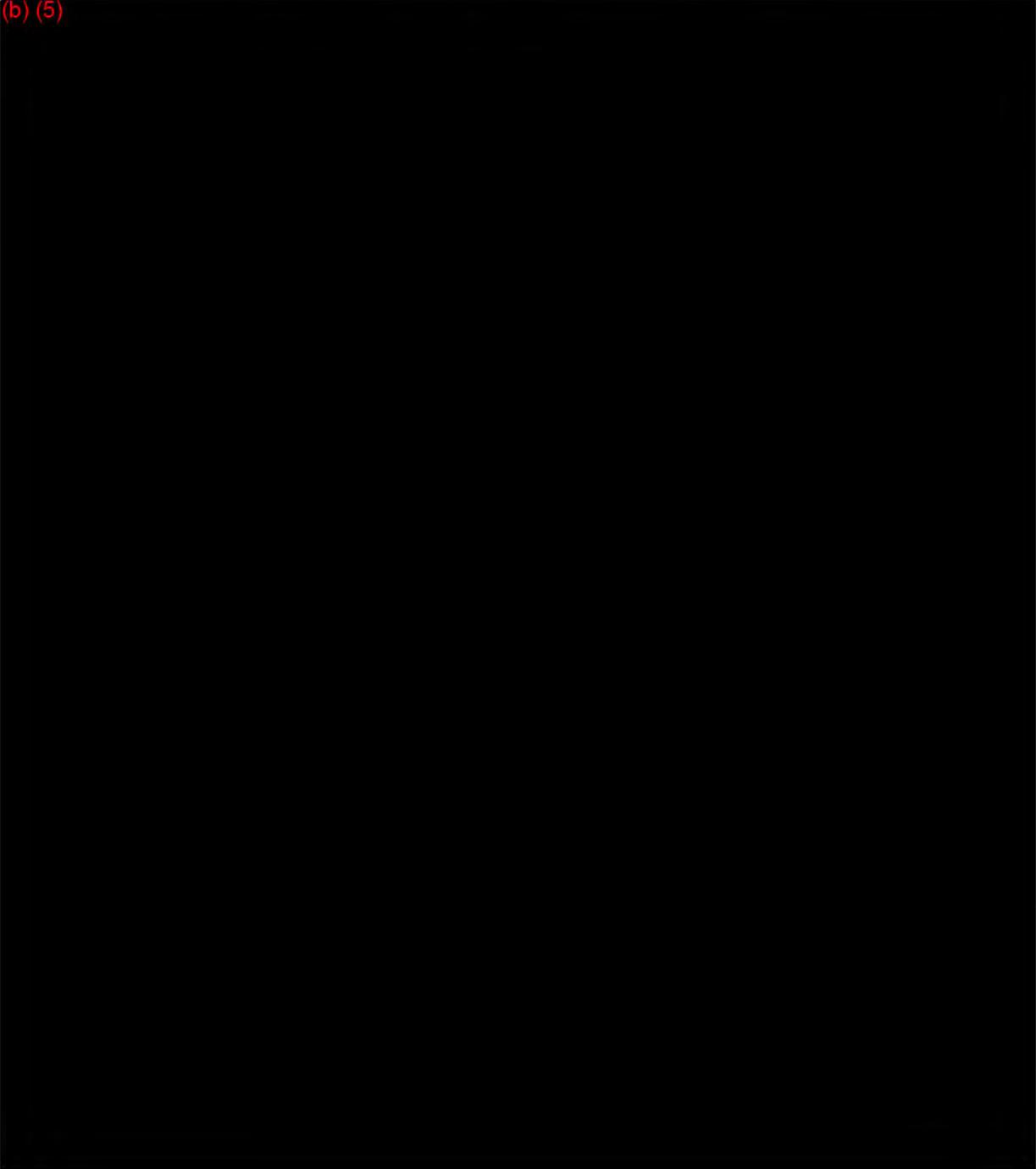
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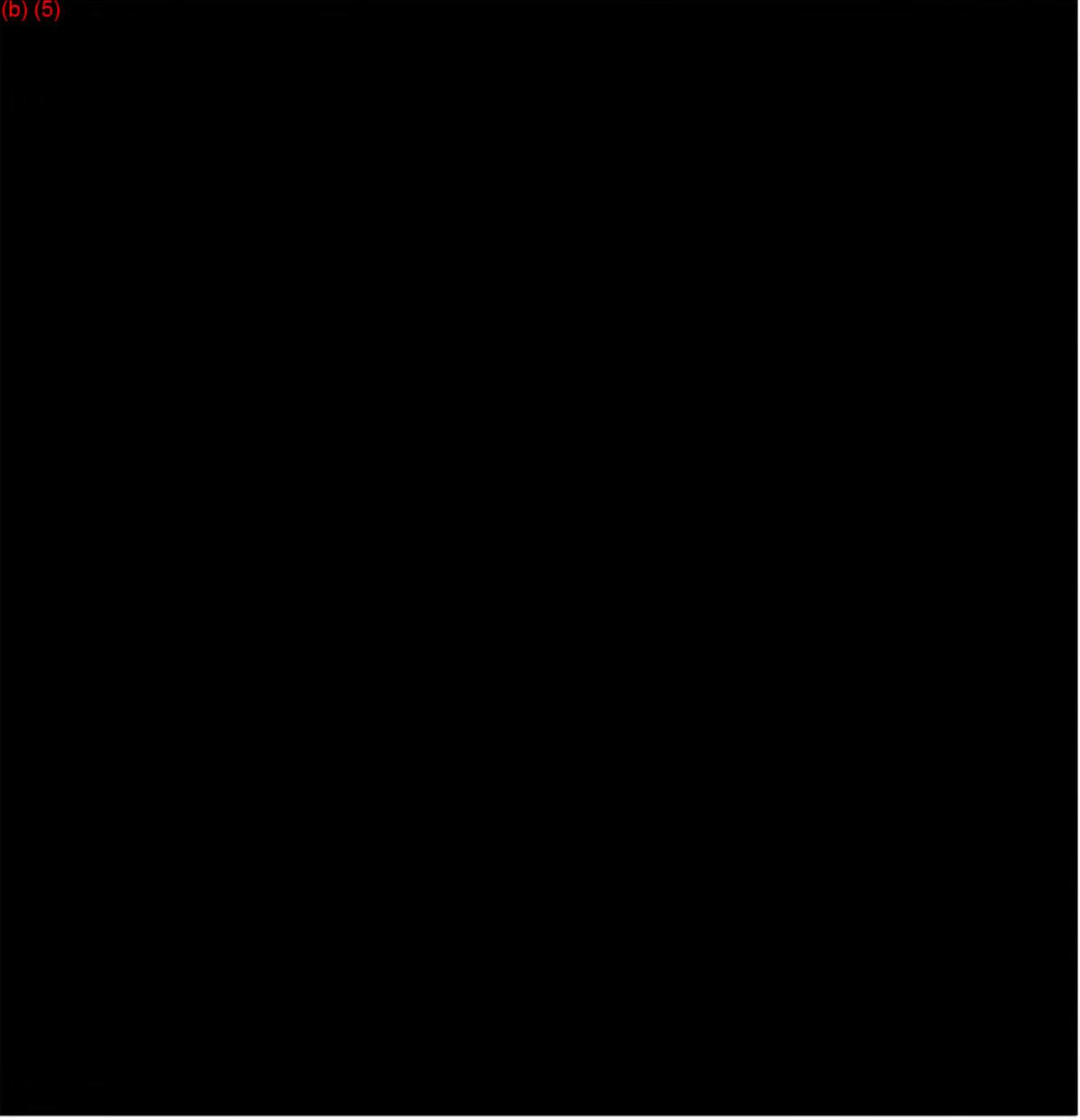
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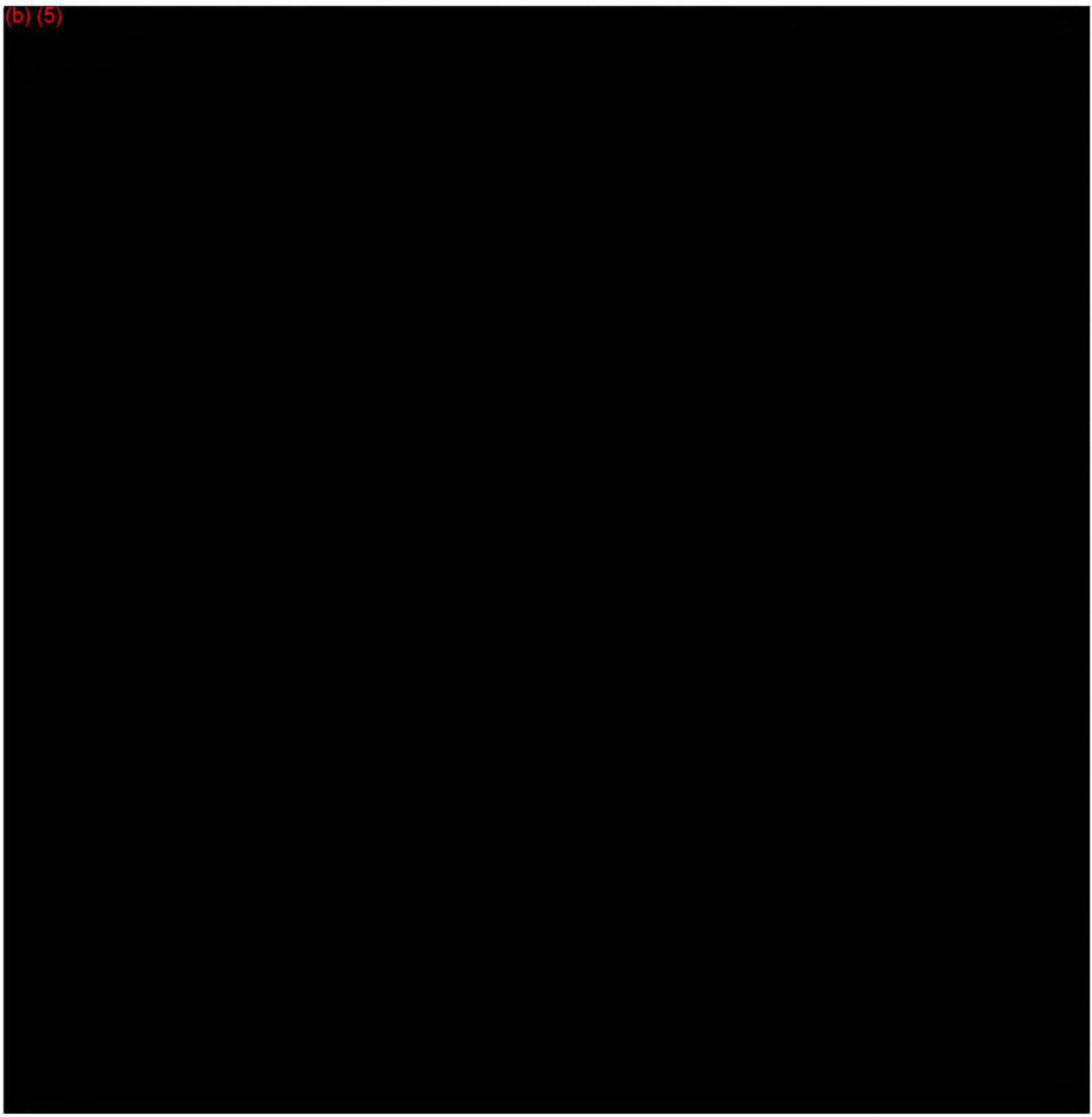
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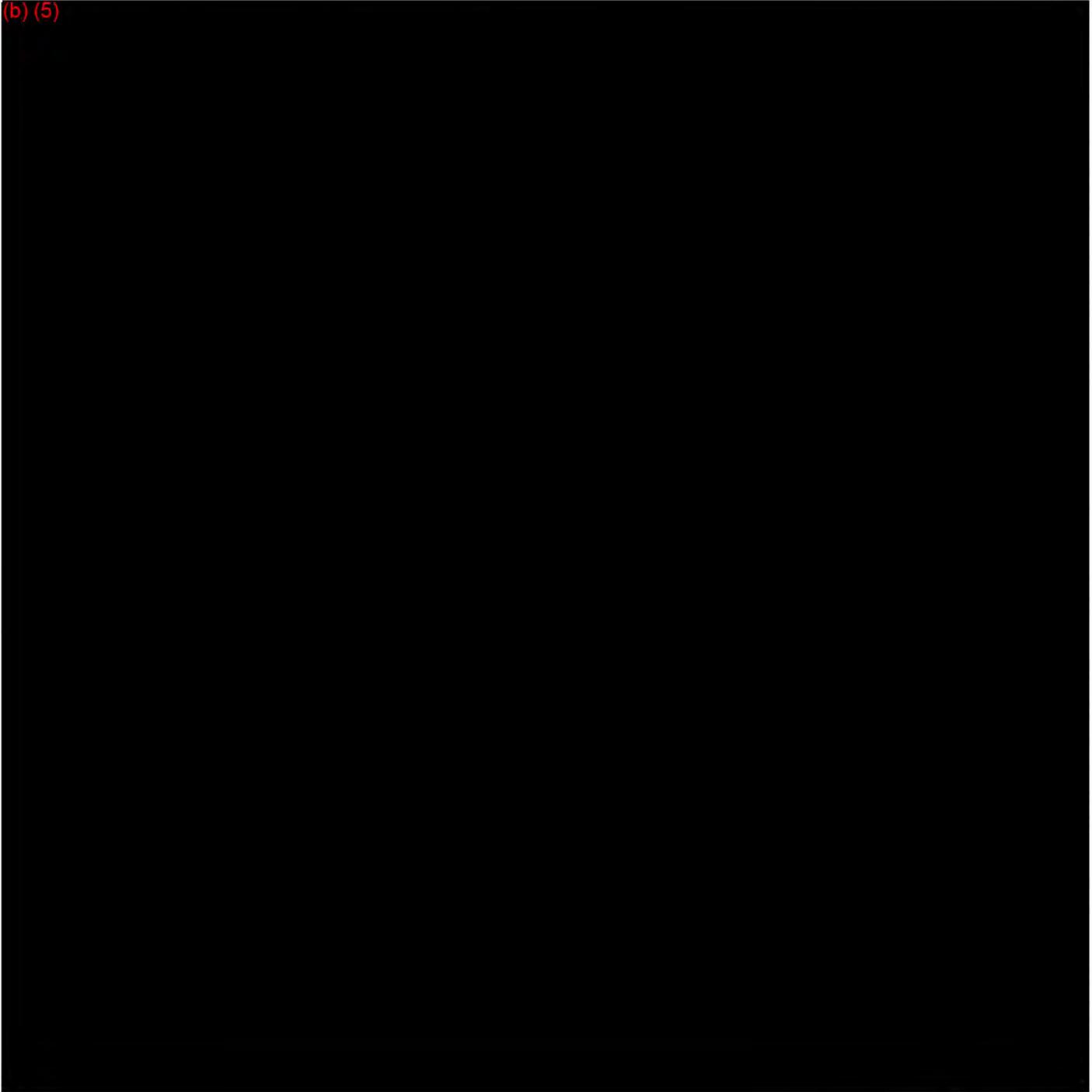
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(b) (5)



(b) (5)



(b) (5)



From: [Sherman, Rachel](#)
To: [Califf, Robert](#)
Subject: Re: memo
Date: Wednesday, September 14, 2016 6:06:06 PM

You hired a wise deputy. You should listen to her.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 14, 2016 at 5:56:22 PM EDT
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Cc: Kraus, Tom <Tom.Kraus@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>
Subject: Fwd: memo

Ouch 2

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: September 14, 2016 at 5:35:44 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Subject: RE: memo

Rob

Thanks for providing an opportunity to review your draft memo regarding the eteplirsen dispute. I am responding just to you since some of the issues I raise below are sensitive. I would be happy to speak with you privately to discuss my concerns in greater detail if you would be open to that.

I ask that you remove reference to quoting me from the July 12, 2016, e-mail that "reasonable people can disagree." I think as used it is mischaracterized and used out of context. I strongly disagree with Janet's decision and do not want my words in a single e-mail to suggest that is not the case.

As to footnote 7, I think the review team needs to weigh in, but it was my impression that use

of corticosteroids has been interpreted based on data to have changed the course of the disease in DMD. We currently have a pending NDA for use of a corticosteroid in DMD.

You note on page 3 that due to the serious defects in the development program, "it is impossible to use much of the resulting trial evidence in regulatory decision-making, including reasonable extrapolation to clinical care." Yet you later support Janet's conclusion that the sponsor has provided data from "two adequate and well-controlled trials." I can find no effort to reconcile these very different statements.

On page 4, you state "there is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence..." This implies she took these actions BEFORE reaching a decision on the application, which is clearly not correct given her statement to the review team of her intention to overrule them and approve the drug BEFORE they had completed their reviews. Keep in mind this occurred after an AC meeting at which the majority of the panel voted against both AA and full approval. It is also clear that she was prepared to approve the drug over the team's objections by the original PDUFA goal date and only reluctantly agreed to press the sponsor for additional data on dystrophin production from the ongoing open-label trial. While I am glad she agreed to go along with that request, convincing her to take what seemed like a very logical action was not easy. So, I find it hard to reconcile your statements about the process with the actions taken. Keep in mind that the usual course of action would be for the Office to issue a CR letter and then the sponsor could submit a FDRR that would first come to me and only if I supported the Office would an FDRR go to the Center Director. In this case that process was bypassed.

On page 4 you state that Dr. Woodcock "finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is "reasonably likely" to predict clinical benefit." This statement defies any sense of scientific reason (would one molecule of dystrophin be enough) and goes directly to Dr. Unger's concern that "any" level of protein seems to be enough for Janet to support approval. You then go on to reference Janet's regression analyses from her memo suggesting a correlation between dystrophin production and clinical outcomes. As I have noted to you on several occasions, I find this to be a scientifically invalid analysis that compares the endpoint value for dystrophin to a delta in a clinical endpoint. This analysis simply shows a correlation between higher levels of dystrophin, without regard to drug effect (there is no delta for dystrophin change that is due to drug), and cannot support the conclusion she reached. Your citation of this analysis is troubling.

You make reference in several places to a "totality of evidence" standard. That is not the statutory standard for demonstration of effectiveness and FDA has always stated that the statutory standard for demonstration of an effect on a surrogate endpoint for AA is the same as for regular approval (i.e., substantial evidence). Perhaps you are using "totality of evidence" to support the decision that the data provided on the surrogate are reasonably

likely to predict clinical benefit, but there must be substantial evidence of the drug's effect on the surrogate and the data are very weak to meet that standard.

You dismiss the concerns about Janet's level of involvement in this review and her role at the AC by suggesting this is simply part of her leadership style. I have worked with Janet for over 20 years and I can say without a doubt that her involvement in this case far exceeds her usual "hands on" approach. You note that there were 14 Center director briefings related to this case, that is clearly not the "norm" for how CDER operates. You also suggest that because CDER has been successful under her leadership that suggests that her intense involvement in this case does not raise concern. I see that as true, true, and unrelated. The question in this case is not whether she has overall been an effective leader of CDER, but whether she acted appropriately and without bias in the current case, something I don't think you effectively address given the evidence and the seriousness of the allegations and concerns expressed.

As to your footnote 23, there are direct statements that Janet made to the team that contradict the statements you reference from your interview with her. I am happy to discuss these statements with you further. In addition, Janet has had frequent private conversations with the sponsor and the stakeholder community. To my knowledge, she has not documented the substance of those conversations to the record, as is required under FDA regulations. That leaves a gap of knowledge to evaluate the concerns raised by the review team and Dr. Borio.

I do not find your statements about how this case does not lower the bar for future drug approvals convincing. I share the concerns voiced by Drs. Unger and Borio about the potential adverse impact on FDA's ability to reach science-based conclusions on future applications.

On page 9 it would be nice to see you call explicitly for retraction of the publications that have now been discredited.

Also on page 9 it is ironic that you attribute to Janet the idea of randomizing early in order to generate good evidence. That is exactly what the review team planned to require of Sarepta after the results of the 12-patient study became available, but it was Janet that pressed that a new randomized trial not be required. So, if Janet had followed the normal CDER process in this case the review team would have required placebo-controlled trials, as they did for drisapersen (b) (4), and we would have better data on which to make a decision. I would note that Janet did not and has not involved herself in the drisapersen (b) (4) cases to the same degree as eteplirsen. Drisapersen arguably (b) (4); they had a positive phase 2 trial and a second trial that leaned favorably on a clinical endpoint. Janet did not object to the division asking for a large phase 3 trial and did not object to ODE1's decision to to issue a CR letter based on (b) (4). I think it is reasonable to question why she devoted so much attention to eteplirsen and not the other (b) drugs. One could speculate that she too was misled by the early reports on

dystrophin production that were later discredited.

The overall tone of your memo seems to say that you conclude that Janet behaved and conducted herself appropriately in this case. That is at odds with the experience of the review team and is counter to the team-based, collegial working environment that we hope to create at FDA so we can accomplish our important public health mission. This validation from your level of her actions and behavior is worrisome. While I understand your desire not to undercut her role as Center Director, her actions have at best created a serious appearance of bias among the review team members and that has created distrust and a sense of undue pressure to "come around" to her way of thinking. Even if you uphold her decision I would think you should counsel her about how her behavior and actions have undermined her credibility among the review staff and should be avoided in future similar cases. Effective leaders must have the trust and respect of their staff. As I noted in our call last week, there are frequent disagreements about data and actions in CDER, and that is healthy and encouraged so we can ensure we hear all voices as we make decision, what is not healthy is a situation where the actions of a leader creates the appearance of bias since this undermines the trust necessary for the review team to conclude that the action was fair and move on.

I understand this appeal has placed you in a very difficult position. I also understand that you have made your decision. I hope, that my comments can help you to structure your decisional memo to avoid similar situations in the future. As you know, I had planned to retire from FDA last spring. I have delayed my departure for a variety of reasons, but one of the most important reasons is that Janet has told me she plans to serve as acting in my place as head of OND once I leave. I am very concerned about the impact of that decision on the future of the new drugs review program and would be happy to discuss those concerns further.

John

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD

Commissioner, Food and Drugs

From: [Sherman, Rachel](#)
To: [Conover, Katie](#); [Califf, Robert](#); [Kraus, Tom](#); [Dickinson, Elizabeth \(FDA\)](#); [Rodriguez, Jennifer](#)
Subject: Re: Follow up on Eteplirsen
Date: Wednesday, September 14, 2016 6:57:43 AM

I can.

Two thoughts - I think it would be enough to release Ellis' decision all memo and Janet's overrule if we need to release reviews right now. Those represent the agency decisions. But in my 18 months outside I saw the letter and labeling posted in 1 to 2 days - I don't recall a review coming out that fast. Might be worth checking with CDER.

Also, I did read the filbanserin reviews when they were posted and I do not recall seeing an appeal document.

From: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Date: September 14, 2016 at 6:49:08 AM EDT
To: Kraus, Tom <Tom.Kraus@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>, Califf, Robert <RMC1@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>
Subject: Re: Follow up on Eteplirsen

Any chance we could all talk briefly this morning?

From: Califf, Robert
Sent: Tuesday, September 13, 2016 8:52 PM
To: Dickinson, Elizabeth (FDA); Sherman, Rachel; Kraus, Tom; Conover, Katie; Rodriguez, Jennifer
Subject: FW: Follow up on Eteplirsen

See below. Open for ideas here,

rmc

From: Unger, Ellis
Sent: Tuesday, September 13, 2016 4:28 PM
To: Califf, Robert
Cc: Jenkins, John K
Subject: RE: Follow up on Eteplirsen

I will add that I would like to know when it would be OK to share Dr. Borio's memorandum with the review team. They would really appreciate being able to see it.

From: Jenkins, John K
Sent: Tuesday, September 13, 2016 3:58 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: RE: Follow up on Eteplirsen

Rob

As to the issue of when to release documents, I was just reminded that there is a statutory requirement that we release a "high level summary" review within 48 hours of NME approvals. Usually we meet this by releasing the division director review. In this case that would not make sense given that the division level review (Eric Bastings) argues against approval. I guess we could release Dr. Woodcock's memo to meet this obligation, but her memo does not really address the entire range of issues for the application that would typically be included in the division director memo. Again, my preference would be to release the documents I listed in item 5 below at the time of approval. Such an approach provides the most transparency and will avoid a "rebound" of media coverage a month or so later about the details of the internal dispute.

John

From: Califf, Robert
Sent: Sunday, September 11, 2016 7:13 AM
To: Jenkins, John K; Woodcock, Janet; Unger, Ellis
Subject: RE: Follow up on Eteplirsen

John,

Thanks for putting this list together. Much of this is in CDER's baileywick, but I want to be sure I do what I need to do. See below:

From: Jenkins, John K
Sent: Friday, September 09, 2016 4:09 PM
To: Califf, Robert; Woodcock, Janet; Unger, Ellis
Cc: Jenkins, John K
Subject: Follow up on Eteplirsen

Rob

Do we have any follow up on the items we discussed yesterday and timelines? I just had my regular meeting with Ellis and we discussed the planned action. Some issues that need to be sorted out:

1. Timeline for approval action.

My understanding is that we're aiming for a week from tomorrow. Please let me know if that is not

feasible.

2. Verification that we have reached final agreement on the labeling/PMRs with the sponsor. Ellis was not sure that there was final agreement on the labeling. Our usual practice/policy is to ensure that the sponsor has agreed to the labeling before approval, which is usually accomplished by the division sending the final draft of the label to the sponsor and the sponsor formally returning that to us indicating their concurrence. We can check to see if we have documentation of that agreement, or if there is a need to ask Sarepta to submit as final the most recent version of the labeling we sent them. Ellis can follow up and confirm the status. If there are to be any changes to the most recent version of the final draft label that the division sent to the sponsor, we would ask that we be included in reviewing those edits. Same for the PMR.

Will follow with interest.

3. Timeline for Rob to meet with review team. Since the review team will have to be involved in some of the work to finalize action on the application, we recommend this meeting occur soon.

OK with me-I want to meet with them. It's a rough couple of weeks coming up so we'll have to do some rearranging. I'm out of town Wed and Thursday of this week and in town all week next week, but have a total of 12 "events" at which I have to make remarks. But I'm sure we can work it out on the schedule.

4. Timeline for sharing Rob's review memo with Ellis and me. Ideally this should occur in advance of the meeting with the review team so we can understand the context of Rob's decision.

Will get back with you later today.

5. Plans for the press release and release of documents that support the approval. Our normal process is to release the approval letter and the labeling on the day of approval, followed some time later (I think we have 30 days) by the redacted action package. In this case, we would strongly advocate for releasing the most important memoranda at the time of approval to ensure transparency for the action. The more complete action package could then be released on the usual timeline (e.g., the CMC review, the pharm/tox review). In our view, the redacted documents that should be released at the time of approval would include the Cross Disciplinary Team Leader (CDTL) memo (Farkas), the deputy division director memo (Bastings), the ODE director decisional memo (Ellis), the Center Director decisional memo, Ellis' appeal memo, the acting Chief Scientist memo, and Rob's decisional memo. We strongly advocate for transparency in this case and if you agree these documents will need to be redacted on an expedited timeline.

Our plan has been as you say but to release all the memos at the time of all the other documents rather than with the approval letter and labeling. I have no particular reason to hold information

back other than to give people all the information at one time. Glad to continue to discuss.

6. The draft press release. Again, we strongly advocate for transparency in the press release about the differing opinions, the appeal, and how the appeal was decided.

We will be transparent. The question is timing as above.

7. Any plans for press availability to discuss the approval. In the past for controversial/high profile actions we have scheduled a media call where we describe the basis for the action and take questions from reporters. We have also often scheduled a separate briefing for stakeholders.

OEA had not planned a media call to my knowledge. For sure there will be a lot of media interest and questions.

I spent yesterday cleaning up a lot of other things and am available today if we need to talk.

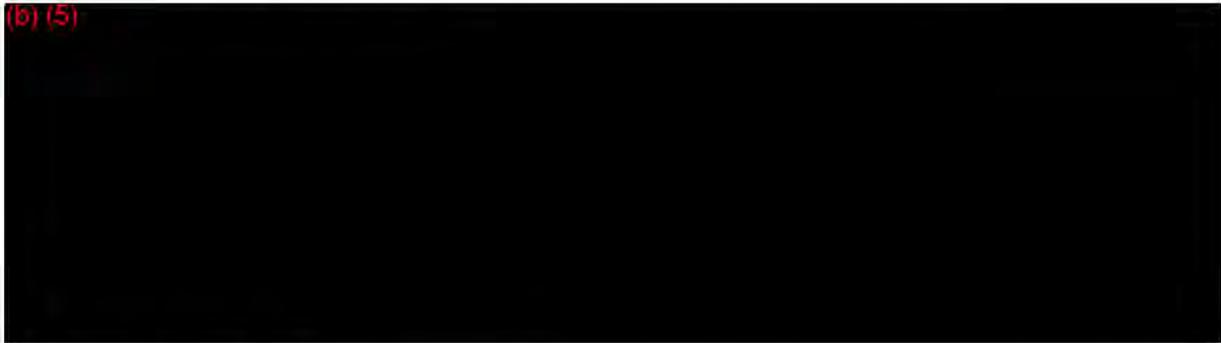
John

From: [Sherman, Rachel](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [Rodriguez, Jennifer](#); [Kraus, Tom](#); [Califf, Robert](#); [Conover, Katie](#)
Subject: RE: Follow up on Eteplirsen
Date: Wednesday, September 14, 2016 7:58:59 AM

Please see my next email (from this am, not last night). I agree with Liz.

From: Dickinson, Elizabeth (FDA)
Sent: Wednesday, September 14, 2016 7:56 AM
To: Sherman, Rachel; Rodriguez, Jennifer; Kraus, Tom; Califf, Robert; Conover, Katie
Subject: RE: Follow up on Eteplirsen

(b) (5)



From: Sherman, Rachel
Sent: Tuesday, September 13, 2016 10:35 PM
To: Rodriguez, Jennifer; Kraus, Tom; Califf, Robert; Dickinson, Elizabeth (FDA); Conover, Katie
Subject: Re: Follow up on Eteplirsen

Based on what he said, I would suggest releasing Ellis' on up.

I agree the review team should see first. Can we a matter of hours.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 13, 2016 at 8:52:21 PM EDT
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Kraus, Tom <Tom.Kraus@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>
Subject: FW: Follow up on Eteplirsen

See below. Open for ideas here.

rmc

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To: Califf, Robert
Cc: Jenkins, John K

Subject: RE: Follow up on Eteplirsen

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Cc: Jenkins, John K
Subject: RE: Follow up on Eteplirsen

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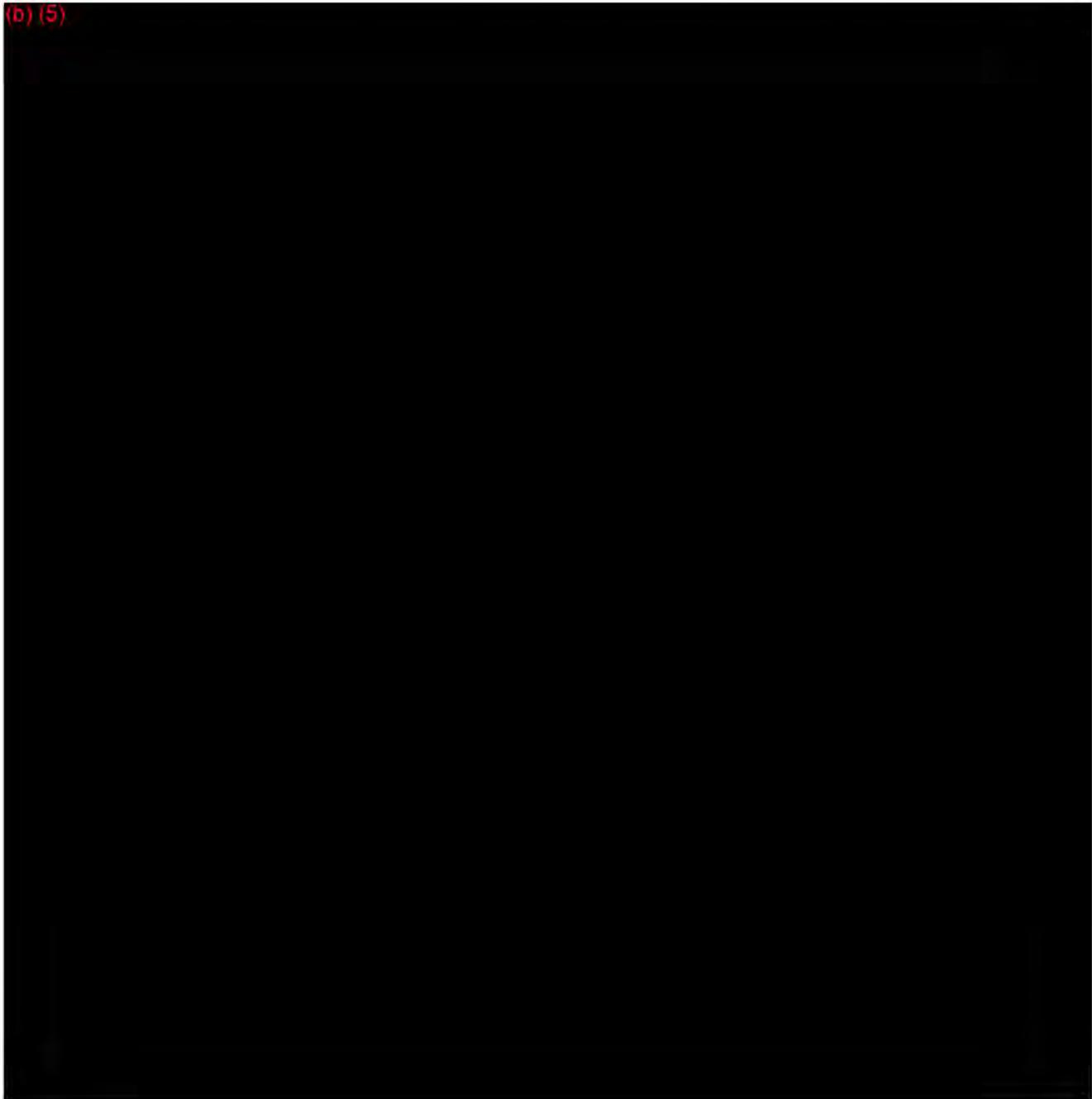
John

From: [Borio, Luciana](#)
To: [Califf, Robert](#); [Woodcock, Janet](#); [Jenkins, John K](#); [Unger, Ellis](#)
Subject: RE: memo
Date: Wednesday, September 14, 2016 5:29:46 PM
Attachments: [2016_Sept_012_R2_Eteplirsen_CLEAN Borio.doc](#)

Dear Dr. Califf,

Thank you for the opportunity to review a draft of your decisional memo on Dr. Unger's appeal related to eteplirsen. Attached is a red-line version with some minor edits (to ensure accuracy) and two embedded comments. I have a few overarching comments that I include here:

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(b) (5)

I would be glad to discuss any concerns or questions you might have about my comments or suggested edits.

Sincerely,

Luciana Borio, M.D.
Acting Chief Scientist
Food and Drug Administration
White Oak Building 1, Room 3317
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel. (301)796-4637

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

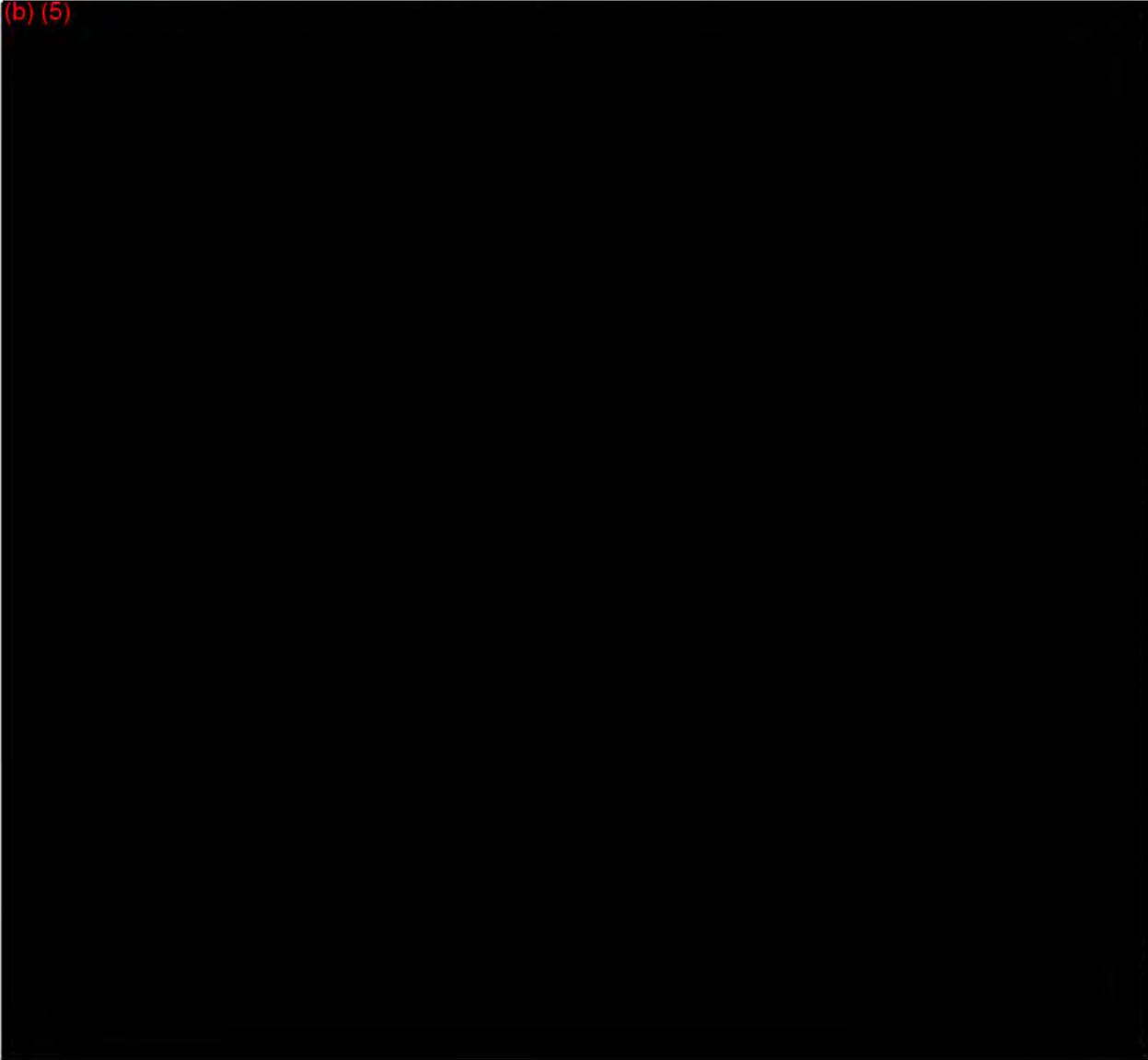
I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD

Commissioner, Food and Drugs

**Scientific Dispute Regarding Approval of Sarepta Therapeutics'
Eteplirsen – Commissioner's Decision**

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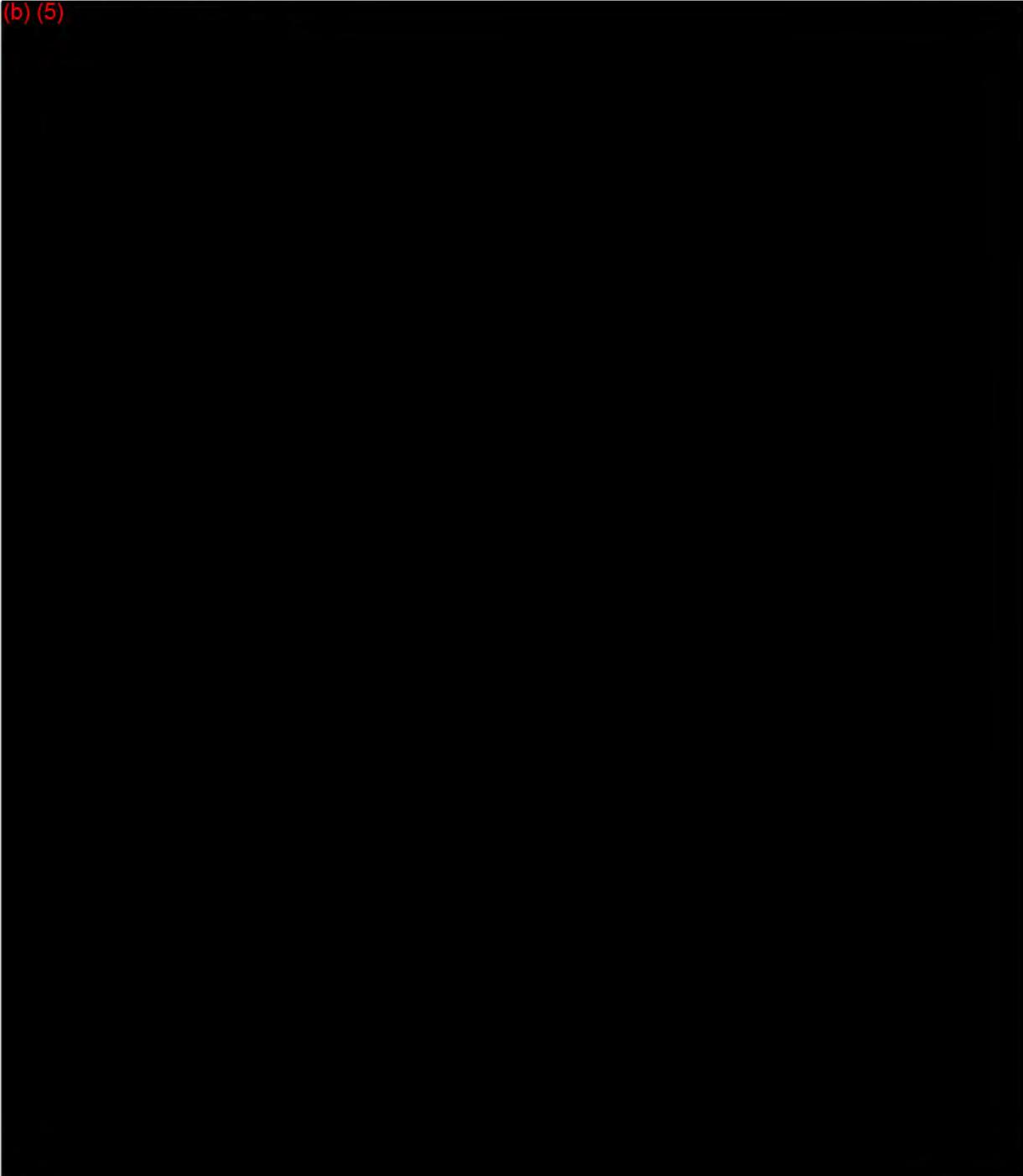


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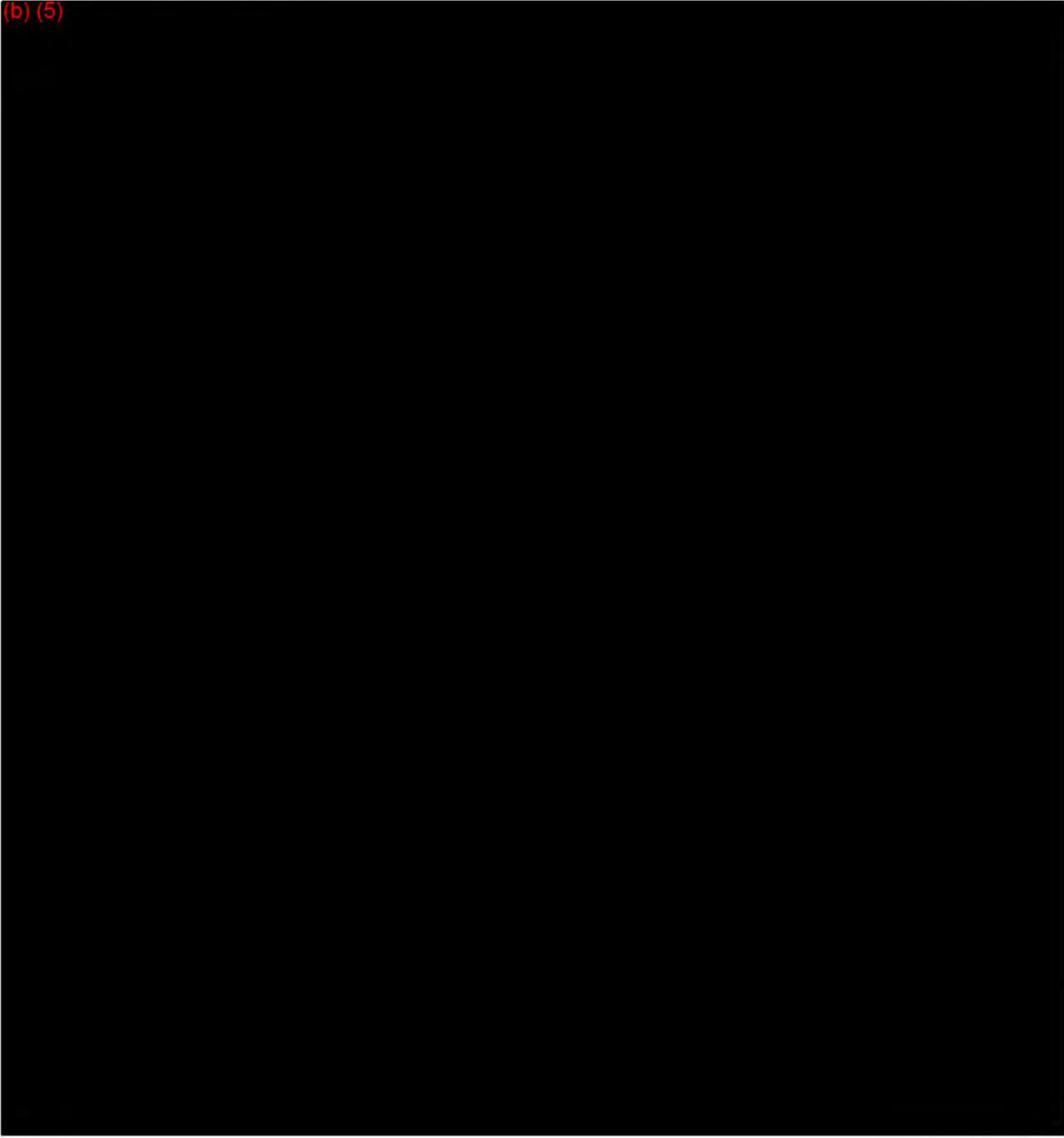
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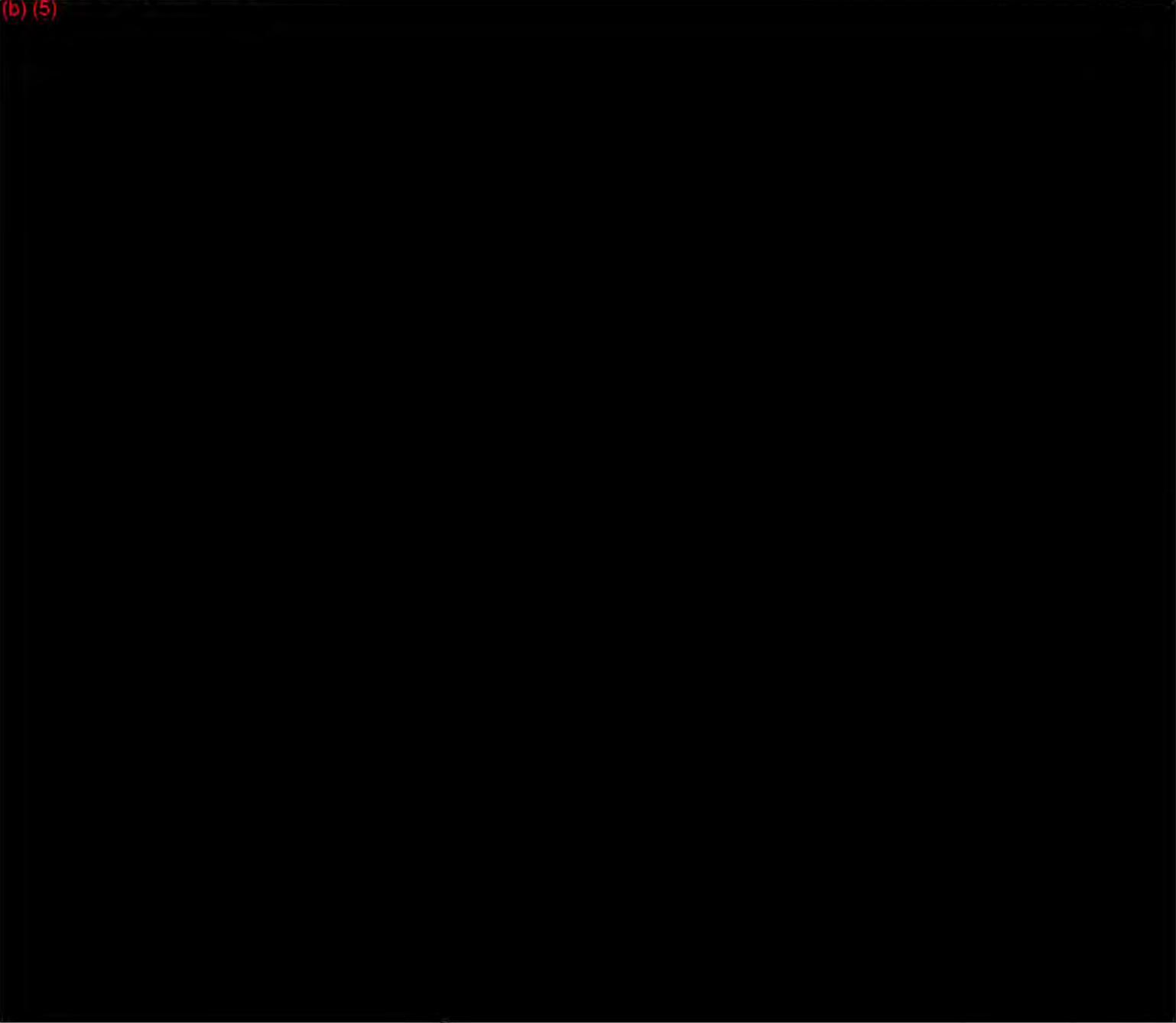


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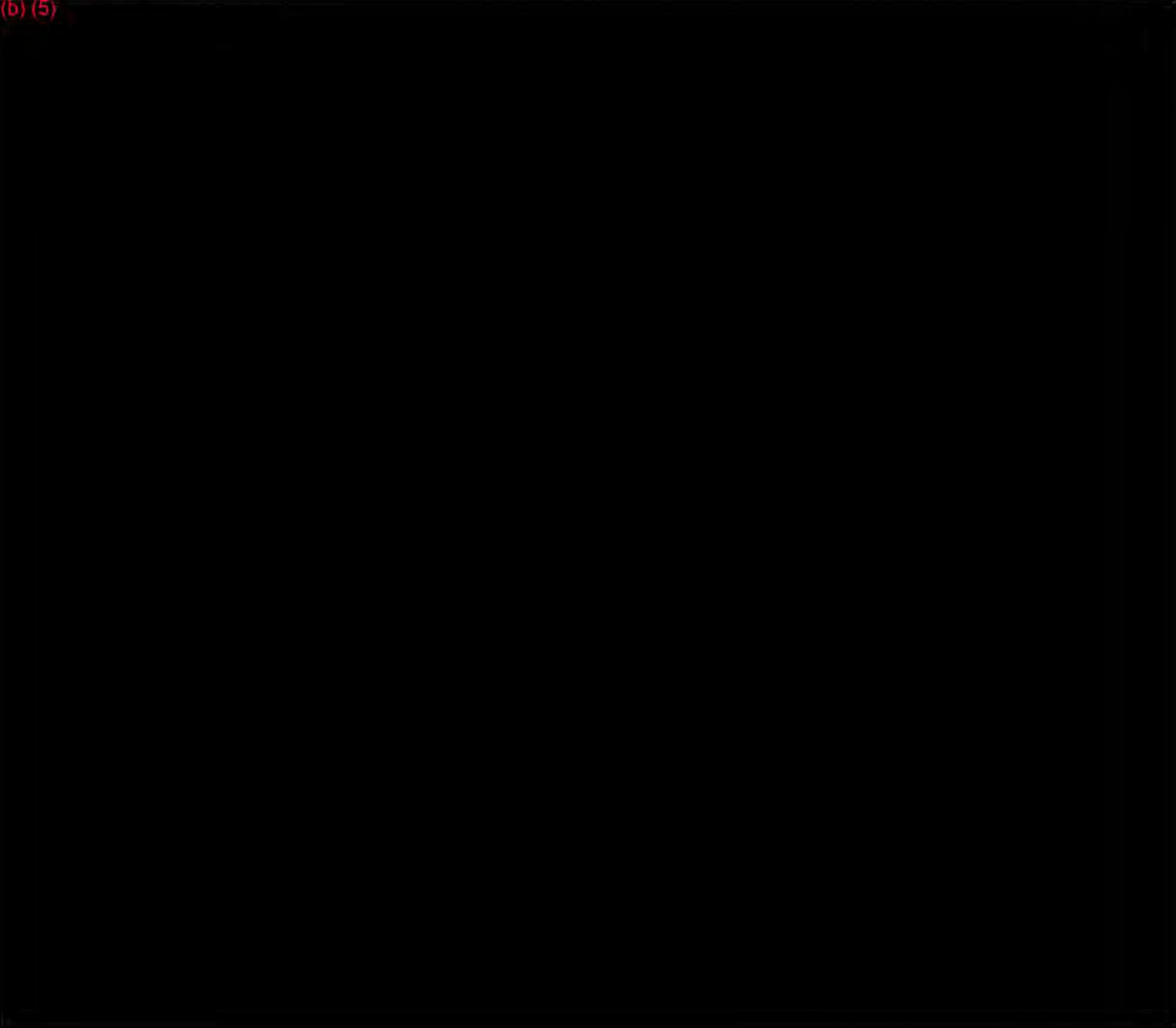
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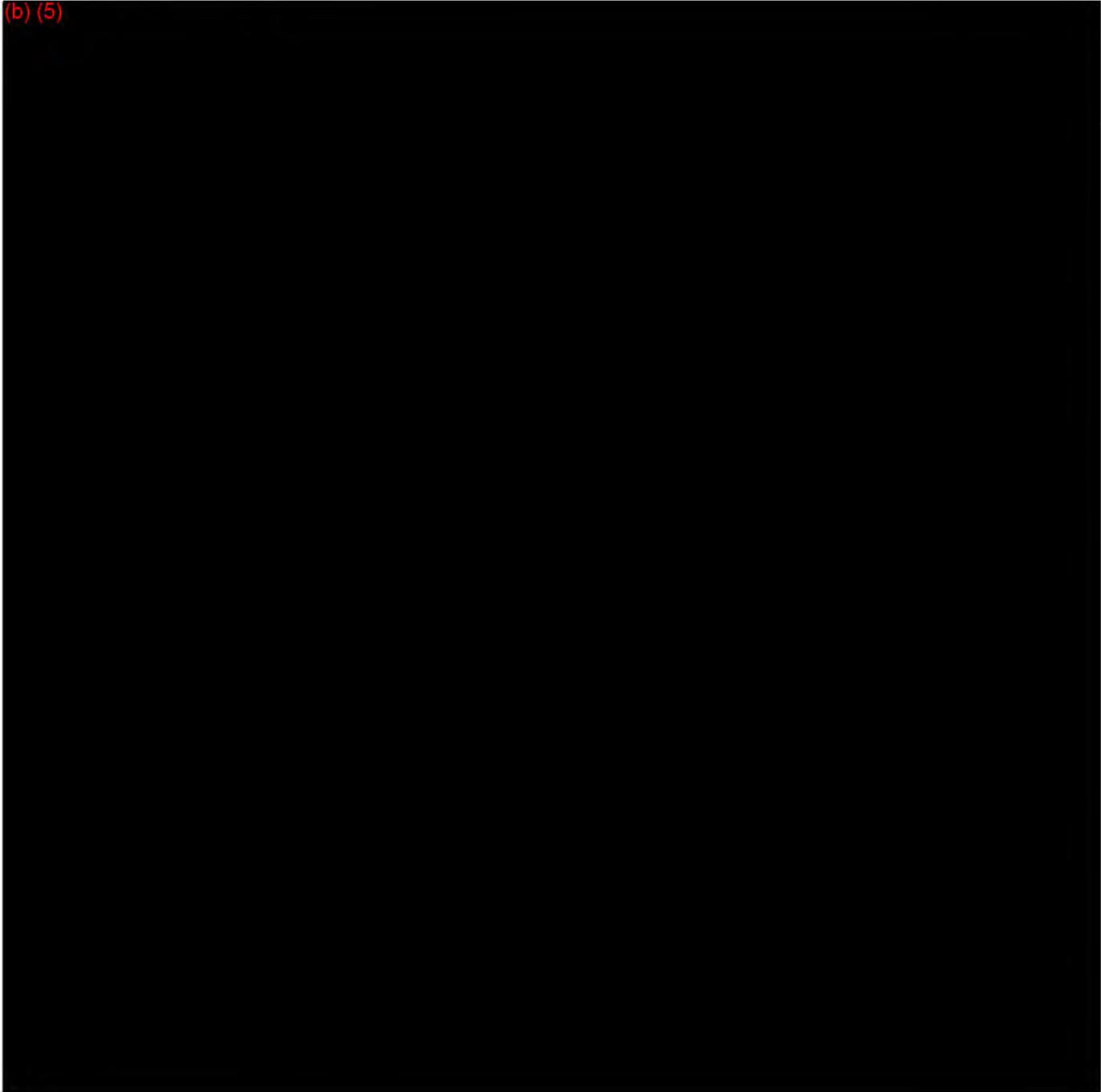


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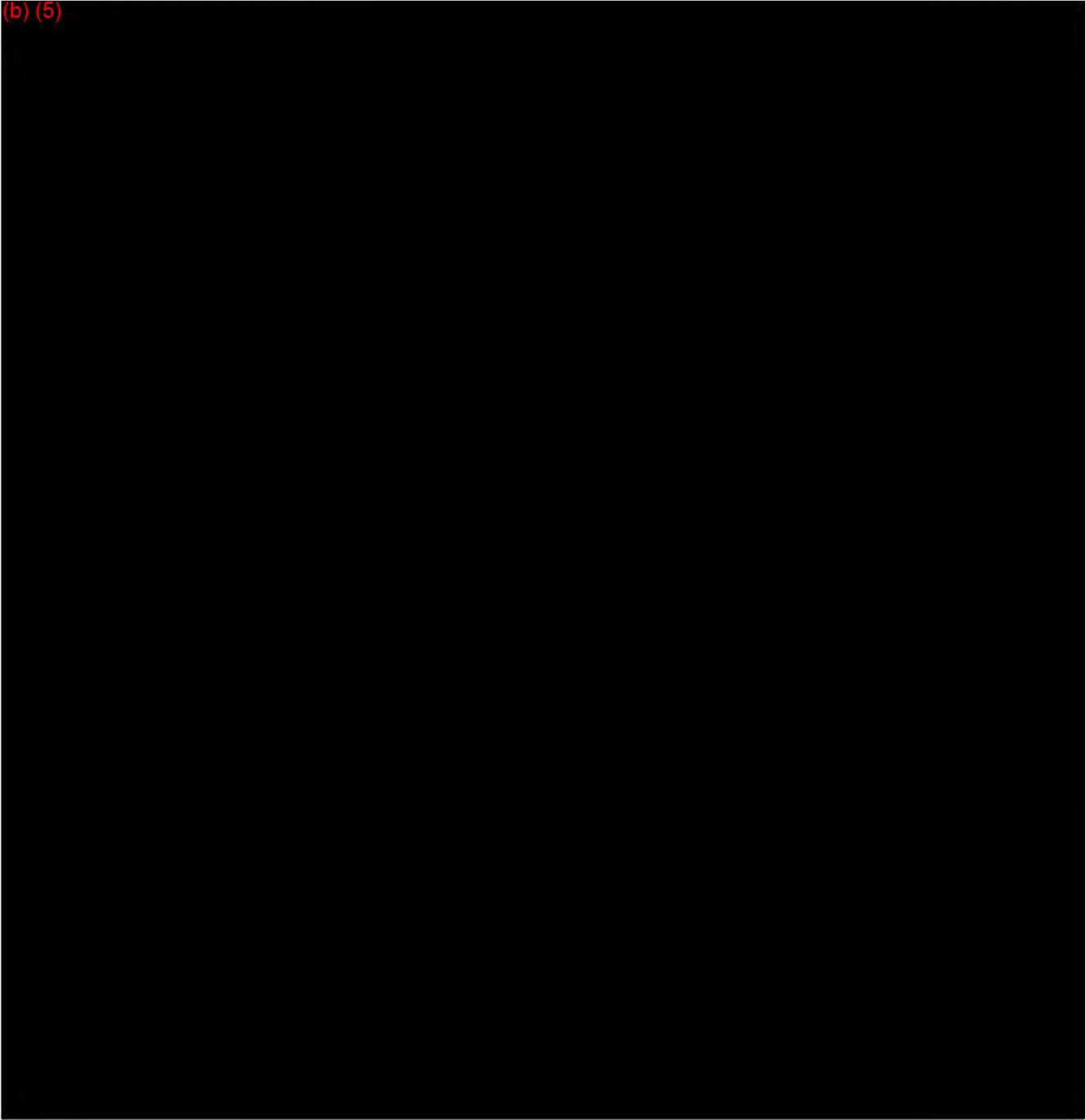


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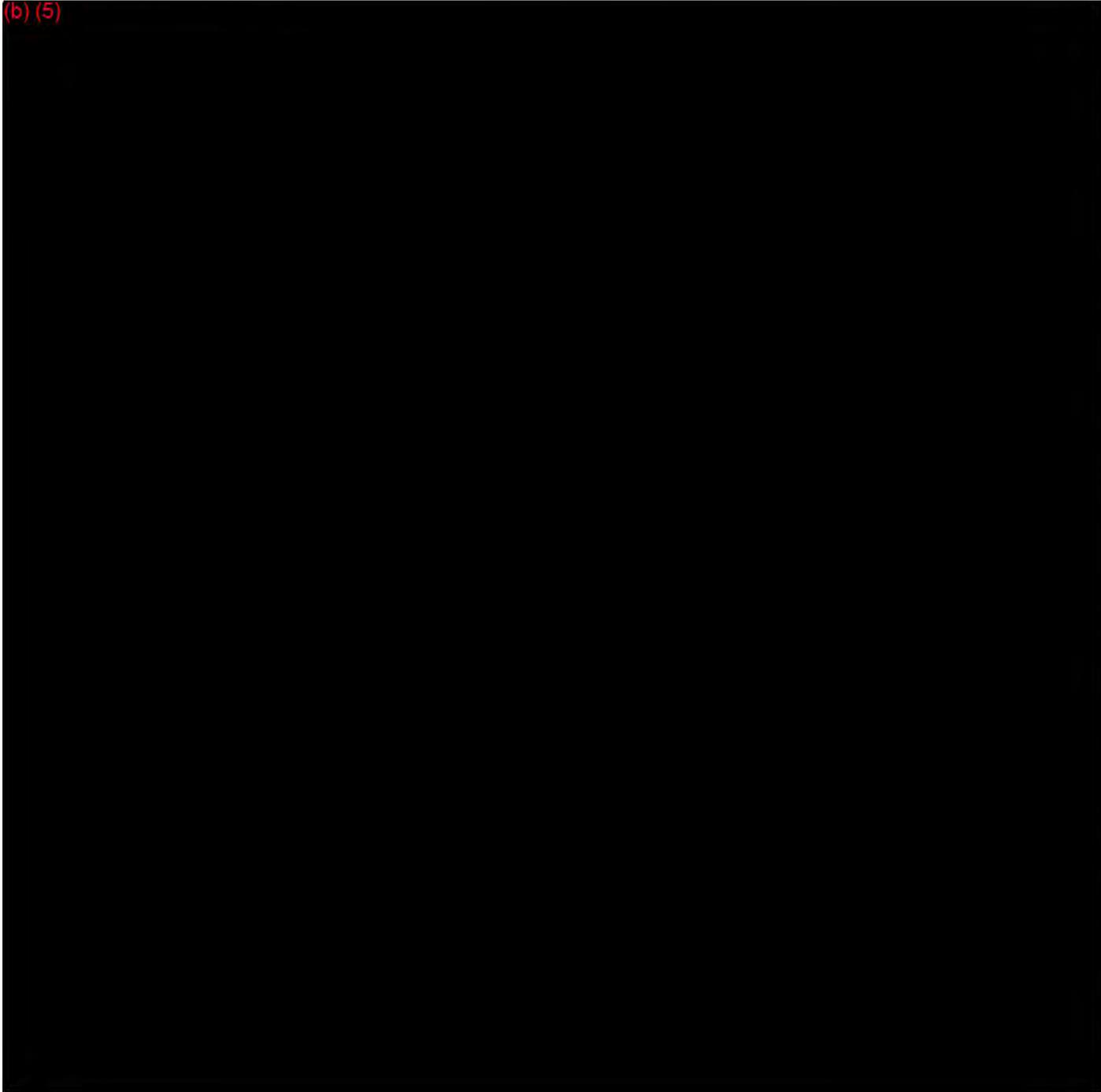


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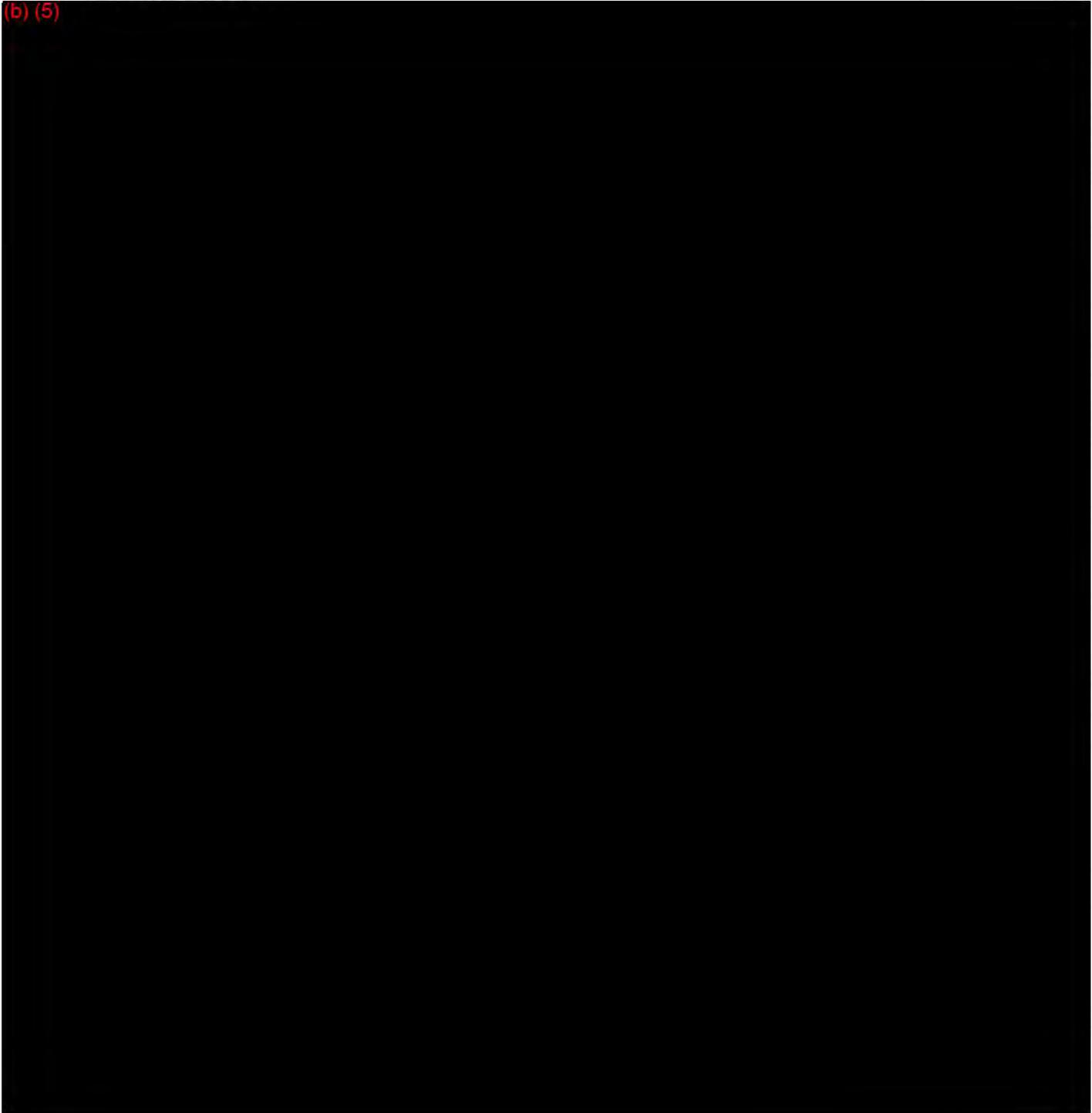


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PROCESS/CONFIDENTIAL

(b) (5)



| DRAFT RMC ~~8/14/2017 11:24 AM~~ ~~9/14/2016 5:03 PM~~ ~~9/14/2016 10:45 AM~~ DELIBERATIVE
PROCESS/CONFIDENTIAL

(b) (5)



From: Sherman, Rachel
To: Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo
Date: Wednesday, September 14, 2016 8:58:49 PM

Hi all,

I had a long chat with Deborah. She had a nice addition, something to the effect that (b) (5)

[REDACTED]

Rachel

From: Sherman, Rachel
Sent: Wednesday, September 14, 2016 6:55 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Just you, Liz and Jonathan,

If you like the email below I will ask Jonathan to tune up and then we will get it to Liz.

I am very conscious that others have been quoted in other memos and did not have the opportunity to object. That point was the only one that gave me pause. The others are (to use Liz's phrase) relitigating a decision you have already made.

I almost added a statement about not wanting to hold up the action but I think that's implied and best left off.

Rachel

Dear John,

(b) (5)

[REDACTED]

Best regards,
Rob

From: Califf, Robert
Sent: Wednesday, September 14, 2016 5:56 PM
To: Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Conover, Katie; Kraus, Tom
Subject: Fwd: memo

Ouch 2

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: September 14, 2016 at 5:35:44 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Subject: RE: memo

Rob

Thanks for providing an opportunity to review your draft memo regarding the eteplirsen dispute. I am responding just to you since some of the issues I raise below are sensitive. I would be happy to speak with you privately to discuss my concerns in greater detail if you would be open to that.

I ask that you remove reference to quoting me from the July 12, 2016, e-mail that "reasonable people can disagree." I think as used it is mischaracterized and used out of context. I strongly disagree with Janet's decision and do not want my words in a single e-mail to suggest that is not the case.

As to footnote 7, I think the review team needs to weigh in, but it was my impression that use of corticosteroids has been interpreted based on data to have changed the course of the disease in DMD. We currently have a pending NDA for use of a corticosteroid in DMD.

You note on page 3 that due to the serious defects in the development program, "it is impossible to use much of the resulting trial evidence in regulatory decision-making, including reasonable extrapolation to clinical care." Yet you later support Janet's conclusion that the sponsor has provided data from "two adequate and well-controlled trials." I can find no effort to reconcile these very different statements.

On page 4, you state “there is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence...” This implies she took these actions BEFORE reaching a decision on the application, which is clearly not correct given her statement to the review team of her intention to overrule them and approve the drug BEFORE they had completed their reviews. Keep in mind this occurred after an AC meeting at which the majority of the panel voted against both AA and full approval. It is also clear that she was prepared to approve the drug over the team’s objections by the original PDUFA goal date and only reluctantly agreed to press the sponsor for additional data on dystrophin production from the ongoing open-label trial. While I am glad she agreed to go along with that request, convincing her to take what seemed like a very logical action was not easy. So, I find it hard to reconcile your statements about the process with the actions taken. Keep in mind that the usual course of action would be for the Office to issue a CR letter and then the sponsor could submit a FDRR that would first come to me and only if I supported the Office would an FDRR go to the Center Director. In this case that process was bypassed.

On page 4 you state that Dr. Woodcock “finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is “reasonably likely” to predict clinical benefit.” This statement defies any sense of scientific reason (would one molecule of dystrophin be enough) and goes directly to Dr. Unger’s concern that “any” level of protein seems to be enough for Janet to support approval. You then go on to reference Janet’s regression analyses from her memo suggesting a correlation between dystrophin production and clinical outcomes. As I have noted to you on several occasions, I find this to be a scientifically invalid analysis that compares the endpoint value for dystrophin to a delta in a clinical endpoint. This analysis simply shows a correlation between higher levels of dystrophin, without regard to drug effect (there is no delta for dystrophin change that is due to drug), and cannot support the conclusion she reached. Your citation of this analysis is troubling.

You make reference in several places to a “totality of evidence” standard. That is not the statutory standard for demonstration of effectiveness and FDA has always stated that the statutory standard for demonstration of an effect on a surrogate endpoint for AA is the same as for regular approval (i.e., substantial evidence). Perhaps you are using “totality of evidence” to support the decision that the data provided on the surrogate are reasonably likely to predict clinical benefit, but there must be substantial evidence of the drug’s effect on the surrogate and the data are very weak to meet that standard.

You dismiss the concerns about Janet’s level of involvement in this review and her role at the AC by suggesting this is simply part of her leadership style. I have worked with Janet for over 20 years and I can say without a doubt that her involvement in this case far exceeds her usual “hands on” approach. You note that there were 14 Center director briefings related to this case, that is clearly not the “norm” for how CDER operates. You also suggest that because CDER has been successful under her leadership that suggests that her intense involvement in

this case does not raise concern. I see that as true, true, and unrelated. The question in this case is not whether she has overall been an effective leader of CDER, but whether she acted appropriately and without bias in the current case, something I don't think you effectively address given the evidence and the seriousness of the allegations and concerns expressed.

As to your footnote 23, there are direct statements that Janet made to the team that contradict the statements you reference from your interview with her. I am happy to discuss these statements with you further. In addition, Janet has had frequent private conversations with the sponsor and the stakeholder community. To my knowledge, she has not documented the substance of those conversations to the record, as is required under FDA regulations. That leaves a gap of knowledge to evaluate the concerns raised by the review team and Dr. Borio.

I do not find your statements about how this case does not lower the bar for future drug approvals convincing. I share the concerns voiced by Drs. Unger and Borio about the potential adverse impact on FDA's ability to reach science-based conclusions on future applications.

On page 9 it would be nice to see you call explicitly for retraction of the publications that have now been discredited.

Also on page 9 it is ironic that you attribute to Janet the idea of randomizing early in order to generate good evidence. That is exactly what the review team planned to require of Sarepta after the results of the 12-patient study became available, but it was Janet that pressed that a new randomized trial not be required. So, if Janet had followed the normal CDER process in this case the review team would have required placebo-controlled trials, as they did for drisapersen (b) (4), and we would have better data on which to make a decision. I would note that Janet did not and has not involved herself in the drisapersen (b) (4) cases to the same degree as eteplirsen. Drisapersen arguably (b) (4) they had a positive phase 2 trial and a second trial that leaned favorably on a clinical endpoint. Janet did not object to the division asking for a large phase 3 trial and did not object to ODE1's decision to to issue a CR letter based on (b) (4). I think it is reasonable to question why she devoted so much attention to eteplirsen and not the other (b) (4) drugs. One could speculate that she too was misled by the early reports on dystrophin production that were later discredited.

The overall tone of your memo seems to say that you conclude that Janet behaved and conducted herself appropriately in this case. That is at odds with the experience of the review team and is counter to the team-based, collegial working environment that we hope to create at FDA so we can accomplish our important public health mission. This validation from your level of her actions and behavior is worrisome. While I understand your desire not to undercut her role as Center Director, her actions have at best created a serious appearance of bias among the review team members and that has created distrust and a sense of undue pressure

to “come around” to her way of thinking. Even if you uphold her decision I would think you should counsel her about how her behavior and actions have undermined her credibility among the review staff and should be avoided in future similar cases. Effective leaders must have the trust and respect of their staff. As I noted in our call last week, there are frequent disagreements about data and actions in CDER, and that is healthy and encouraged so we can ensure we hear all voices as we make decision, what is not healthy is a situation where the actions of a leader creates the appearance of bias since this undermines the trust necessary for the review team to conclude that the action was fair and move on.

I understand this appeal has placed you in a very difficult position. I also understand that you have made your decision. I hope, that my comments can help you to structure your decisional memo to avoid similar situations in the future. As you know, I had planned to retire from FDA last spring. I have delayed my departure for a variety of reasons, but one of the most important reasons is that Janet has told me she plans to serve as acting in my place as head of OND once I leave. I am very concerned about the impact of that decision on the future of the new drugs review program and would be happy to discuss those concerns further.
John

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board’s memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect

extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD
Commissioner, Food and Drugs

From: [Califf, Robert](#)
To: [McCall, Jonathan *](#)
Cc: [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Kraus, Tom](#); [Conover, Katie](#); [Rodriguez, Jennifer](#)
Subject: RE: Eteplirsen decision memo and supporting materials for your review
Date: Thursday, September 15, 2016 9:15:00 PM
Attachments: [20160915 Memo to File re Commissioner Decision 9-15-16_JMrs\(occ\)_CLEAN_rmc.doc](#)

Comments added. Hopefully this will do it. Should be easy for you to check out.

rmc

From: McCall, Jonathan *
Sent: Thursday, September 15, 2016 4:56 PM
To: Califf, Robert
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom
Subject: Eteplirsen decision memo and supporting materials for your review

Hello Dr. Califf –

Here is the current version of the eteplirsen memo:

<< File: 2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ).doc >> << File: 2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ)_Commented.doc >>

Here is the memo to file:

<< File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN.doc >> << File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_COMMENTED.doc >>

And here are the response cover notes:

<< File: 20160915 response notesrs_JM_CLEAN.doc >> << File: 20160915 response notesrs_JM_TRACKED.doc >>

Thanks!

--

Jonathan

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Attorney-Client Privilege

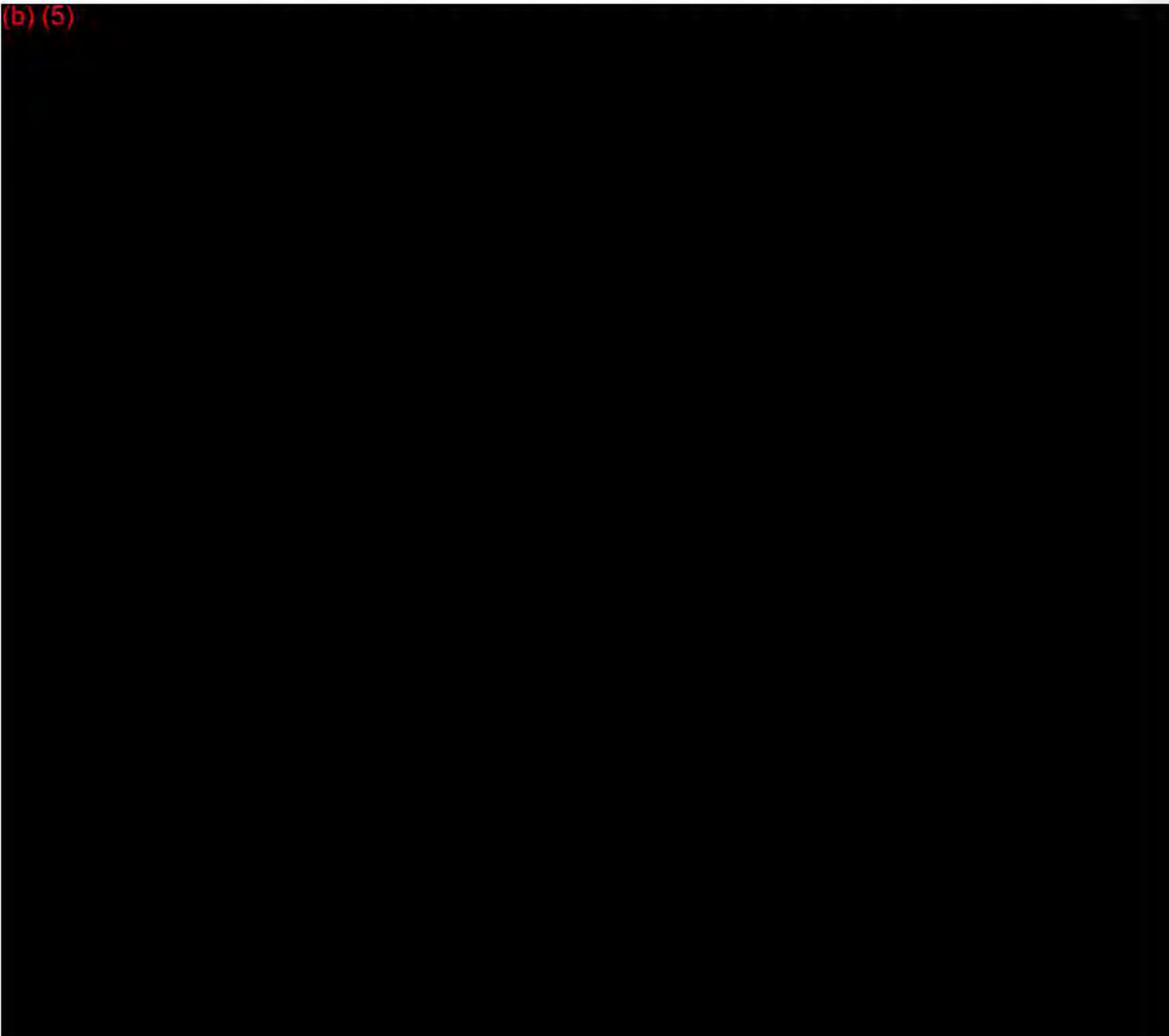
MEMO TO FILE

FROM: Robert Califf, M.D., Commissioner of Food and Drugs

DATE:

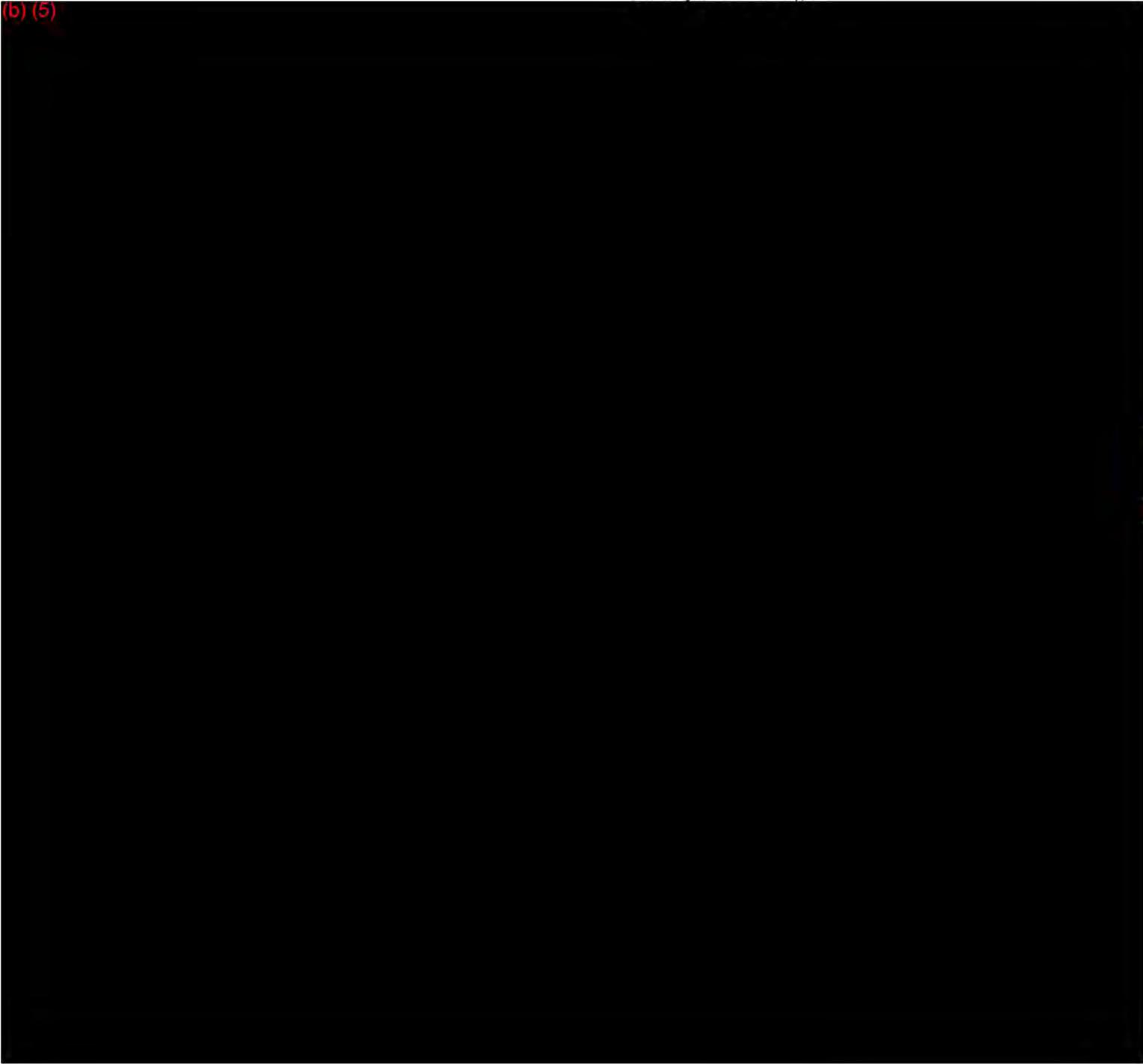
RE: Process for Commissioner's Decision about the Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics' Eteplirsen (NDA 206488)

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Deliberative Process Privilege
Attorney-Client Privilege

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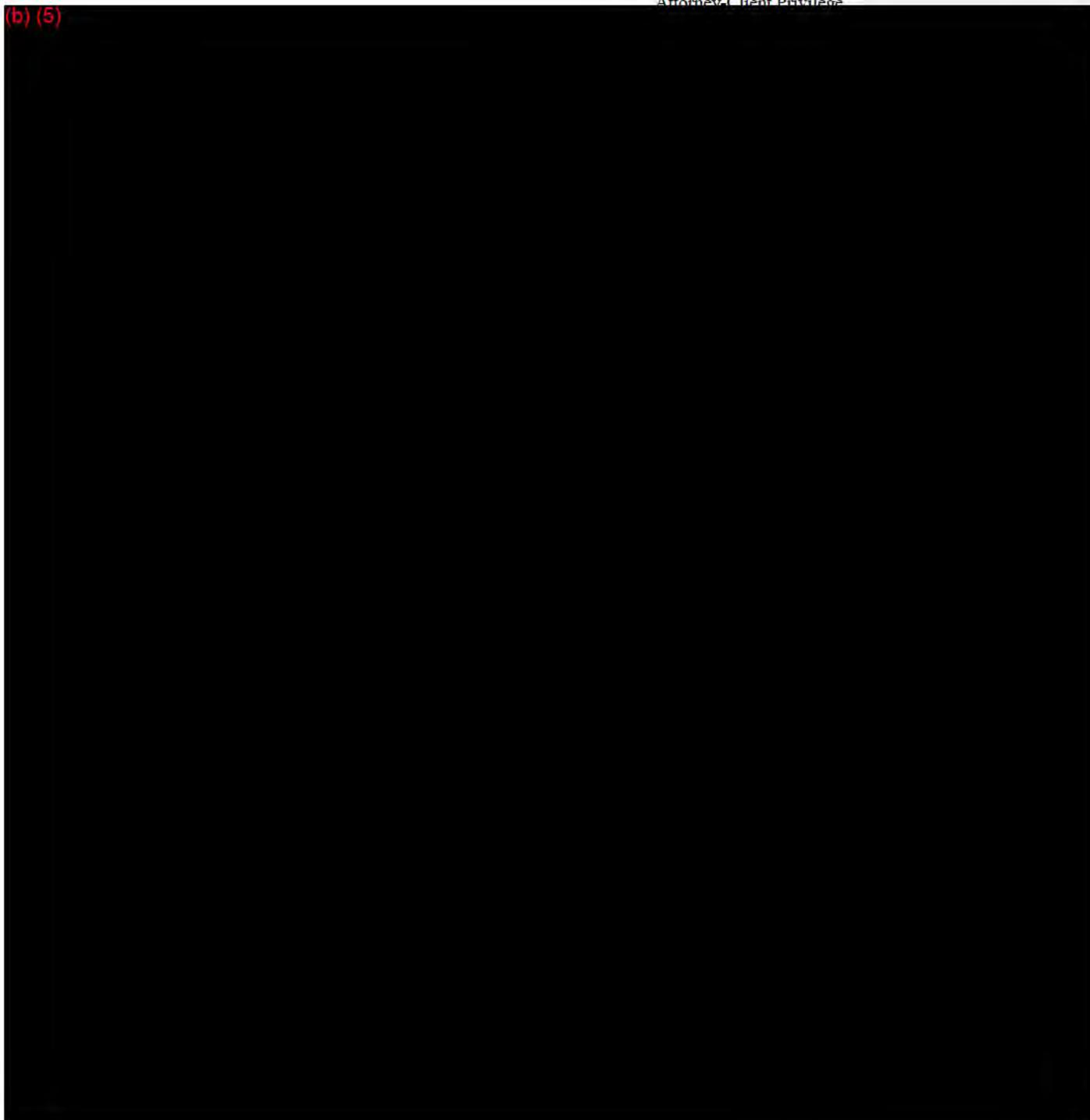
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Deliberative Process Privilege

Attorney-Client Privilege

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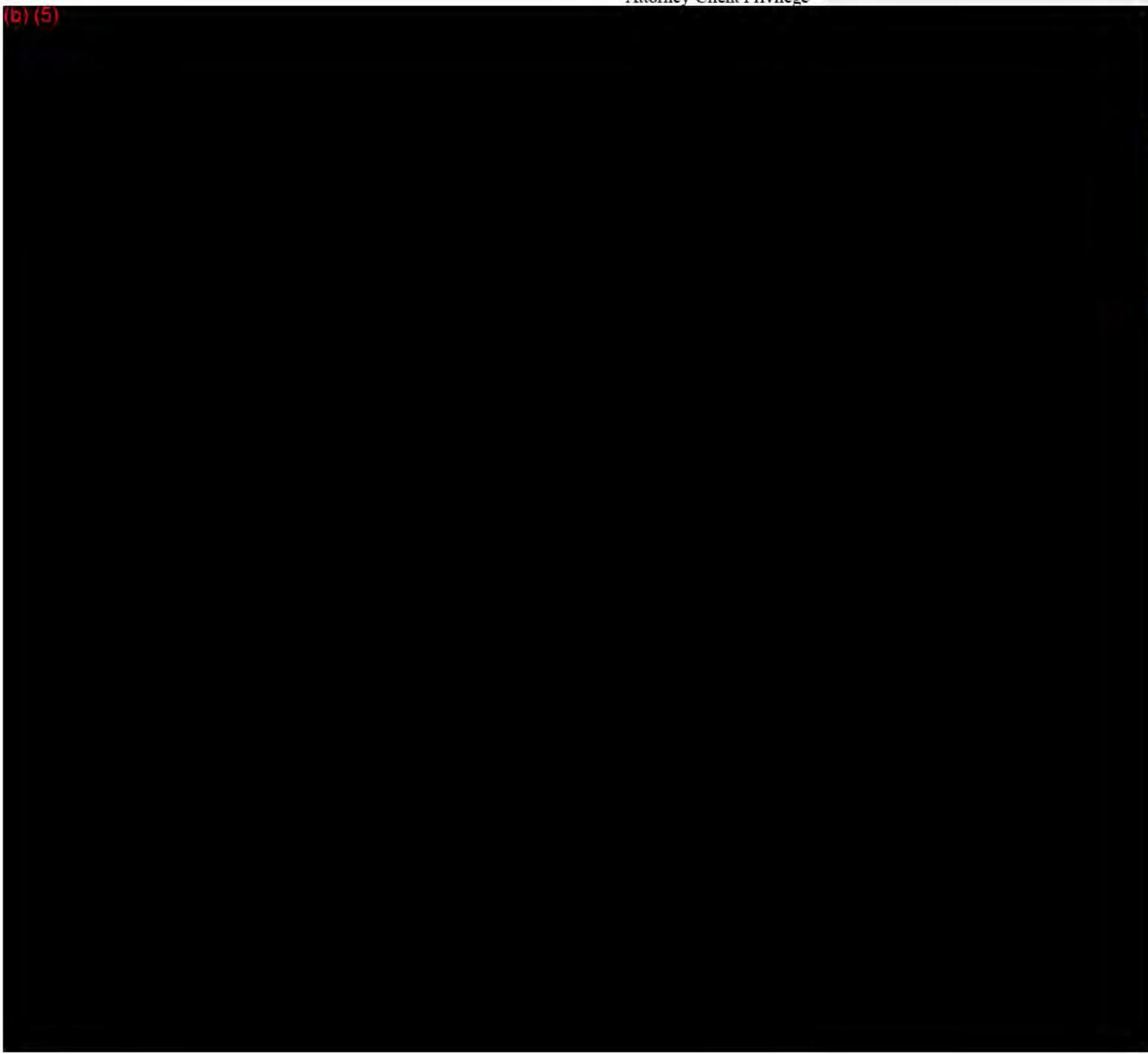


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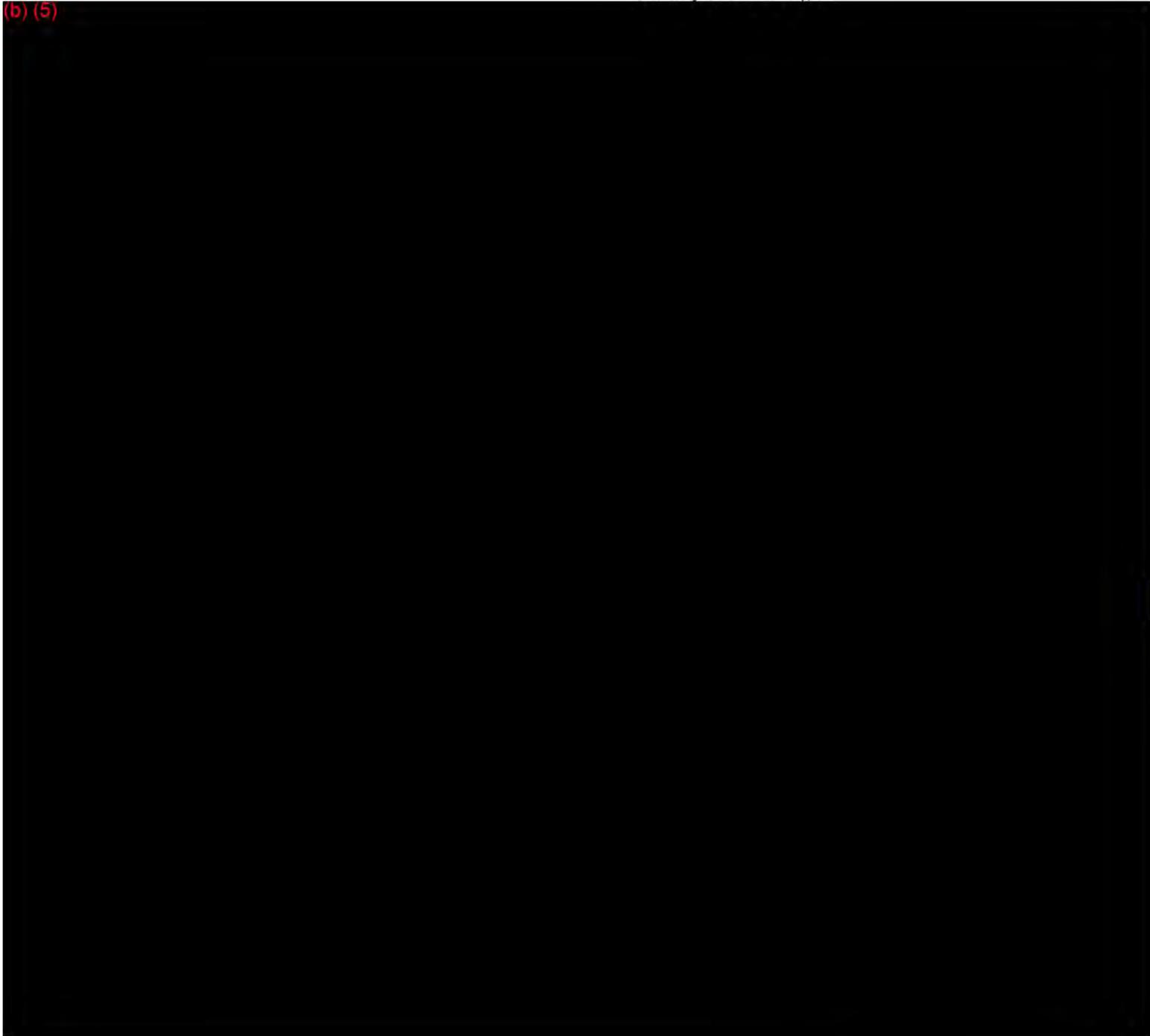
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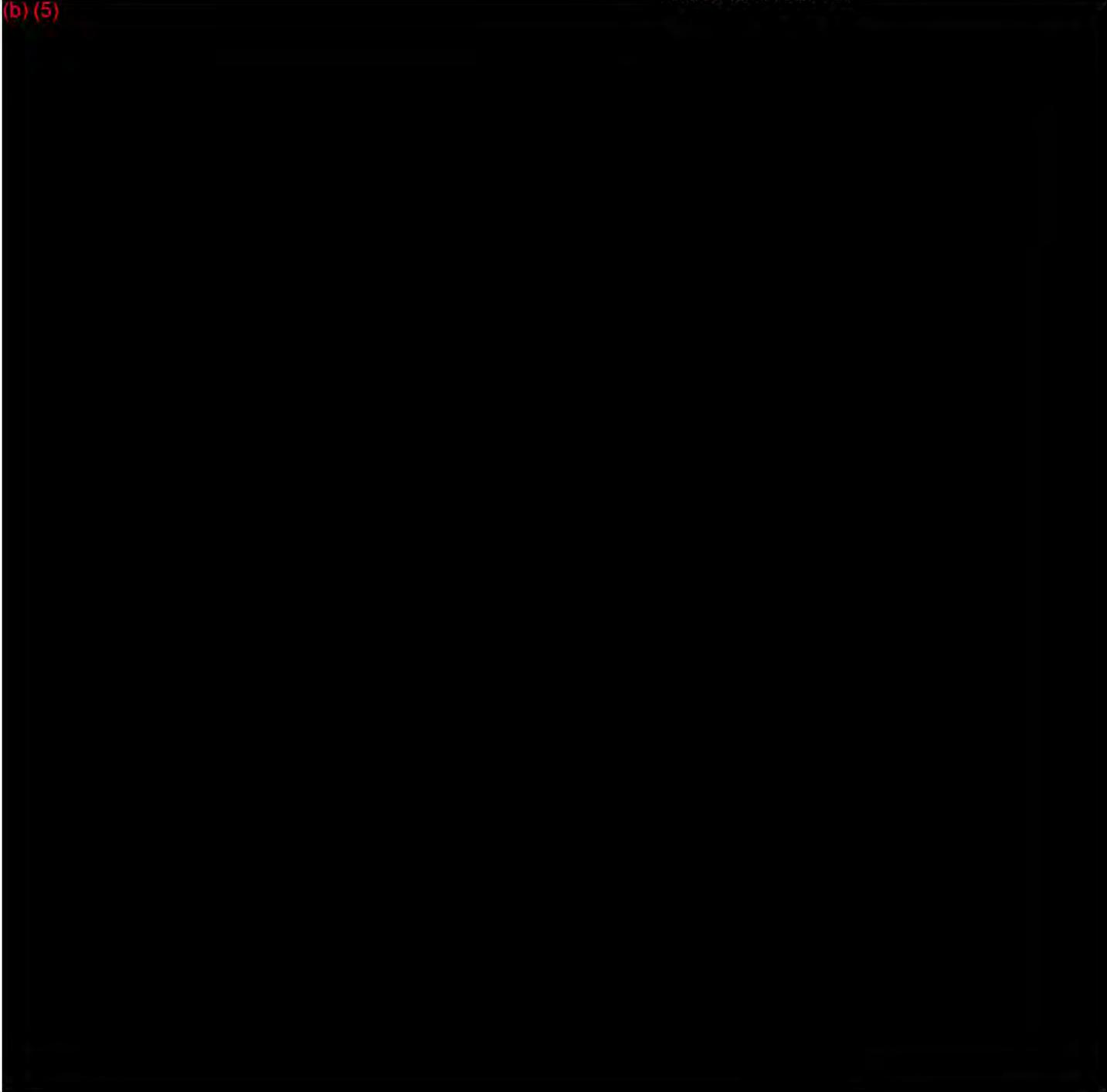
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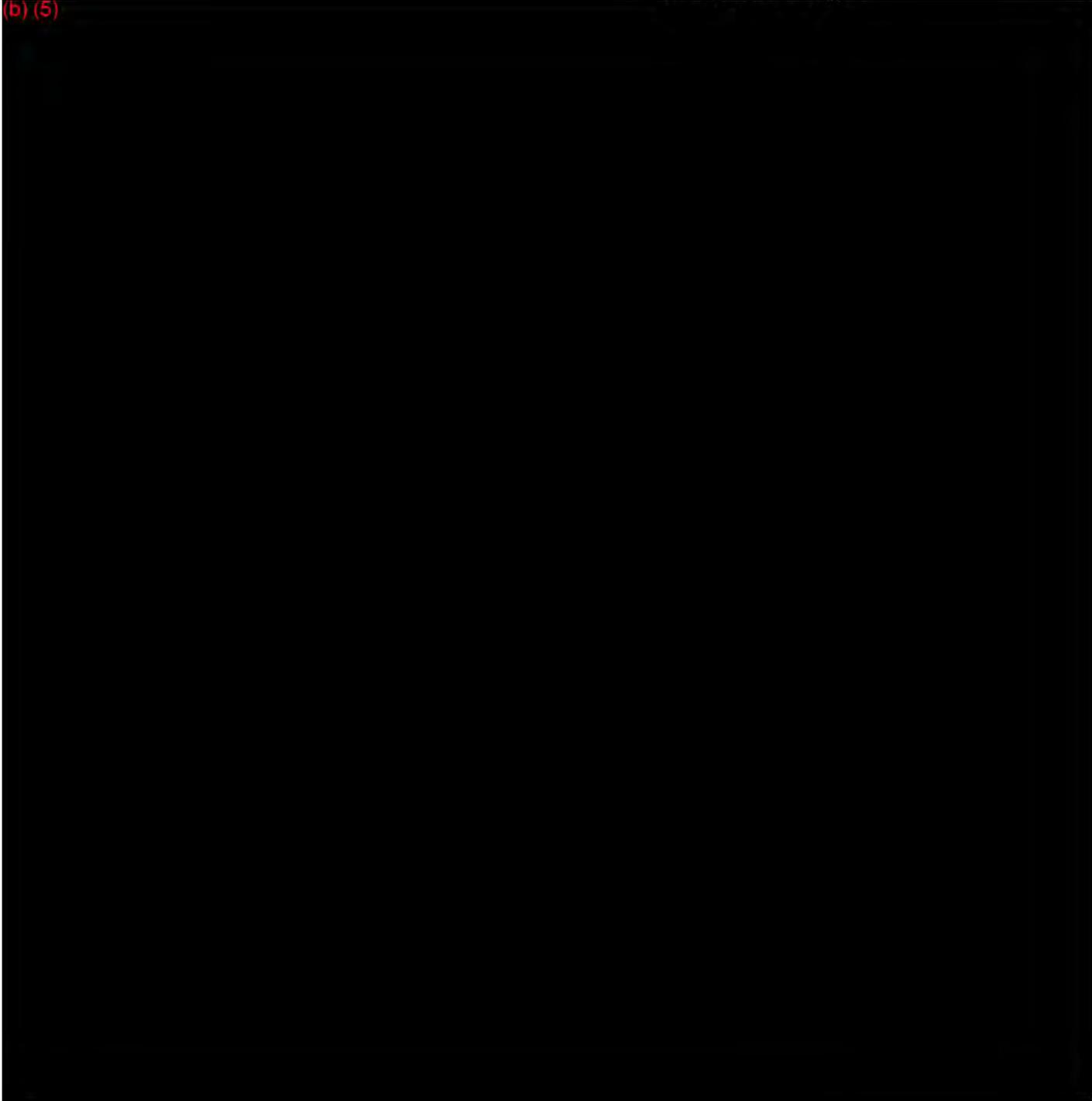
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Attorney-Client Privilege

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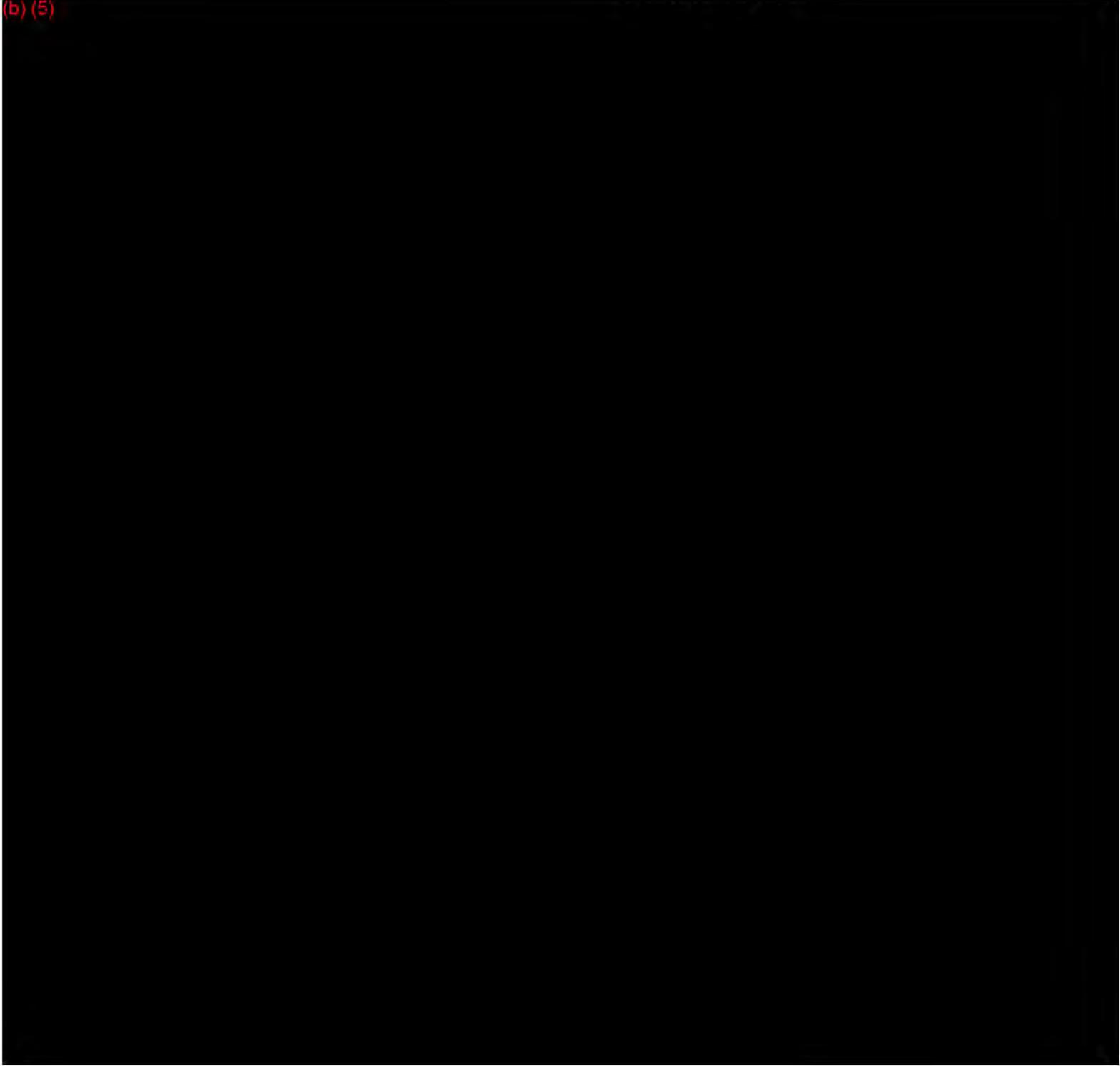
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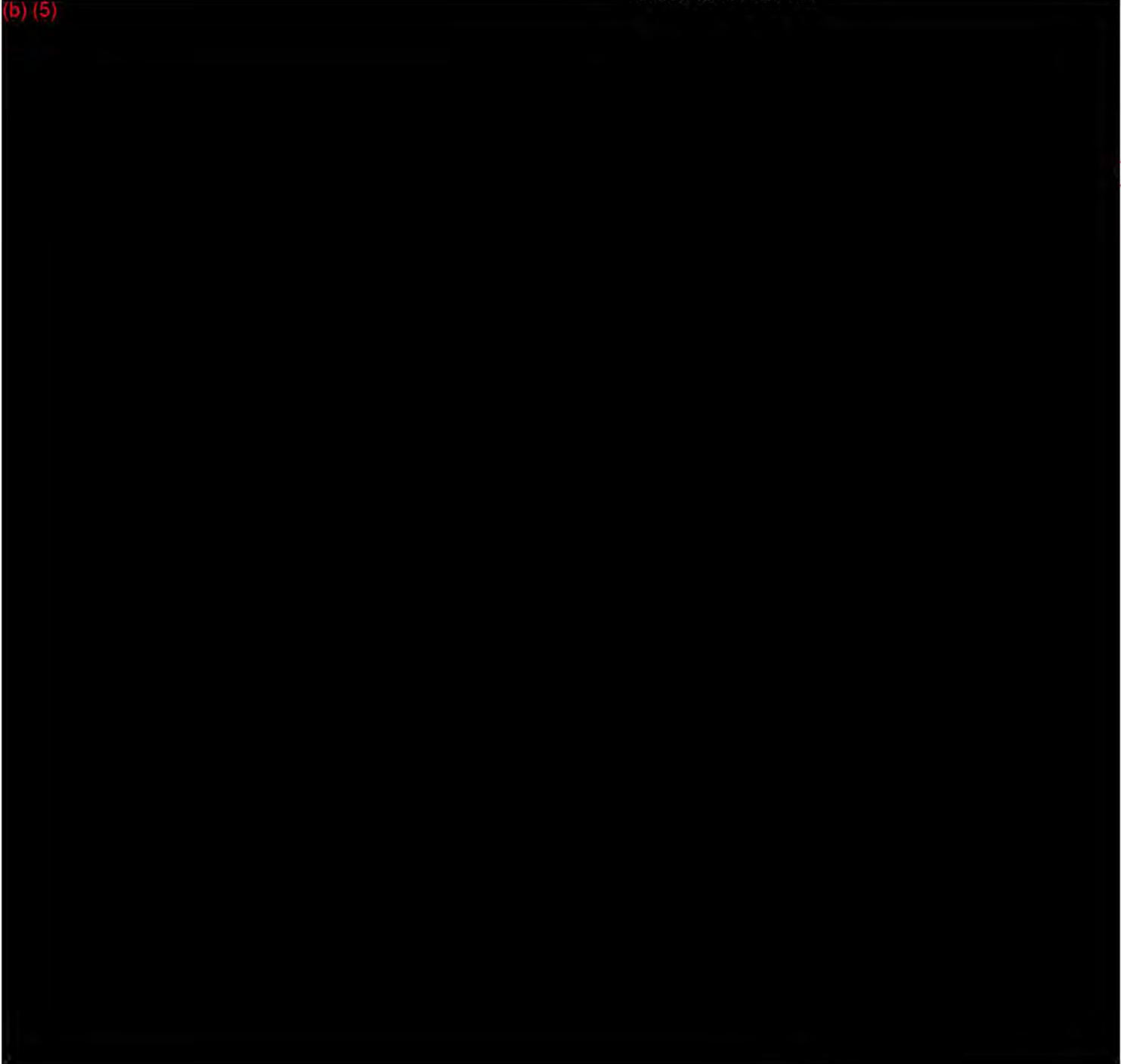
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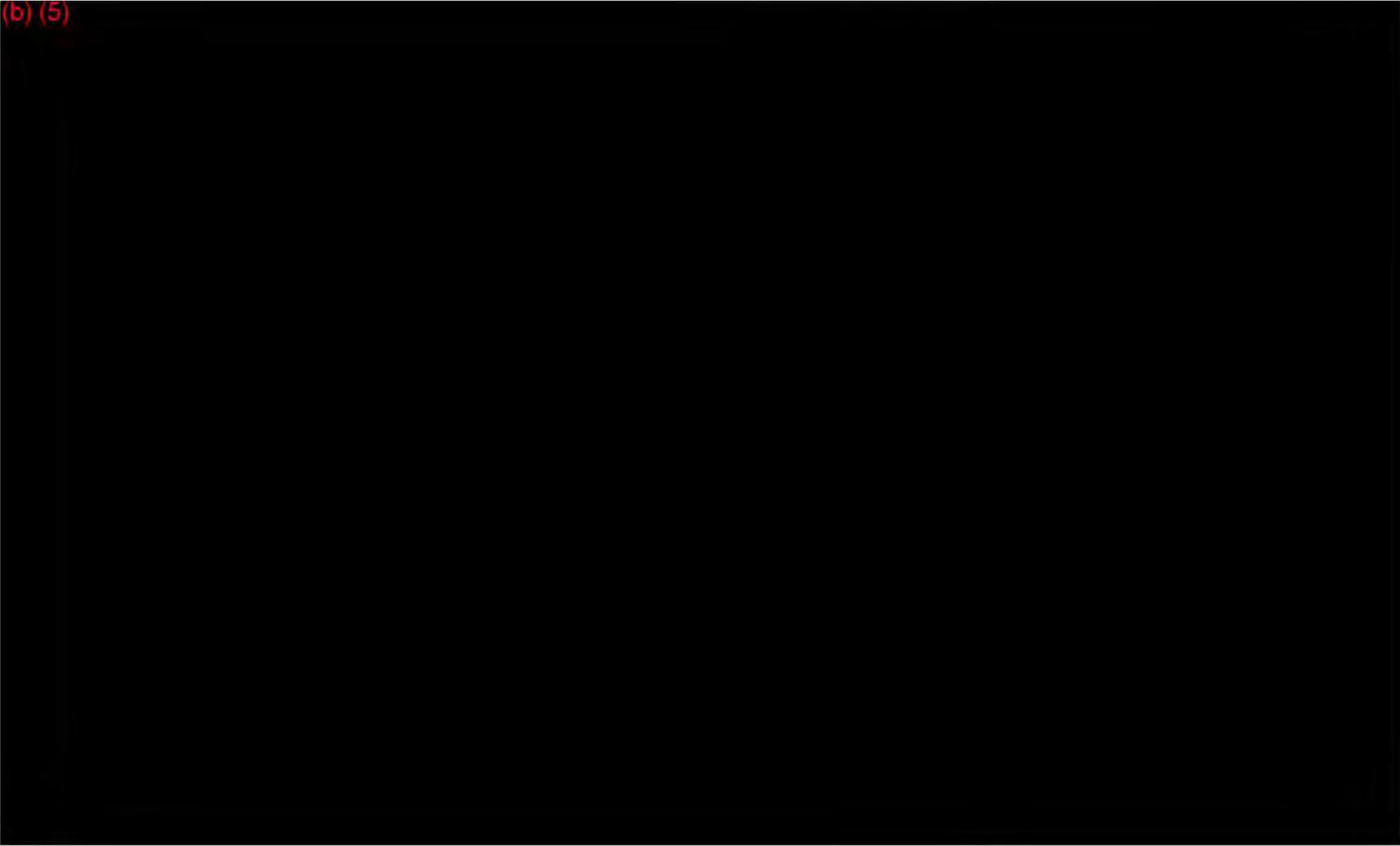
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Attorney-Client Privilege

(b) (5)



FDAOC0002058

(b) (5)



Smith, Celeste

To: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Proposed notes to go with responses:

To Dr. Borio:

Dear Lu,

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 6:15 AM
To: Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Hi,

I think the holes are filled.

What next? It sounds as if you want to say something about the (b) (5)

(b) (5)



Rachel,

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 15, 2016 at 5:47:49 AM EDT
To: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>
Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Subject: RE: memo

See below for my comments. The question is the format of the response to Ellis, John and Lu. I'm guessing this format is good and if someone can do a draft I can edit tonight, or I can do a draft tonight for editing tomorrow.

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Wednesday, September 14, 2016 11:38 PM
To: Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

(b) (5)

From: Sherman, Rachel
Sent: Wednesday, September 14, 2016 7:32 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Chasan-Sloan, Deborah (FDA)
Subject: RE: memo

Hi,

Liz wisely advised (b) (5)

Limiting this to those who worked on the memo draft.

Rachel

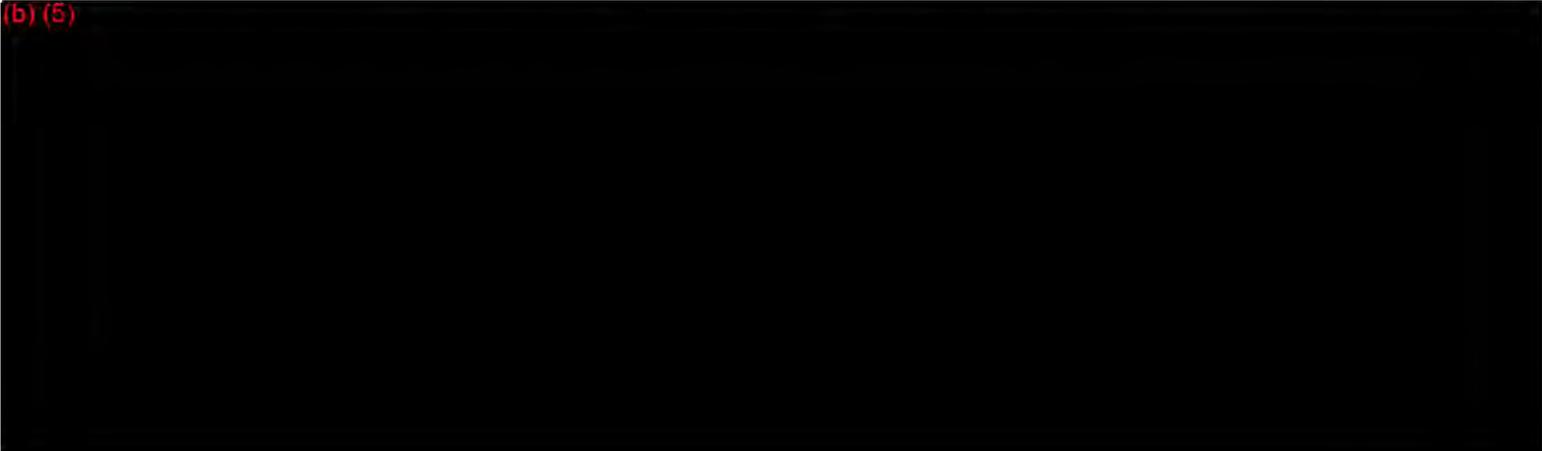
From: Califf, Robert
Sent: Wednesday, September 14, 2016 5:56 PM
To: Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Conover, Katie; Kraus, Tom
Subject: Fwd: memo

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: September 14, 2016 at 5:35:44 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>
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Rob
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1. I ask that you remove reference to quoting me from the July 12, 2016, e-mail that “reasonable people can disagree.” I think as used it is mischaracterized and used out of context. I strongly disagree with Janet’s decision and do not want my words in a single e-mail to suggest that is not the case.

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2. As to footnote 7, I think the review team needs to weigh in, but it was my impression that use of corticosteroids has been interpreted based on data to have changed the course of the disease in DMD. We currently have a pending NDA for use of a corticosteroid in DMD.

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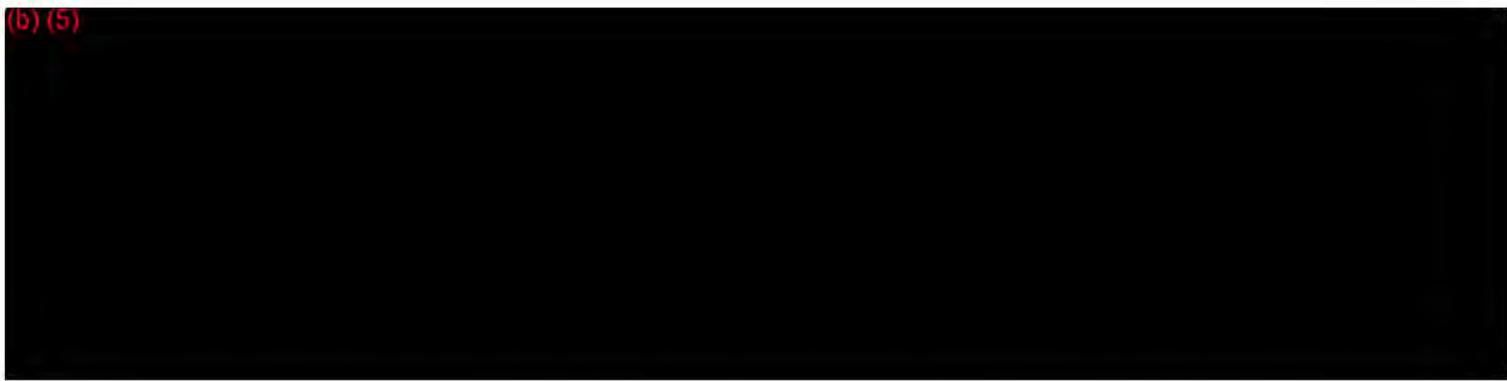
3. You note on page 3 that due to the serious defects in the development program, “it is impossible to use much of the resulting trial evidence in regulatory decision-making, including reasonable extrapolation to clinical care.” Yet you later support Janet’s conclusion that the sponsor has provided data from “two adequate and well-controlled trials.” I can find no effort to reconcile these very different statements.

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4. On page 4, you state “there is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence...” This implies she took these actions BEFORE reaching a decision on the application, which is clearly not correct given her statement to the review team of her intention to overrule them and approve the drug BEFORE they had completed their reviews. Keep in mind this occurred after an AC meeting at which the majority of the panel voted against both AA and full approval. It is also clear that she was prepared to approve the drug over the team’s objections by the original PDUFA goal date and only reluctantly agreed to press the sponsor for additional data on dystrophin production from the ongoing open-label trial. While I am glad she agreed to go along with that request, convincing her to take what seemed like a very logical action was not easy. So, I find it hard to reconcile your statements about the process with the actions taken. Keep in mind that the usual course of action would be for the Office to issue a CR letter and then the sponsor could submit a FDRR that would first come to me and only if I supported the Office would an FDRR go to the Center Director. In this case that process was bypassed.

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5. On page 4 you state that Dr. Woodcock “finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is “reasonably likely” to predict clinical benefit.” This statement defies any sense of scientific reason (would one molecule of dystrophin be enough) and goes directly to Dr. Unger’s concern that “any” level of protein seems to be enough for Janet to support approval. You then go on to reference Janet’s regression analyses from her memo suggesting a correlation between dystrophin production and clinical outcomes. As I have noted to you on several occasions, I find this to be a scientifically invalid analysis that compares the endpoint value for dystrophin to a delta in a clinical endpoint. This analysis simply shows a correlation between higher levels of dystrophin, without regard to drug effect (there is no delta for dystrophin change that is due to drug), and cannot support the conclusion she reached. Your citation of this analysis is troubling.

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6. You make reference in several places to a “totality of evidence” standard. That is not the statutory standard for demonstration of effectiveness and FDA has always stated that the statutory standard for demonstration of an effect on a surrogate endpoint for AA is the same as for regular approval (i.e., substantial evidence). Perhaps you are using “totality of evidence” to support the decision that the data provided on the surrogate are reasonably likely to predict clinical benefit, but there must be substantial evidence of the drug’s effect on the surrogate and the data are very weak to meet that standard.

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7. You dismiss the concerns about Janet’s level of involvement in this review and her role at the AC by suggesting this is simply part of her leadership style. I have worked with Janet for over 20 years and I can say without a doubt that her involvement in this case far exceeds her usual “hands on” approach. You note that there were

14 Center director briefings related to this case, that is clearly not the “norm” for how CDER operates. You also suggest that because CDER has been successful under her leadership that suggests that her intense involvement in this case does not raise concern. I see that as true, true, and unrelated. The question in this case is not whether she has overall been an effective leader of CDER, but whether she acted appropriately and without bias in the current case, something I don’t think you effectively address given the evidence and the seriousness of the allegations and concerns expressed.

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8. As to your footnote 23, there are direct statements that Janet made to the team that contradict the statements you reference from your interview with her. I am happy to discuss these statements with you further. In addition, Janet has had frequent private conversations with the sponsor and the stakeholder community. To my knowledge, she has not documented the substance of those conversations to the record, as is required under FDA regulations. That leaves a gap of knowledge to evaluate the concerns raised by the review team and Dr. Borio.
9. I do not find your statements about how this case does not lower the bar for future drug approvals convincing. I share the concerns voiced by Drs. Unger and Borio about the potential adverse impact on FDA’s ability to reach science-based conclusions on future applications.

(b) (5)

10. On page 9 it would be nice to see you call explicitly for retraction of the publications that have now been discredited.

(b) (5)

11. Also on page 9 it is ironic that you attribute to Janet the idea of randomizing early in order to generate good evidence. That is exactly what the review team planned to require of Sarepta after the results of the 12-patient study became available, but it was Janet that pressed that a new randomized trial not be required. So, if Janet had followed the normal CDER process in this case the review team would have required placebo-controlled trials, as they did for drisapersen (b) (4), and we would have better data on which to make a decision. I would note that Janet did not and has not involved herself in the drisapersen (b) (4) cases to the same degree as eteplirsen. Drisapersen arguably (b) (4); they had a positive phase 2 trial and a second trial that leaned favorably on a clinical endpoint. Janet did not object to the division asking for a large phase 3 trial and did not object to ODE1’s decision to to issue a CR letter based on (b) (4). I think it is reasonable to question why she devoted so much attention to eteplirsen and not the other (b) (4) drugs. One could speculate that she too was misled by the early reports on dystrophin production that were later discredited.

12. The overall tone of your memo seems to say that you conclude that Janet behaved and conducted herself appropriately in this case. That is at odds with the experience of the review team and is counter to the team-based, collegial working environment that we hope to create at FDA so we can accomplish our important public health mission. This validation from your level of her actions and behavior is worrisome. While I understand your desire not to undercut her role as Center Director, her actions have at best created a serious appearance of bias among the review team members and that has created distrust and a sense of undue pressure to “come around” to her way of thinking. Even if you uphold her decision I would think you should counsel her about how her behavior and actions have undermined her credibility among the review staff and should be avoided in future similar cases. Effective leaders must have the trust and respect of their staff. As I noted in our call last week, there are frequent disagreements about data and actions in CDER, and that is healthy and encouraged so we can ensure we hear all voices as we make decision, what is not healthy is a situation where the actions of a leader creates the appearance of bias since this undermines the trust necessary for the review team to conclude that the action was fair and move on.

I understand this appeal has placed you in a very difficult position. I also understand that you have made your decision. I hope, that my comments can help you to structure your decisional memo to avoid similar situations in the future. As you know, I had planned to retire from FDA last spring. I have delayed my departure for a variety of reasons, but one of the most important reasons is that Janet has told me she plans to serve as acting in my place as head of OND once I leave. I am very concerned about the impact of that decision on the future of the new drugs review program and would be happy to discuss those concerns further.

John

From: Califf, Robert

Sent: Tuesday, September 13, 2016 6:40 PM

To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana

Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities. I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD
Commissioner, Food and Drugs

From: [Califf, Robert](#)
To: [McCall, Jonathan *](#)
Cc: [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Kraus, Tom](#)
Subject: RE: Eteplirsen decision memo and supporting materials for your review
Date: Thursday, September 15, 2016 9:21:00 PM
Attachments: [20160915 response notesrs_JM_CLEAN_rmc.doc](#)

One minor change on response note.

rmc

From: McCall, Jonathan *
Sent: Thursday, September 15, 2016 4:56 PM
To: Califf, Robert
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom
Subject: Eteplirsen decision memo and supporting materials for your review

Hello Dr. Califf –

Here is the current version of the eteplirsen memo:

<< File: 2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ).doc >> << File: 2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ)_Commented.doc >>

Here is the memo to file:

<< File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN.doc >> << File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_COMMENTED.doc >>

And here are the response cover notes:

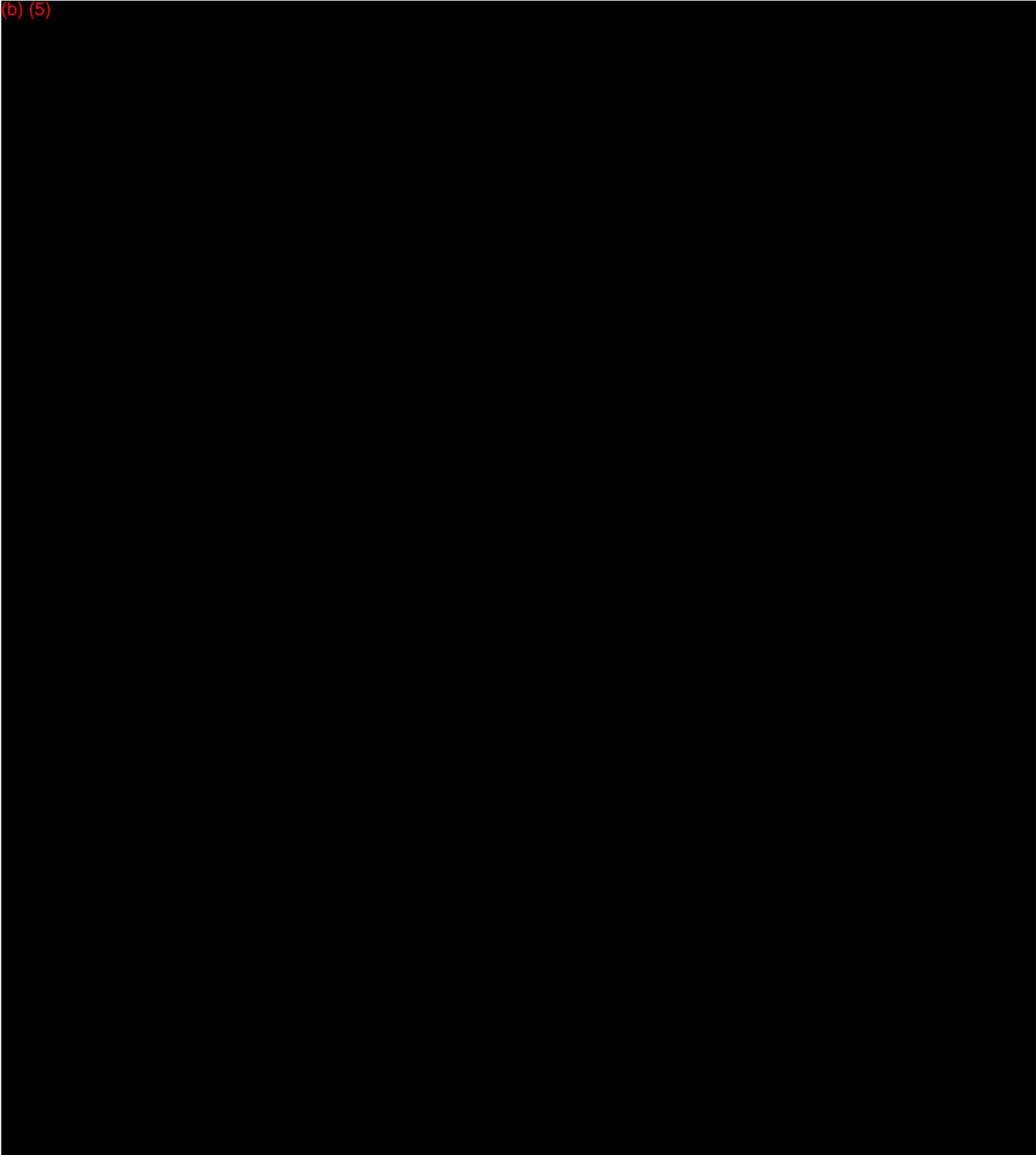
<< File: 20160915 response notesrs_JM_CLEAN.doc >> << File: 20160915 response notesrs_JM_TRACKED.doc >>

Thanks!

--

Jonathan

(b) (5)



From: Sherman, Rachel
To: Califf, Robert; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo
Date: Thursday, September 15, 2016 8:33:37 AM

Hi,

Memo – we want one memo that incorporates any changes.

Cover email – you have written individual ones so I assume that is what you want.

(b) (5)

So, here's my suggestion for going forward:

I am free until – I will do as much as I can on the cover emails (easy) and memo (harder).

I will then send it to Jonathan who will fill in as many blanks as he can.

He will then send to Deborah and Liz who will do the same.

Deborah and Liz will send what they have to Rob at the end of the day and he can look this evening.

Does that work?

From: Califf, Robert
Sent: Thursday, September 15, 2016 8:28 AM
To: Dickinson, Elizabeth (FDA); Sherman, Rachel; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

I'm really tied up till this evening. Do we want one memo or one for each person?

From: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Date: September 15, 2016 at 8:22:22 AM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Subject: RE: memo

(b) (5)

(b) (5)

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 7:56 AM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Okay, I'm lost.

You have drafted the cover notes – so now onto JM, then OCC, then back to you.

But you reference embedded text. That where I am lost – do you want us to clean up what we all added and forward those?

If so, I think OCC needs to concur.

From: Califf, Robert
Sent: Thursday, September 15, 2016 6:56 AM
To: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Here are the proposed intros to responses

rmc

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 6:52 AM
To: Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Okay, sorry I missed this.

I can draft the email this am. I can work on the memo but it may not be until late afternoon.
If someone else can start my feelings won't be hurt.

So email RS to JM to OCC to RMC.

Memo TBD.

OCC (b) (5)

From: Califf, Robert <RMC1@fda.hhs.gov>

Date: September 15, 2016 at 5:47:49 AM EDT

To: Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>

Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>

Subject: RE: memo

See below for my comments. The question is the format of the response to Ellis, John and Lu. I'm guessing this format is good and if someone can do a draft I can edit tonight, or I can do a draft tonight for editing tomorrow.

rmc

From: Chasan-Sloan, Deborah (FDA)

Sent: Wednesday, September 14, 2016 11:38 PM

To: Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA)

Cc: McCall, Jonathan *

Subject: RE: memo

(b) (5)



From: Sherman, Rachel

Sent: Wednesday, September 14, 2016 7:32 PM

To: Califf, Robert; Dickinson, Elizabeth (FDA)

Cc: McCall, Jonathan *; Chasan-Sloan, Deborah (FDA)

Subject: RE: memo

Hi,

Liz wisely advised (b) (5)



Limiting this to those who worked on the memo draft.

Rachel

From: Califf, Robert

Sent: Wednesday, September 14, 2016 5:56 PM

To: Dickinson, Elizabeth (FDA); Sherman, Rachel

Cc: Conover, Katie; Kraus, Tom

Subject: Fwd: memo

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>

Date: September 14, 2016 at 5:35:44 PM EDT

To: Califf, Robert <RMC1@fda.hhs.gov>

Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>

Subject: RE: memo

Rob

Thanks for providing an opportunity to review your draft memo regarding the eteplirsen dispute. I am responding just to you since some of the issues I raise below are sensitive. I would be happy to speak with you privately to discuss my concerns in greater detail if you would be open to that.

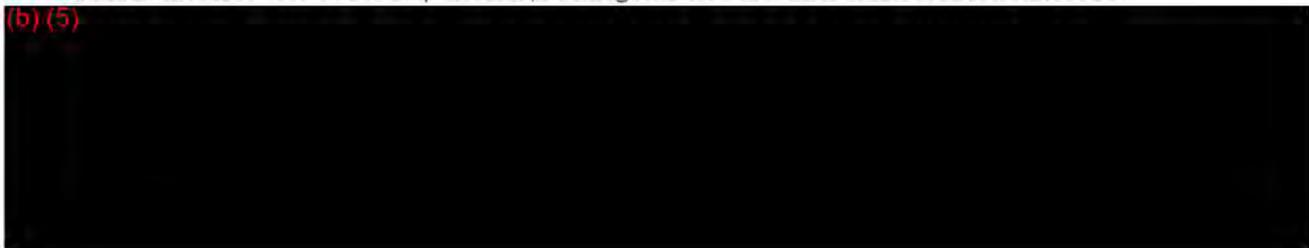
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(b) (5)



As to footnote 7, I think the review team needs to weigh in, but it was my impression that use of corticosteroids has been interpreted based on data to have changed the course of the disease in DMD. We currently have a pending NDA for use of a corticosteroid in DMD.

(b) (5)



You note on page 3 that due to the serious defects in the development program, "it is impossible to use much of the resulting trial evidence in regulatory decision-making, including reasonable extrapolation to clinical care." Yet you later support Janet's conclusion that the sponsor has provided data from "two adequate and well-controlled trials." I can find no effort to reconcile these very different statements.

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On page 4, you state "there is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence..." This implies she took these actions BEFORE reaching a decision on the application, which is clearly not correct given her statement to the review team of her intention to overrule them and approve the drug BEFORE they had completed their reviews. Keep in mind this occurred after an AC meeting at which the majority of the panel voted against both AA and full approval. It is also clear that she was prepared to approve the drug over the team's objections by the original PDUFA goal date and only reluctantly agreed to press the sponsor for additional data on dystrophin production from the ongoing open-label trial. While I am glad she agreed to go along with that request, convincing her to take what seemed like a very logical action was not easy. So, I find it hard to reconcile your statements about the process with the actions taken. Keep in mind that the usual course of action would be for the Office to issue a CR letter and then the sponsor could submit a FDRR that would first come to me and only if I supported the Office would an FDRR go to the Center Director. In this case that process was bypassed.

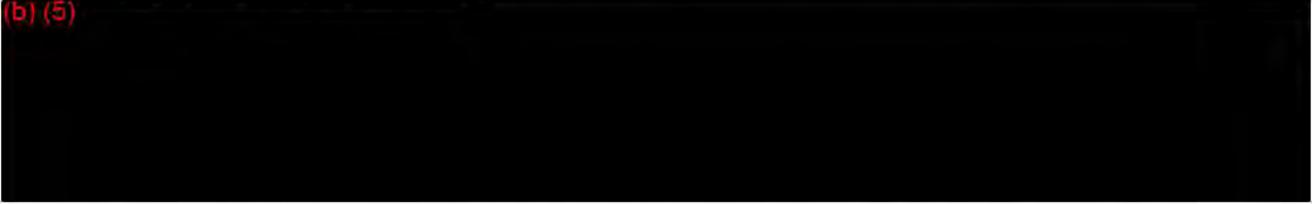
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On page 4 you state that Dr. Woodcock "finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is "reasonably likely" to predict clinical benefit." This statement defies any sense of scientific reason (would one molecule of dystrophin be enough) and goes directly to Dr. Unger's concern that "any" level of protein seems to be enough for Janet to support

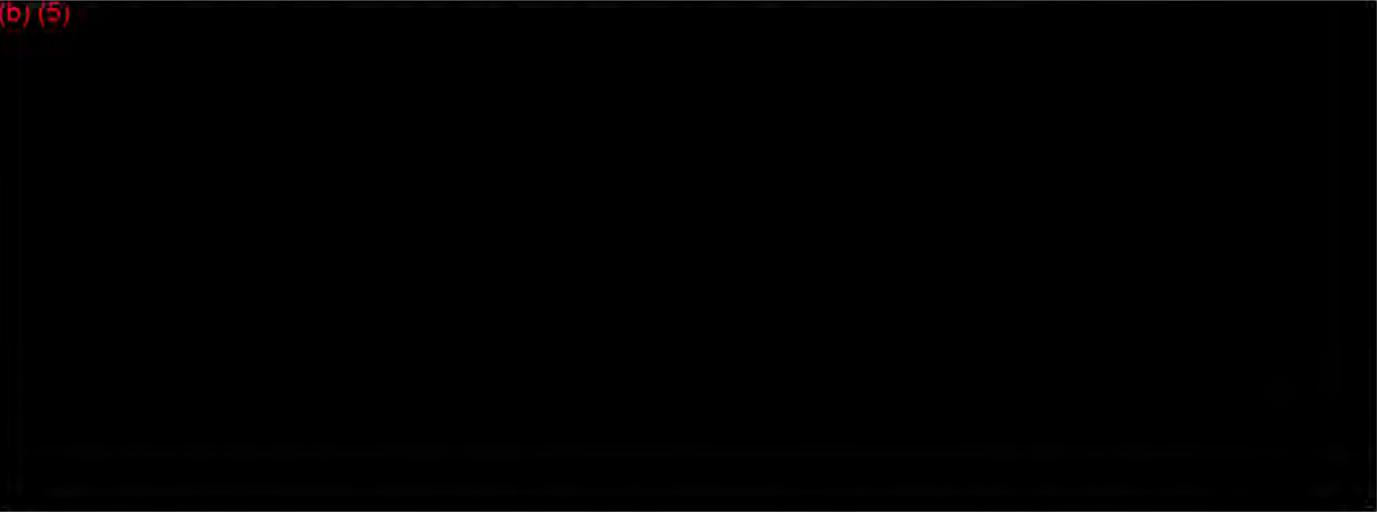
approval. You then go on to reference Janet's regression analyses from her memo suggesting a correlation between dystrophin production and clinical outcomes. As I have noted to you on several occasions, I find this to be a scientifically invalid analysis that compares the endpoint value for dystrophin to a delta in a clinical endpoint. This analysis simply shows a correlation between higher levels of dystrophin, without regard to drug effect (there is no delta for dystrophin change that is due to drug), and cannot support the conclusion she reached. Your citation of this analysis is troubling.

(b) (5)

A large black rectangular redaction box covering several lines of text.

You make reference in several places to a "totality of evidence" standard. That is not the statutory standard for demonstration of effectiveness and FDA has always stated that the statutory standard for demonstration of an effect on a surrogate endpoint for AA is the same as for regular approval (i.e., substantial evidence). Perhaps you are using "totality of evidence" to support the decision that the data provided on the surrogate are reasonably likely to predict clinical benefit, but there must be substantial evidence of the drug's effect on the surrogate and the data are very weak to meet that standard.

(b) (5)

A large black rectangular redaction box covering several lines of text.

You dismiss the concerns about Janet's level of involvement in this review and her role at the AC by suggesting this is simply part of her leadership style. I have worked with Janet for over 20 years and I can say without a doubt that her involvement in this case far exceeds her usual "hands on" approach. You note that there were 14 Center director briefings related to this case, that is clearly not the "norm" for how CDER operates. You also suggest that because CDER has been successful under her leadership that suggests that her intense involvement in this case does not raise concern. I see that as true, true, and unrelated. The question in this case is not whether she has overall been an effective leader of CDER, but whether she acted appropriately and without bias in the current case, something I don't think you effectively

address given the evidence and the seriousness of the allegations and concerns expressed.

(b) (5)

As to your footnote 23, there are direct statements that Janet made to the team that contradict the statements you reference from your interview with her. I am happy to discuss these statements with you further. In addition, Janet has had frequent private conversations with the sponsor and the stakeholder community. To my knowledge, she has not documented the substance of those conversations to the record, as is required under FDA regulations. That leaves a gap of knowledge to evaluate the concerns raised by the review team and Dr. Borio.

I do not find your statements about how this case does not lower the bar for future drug approvals convincing. I share the concerns voiced by Drs. Unger and Borio about the potential adverse impact on FDA's ability to reach science-based conclusions on future applications.

(b) (5)

On page 9 it would be nice to see you call explicitly for retraction of the publications that have now been discredited.

(b) (5)

Also on page 9 it is ironic that you attribute to Janet the idea of randomizing early in order to generate good evidence. That is exactly what the review team planned to require of Sarepta after the results of the 12-patient study became available, but it was Janet that pressed that a new randomized trial not be required. So, if Janet had followed the normal CDER process in this case the review team would have required placebo-controlled trials, as they did for drisapersen (b) (4), and we would have better data on which to make a decision. I would note that Janet did not and has not involved herself in the drisapersen (b) (4) cases to the same degree as eteplirsen. Drisapersen arguably (b) (4); they had a positive phase 2 trial and a second trial that leaned favorably on a clinical endpoint. Janet did not object to the division asking for a large phase 3 trial and did not object to ODE1's decision to to issue a CR letter based on (b) (4).

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John

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Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

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Robert M. Califf, MD
Commissioner, Food and Drugs

From: [Califf, Robert](#)
To: [McCall, Jonathan *](#)
Cc: [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Kraus, Tom](#)
Subject: RE: Eteplirsen decision memo and supporting materials for your review
Date: Thursday, September 15, 2016 9:42:00 PM

I think the memo is about as good as its going to get.

rmc

From: McCall, Jonathan *
Sent: Thursday, September 15, 2016 4:56 PM
To: Califf, Robert
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom
Subject: Eteplirsen decision memo and supporting materials for your review

Hello Dr. Califf –

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Thanks!

--

Jonathan

From: [Sherman, Rachel](#)
To: [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Cc: [McCall, Jonathan *](#)
Subject: RE: memo
Date: Thursday, September 15, 2016 1:09:17 PM
Attachments: [20160915 response notesrs.doc](#)

Hi all,

My suggested edits to Rob's cover notes.

Jonathan, you're next up then onto Deborah and then back to Rob.

Thanks!

Rachel

From: Califf, Robert
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To: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
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Memo TBD.

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Date: September 15, 2016 at 5:47:49 AM EDT

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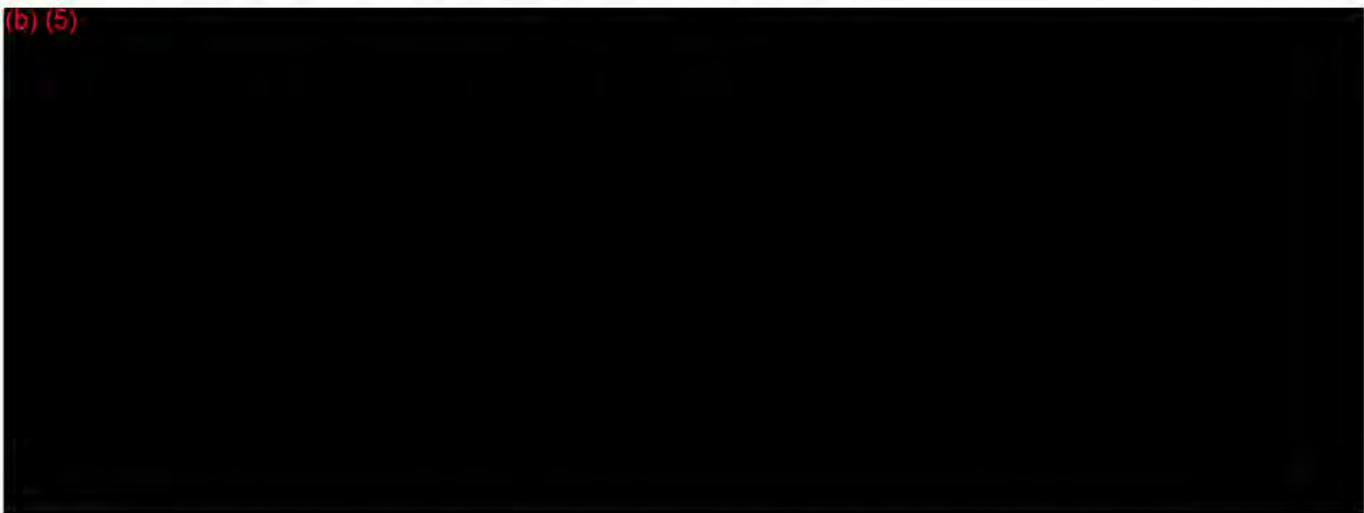
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You make reference in several places to a “totality of evidence” standard. That is not the statutory standard for demonstration of effectiveness and FDA has always stated that the statutory standard for demonstration of an effect on a surrogate endpoint for AA is the same as for regular approval (i.e., substantial evidence). Perhaps you are using “totality of evidence” to support the decision that the data provided on the surrogate are reasonably likely to predict clinical benefit, but there must be substantial evidence of the drug’s effect on the surrogate and the data are very weak to meet that standard.

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You dismiss the concerns about Janet’s level of involvement in this review and her role at the AC by suggesting this is simply part of her leadership style. I have worked with Janet for over 20 years and I can say without a doubt that her involvement in this case far exceeds her usual “hands on” approach. You note that there were 14 Center director briefings related to this case, that is clearly not the “norm” for how CDER operates. You also suggest that because CDER has been successful under her leadership that suggests that her intense involvement in this case does not raise concern. I see that as true, true, and unrelated. The question in this case is not whether she has overall been an effective leader of CDER, but whether she acted appropriately and without bias in the current case, something I don’t think you effectively address given the evidence and the seriousness of the allegations and concerns expressed.

(b) (5)

As to your footnote 23, there are direct statements that Janet made to the team that contradict the statements you reference from your interview with her. I am happy to discuss these statements with you further. In addition, Janet has had frequent private conversations with the sponsor and the stakeholder community. To my knowledge, she has not documented the substance of those conversations to the record, as is required under FDA regulations. That leaves a gap of knowledge to evaluate the concerns raised by the review team and Dr. Borio.

I do not find your statements about how this case does not lower the bar for future drug approvals convincing. I share the concerns voiced by Drs. Unger and Borio about the potential adverse impact on FDA's ability to reach science-based conclusions on future applications.

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On page 9 it would be nice to see you call explicitly for retraction of the publications that have now been discredited.

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Also on page 9 it is ironic that you attribute to Janet the idea of randomizing early in order to generate good evidence. That is exactly what the review team planned to require of Sarepta after the results of the 12-patient study became available, but it was Janet that pressed that a new randomized trial not be required. So, if Janet had followed the normal CDER process in this case the review team would have required placebo-controlled trials, as they did for drisapersen (b) (4), and we would have better data on which to make a decision. I would note that Janet did not and has not involved herself in the drisapersen (b) (4) cases to the same degree as eteplirsen. Drisapersen arguably (b) (4); they had a positive phase 2 trial and a second trial that leaned favorably on a clinical endpoint. Janet did not object to the division asking for a large phase 3 trial and did not object to ODE1's decision to issue a CR letter based on (b) (4). I think it is reasonable to question why she devoted so much attention to eteplirsen and not the

other (b) drugs. One could speculate that she too was misled by the early reports on dystrophin production that were later discredited.

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The overall tone of your memo seems to say that you conclude that Janet behaved and conducted herself appropriately in this case. That is at odds with the experience of the review team and is counter to the team-based, collegial working environment that we hope to create at FDA so we can accomplish our important public health mission. This validation from your level of her actions and behavior is worrisome. While I understand your desire not to undercut her role as Center Director, her actions have at best created a serious appearance of bias among the review team members and that has created distrust and a sense of undue pressure to "come around" to her way of thinking. Even if you uphold her decision I would think you should counsel her about how her behavior and actions have undermined her credibility among the review staff and should be avoided in future similar cases. Effective leaders must have the trust and respect of their staff. As I noted in our call last week, there are frequent disagreements about data and actions in CDER, and that is healthy and encouraged so we can ensure we hear all voices as we make decision, what is not healthy is a situation where the actions of a leader creates the appearance of bias since this undermines the trust necessary for the review team to conclude that the action was fair and move on.

I understand this appeal has placed you in a very difficult position. I also understand that you have made your decision. I hope, that my comments can help you to structure your decisional memo to avoid similar situations in the future. As you know, I had planned to retire from FDA last spring. I have delayed my departure for a variety of reasons, but one of the most important reasons is that Janet has told me she plans to serve as acting in my place as head of OND once I leave. I am very concerned about the impact of that decision on the future of the new drugs review program and would be happy to discuss those concerns further.

John

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we

have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD
Commissioner, Food and Drugs

(b) (5)



From: [Califf, Robert](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [McCall, Jonathan *](#)
Cc: [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Kraus, Tom](#); [Conover, Katie](#); [Rodriguez, Jennifer](#)
Subject: RE: Eteplirsen decision memo and supporting materials for your review
Date: Thursday, September 15, 2016 10:41:00 PM

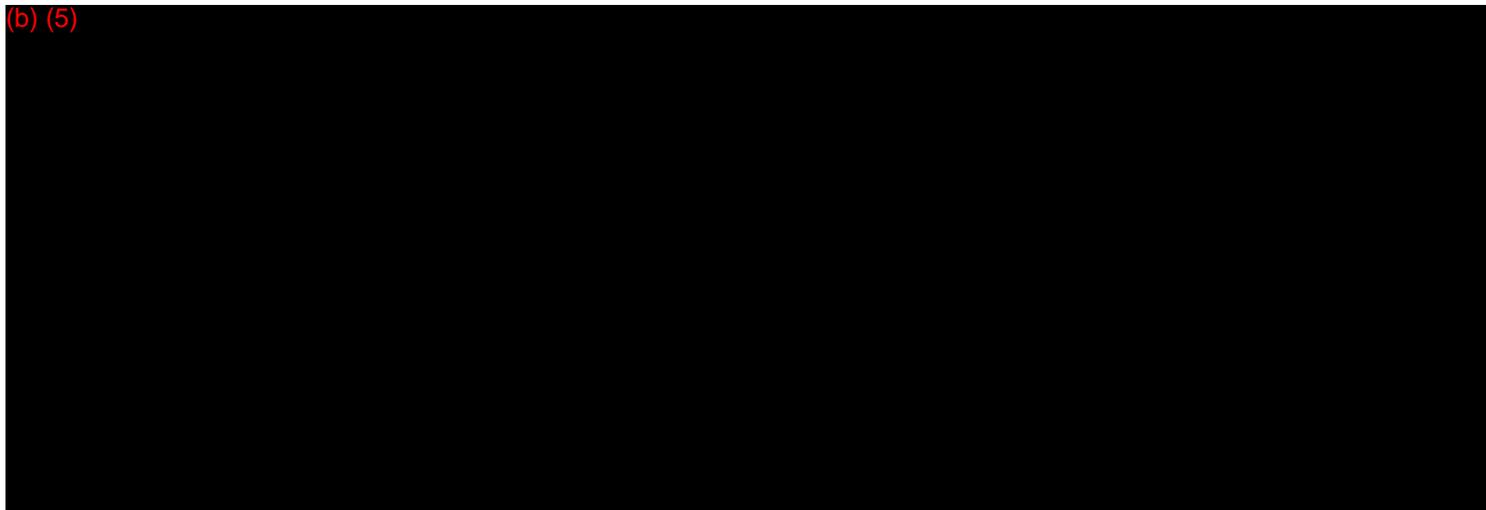
Looks good

rmc

From: Dickinson, Elizabeth (FDA)
Sent: Thursday, September 15, 2016 10:36 PM
To: Califf, Robert; McCall, Jonathan *
Cc: Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Kraus, Tom; Conover, Katie; Rodriguez, Jennifer
Subject: RE: Eteplirsen decision memo and supporting materials for your review

<< File: 2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ) (2)(dcs)(ehd) (2).doc >> << File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN (dcs).doc >> << File: Electronic Letterhead for White Oak3.doc >>

(b) (5)



From: Califf, Robert
Sent: Thursday, September 15, 2016 9:16 PM
To: McCall, Jonathan *
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom; Conover, Katie; Rodriguez, Jennifer
Subject: RE: Eteplirsen decision memo and supporting materials for your review

<< File: 20160915 Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN_rmc.doc >>

Comments added. Hopefully this will do it. Should be easy for you to check out.

rmc

From: McCall, Jonathan *
Sent: Thursday, September 15, 2016 4:56 PM
To: Califf, Robert
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom
Subject: Eteplirsen decision memo and supporting materials for your review

Hello Dr. Califf –

Here is the current version of the eteplirsen memo:

<< File: 2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ).doc >> << File:
2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ)_Commented.doc >>

Here is the memo to file:

<< File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN.doc >> << File:
Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_COMMENTED.doc >>

And here are the response cover notes:

<< File: 20160915 response notesrs_JM_CLEAN.doc >> << File: 20160915 response
notesrs_JM_TRACKED.doc >>

Thanks!

--

Jonathan

From: [McCall, Jonathan *](#)
To: [Sherman, Rachel](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: RE: memo
Date: Thursday, September 15, 2016 4:15:22 PM
Attachments: [20160915 response notesrs JM.doc](#)

My edits appended.

Thanks!

--
J

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 1:09 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Hi all,

My suggested edits to Rob's cover notes.

Jonathan, you're next up then onto Deborah and then back to Rob.

Thanks!

Rachel

From: Califf, Robert
Sent: Thursday, September 15, 2016 6:56 AM
To: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Here are the proposed intros to responses

rmc

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 6:52 AM
To: Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Okay, sorry I missed this.

I can draft the email this am. I can work on the memo but it may not be until late afternoon.
If someone else can start my feelings won't be hurt.

So email RS to JM to OCC to RMC.

Memo TBD.

OCC (b) (5) [REDACTED].

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 15, 2016 at 5:47:49 AM EDT
To: Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Subject: RE: memo

See below for my comments. The question is the format of the response to Ellis, John and Lu. I'm guessing this format is good and if someone can do a draft I can edit tonight, or I can do a draft tonight for editing tomorrow.

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Wednesday, September 14, 2016 11:38 PM
To: Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

(b) (5) [REDACTED]

From: Sherman, Rachel
Sent: Wednesday, September 14, 2016 7:32 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Chasan-Sloan, Deborah (FDA)
Subject: RE: memo

Hi,

Liz wisely advised (b) (5) [REDACTED]
[REDACTED]

Limiting this to those who worked on the memo draft.

Rachel

From: Califf, Robert
Sent: Wednesday, September 14, 2016 5:56 PM
To: Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Conover, Katie; Kraus, Tom
Subject: Fwd: memo

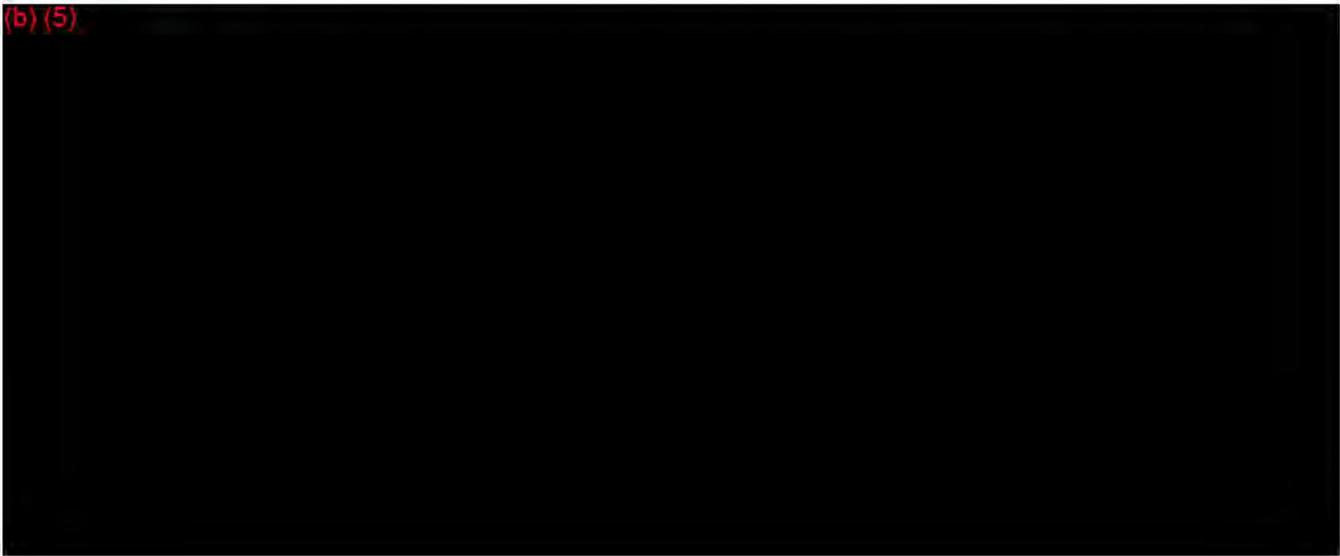
From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: September 14, 2016 at 5:35:44 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Subject: RE: memo

Rob

Thanks for providing an opportunity to review your draft memo regarding the eteplirsen dispute. I am responding just to you since some of the issues I raise below are sensitive. I would be happy to speak with you privately to discuss my concerns in greater detail if you would be open to that.

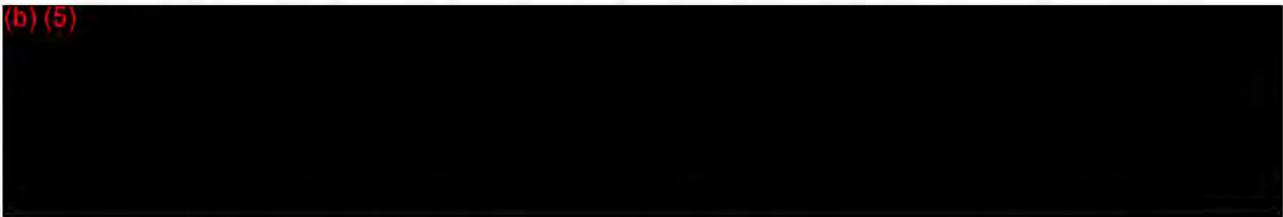
I ask that you remove reference to quoting me from the July 12, 2016, e-mail that "reasonable people can disagree." I think as used it is mischaracterized and used out of context. I strongly disagree with Janet's decision and do not want my words in a single e-mail to suggest that is not the case.

(b) (5)



As to footnote 7, I think the review team needs to weigh in, but it was my impression that use of corticosteroids has been interpreted based on data to have changed the course of the disease in DMD. We currently have a pending NDA for use of a corticosteroid in DMD.

(b) (5)



You note on page 3 that due to the serious defects in the development program, “it is impossible to use much of the resulting trial evidence in regulatory decision-making, including reasonable extrapolation to clinical care.” Yet you later support Janet’s conclusion that the sponsor has provided data from “two adequate and well-controlled trials.” I can find no effort to reconcile these very different statements.

(b) (5)



On page 4, you state “there is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence...” This implies she took these actions BEFORE reaching a decision on the application, which is clearly not correct given her statement to the review team of her intention to overrule them and approve the drug BEFORE they had completed their reviews. Keep in mind this occurred after an AC meeting at which the majority of the panel voted against both AA and full approval. It is also clear that she was prepared to approve the drug over the team’s objections by the original PDUFA goal date and only reluctantly agreed to press the sponsor for additional data on dystrophin production from the ongoing open-label trial. While I am glad she agreed to go along with that request, convincing her to take what seemed like a very logical action was not easy. So, I find it hard to reconcile your statements about the process with the actions taken. Keep in mind that the usual course of action would be for the Office to issue a CR letter and then the sponsor could submit a FDRR that would first come to me and only if I supported the Office would an FDRR go to the Center Director. In this case that process was bypassed.

(b) (5)



(b) (5)



On page 4 you state that Dr. Woodcock “finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is “reasonably likely” to predict clinical benefit.” This statement defies any sense of scientific reason (would one molecule of dystrophin be enough) and goes directly to Dr. Unger’s concern that “any” level of protein seems to be enough for Janet to support approval. You then go on to reference Janet’s regression analyses from her memo suggesting a correlation between dystrophin production and clinical outcomes. As I have noted to you on several occasions, I find this to be a scientifically invalid analysis that compares the endpoint value for dystrophin to a delta in a clinical endpoint. This analysis simply shows a correlation between higher levels of dystrophin, without regard to drug effect (there is no delta for dystrophin change that is due to drug), and cannot support the conclusion she reached. Your citation of this analysis is troubling.

(b) (5)



You make reference in several places to a “totality of evidence” standard. That is not the statutory standard for demonstration of effectiveness and FDA has always stated that the statutory standard for demonstration of an effect on a surrogate endpoint for AA is the same as for regular approval (i.e., substantial evidence). Perhaps you are using “totality of evidence” to support the decision that the data provided on the surrogate are reasonably likely to predict clinical benefit, but there must be substantial evidence of the drug’s effect on the surrogate and the data are very weak to meet that standard.

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John

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

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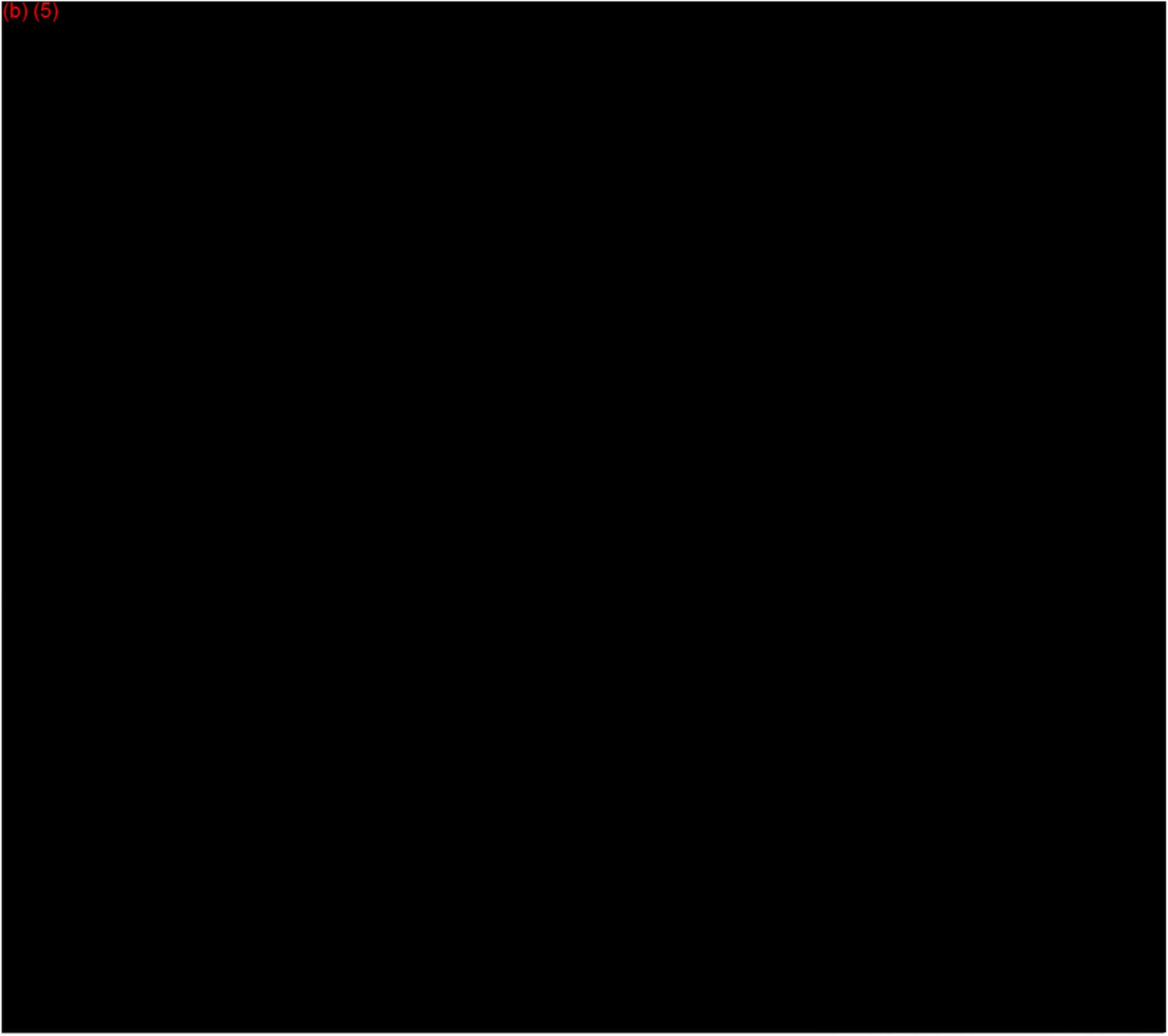
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Robert M. Califf, MD
Commissioner, Food and Drugs

(b) (5)



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From: [Chasan-Sloan, Deborah \(FDA\)](#)
To: [Sherman, Rachel](#); [McCall, Jonathan *](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: memo
Date: Thursday, September 15, 2016 4:31:02 PM
Attachments: [2016_Sept_012_R2_Eteplirsen_CLEAN_Borio_rmc_JM-CLEAN\(occ\).doc](#)
Importance: High

(b) (5)



From: Sherman, Rachel
Sent: Thursday, September 15, 2016 4:25 PM
To: [McCall, Jonathan *](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: RE: memo

Hi all,

Rob's flight is at 5, not 530. Whatever we have finished by 450 please send to Jonathan who will consolidate into a single email.

The rest we can get him later.

Thanks!

From: [McCall, Jonathan *](#)
Sent: Thursday, September 15, 2016 4:15 PM
To: [Sherman, Rachel](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: RE: memo

My edits appended.

Thanks!

—
J

From: Sherman, Rachel
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rmc

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OCC (b) (5)

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 15, 2016 at 5:47:49 AM EDT
To: Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Subject: RE: memo

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rmc

FDAOC0002101

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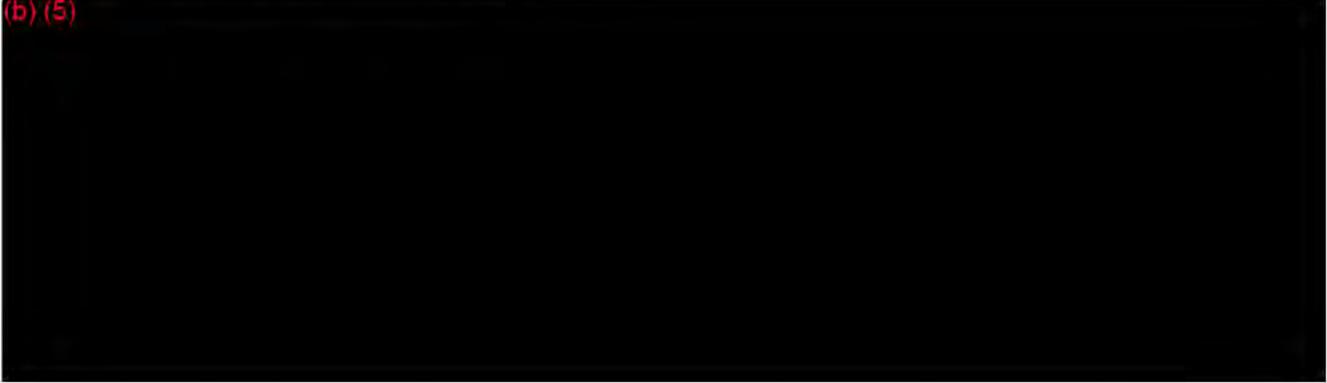
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On page 4, you state “there is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence...” This implies she took these actions BEFORE reaching a decision on

the application, which is clearly not correct given her statement to the review team of her intention to overrule them and approve the drug BEFORE they had completed their reviews. Keep in mind this occurred after an AC meeting at which the majority of the panel voted against both AA and full approval. It is also clear that she was prepared to approve the drug over the team's objections by the original PDUFA goal date and only reluctantly agreed to press the sponsor for additional data on dystrophin production from the ongoing open-label trial. While I am glad she agreed to go along with that request, convincing her to take what seemed like a very logical action was not easy. So, I find it hard to reconcile your statements about the process with the actions taken. Keep in mind that the usual course of action would be for the Office to issue a CR letter and then the sponsor could submit a FDRR that would first come to me and only if I supported the Office would an FDRR go to the Center Director. In this case that process was bypassed.

(b) (5)



On page 4 you state that Dr. Woodcock "finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is "reasonably likely" to predict clinical benefit." This statement defies any sense of scientific reason (would one molecule of dystrophin be enough) and goes directly to Dr. Unger's concern that "any" level of protein seems to be enough for Janet to support approval. You then go on to reference Janet's regression analyses from her memo suggesting a correlation between dystrophin production and clinical outcomes. As I have noted to you on several occasions, I find this to be a scientifically invalid analysis that compares the endpoint value for dystrophin to a delta in a clinical endpoint. This analysis simply shows a correlation between higher levels of dystrophin, without regard to drug effect (there is no delta for dystrophin change that is due to drug), and cannot support the conclusion she reached. Your citation of this analysis is troubling.

(b) (5)



You make reference in several places to a "totality of evidence" standard. That is not the

statutory standard for demonstration of effectiveness and FDA has always stated that the statutory standard for demonstration of an effect on a surrogate endpoint for AA is the same as for regular approval (i.e., substantial evidence). Perhaps you are using "totality of evidence" to support the decision that the data provided on the surrogate are reasonably likely to predict clinical benefit, but there must be substantial evidence of the drug's effect on the surrogate and the data are very weak to meet that standard.

(b) (5)



You dismiss the concerns about Janet's level of involvement in this review and her role at the AC by suggesting this is simply part of her leadership style. I have worked with Janet for over 20 years and I can say without a doubt that her involvement in this case far exceeds her usual "hands on" approach. You note that there were 14 Center director briefings related to this case, that is clearly not the "norm" for how CDER operates. You also suggest that because CDER has been successful under her leadership that suggests that her intense involvement in this case does not raise concern. I see that as true, true, and unrelated. The question in this case is not whether she has overall been an effective leader of CDER, but whether she acted appropriately and without bias in the current case, something I don't think you effectively address given the evidence and the seriousness of the allegations and concerns expressed.

(b) (5)



As to your footnote 23, there are direct statements that Janet made to the team that contradict the statements you reference from your interview with her. I am happy to discuss these statements with you further. In addition, Janet has had frequent private conversations with the sponsor and the stakeholder community. To my knowledge, she has not documented the substance of those conversations to the record, as is required under FDA regulations. That leaves a gap of knowledge to evaluate the concerns raised by the review team and Dr. Borio.

I do not find your statements about how this case does not lower the bar for future drug approvals convincing. I share the concerns voiced by Drs. Unger and Borio about the potential adverse impact on FDA's ability to reach science-based conclusions on future applications.

(b) (5)



On page 9 it would be nice to see you call explicitly for retraction of the publications that have now been discredited.

(b) (5)



Also on page 9 it is ironic that you attribute to Janet the idea of randomizing early in order to generate good evidence. That is exactly what the review team planned to require of Sarepta after the results of the 12-patient study became available, but it was Janet that pressed that a new randomized trial not be required. So, if Janet had followed the normal CDER process in this case the review team would have required placebo-controlled trials, as they did for drisapersen (b) (4), and we would have better data on which to make a decision. I would note that Janet did not and has not involved herself in the drisapersen (b) (4) cases to the same degree as eteplirsen. Drisapersen arguably (b) (4) they had a positive phase 2 trial and a second trial that leaned favorably on a clinical endpoint. Janet did not object to the division asking for a large phase 3 trial and did not object to ODE1's decision to to issue a CR letter based on (b) (4). I think it is reasonable to question why she devoted so much attention to eteplirsen and not the other (b) (4) drugs. One could speculate that she too was misled by the early reports on dystrophin production that were later discredited.

(b) (5)



The overall tone of your memo seems to say that you conclude that Janet behaved and conducted herself appropriately in this case. That is at odds with the experience of the review team and is counter to the team-based, collegial working environment that we hope to create at FDA so we can accomplish our important public health mission. This validation from your level of her actions and behavior is worrisome. While I understand your desire not to undercut her role as Center Director, her actions have at best created a serious appearance of bias

among the review team members and that has created distrust and a sense of undue pressure to “come around” to her way of thinking. Even if you uphold her decision I would think you should counsel her about how her behavior and actions have undermined her credibility among the review staff and should be avoided in future similar cases. Effective leaders must have the trust and respect of their staff. As I noted in our call last week, there are frequent disagreements about data and actions in CDER, and that is healthy and encouraged so we can ensure we hear all voices as we make decision, what is not healthy is a situation where the actions of a leader creates the appearance of bias since this undermines the trust necessary for the review team to conclude that the action was fair and move on.

I understand this appeal has placed you in a very difficult position. I also understand that you have made your decision. I hope, that my comments can help you to structure your decisional memo to avoid similar situations in the future. As you know, I had planned to retire from FDA last spring. I have delayed my departure for a variety of reasons, but one of the most important reasons is that Janet has told me she plans to serve as acting in my place as head of OND once I leave. I am very concerned about the impact of that decision on the future of the new drugs review program and would be happy to discuss those concerns further.
John

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board’s memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect

extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

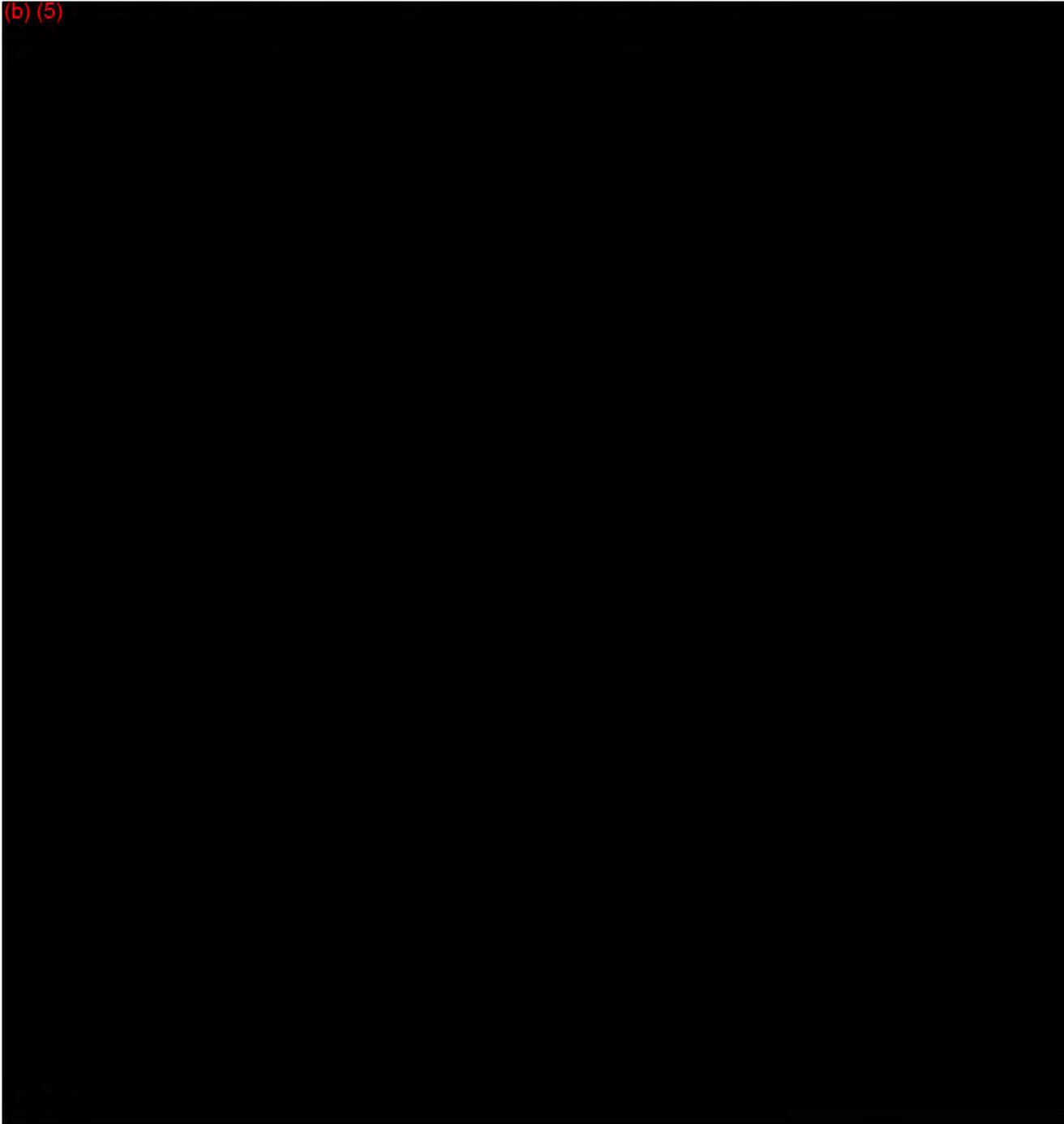
Robert M. Califf, MD
Commissioner, Food and Drugs

**Scientific Dispute Regarding Approval of Sarepta Therapeutics'
Eteplirsen – Commissioner's Decision**

(b) (5)



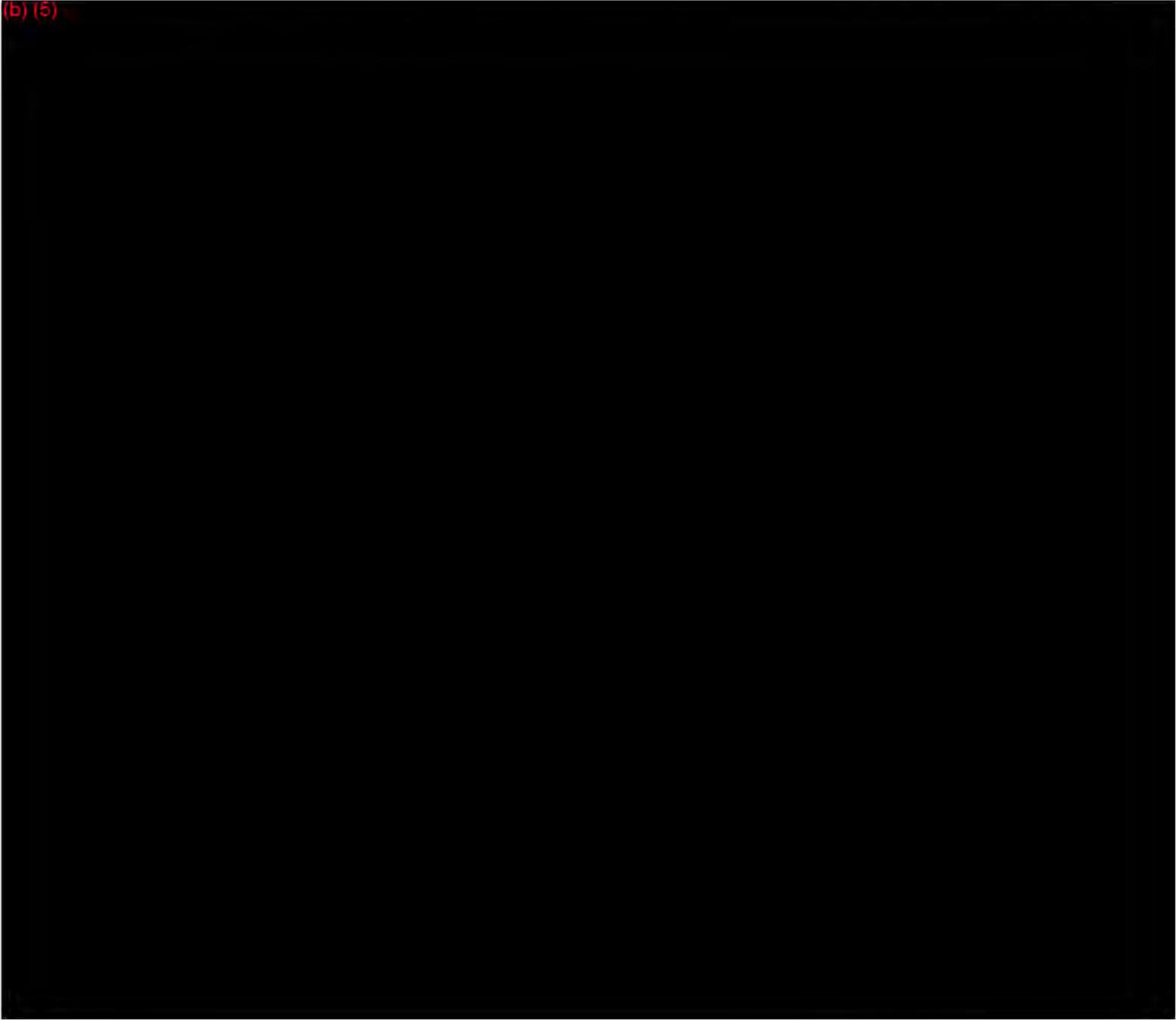
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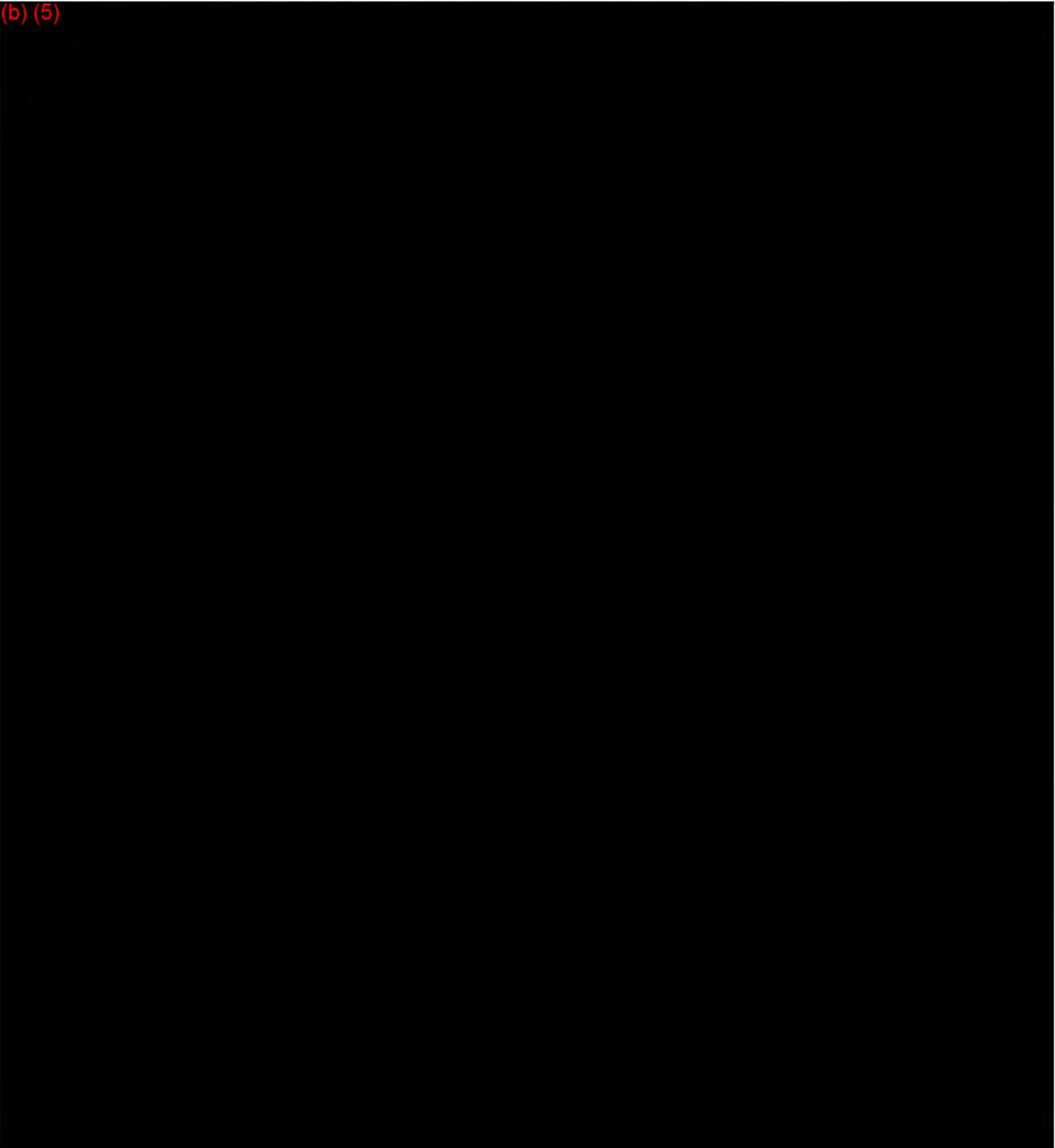
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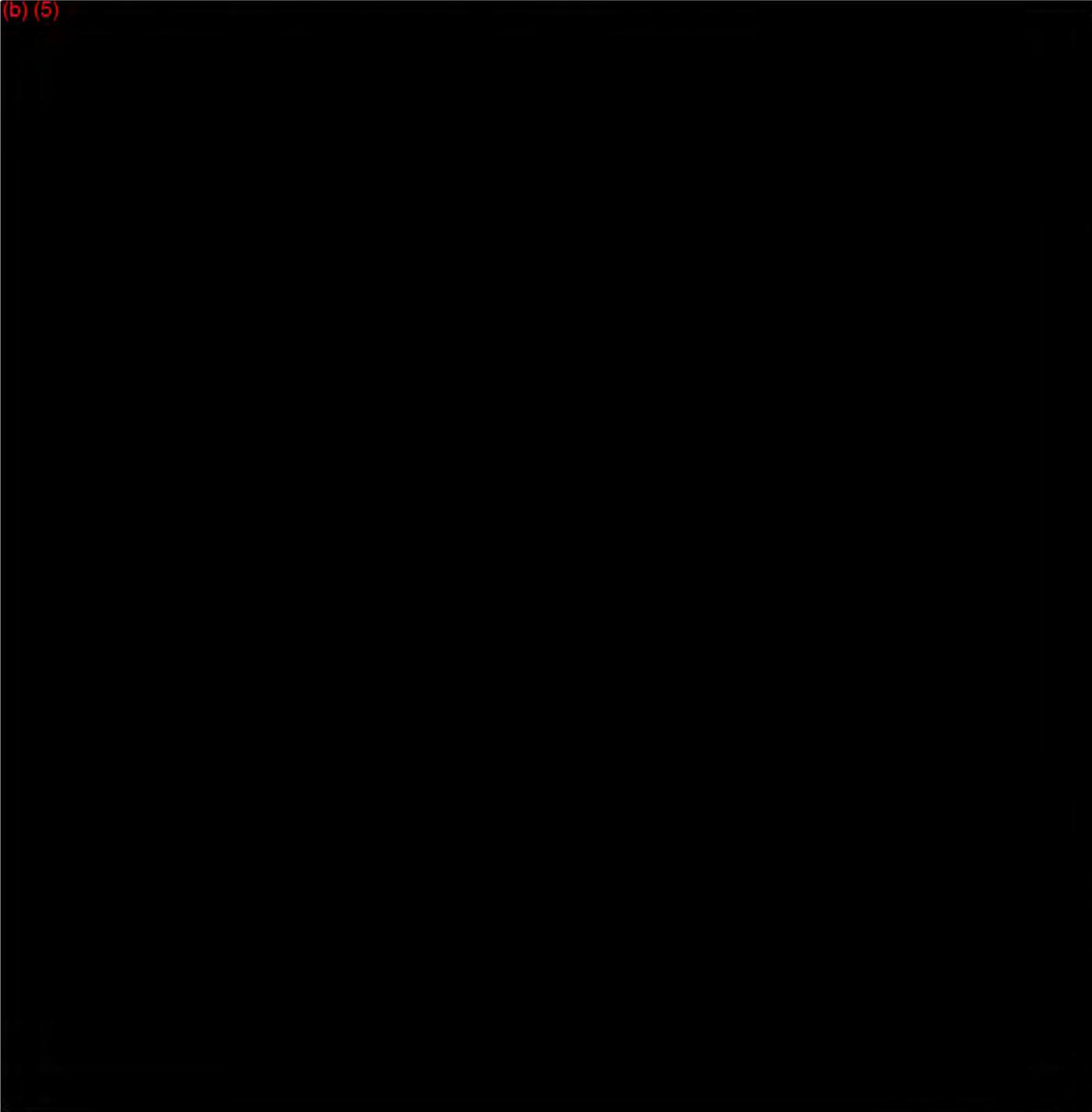
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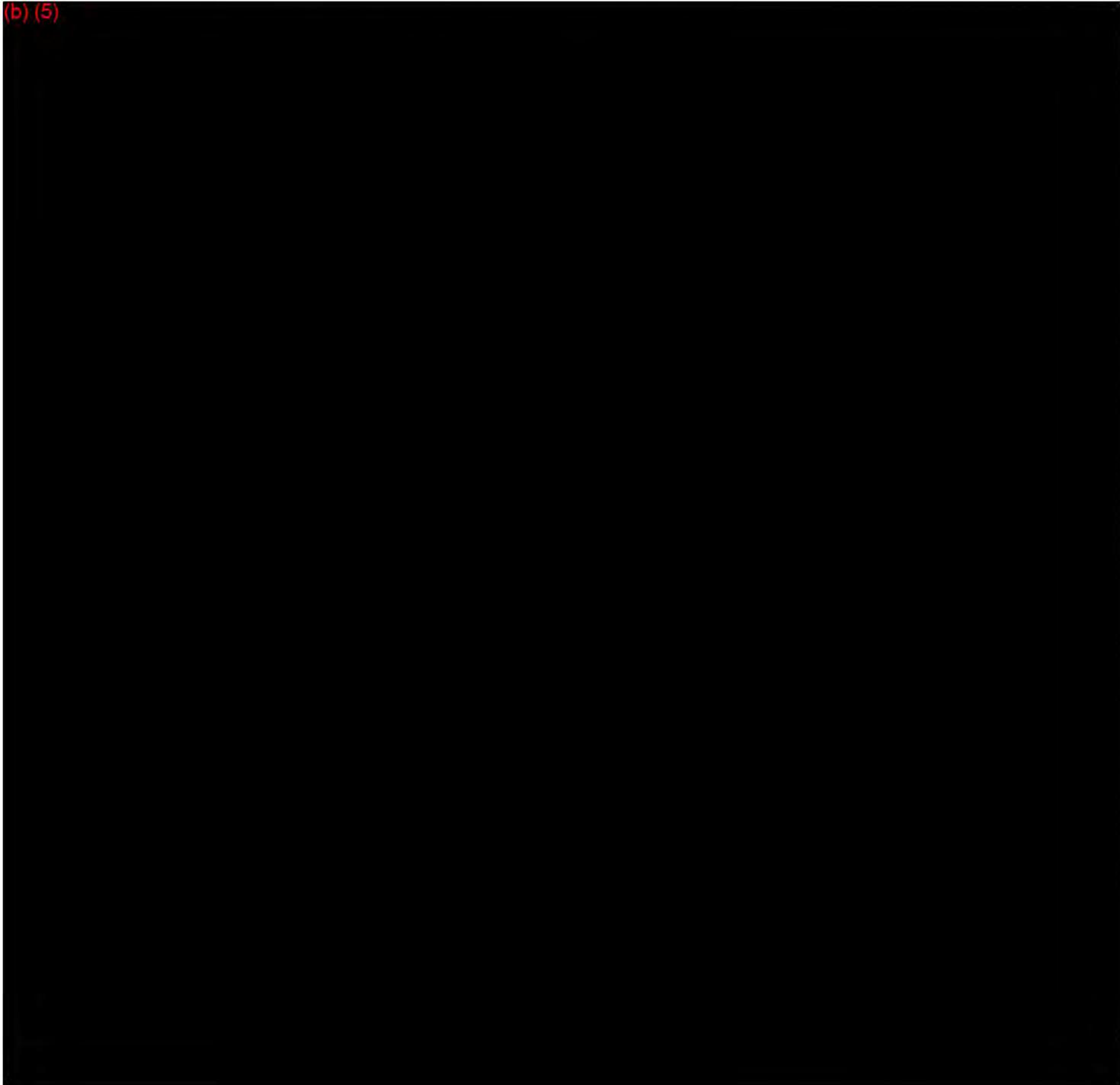
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(b) (5)



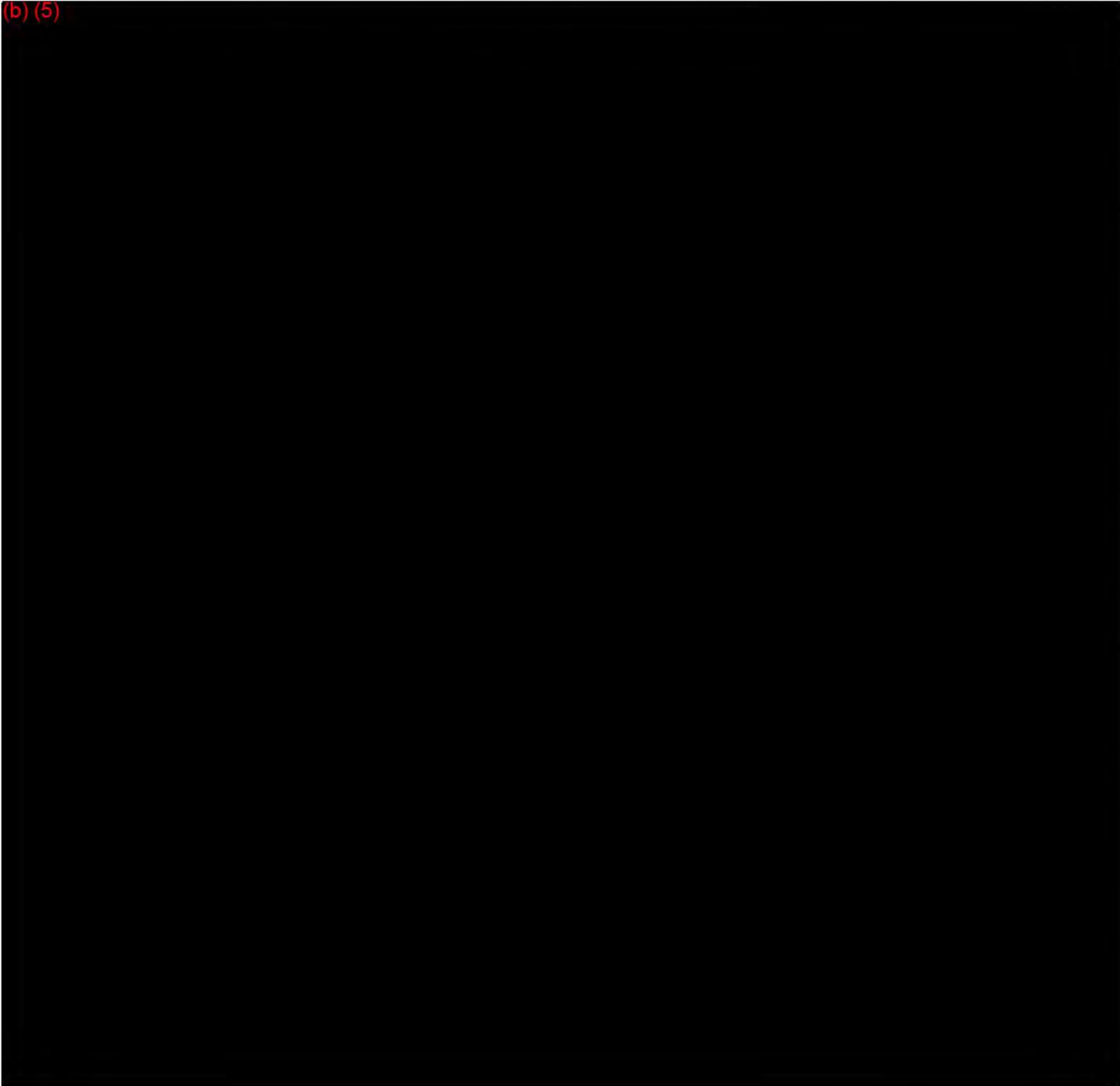
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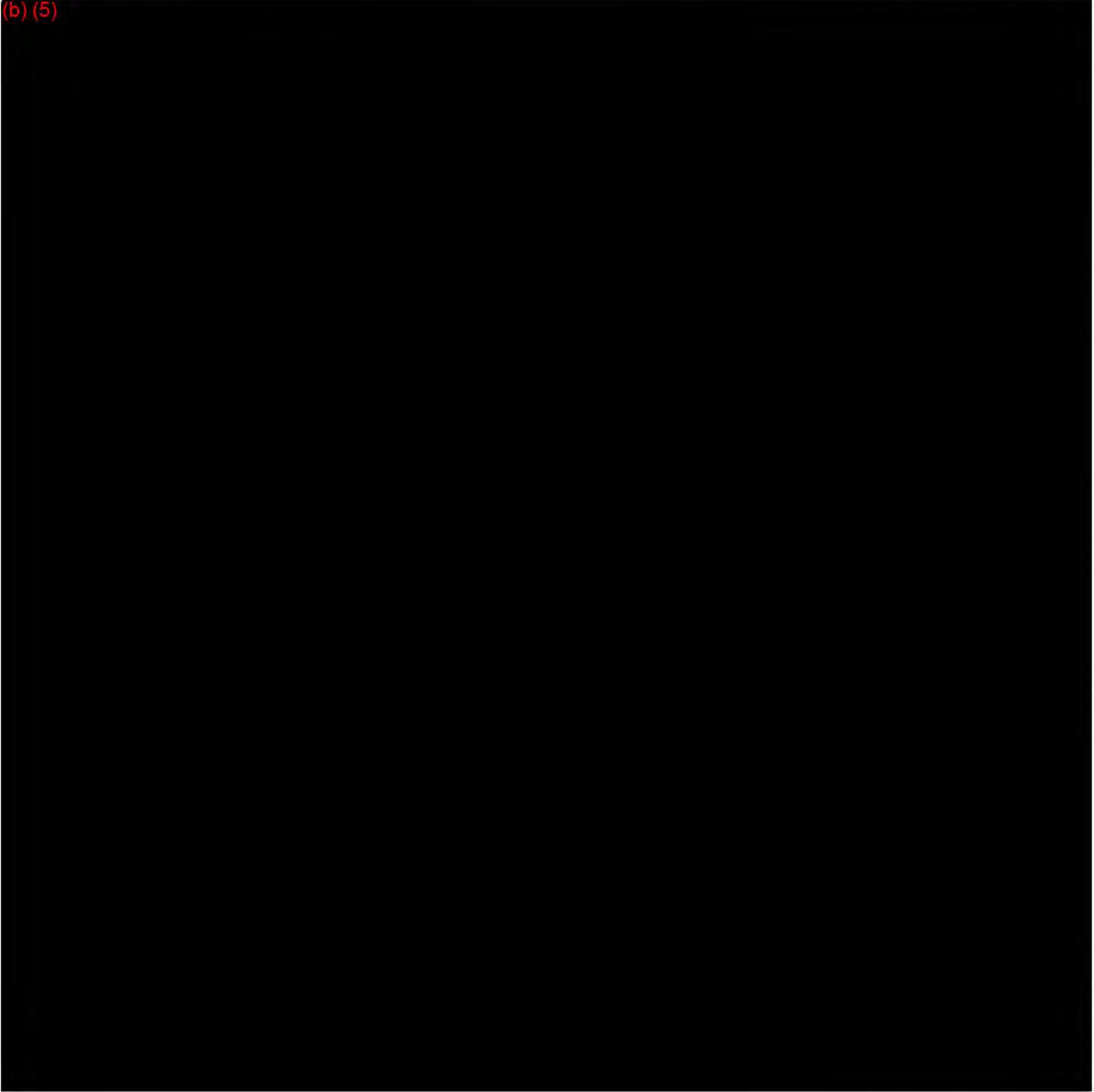
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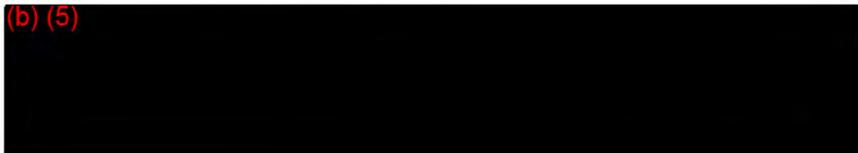
(b) (5)



(b) (5)



(b) (5)



From: Sherman, Rachel
To: Califf, Robert; Chasan-Sloan, Deborah (FDA); Dickinson, Elizabeth (FDA); McCall, Jonathan *
Subject: RE: memo
Date: Thursday, September 15, 2016 5:30:04 PM

I hope you brought the pup back with you!

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 15, 2016 at 5:28:39 PM EDT
To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>
Subject: RE: memo

Thanks to all of you for your work on this. I will have it all back this evening. I'm on board and ready to be airborne after half the day with politicians eyeing the transition and half the day with an amazing tour of our mail import facility at JFK, including hands on training with a K9 who pick out the bad stuff from any pile of boxes.

rmc

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 4:32 PM
To: Chasan-Sloan, Deborah (FDA); McCall, Jonathan *; Califf, Robert; Dickinson, Elizabeth (FDA)
Subject: RE: memo

Score!

From: Chasan-Sloan, Deborah (FDA)
Sent: Thursday, September 15, 2016 4:31 PM
To: Sherman, Rachel; McCall, Jonathan *; Califf, Robert; Dickinson, Elizabeth (FDA)
Subject: RE: memo
Importance: High

(b) (5)

A large black rectangular redaction box covers the body of the email. The text "(b) (5)" is written in red at the top left corner of the redaction.

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 4:25 PM
To: McCall, Jonathan *; Califf, Robert; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Subject: RE: memo

Hi all,

Rob's flight is at 5, not 530. Whatever we have finished by 450 please send to Jonathan who will consolidate into a single email.

The rest we can get him later.

Thanks!

From: McCall, Jonathan *
Sent: Thursday, September 15, 2016 4:15 PM
To: Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Subject: RE: memo

My edits appended.

Thanks!

--
J

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 1:09 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Hi all,

My suggested edits to Rob's cover notes.

Jonathan, you're next up then onto Deborah and then back to Rob.

Thanks!

Rachel

From: Califf, Robert
Sent: Thursday, September 15, 2016 6:56 AM
To: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Here are the proposed intros to responses

rmc

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 6:52 AM
To: Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Okay, sorry I missed this.

I can draft the email this am. I can work on the memo but it may not be until late afternoon.
If someone else can start my feelings won't be hurt.

So email RS to JM to OCC to RMC.

Memo TBD.

OCC (b) (5)

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 15, 2016 at 5:47:49 AM EDT
To: Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Subject: RE: memo

See below for my comments. The question is the format of the response to Ellis, John and Lu. I'm guessing this format is good and if someone can do a draft I can edit tonight, or I can do a draft tonight for editing tomorrow.

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Wednesday, September 14, 2016 11:38 PM
To: Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

(b) (5)

From: Sherman, Rachel
Sent: Wednesday, September 14, 2016 7:32 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Chasan-Sloan, Deborah (FDA)
Subject: RE: memo

Hi,

Liz wisely advised (b) (5)

Limiting this to those who worked on the memo draft.

Rachel

From: Califf, Robert
Sent: Wednesday, September 14, 2016 5:56 PM
To: Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Conover, Katie; Kraus, Tom
Subject: Fwd: memo

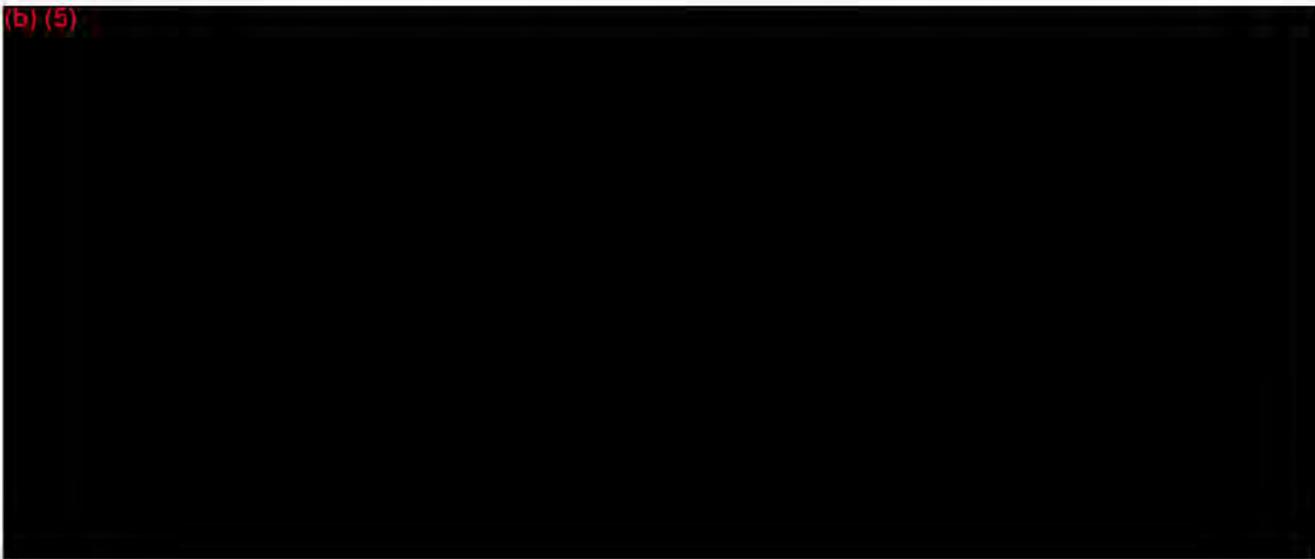
From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: September 14, 2016 at 5:35:44 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Subject: RE: memo

Rob

Thanks for providing an opportunity to review your draft memo regarding the eteplirsen dispute. I am responding just to you since some of the issues I raise below are sensitive. I would be happy to speak with you privately to discuss my concerns in greater detail if you would be open to that.

I ask that you remove reference to quoting me from the July 12, 2016, e-mail that "reasonable people can disagree." I think as used it is mischaracterized and used out of context. I strongly disagree with Janet's decision and do not want my words in a single e-mail to suggest that is not the case.

(b) (5)



As to footnote 7, I think the review team needs to weigh in, but it was my impression that use of corticosteroids has been interpreted based on data to have changed the course of the disease in DMD. We currently have a pending NDA for use of a corticosteroid in DMD.

(b) (5)

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You note on page 3 that due to the serious defects in the development program, “it is impossible to use much of the resulting trial evidence in regulatory decision-making, including reasonable extrapolation to clinical care.” Yet you later support Janet’s conclusion that the sponsor has provided data from “two adequate and well-controlled trials.” I can find no effort to reconcile these very different statements.

(b) (5)

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On page 4, you state “there is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence...” This implies she took these actions BEFORE reaching a decision on the application, which is clearly not correct given her statement to the review team of her intention to overrule them and approve the drug BEFORE they had completed their reviews. Keep in mind this occurred after an AC meeting at which the majority of the panel voted against both AA and full approval. It is also clear that she was prepared to approve the drug over the team’s objections by the original PDUFA goal date and only reluctantly agreed to press the sponsor for additional data on dystrophin production from the ongoing open-label trial. While I am glad she agreed to go along with that request, convincing her to take what seemed like a very logical action was not easy. So, I find it hard to reconcile your statements about the process with the actions taken. Keep in mind that the usual course of action would be for the Office to issue a CR letter and then the sponsor could submit a FDRR that would first come to me and only if I supported the Office would an FDRR go to the Center Director. In this case that process was bypassed.

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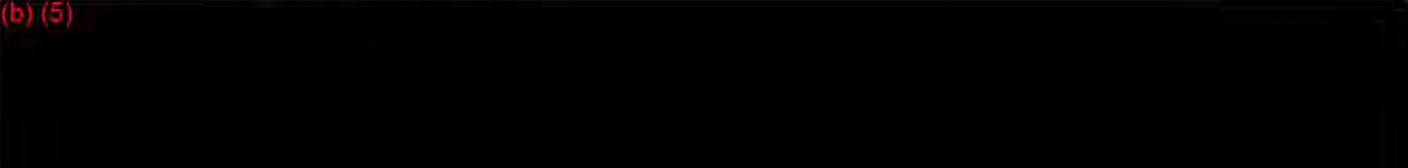
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AC by suggesting this is simply part of her leadership style. I have worked with Janet for over 20 years and I can say without a doubt that her involvement in this case far exceeds her usual "hands on" approach. You note that there were 14 Center director briefings related to this case, that is clearly not the "norm" for how CDER operates. You also suggest that because CDER has been successful under her leadership that suggests that her intense involvement in this case does not raise concern. I see that as true, true, and unrelated. The question in this case is not whether she has overall been an effective leader of CDER, but whether she acted appropriately and without bias in the current case, something I don't think you effectively address given the evidence and the seriousness of the allegations and concerns expressed.

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As to your footnote 23, there are direct statements that Janet made to the team that contradict the statements you reference from your interview with her. I am happy to discuss these statements with you further. In addition, Janet has had frequent private conversations with the sponsor and the stakeholder community. To my knowledge, she has not documented the substance of those conversations to the record, as is required under FDA regulations. That leaves a gap of knowledge to evaluate the concerns raised by the review team and Dr. Borio.

I do not find your statements about how this case does not lower the bar for future drug approvals convincing. I share the concerns voiced by Drs. Unger and Borio about the potential adverse impact on FDA's ability to reach science-based conclusions on future applications.

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new randomized trial not be required. So, if Janet had followed the normal CDER process in this case the review team would have required placebo-controlled trials, as they did for drisapersen (b) (4), and we would have better data on which to make a decision. I would note that Janet did not and has not involved herself in the drisapersen (b) (4) cases to the same degree as eteplirsen. Drisapersen arguably (b) (4); they had a positive phase 2 trial and a second trial that leaned favorably on a clinical endpoint. Janet did not object to the division asking for a large phase 3 trial and did not object to ODE1's decision to issue a CR letter based on (b) (4) trial. I think it is reasonable to question why she devoted so much attention to eteplirsen and not the other (b) drugs. One could speculate that she too was misled by the early reports on dystrophin production that were later discredited.

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The overall tone of your memo seems to say that you conclude that Janet behaved and conducted herself appropriately in this case. That is at odds with the experience of the review team and is counter to the team-based, collegial working environment that we hope to create at FDA so we can accomplish our important public health mission. This validation from your level of her actions and behavior is worrisome. While I understand your desire not to undercut her role as Center Director, her actions have at best created a serious appearance of bias among the review team members and that has created distrust and a sense of undue pressure to "come around" to her way of thinking. Even if you uphold her decision I would think you should counsel her about how her behavior and actions have undermined her credibility among the review staff and should be avoided in future similar cases. Effective leaders must have the trust and respect of their staff. As I noted in our call last week, there are frequent disagreements about data and actions in CDER, and that is healthy and encouraged so we can ensure we hear all voices as we make decision, what is not healthy is a situation where the actions of a leader creates the appearance of bias since this undermines the trust necessary for the review team to conclude that the action was fair and move on.

I understand this appeal has placed you in a very difficult position. I also understand that you have made your decision. I hope, that my comments can help you to structure your decisional memo to avoid similar situations in the future. As you know, I had planned to retire from FDA last spring. I have delayed my departure for a variety of reasons, but one of the most important reasons is that Janet has told me she plans to serve as acting in my place as head of OND once I leave. I am very concerned about the impact of that decision on the future of the new drugs review program and would be happy to discuss those concerns further.
John

From: Califf, Robert

FDAOC0002128

Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

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First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD
Commissioner, Food and Drugs

From: [Sherman, Rachel](#)
To: [Dickinson, Elizabeth \(FDA\)](#); [Califf, Robert](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Cc: [McCall, Jonathan *](#)
Subject: RE: memo
Date: Thursday, September 15, 2016 8:34:57 AM

I don't know what that means. Are you available to talk?

From: Dickinson, Elizabeth (FDA)
Sent: Thursday, September 15, 2016 8:34 AM
To: [Califf, Robert](#); [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Cc: [McCall, Jonathan *](#)
Subject: Re: memo

(b) (5)



From: [Califf, Robert](#)
Sent: Thursday, September 15, 2016 8:27 AM
To: [Dickinson, Elizabeth \(FDA\)](#); [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Cc: [McCall, Jonathan *](#)
Subject: RE: memo

I'm really tied up till this evening. Do we want one memo or one for each person?

From: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Date: September 15, 2016 at 8:22:22 AM EDT
To: [Califf, Robert <RMC1@fda.hhs.gov>](mailto:RMC1@fda.hhs.gov), [Chasan-Sloan, Deborah \(FDA\) <Deborah.Chasan-Sloan@fda.hhs.gov>](mailto:Deborah.Chasan-Sloan@fda.hhs.gov), [Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>](mailto:Rachel.Sherman@fda.hhs.gov)
Cc: [McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>](mailto:Jonathan.McCall@fda.hhs.gov)
Subject: RE: memo

(b) (5)



From: Sherman, Rachel
Sent: Thursday, September 15, 2016 7:56 AM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Okay, I'm lost.

You have drafted the cover notes – so now onto JM, then OCC, then back to you.

But you reference embedded text. That where I am lost – do you want us to clean up what we all added and forward those?

If so, I think OCC needs to concur.

From: Califf, Robert
Sent: Thursday, September 15, 2016 6:56 AM
To: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Here are the proposed intros to responses

rmc

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 6:52 AM
To: Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Okay, sorry I missed this.

I can draft the email this am. I can work on the memo but it may not be until late afternoon.
If someone else can start my feelings won't be hurt.

So email RS to JM to OCC to RMC.

Memo TBD.

OCC (b) (5)

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 15, 2016 at 5:47:49 AM EDT
To: Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Subject: RE: memo

See below for my comments. The question is the format of the response to Ellis, John and Lu. I'm guessing this format is good and if someone can do a draft I can edit tonight, or I can do a draft tonight for editing tomorrow.

rnc

From: Chasan-Sloan, Deborah (FDA)
Sent: Wednesday, September 14, 2016 11:38 PM
To: Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

(b) (5)



From: Sherman, Rachel
Sent: Wednesday, September 14, 2016 7:32 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Chasan-Sloan, Deborah (FDA)
Subject: RE: memo

Hi,

Liz wisely advised (b) (5)



Limiting this to those who worked on the memo draft.

Rachel

From: Califf, Robert
Sent: Wednesday, September 14, 2016 5:56 PM
To: Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Conover, Katie; Kraus, Tom
Subject: Fwd: memo

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>

Date: September 14, 2016 at 5:35:44 PM EDT

To: Califf, Robert <RMC1@fda.hhs.gov>

Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>

Subject: RE: memo

Rob

Thanks for providing an opportunity to review your draft memo regarding the eteplirsen dispute. I am responding just to you since some of the issues I raise below are sensitive. I would be happy to speak with you privately to discuss my concerns in greater detail if you would be open to that.

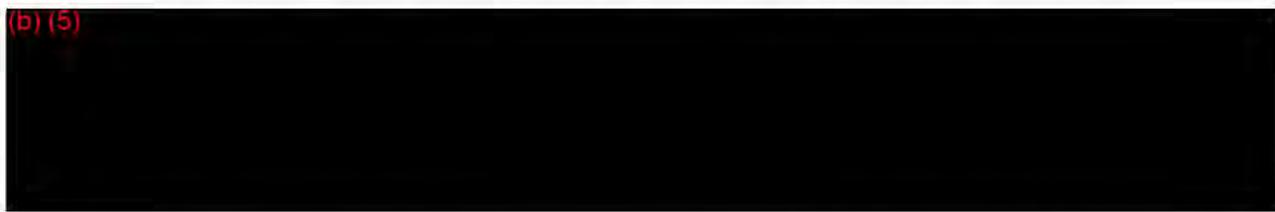
I ask that you remove reference to quoting me from the July 12, 2016, e-mail that "reasonable people can disagree." I think as used it is mischaracterized and used out of context. I strongly disagree with Janet's decision and do not want my words in a single e-mail to suggest that is not the case.

(b) (5)



As to footnote 7, I think the review team needs to weigh in, but it was my impression that use of corticosteroids has been interpreted based on data to have changed the course of the disease in DMD. We currently have a pending NDA for use of a corticosteroid in DMD.

(b) (5)



You note on page 3 that due to the serious defects in the development program, "it is

impossible to use much of the resulting trial evidence in regulatory decision-making, including reasonable extrapolation to clinical care.” Yet you later support Janet’s conclusion that the sponsor has provided data from “two adequate and well-controlled trials.” I can find no effort to reconcile these very different statements.

(b) (5)

A large black rectangular redaction box covering several lines of text.

On page 4, you state “there is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence...” This implies she took these actions BEFORE reaching a decision on the application, which is clearly not correct given her statement to the review team of her intention to overrule them and approve the drug BEFORE they had completed their reviews. Keep in mind this occurred after an AC meeting at which the majority of the panel voted against both AA and full approval. It is also clear that she was prepared to approve the drug over the team’s objections by the original PDUFA goal date and only reluctantly agreed to press the sponsor for additional data on dystrophin production from the ongoing open-label trial. While I am glad she agreed to go along with that request, convincing her to take what seemed like a very logical action was not easy. So, I find it hard to reconcile your statements about the process with the actions taken. Keep in mind that the usual course of action would be for the Office to issue a CR letter and then the sponsor could submit a FDRR that would first come to me and only if I supported the Office would an FDRR go to the Center Director. In this case that process was bypassed.

(b) (5)

A large black rectangular redaction box covering several lines of text.

On page 4 you state that Dr. Woodcock “finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is “reasonably likely” to predict clinical benefit.” This statement defies any sense of scientific reason (would one molecule of dystrophin be enough) and goes directly to Dr. Unger’s concern that “any” level of protein seems to be enough for Janet to support approval. You then go on to reference Janet’s regression analyses from her memo suggesting a correlation between dystrophin production and clinical outcomes. As I have noted to you on

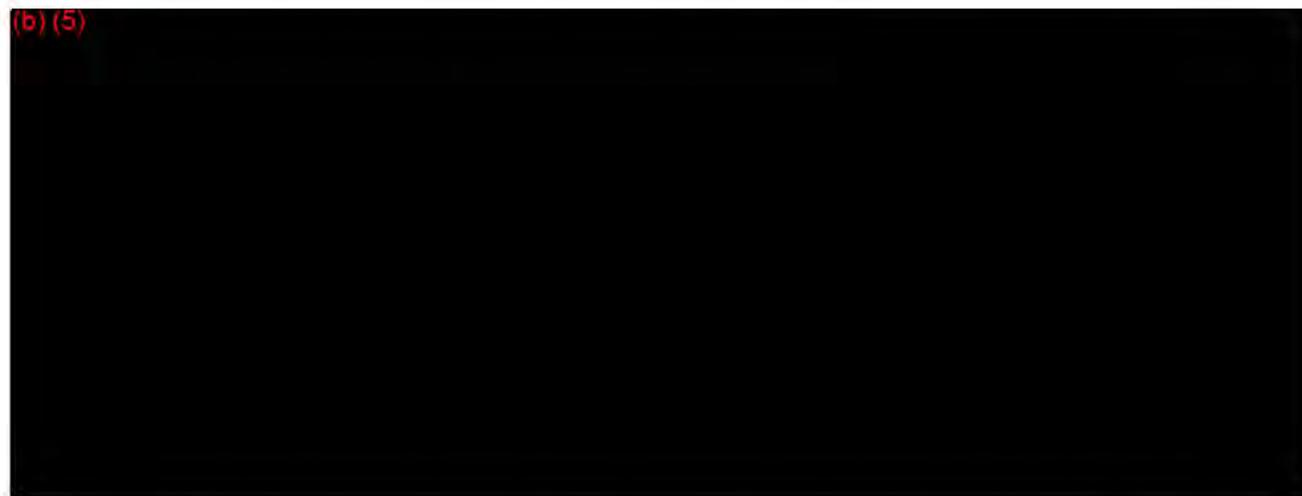
several occasions, I find this to be a scientifically invalid analysis that compares the endpoint value for dystrophin to a delta in a clinical endpoint. This analysis simply shows a correlation between higher levels of dystrophin, without regard to drug effect (there is no delta for dystrophin change that is due to drug), and cannot support the conclusion she reached. Your citation of this analysis is troubling.

(b) (5)



You make reference in several places to a “totality of evidence” standard. That is not the statutory standard for demonstration of effectiveness and FDA has always stated that the statutory standard for demonstration of an effect on a surrogate endpoint for AA is the same as for regular approval (i.e., substantial evidence). Perhaps you are using “totality of evidence” to support the decision that the data provided on the surrogate are reasonably likely to predict clinical benefit, but there must be substantial evidence of the drug’s effect on the surrogate and the data are very weak to meet that standard.

(b) (5)



You dismiss the concerns about Janet’s level of involvement in this review and her role at the AC by suggesting this is simply part of her leadership style. I have worked with Janet for over 20 years and I can say without a doubt that her involvement in this case far exceeds her usual “hands on” approach. You note that there were 14 Center director briefings related to this case, that is clearly not the “norm” for how CDER operates. You also suggest that because CDER has been successful under her leadership that suggests that her intense involvement in this case does not raise concern. I see that as true, true, and unrelated. The question in this case is not whether she has overall been an effective leader of CDER, but whether she acted appropriately and without bias in the current case, something I don’t think you effectively address given the evidence and the seriousness of the allegations and concerns expressed.

(b) (5)

As to your footnote 23, there are direct statements that Janet made to the team that contradict the statements you reference from your interview with her. I am happy to discuss these statements with you further. In addition, Janet has had frequent private conversations with the sponsor and the stakeholder community. To my knowledge, she has not documented the substance of those conversations to the record, as is required under FDA regulations. That leaves a gap of knowledge to evaluate the concerns raised by the review team and Dr. Borio.

I do not find your statements about how this case does not lower the bar for future drug approvals convincing. I share the concerns voiced by Drs. Unger and Borio about the potential adverse impact on FDA's ability to reach science-based conclusions on future applications.

(b) (5)

. On page 9 it would be nice to see you call explicitly for retraction of the publications that have now been discredited.

(b) (5)

. Also on page 9 it is ironic that you attribute to Janet the idea of randomizing early in order to generate good evidence. That is exactly what the review team planned to require of Sarepta after the results of the 12-patient study became available, but it was Janet that pressed that a new randomized trial not be required. So, if Janet had followed the normal CDER process in this case the review team would have required placebo-controlled trials, as they did for drisapersen (b) (4), and we would have better data on which to make a decision. I would note that Janet did not and has not involved herself in the drisapersen (b) (4) cases to the same degree as eteplirsen. Drisapersen arguably (b) (4); they had a positive phase 2 trial and a second trial that leaned favorably on a clinical endpoint. Janet did not object to the division asking for a large phase 3 trial and did not object to ODE1's decision to issue a CR letter based on (b) (4). I think it is reasonable to question why she devoted so much attention to eteplirsen and not the

other (b) drugs. One could speculate that she too was misled by the early reports on dystrophin production that were later discredited.

(b) (5)

The overall tone of your memo seems to say that you conclude that Janet behaved and conducted herself appropriately in this case. That is at odds with the experience of the review team and is counter to the team-based, collegial working environment that we hope to create at FDA so we can accomplish our important public health mission. This validation from your level of her actions and behavior is worrisome. While I understand your desire not to undercut her role as Center Director, her actions have at best created a serious appearance of bias among the review team members and that has created distrust and a sense of undue pressure to "come around" to her way of thinking. Even if you uphold her decision I would think you should counsel her about how her behavior and actions have undermined her credibility among the review staff and should be avoided in future similar cases. Effective leaders must have the trust and respect of their staff. As I noted in our call last week, there are frequent disagreements about data and actions in CDER, and that is healthy and encouraged so we can ensure we hear all voices as we make decision, what is not healthy is a situation where the actions of a leader creates the appearance of bias since this undermines the trust necessary for the review team to conclude that the action was fair and move on.

I understand this appeal has placed you in a very difficult position. I also understand that you have made your decision. I hope, that my comments can help you to structure your decisional memo to avoid similar situations in the future. As you know, I had planned to retire from FDA last spring. I have delayed my departure for a variety of reasons, but one of the most important reasons is that Janet has told me she plans to serve as acting in my place as head of OND once I leave. I am very concerned about the impact of that decision on the future of the new drugs review program and would be happy to discuss those concerns further.

John

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we

have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board's memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD
Commissioner, Food and Drugs

From: Dickinson, Elizabeth (FDA)
To: Califf, Robert; McCall, Jonathan *
Cc: Sherman, Rachel; Chasan-Sloan, Deborah (FDA); Kraus, Tom; Conover, Katie; Rodriguez, Jennifer
Subject: RE: Eteplirsen decision memo and supporting materials for your review
Date: Thursday, September 15, 2016 10:35:49 PM
Attachments: [2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN\(occ\)\(2\)\(dcs\)\(ehd\)\(2\).doc](#)
[Electronic Letterhead for White Oak3.doc](#)
[Memo to File re Commissioner Decision 9-15-16_JMrs\(occ\)_CLEAN\(dcs\).doc](#)

(b) (5)



From: Califf, Robert
Sent: Thursday, September 15, 2016 9:16 PM
To: McCall, Jonathan *
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom; Conover, Katie; Rodriguez, Jennifer
Subject: RE: Eteplirsen decision memo and supporting materials for your review

<< File: 20160915 Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN_rmc.doc >>

Comments added. Hopefully this will do it. Should be easy for you to check out.

rmc

From: McCall, Jonathan *
Sent: Thursday, September 15, 2016 4:56 PM
To: Califf, Robert
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom
Subject: Eteplirsen decision memo and supporting materials for your review

Hello Dr. Califf –

Here is the current version of the eteplirsen memo:

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2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ)_Commented.doc >>

Here is the memo to file:

<< File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN.doc >> << File:
Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_COMMENTED.doc >>

And here are the response cover notes:

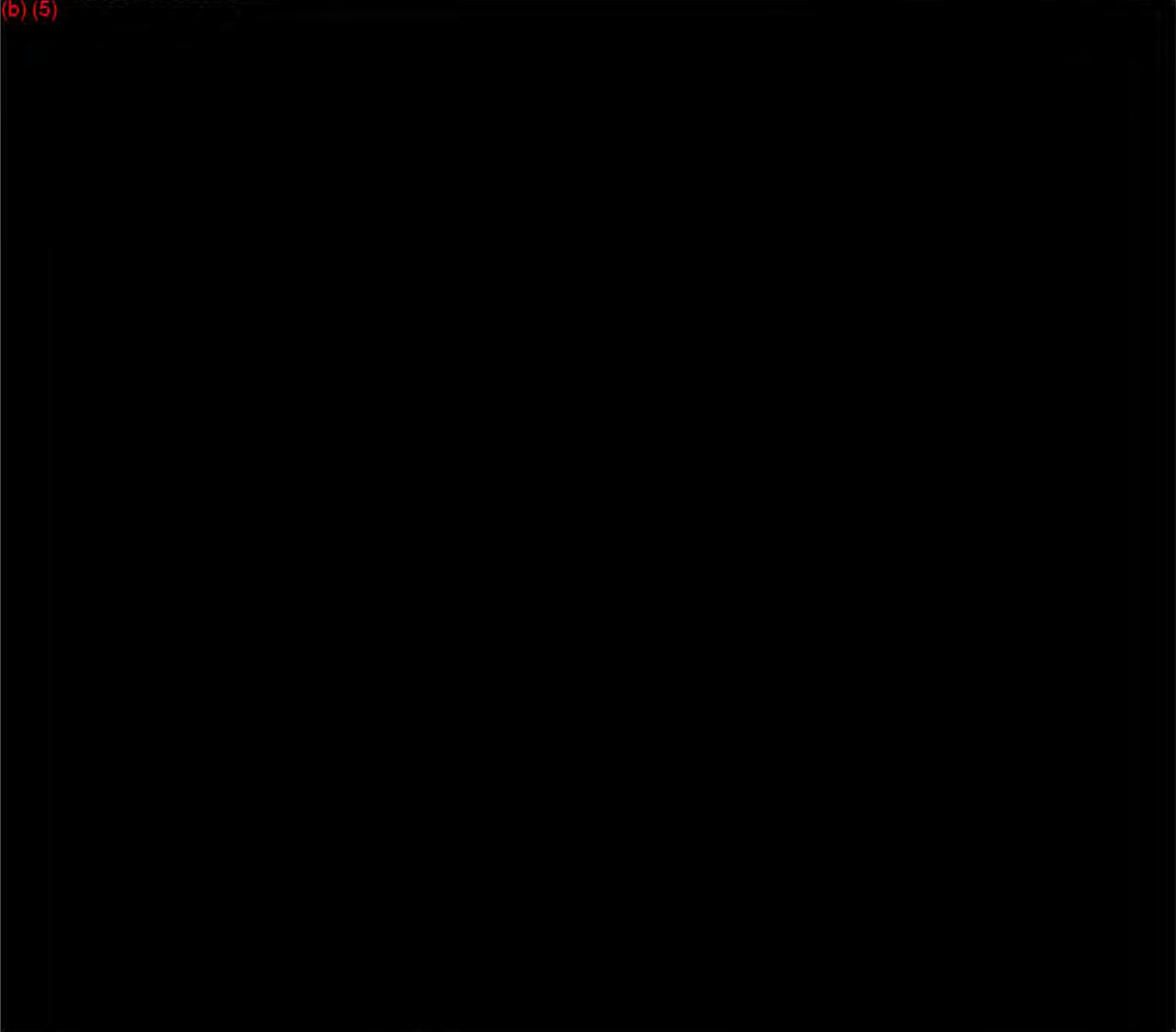
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notesrs_JM_TRACKED.doc >>

Thanks!

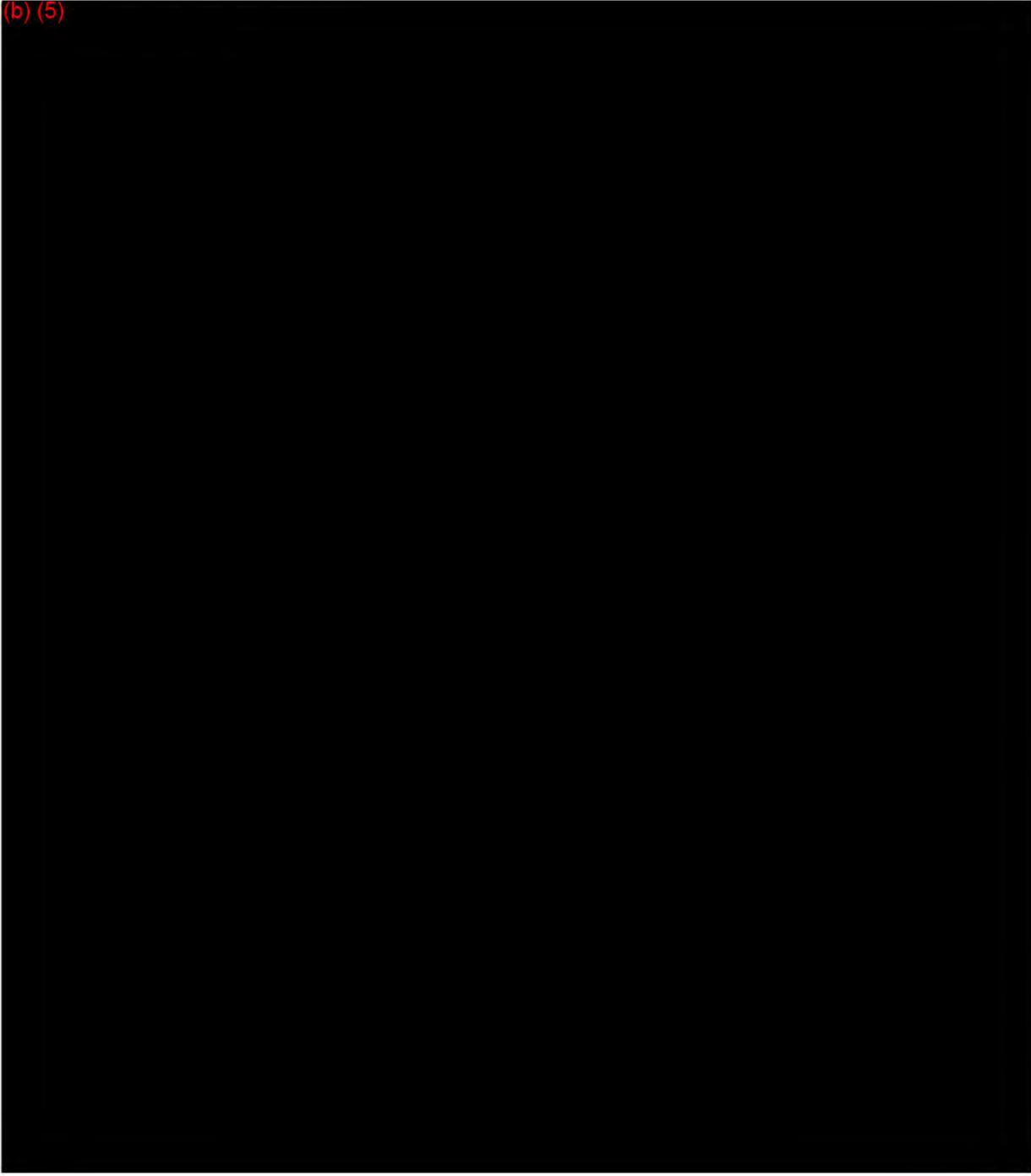
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Jonathan

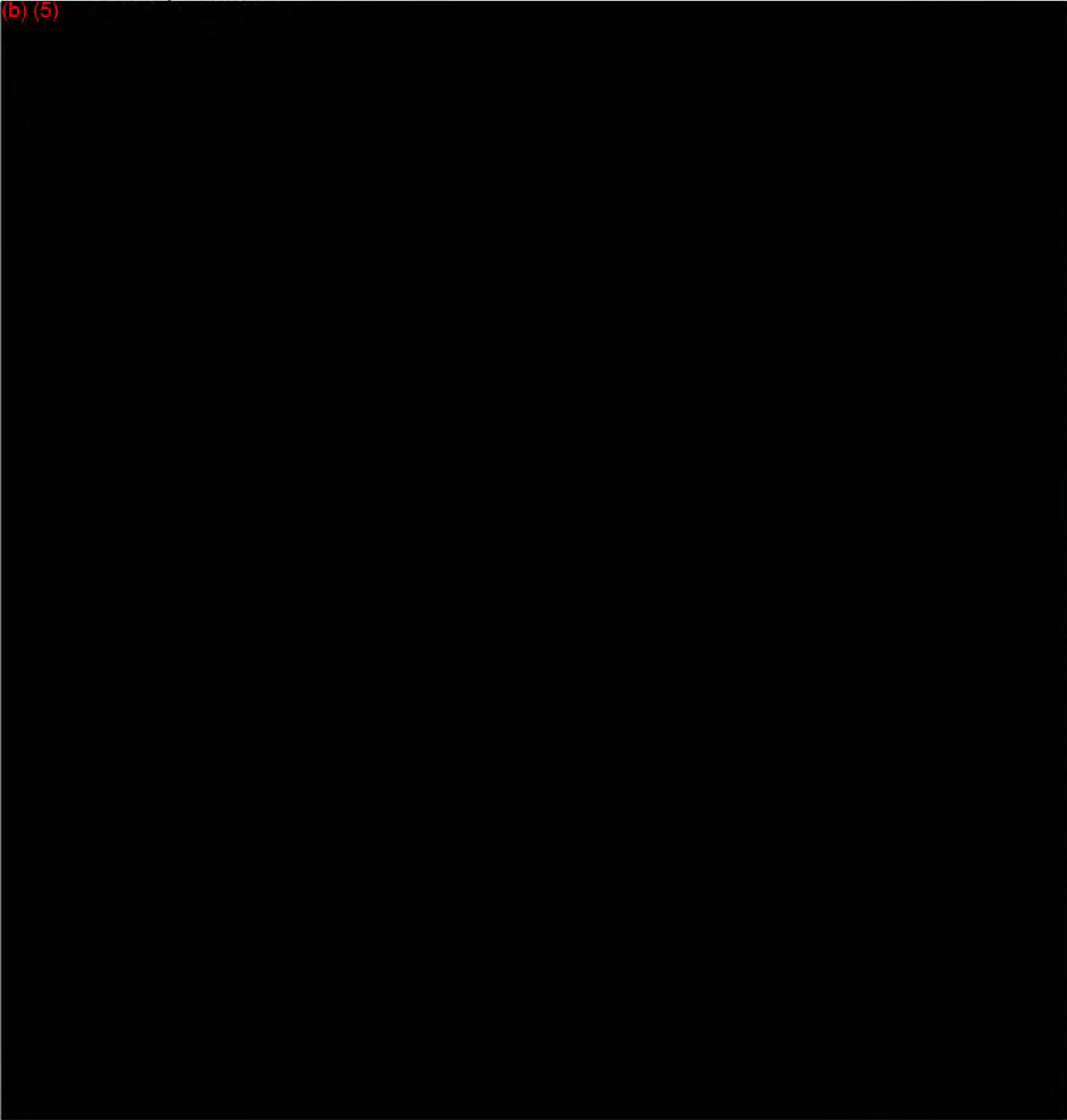
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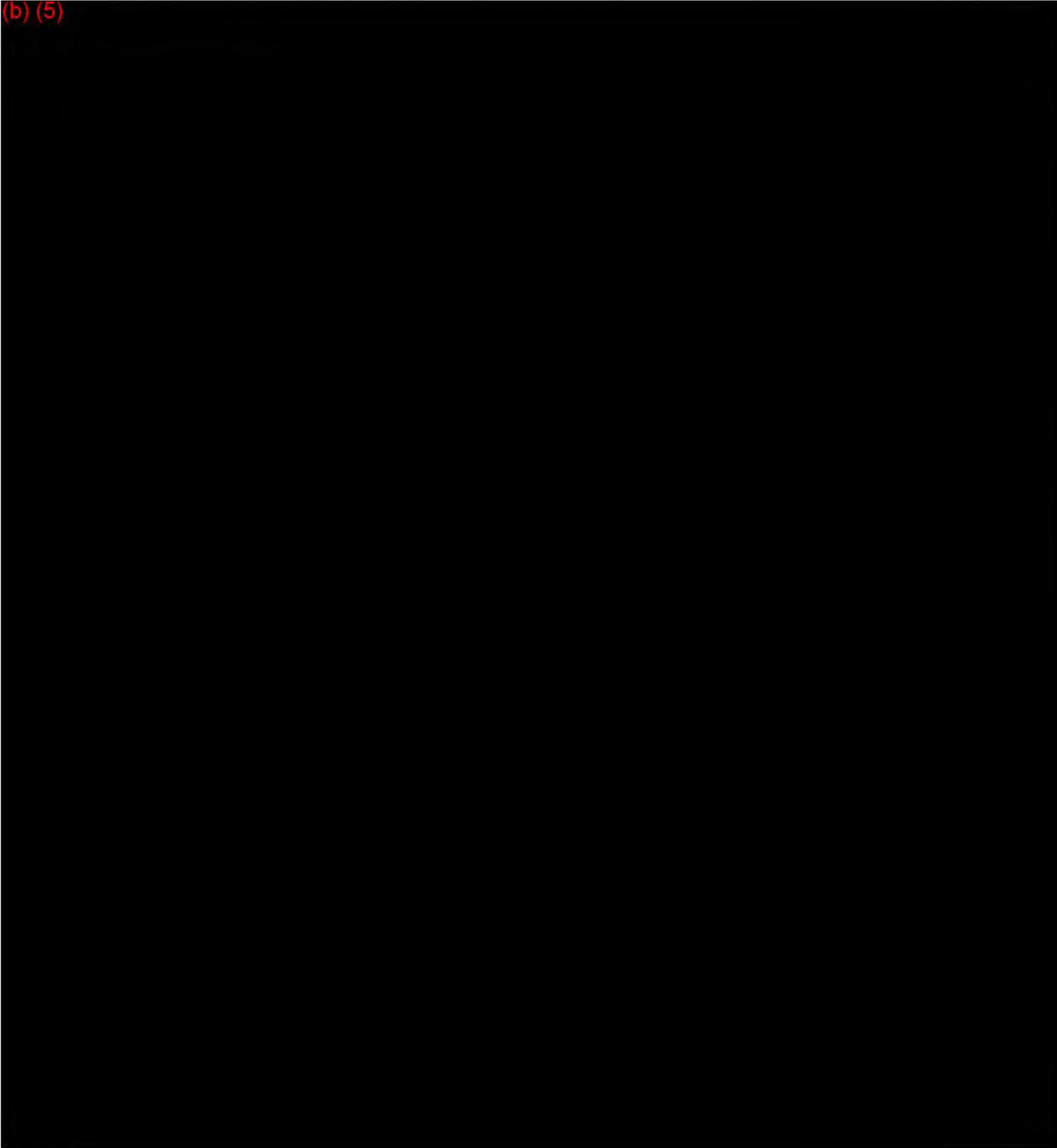


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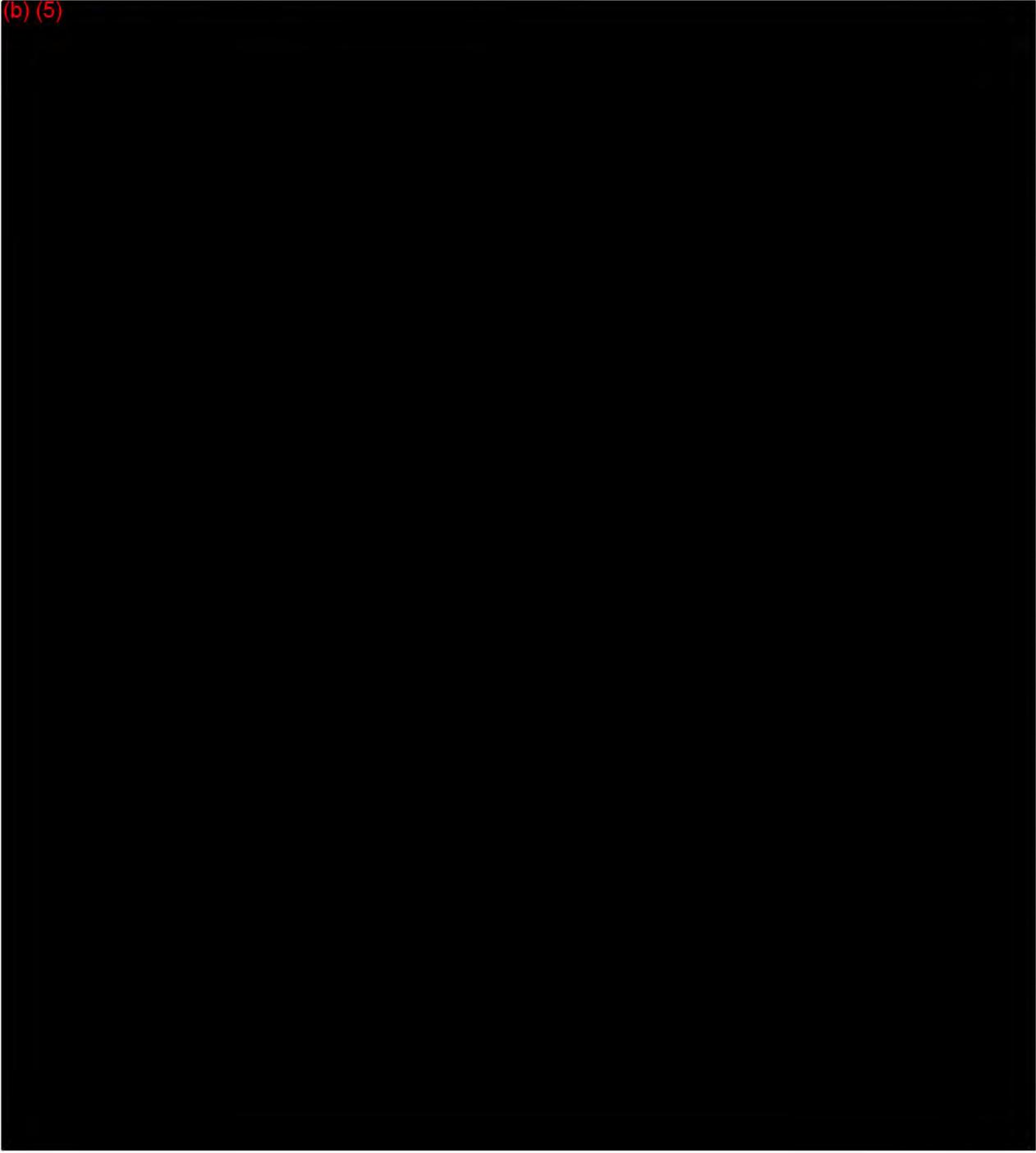
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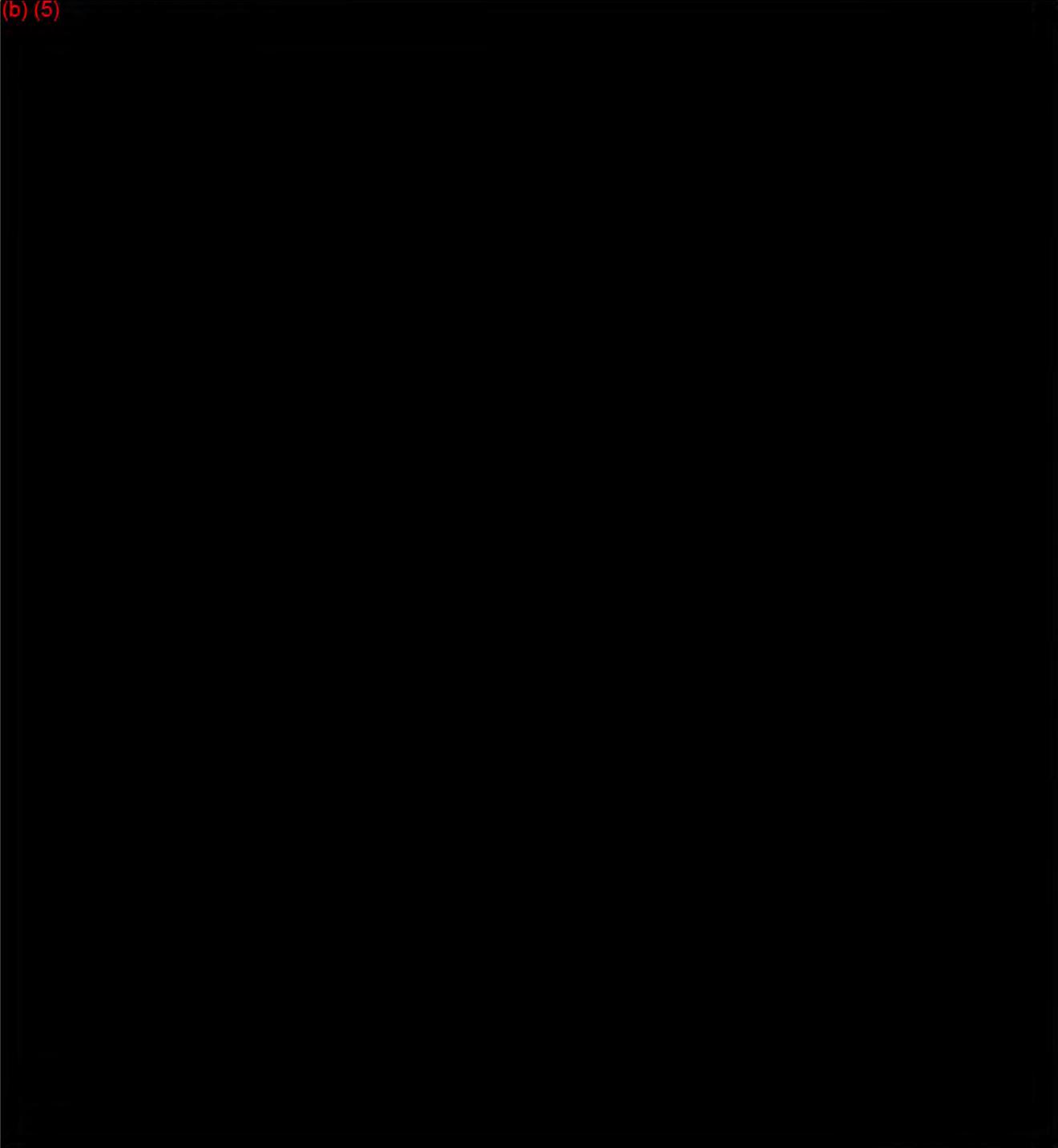
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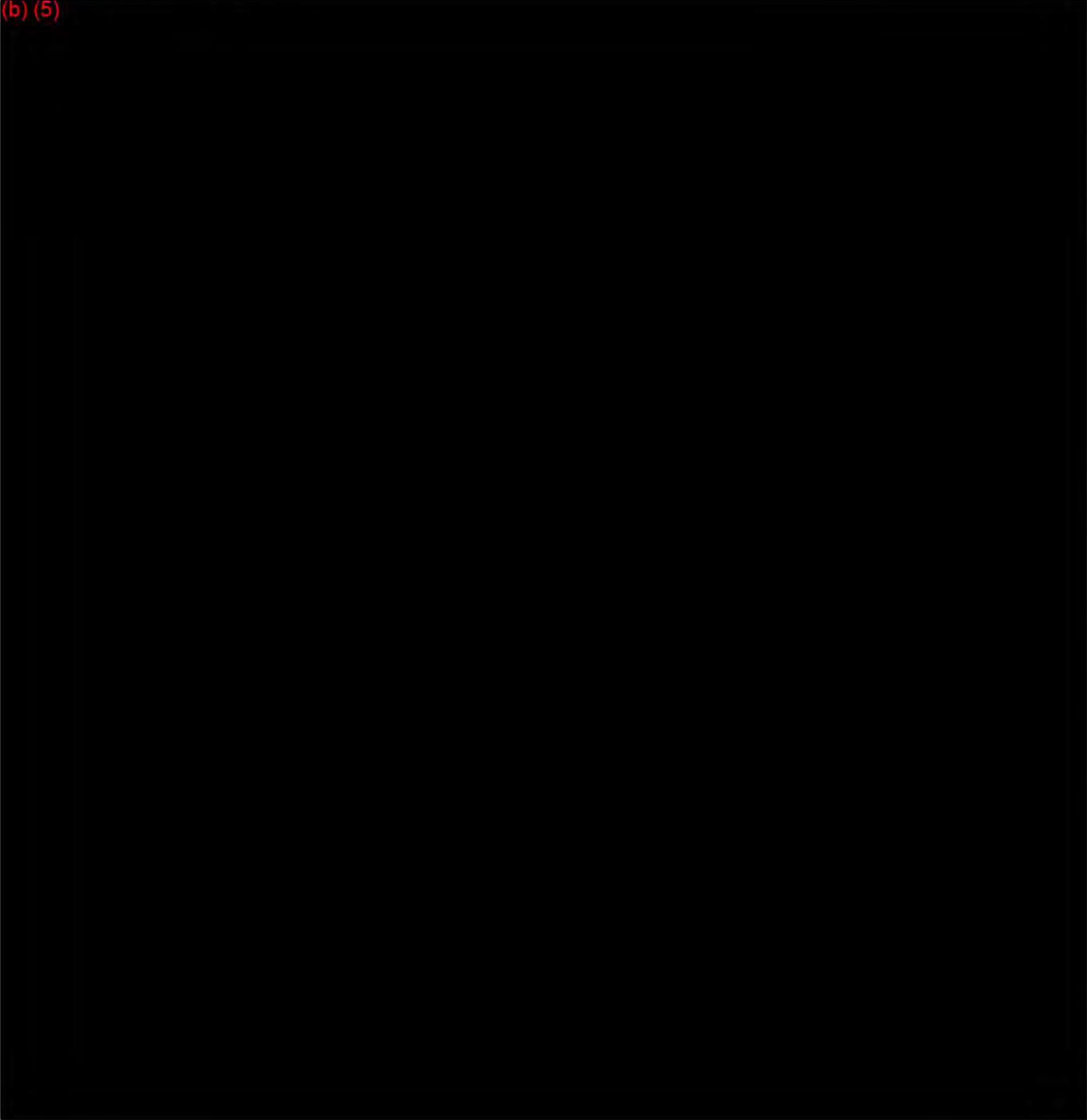


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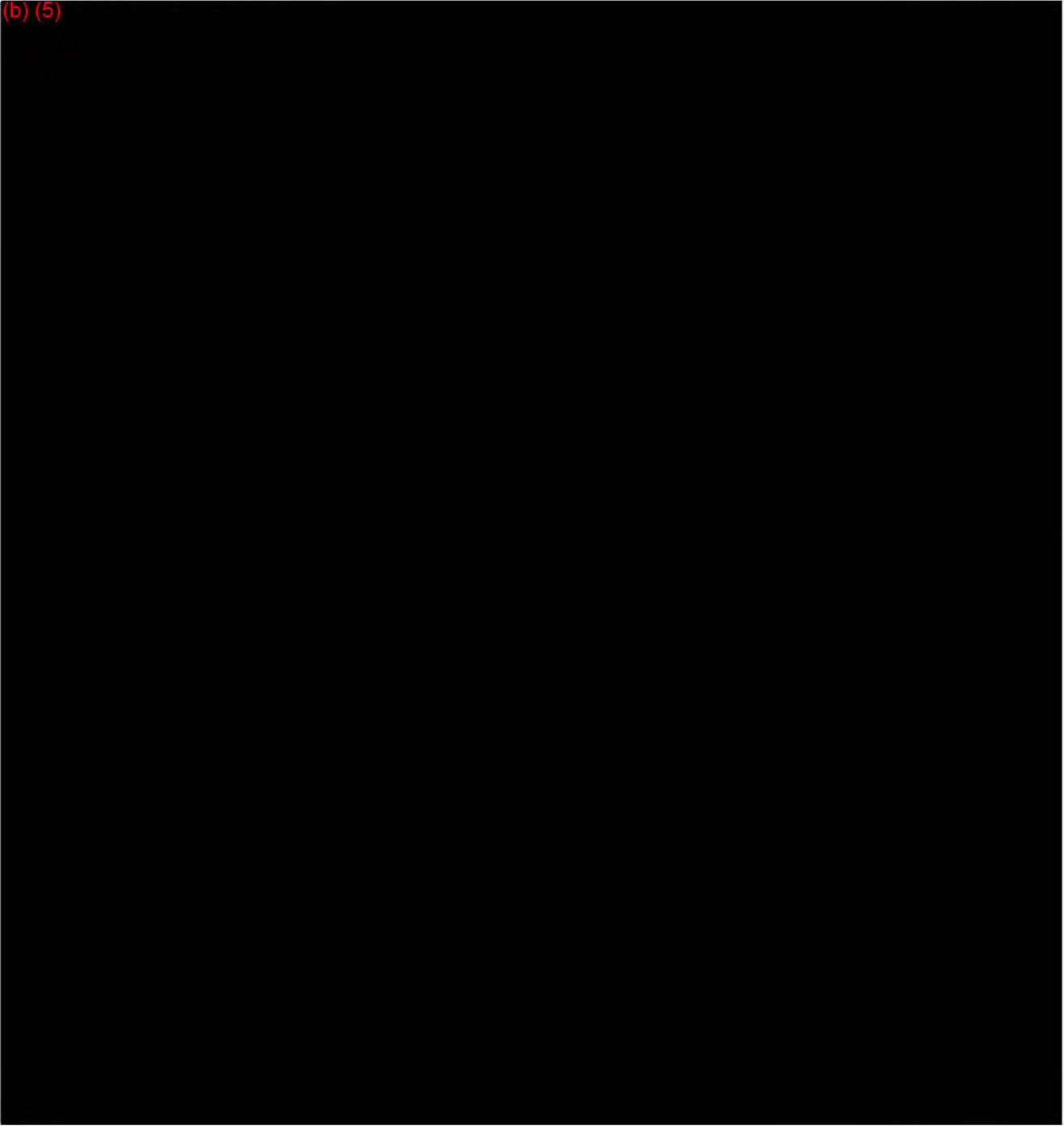
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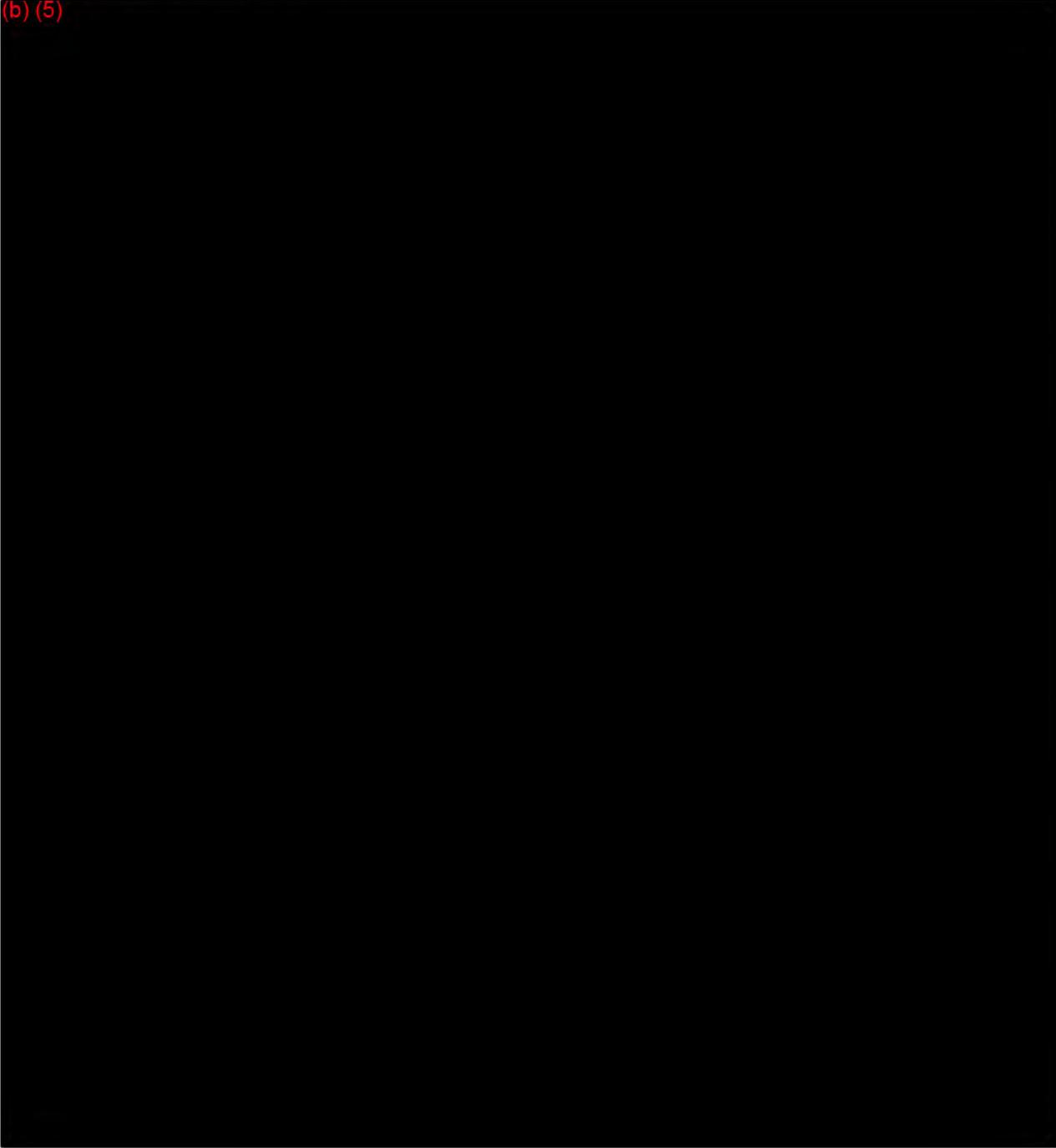
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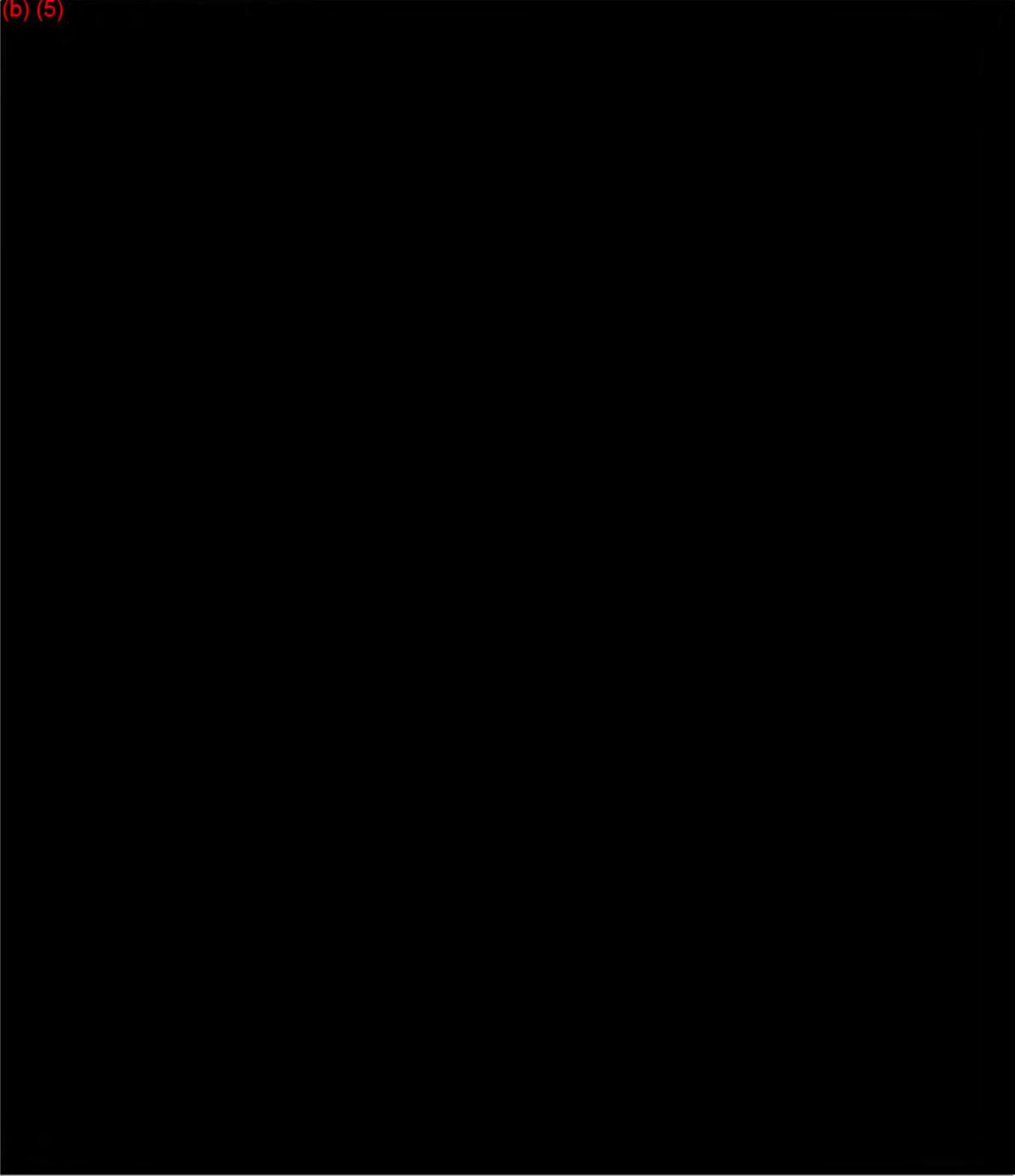


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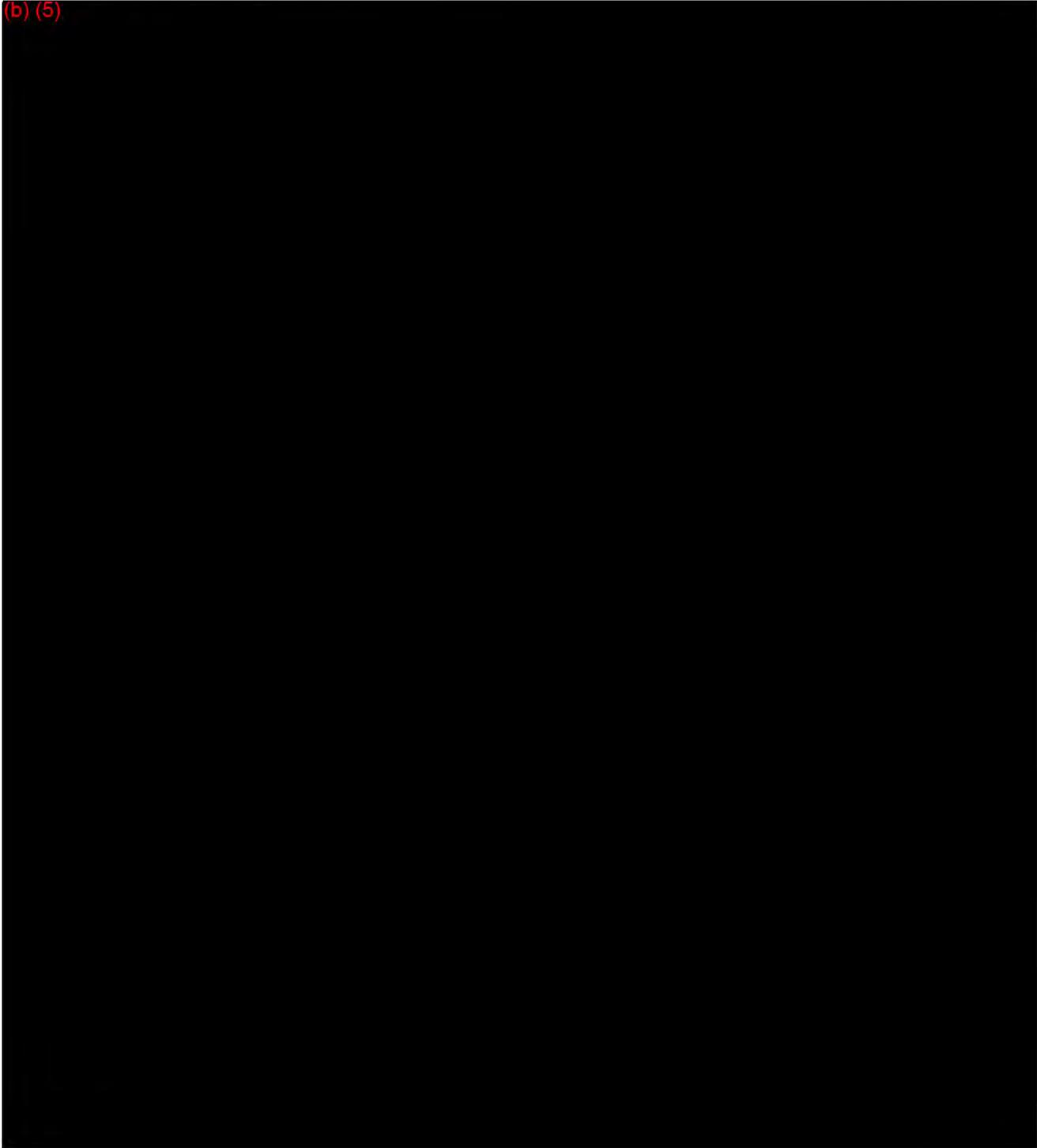


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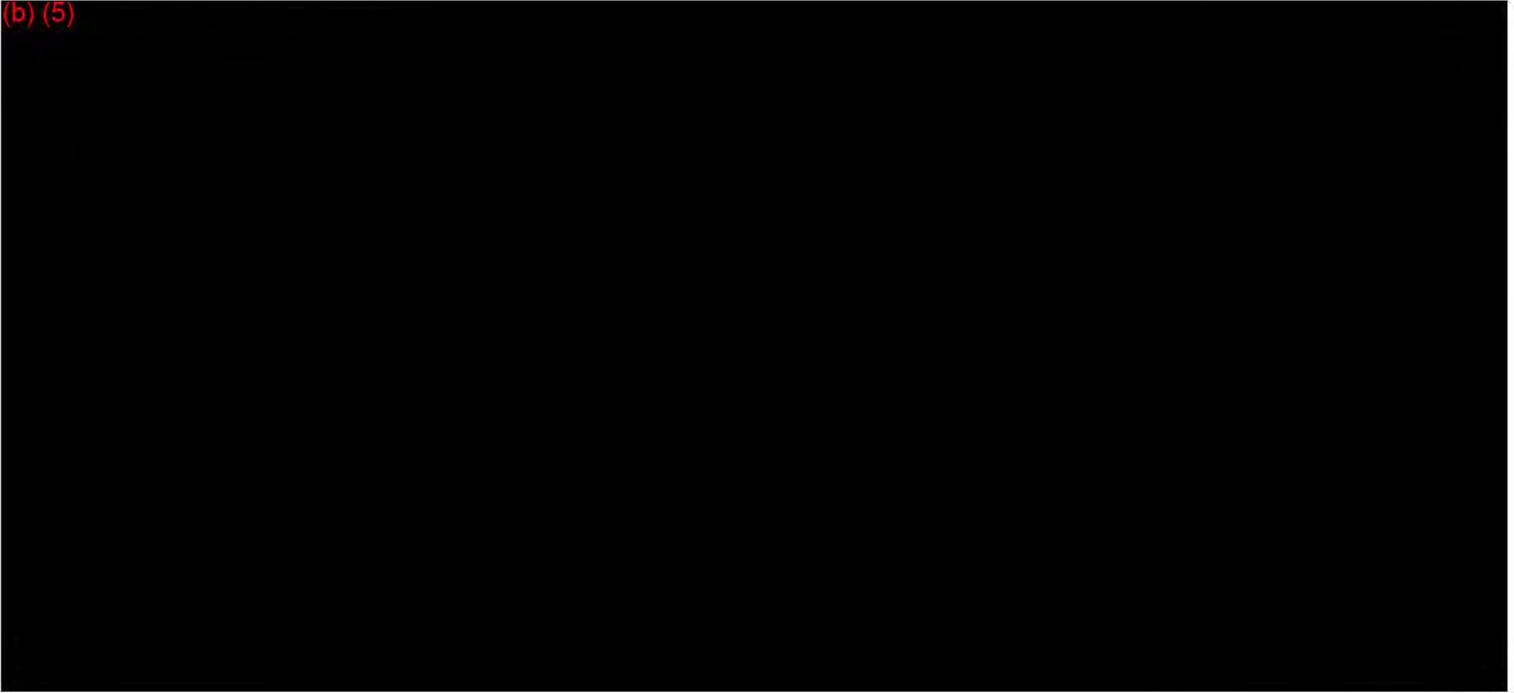


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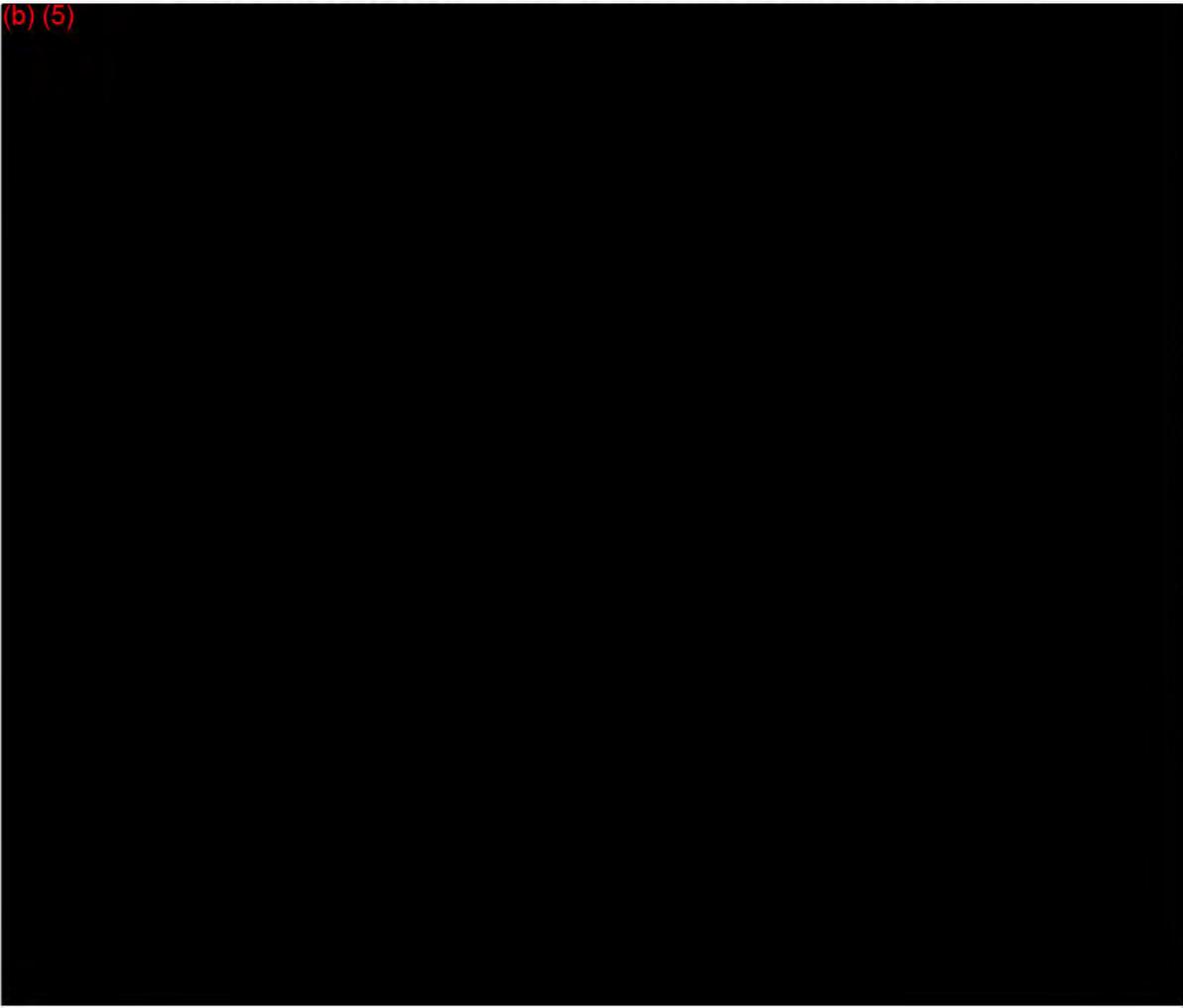
MEMO TO FILE

FROM: Robert Califf, M.D., Commissioner of Food and Drugs

DATE:

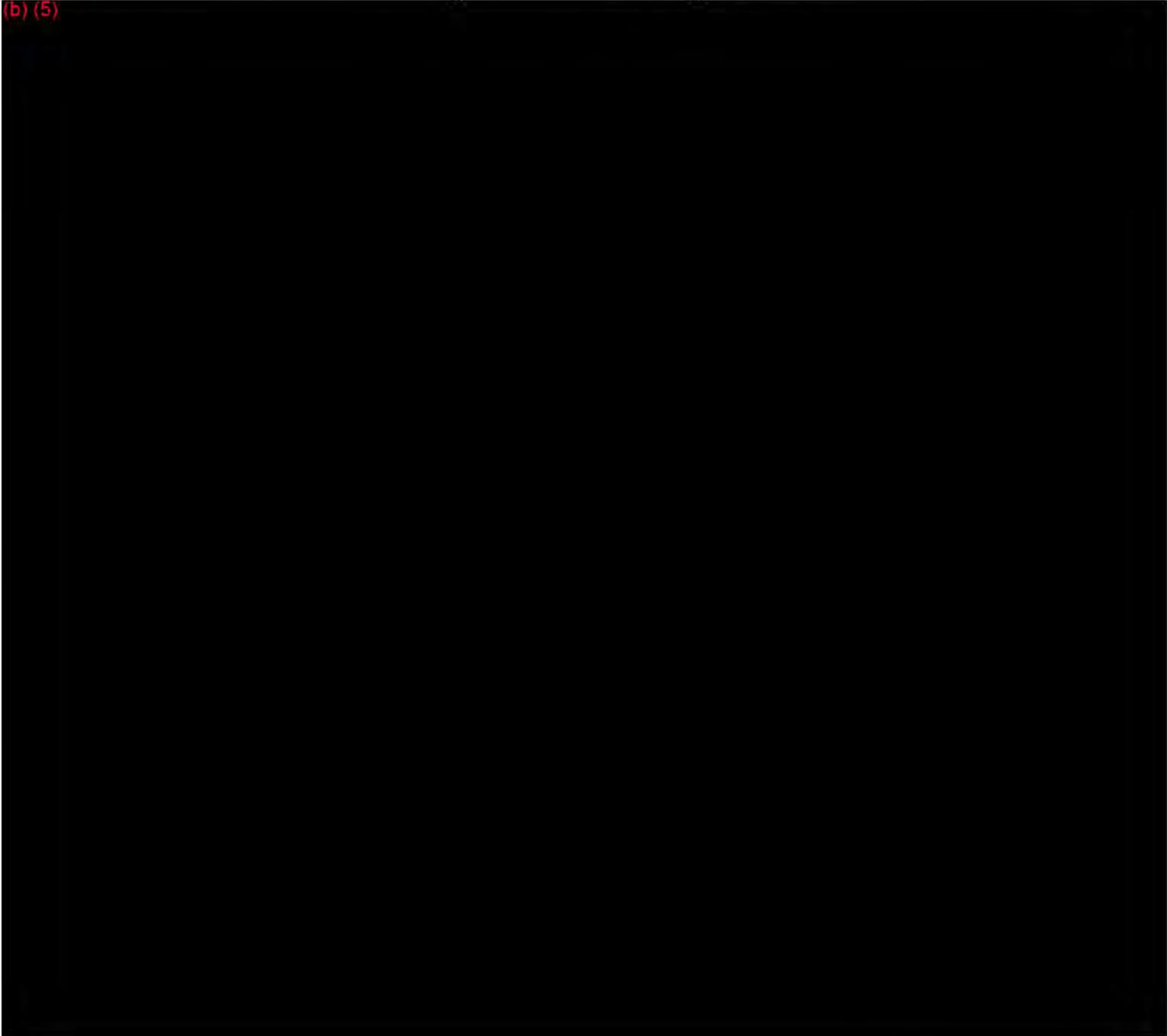
**RE: Process for Commissioner's Decision about the Scientific Dispute Regarding
Accelerated Approval of Sarepta Therapeutics' Eteplirsen (NDA 206488)**

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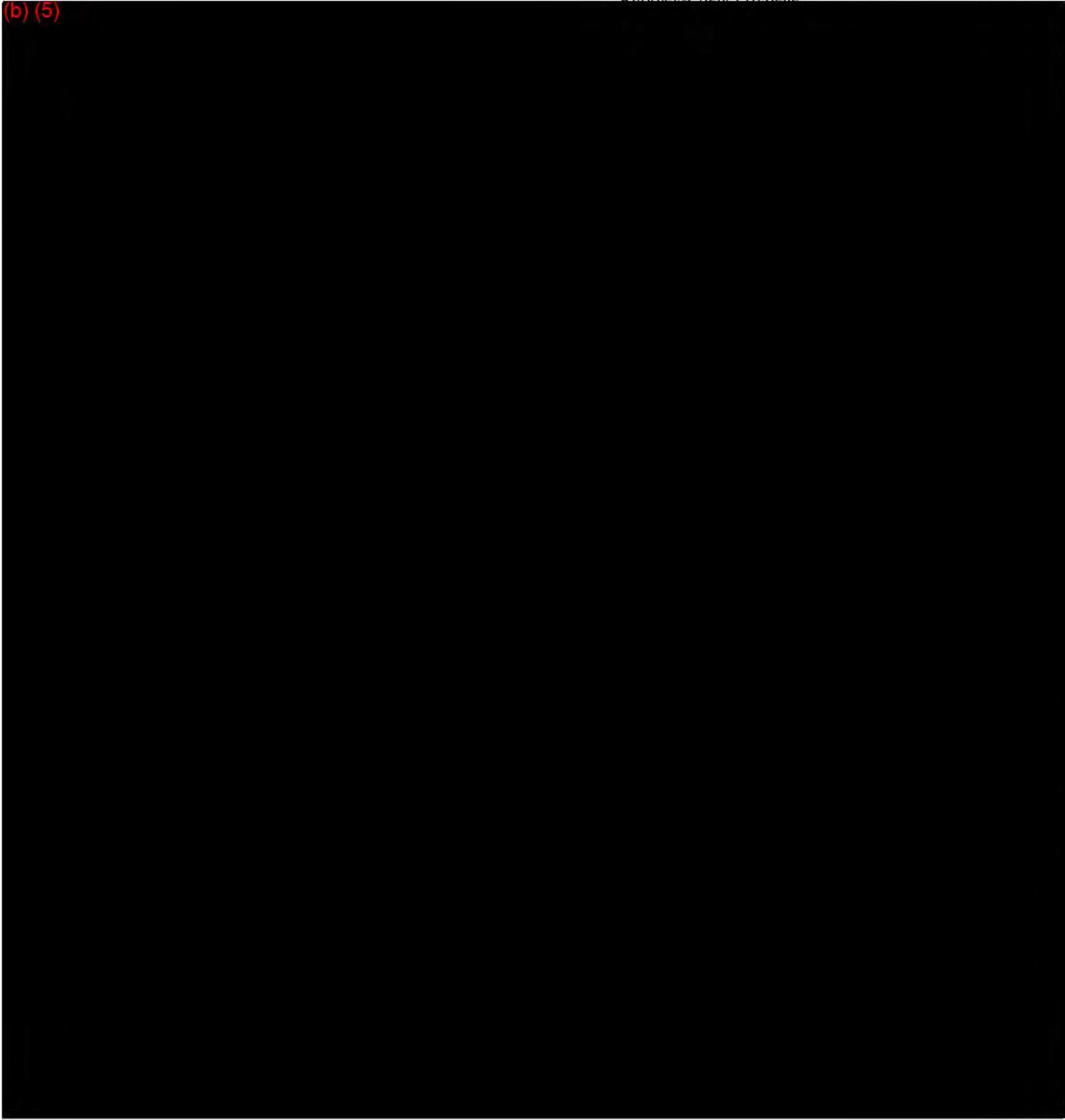


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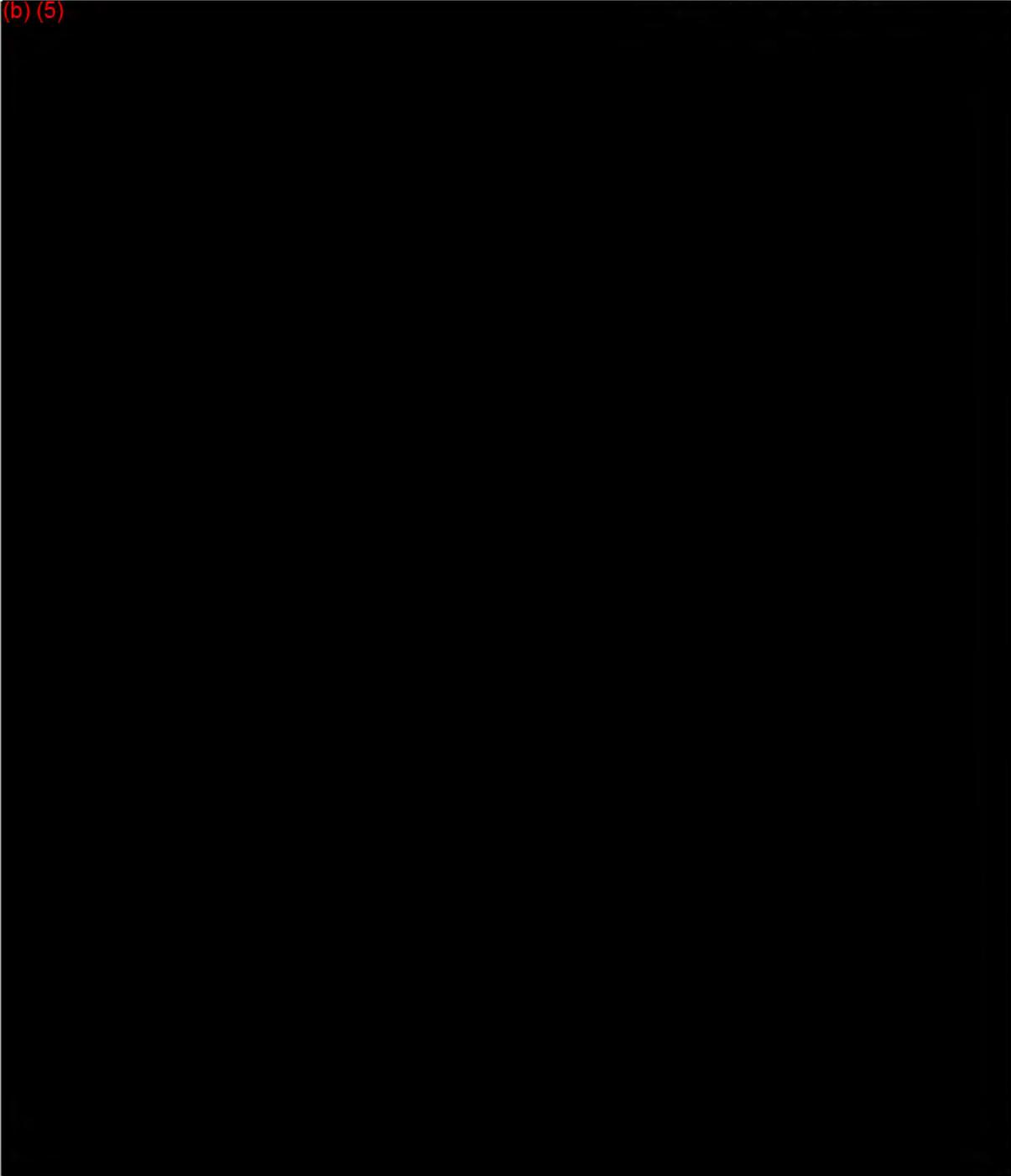
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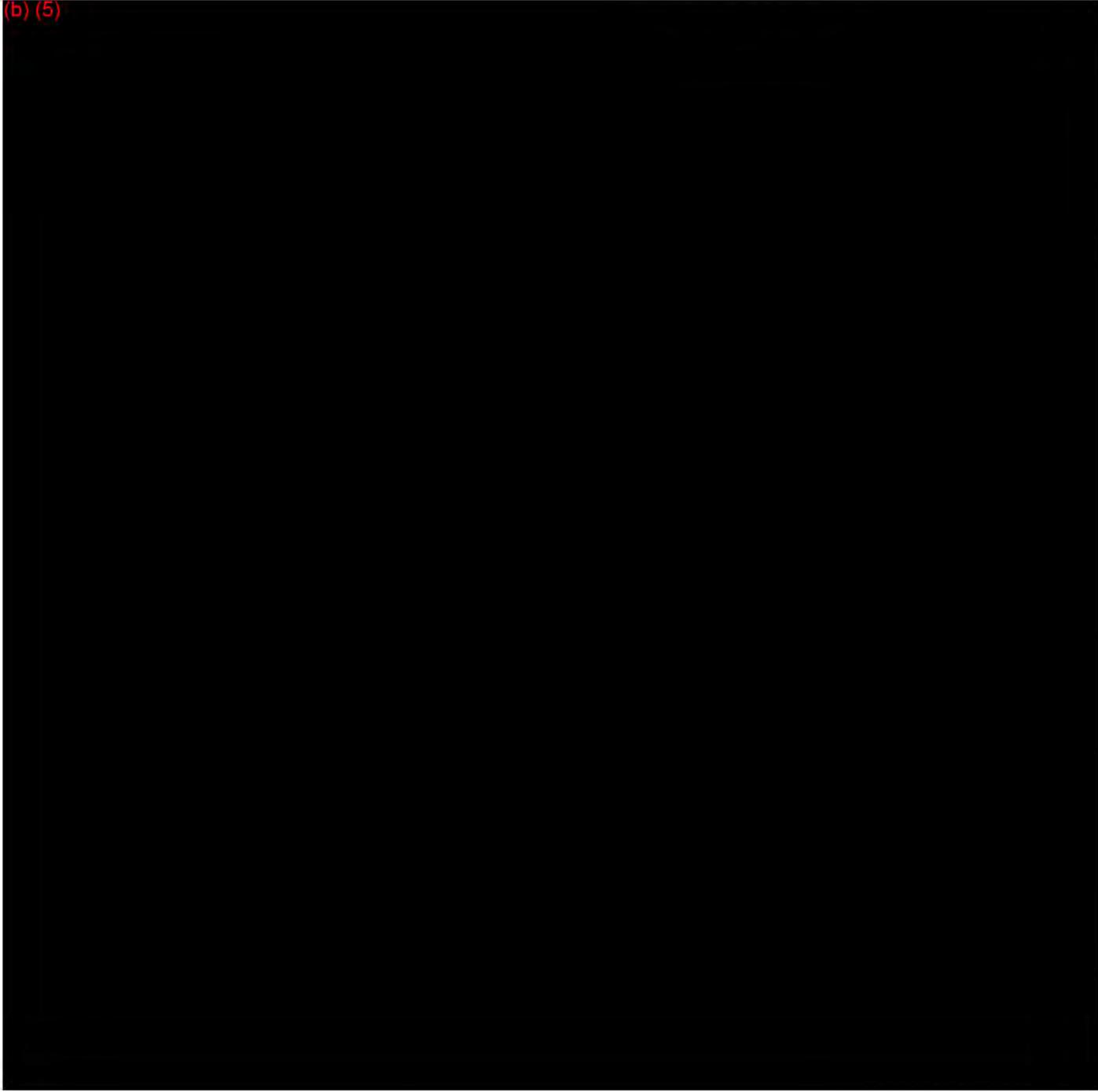
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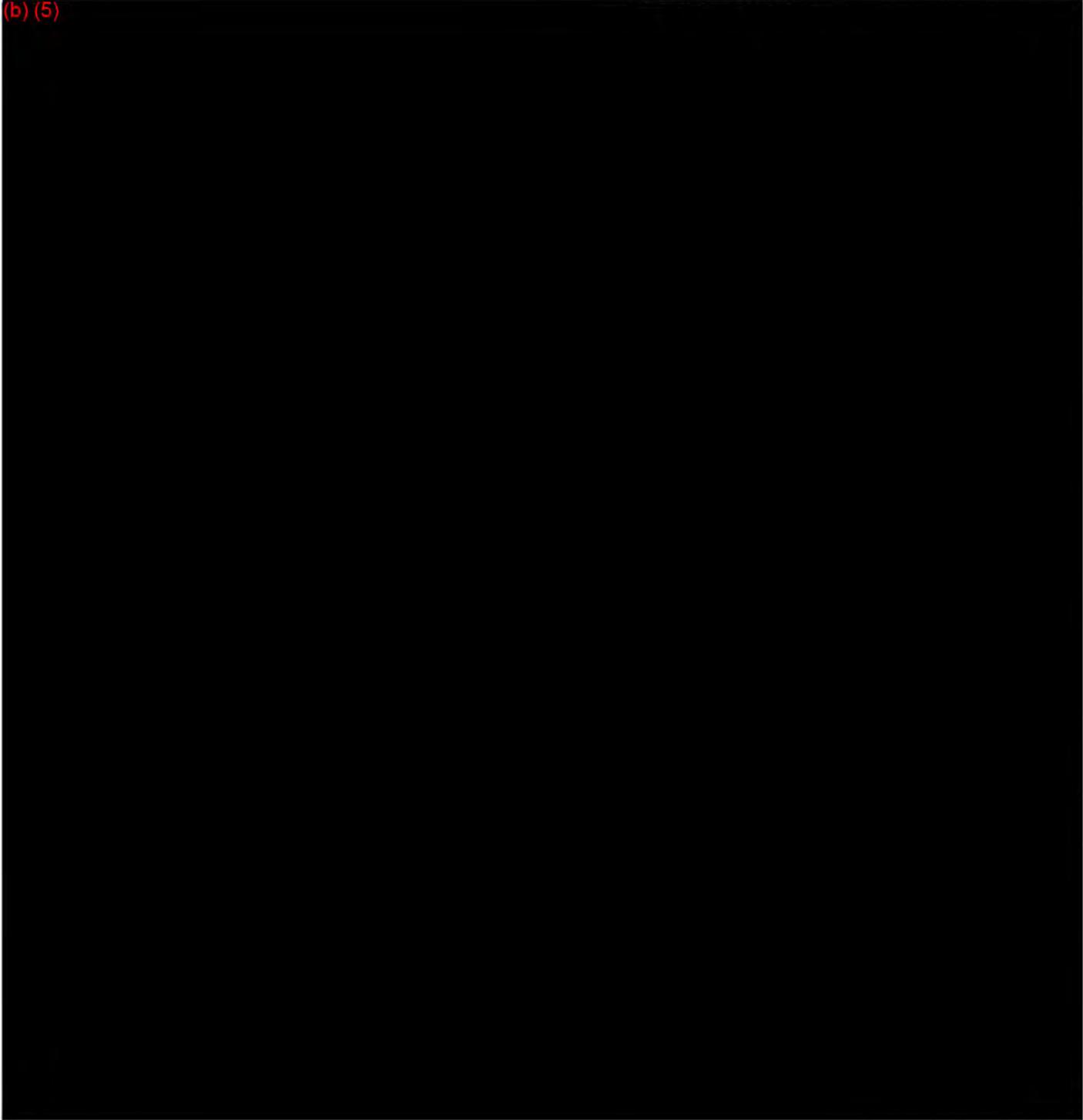
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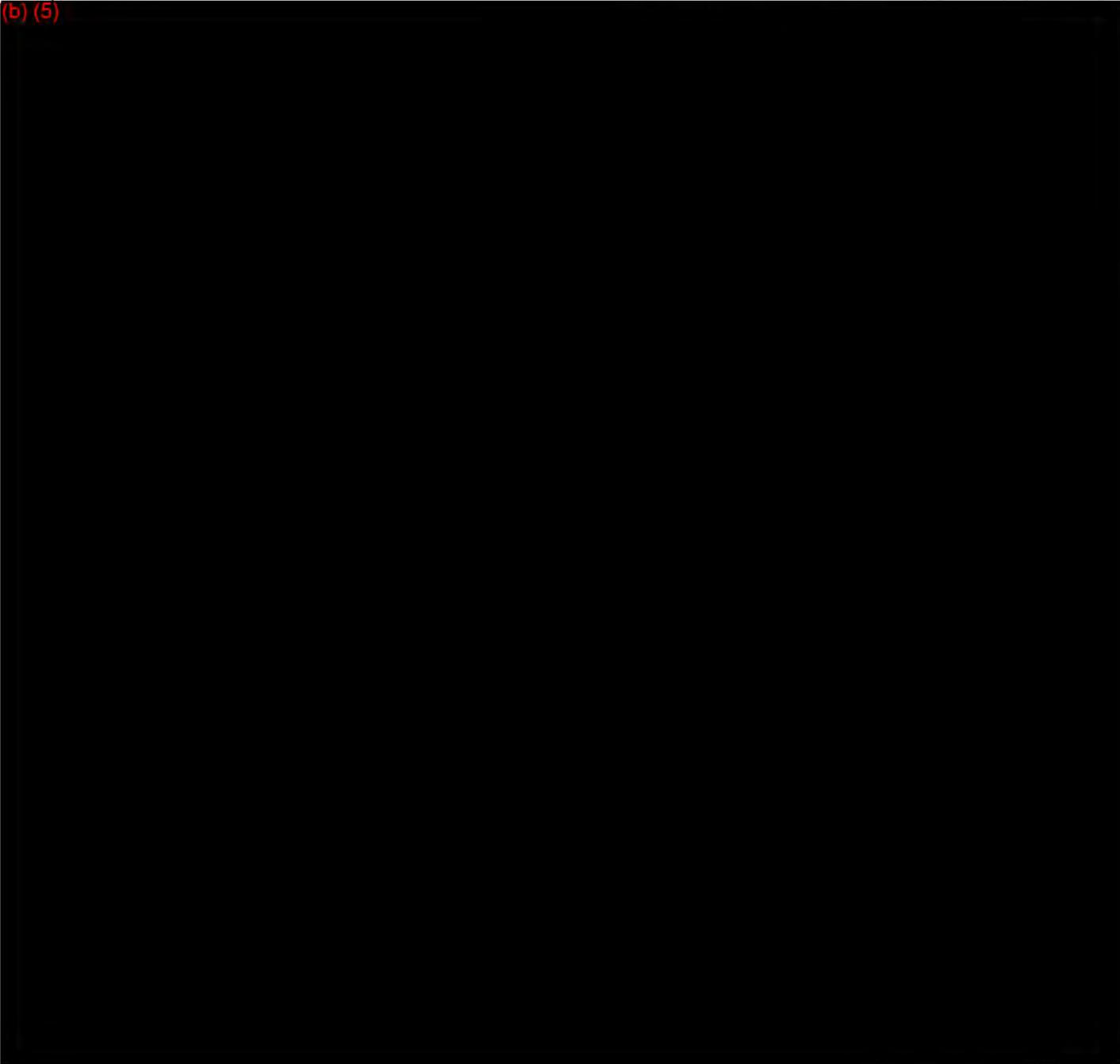
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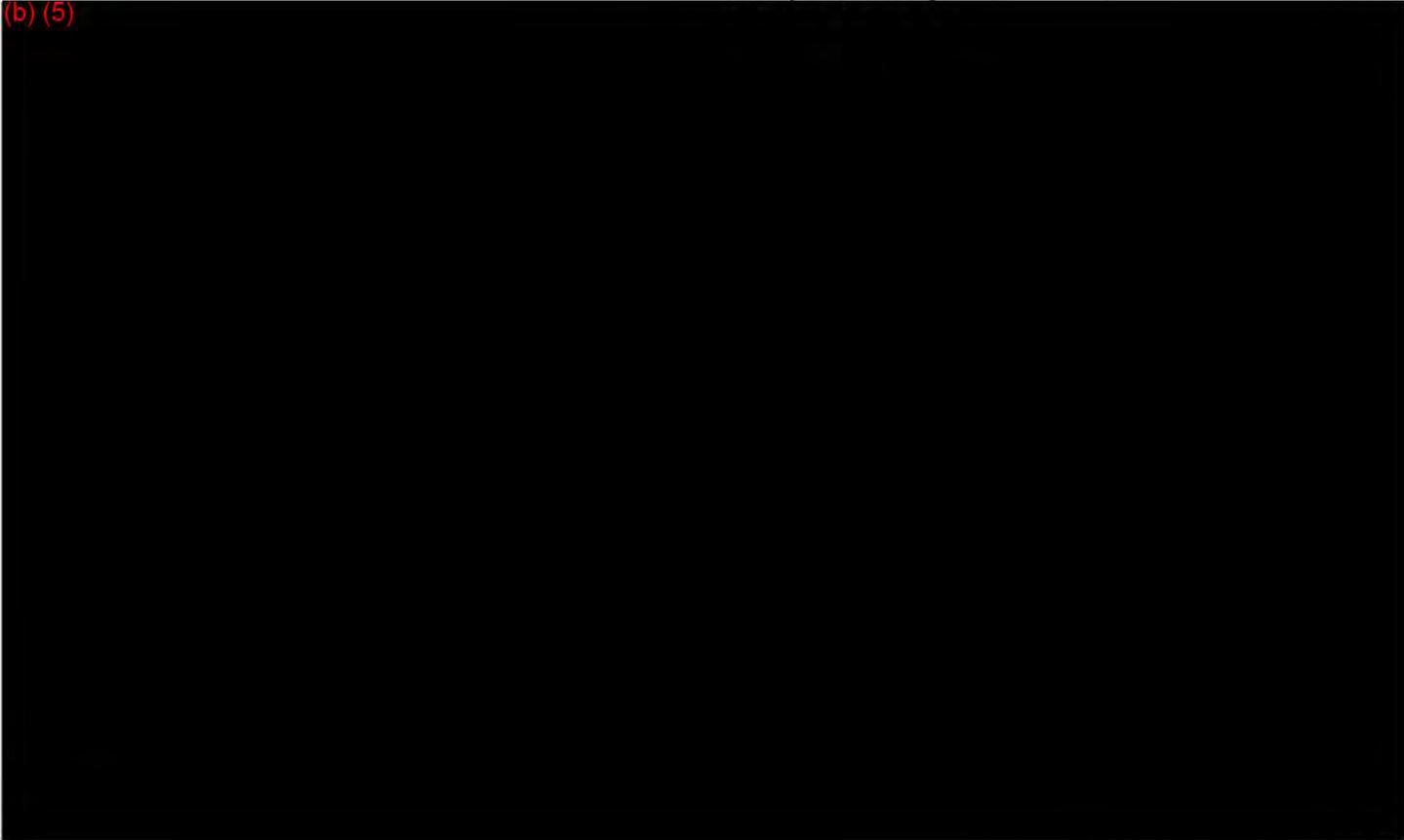
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From: [McCall, Jonathan *](#)
To: [Sherman, Rachel](#)
Cc: [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Califf, Robert](#)
Subject: RE: My suggested edits to the decisional memo
Date: Thursday, September 15, 2016 10:27:39 AM
Attachments: [2016_Sept_012_R2_Eteplirsen_CLEAN Borio rmc JM-CLEAN.doc](#)
[2016_Sept_012_R2_Eteplirsen_CLEAN Borio rmc JM-TRACKED.doc](#)

Hello all –

I am attaching tracked and clean copies of the latest version of the decisional memo. I've removed

(b) (5)

Dr. Califf may want to review my phrasing here; this would normally happen through a process of correspondence and response mediated and adjudicated by the publishing journal, but I wasn't clear on the mechanics of that would work in this situation.

I'll be standing by for any further changes.

Thanks!

–

J

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 9:21 AM
To: McCall, Jonathan *
Cc: Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Califf, Robert
Subject: My suggested edits to the decisional memo

Based on Dr. Jenkin's comments and Dr. Califf's responses:

- Remove quote
- Insert a footnote on page 9 to indicate that (b) (5) [redacted] (Jonathan you probably know exactly what to say – is it a letter to the editor or do the authors or something else).

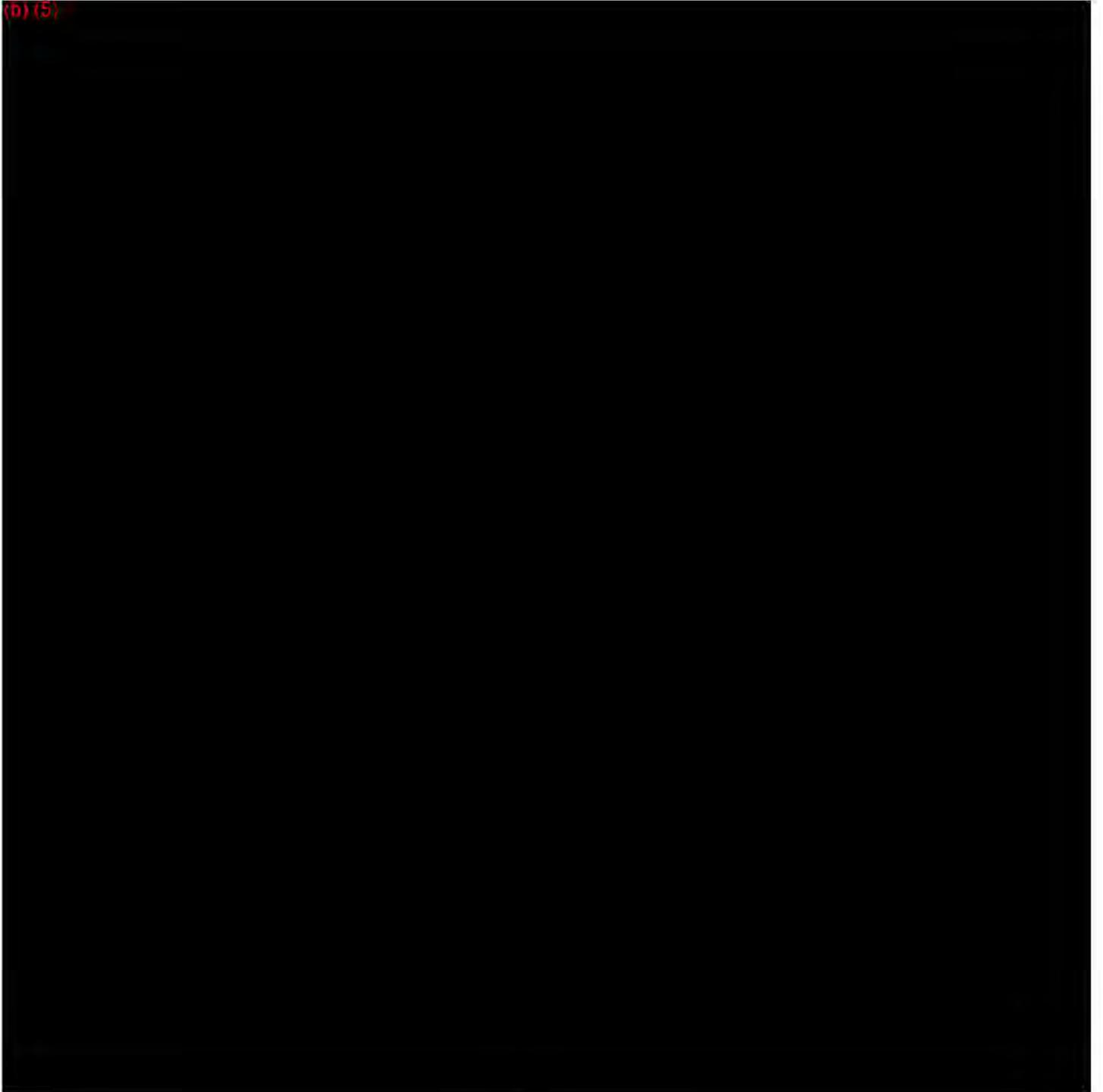
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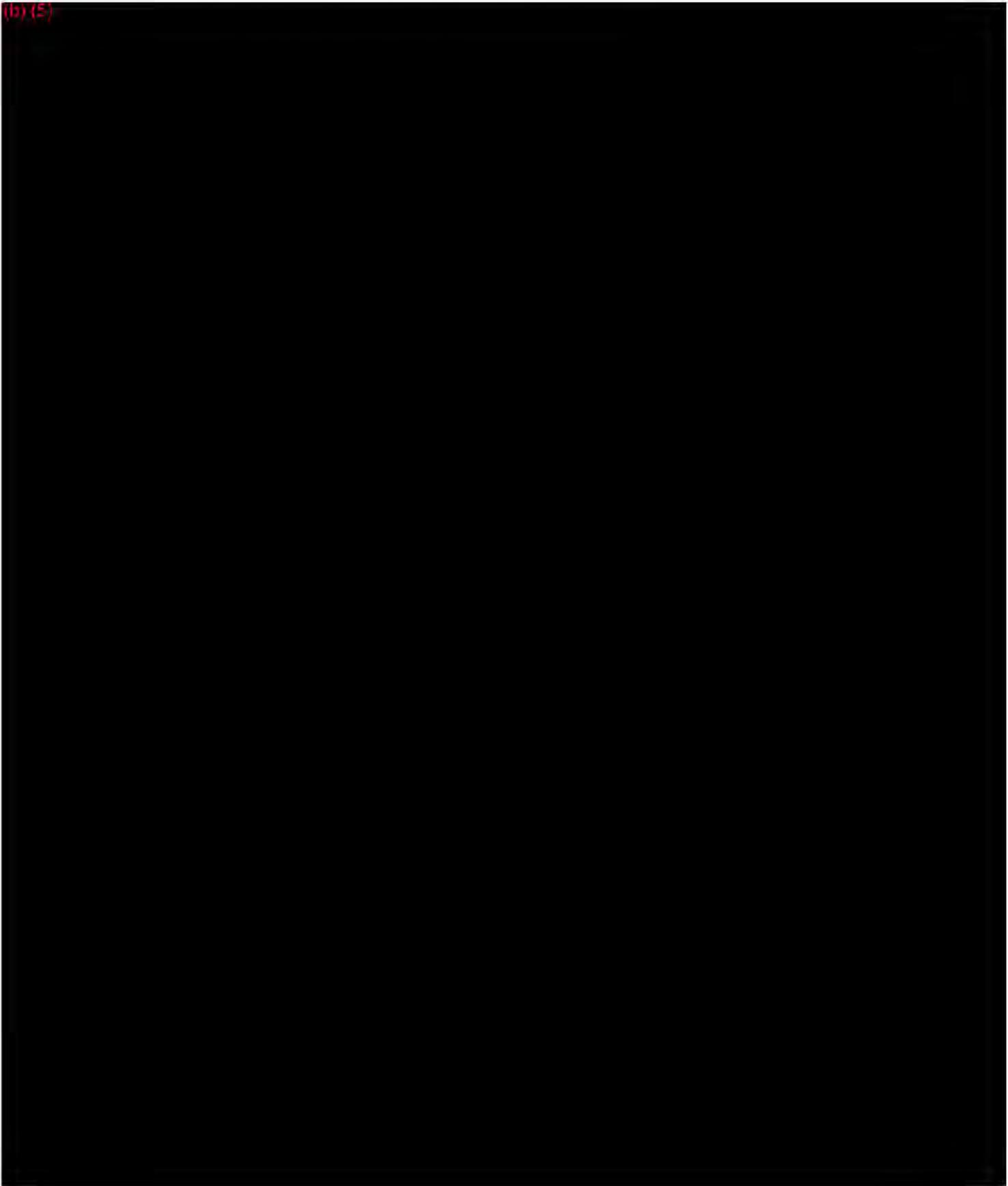


**Scientific Dispute Regarding Approval of Sarepta Therapeutics’
Eteplirsen – Commissioner’s Decision**

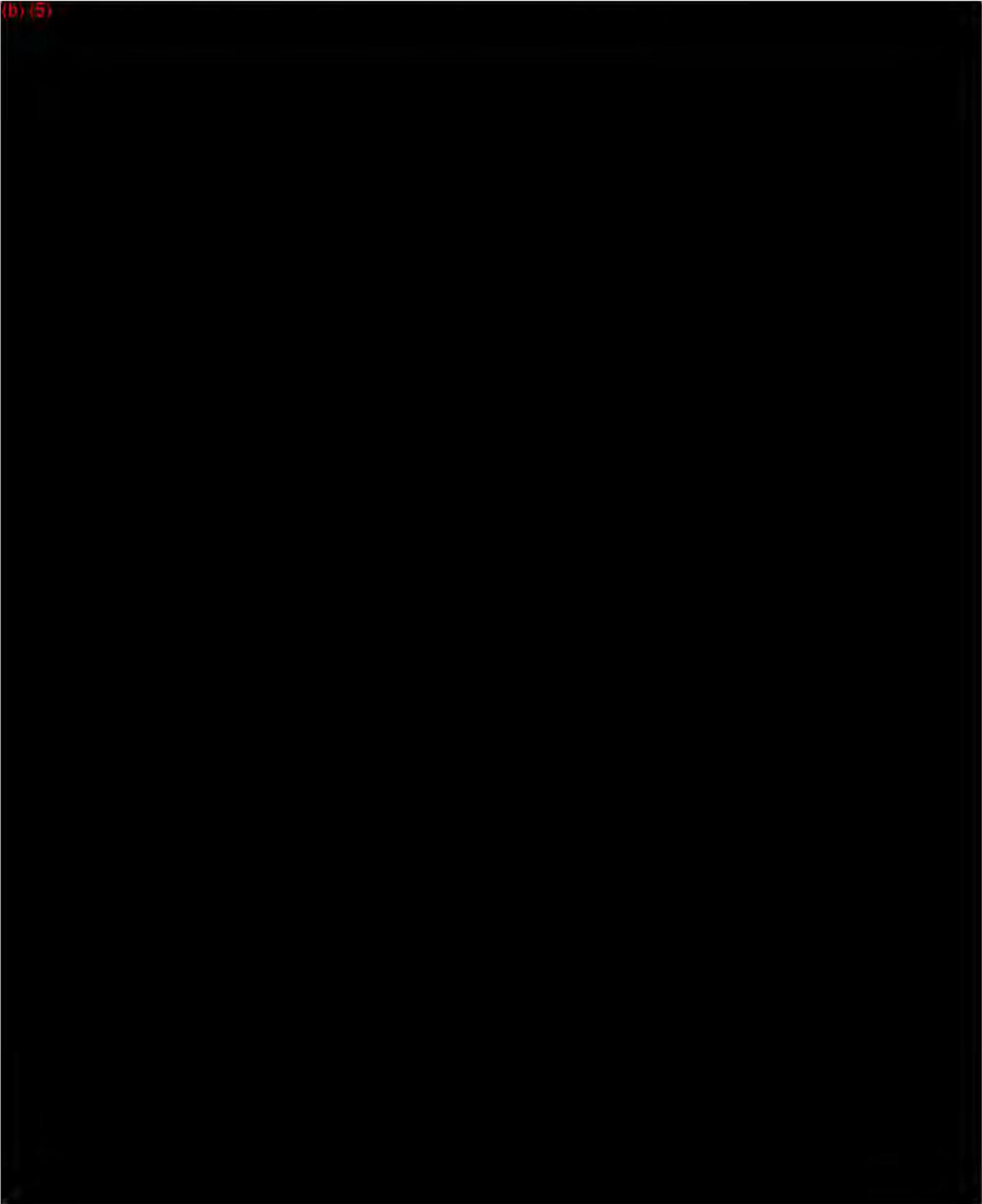
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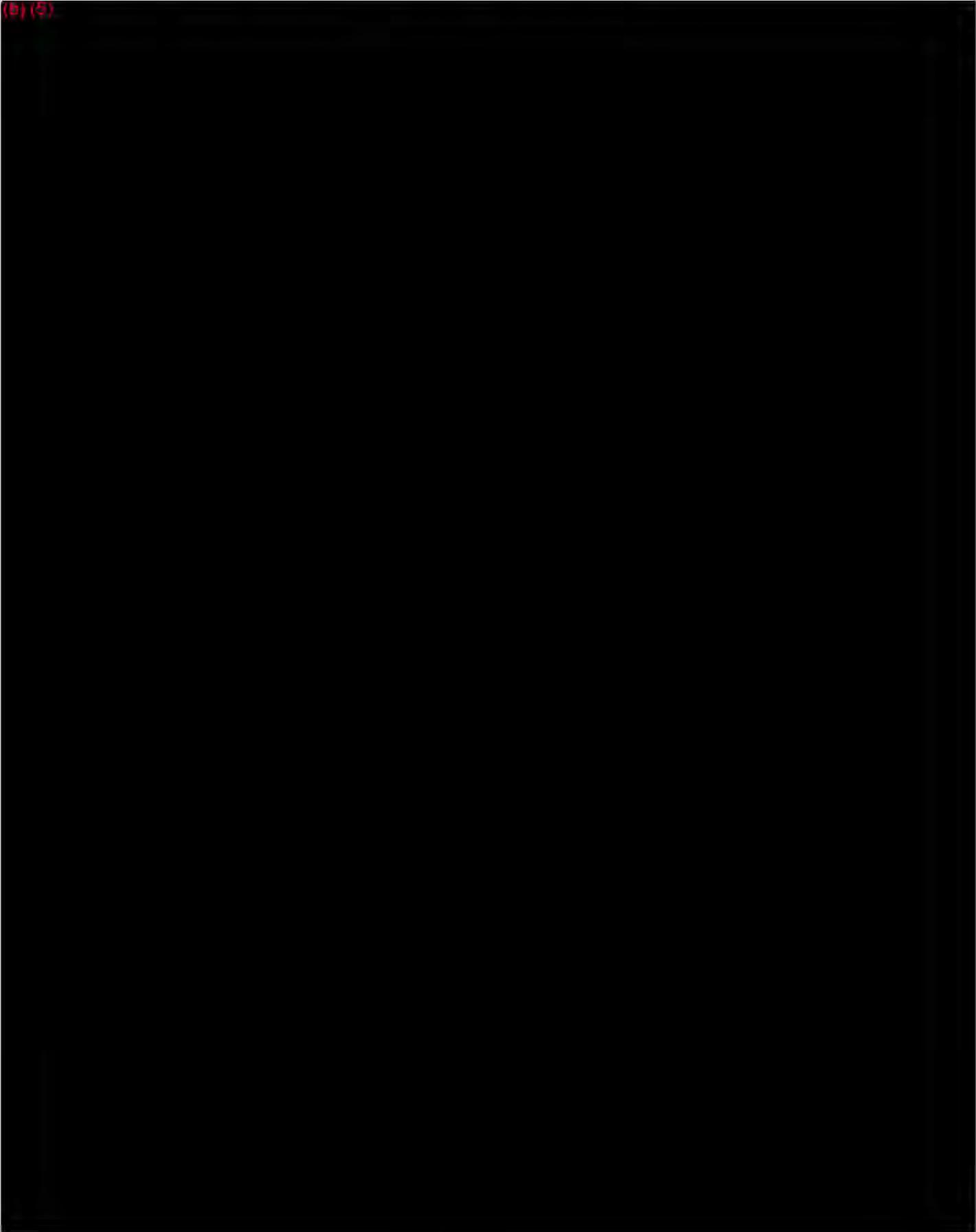
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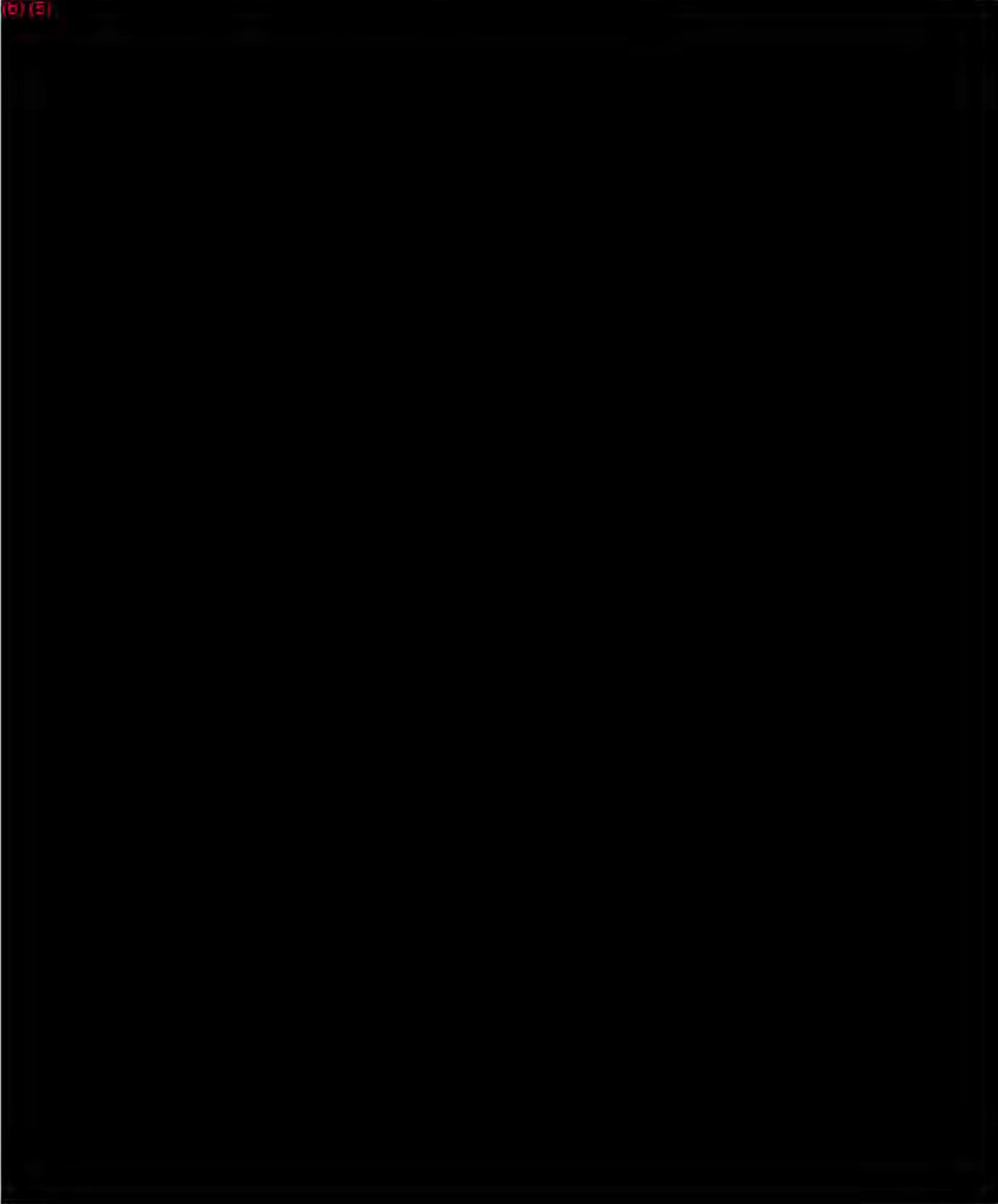
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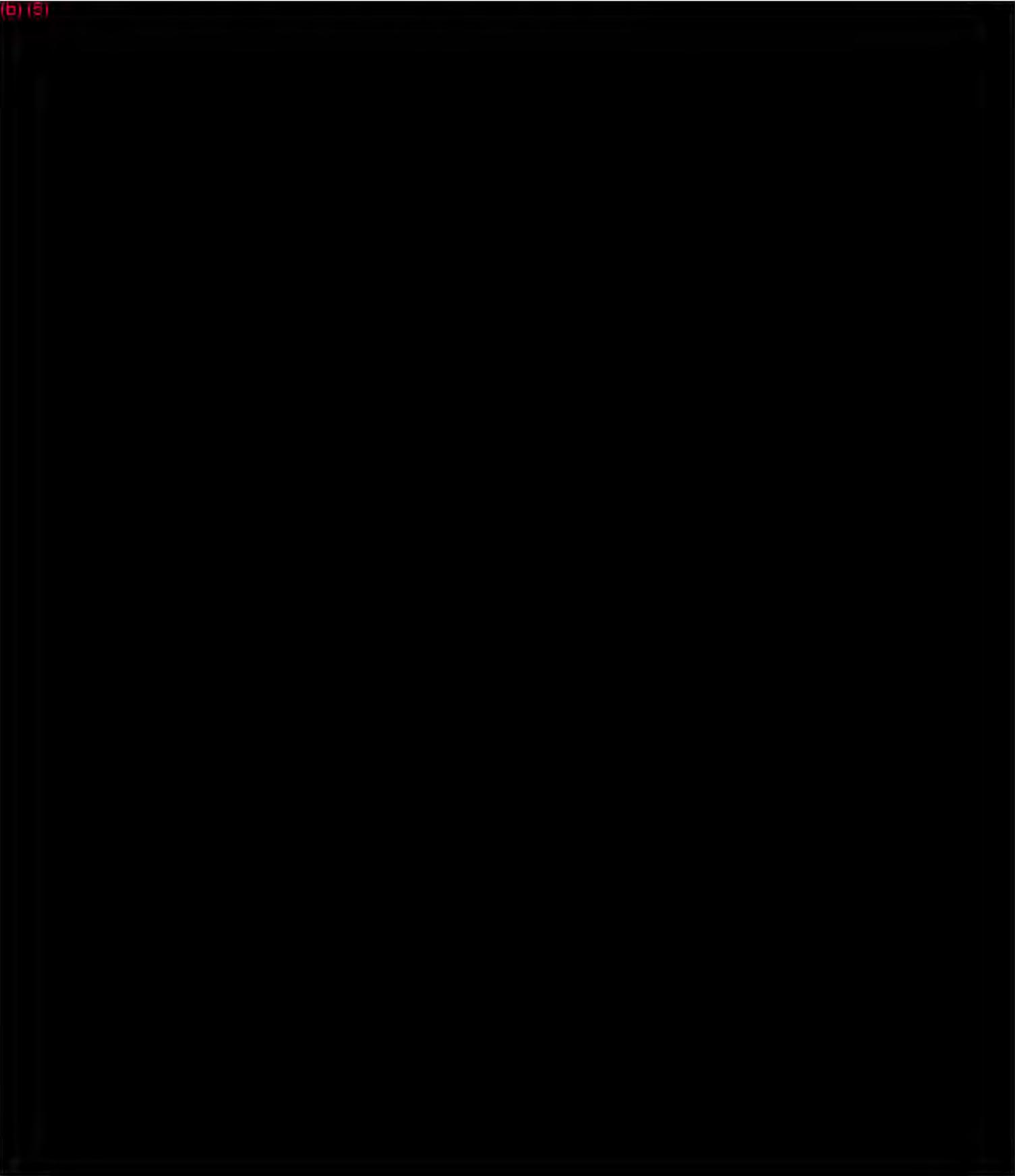
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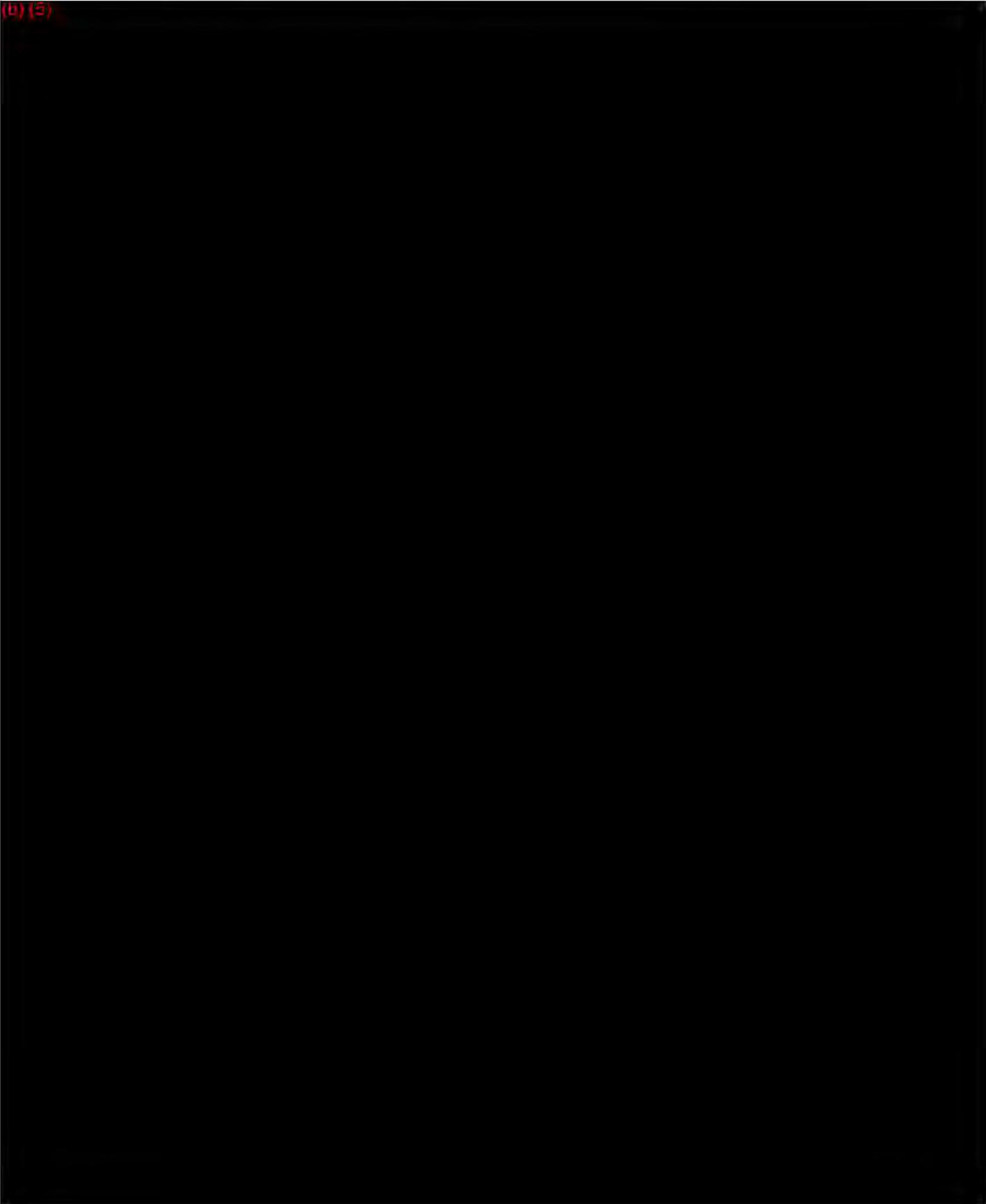
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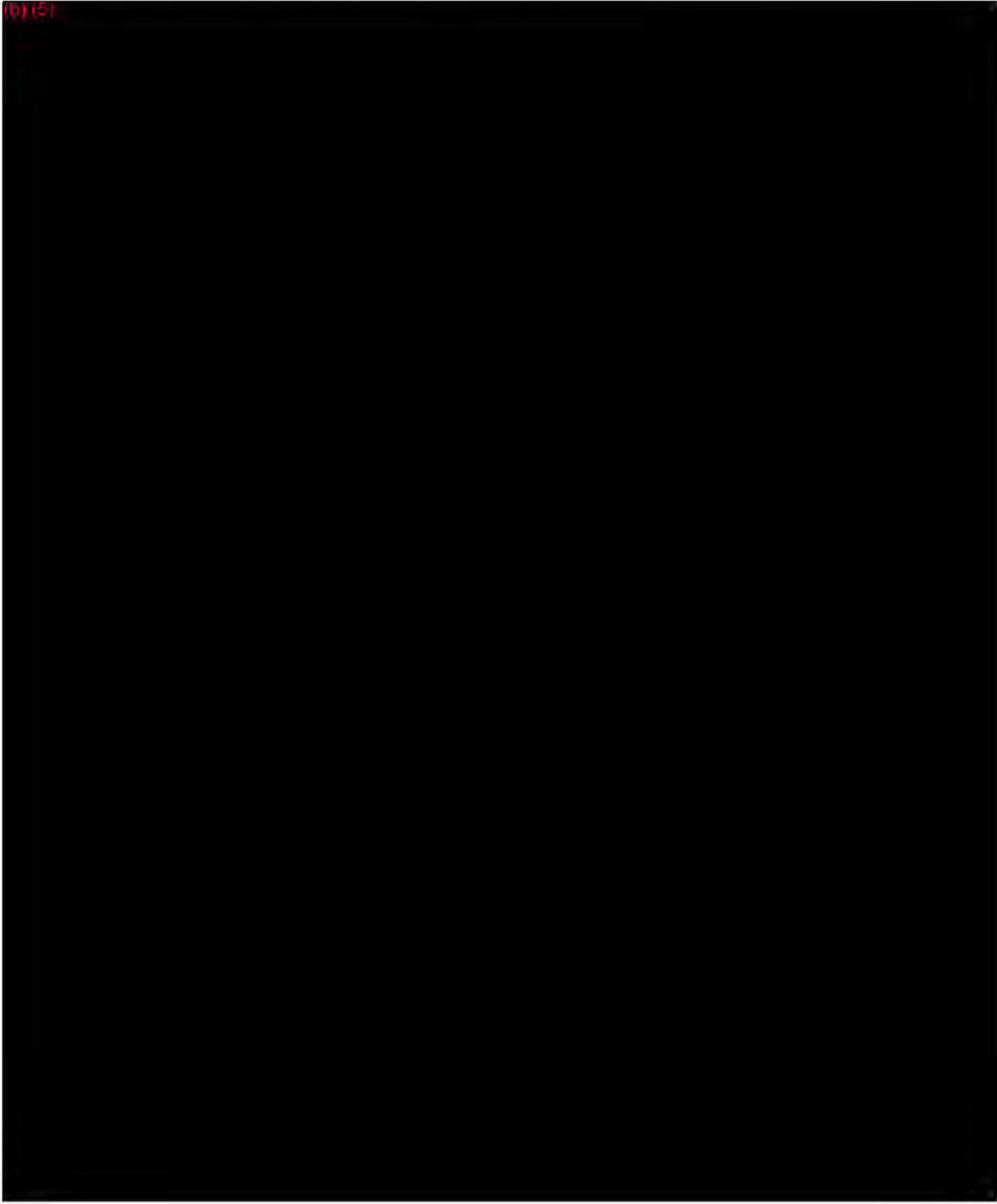
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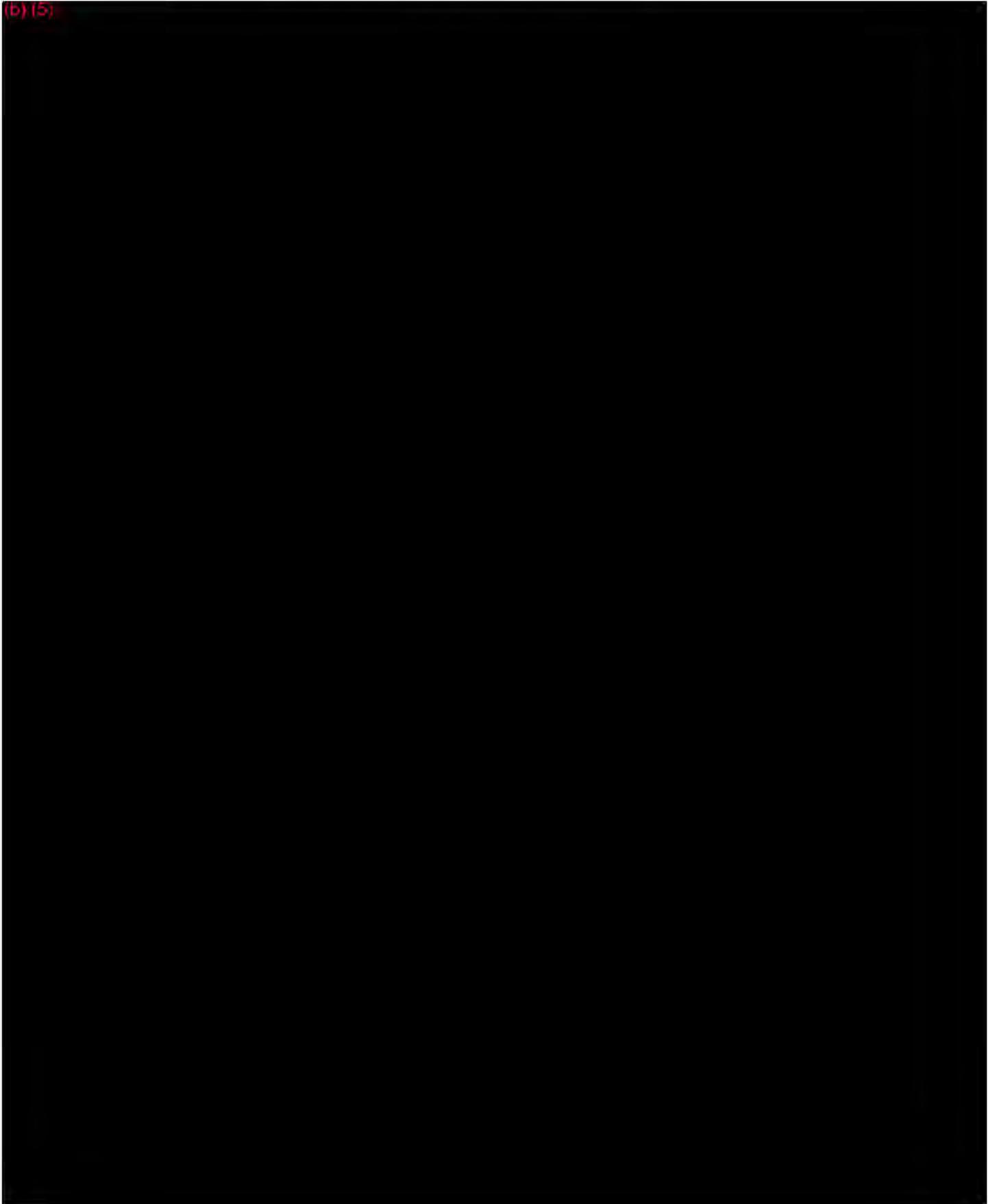
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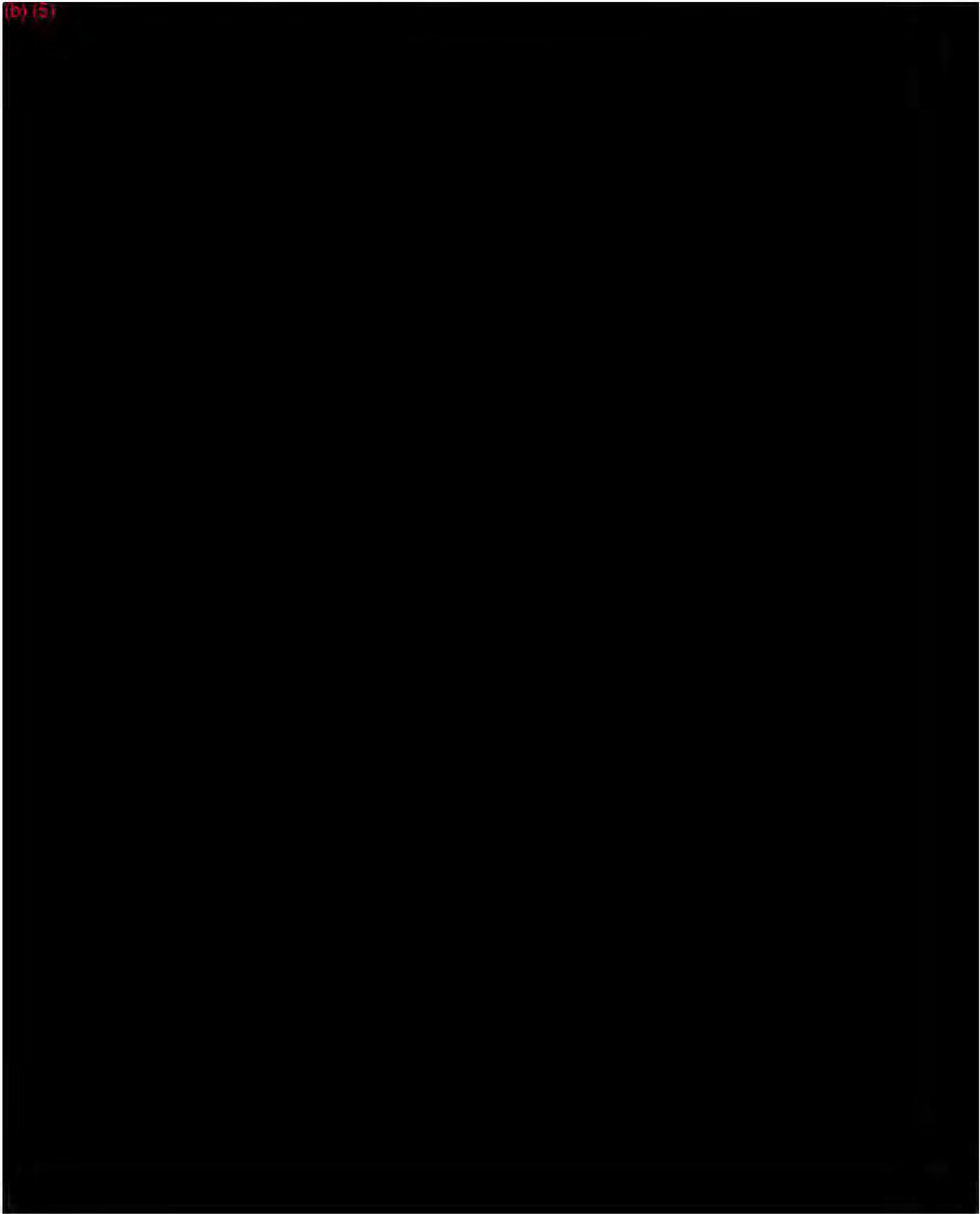
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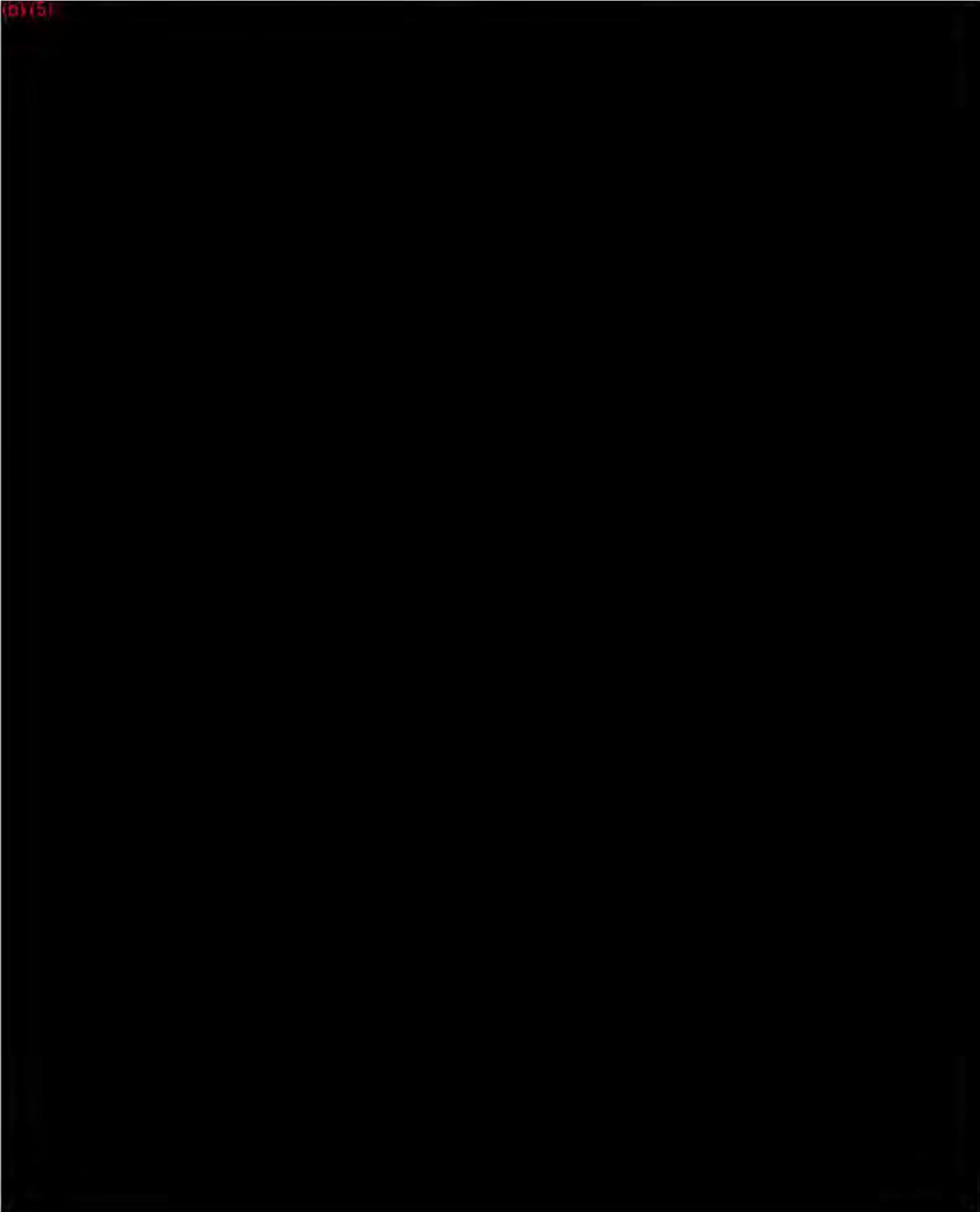
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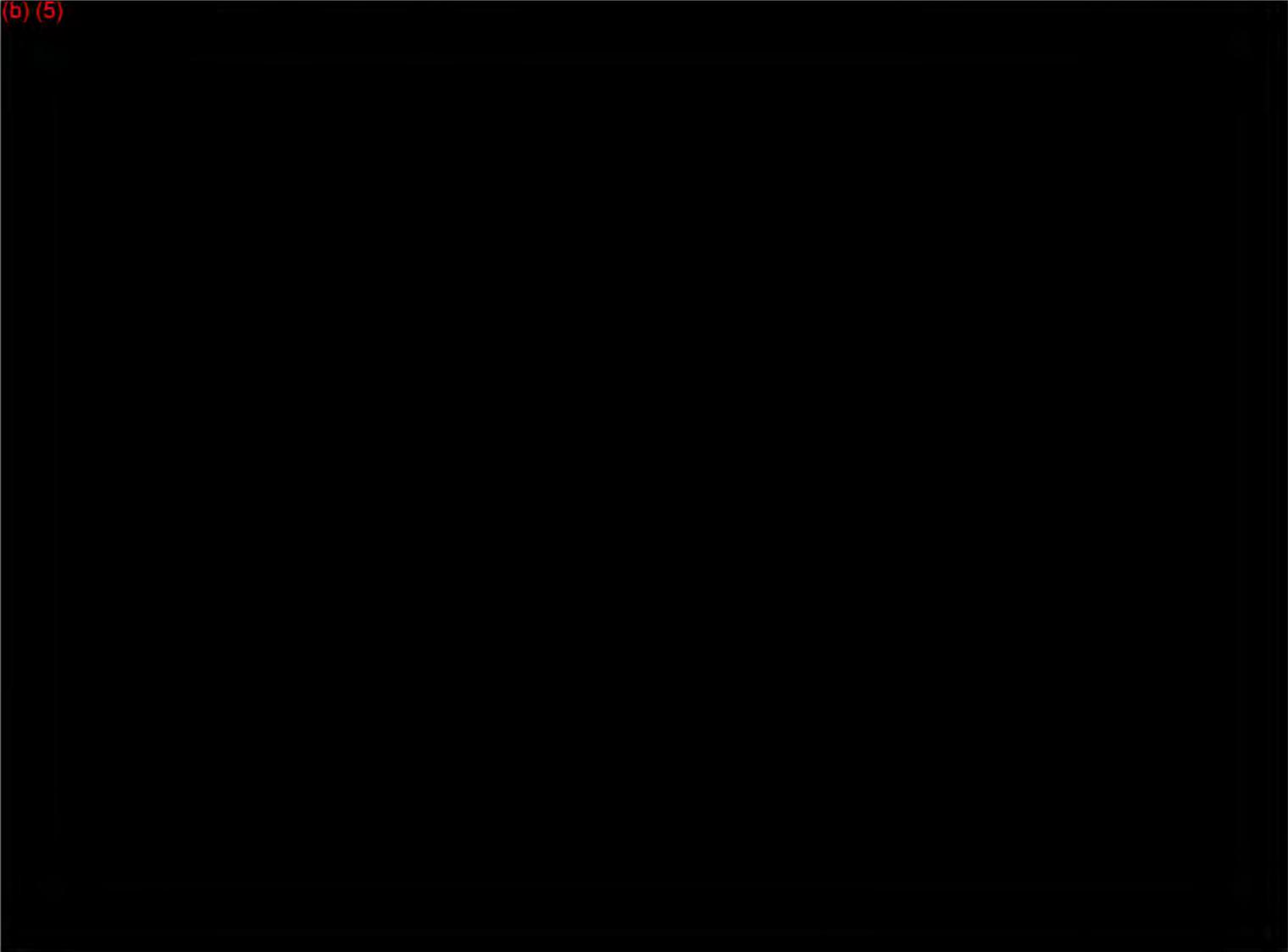


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**Scientific Dispute Regarding Approval of Sarepta Therapeutics'
Eteplirsen – Commissioner’s Decision**

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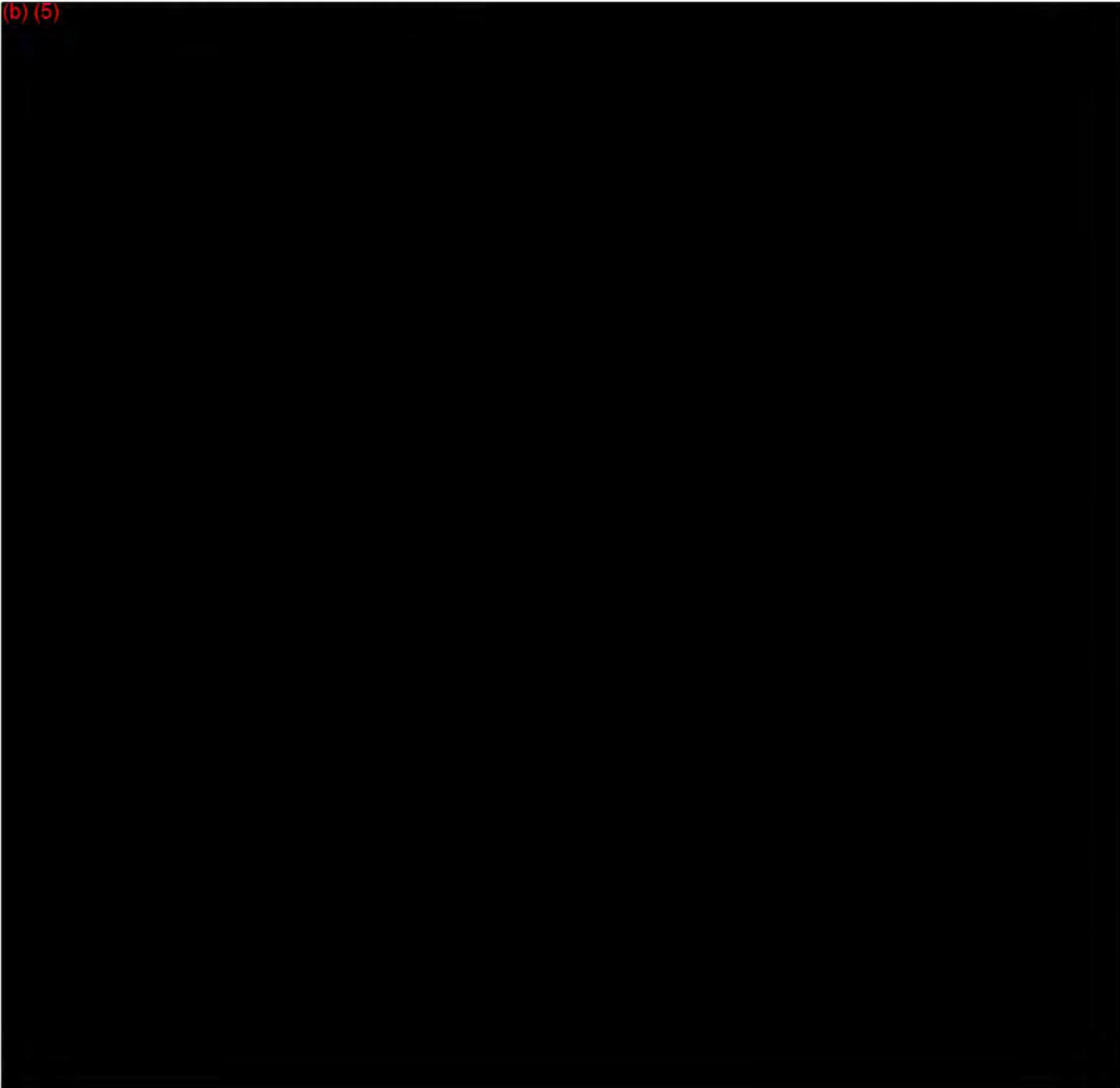




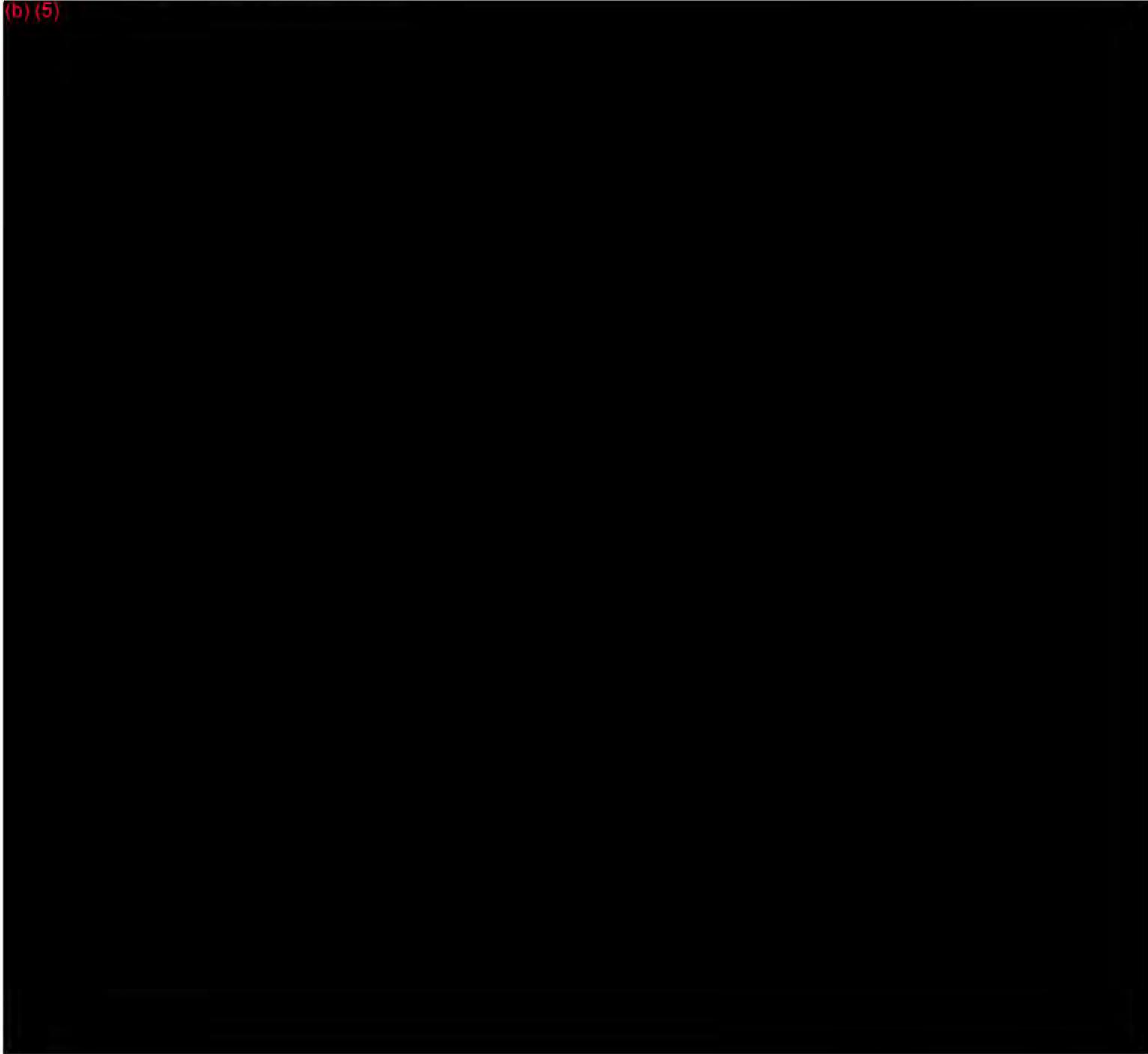
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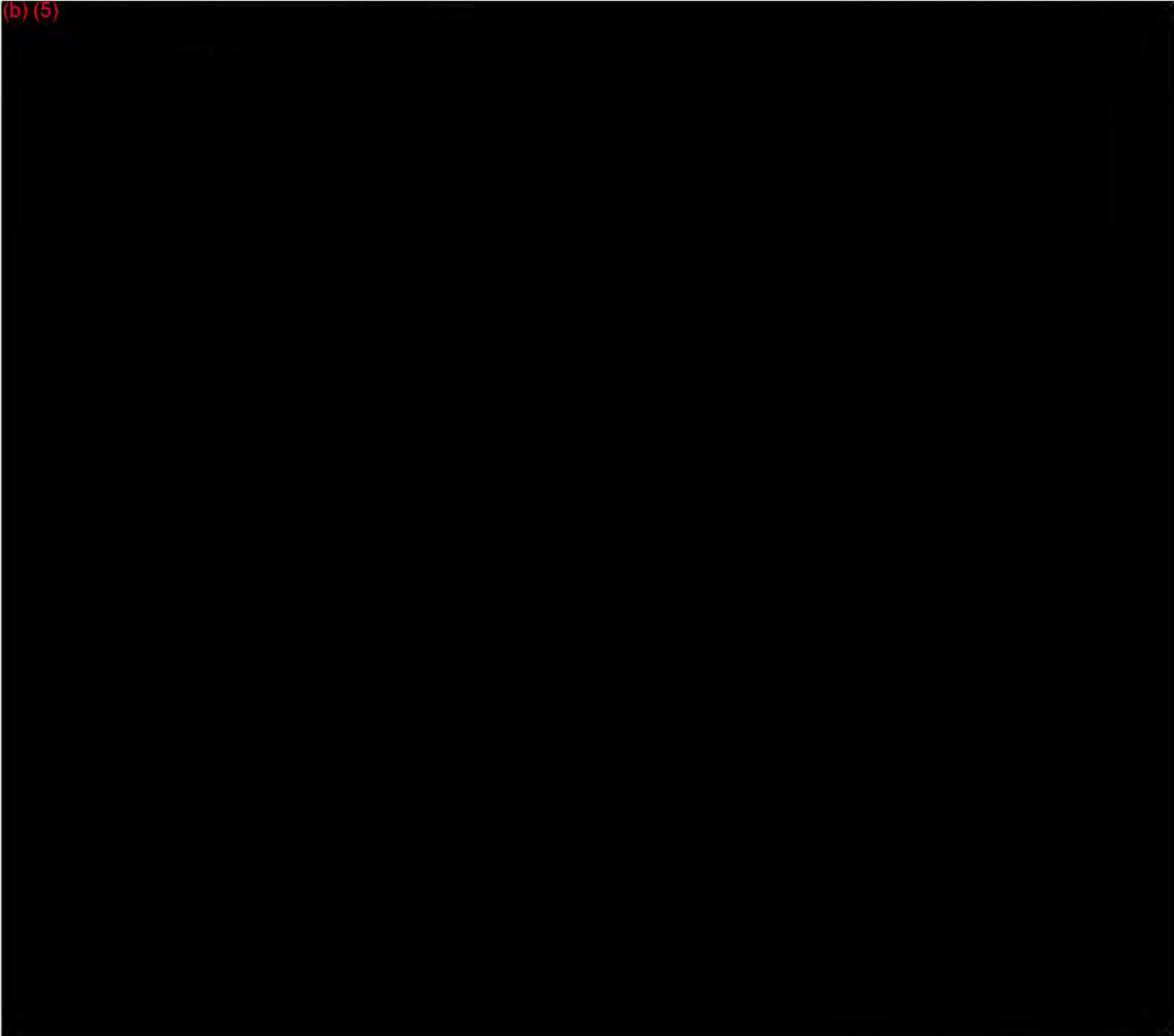
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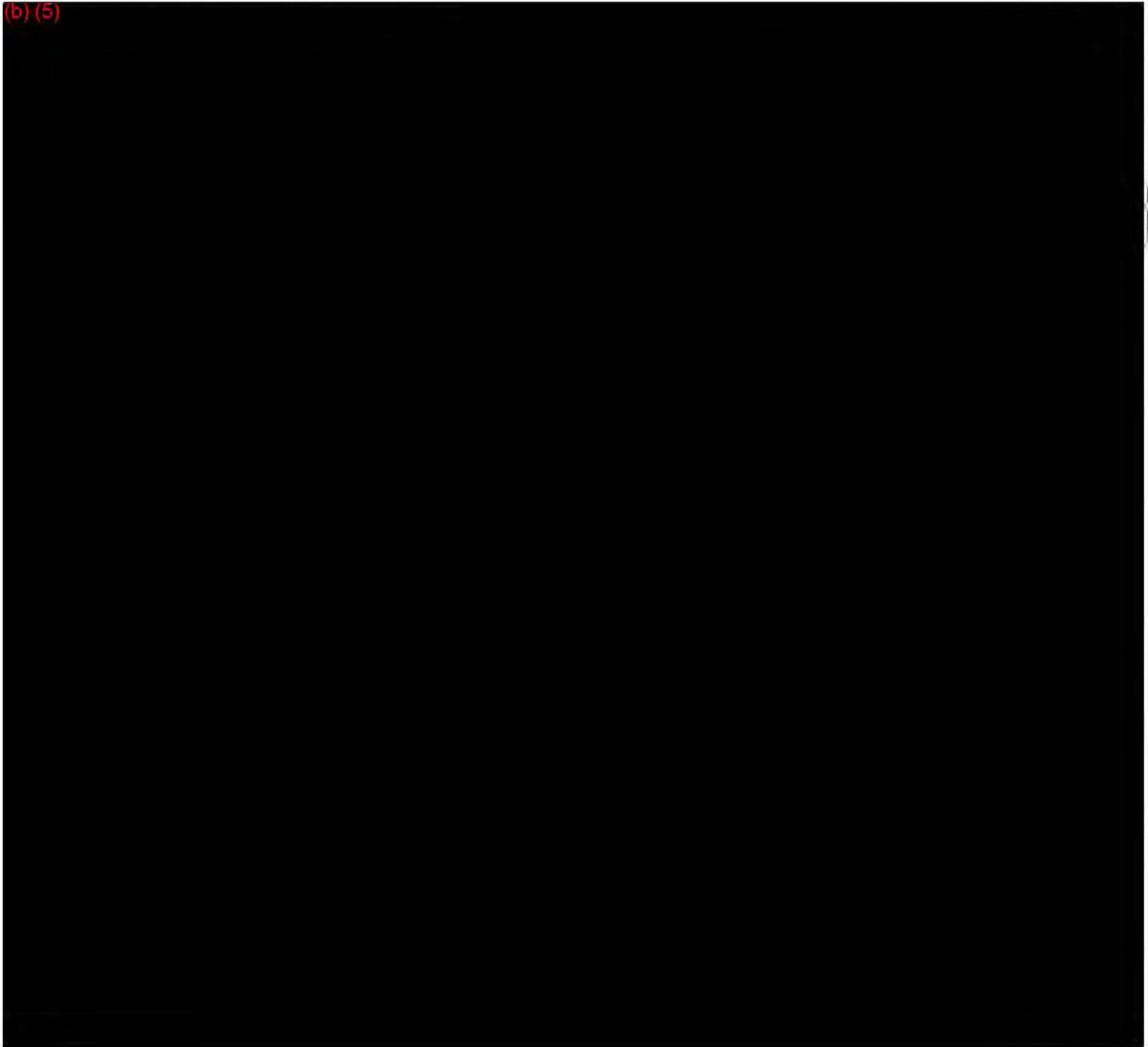
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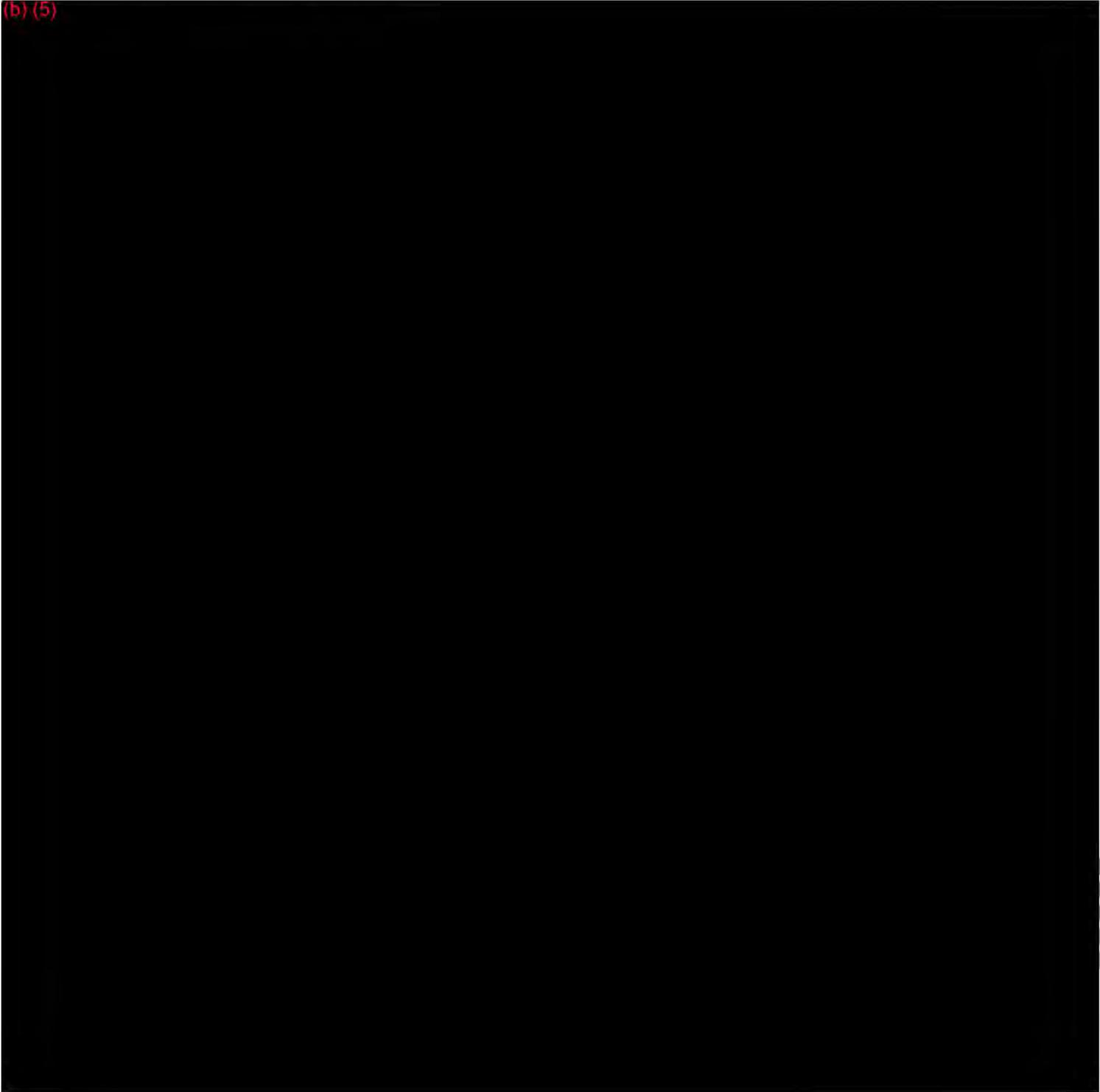
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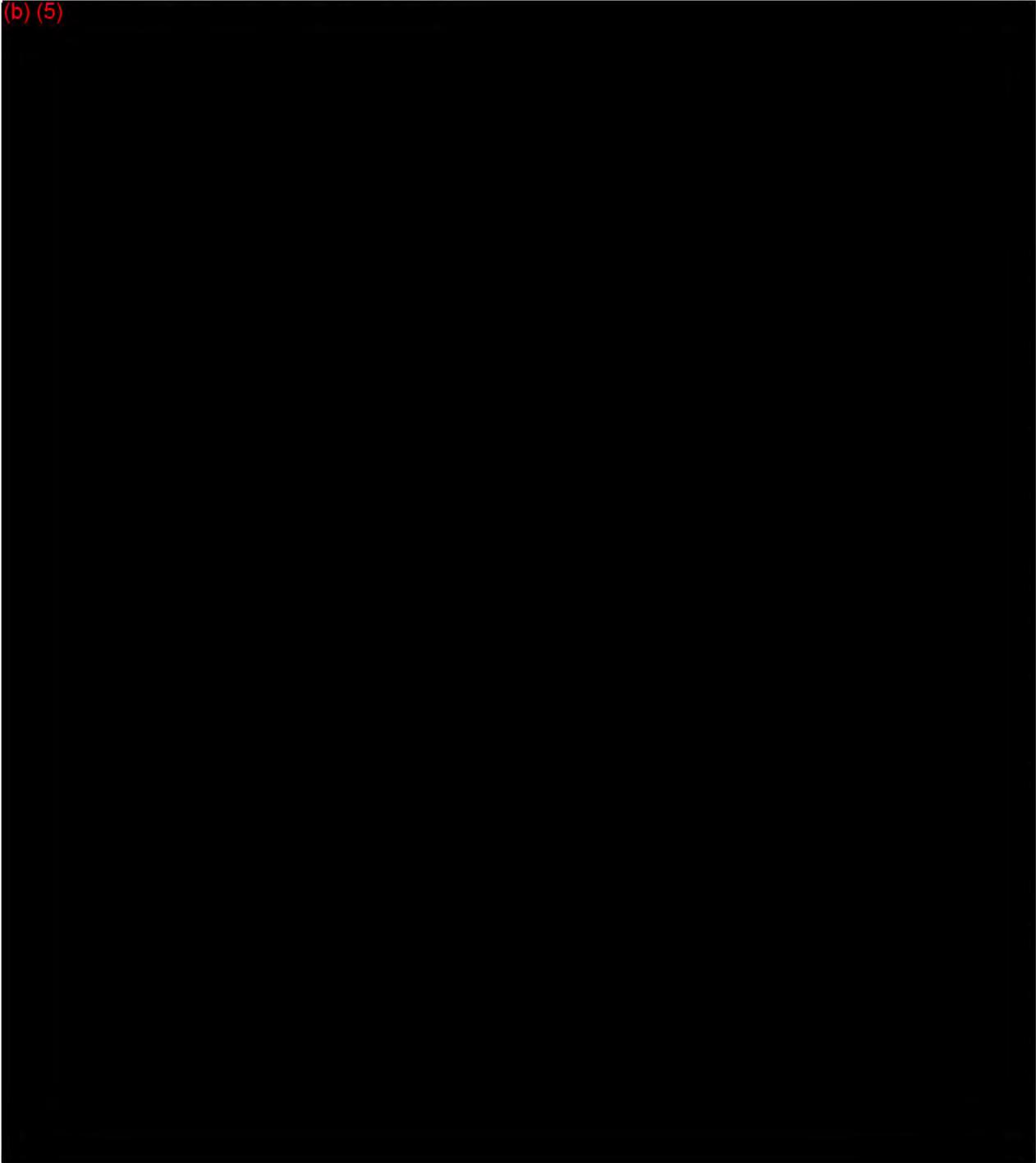
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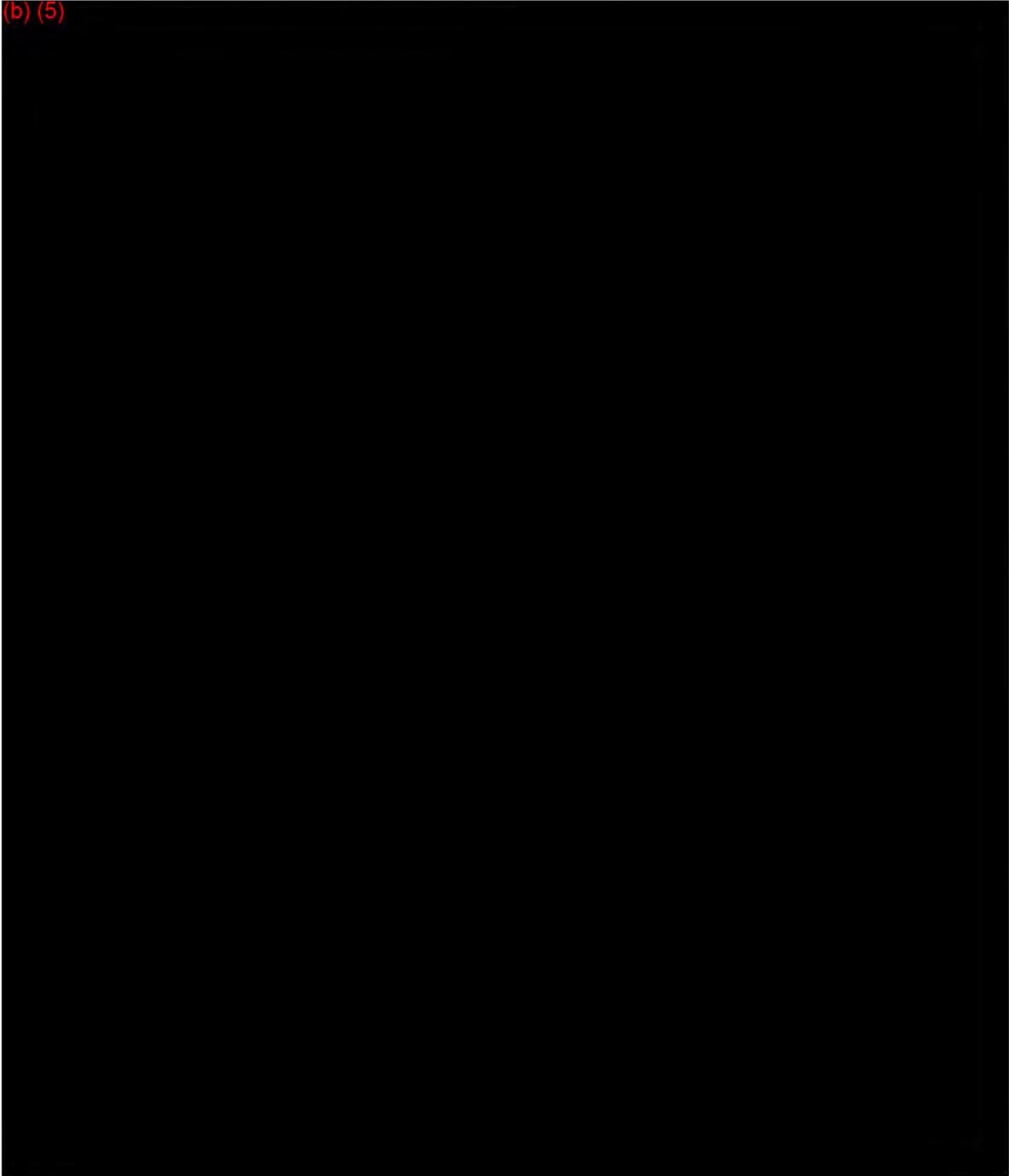
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DRAFT RMC 8/14/2017 11:25 AM 9/15/2016 8:40 AM 9/14/2016 10:43 PM 9/14/2016 5:03 PM 9/14/2016 10:45 AM DELIBERATIVE PROCESS/CONFIDENTIAL

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From: [Sherman, Rachel](#)
To: [McCall, Jonathan *](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#)
Cc: [Kraus, Tom](#)
Subject: RE: We have a plan
Date: Thursday, September 15, 2016 4:06:46 PM
Attachments: [Memo to File re Commissioner Decision 9-15-16 JMrs.doc](#)

Hi all,

This looks great.

Deborah – I've inserted two questions for you (page 6 and the last page). I've also tinkered a little

After Deborah, please return to Jonathan.

Jonathan – can you add the dates Caitlin provided, clean up and then send to Rob?

In terms of competing priorities, as we don't have to redact this one the emails and decisional memo are higher priority.

Thanks!!
Rachel

From: McCall, Jonathan *
Sent: Thursday, September 15, 2016 3:02 PM
To: Chasan-Sloan, Deborah (FDA); Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: Kraus, Tom
Subject: RE: We have a plan

Hello all –

I have tried to distill the responses a bit and apply a uniform tone. Please feel free to edit or overrule and restore the original text. There was one point (noted with comments) where there didn't seem to be a preliminary response to work from.

Best,

Jonathan

From: Chasan-Sloan, Deborah (FDA)
Sent: Thursday, September 15, 2016 1:00 PM
To: Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Kraus, Tom
Subject: RE: We have a plan

(b) (5)



From: Sherman, Rachel
Sent: Thursday, September 15, 2016 12:48 PM
To: Chasan-Sloan, Deborah (FDA); Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Kraus, Tom
Subject: RE: We have a plan

Okay, one question – I assume we need to put in the comments that don't have a response and then Jonathan was going to craft something to the effect of "this doesn't need a response".

Do you agree that's what should be done?

From: Chasan-Sloan, Deborah (FDA)
Sent: Thursday, September 15, 2016 12:46 PM
To: Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Kraus, Tom
Subject: RE: We have a plan

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A large black rectangular redaction box covers the majority of the email body content between the second and third email headers.

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 12:43 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Chasan-Sloan, Deborah (FDA); Kraus, Tom
Subject: RE: We have a plan

Hi,

Jonathan may well have started – perhaps Deborah and Jonathan should connect?

Just spoke to Tom about when Rob's decisional memo will be ready for redaction. I thought not until tomorrow am. Do you all agree?

From: Califf, Robert
Sent: Thursday, September 15, 2016 9:33 AM
To: Sherman, Rachel; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Chasan-Sloan, Deborah (FDA)
Subject: Re: We have a plan

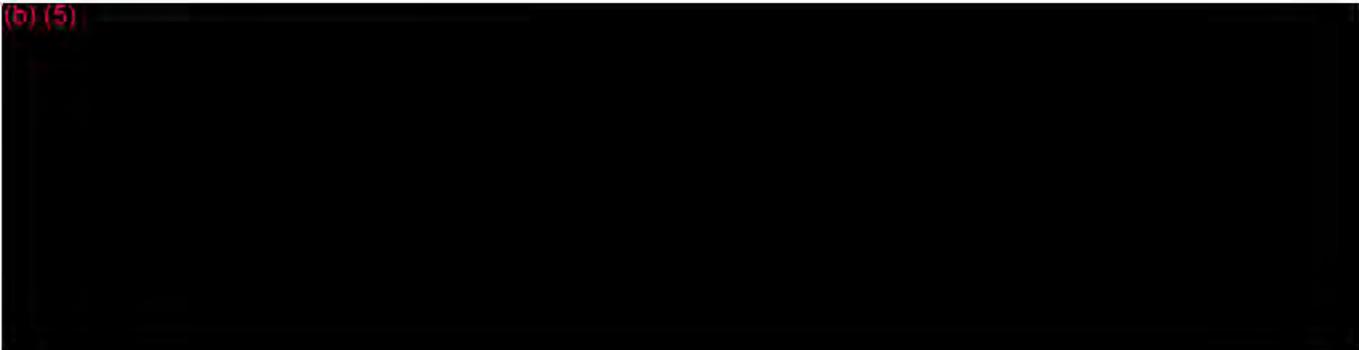
Yes

From: Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Date: September 15, 2016 at 9:30:52 AM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>, Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>

Subject: Re: We have a plan

All,

(b) (5)



From: Sherman, Rachel

Sent: Thursday, September 15, 2016 9:09 AM

To: Califf, Robert

Cc: McCall, Jonathan *; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)

Subject: We have a plan

When you have a moment call and I can review with you.

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MEMO TO FILE

FROM: Robert Califf, M.D., Commissioner of Food and Drugs

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DATE:

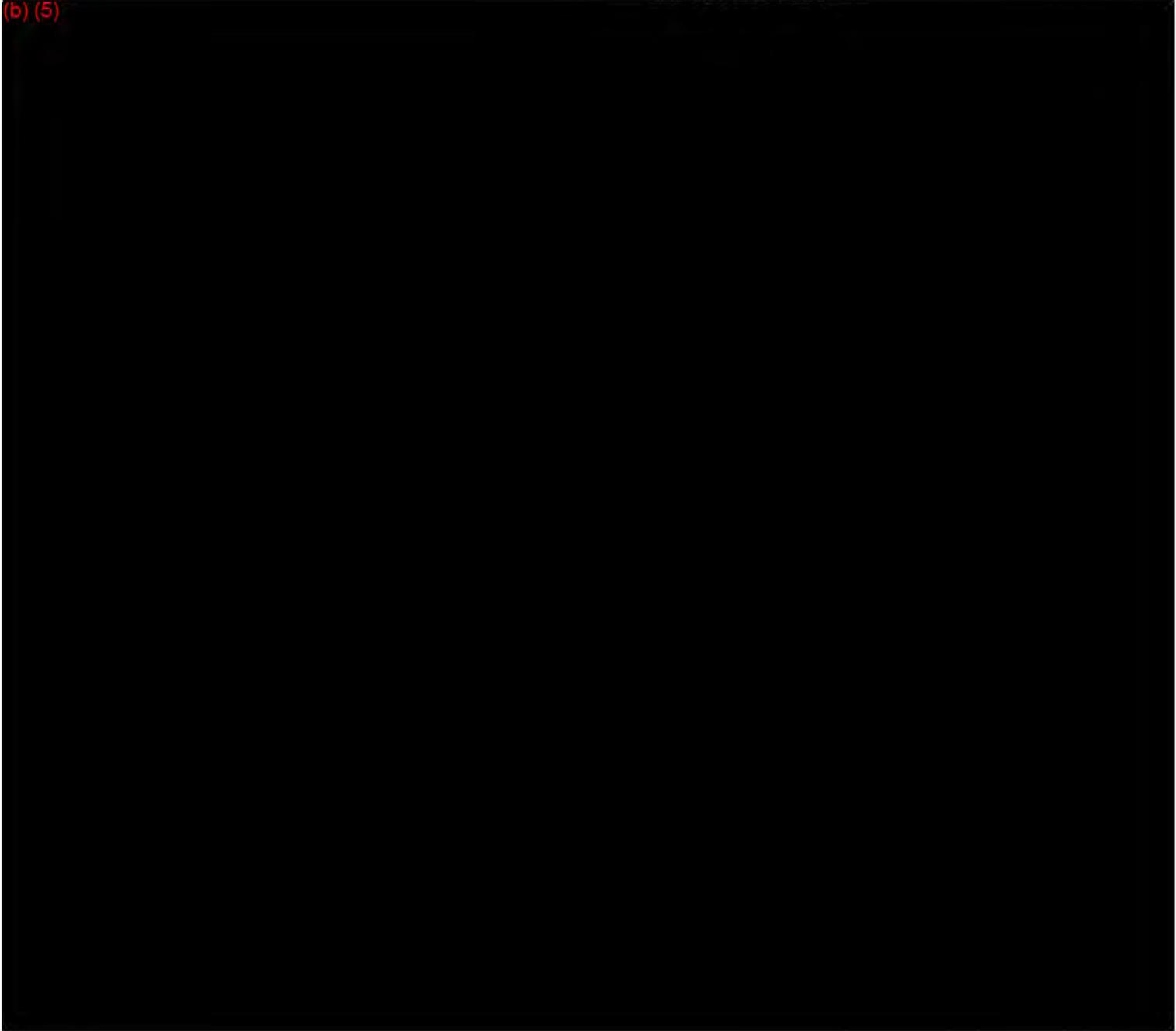
RE: Process for Commissioner's Decision about the Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics' Eteplirsen (NDA 206488)

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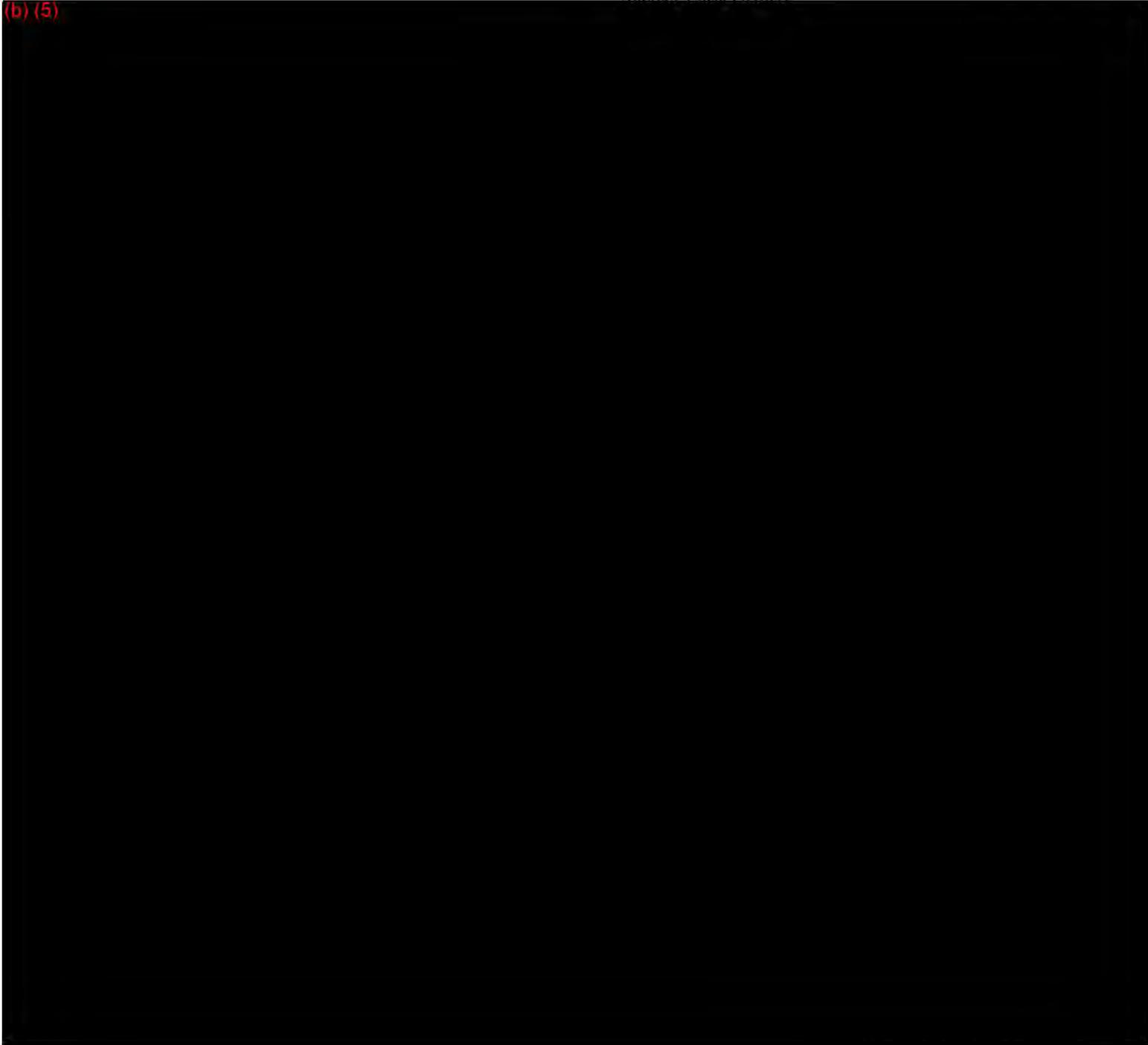


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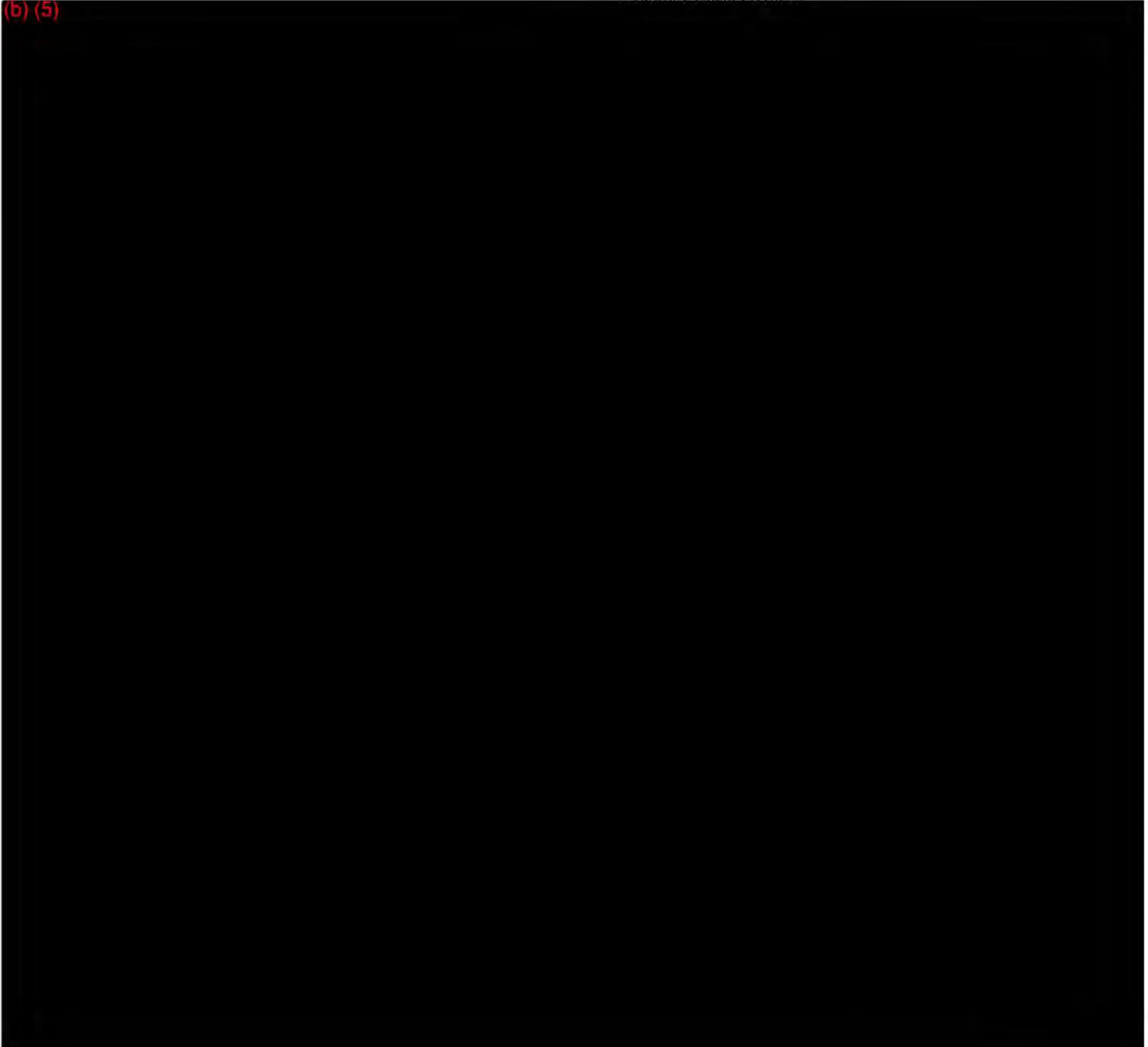


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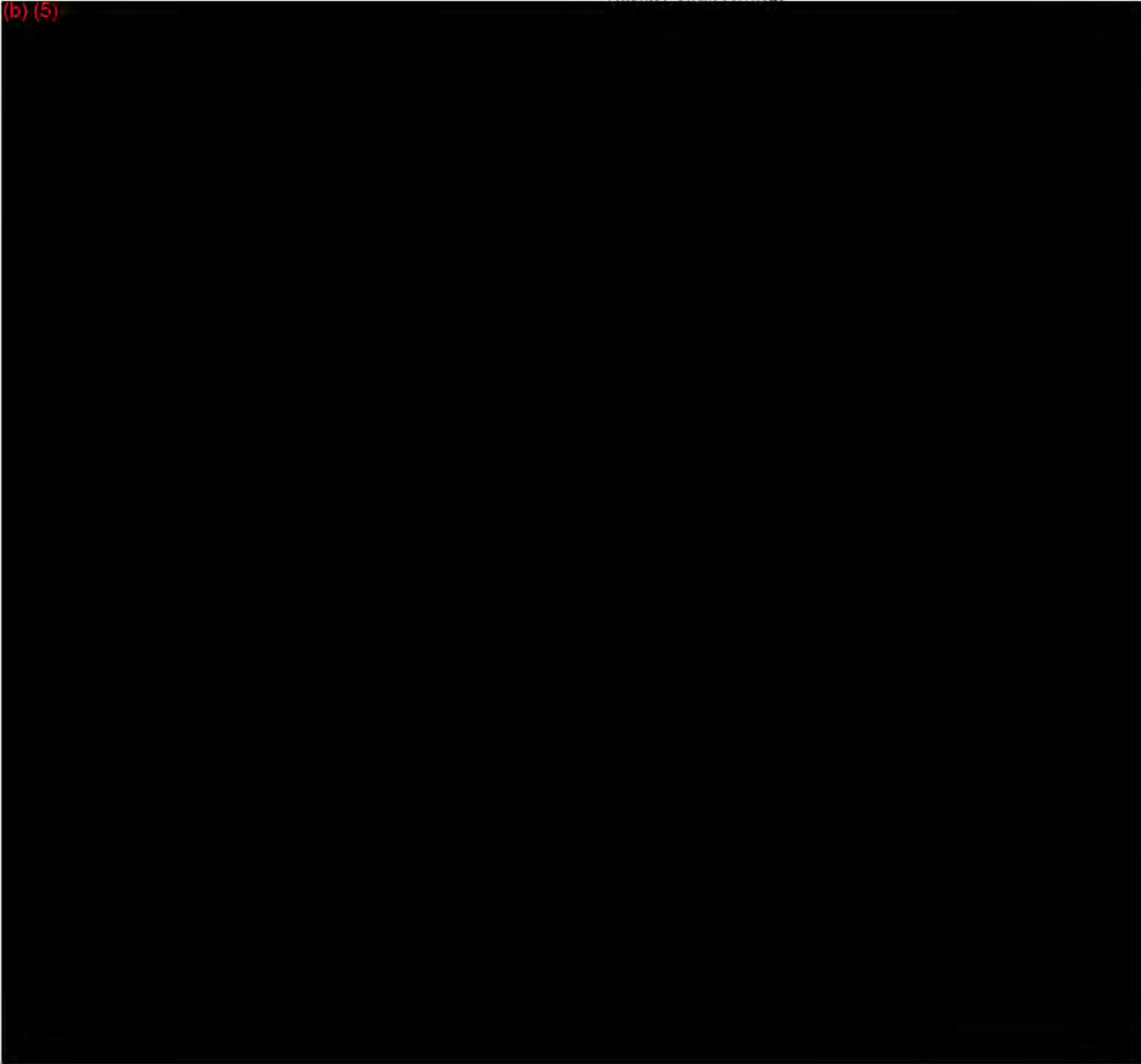
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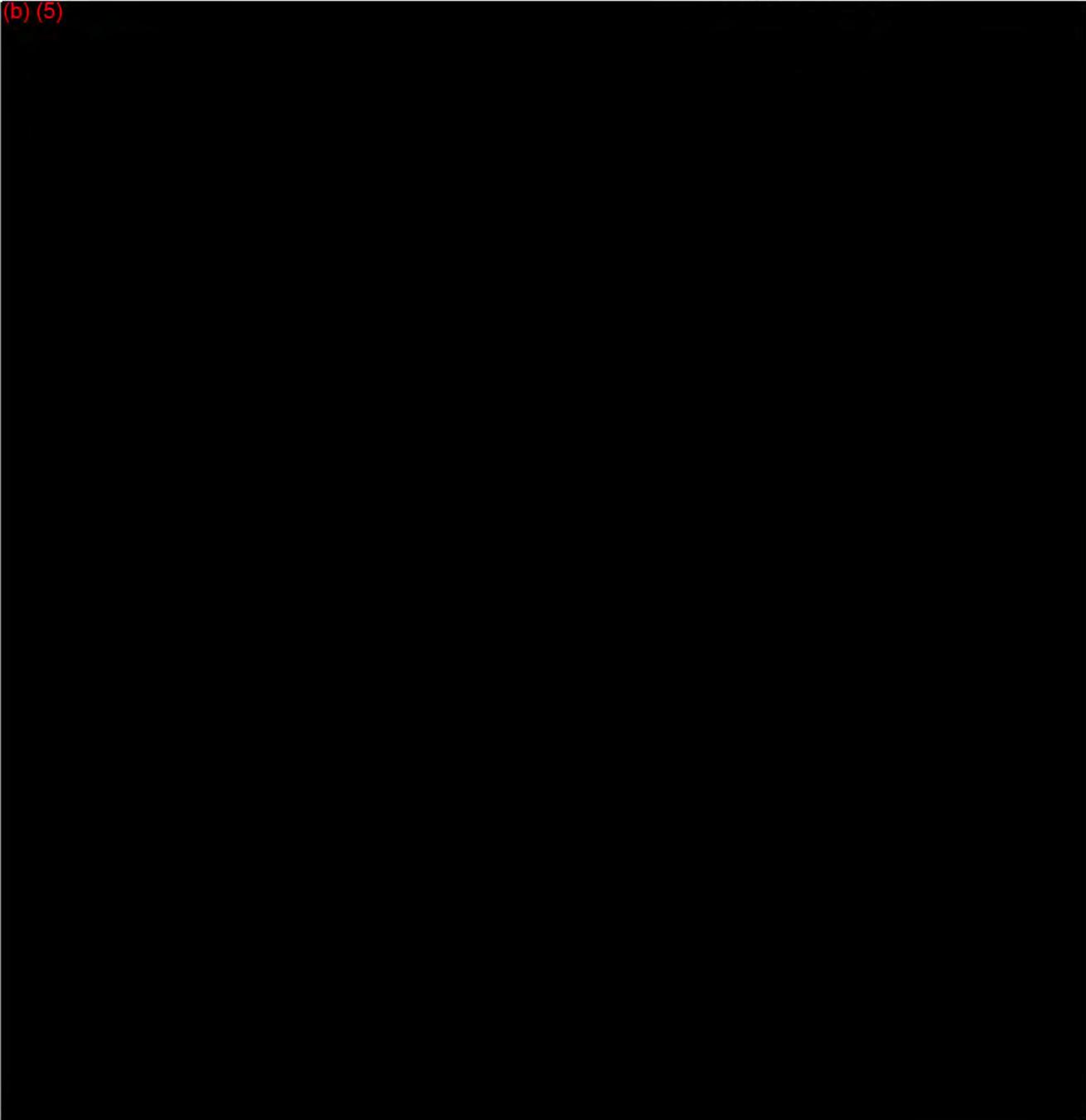
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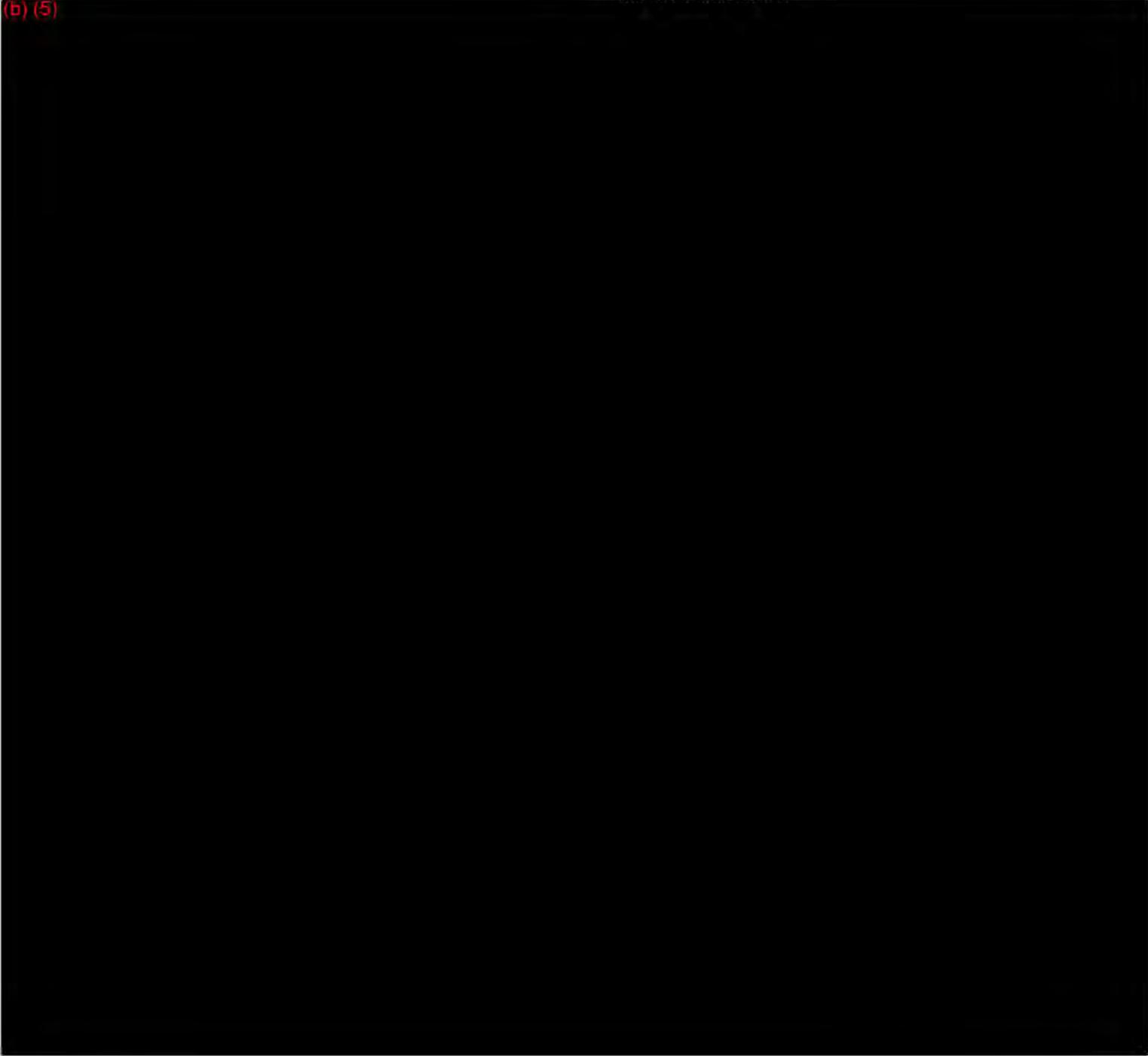
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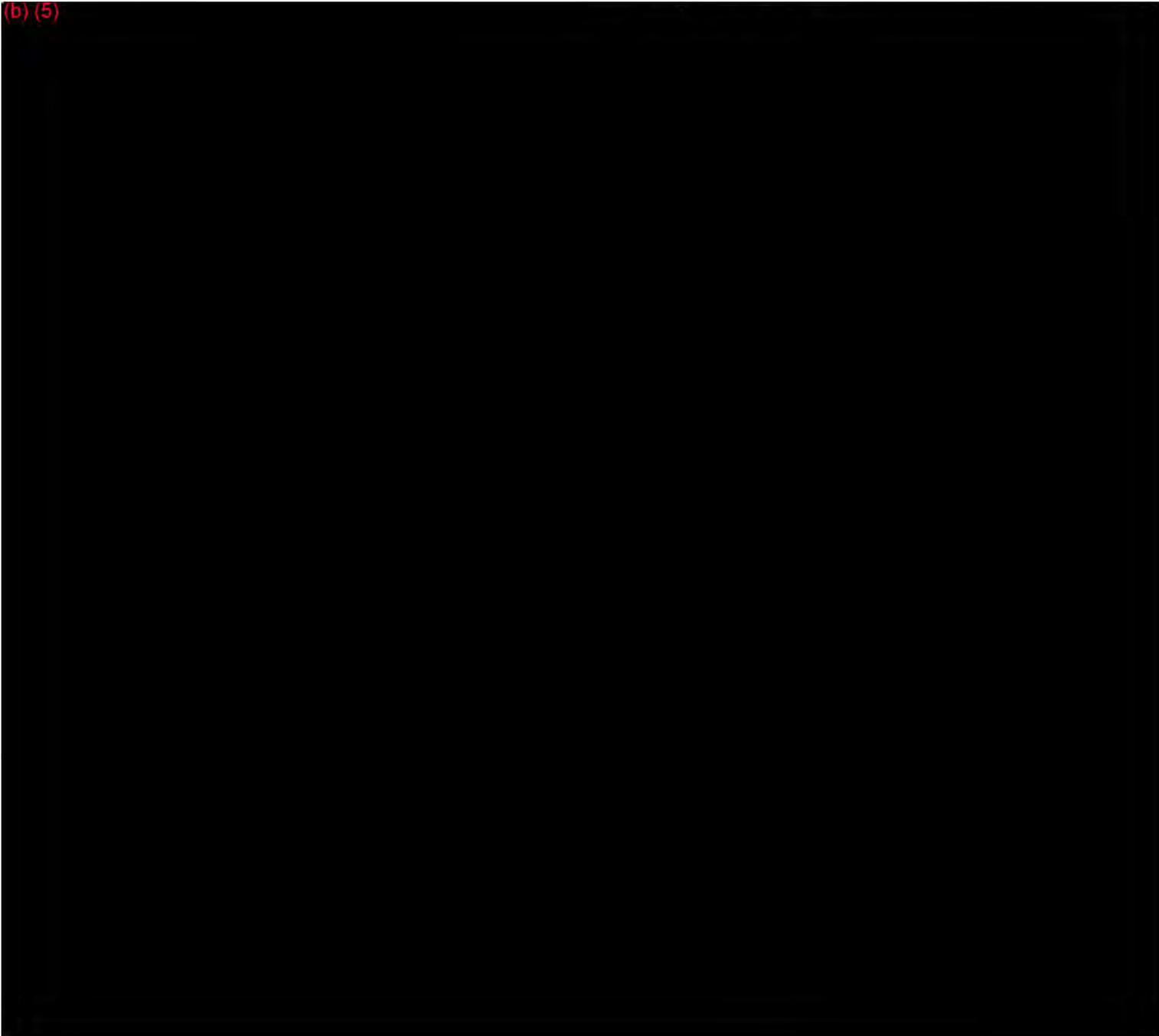
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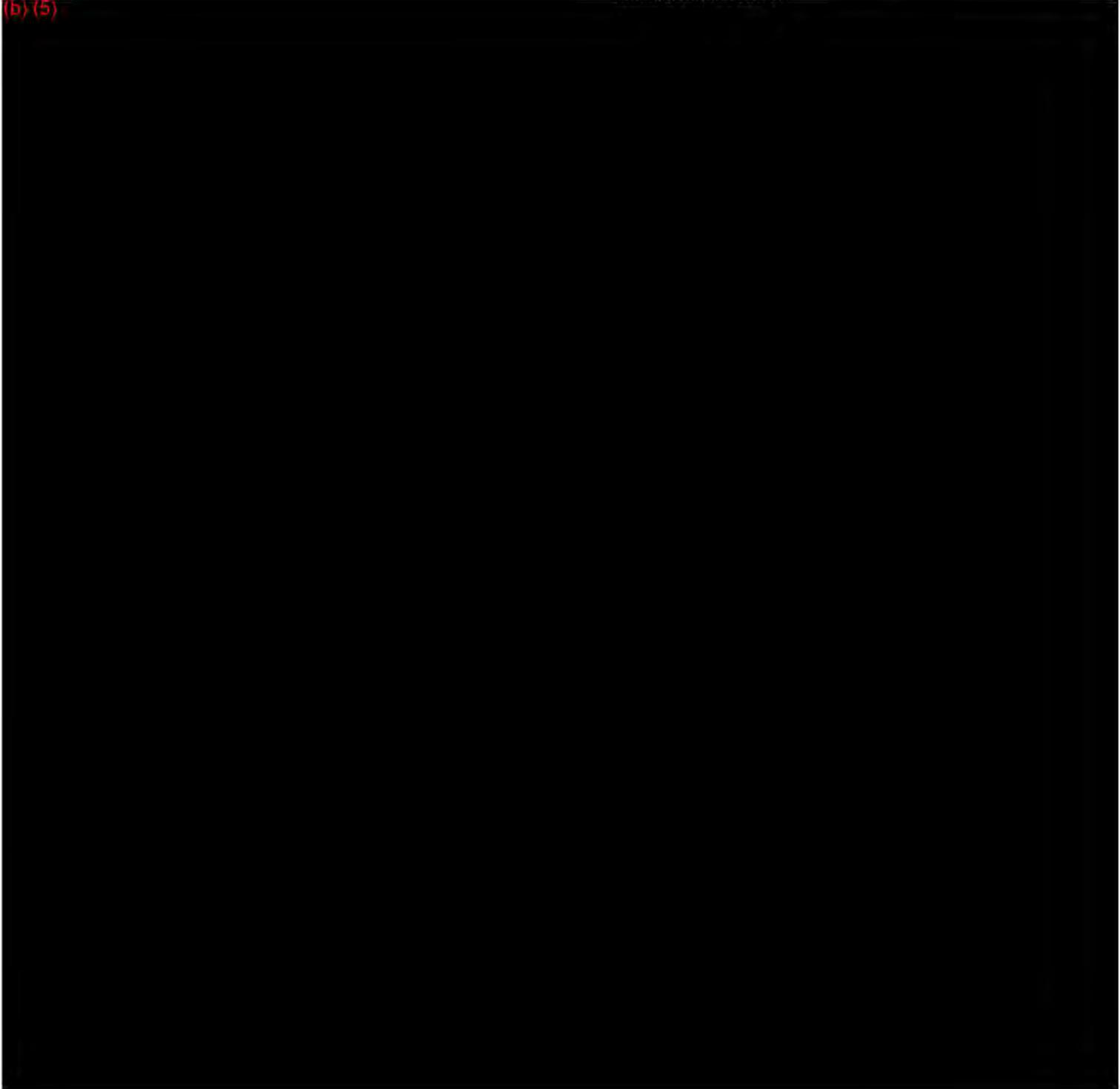
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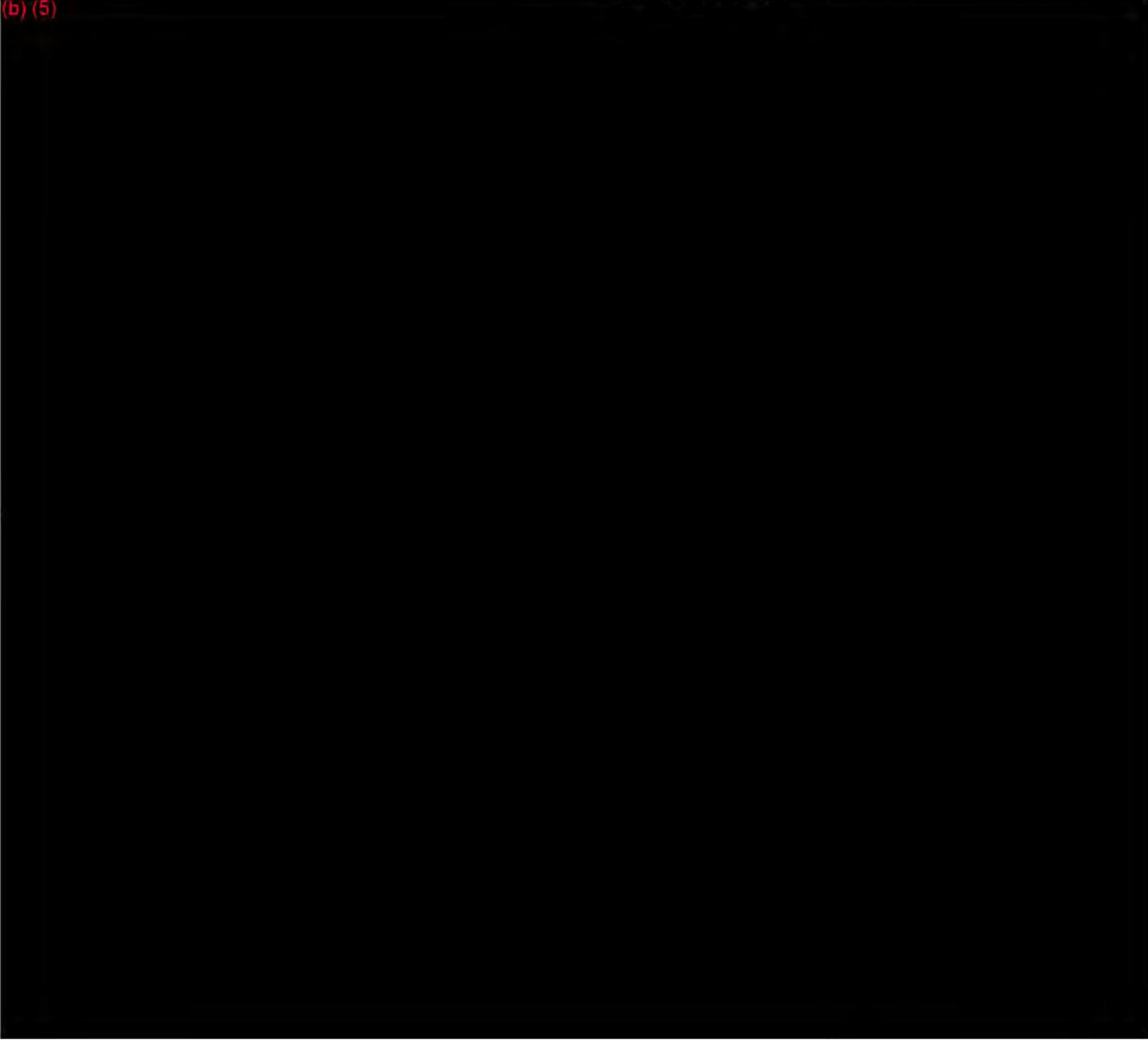
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Attorney-Client Privilege

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From: [Chasan-Sloan, Deborah \(FDA\)](#)
To: [Sherman, Rachel](#); [McCall, Jonathan *](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: Memo to file - FOR DR. CALIFF'S REVIEW
Date: Thursday, September 15, 2016 4:46:31 PM
Attachments: [Memo to File re Commissioner Decision 9-15-16 jMrs\(occ\).doc](#)
Importance: High

(b) (5)



From: Sherman, Rachel
Sent: Thursday, September 15, 2016 4:25 PM
To: [McCall, Jonathan *](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: RE: memo

Hi all,

Rob's flight is at 5, not 530. Whatever we have finished by 450 please send to Jonathan who will consolidate into a single email.

The rest we can get him later.

Thanks!

From: [McCall, Jonathan *](#)
Sent: Thursday, September 15, 2016 4:15 PM
To: [Sherman, Rachel](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: RE: memo

My edits appended.

Thanks!

-

J

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 1:09 PM
To: [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Cc: [McCall, Jonathan *](#)
Subject: RE: memo

Hi all,

My suggested edits to Rob's cover notes.

Jonathan, you're next up then onto Deborah and then back to Rob.

Thanks!

Rachel

From: Califf, Robert
Sent: Thursday, September 15, 2016 6:56 AM
To: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Here are the proposed intros to responses

rmc

From: Sherman, Rachel
Sent: Thursday, September 15, 2016 6:52 AM
To: Dickinson, Elizabeth (FDA); Califf, Robert; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

Okay, sorry I missed this.

I can draft the email this am. I can work on the memo but it may not be until late afternoon.
If someone else can start my feelings won't be hurt.

So email RS to JM to OCC to RMC.

Memo TBD.

OCC (b) (5) -

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 15, 2016 at 5:47:49 AM EDT
To: Chasan-Sloan, Deborah (FDA) <Deborah.Chasan-Sloan@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Cc: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Subject: RE: memo

See below for my comments. The question is the format of the response to Ellis, John and Lu. I'm guessing this format is good and if someone can do a draft I can edit tonight, or I can do a draft tonight for editing tomorrow.

rmc

From: Chasan-Sloan, Deborah (FDA)
Sent: Wednesday, September 14, 2016 11:38 PM
To: Sherman, Rachel; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *
Subject: RE: memo

(b) (5)

From: Sherman, Rachel
Sent: Wednesday, September 14, 2016 7:32 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Chasan-Sloan, Deborah (FDA)
Subject: RE: memo

Hi,

Liz wisely advised (b) (5)

Limiting this to those who worked on the memo draft.

Rachel

From: Califf, Robert
Sent: Wednesday, September 14, 2016 5:56 PM
To: Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Conover, Katie; Kraus, Tom
Subject: Fwd: memo

From: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Date: September 14, 2016 at 5:35:44 PM EDT
To: Califf, Robert <RMC1@fda.hhs.gov>
Cc: Jenkins, John K <John.Jenkins@fda.hhs.gov>
Subject: RE: memo

Rob

Thanks for providing an opportunity to review your draft memo regarding the eteplirsen dispute. I am responding just to you since some of the issues I raise below are sensitive. I would be happy to speak with you privately to discuss my concerns in greater detail if you

would be open to that.

I ask that you remove reference to quoting me from the July 12, 2016, e-mail that “reasonable people can disagree.” I think as used it is mischaracterized and used out of context. I strongly disagree with Janet’s decision and do not want my words in a single e-mail to suggest that is not the case.

(b) (5)



As to footnote 7, I think the review team needs to weigh in, but it was my impression that use of corticosteroids has been interpreted based on data to have changed the course of the disease in DMD. We currently have a pending NDA for use of a corticosteroid in DMD.

(b) (5)



You note on page 3 that due to the serious defects in the development program, “it is impossible to use much of the resulting trial evidence in regulatory decision-making, including reasonable extrapolation to clinical care.” Yet you later support Janet’s conclusion that the sponsor has provided data from “two adequate and well-controlled trials.” I can find no effort to reconcile these very different statements.

(b) (5)



On page 4, you state “there is also abundant evidence that Dr. Woodcock heard and read all the scientific evidence...” This implies she took these actions BEFORE reaching a decision on

the application, which is clearly not correct given her statement to the review team of her intention to overrule them and approve the drug BEFORE they had completed their reviews. Keep in mind this occurred after an AC meeting at which the majority of the panel voted against both AA and full approval. It is also clear that she was prepared to approve the drug over the team's objections by the original PDUFA goal date and only reluctantly agreed to press the sponsor for additional data on dystrophin production from the ongoing open-label trial. While I am glad she agreed to go along with that request, convincing her to take what seemed like a very logical action was not easy. So, I find it hard to reconcile your statements about the process with the actions taken. Keep in mind that the usual course of action would be for the Office to issue a CR letter and then the sponsor could submit a FDRR that would first come to me and only if I supported the Office would an FDRR go to the Center Director. In this case that process was bypassed.

(b) (5)



On page 4 you state that Dr. Woodcock "finds no rational basis for identifying a specific threshold value for dystrophin levels that would be needed to support a determination that a particular level is "reasonably likely" to predict clinical benefit." This statement defies any sense of scientific reason (would one molecule of dystrophin be enough) and goes directly to Dr. Unger's concern that "any" level of protein seems to be enough for Janet to support approval. You then go on to reference Janet's regression analyses from her memo suggesting a correlation between dystrophin production and clinical outcomes. As I have noted to you on several occasions, I find this to be a scientifically invalid analysis that compares the endpoint value for dystrophin to a delta in a clinical endpoint. This analysis simply shows a correlation between higher levels of dystrophin, without regard to drug effect (there is no delta for dystrophin change that is due to drug), and cannot support the conclusion she reached. Your citation of this analysis is troubling.

(b) (5)



You make reference in several places to a "totality of evidence" standard. That is not the

statutory standard for demonstration of effectiveness and FDA has always stated that the statutory standard for demonstration of an effect on a surrogate endpoint for AA is the same as for regular approval (i.e., substantial evidence). Perhaps you are using "totality of evidence" to support the decision that the data provided on the surrogate are reasonably likely to predict clinical benefit, but there must be substantial evidence of the drug's effect on the surrogate and the data are very weak to meet that standard.

(b) (5)



You dismiss the concerns about Janet's level of involvement in this review and her role at the AC by suggesting this is simply part of her leadership style. I have worked with Janet for over 20 years and I can say without a doubt that her involvement in this case far exceeds her usual "hands on" approach. You note that there were 14 Center director briefings related to this case, that is clearly not the "norm" for how CDER operates. You also suggest that because CDER has been successful under her leadership that suggests that her intense involvement in this case does not raise concern. I see that as true, true, and unrelated. The question in this case is not whether she has overall been an effective leader of CDER, but whether she acted appropriately and without bias in the current case, something I don't think you effectively address given the evidence and the seriousness of the allegations and concerns expressed.

(b) (5)



As to your footnote 23, there are direct statements that Janet made to the team that contradict the statements you reference from your interview with her. I am happy to discuss these statements with you further. In addition, Janet has had frequent private conversations with the sponsor and the stakeholder community. To my knowledge, she has not documented the substance of those conversations to the record, as is required under FDA regulations. That leaves a gap of knowledge to evaluate the concerns raised by the review team and Dr. Borio.

I do not find your statements about how this case does not lower the bar for future drug approvals convincing. I share the concerns voiced by Drs. Unger and Borio about the potential adverse impact on FDA's ability to reach science-based conclusions on future applications.

(b) (5)



.. On page 9 it would be nice to see you call explicitly for retraction of the publications that have now been discredited.

(b) (5)



.. Also on page 9 it is ironic that you attribute to Janet the idea of randomizing early in order to generate good evidence. That is exactly what the review team planned to require of Sarepta after the results of the 12-patient study became available, but it was Janet that pressed that a new randomized trial not be required. So, if Janet had followed the normal CDER process in this case the review team would have required placebo-controlled trials, as they did for drisapersen (b) (4), and we would have better data on which to make a decision. I would note that Janet did not and has not involved herself in the drisapersen (b) (4) cases to the same degree as eteplirsen. Drisapersen arguably (b) (4) they had a positive phase 2 trial and a second trial that leaned favorably on a clinical endpoint. Janet did not object to the division asking for a large phase 3 trial and did not object to ODE1's decision to to issue a CR letter based on (b) (4). I think it is reasonable to question why she devoted so much attention to eteplirsen and not the other (b) (4) drugs. One could speculate that she too was misled by the early reports on dystrophin production that were later discredited.

(b) (5)



.. The overall tone of your memo seems to say that you conclude that Janet behaved and conducted herself appropriately in this case. That is at odds with the experience of the review team and is counter to the team-based, collegial working environment that we hope to create at FDA so we can accomplish our important public health mission. This validation from your level of her actions and behavior is worrisome. While I understand your desire not to undercut her role as Center Director, her actions have at best created a serious appearance of bias

among the review team members and that has created distrust and a sense of undue pressure to “come around” to her way of thinking. Even if you uphold her decision I would think you should counsel her about how her behavior and actions have undermined her credibility among the review staff and should be avoided in future similar cases. Effective leaders must have the trust and respect of their staff. As I noted in our call last week, there are frequent disagreements about data and actions in CDER, and that is healthy and encouraged so we can ensure we hear all voices as we make decision, what is not healthy is a situation where the actions of a leader creates the appearance of bias since this undermines the trust necessary for the review team to conclude that the action was fair and move on.

I understand this appeal has placed you in a very difficult position. I also understand that you have made your decision. I hope, that my comments can help you to structure your decisional memo to avoid similar situations in the future. As you know, I had planned to retire from FDA last spring. I have delayed my departure for a variety of reasons, but one of the most important reasons is that Janet has told me she plans to serve as acting in my place as head of OND once I leave. I am very concerned about the impact of that decision on the future of the new drugs review program and would be happy to discuss those concerns further.
John

From: Califf, Robert
Sent: Tuesday, September 13, 2016 6:40 PM
To: Woodcock, Janet; Jenkins, John K; Unger, Ellis; Borio, Luciana
Subject: memo

Dear Colleagues,

Today I am providing to you a copy of the penultimate draft of my decisional memorandum. Although I believe the contents are self-explanatory, there are a few points that I wish to emphasize.

First, I deeply appreciate the dedication to our shared mission displayed by everyone involved in this process.

Second, I am heartened that our processes and policies worked as they should, and that we have resolved a matter of great complexity in an orderly and transparent manner.

Third, I believe this appeal highlights a critical point: it is precisely in circumstances where the evidentiary basis for our decisions is less strong that judgment and opinion necessarily assume greater prominence. We must redouble our efforts to ensure that our system for evidence generation is as robust as possible.

Finally, it is precisely because of the complexity of the subject matter and the subtle regulatory judgment required that I have come to the following major conclusions:

- All applicable processes and procedures were followed;
- The appealing parties had ample opportunity to present their views; and
- The decision to grant accelerated approval was made following consideration of all relevant scientific evidence.

I elected to review the scientific basis for this regulatory action to ensure that I fully understood the positions of both parties and to evaluate whether an additional expert panel, as recommended in the Scientific Dispute Process Review Board’s memorandum, would be needed. I have concluded that although I believe that both views are rational and reflect

extraordinary dedication to the topic, there is no basis upon which I should overrule Dr. Woodcock's decision, and that additional external review is not indicated. Furthermore, I have evaluated and am satisfied with the post-marketing requirements that have been developed and understand that the Center for Drug Evaluation and Research will closely monitor the sponsor's compliance with these requirements.

I look forward to continued vigorous discussion and debate as we continue to move this field forward. Thank you for your determination, dedication, and perseverance in serving the patient and healthcare communities.

I would request that you maintain this memorandum in confidence and do not further distribute it until such time as my decision has been made available in final form. If you identify any significant factual errors in this document, please advise me by COB Wednesday, September 14.

Robert M. Califf, MD
Commissioner, Food and Drugs

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MEMO TO FILE

FROM: Robert Califf, M.D., Commissioner of Food and Drugs

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DATE:

RE: Process for Commissioner's Decision about the Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics' Eteplirsen (NDA 206488)

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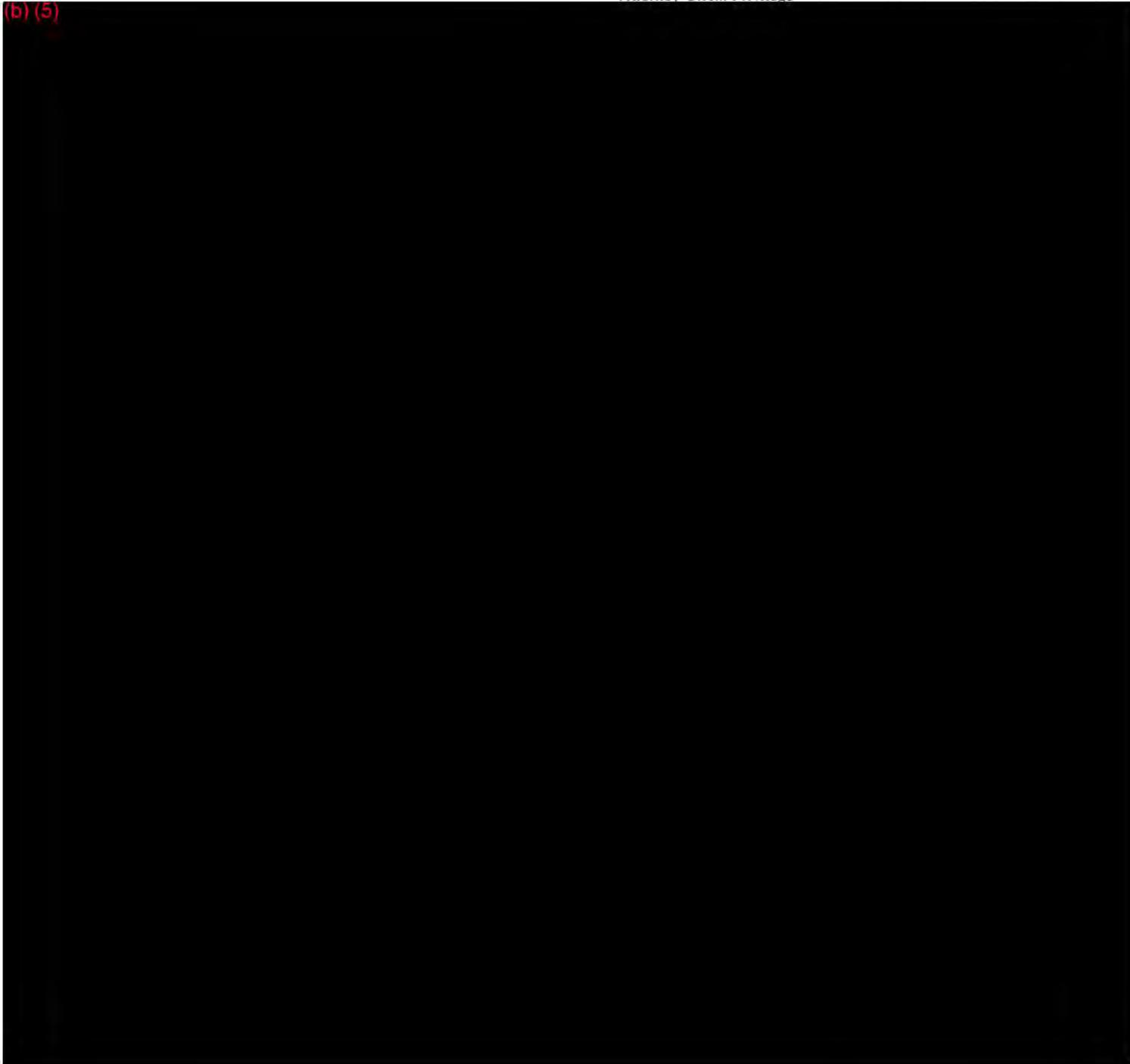
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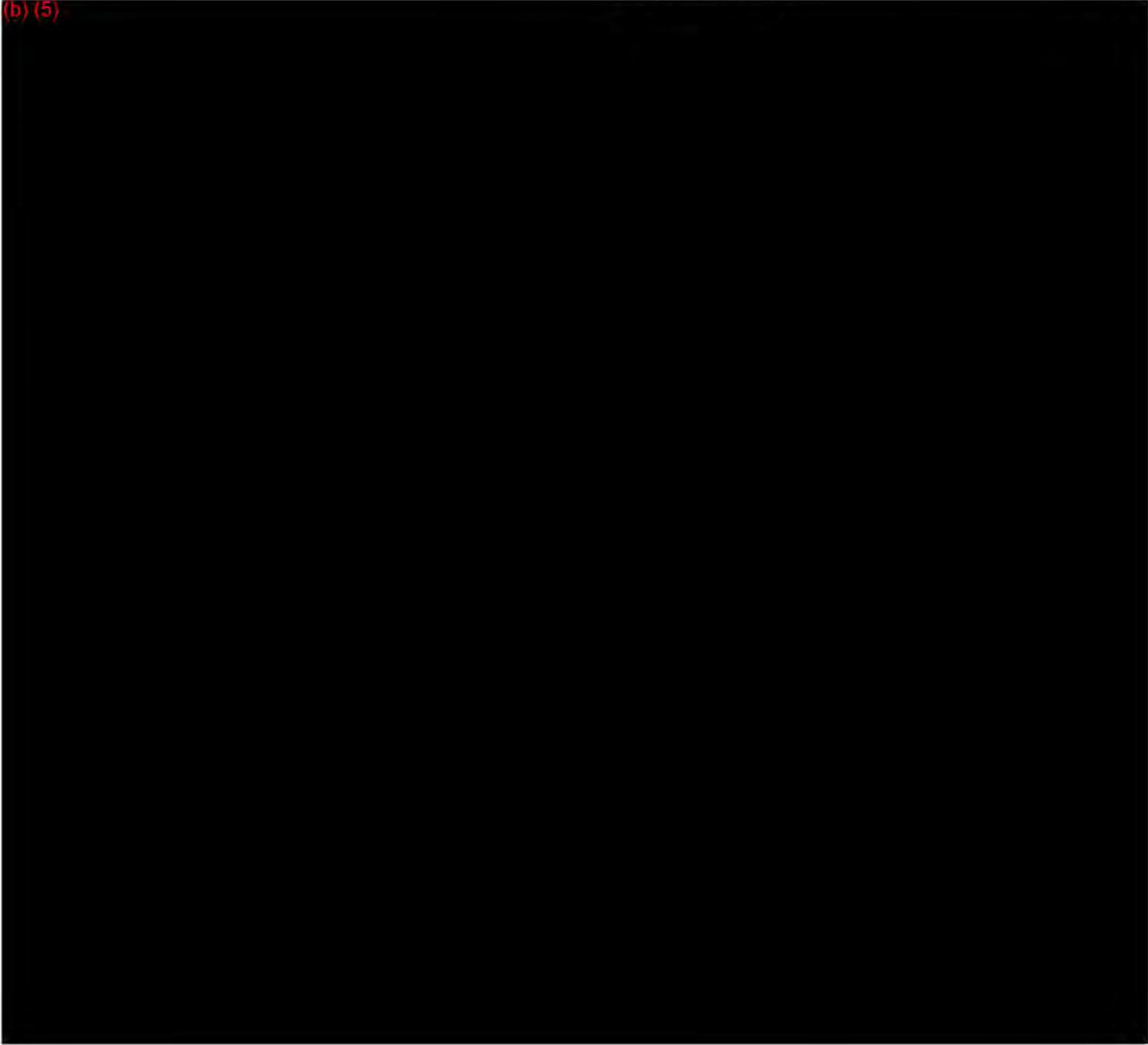
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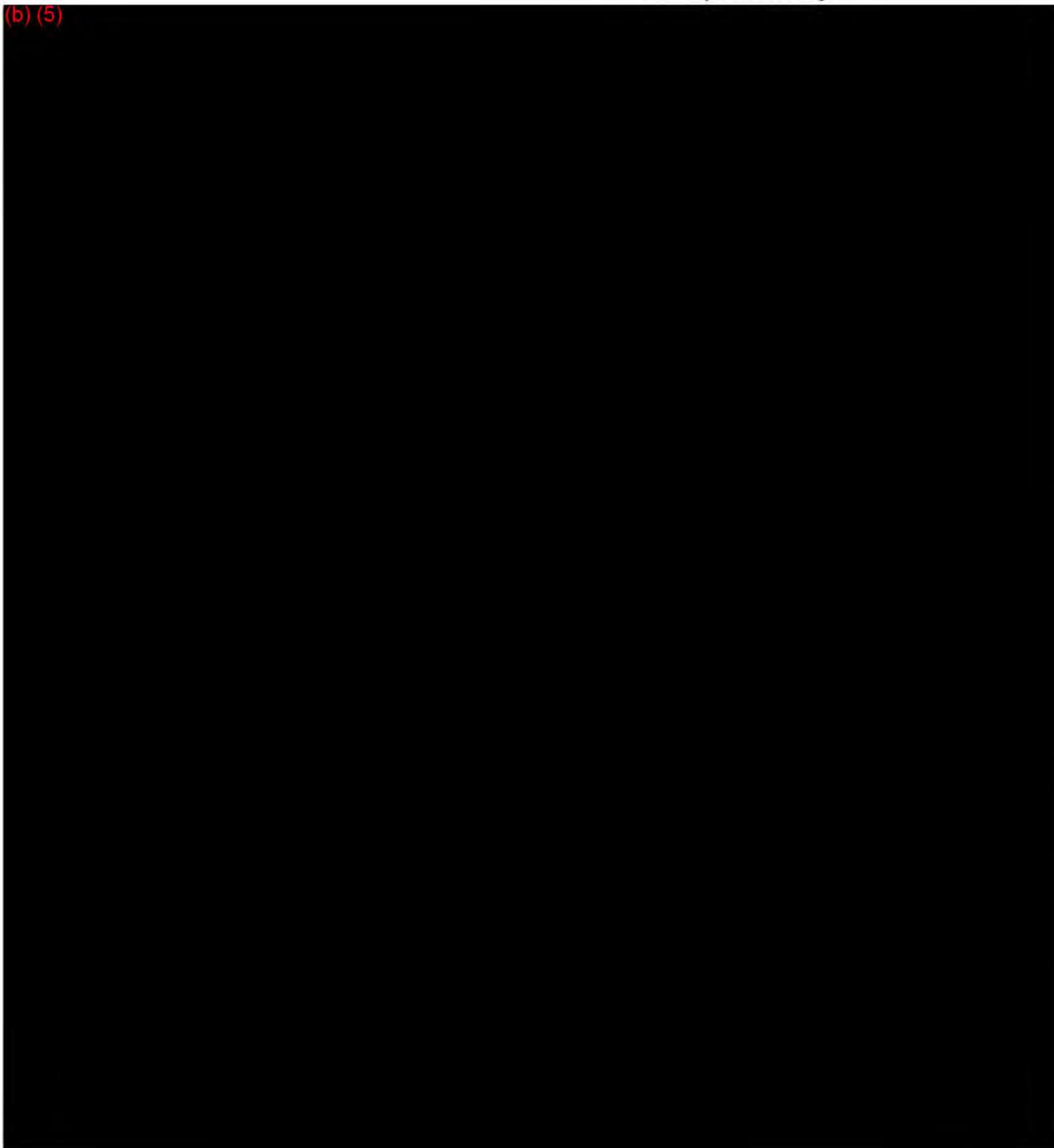
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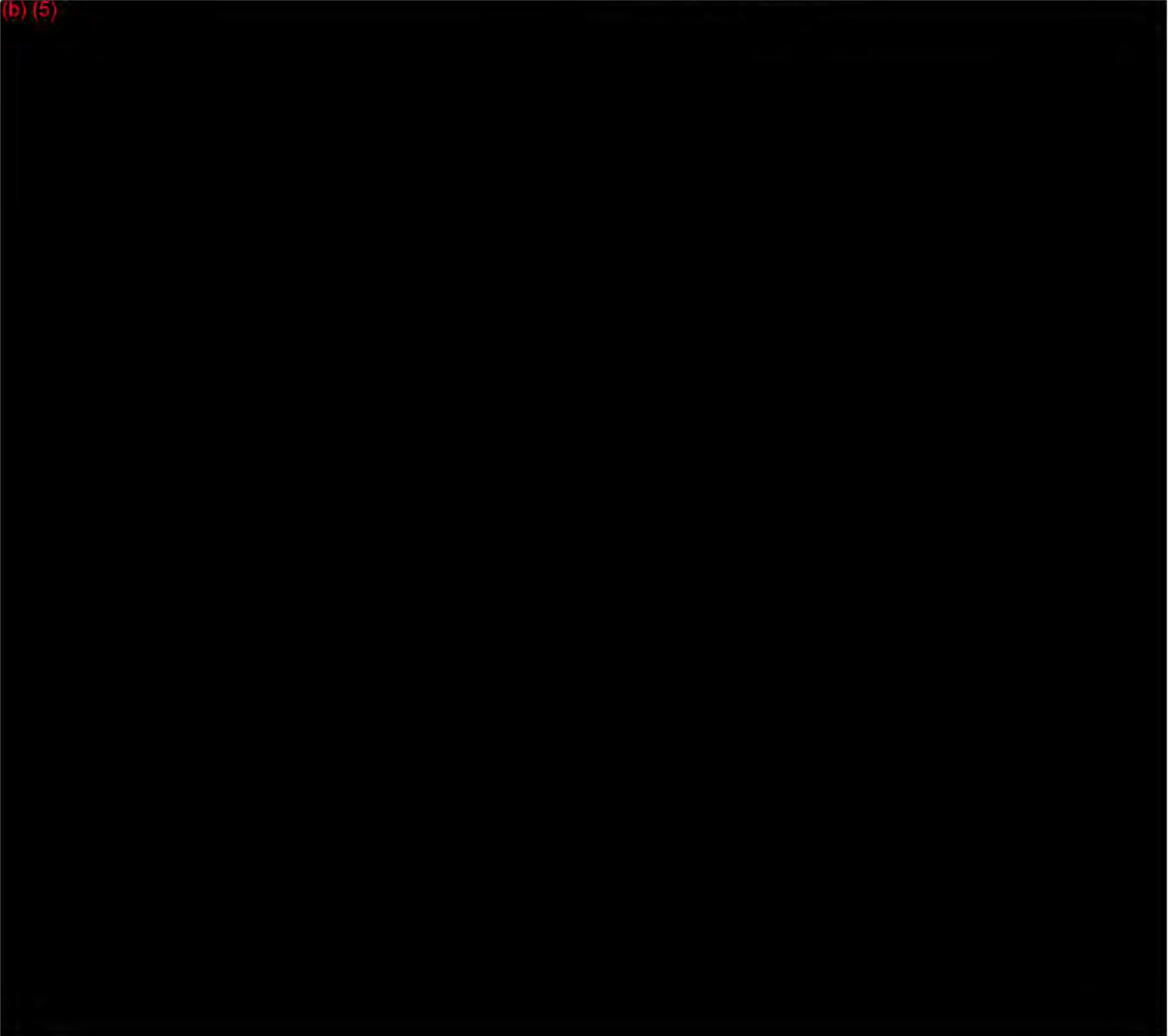
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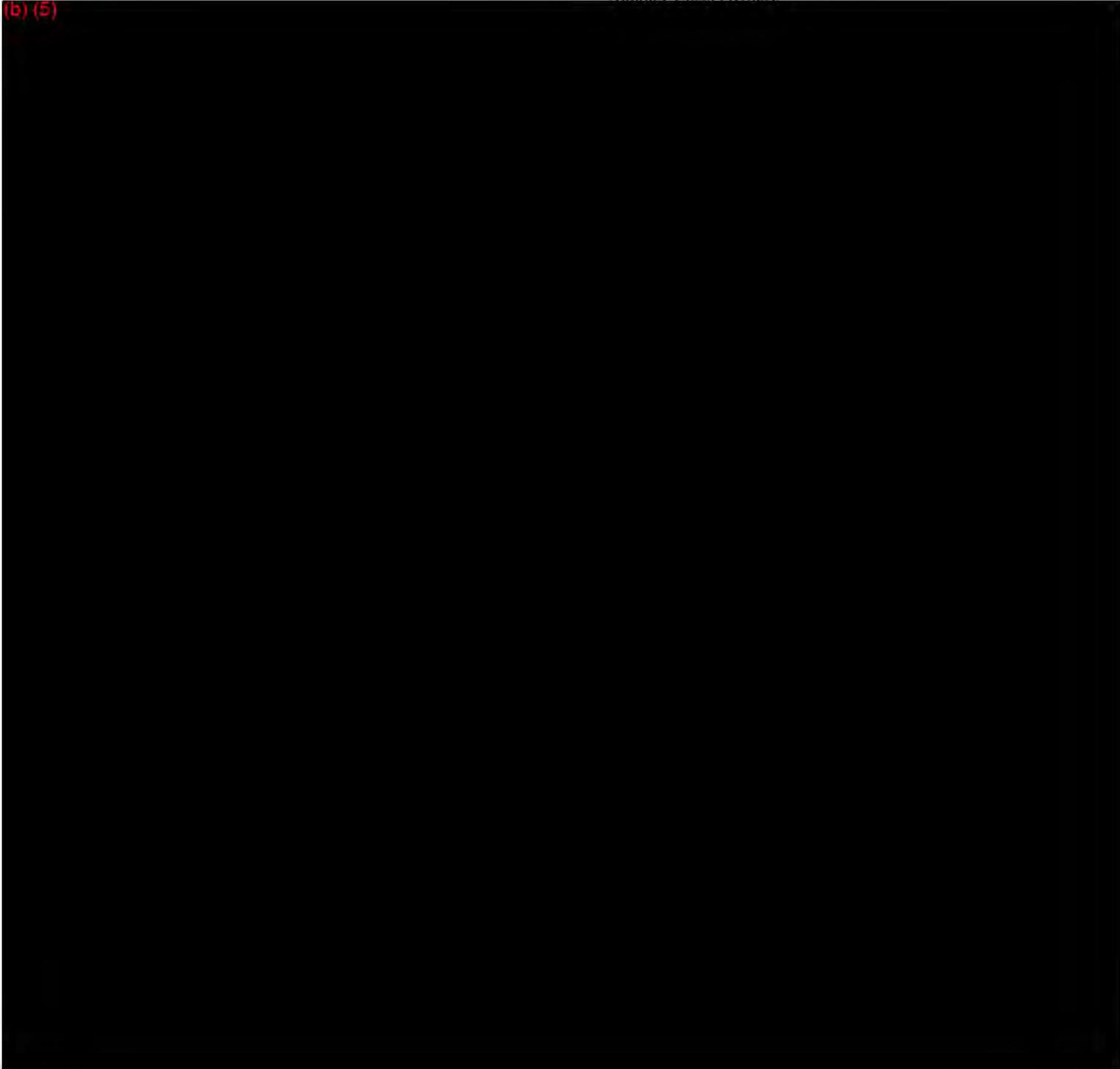


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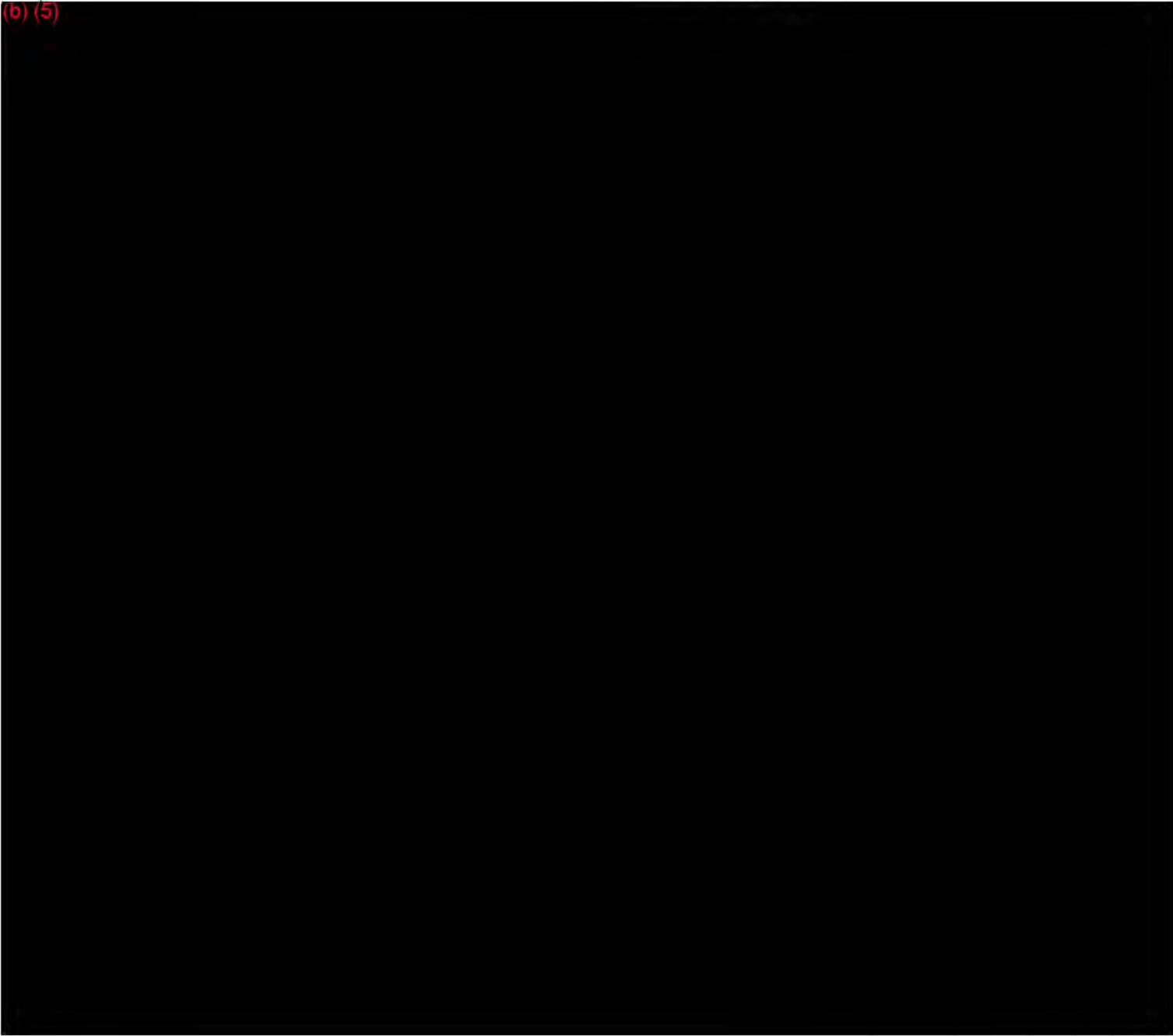
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Attorney-Client Privilege

(b) (5)



From: [Califf, Robert](#)
To: [Sherman, Rachel](#); [Chasan-Sloan, Deborah \(FDA\)](#); [McCall, Jonathan *](#)
Cc: [Dickinson, Elizabeth \(FDA\)](#); [Kraus, Tom](#)
Subject: RE: Eteplirsen decision memo and supporting materials for your review
Date: Friday, September 16, 2016 7:04:00 AM

agree

Robert M Califf MD

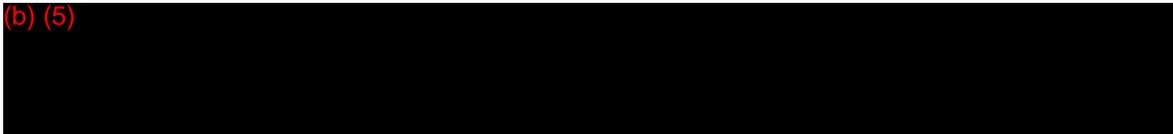
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Friday, September 16, 2016 6:51 AM
To: Chasan-Sloan, Deborah (FDA); Califf, Robert; McCall, Jonathan *
Cc: Dickinson, Elizabeth (FDA); Kraus, Tom
Subject: RE: Eteplirsen decision memo and supporting materials for your review

Looks good to me; Rob, if you like them these are good to go.

From: Chasan-Sloan, Deborah (FDA)
Sent: Thursday, September 15, 2016 11:59 PM
To: Califf, Robert; McCall, Jonathan *
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Kraus, Tom
Subject: RE: Eteplirsen decision memo and supporting materials for your review

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A large black rectangular redaction box covers the majority of the email body content between the second and third email headers.

<< File: 20160915 response notesrs_JM_CLEAN_rmc.doc >>

From: Califf, Robert
Sent: Thursday, September 15, 2016 9:22 PM
To: McCall, Jonathan *
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom
Subject: RE: Eteplirsen decision memo and supporting materials for your review

<< File: 20160915 response notesrs_JM_CLEAN_rmc.doc >>

One minor change on response note.

rmc

From: McCall, Jonathan *
Sent: Thursday, September 15, 2016 4:56 PM
To: Califf, Robert
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom

Subject: Eteplirsen decision memo and supporting materials for your review

Hello Dr. Califf –

Here is the current version of the eteplirsen memo:

<< File: 2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ).doc >> << File: 2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ)_Commented.doc >>

Here is the memo to file:

<< File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN.doc >> << File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_COMMENTED.doc >>

And here are the response cover notes:

<< File: 20160915 response notesrs_JM_CLEAN.doc >> << File: 20160915 response notesrs_JM_TRACKED.doc >>

Thanks!

--

Jonathan

From: Dickinson, Elizabeth (FDA)
To: Kraus, Tom; Sherman, Rachel; Conover, Katie; Califf, Robert
Cc: Chasan-Sloan, Deborah (FDA)
Subject: Pink Sheet
Date: Friday, September 16, 2016 8:19:38 AM

FDA Neurology Clinical Team Leader Departure May Be Mountain Disguised As Molehill

Executive Summary

Attention to the departure of neurology reviewer Ron Farkas from FDA has focused on what it means for Sarepta's eteplirsen application, but there are larger regulatory environment issues that deserve more scrutiny.

Like most controversies today, it started with a tweet.

"Seems like Ron Farkas is no longer at the [@US_FDA](#) cc [\\$SRPT](#)" Jenn McNary, one of the most active Duchenne Muscular Dystrophy patient advocates and a mother of a son with DMD, wrote on Sept. 13 using the stock ticker symbol for **Sarepta Therapeutics Inc.**, the sponsor of eteplirsen.

The reaction on social media was fast and furious: reporters and investors attempted to confirm with FDA and Parexel – the rumored new employer of Farkas – that the reviewer had indeed left the agency.

Farkas was Division of Neurology Products clinical team leader who conducted the review of Sarepta's DMD drug eteplirsen. His review was overwhelmingly negative and concluded that not only was there not substantial evidence of an effect from eteplirsen but there was no evidence at all. (Also see "[Sarepta, FDA And The Dangers Of Strong Early Results](#)" - Pink Sheet, 2 May, 2016.)

McNary's tweet in turn led to Wall Street speculation and stories confirming Farkas had left FDA and that it was a positive development – if not confirmation – that eteplirsen will get accelerated approval. The application has survived bumps at FDA but remains a possibility for an accelerated approval.

But reading the tea leaves of the Farkas departure solely as another piece in the up-or-down decision on the Sarepta drug misses a potentially broader significance to the event. There are other messages and reverberations that may last longer.

Personal Enmity Towards Reviewers

The first is the personalization of enmity toward an FDA reviewer. Farkas was

painted as enemy number one for what some believed was an obstructionist position on the eteplirsen application for a deadly disease in young boys. Farkas has been negative on other recent applications. He reviewed **BioMarin Pharmaceutical Inc.**'s DMD drug drisapersen that was rejected by FDA and probably had an important role in FDA's decision to refuse-to-file **PTC Therapeutics Inc.**'s application for ataluren.

Farkas also was negative on Merck's sleep drug suvorexant that led to a big write-up in the *New Yorker* titled "**The Big Sleep.**" But that's not always the case. He supported approval of Vanda's non-24 sleep drug tasimelteon for the blind that was approved by FDA.

Removing emotion from the case of eteplirsen, Farkas applied the FDA's long-established regulatory standards to the review and made it very clear that the application fell well short of the threshold for approval in his opinion as primary reviewer.

Tough standards come into conflict with applications for life-threatening conditions at FDA: it is part of the territory.

For many reasons, though, the eteplirsen application reached an almost unprecedented level of political and patient sensitivity. Therefore, Farkas' position as lead reviewer and regulatory determination were magnified. What reviewer will want to take on an application like eteplirsen in the future?

Not Farkas' Call To Make

Lost in the focus on Farkas is the fact that Division Director Billy Dunn and Deputy Director Eric Bastings both expressed the same position as Farkas regarding the eteplirsen application. Office of Drug Evaluation I Director Ellis Unger appeared to be of the same mind as well given some of his comments at the panel meeting, but it was less clear.

And if an unprecedented level of regulatory flexibility were to be applied to the filing in order to reach an approval decision, it will be done by several layers above Farkas – that was always going to be the case.

The final sign off decision will fall to Unger or could escalate – unlikely but possible in this unusual case – to CDER Director Janet Woodcock, who opened the door for an accelerated approval pathway for eteplirsen during her presentation at the eteplirsen panel review.

Put another way, it was not Farkas' call to make despite the perception that he was the implacable roadblock to the application.

Bolstering Review Morale

The second issue: this is what the start of a decline of a peak approval climate looks like. Anyone who watched the April 25 advisory committee review of eteplirsen or who has followed Sarepta can tell you this was a brutal review. And the pressure on the neurology division to approve an application for DMD – particularly eteplirsen – has not been lost on other reviewers in different divisions.

In other words, everybody is watching this application but FDA reviewers are watching the eteplirsen outcome too.

If a myth or storyline develops that Farkas left FDA because management overruled him due to external pressure, that would create a significant problem for FDA internally. Senior FDA officials have worked tirelessly and successfully to remove that distraction and create an almost peerless period of pro-innovation, approvals, cutting edge regulatory science and efficiency.

The risk is that others could follow Farkas out the door, or worse stay on at the agency demoralized and perhaps resentful and fretful of being overridden from management above.

Impossible? No. That is what happened in the nadir of the FDA drug approval process four decades ago – two decades before Woodcock even joined the agency. A general perception first within FDA and then generally in the public of too much bending in favor of applications and industry-bias by FDA managers led to a general collapse of morale and Congressional hearings.

Preventing A Toxic Review Climate

Sarepta has collected many Congressional supporters for its application. So a negative response from Capitol Hill to an eteplirsen approval is not likely. What is dangerous is a sense at the working review levels that management is pushing too hard for approvals. That story – true or false – can be toxic to the NDA review environment.

The Neurology Division's portfolio of diseases includes some of the most high-profile diseases for which there is major unmet need: Alzheimer's, Parkinson's disease, Huntington's disease, multiple sclerosis, epilepsy, migraine, muscular dystrophy, ALS, narcolepsy.

Now that division has lost a senior reviewer at a time when FDA is having great difficulty recruiting young neurologists to staff the division. CDER Director Janet

Woodcock has publicly lamented the fact that newly minted neurologists out of medical school can make as much as an FDA Center Director.

The truth is no one at this point know why Farkas left. His departure and the eteplirsen review may be completely unrelated or a direct cause and effect. But keep watching to see if something bigger may be brewing here.

From the editors of the RPM Report

From: [Rodriguez, Jennifer](#)
To: [Chasan-Sloan, Deborah \(FDA\)](#)
Cc: [Conover, Katie](#); [Califf, Robert](#); [Sherman, Rachel](#); [Kraus, Tom](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: RE: HHS Cleared Comms - Next Steps
Date: Friday, September 16, 2016 10:08:54 AM
Attachments: [Phase II approval QA 9.16.16.doc](#)
[eteplirsen KMOA 9.16.16.doc](#)
[eteplirsen PR 9.16.16ocr.doc](#)
[image001.png](#)
[image002.png](#)
[image003.png](#)
[image004.png](#)
[image005.png](#)
[image006.png](#)

Thank you, Deborah! I have addressed your edits and comments here.

When do you anticipate having the documents you need to conduct your final review?

I am also reaching out to Matt Warren for assistance with the one outstanding QA.

Thanks!

Jen

From: Chasan-Sloan, Deborah (FDA)
Sent: Friday, September 16, 2016 9:34 AM
To: Rodriguez, Jennifer
Cc: Conover, Katie; Califf, Robert; Sherman, Rachel; Kraus, Tom; Dickinson, Elizabeth (FDA)
Subject: RE: HHS Cleared Comms - Next Steps

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From: Rodriguez, Jennifer
Sent: Thursday, September 15, 2016 4:53 PM
To: Califf, Robert; Sherman, Rachel; Kraus, Tom; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: Conover, Katie
Subject: HHS Cleared Comms - Next Steps
Importance: High

Hi All,

Attached please find the HHS cleared comms. This reflects relatively minor edits from HHS, which have been incorporated/addressed.

FDAOC0002232

Liz/Deborah – we would appreciate, for due diligence, if you could review all three documents once more to ensure they OK. Also, (b) (5)

In addition, HHS has signed off on our Hill/Stakeholder outreach plan. They have just asked that we give them a heads up before we take the action so that they are aware.

Please let me know if you have any questions.

Best,
Jen

Jennifer Rodriguez

Deputy Director of Strategy, OMA

Office of Media Affairs

Office of External Affairs

U.S. Food and Drug Administration

Tel: 301-796-8232 / Cell: 202-763-9073

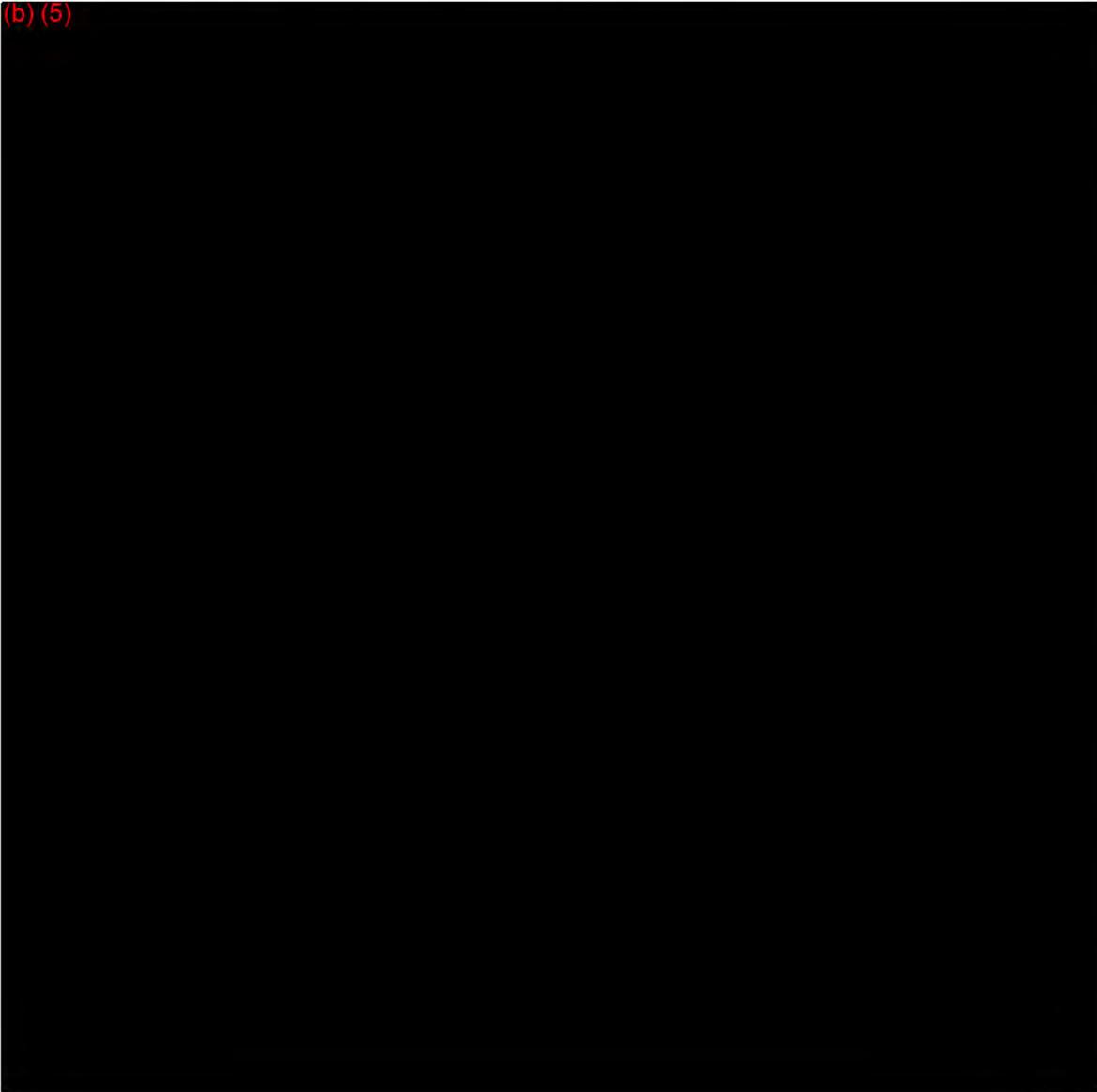
Jennifer.Rodriguez@fda.hhs.gov



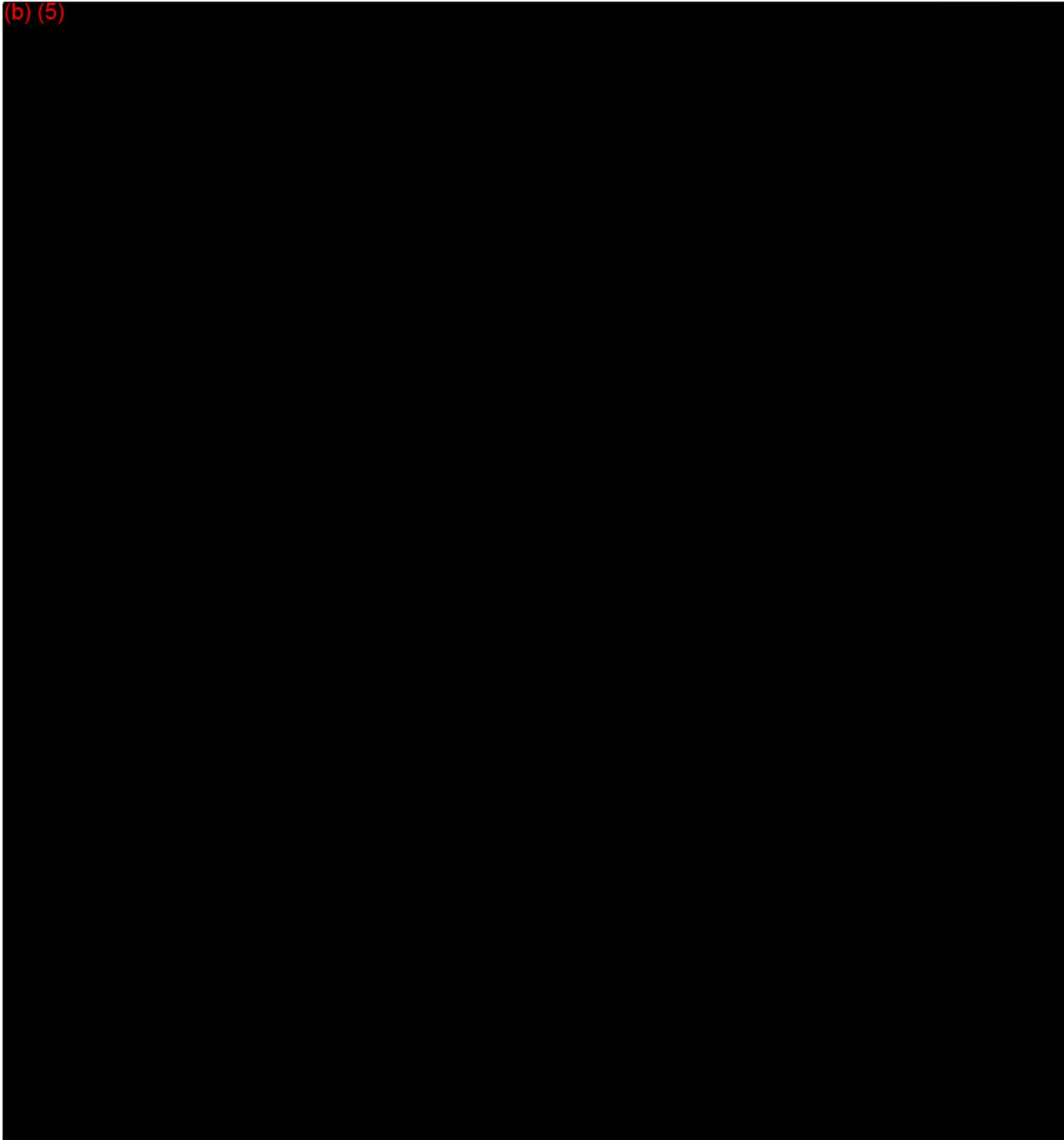
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Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy**

Target date: September 2016

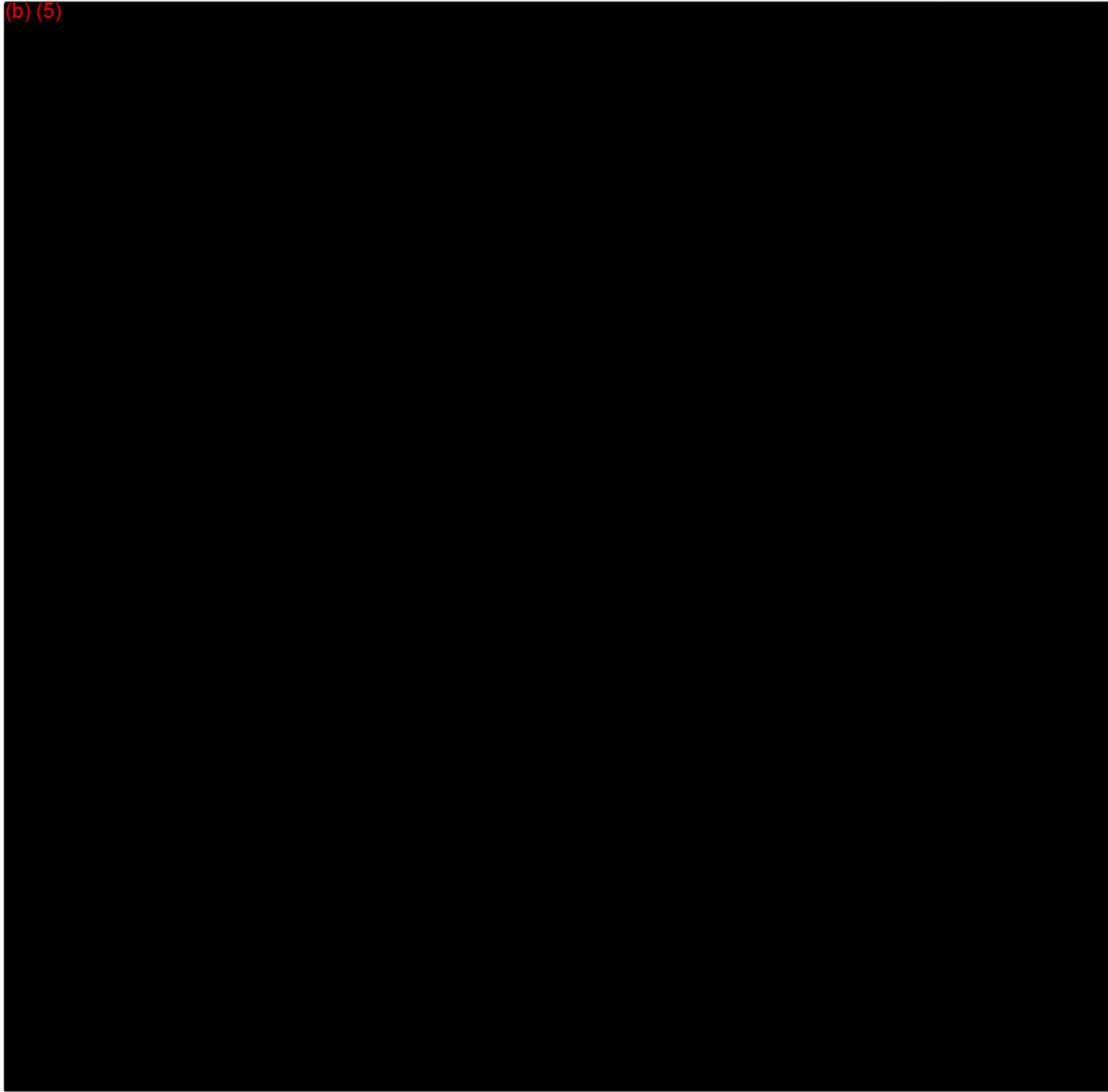
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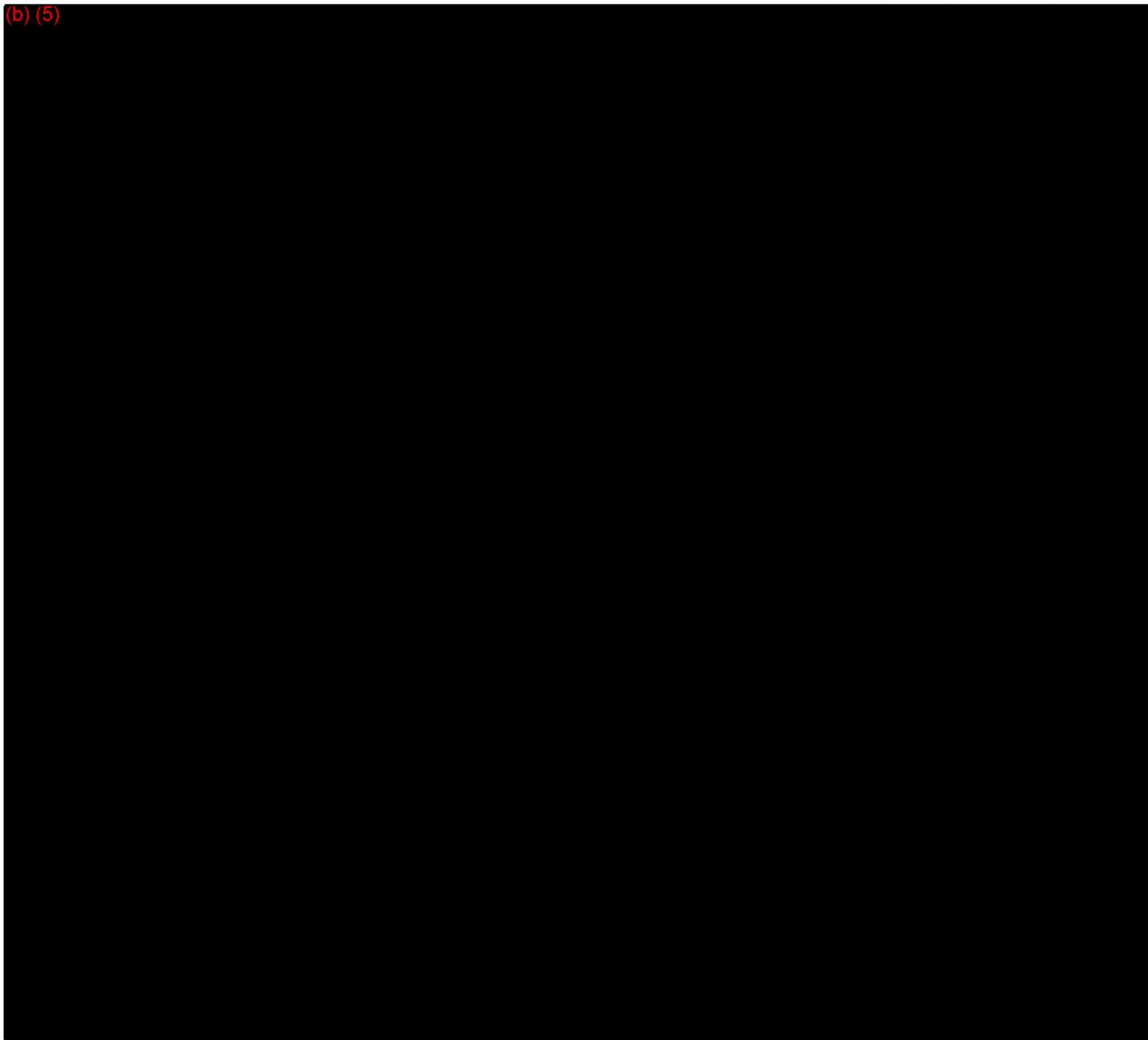
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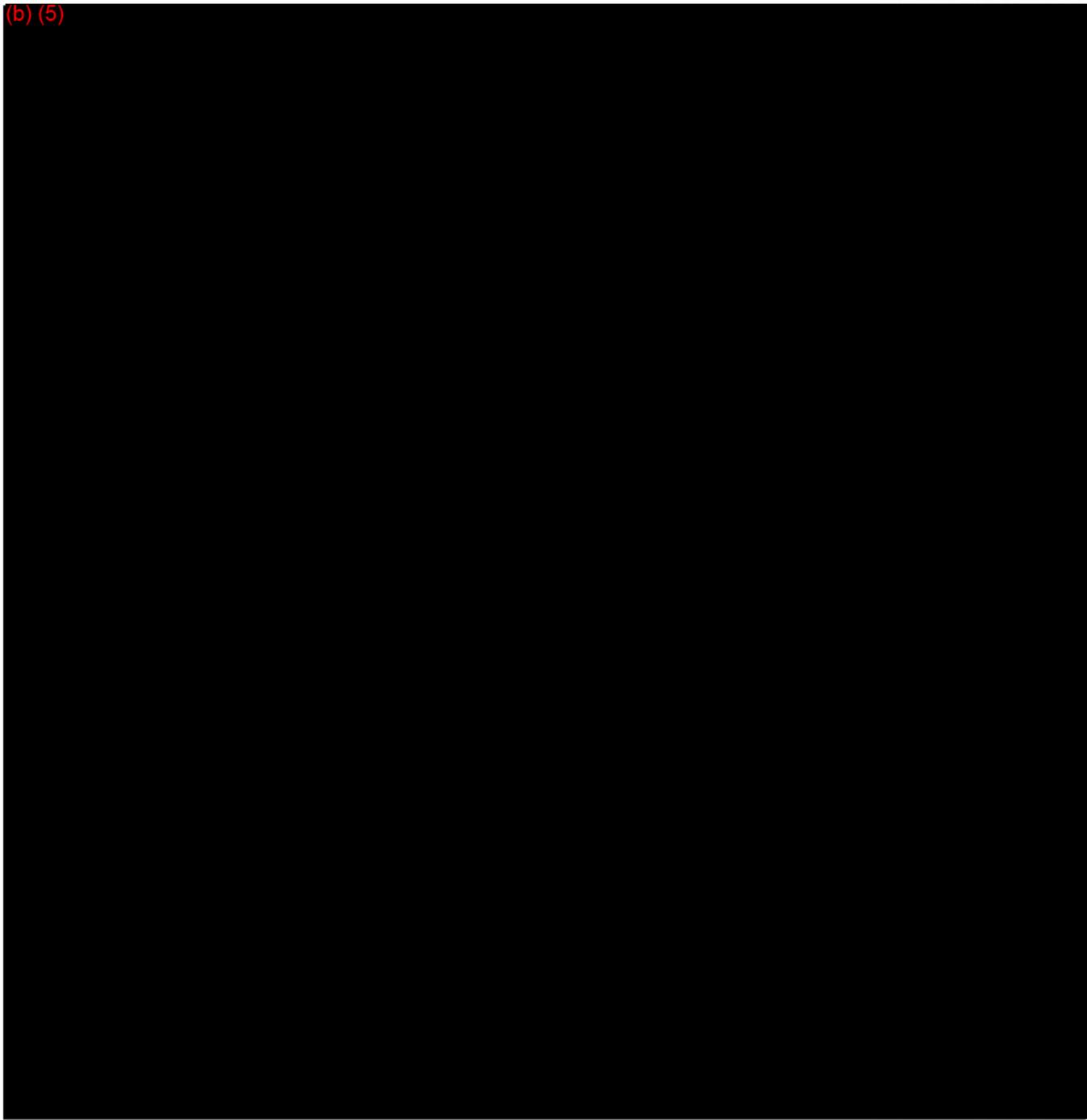
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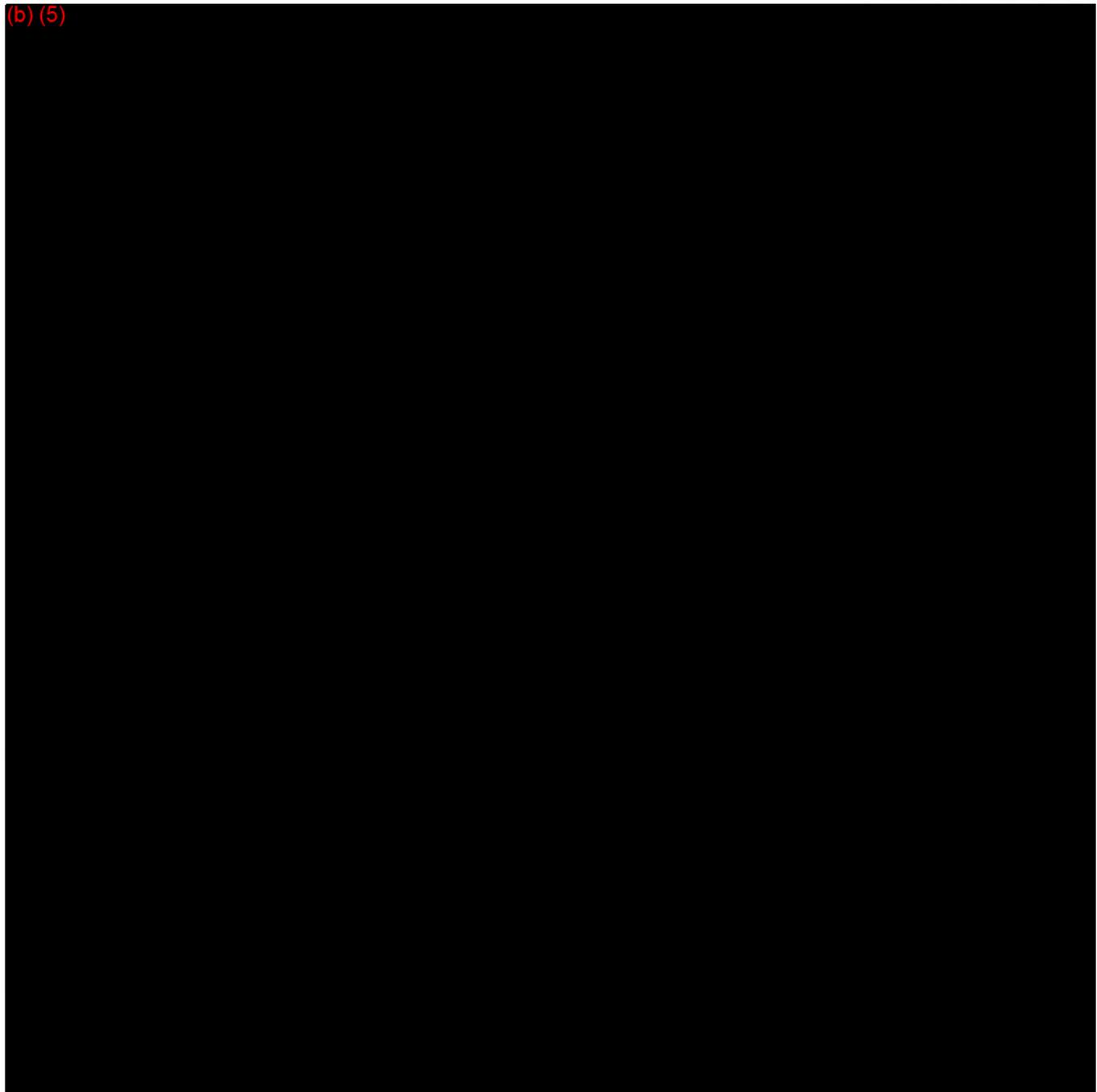
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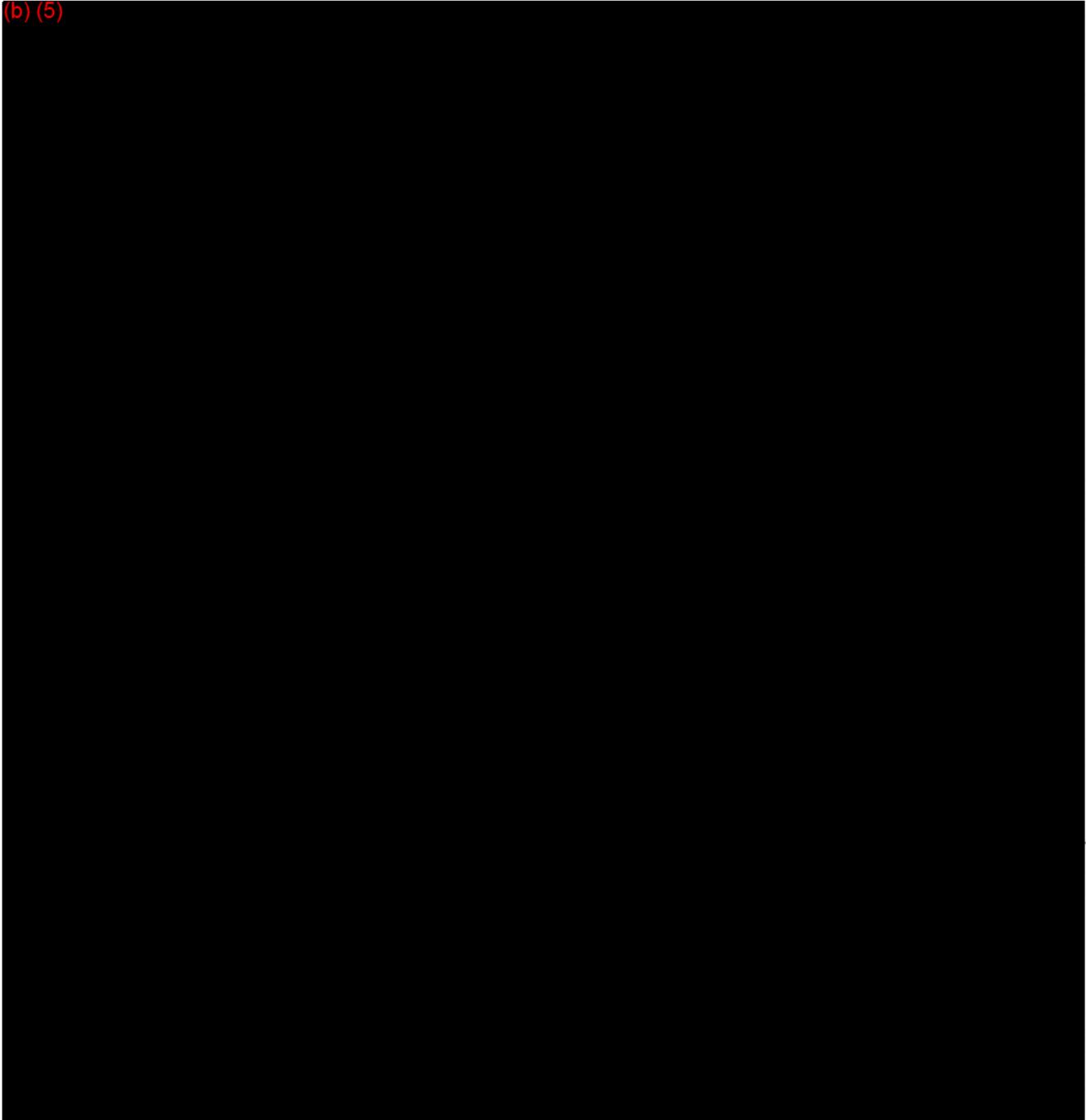
Key Messages & Reactive QA: FDA approval of Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy

Target date: September 2016

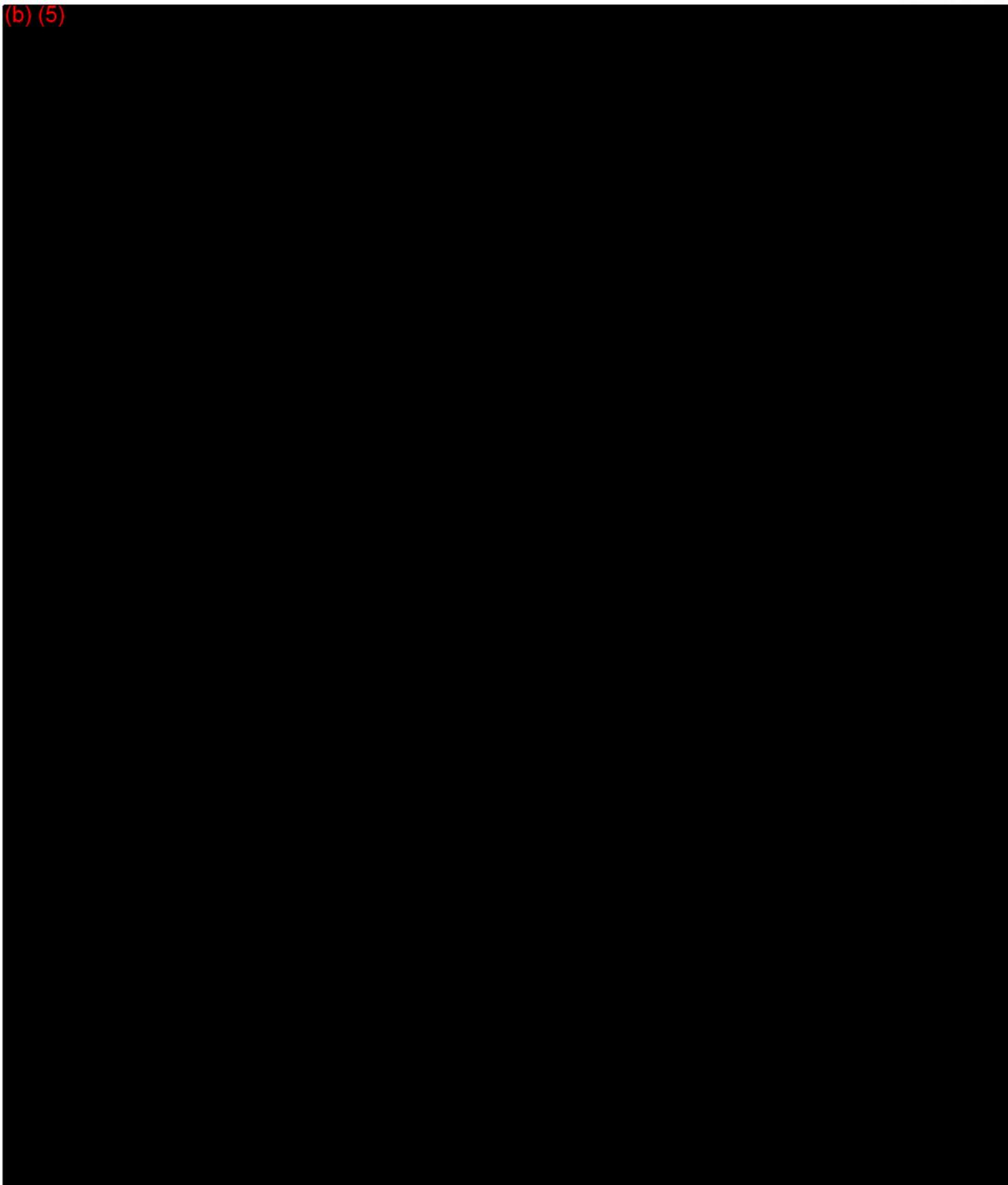
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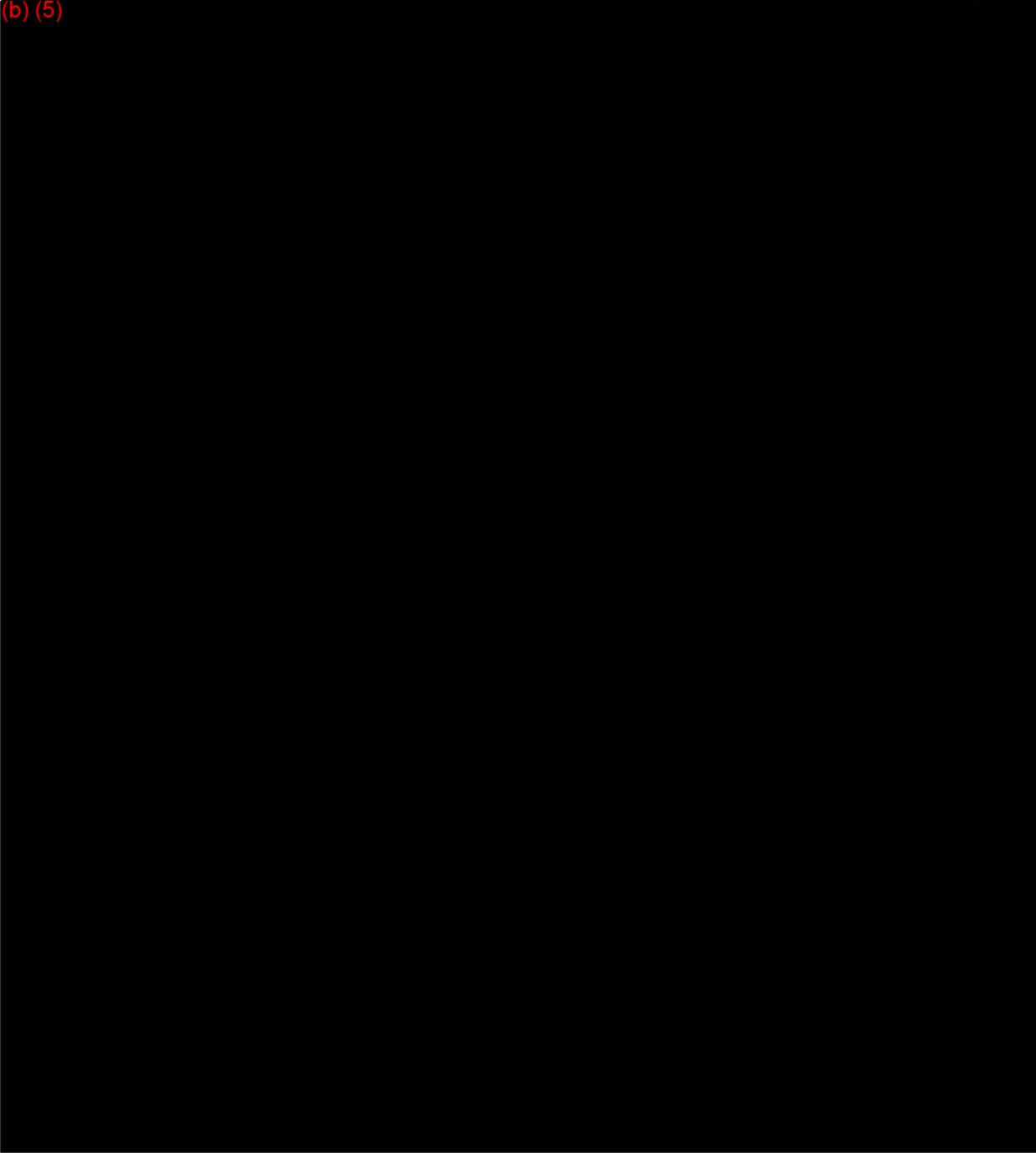
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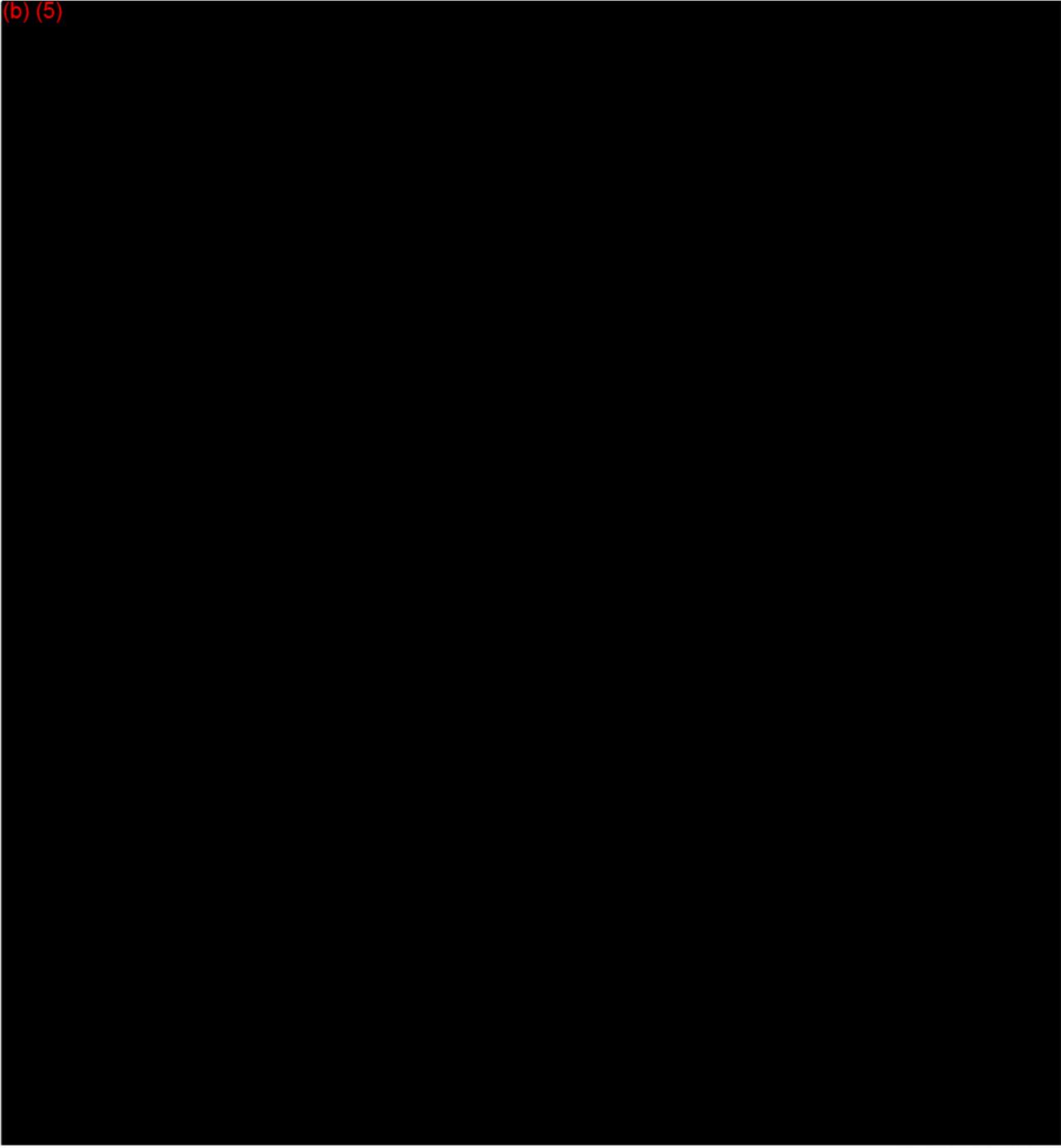
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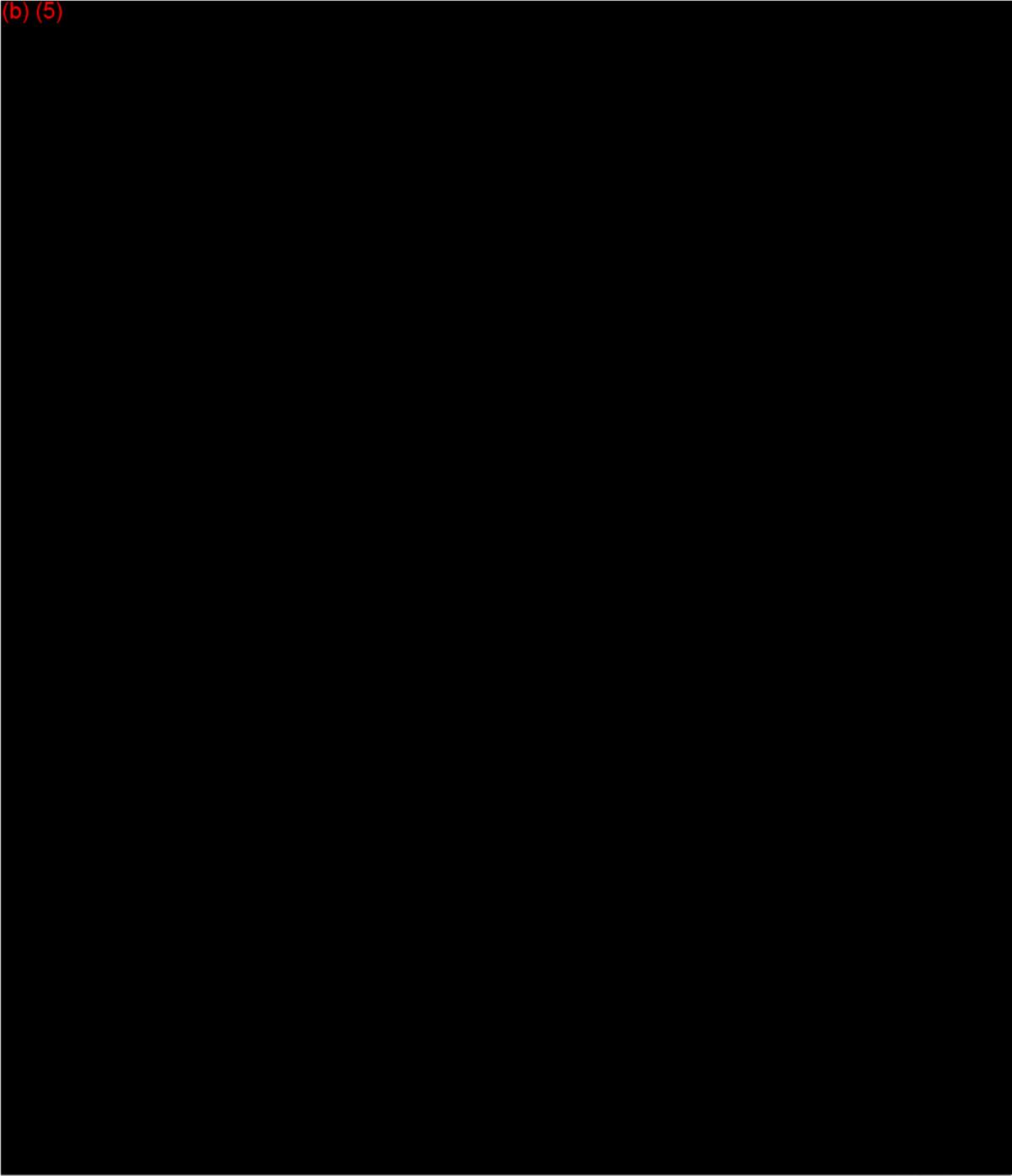
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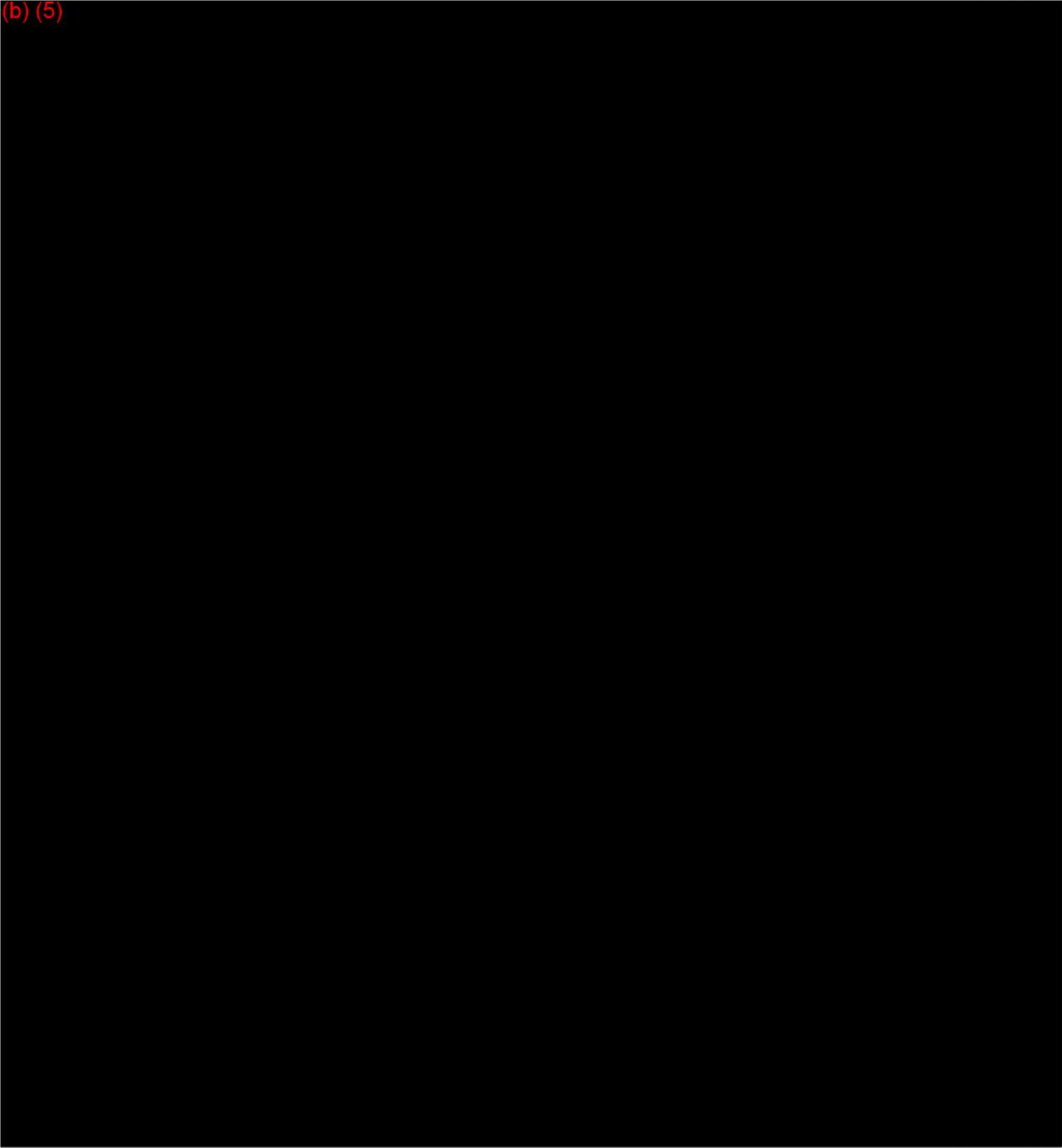
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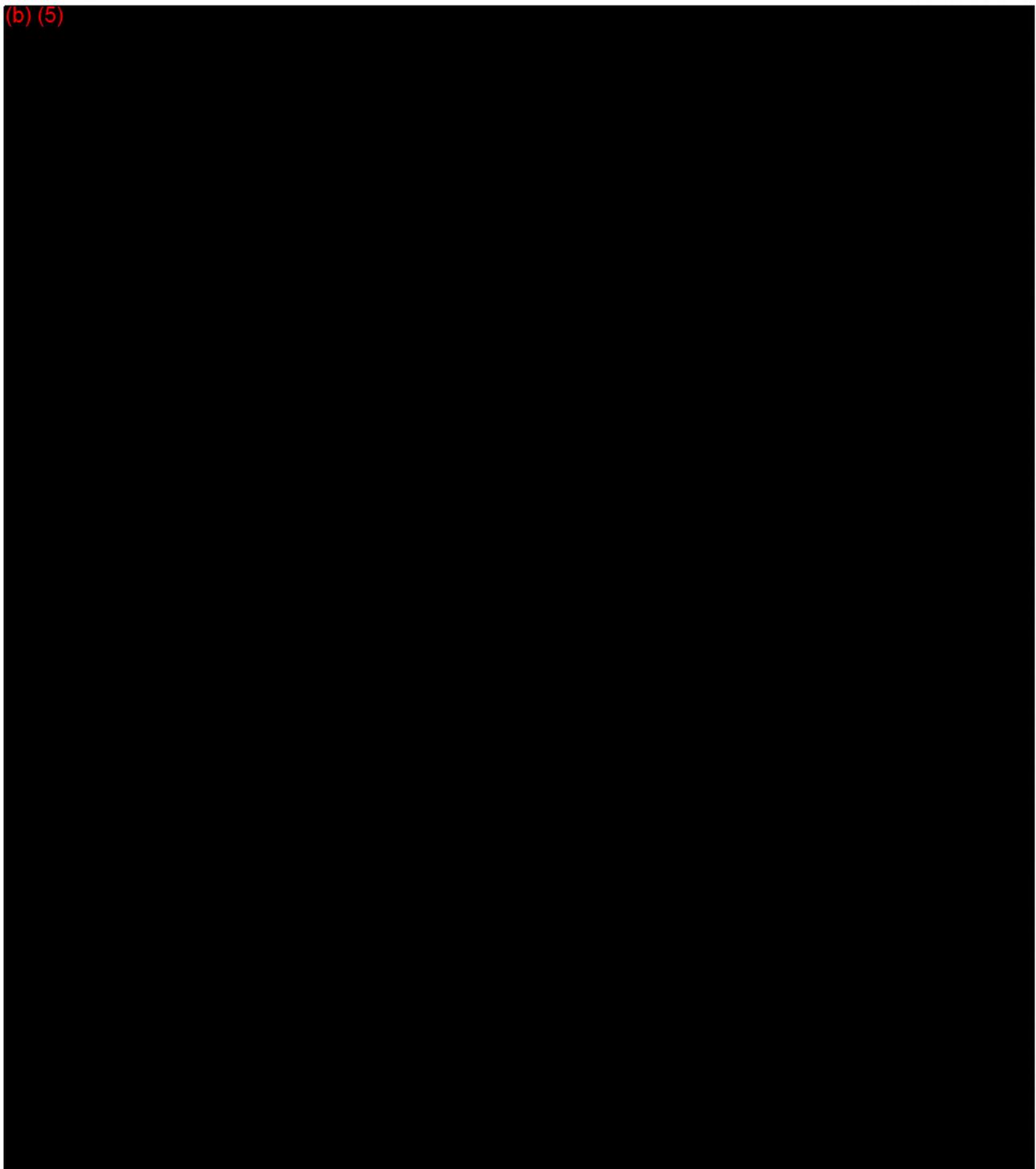
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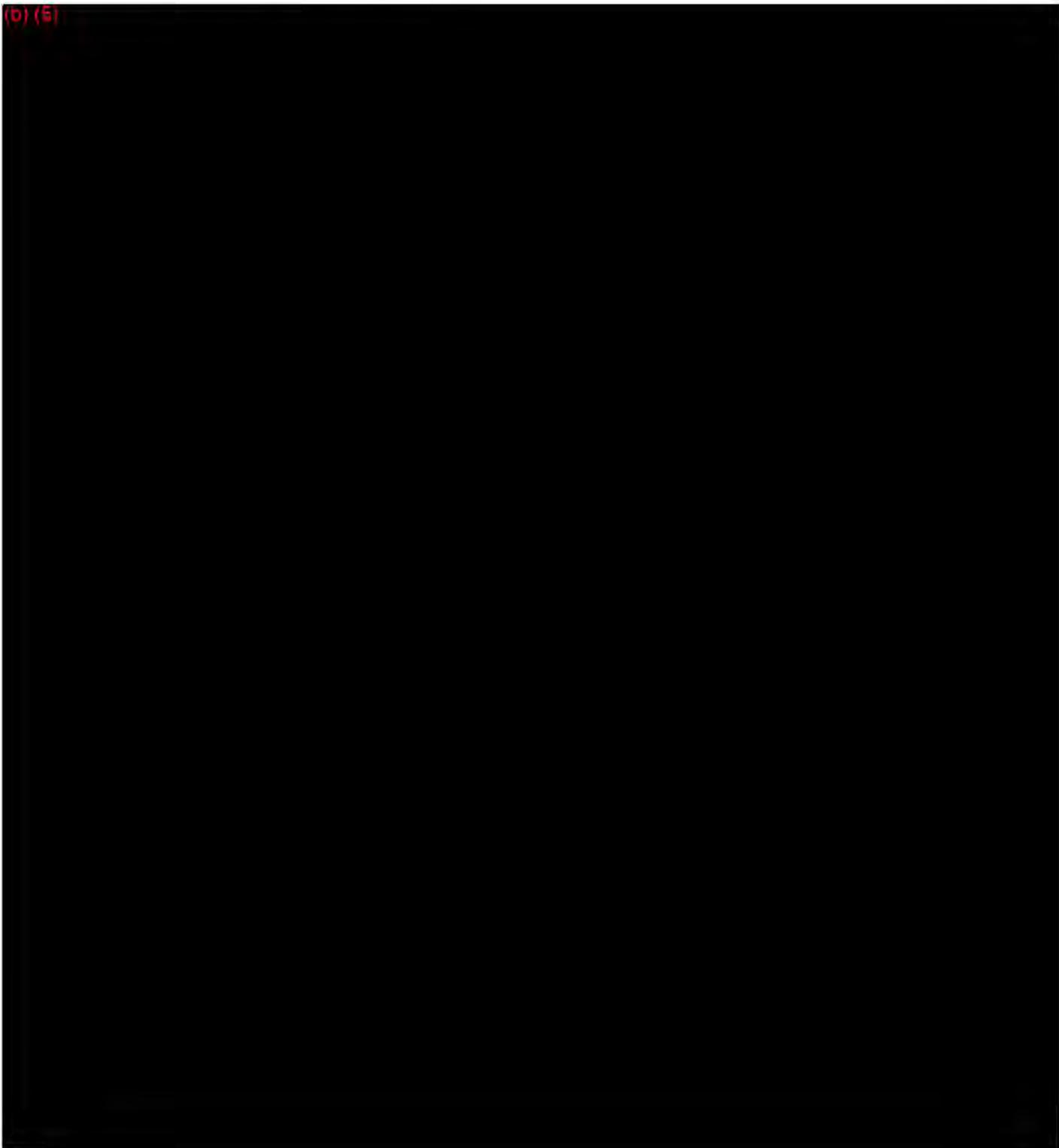
FDA NEWS RELEASE

For Immediate Release: September xx, 2016

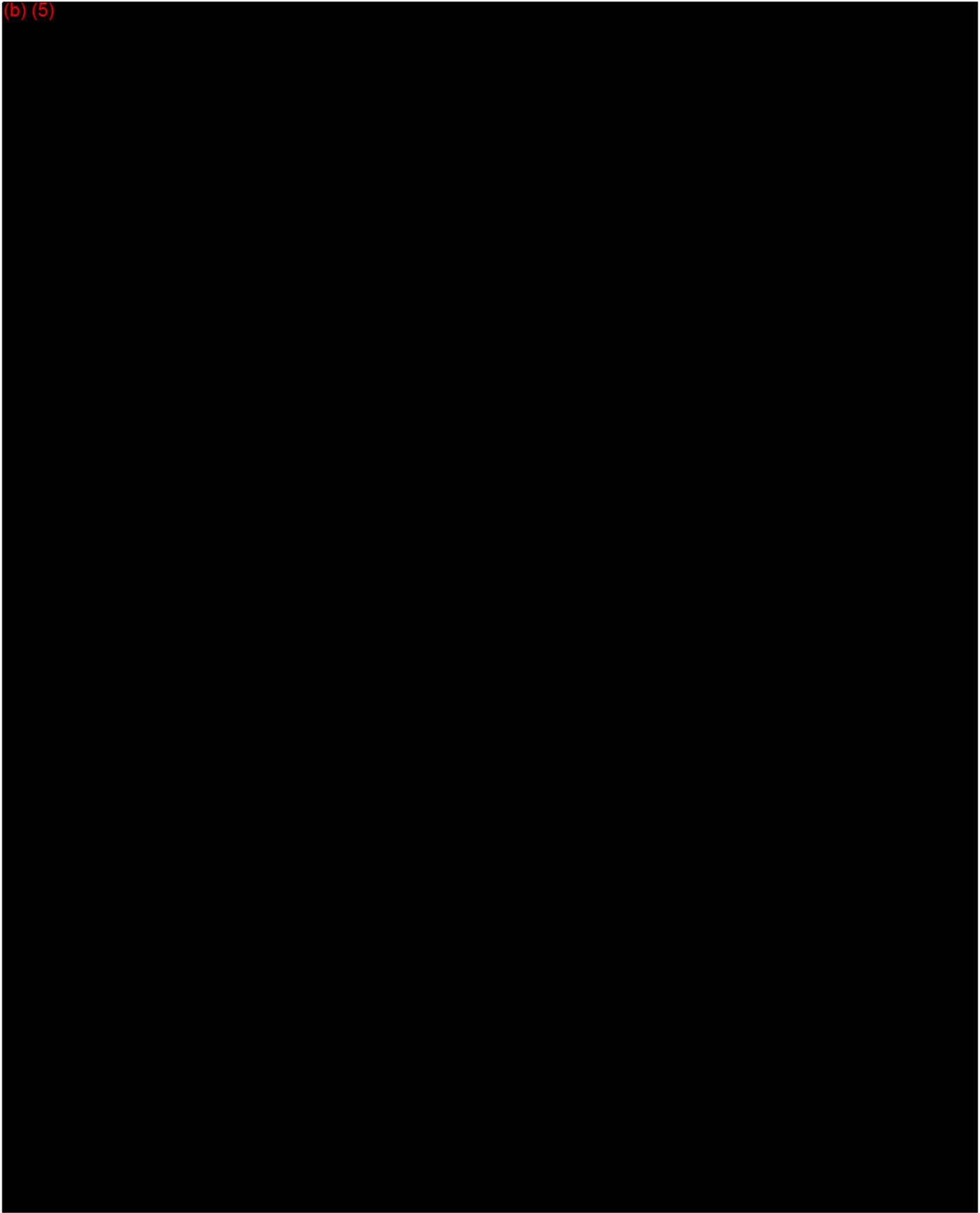
Media Inquiries: Sandy Walsh, 301-796-4669, sandy.walsh@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

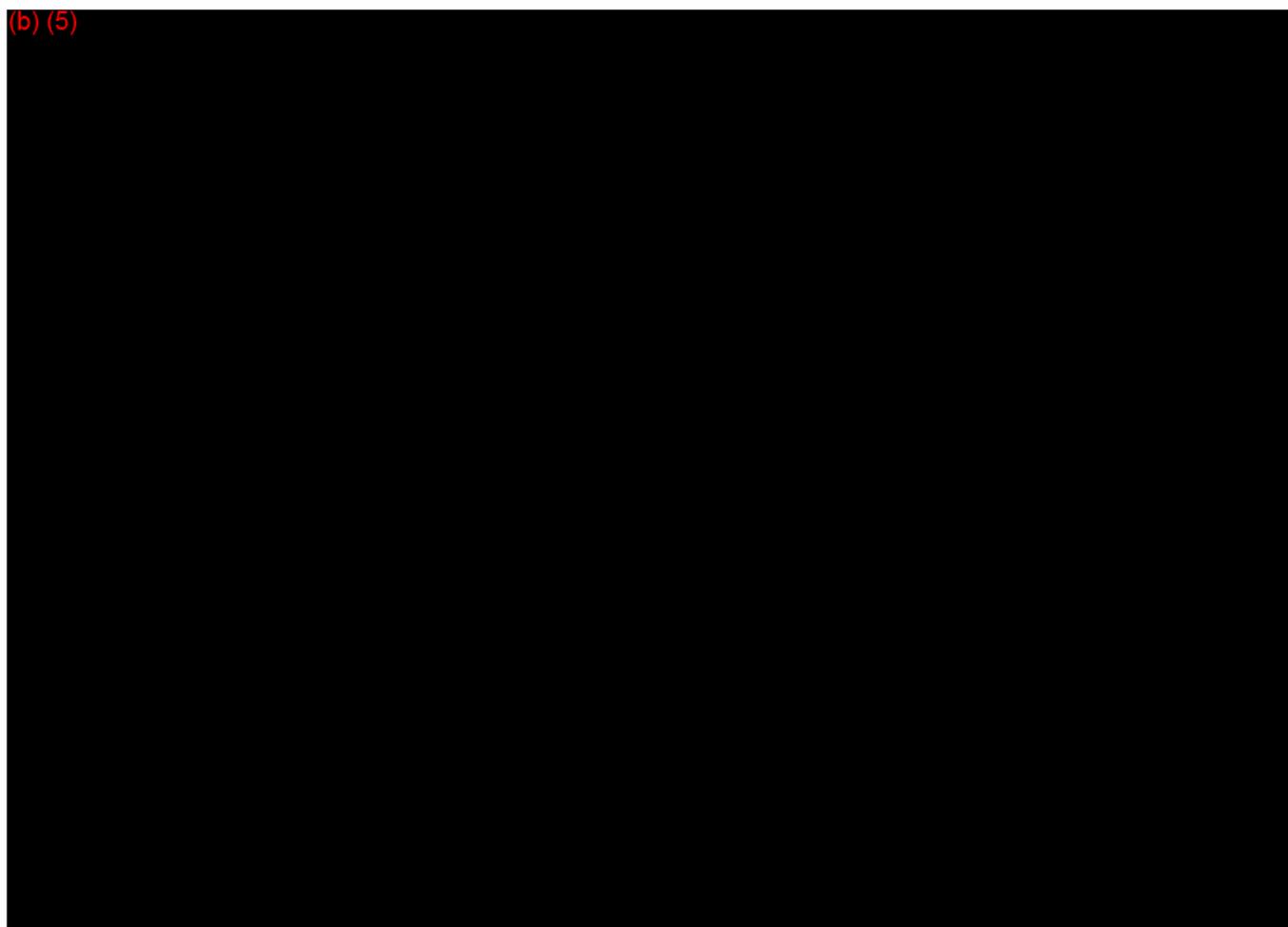
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From: [McCall, Jonathan *](#)
To: [Chasan-Sloan, Deborah \(FDA\)](#); [Califf, Robert](#)
Cc: [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [Kraus, Tom](#); [Conover, Katie](#); [Rodriguez, Jennifer](#)
Subject: RE: Eteplirsen decision memo and supporting materials for your review
Date: Friday, September 16, 2016 10:40:35 AM
Attachments: [Memo-to-file 9-16-2016 JM_CLEAN.doc](#)
[Memo-to-file 9-16-2016 JM_TRACKED.doc](#)

Hello all –

Here are tracked and clean versions of the memo to file. I've tried to regularize the formatting and make clear the separations between statements and responses.

This draft represents a merged version that combined edits from the 10:36 PM 9/15 version from Liz, the version attached to the email below, and incorporates Liz' emailed edits. Please let me know if I missed anything!

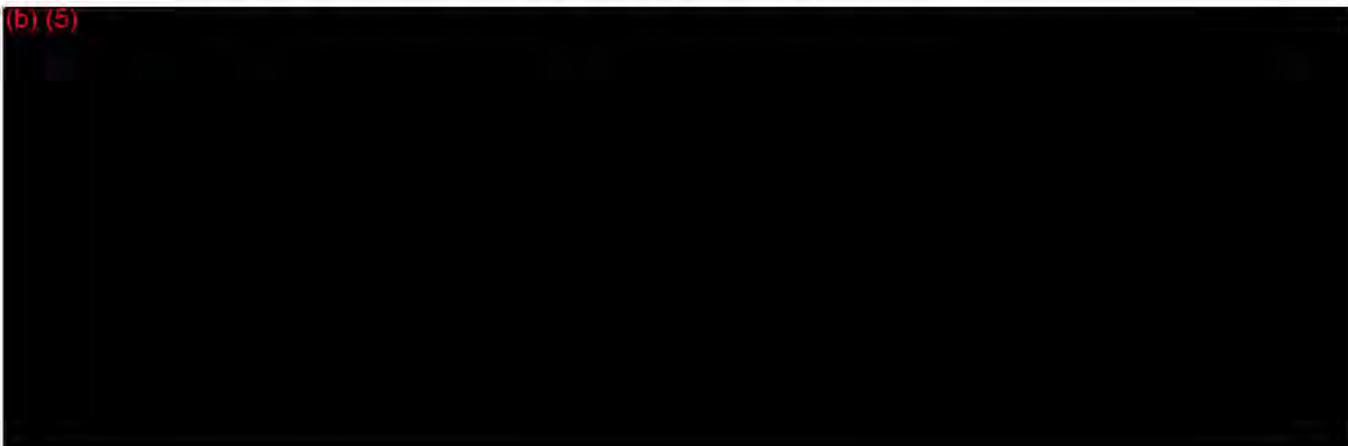
Thanks!

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Jonathan

From: Chasan-Sloan, Deborah (FDA)
Sent: Friday, September 16, 2016 12:38 AM
To: Califf, Robert; McCall, Jonathan *
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Kraus, Tom; Conover, Katie; Rodriguez, Jennifer
Subject: RE: Eteplirsen decision memo and supporting materials for your review

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From: Califf, Robert
Sent: Thursday, September 15, 2016 9:16 PM
To: McCall, Jonathan *

FDAOC0002253

Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom; Conover, Katie; Rodriguez, Jennifer
Subject: RE: Eteplirsen decision memo and supporting materials for your review

<< File: 20160915 Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN_rmc.doc >>

Comments added. Hopefully this will do it. Should be easy for you to check out.

rmc

From: McCall, Jonathan *
Sent: Thursday, September 15, 2016 4:56 PM
To: Califf, Robert
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom
Subject: Eteplirsen decision memo and supporting materials for your review

Hello Dr. Califf –

Here is the current version of the eteplirsen memo:

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Here is the memo to file:

<< File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN.doc >> << File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_COMMENTED.doc >>

And here are the response cover notes:

<< File: 20160915 response notesrs_JM_CLEAN.doc >> << File: 20160915 response notesrs_JM_TRACKED.doc >>

Thanks!

–

Jonathan

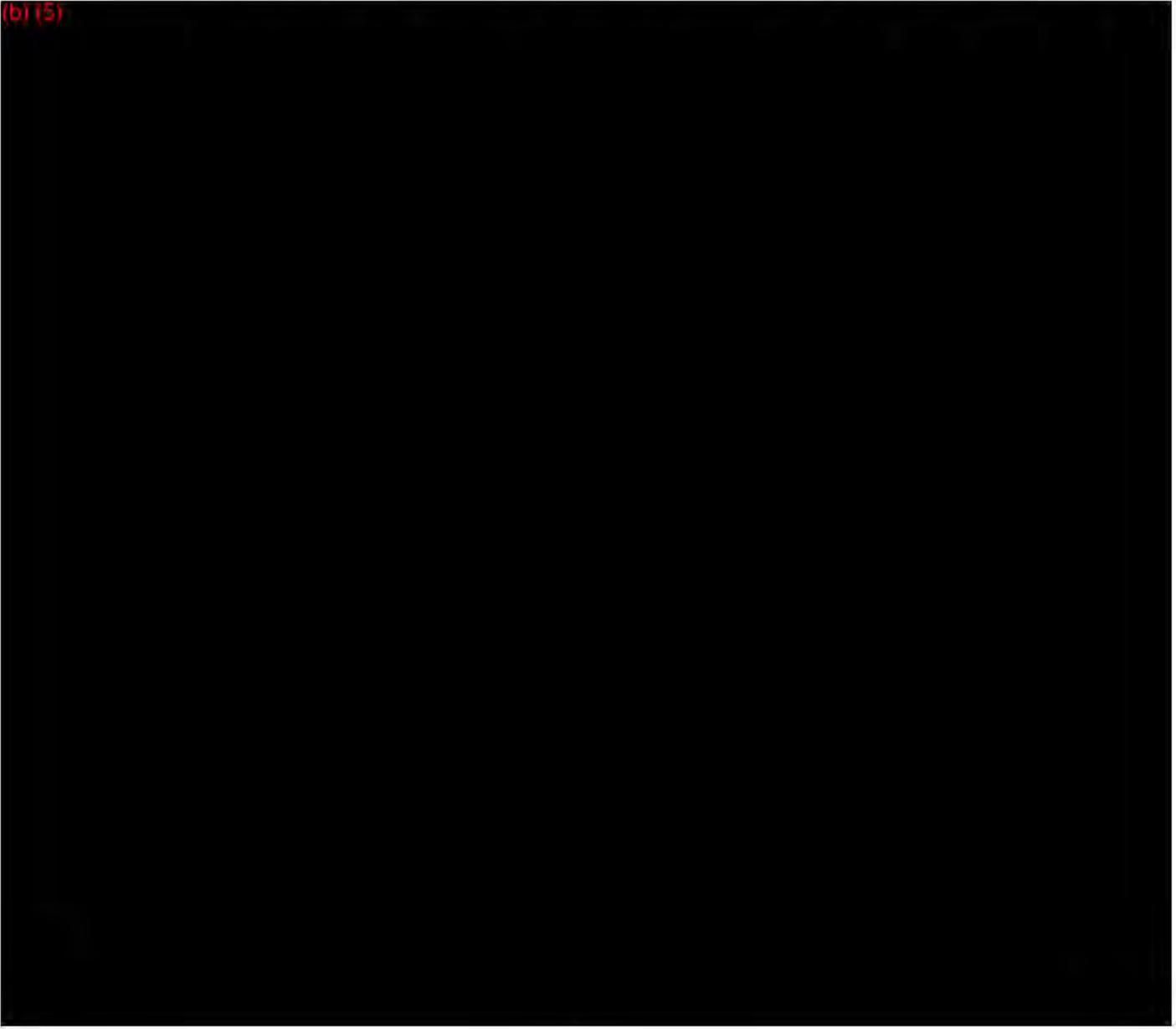
MEMO TO FILE

FROM: Robert Califf, M.D., Commissioner of Food and Drugs

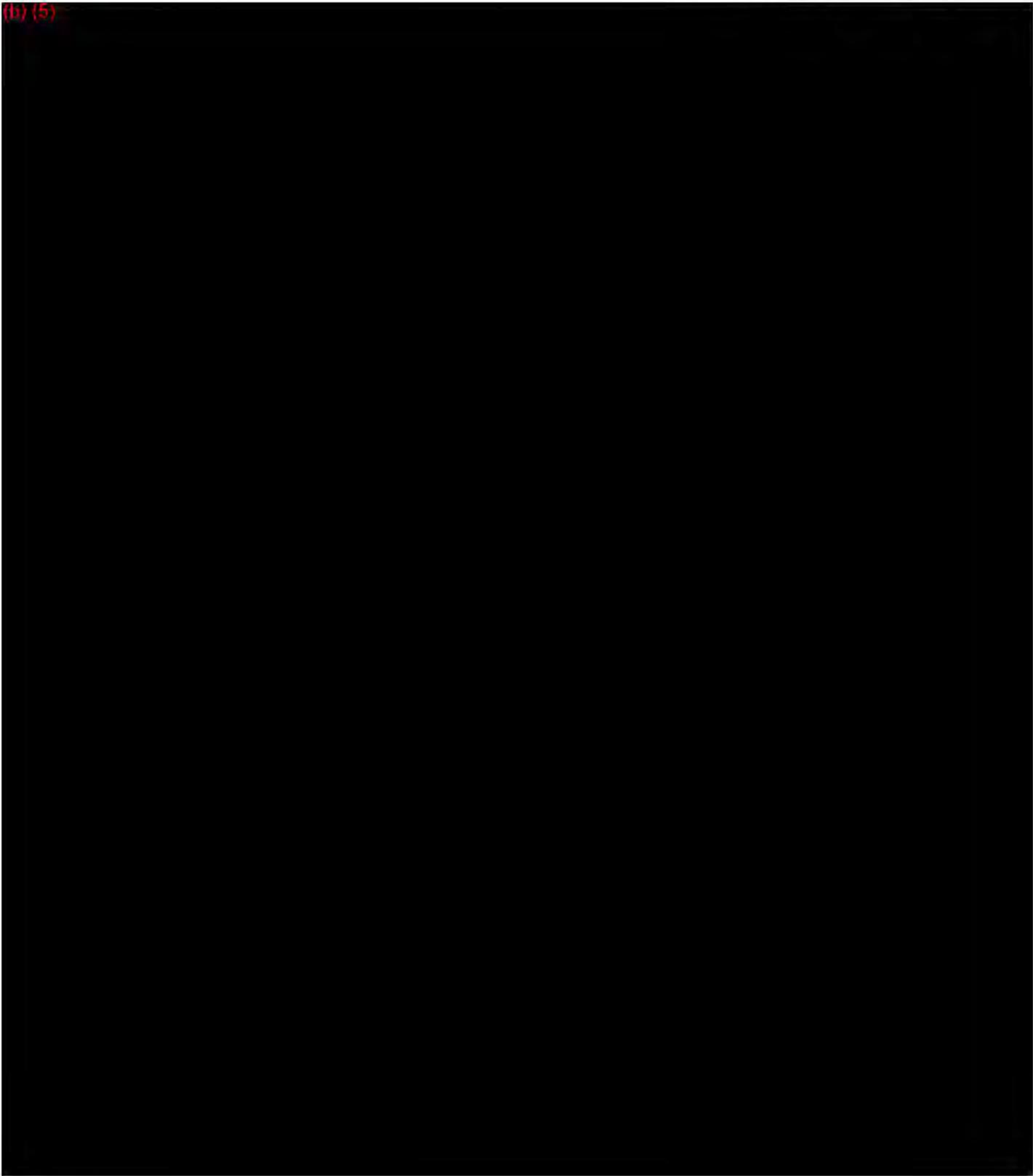
DATE:

RE: Process for Commissioner's Decision about the Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics' Eteplirsen (NDA 206488)

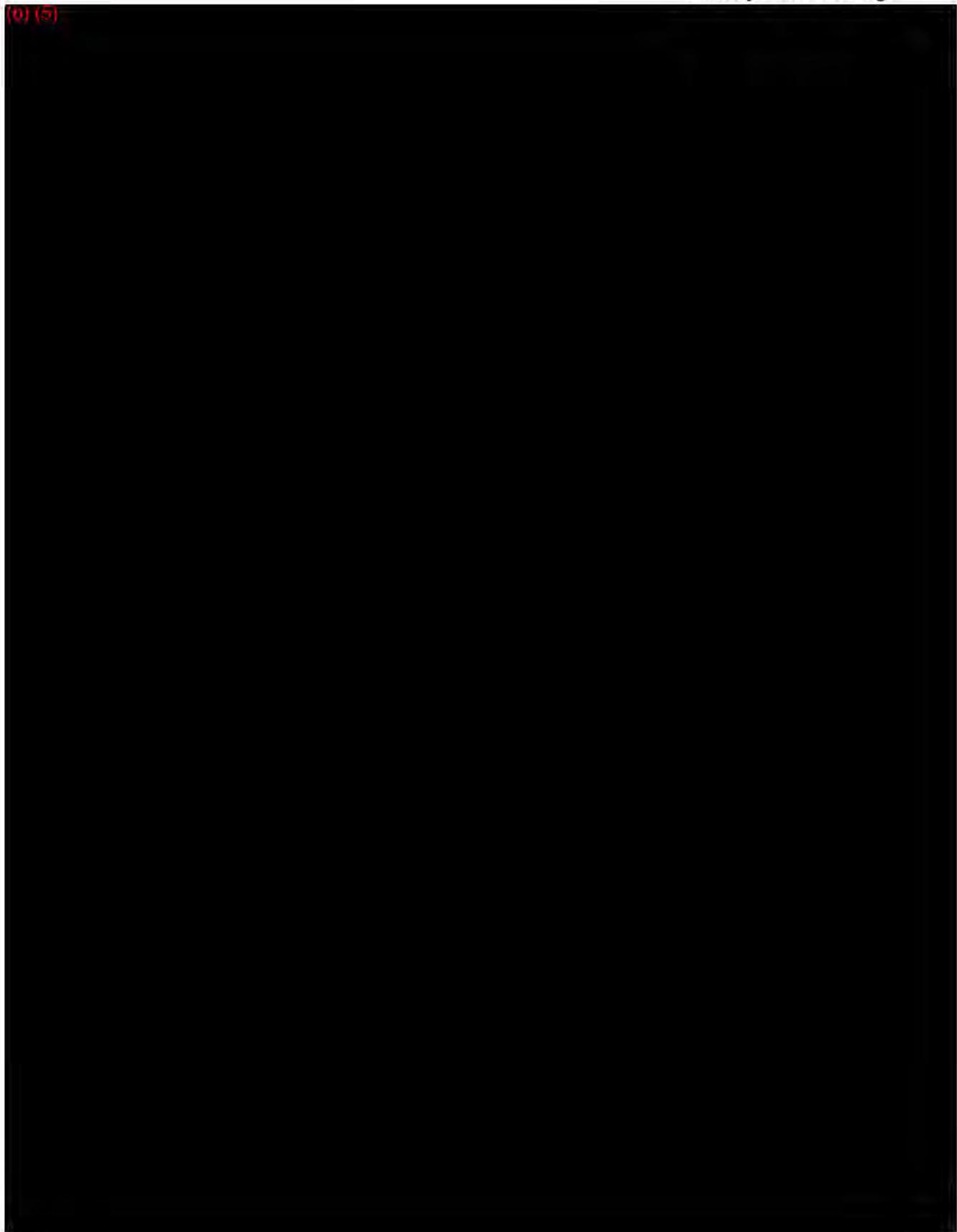
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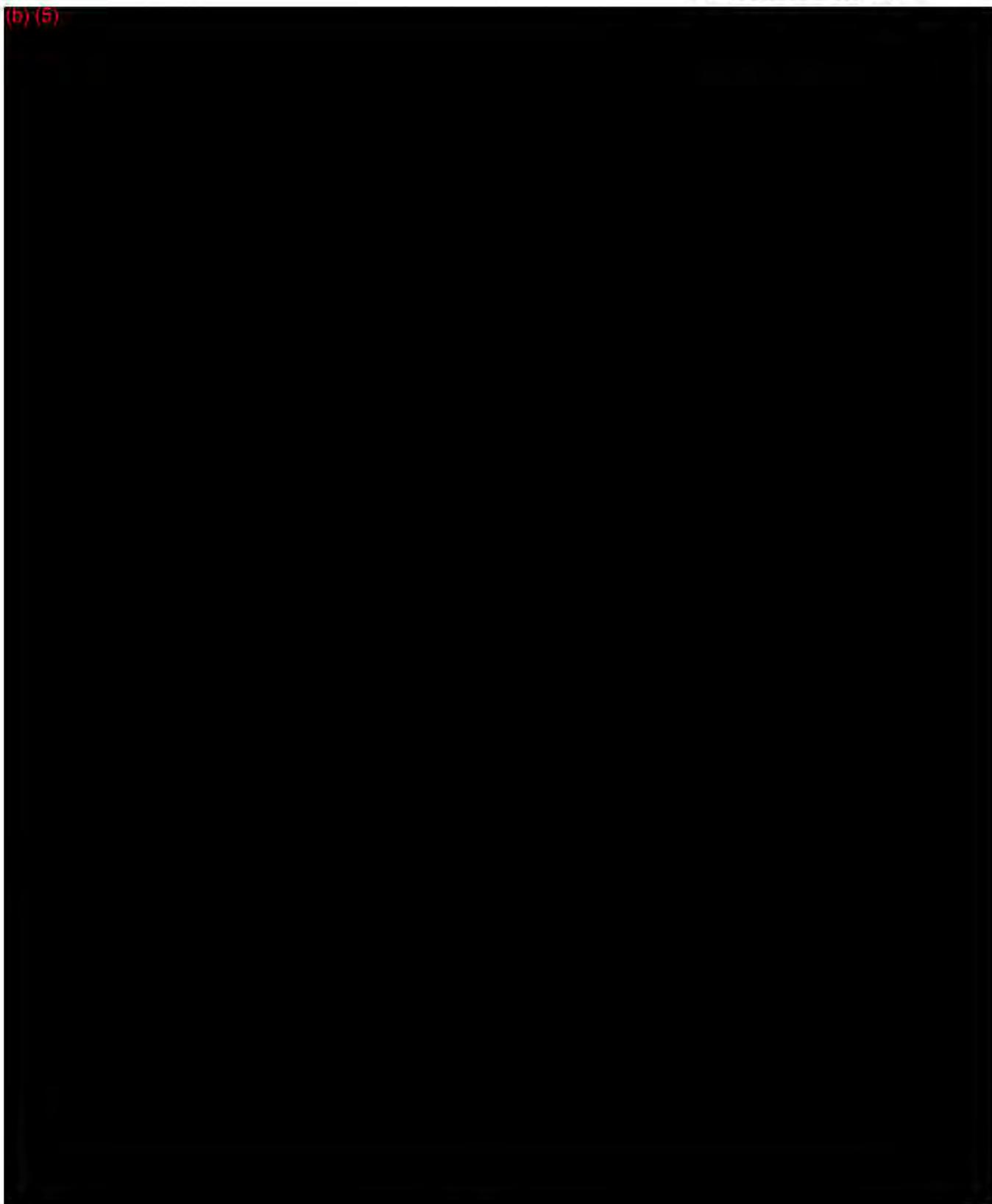
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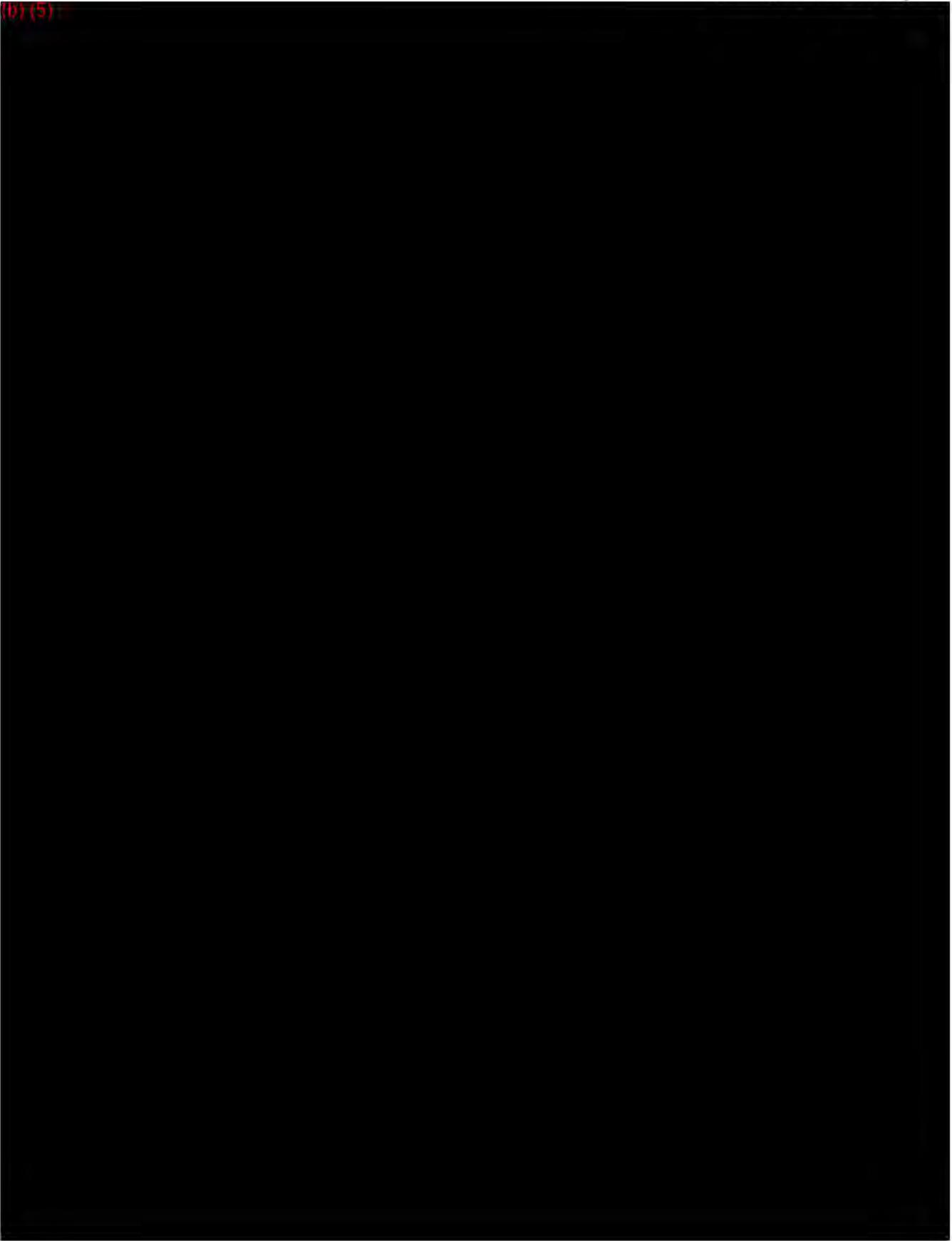
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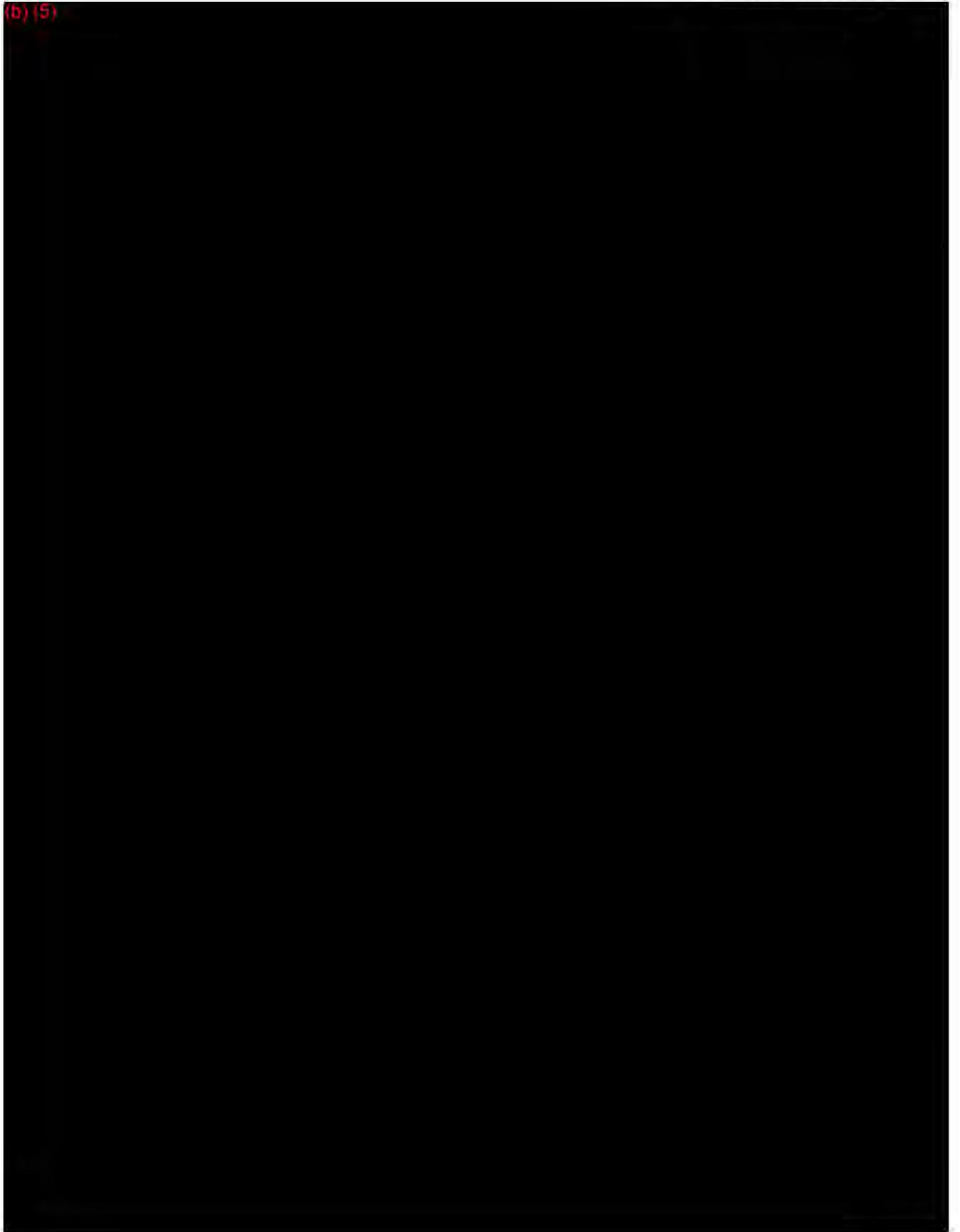
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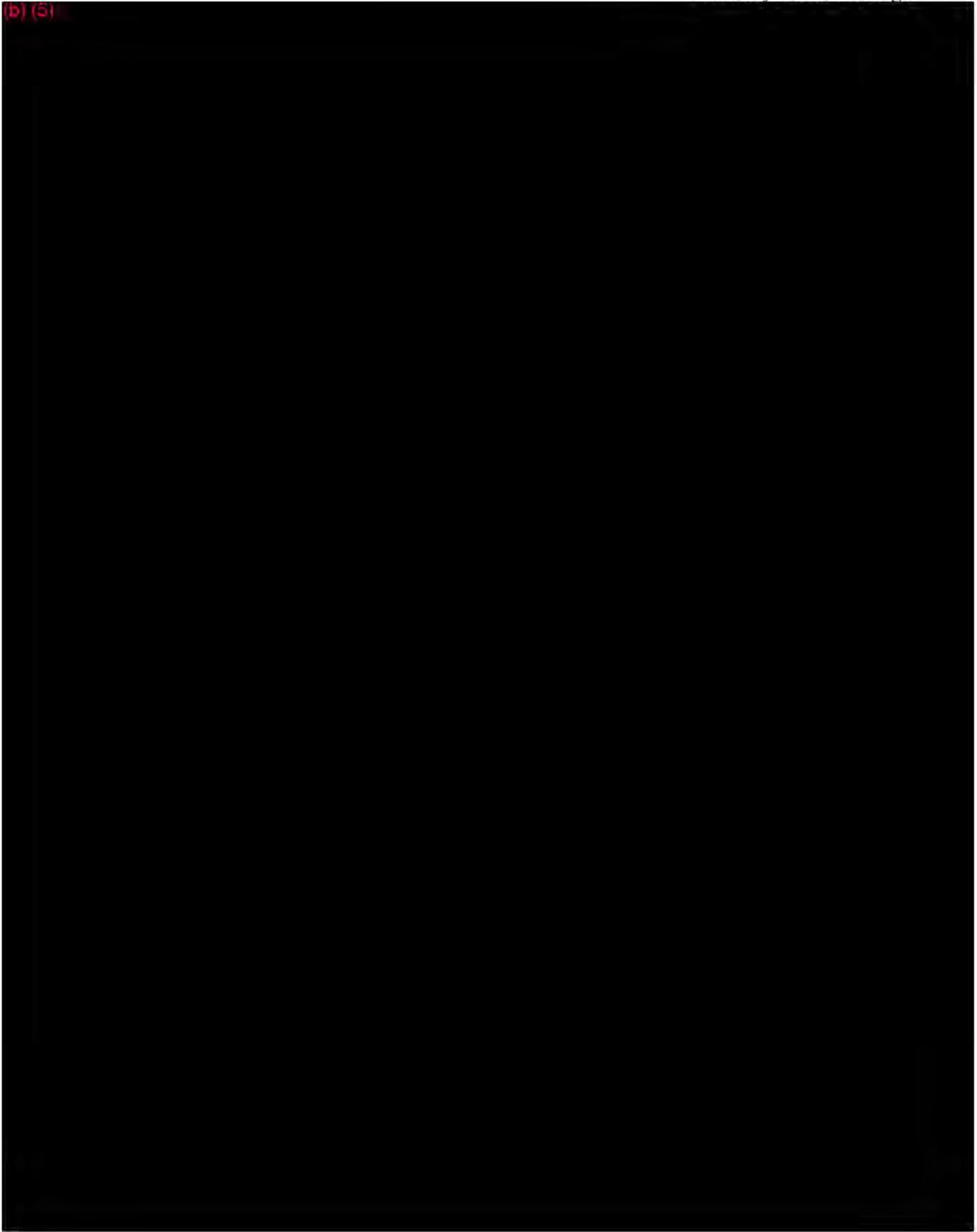
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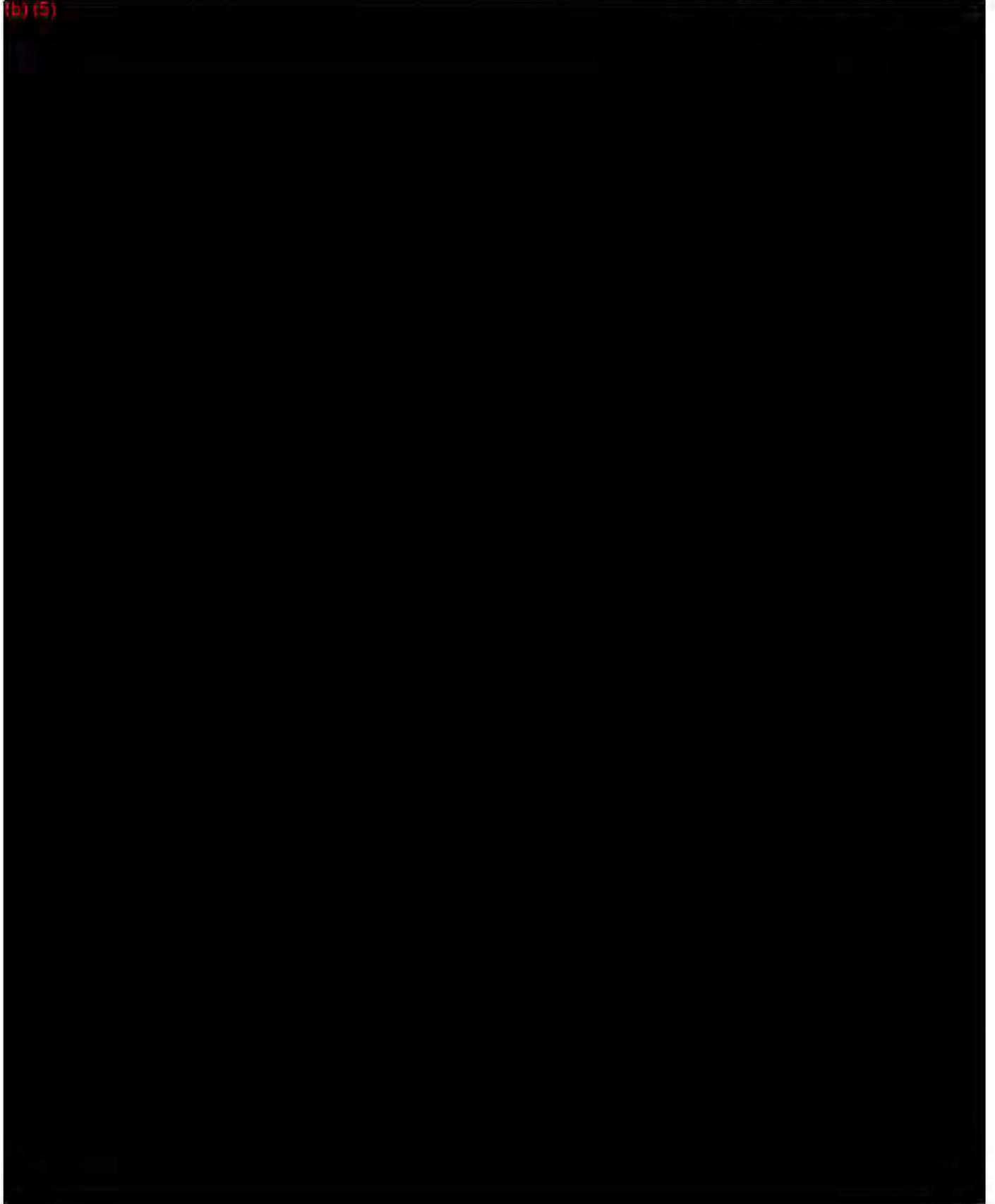
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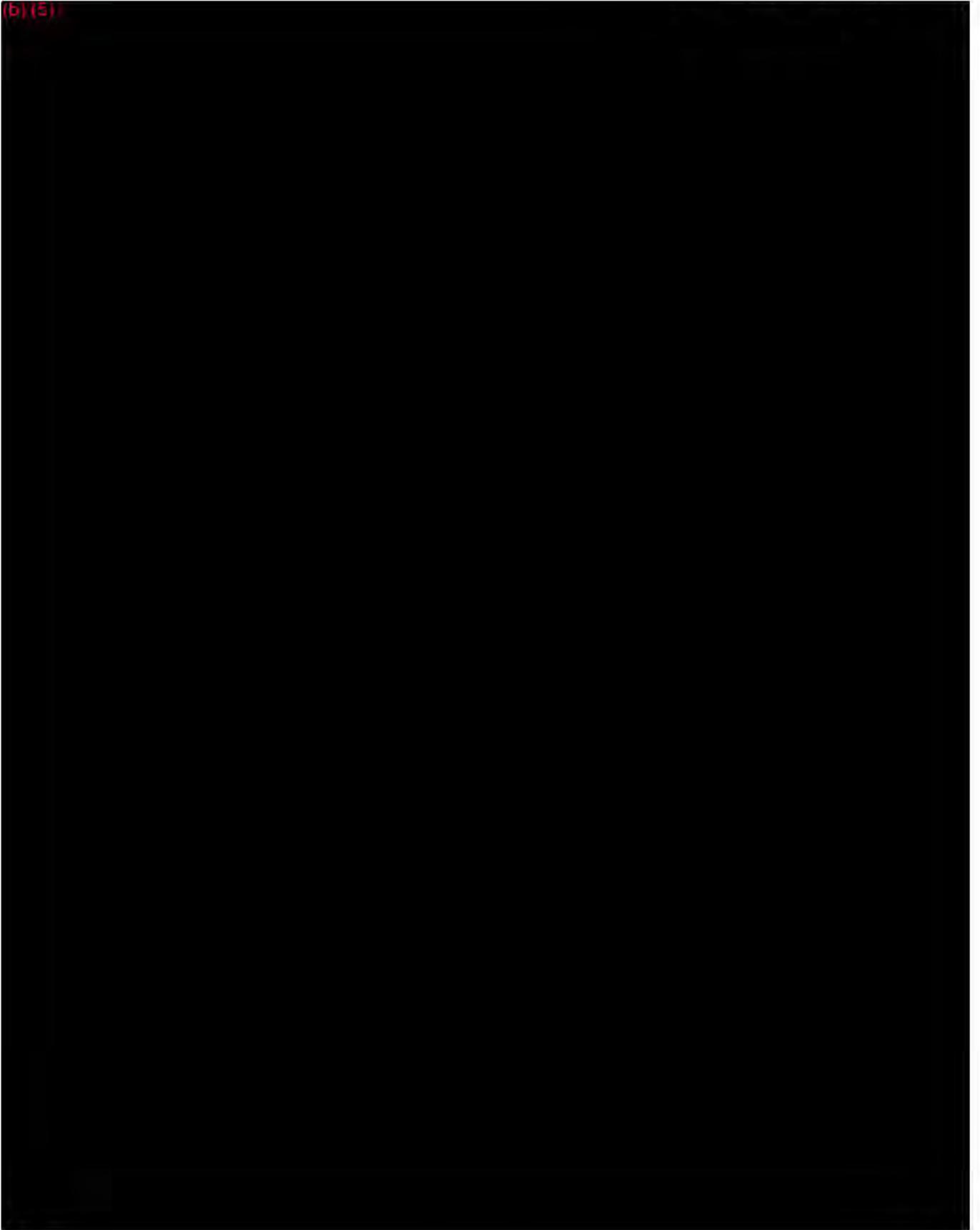
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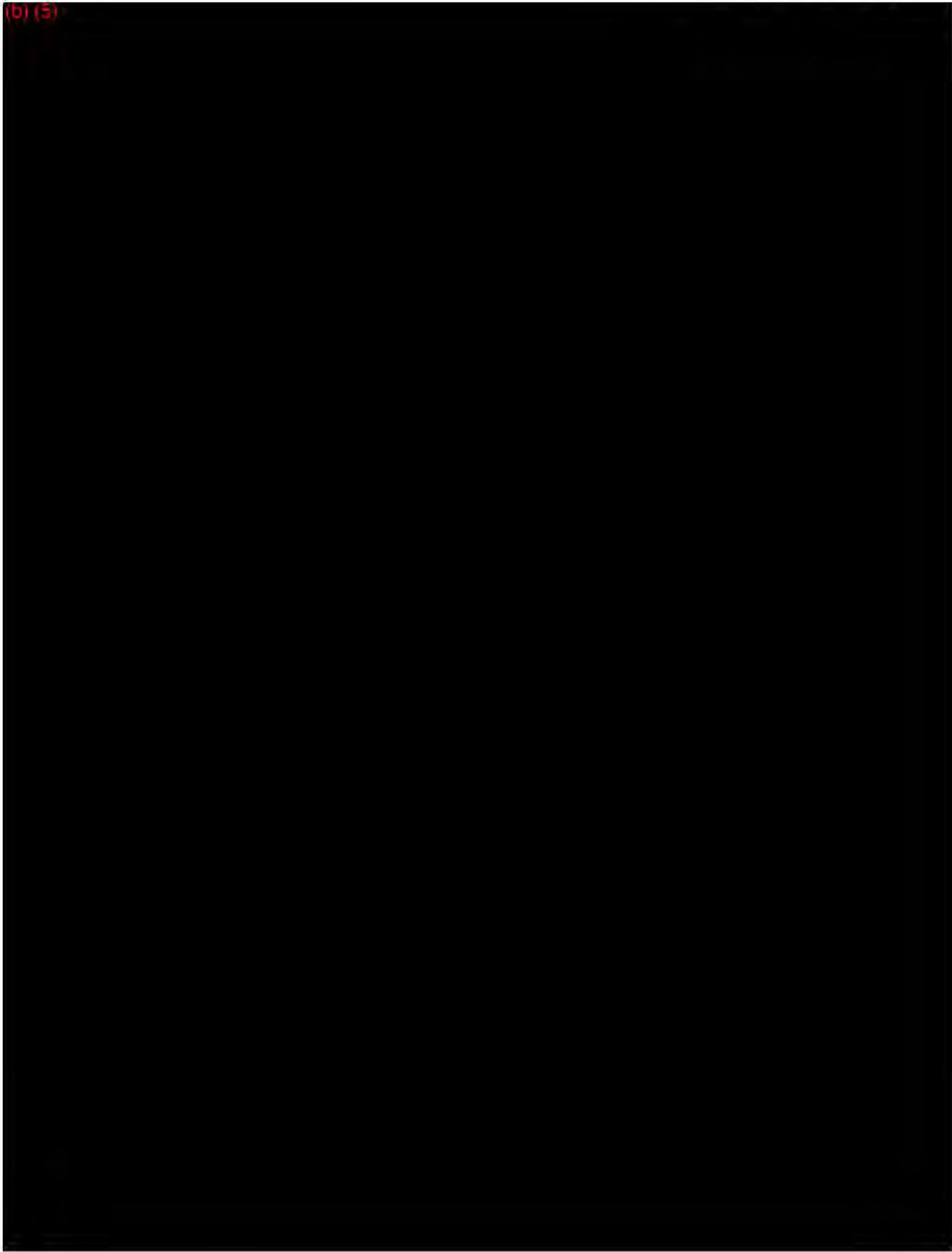
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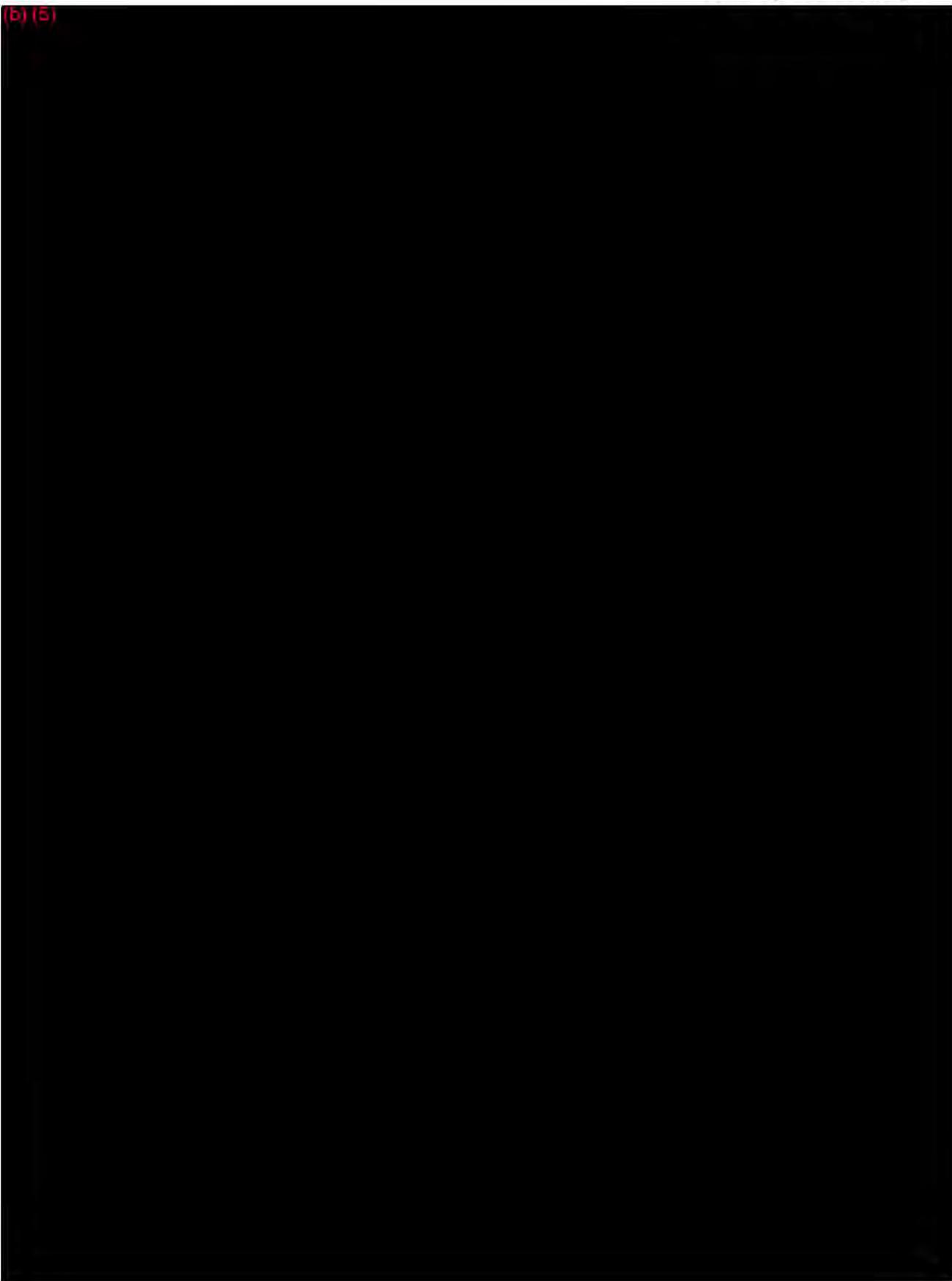
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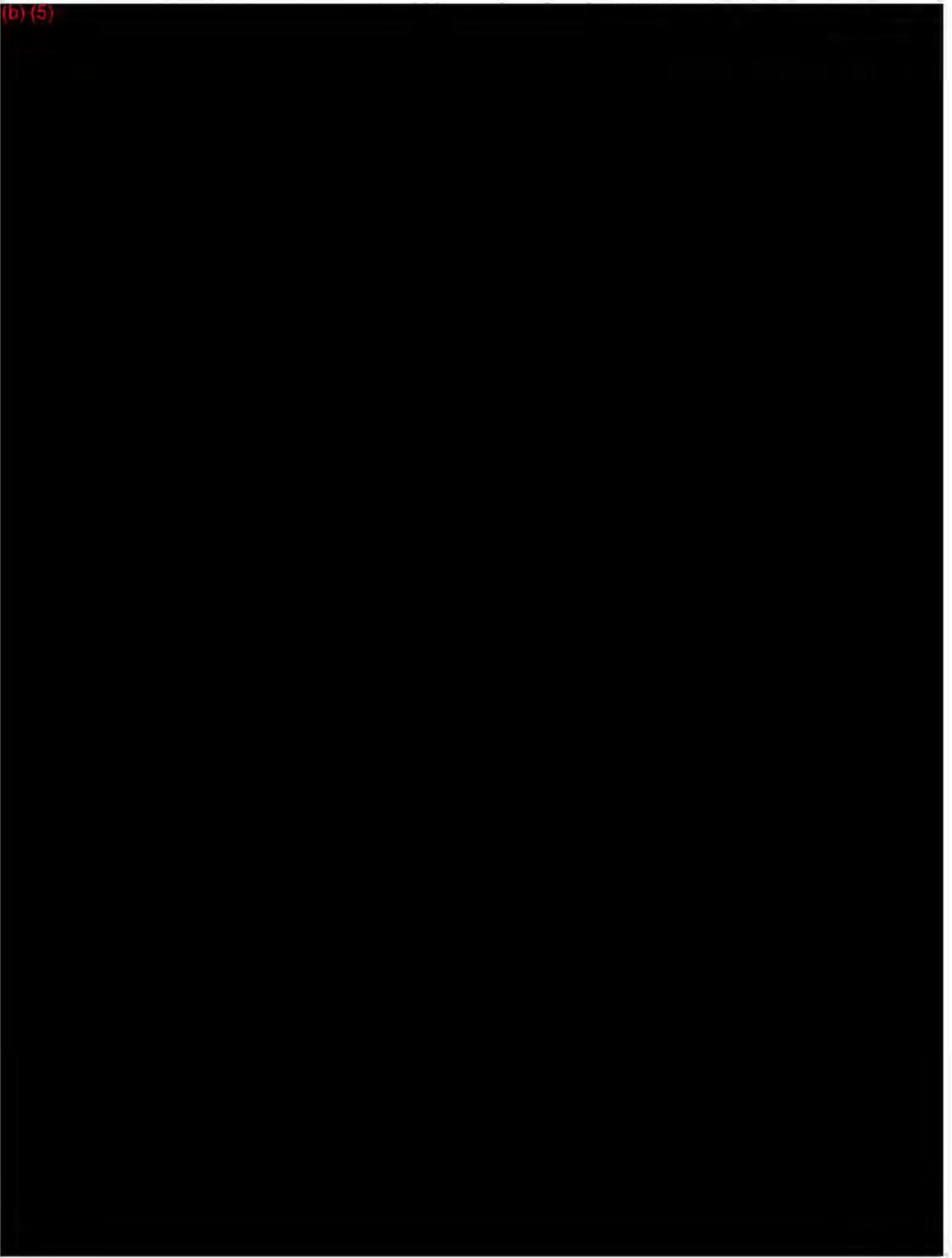
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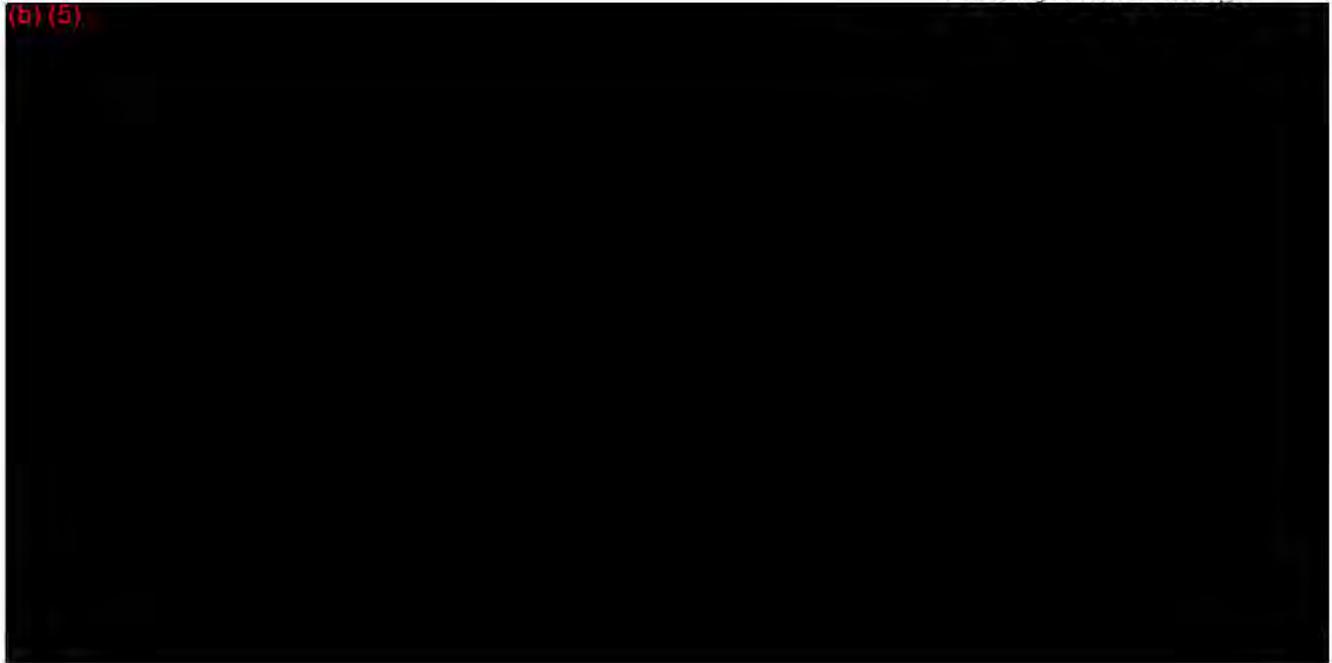
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MEMO TO FILE

FROM: Robert Califf, M.D., Commissioner of Food and Drugs

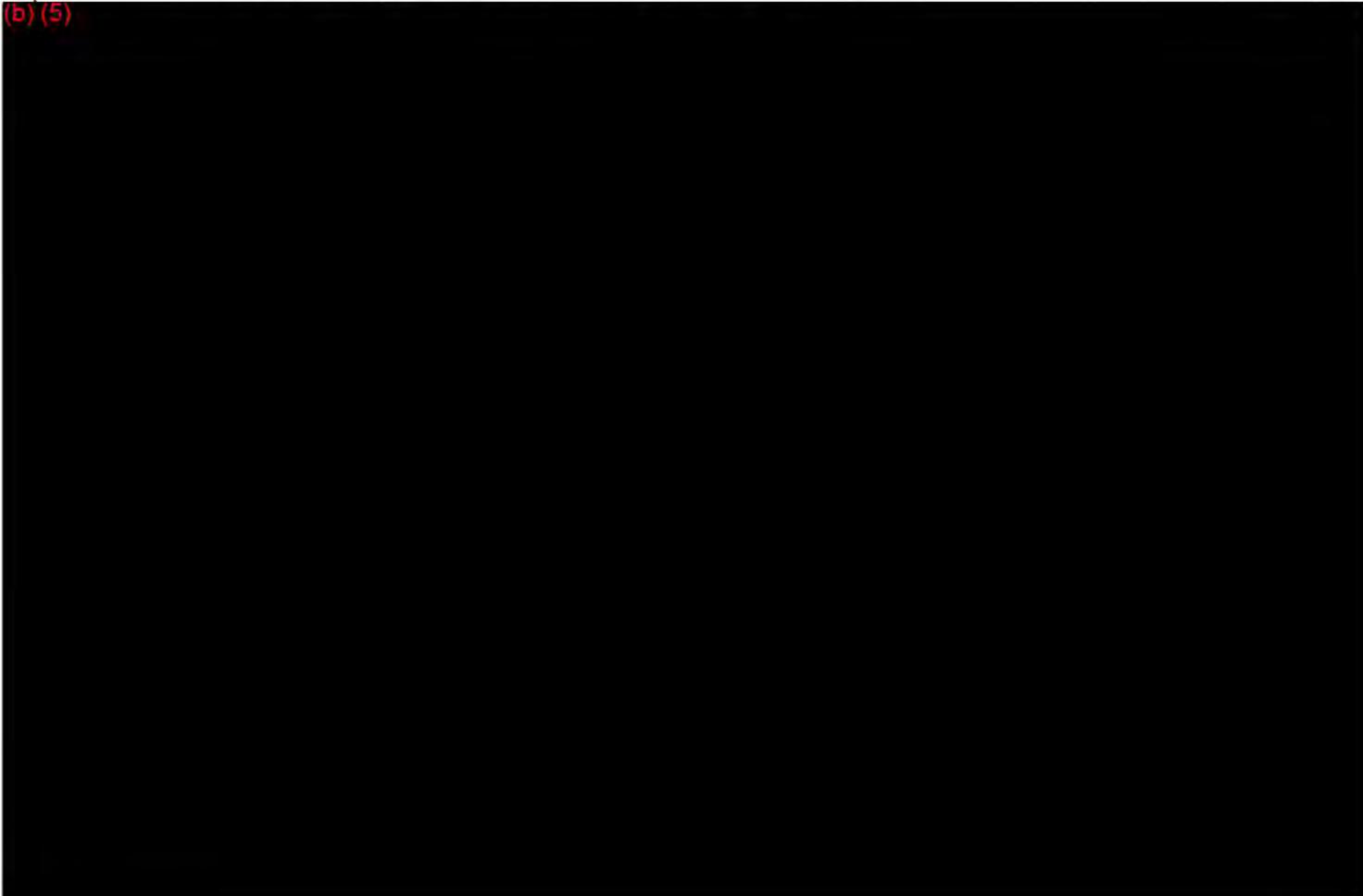
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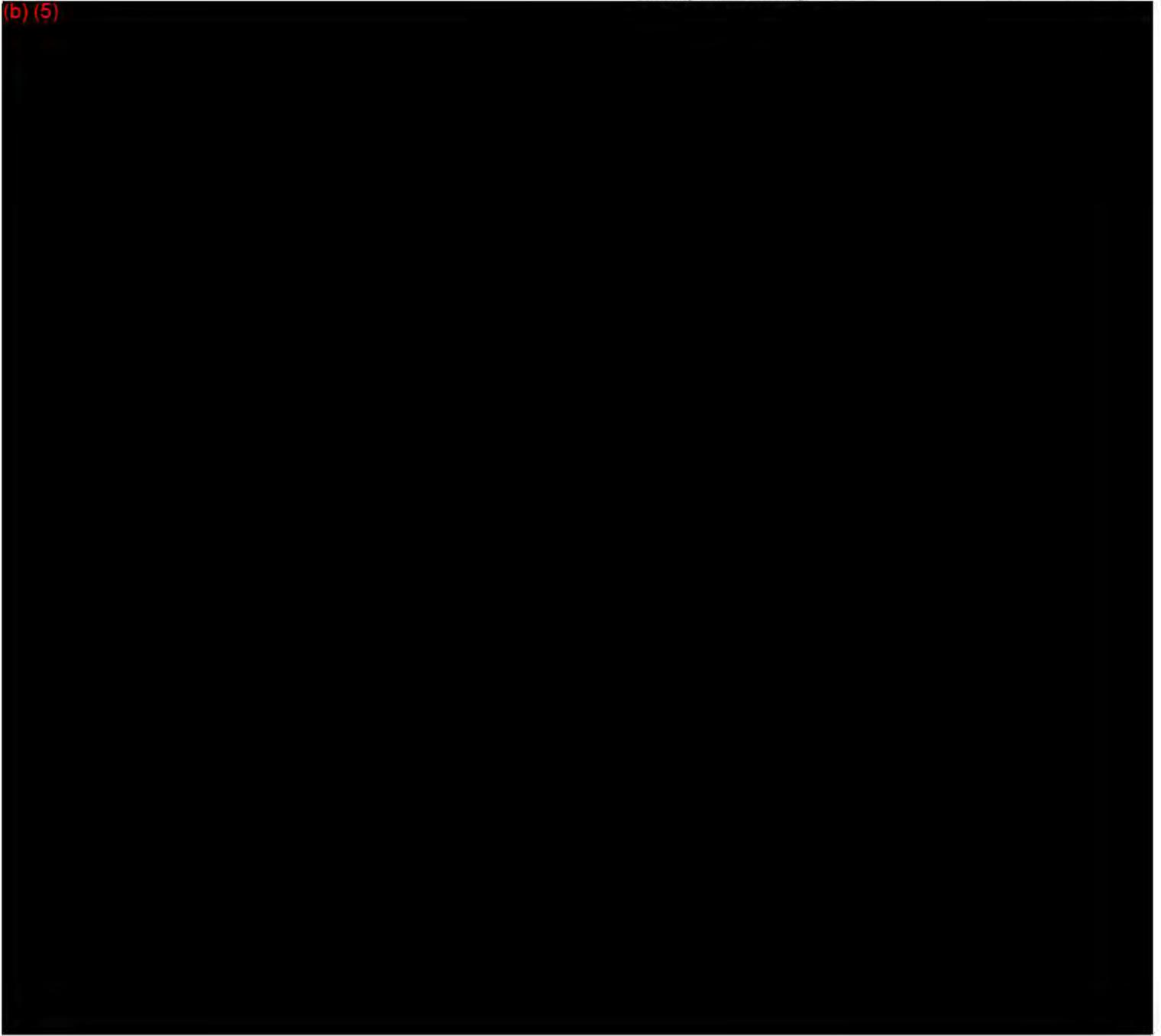
RE: Process for Commissioner's Decision about the Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics' Eteplirsen (NDA 206488)

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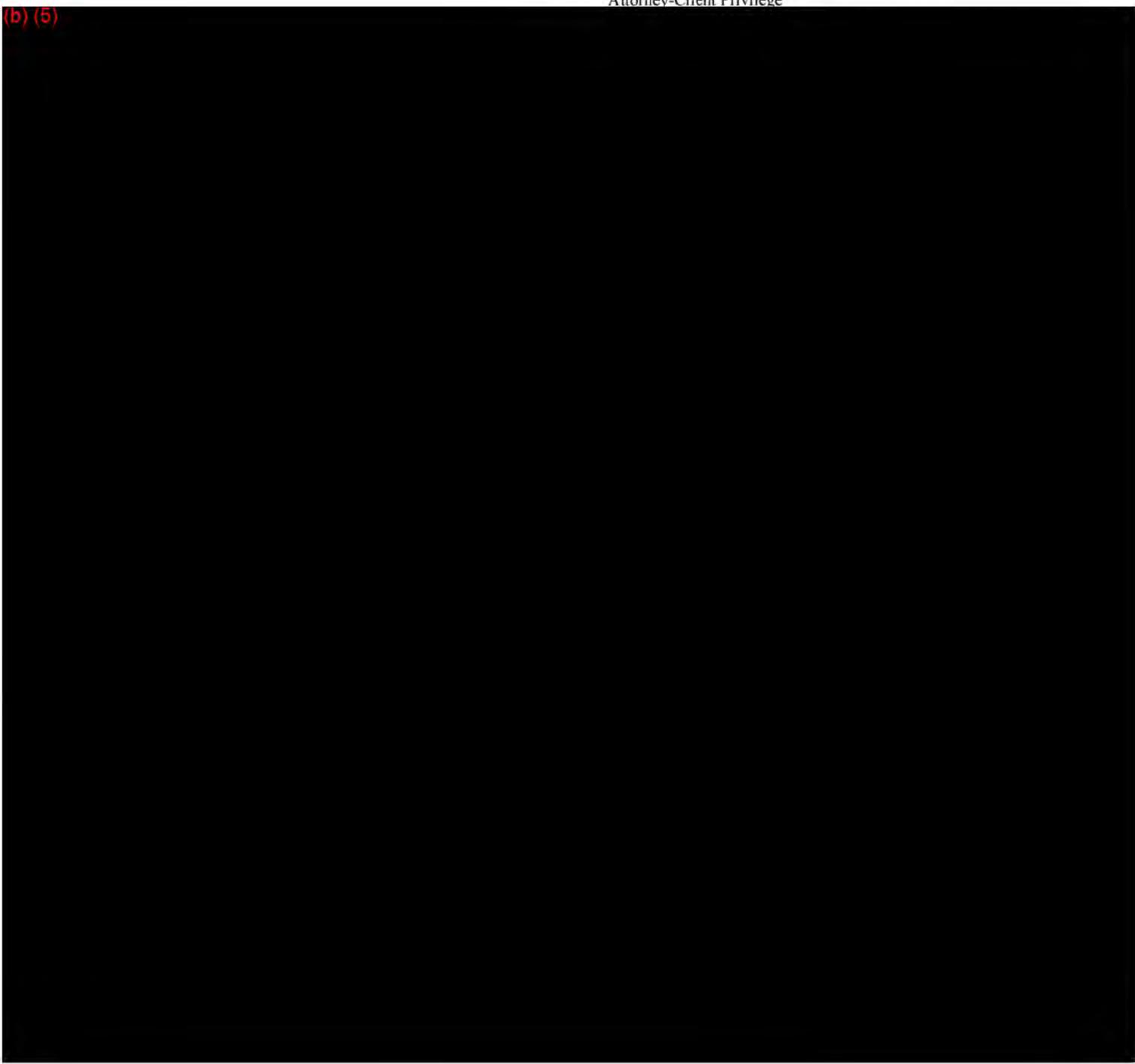
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Deliberative Process Privilege

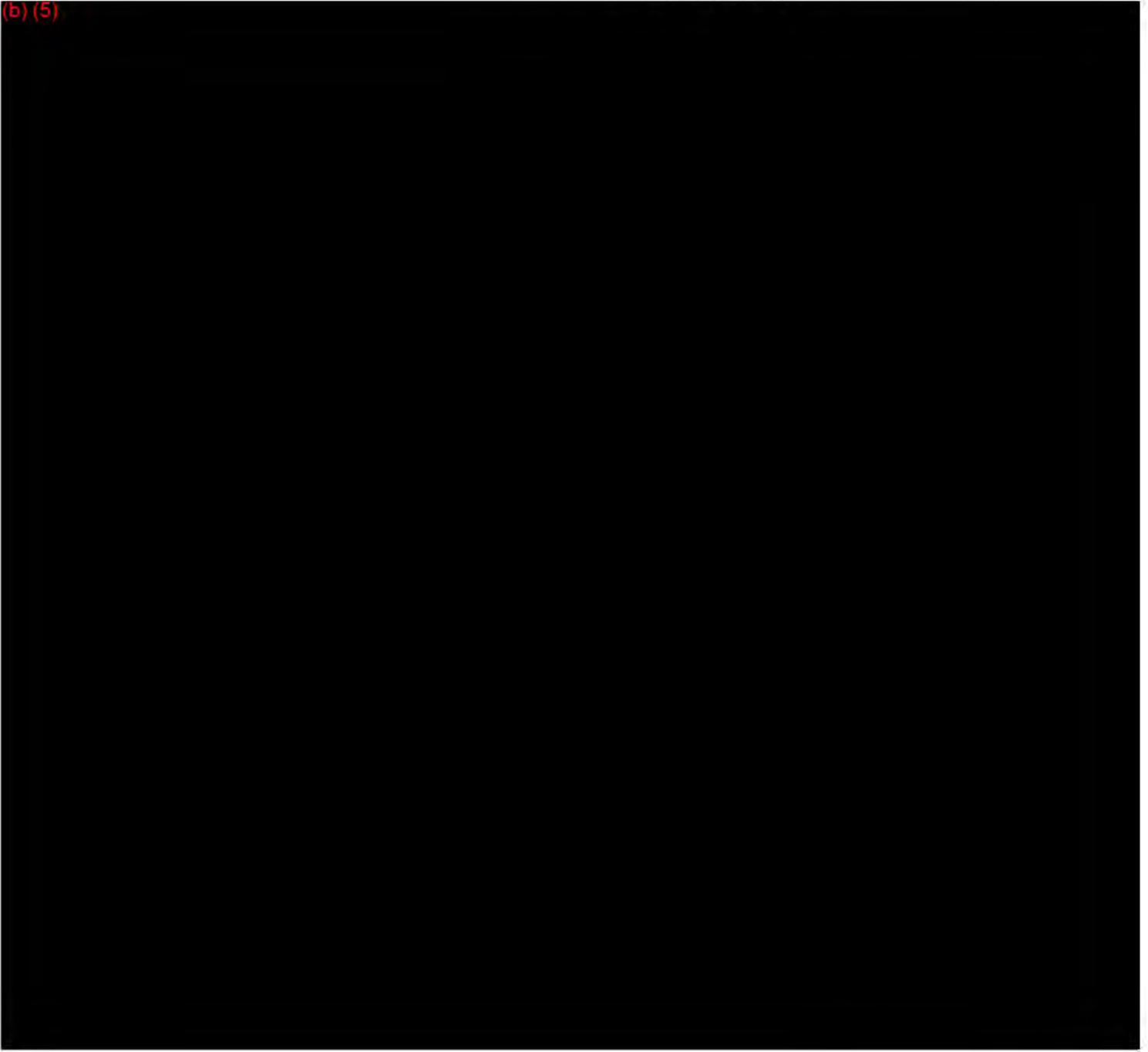
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Deliberative Process Privilege
Attorney-Client Privilege

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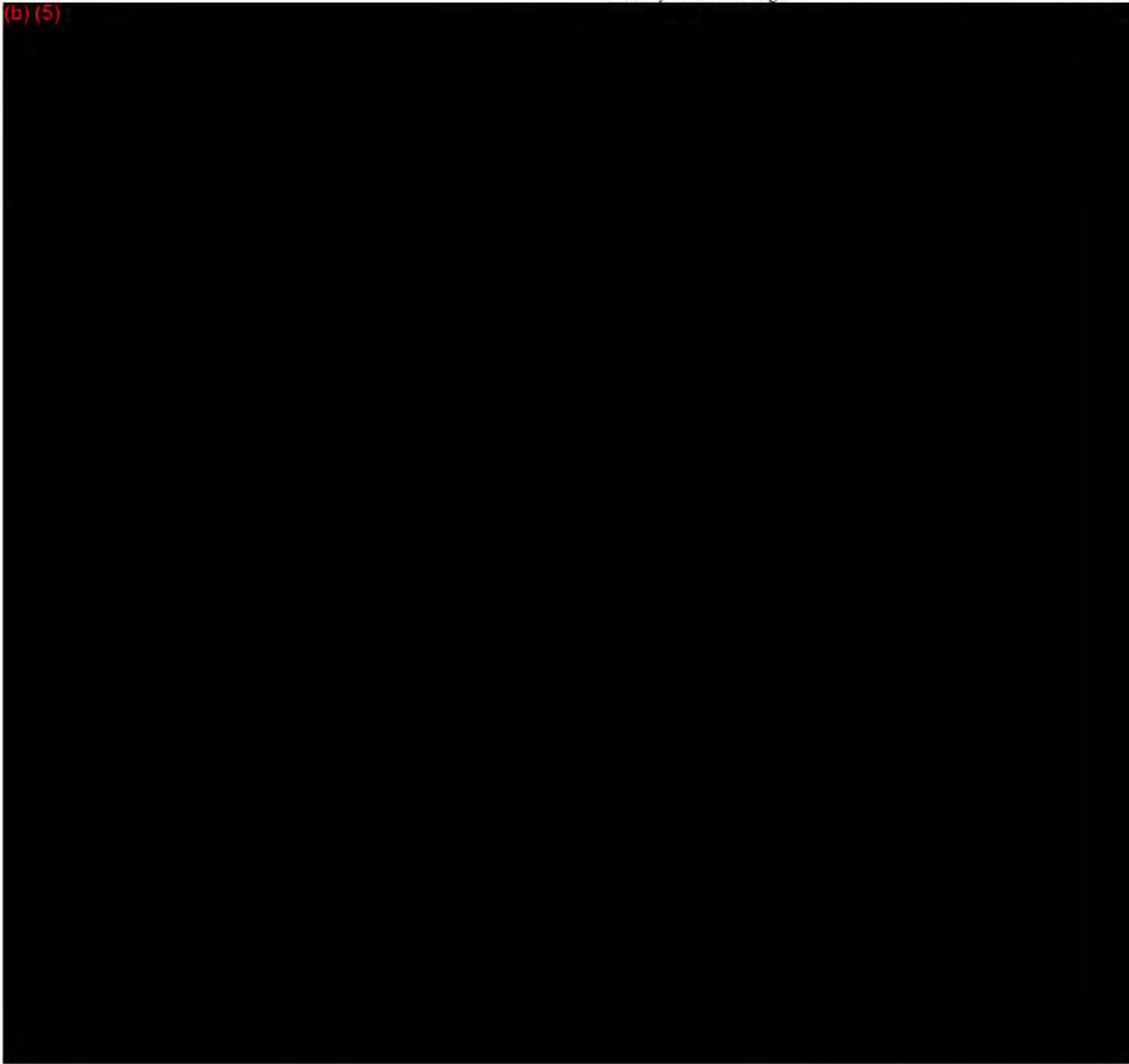


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Deliberative Process Privilege

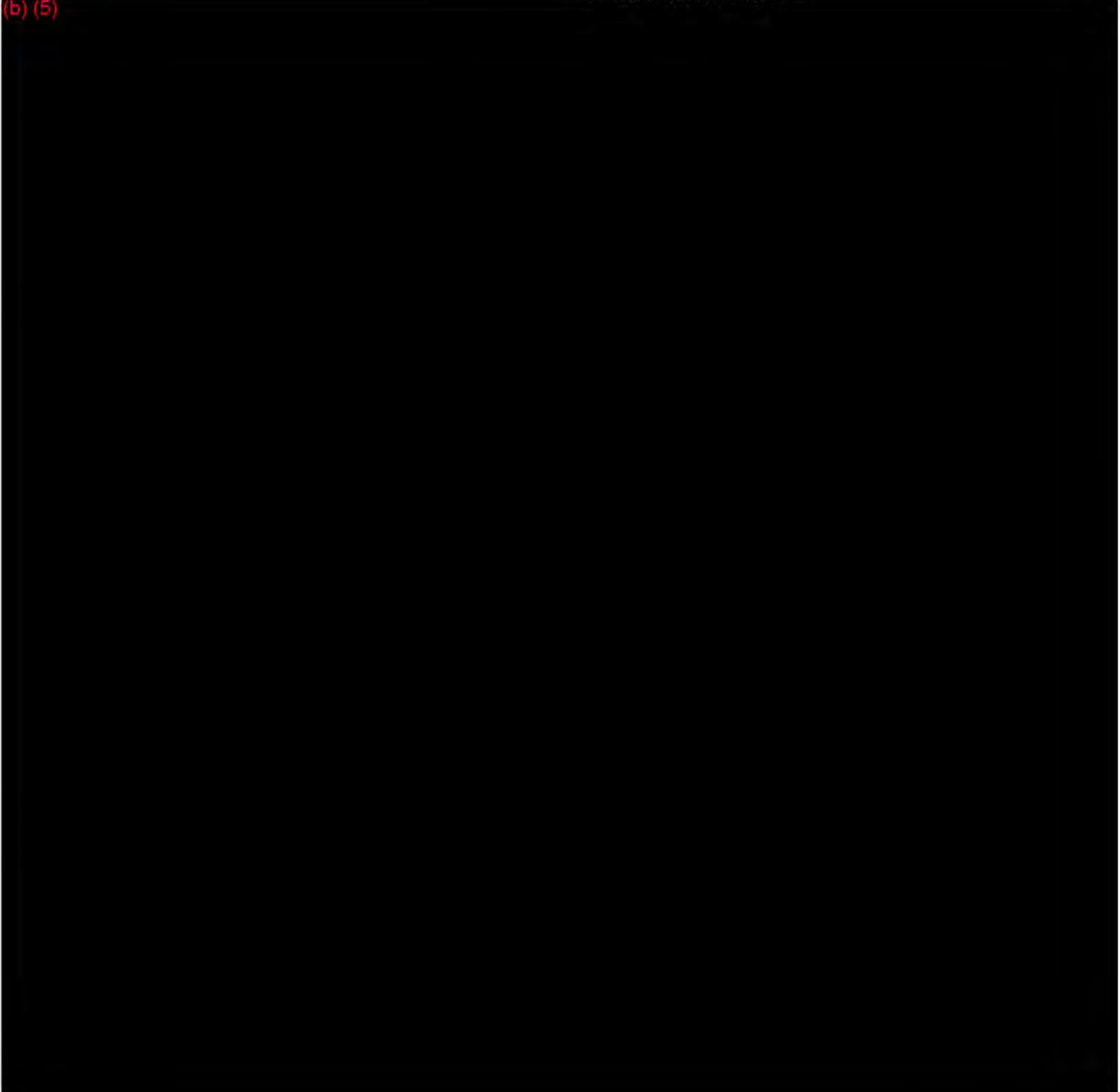
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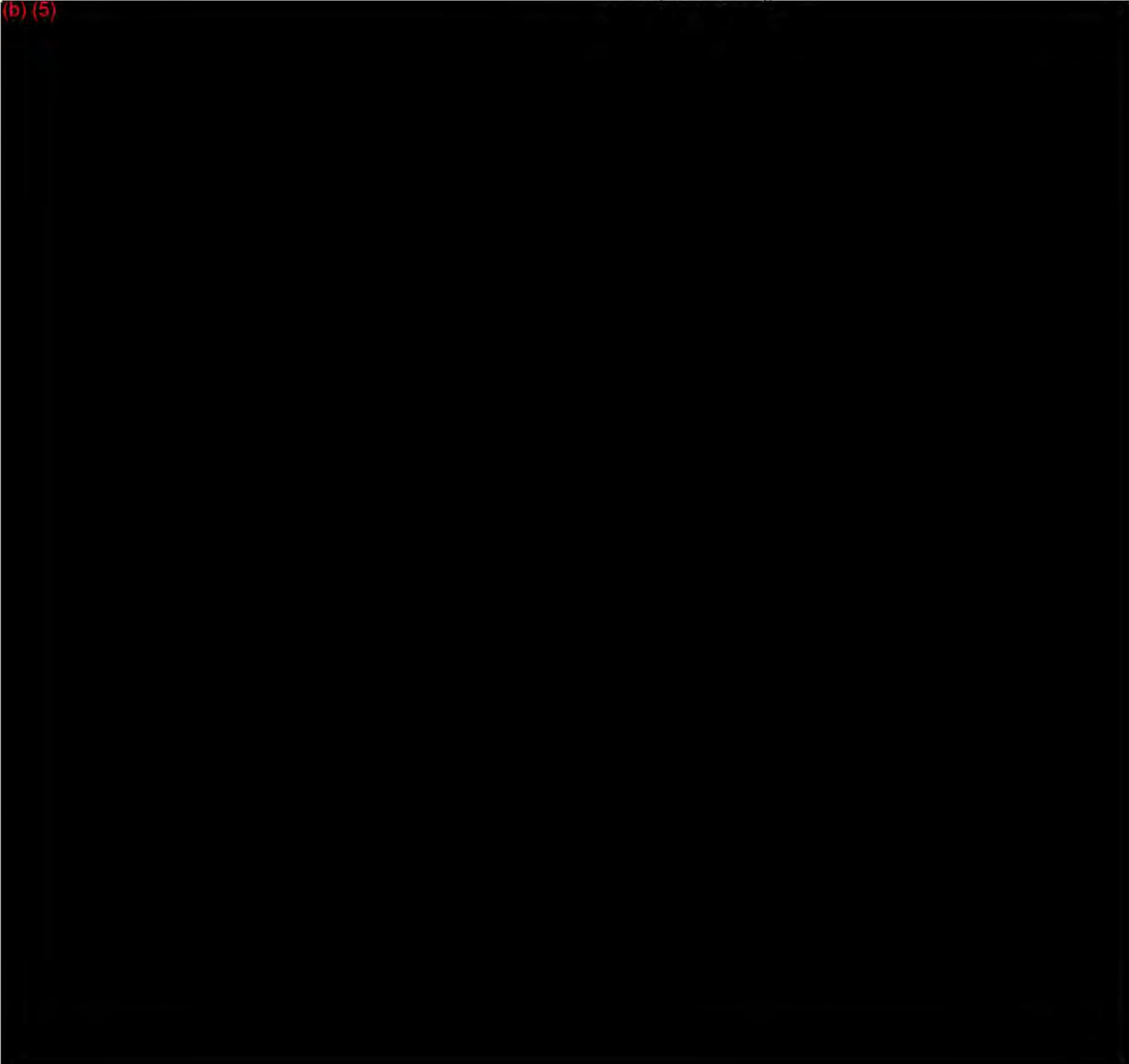
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Deliberative Process Privilege
Attorney-Client Privilege

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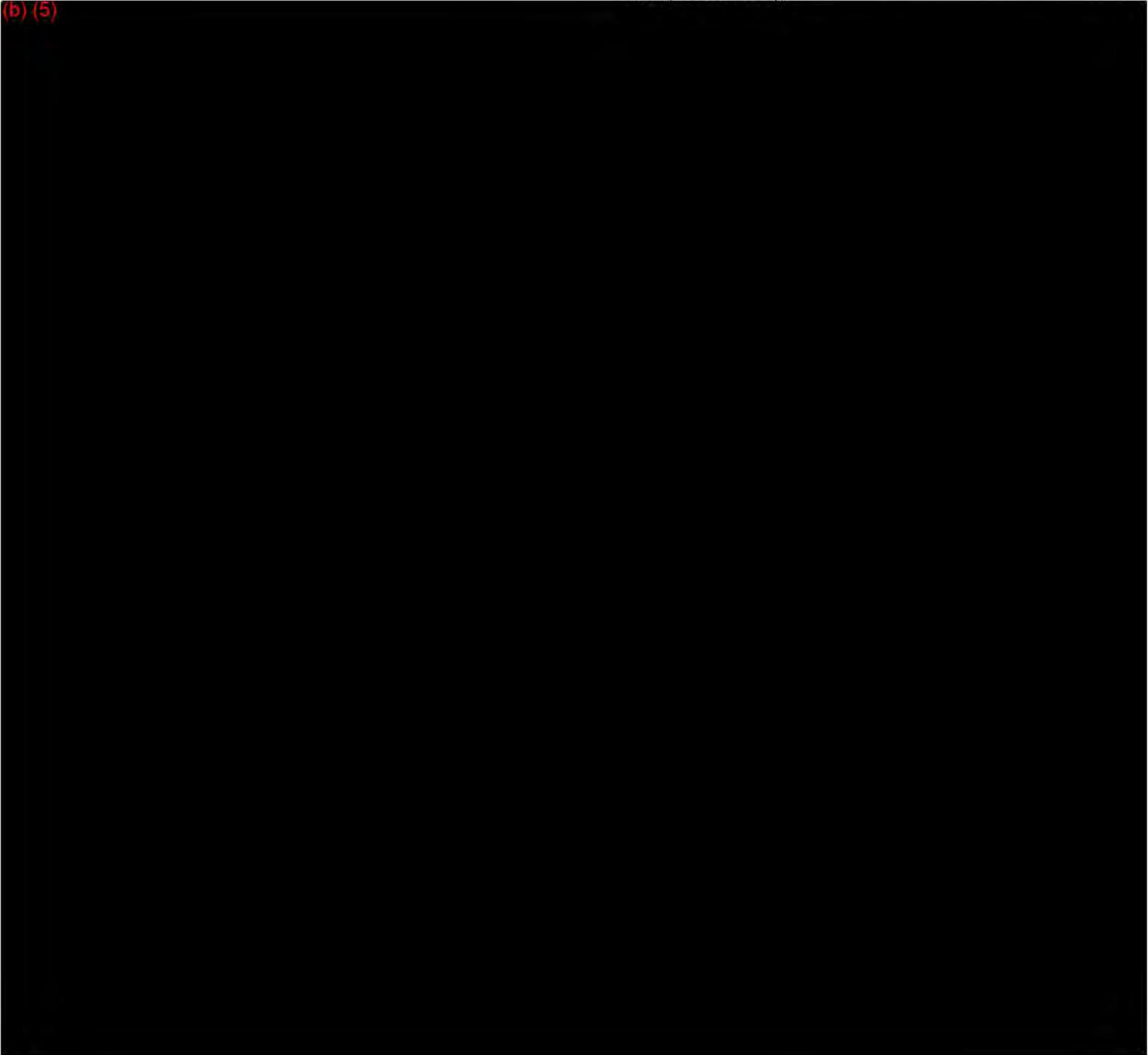
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Deliberative Process Privilege
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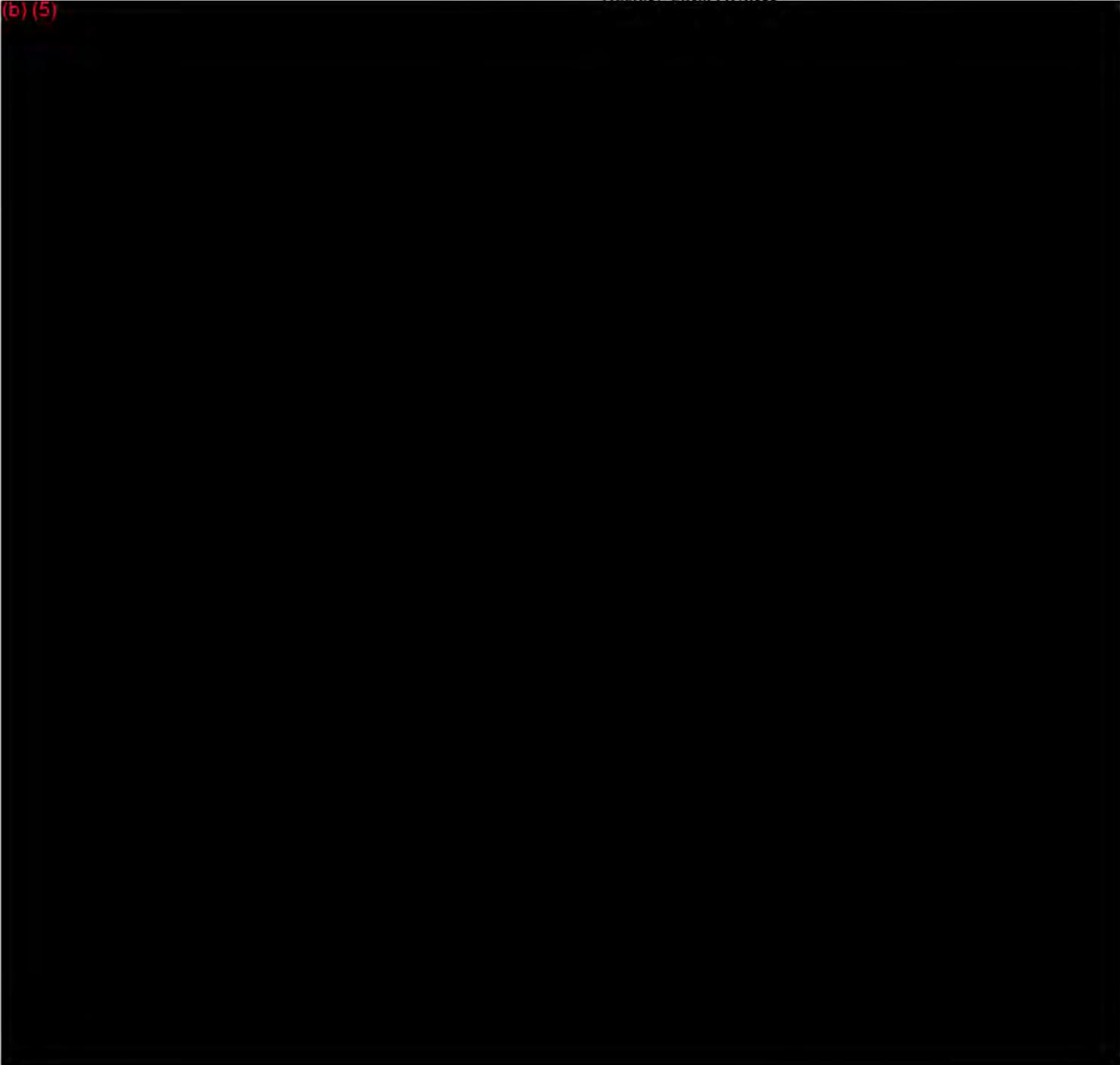
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FDAOC0002276

CONFIDENTIAL – DRAFT 9/15/16
Deliberative Process Privilege
Attorney-Client Privilege

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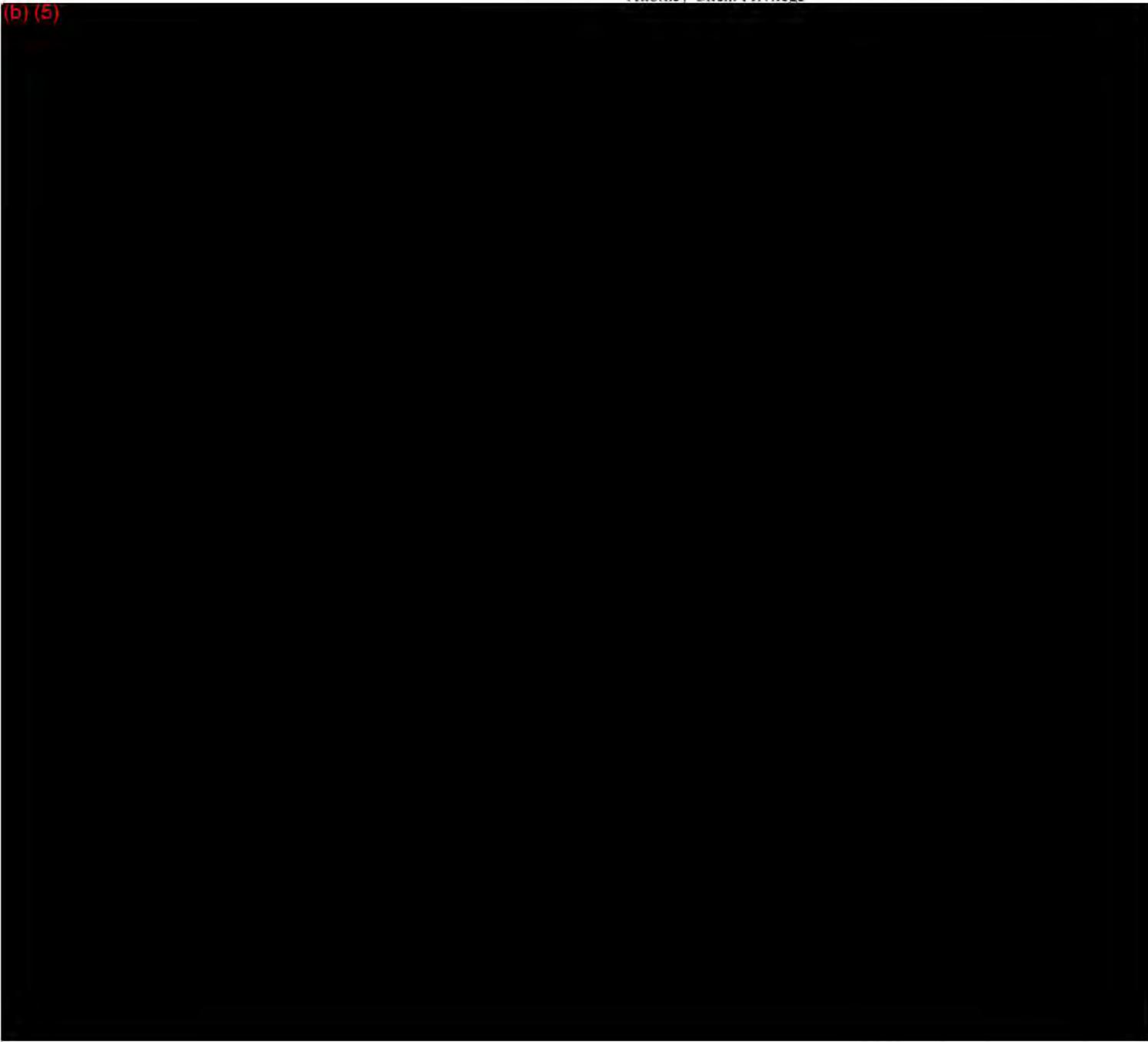


CONFIDENTIAL – DRAFT 9/15/16

Deliberative Process Privilege

Attorney-Client Privilege

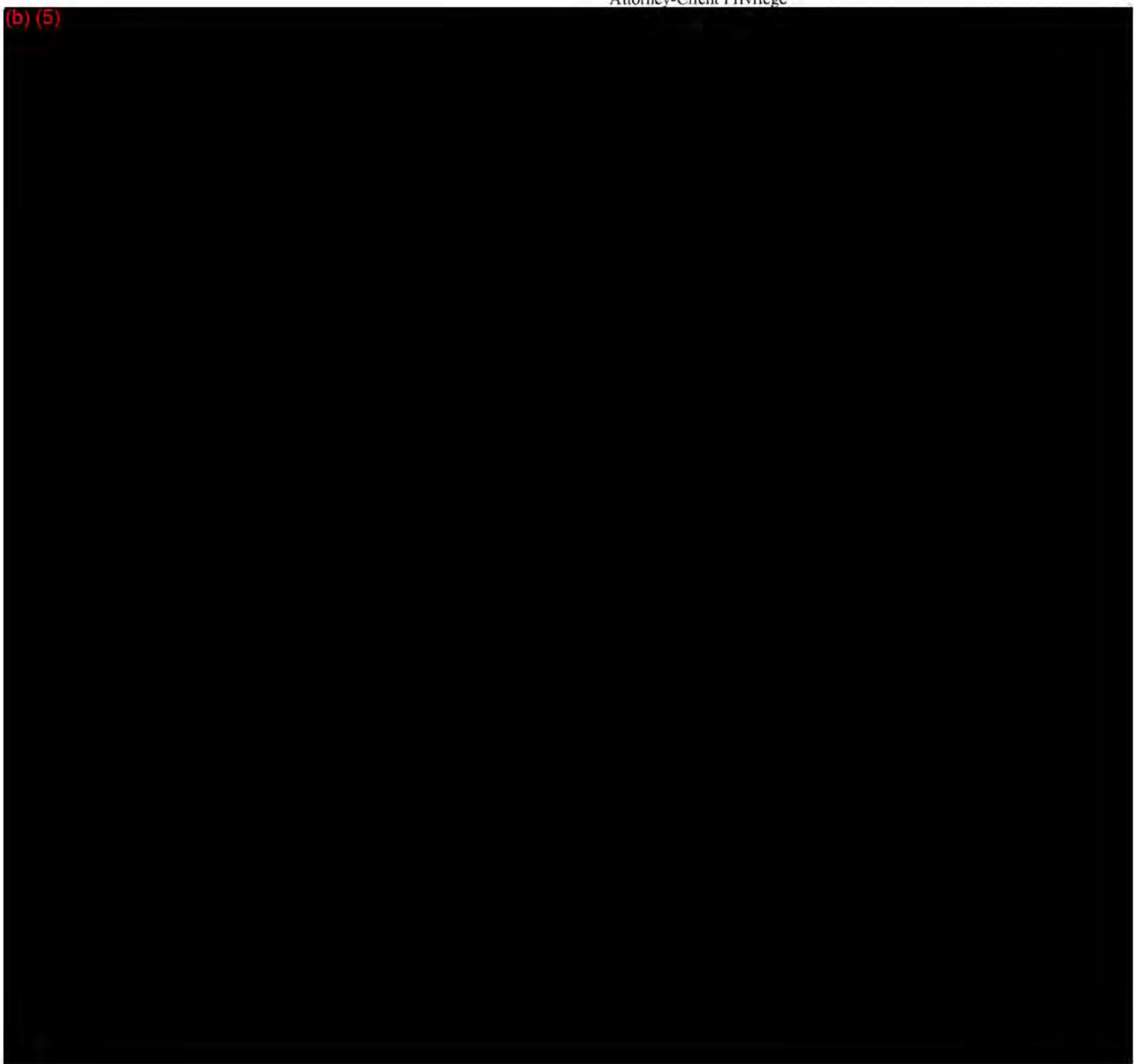
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CONFIDENTIAL – DRAFT 9/15/16
Deliberative Process Privilege
Attorney-Client Privilege

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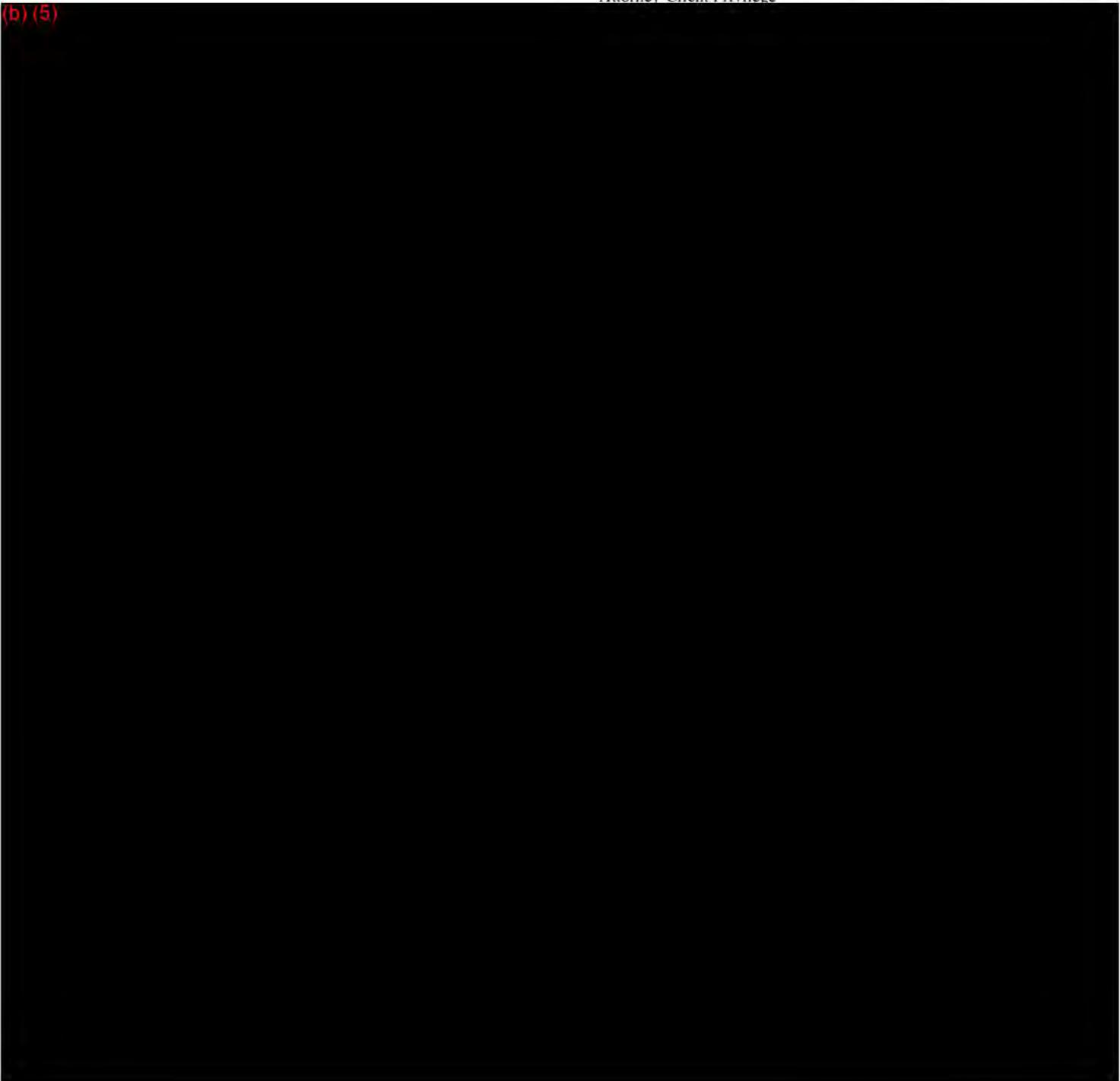
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CONFIDENTIAL – DRAFT 9/15/16

Deliberative Process Privilege

Attorney-Client Privilege

(b) (5)



CONFIDENTIAL – DRAFT 9/15/16
Deliberative Process Privilege
Attorney-Client Privilege

(b) (5)



From: [McCall, Jonathan *](#)
To: [Sherman, Rachel](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: RE: Do I have this right?
Date: Friday, September 16, 2016 11:17:12 AM
Attachments: [Eteplirsen_decisional_DRAFT_16-Sept-2016_CLEAN.doc](#)
[Eteplirsen_decisional_DRAFT_16-Sept-2016_TRACKED.doc](#)

Decisional memo attached (no changes to content). I'm assuming the formatting for the addresses at the top should be left as is?

Please let me know if you need anything else!

Best,

Jonathan

From: Sherman, Rachel
Sent: Friday, September 16, 2016 8:19 AM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: Do I have this right?

Cover emails – with Rob, timing of release TBD

Decisional memo

- Jonathan will clean up and send to RS and OCC
- After RS and OCC – back to RMC/DE to signed, put into PDF
- Timing of release TBD

Memo to file

- Jonathan cleans up sends to OCC
- OCC finalizes and send to Tom
- Tom will figure out what to do with it; will not be released

TO: Janet Woodcock, M.D., Director, CDER
Ellis Unger, M.D., Director, Office of Drug Evaluation I, CDER
Luciana Borio, M.D., Chair, Agency Scientific Dispute Process
Review Board

FROM: Robert M. Califf, M.D., Commissioner, Food and Drugs

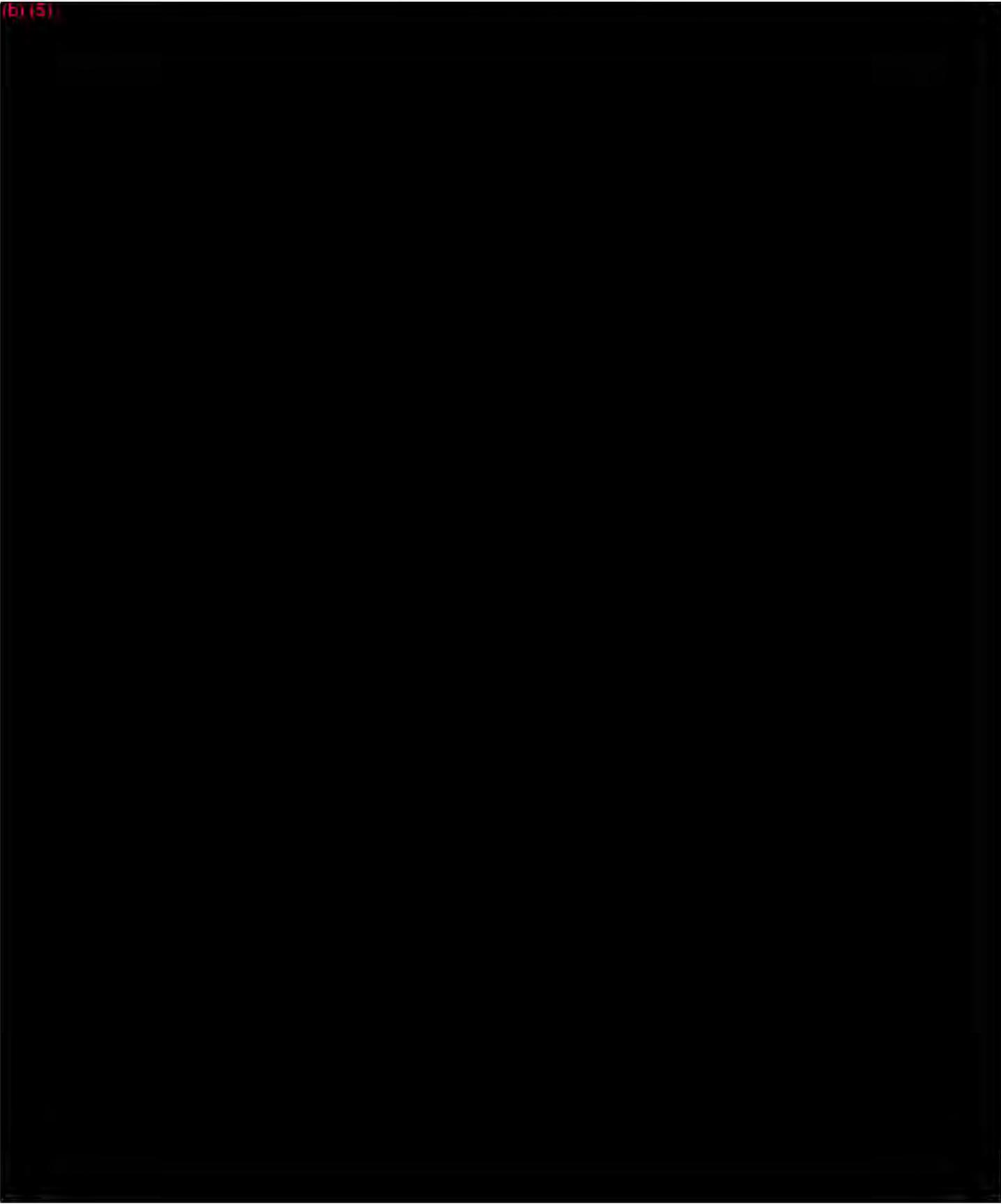
RE: Scientific Dispute Regarding Approval of Sarepta Therapeutics'
Eteplirsen (NDA 206488) – Commissioner's Decision

DATE: September XX, 2016

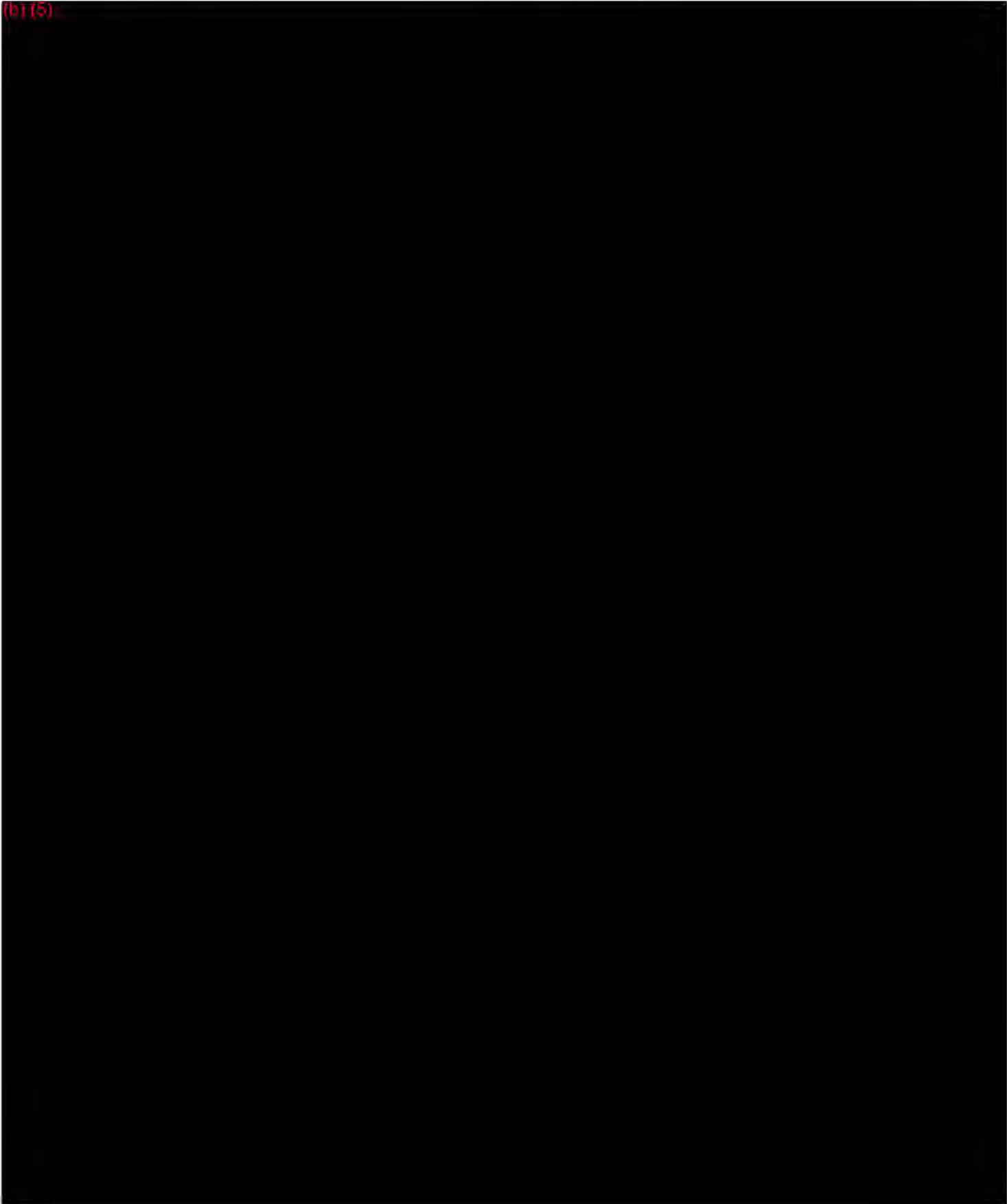
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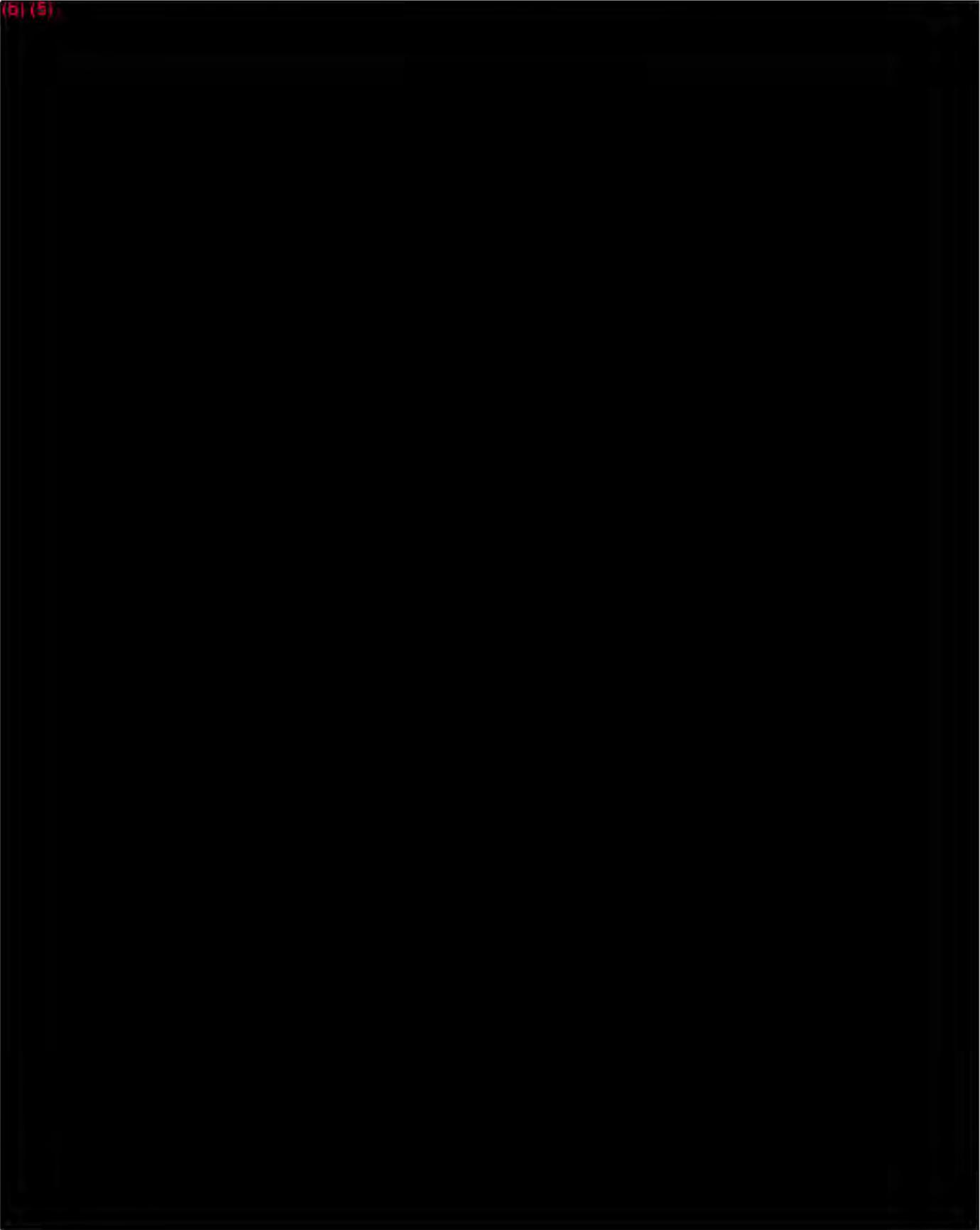
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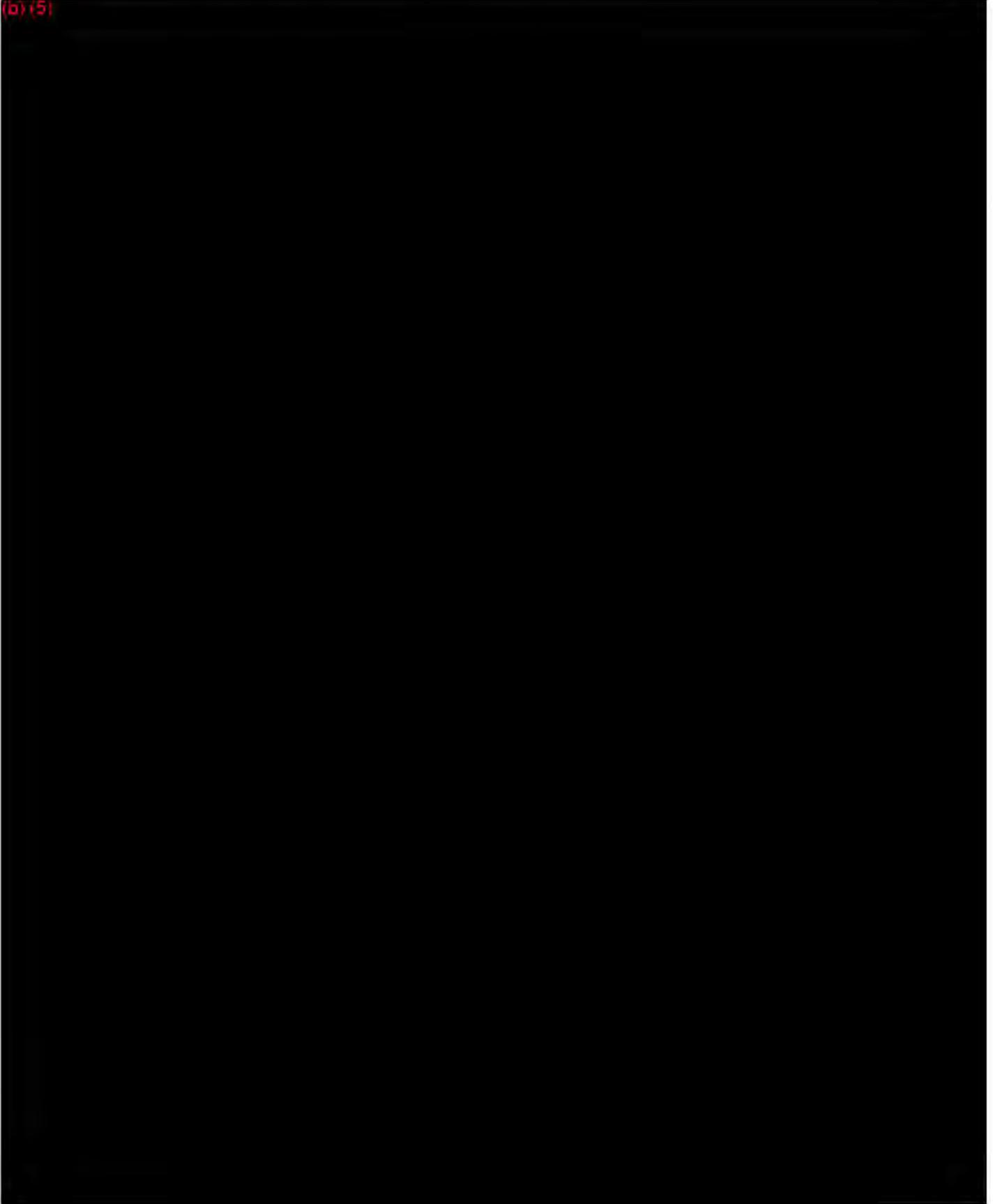
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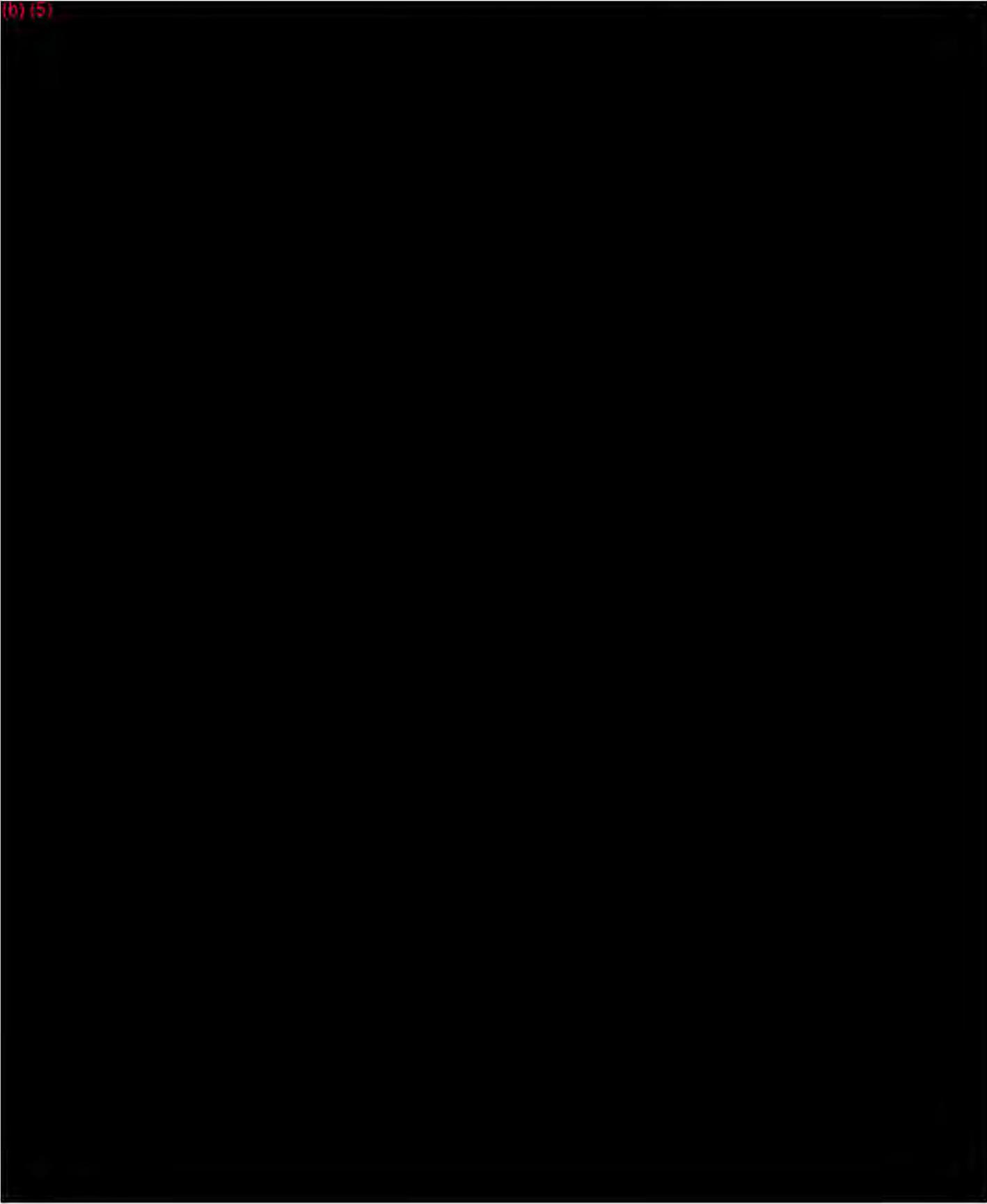
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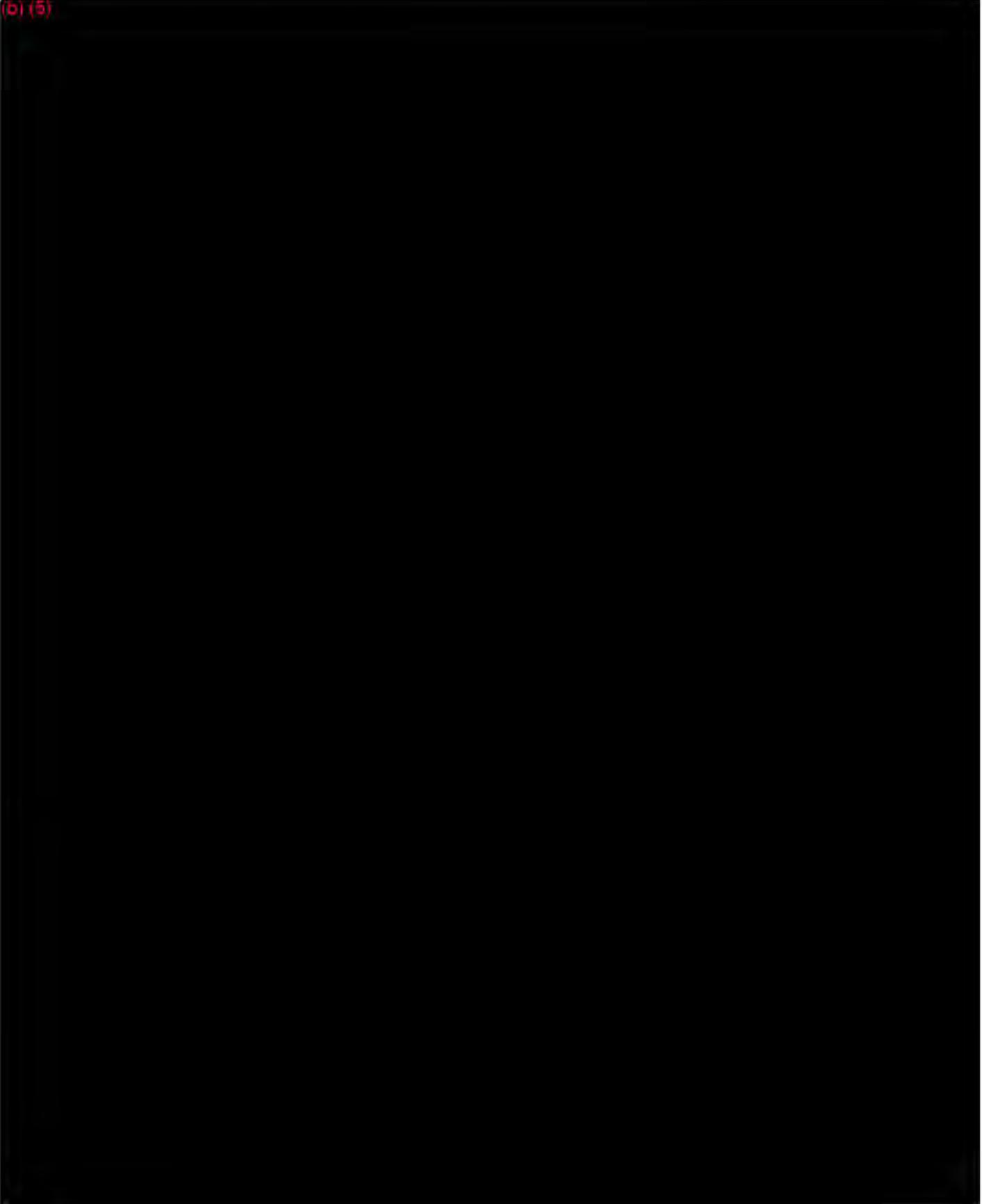
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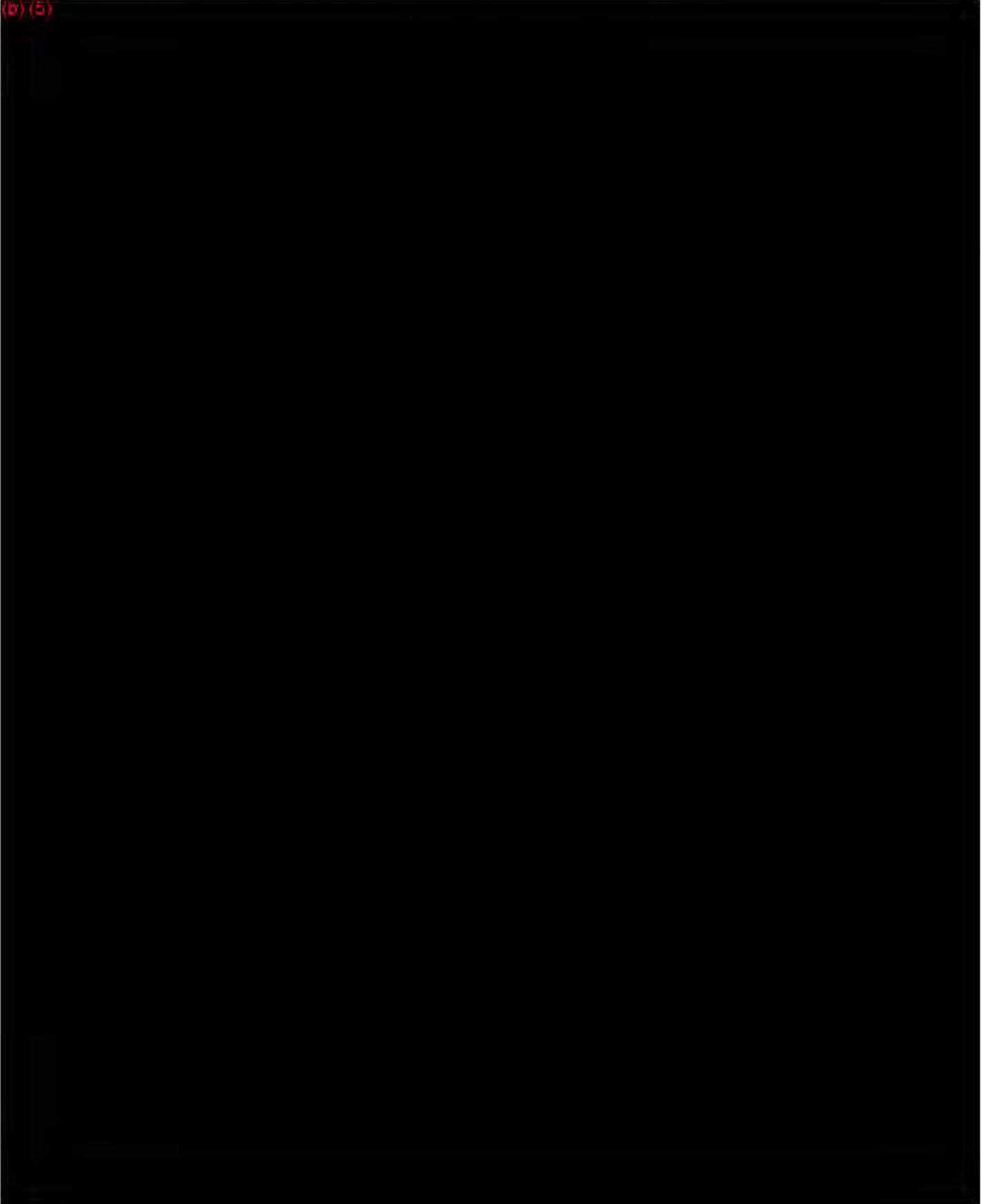
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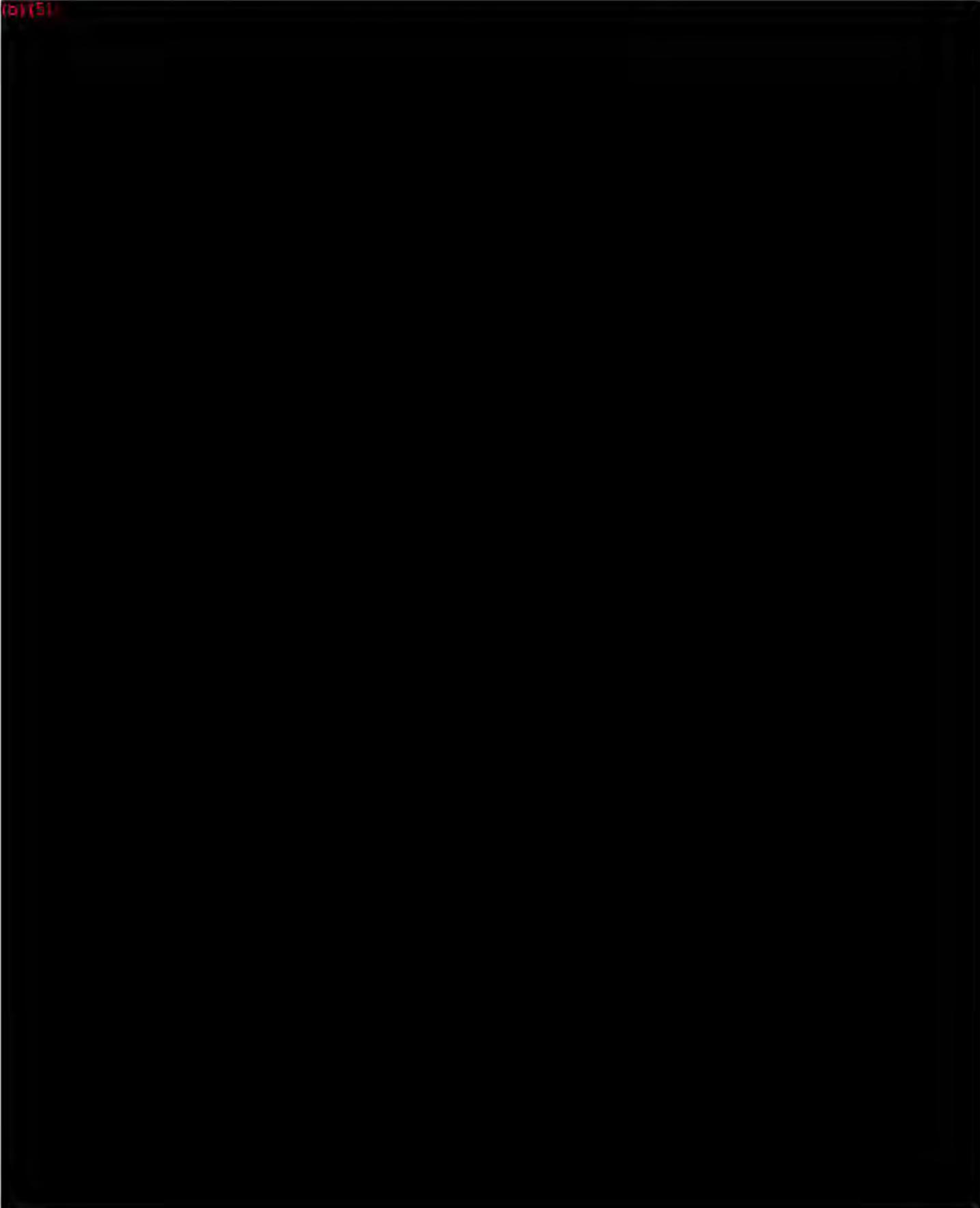
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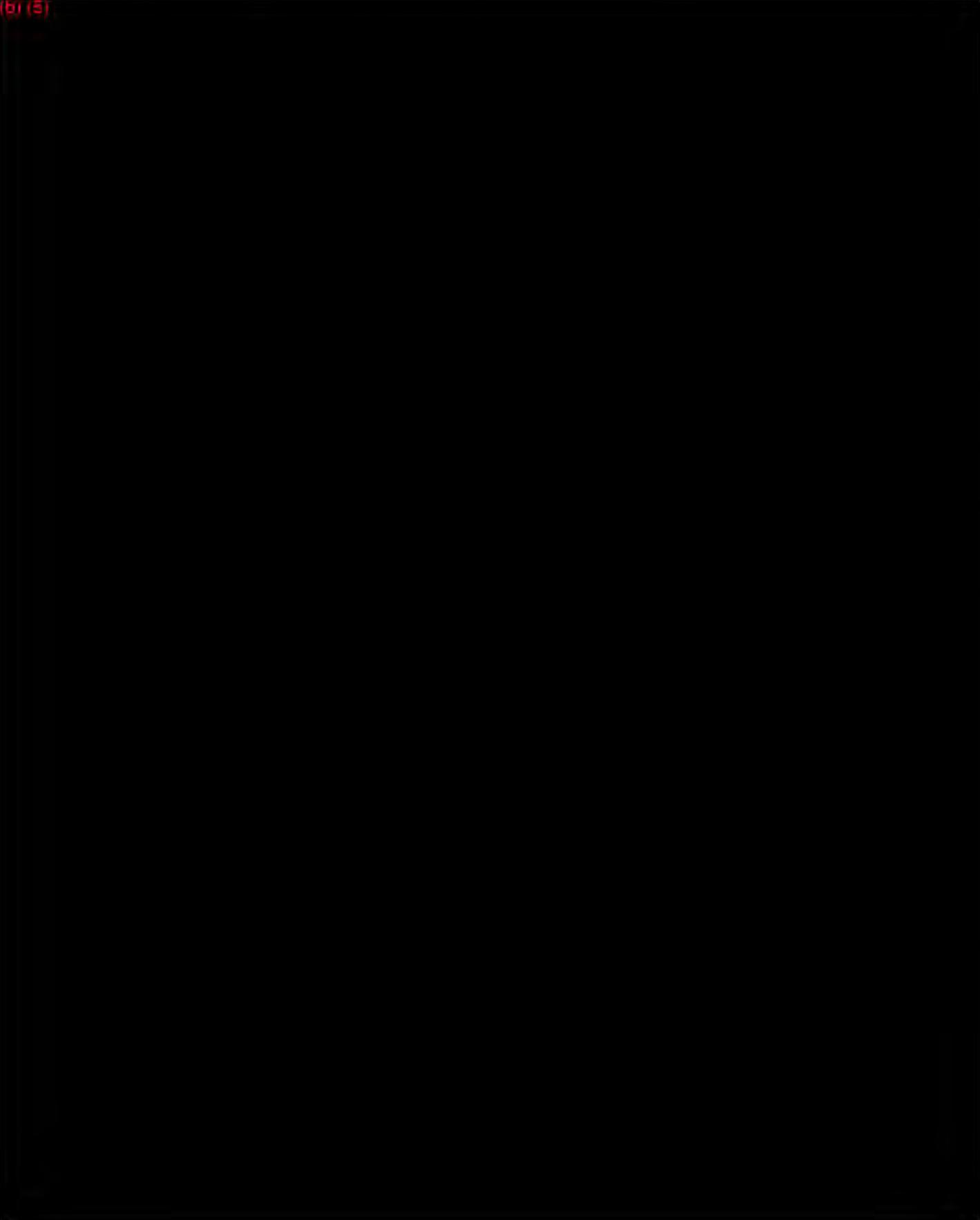
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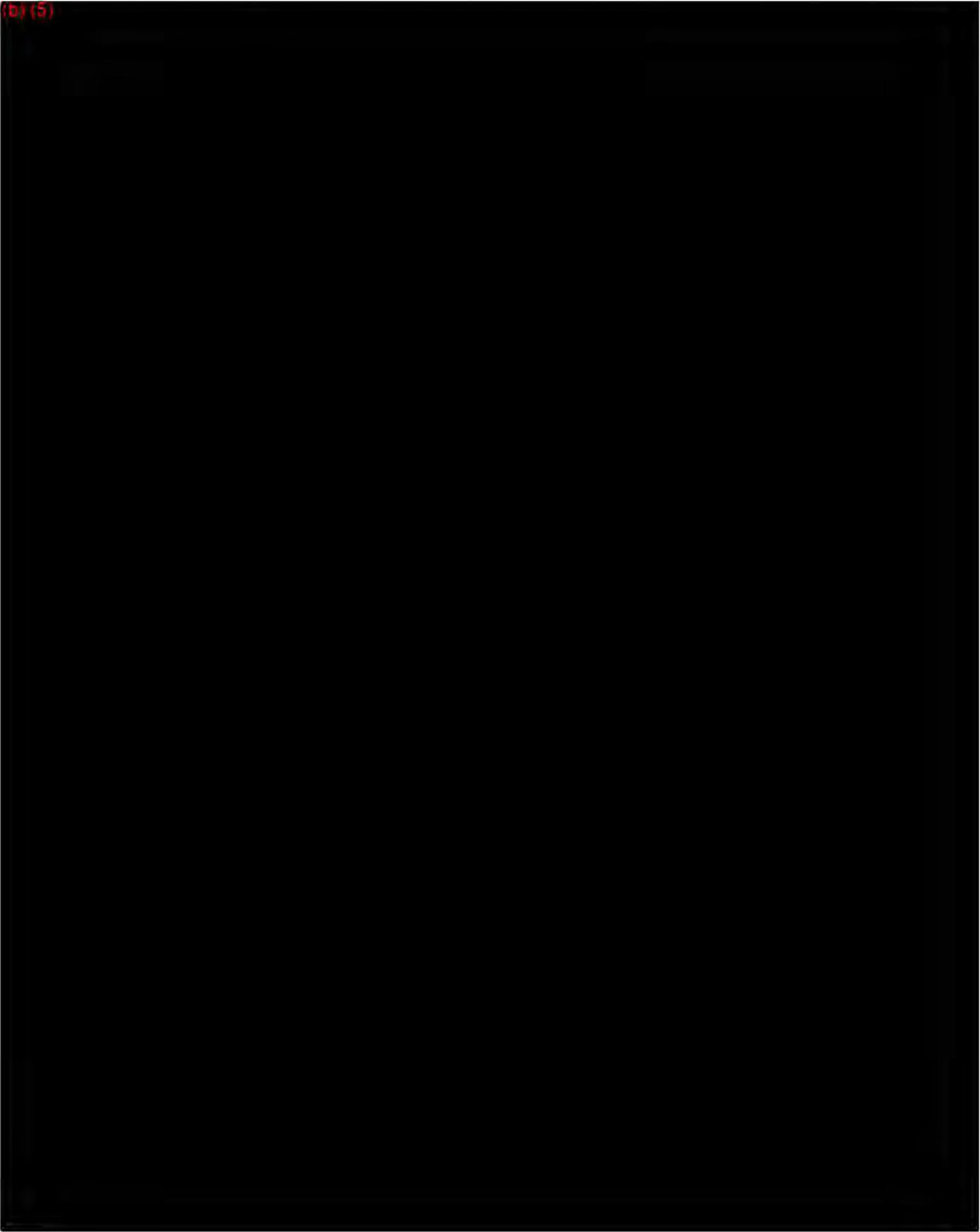
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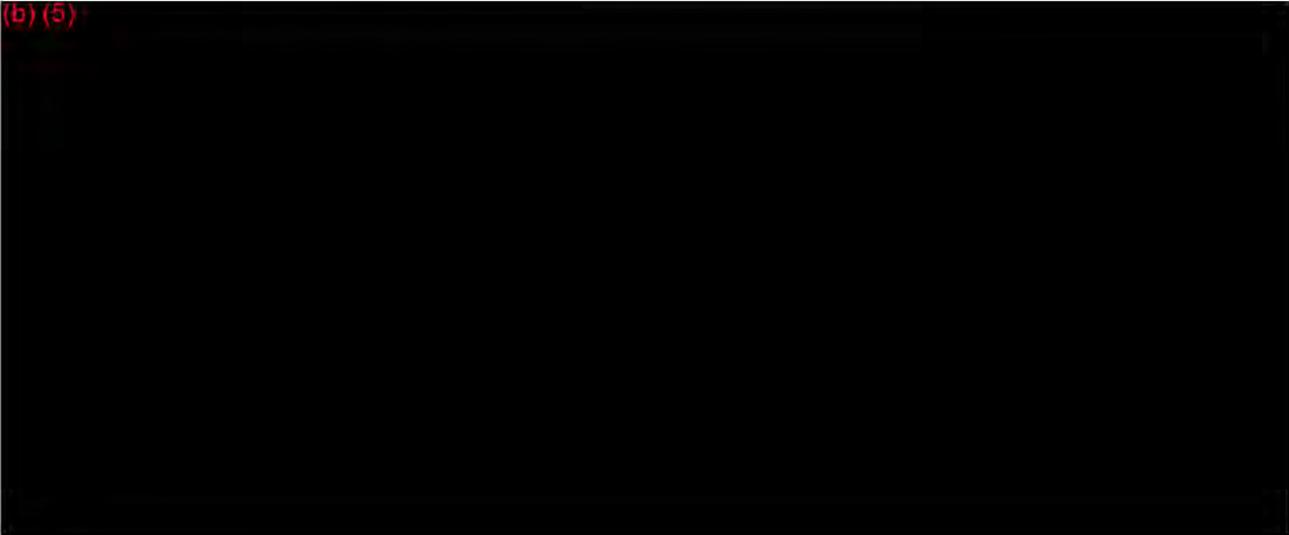
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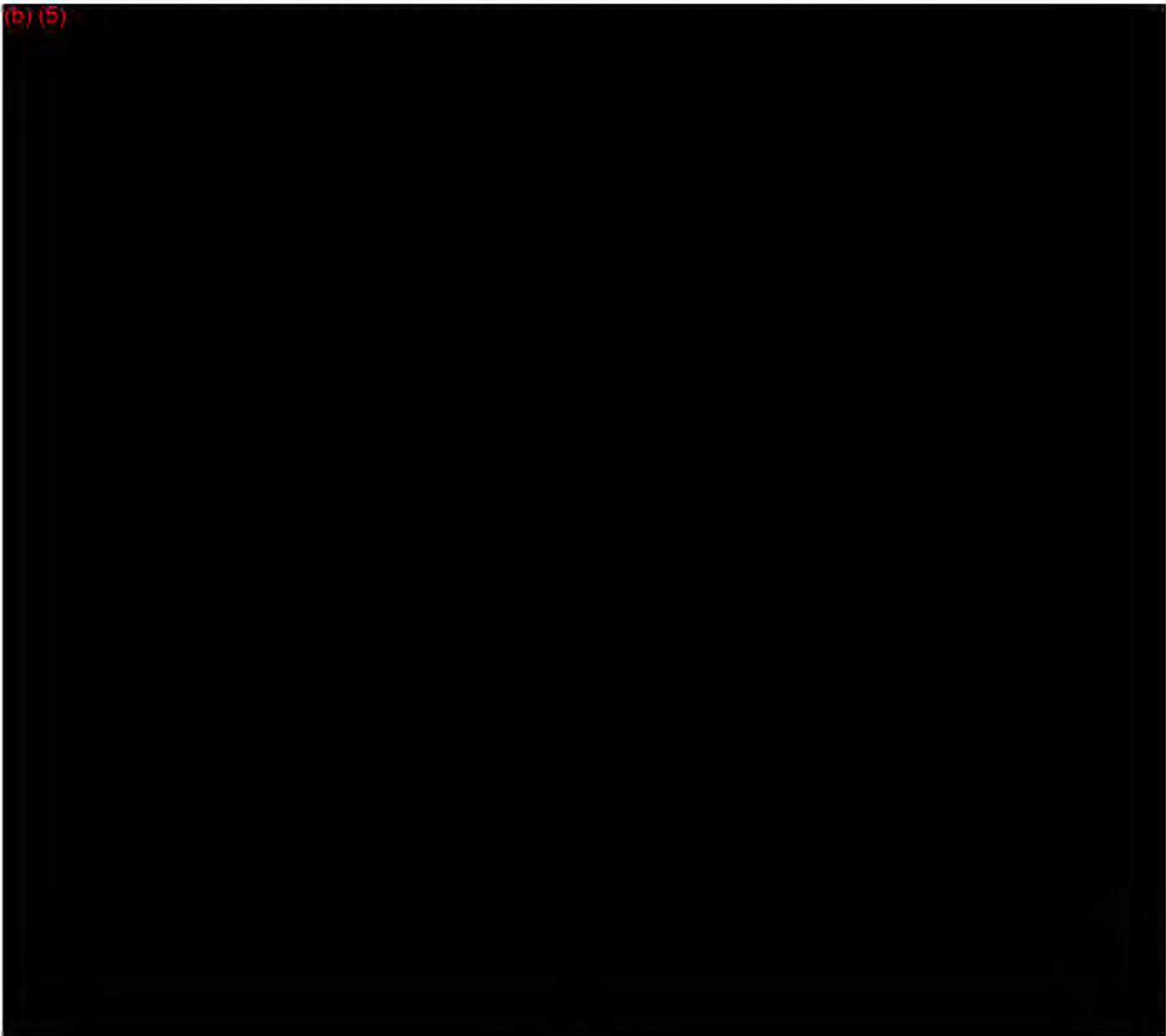
TO: Janet Woodcock, M.D., Director, CDER
Ellis Unger, M.D., Director, Office of Drug Evaluation I, CDER
Luciana Borio, M.D., Chair, Agency Scientific Dispute Process
Review Board

FROM: Robert M. Califf, M.D., Commissioner, Food and Drugs

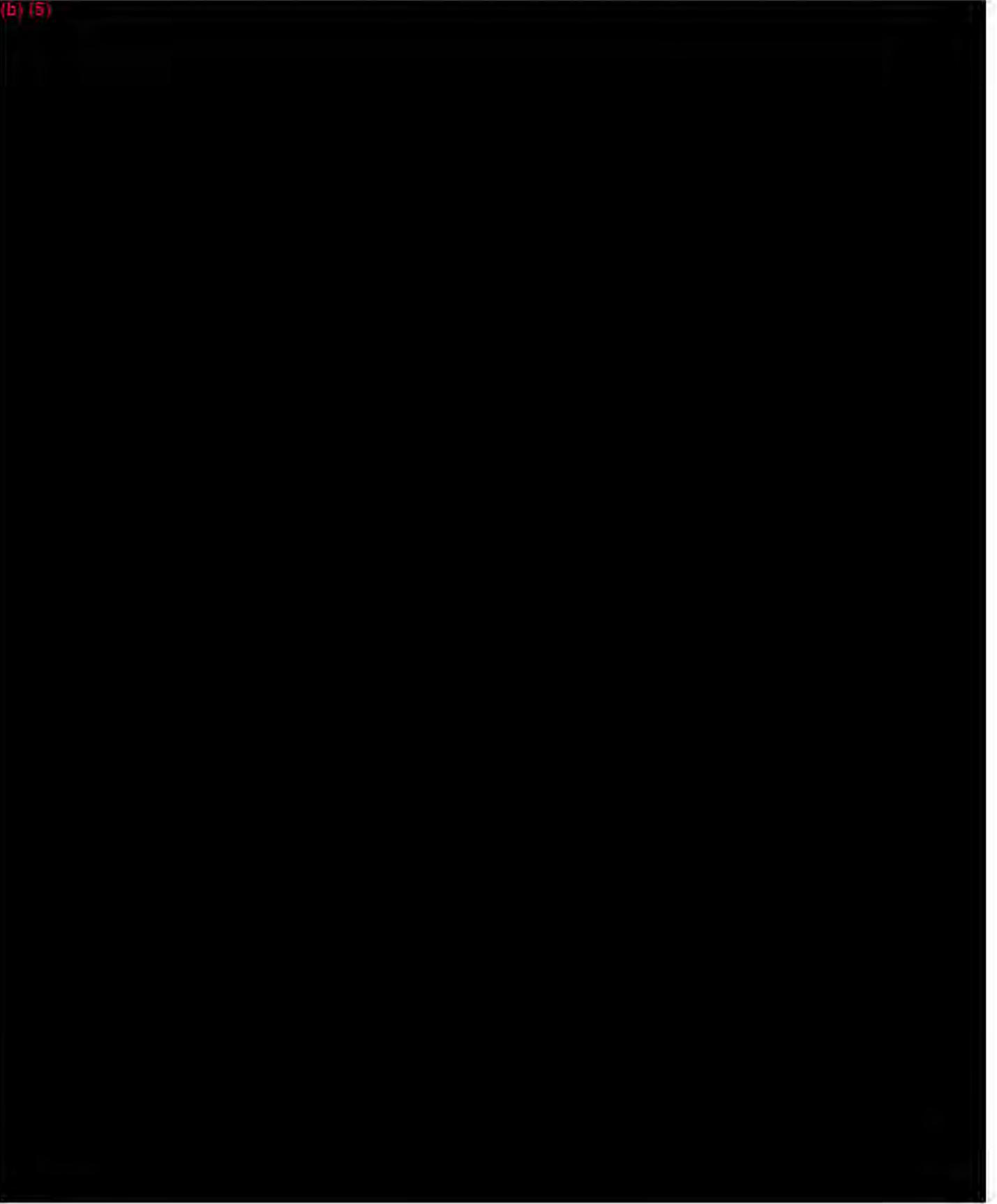
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Eteplirsen (NDA 206488) – Commissioner's Decision

DATE: September XX, 2016

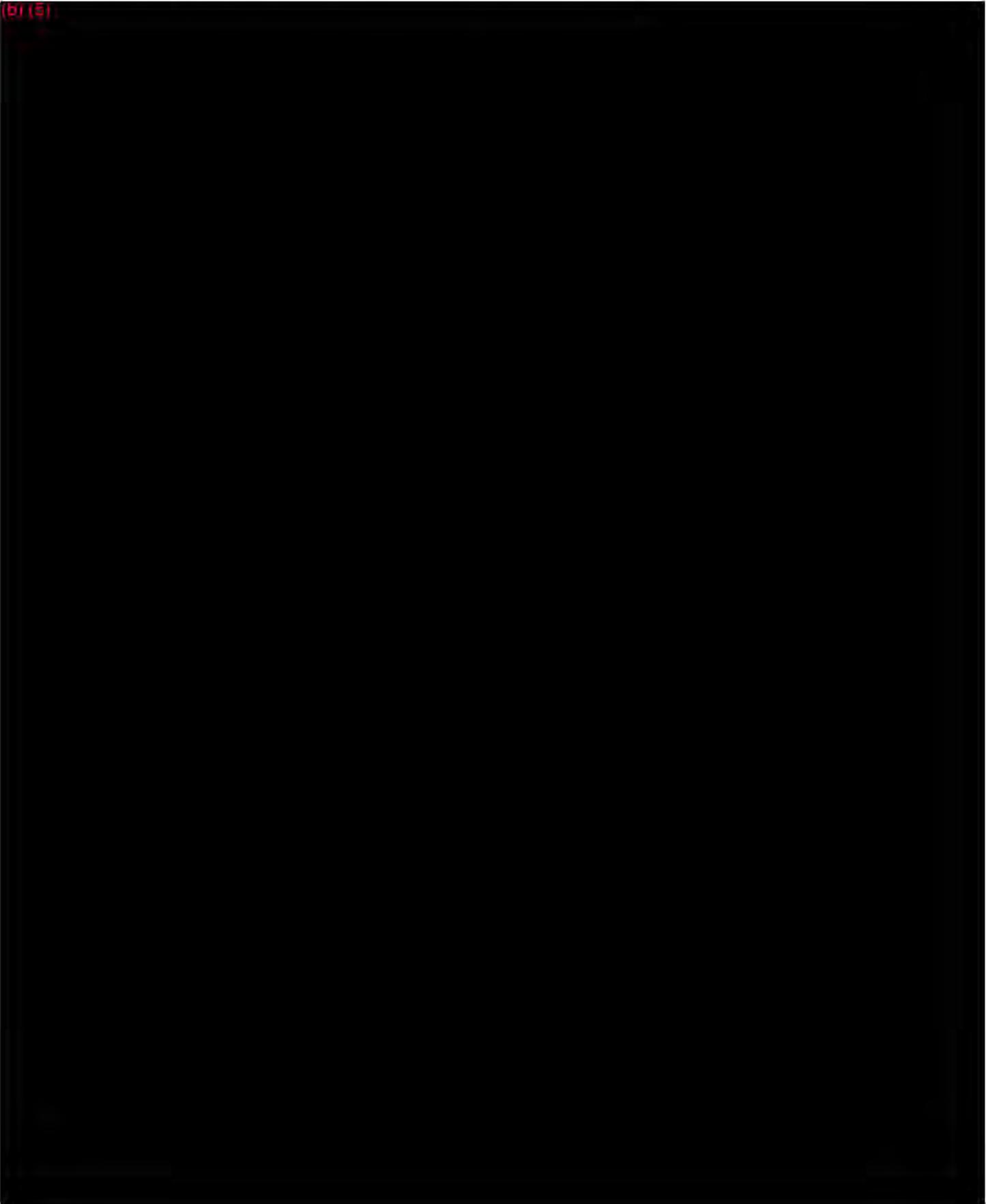
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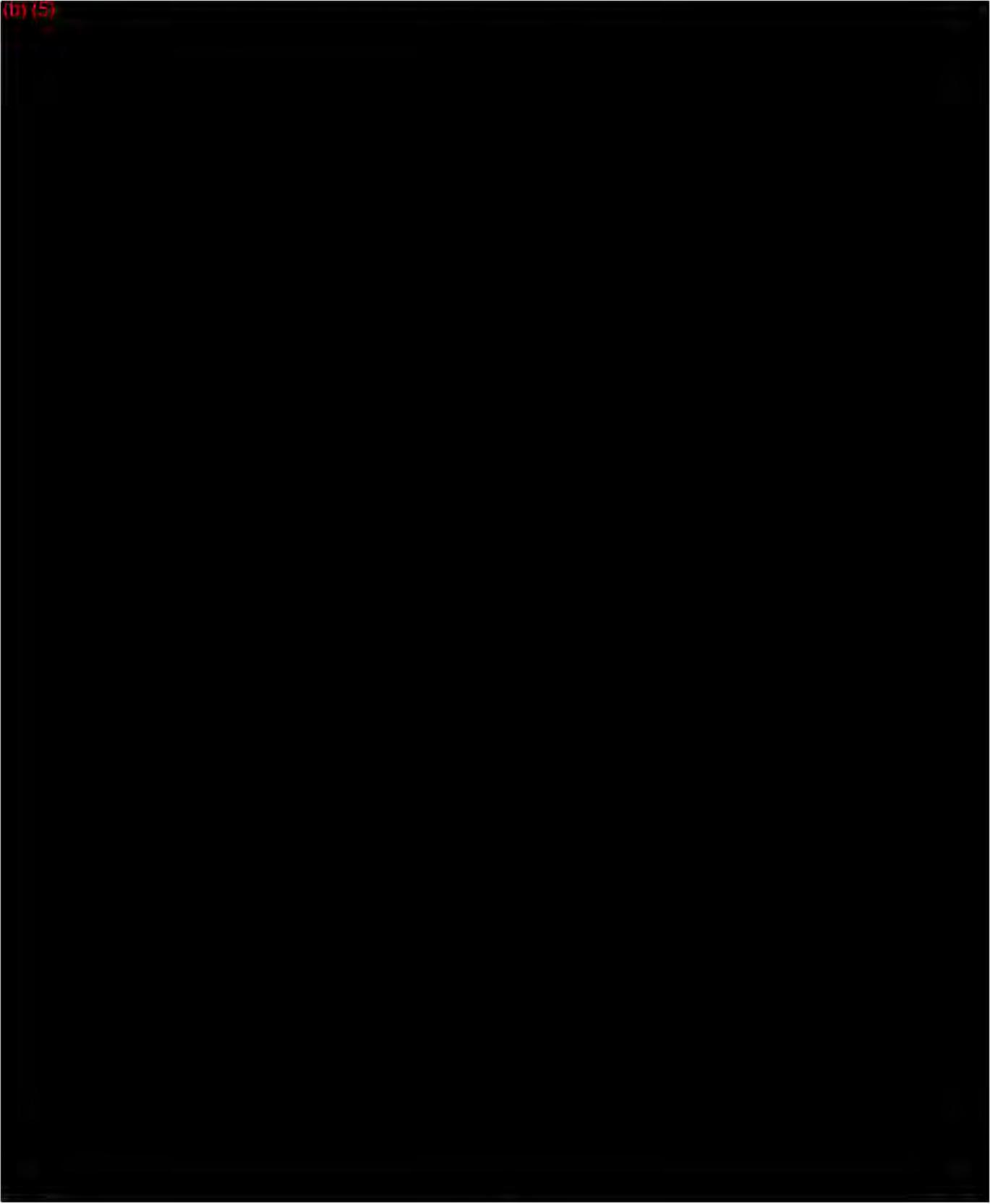
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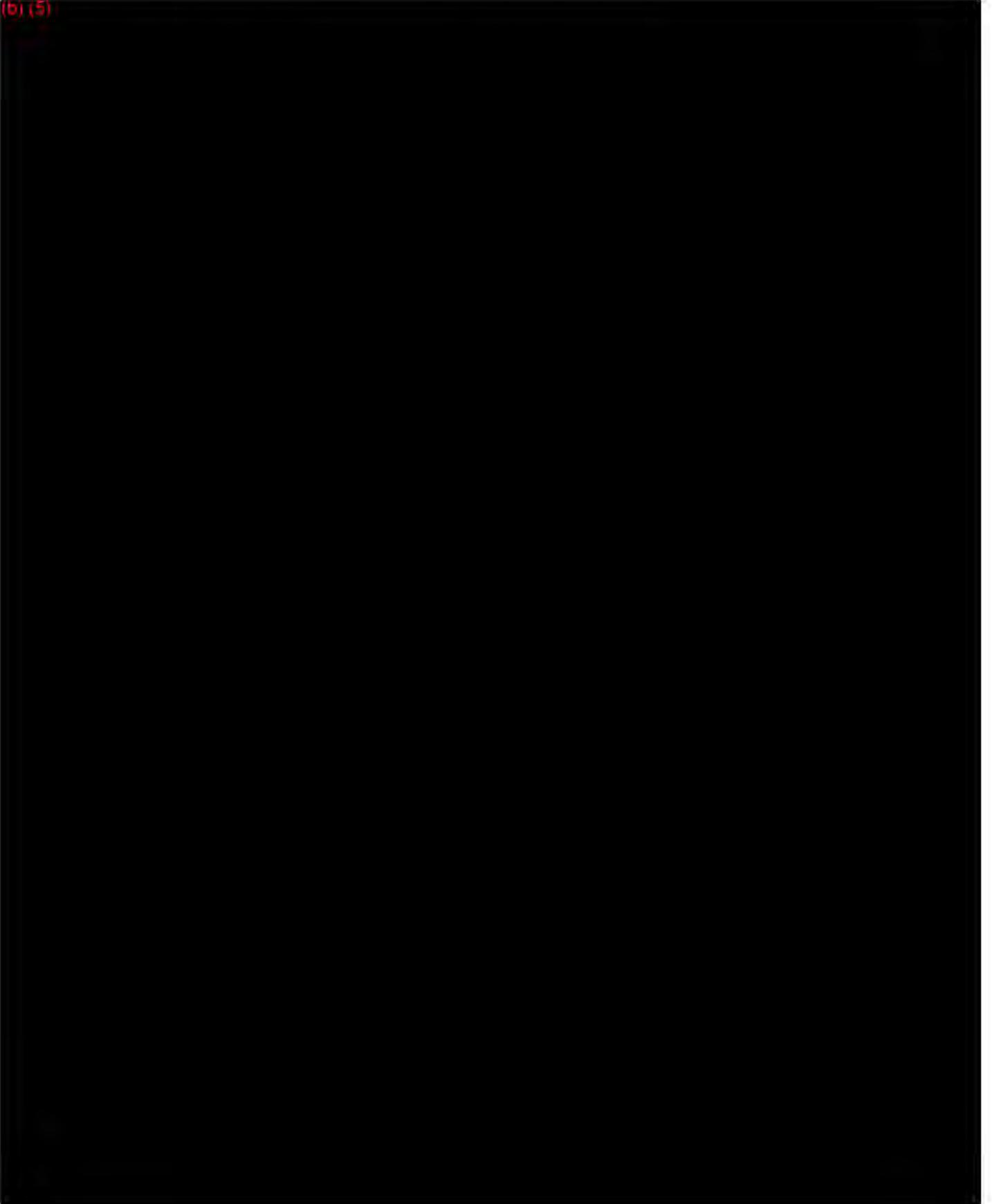
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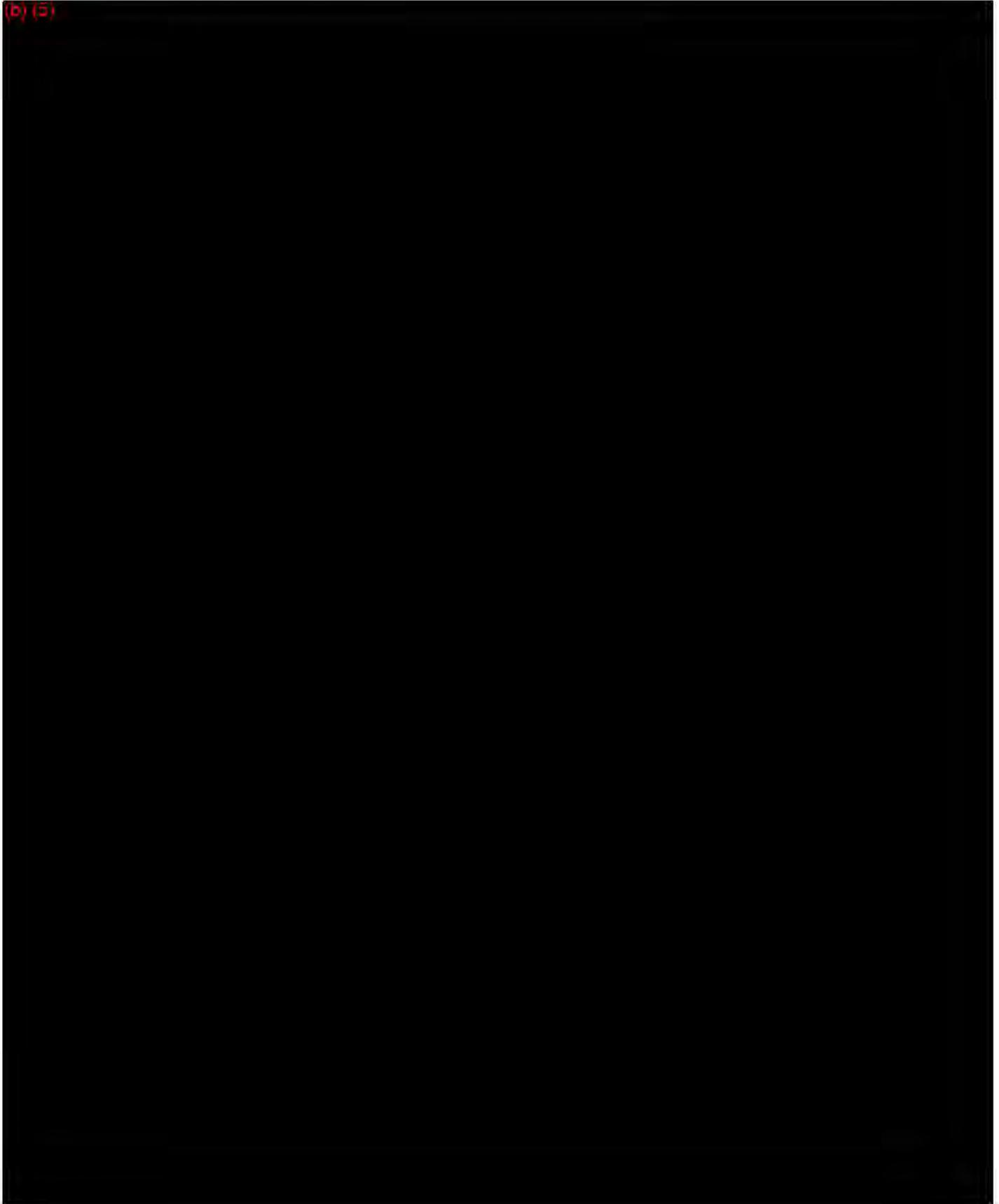
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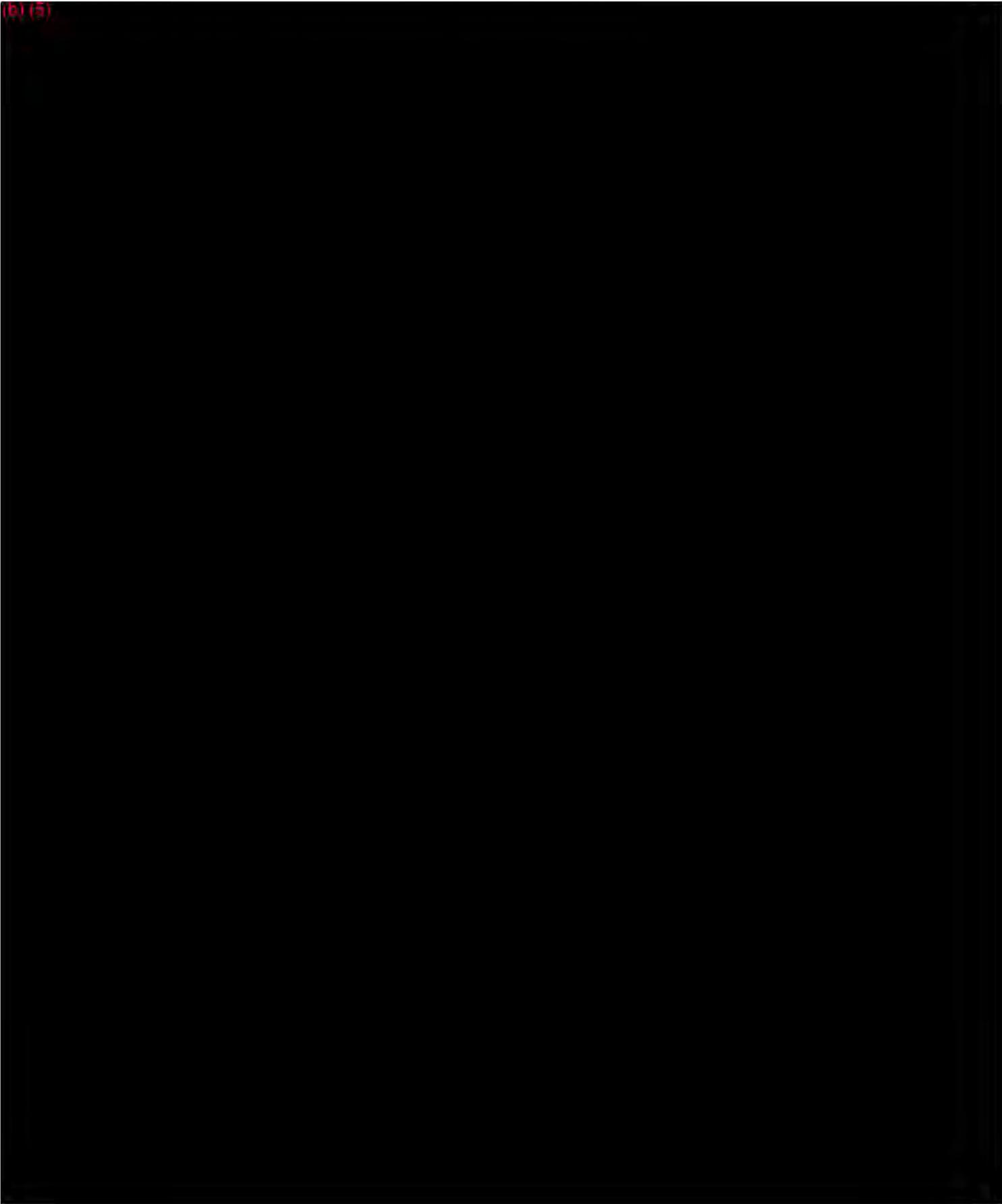


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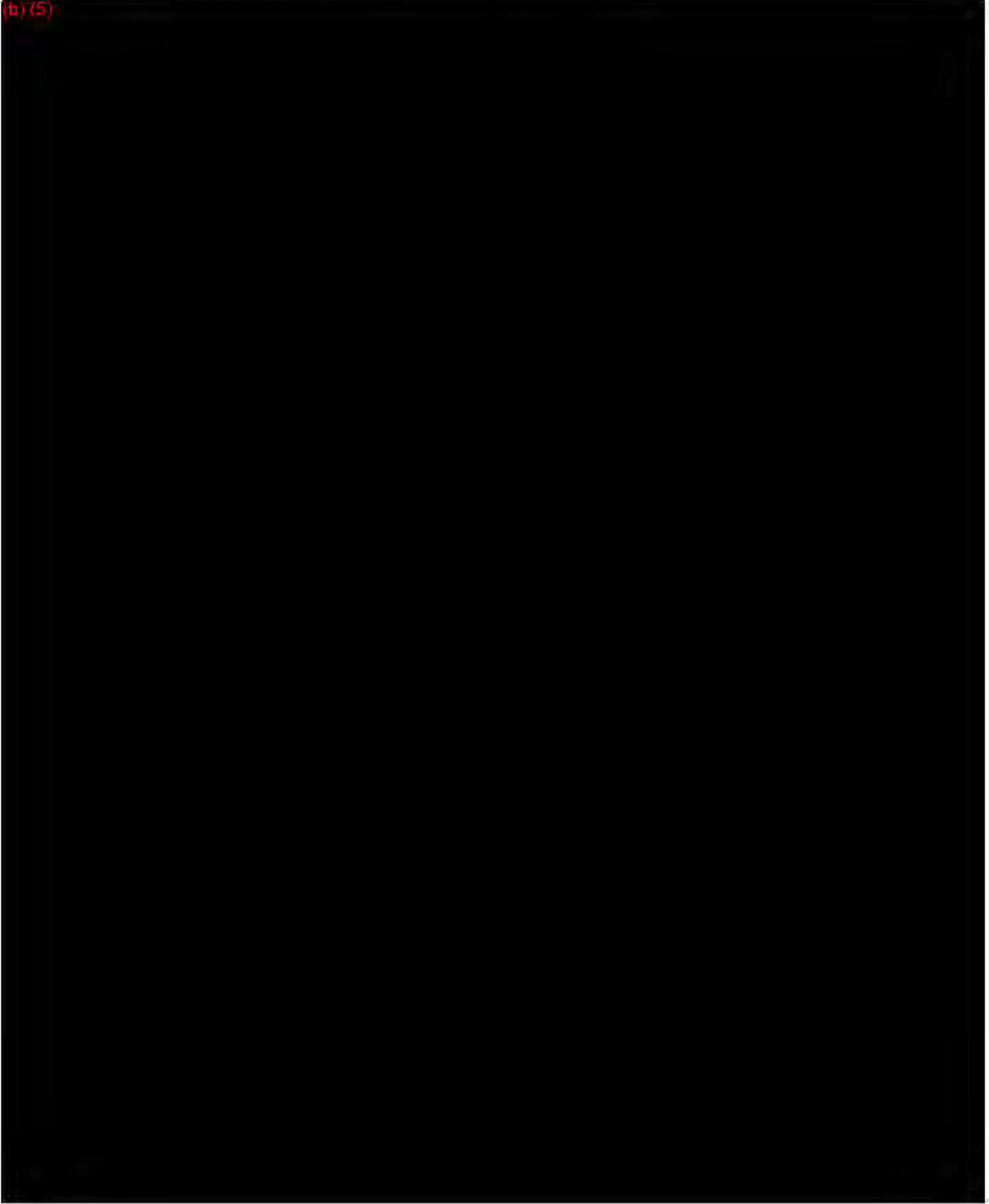
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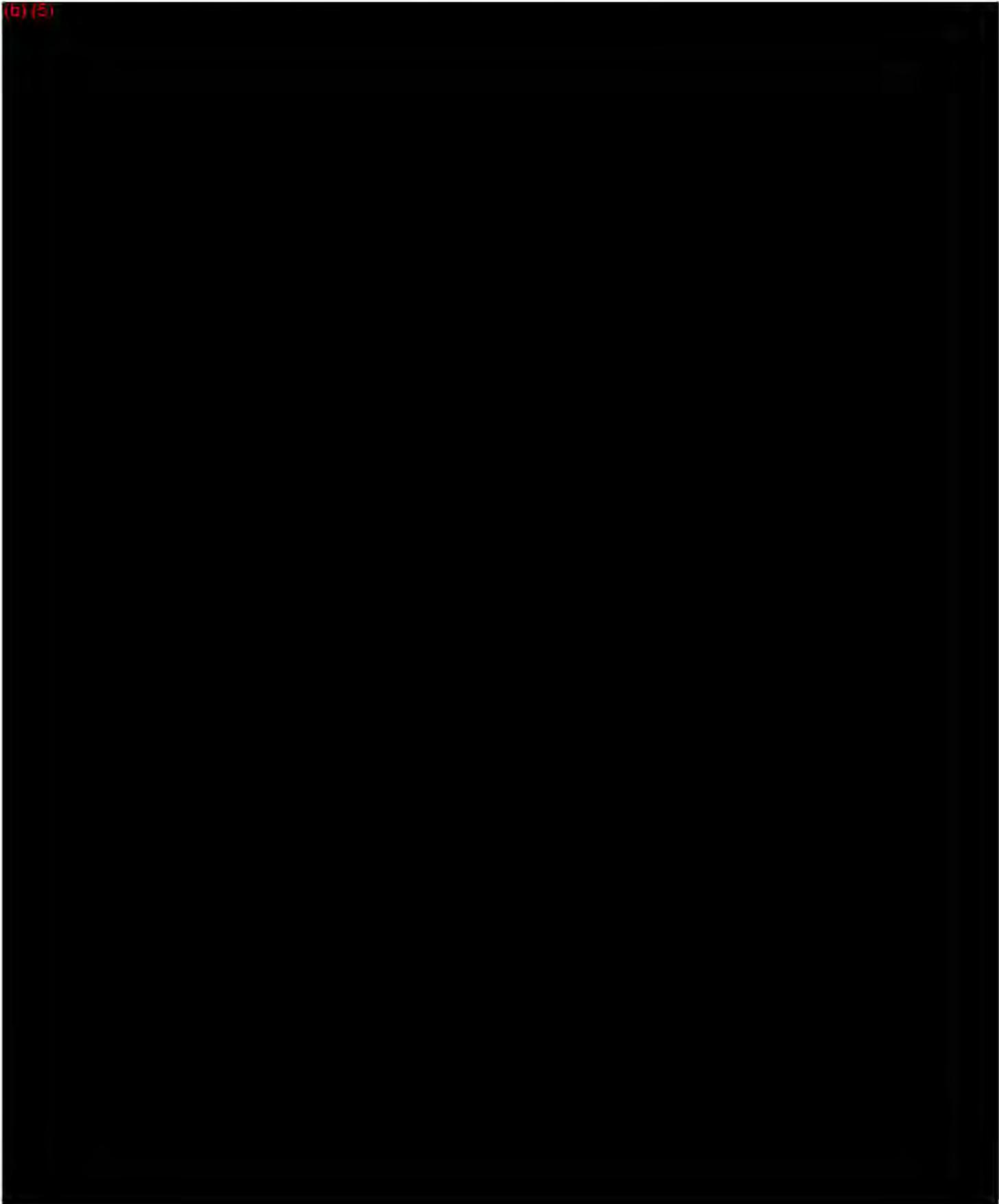


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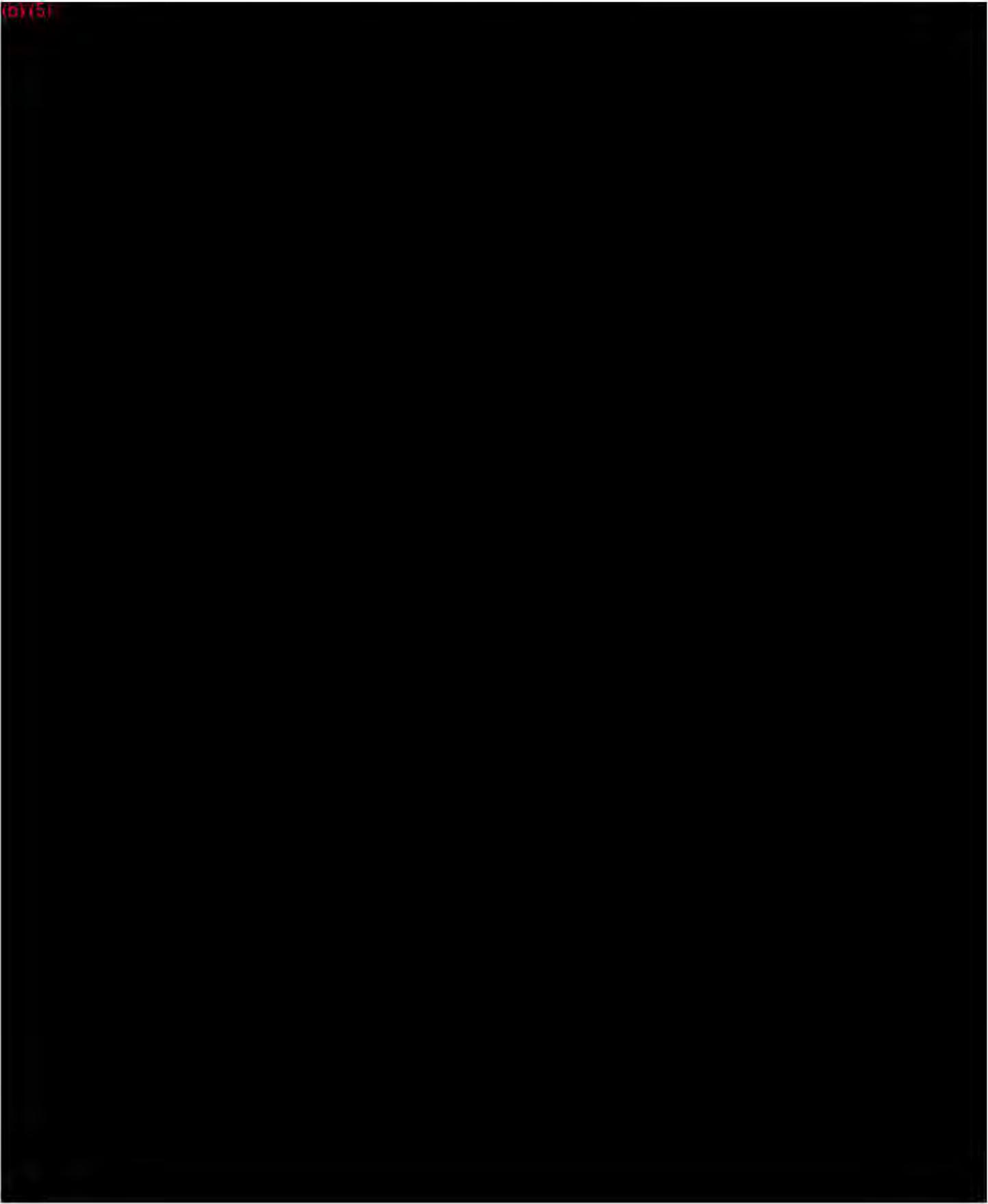
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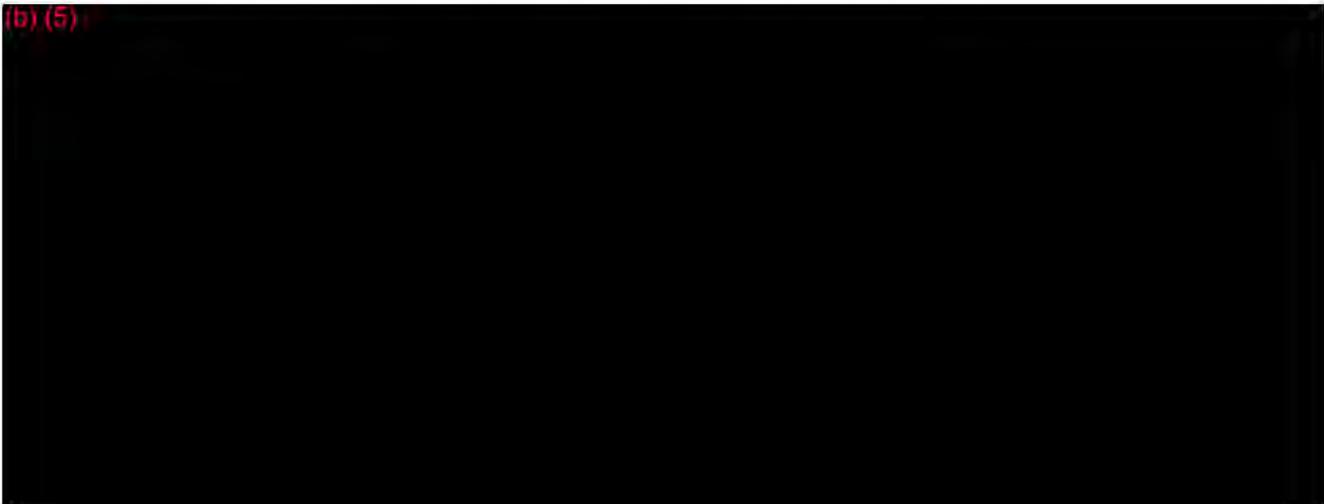
(b) (5)



(b) (5)



(b) (5)



From: [Conover, Katie](#)
To: [Califf, Robert](#); [Kraus, Tom](#); [Dickinson, Elizabeth \(FDA\)](#); [Sharp, Jeremy](#)
Cc: [Quinn, Kathleen](#); [Marchand, Heidi](#); [Rodriguez, Jennifer](#); [Walsh, Sandy](#)
Subject: Primary Patient/Advocacy Organizations' Activities/Reactions to September 19, 2016, Eteplirsen Approval (Collected 10am-3:30pm)
Date: Monday, September 19, 2016 5:20:46 PM

**Primary Patient/Advocacy Organizations' Activities/Reactions to September 19, 2016,
Eteplirsen Approval
(Info collected 10am-3:30pm, September 19, 2016)**

- **Parent Project Muscular Dystrophy (PPMD):**
 - PPMD issues press release: [PPMD Applauds FDA for Landmark Approval of First-Ever Disease-Modifying Drug to Treat Duchenne Muscular Dystrophy--Organization Will Continue to Support Patient Access and Drive Policies and Projects That Support Development and Approval of More Therapies](#).
 - PPMD President quoted "PPMD is thrilled that FDA has granted an Accelerated Approval to Exondys 51, a therapy with the potential to treat 13% of people living with Duchenne, marking the first-ever U.S. approval of a drug to treat this disease," said PPMD Founding President and CEO Pat Furlong."
 - PPMD links to [FDA Press Release](#) (click "Learn More").
 - PPMD's President, Pat Furlong, issues blog [FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy](#).
- **National Organization for Rare Disorders (NORD):**
 - NORD issues press release "[FDA Approves Eteplirsen to Treat Duchenne Muscular Dystrophy](#)" and includes link to [FDA press release](#).
- **CureDuchenne:**
 - CureDuchenne issues press release "[CureDuchenne Celebrates FDA Approval of First Drug for Duchenne Muscular Dystrophy](#)."
- **Muscular Dystrophy Association (MDA):**
 - MDA issues press release (via PR Newswire): "[MDA Celebrates FDA Accelerated Approval of Eteplirsen for Treatment of Duchenne Muscular Dystrophy--Approval](#)"

expected to hasten development of treatments for DMD and related diseases."

- MDA President and CEO, Steven M. Derks quoted--"Today has been a long time in the making," said MDA President and CEO Steven M. Derks. "This is the outcome MDA dreamed of 25 years ago when it was the first to invest in the breakthrough research that led to development of eteplirsen. Throughout this process we have seen the undeniable strength of our community to rally behind MDA's commitment to find treatments for our families. This is an important victory, and we are honored to stand shoulder-to-shoulder with everyone who has fought to make this day a reality."
- MDA published a YouTube program today: "Eteplirsen is Granted Accelerated Approval in US," hosted by Lou Kunkel, Ph.D. Professor of Pediatrics and Genetics, Harvard Medical School, Initial fellowship from MDA led to his discovery of dystrophin gene; highlight key researchers in field in support of approval.
- **CureSMA:**
 - CureSMA President Kenneth Hobby quotes in Xconomy press release "After New Data, FDA Bucks Advisory Panel, Approves Sarepta's Duchenne Drug." Mr. Hobby stated that "Whatever [the FDA does] there is going to set a precedent for other orphan therapeutics coming through," Hobby says. "It's going to have to be the benchmark for other diseases, like SMA."
- **Jett Foundation:**
 - Jett Foundation issues statement on website "Jett Foundation Celebrates Major Milestone in Fight Against Duchenne Muscular Dystrophy."
 - Christine McSherry, Founder Jett Foundation, quoted in statement "The FDA approval of a therapy that treats Duchenne is an event I once never imagined I would witness in Jett's lifetime," McSherry said. "Not only will eteplirsen's approval change the way every mom and dad reacts when they hear their child's diagnosis, it gives hope to an entire generation of children that they too may have the opportunity to live a fuller and more normal life, a life where they can be just like their peers for a little while longer. However, the weeks, months and years of unnecessary and burdensome regulatory barriers that eteplirsen faced came at a massive, and unacceptable, human cost to the Duchenne patient community."
 - Jett Foundation posted FDA press release.

- **National Center for Health Research (NCHR):**

- NCHR posted *Washington Post* article on their website "[FDA grants accelerated approval to controversial muscular dystrophy drug.](#)"
 - Diana Zuckerman, NCHR President, quoted as saying "If this drug can be approved under those conditions, is there any drug that FDA won't approve?" said Diana Zuckerman, president of the National Center for Health Research, a nonprofit research organization. "This drug was based on the strong lobbying of patients and the company, and time will tell whether it will really help these boys or not, and that has always been the question."

Key Patient Advocacy Reactions in Media

- National Center for Health Research's Diana Zuckerman quoted in *Washington Post* article "[FDA grants accelerated approval to controversial muscular dystrophy drug.](#)"
- Cure Duchenne, Fight DMD, and Charley's Fund, featured in *Forbes* article "[Now That FDA Has Approved Muscular Dystrophy Drug Against Advisors' Recommendation, What's Next?](#)"
- Jenn McNary of Jett Foundation quoted in NBC News article "[FDA Approves Controversial Muscular Dystrophy Drug](#)" saying "I can hardly breathe," Jenn McNary, mother of two boys with muscular dystrophy in Saxtons River, Vermont, said by email. "This is what success feels like. I can't wait to hug the boys."

From: [Smith, Fallon](#)
To: [Califf, Robert](#); [Sherman, Rachel](#); [Kraus, Tom](#); [Sharp, Jeremy](#); [Cristinzio, Dayle](#); [Bolek, Michelle](#); [Shreeve, Chris](#); [Rawlings, Kimberly](#); [Woodcock, Janet](#); [Throckmorton, Douglas C](#); [Conover, Katie](#); [Young, Jason](#); [Rebello, Heidi](#); [Rodriguez, Jennifer](#); [Walsh, Sandy](#); [Kotz, Deborah](#); [Marchand, Heidi](#); [Quinn, Kathleen](#); [Scott, Meghan](#)
Subject: RE: Eteplirsen Coverage: BioPharma Dive and Regulatory Focus
Date: Monday, September 19, 2016 11:44:52 AM
Attachments: [image001.png](#)

BioPharma: Sarepta skyrockets as FDA approves DMD drug

By: Ned Pagliarulo and Lisa LaMotta

Dive Brief:

Sarepta Therapeutics on Monday won conditional approval from the Food and Drug Administration for its Duchenne muscular dystrophy (DMD) treatment, after a months-long delay left the company and DMD patients in regulatory limbo.

Sarepta will be required to carry out a clinical trial to confirm the drug's clinical benefit, and the Food and Drug Administration made clear a failure to verify efficacy could lead the regulator to withdraw approval for the treatment.

Shares in Sarepta skyrocketed by over 90% at one point Monday morning, as the FDA's decision resolved a long-standing question of whether the company would be sent back to the drawing board. The drug, now known as Exondys 51 (eteplirsen), is the first approved treatment for DMD.

Dive Insight:

The FDA has signed off on approval of Sarepta's DMD drug after several years of back and forth with the community. While the drug did pass muster for a conditional approval, the decision is a contentious one. Regulators had been originally expected to make a decision on the drug in May.

Advocates for the community have been particularly outspoken and criticized the FDA for passing over drugs from several other companies, including PTC Therapeutics and BioMarin. An advisory committee to the FDA voted against approval of eteplirsen earlier this year, raising further ire from the community.

The regulatory agency and its experts have long claimed that while the unmet need is very high in this case, the drug candidates in development have not shown strong efficacy.

DMD is a genetic disease that affects young boys, many of which die before reaching adulthood. The disease is characterized by muscle wasting and most of these boys lose the ability to walk and eventually succumb to respiratory failure. Advocacy groups — composed largely of parents of the children — have been major supporters of DMD developers and clinical trials seeking to test disease-modifying drugs.

Several companies have pulled out of the space after the FDA made clear there was no path forward for approval for their drugs. BioMarin was forced to announced this spring that it would end pursuit of approval of its drug, Kyndrisa (drisapersen).

###

RAPS: Sarepta Wins Controversial FDA Approval for First DMD Drug

By: Zachary Brennan

The US Food and Drug Administration (FDA) on Monday approved Sarepta Therapeutics' first drug to treat patients with Duchenne muscular dystrophy (DMD), a rare genetic disorder that causes progressive muscle deterioration and weakness in young children.

The approval is highly controversial after a FDA advisory committee voted against approval in April as the outside experts said there was not substantial evidence that the drug is effective in providing clinical benefit, which is the standard for traditional approval. Before that vote and afterwards, the DMD patient community protested vigorously.

DMD, occurring in about one out of every 3,600 male infants worldwide, is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. The first symptoms are usually seen between the ages of three and five, and worsen over time.

The agency said that following the hearing, Sarepta submitted additional data "showing substantial evidence of dystrophin production, although the amount of dystrophin produced was only a small fraction of the normal level."

The injection, known as Exondys 51 (eteplirsen), is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, who constitute approximately 13 percent of the population with DMD.

Ultimately, the new injection, known as Exondys 51, was approved under FDA's accelerated approval program, reserved for drugs to treat serious or life-threatening diseases, and where there is a lack of available therapy.

"Based on the data submitted by the applicant, the Agency has concluded that there is a statistically significant increase in dystrophin production in indicated patients who are exposed to the drug that meets this requirement," FDA said Monday.

That approval followed a contentious scientific disagreement among FDA, with some saying the "statistically significant increase in dystrophin, the surrogate endpoint, of an exceptionally small magnitude does not imply clinical benefit," according to the 126-page approval letter.

Moving forward, FDA said it is requiring Sarepta (company's stock increased in value by more than 80% as of Monday morning and the company also won a rare pediatric priority review voucher as a result of the approval) to conduct a clinical trial to show that the drug preserves motor function, with eteplirsen being compared to placebo.

The required study is designed to assess whether Exondys 51 improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. If the trial

fails to verify clinical benefit, FDA said it “may initiate proceedings to withdraw approval of the drug.

“In this case, flexibility is warranted because of the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a life-limiting disease of children. These factors, combined with the dystrophin production data – and the drug’s low risk profile – led the Agency to approve the drug under the accelerated approval pathway,” FDA said.

Fallon Smith

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-8632
Fallon.Smith@fda.hhs.gov



From: [Conover, Katie](#)
To: [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Sharp, Jeremy](#); [Kraus, Tom](#)
Cc: [Quinn, Kathleen](#); [Rodriguez, Jennifer](#); [Walsh, Sandy](#)
Subject: Updated DMD social media numbers
Date: Tuesday, September 20, 2016 11:02:17 AM
Attachments: [DMD social media report 9 20.doc](#)
[image011.png](#)

Hello all –

An updated social media report for yesterday’s announcement (as of 9 am today)

Katie and team

Katie Conover

Acting Associate Commissioner

Office of External Affairs

U.S. Food and Drug Administration

Tel: 240-402-2402 / Cell: 301-512-9120

priscilla.conover@fda.hhs.gov



DMD Social Media 9/20 A.M. Report

25M+ reach for topic (FDA/DMD) on Twitter

Key Insights Duchenna (DMD) Sep 16, 2016 - Sep 20, 2016

Total Mentions

4431

Previous Period: 983

▲ 351%

Unique Authors

2832

Previous Period: 549

▲ 416%

Trending Topics

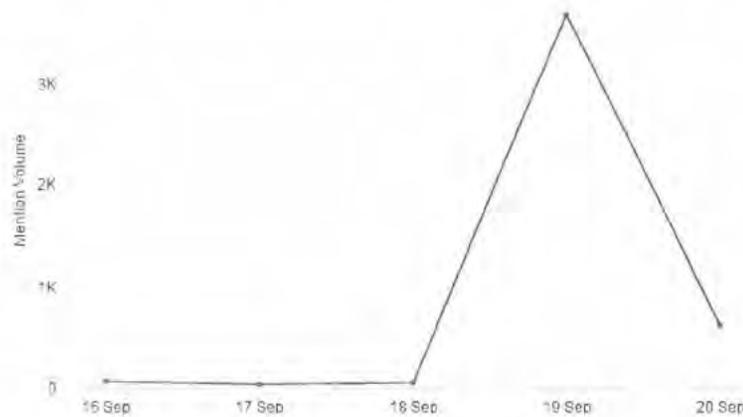
- 1 Sarepta Therapeutics' Exondys 51
- 2 approved a controversial
- 3 FDA approves Sarepta's Duchenne drug

Top News Stories

- 1 Isle of Capri, GM and Halliburton climb
- 2 Reuters Health News Summary
- 3 Business Highlights

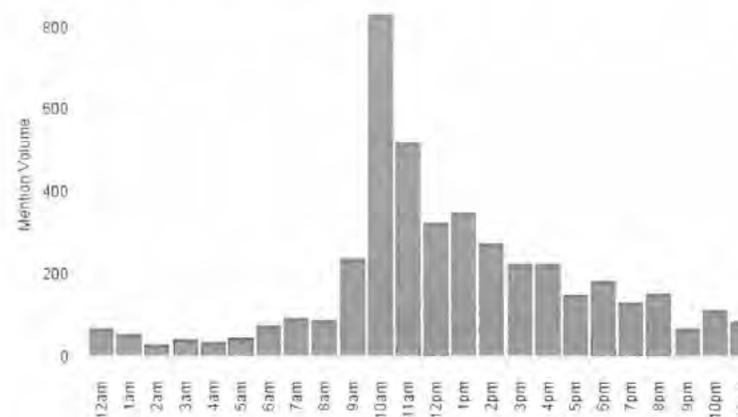
Mentions Over Time by Day

Duchenna (DMD) Sep 16, 2016 - Sep 20, 2016



Mentions by Hour of Day

Duchenna (DMD) Sep 16, 2016 - Sep 20, 2016



Twitter Insights Duchenna (DMD) Sep 16, 2016 - Sep 20, 2016

Top Stories	TWEETS	RETWEETS	ALL TWEETS	IMPRESSIONS	Top Hashtags	TWEETS	RETWEETS	ALL TWEETS	IMPRESSIONS
fda.gov/NewsEvents/Newsroom	96	109	205	642402	#duchenna	75	158	233	610195
fda.gov/NewsEvents/Newsroom	58	105	163	546595	#dmd	97	102	199	835894
reuters.com/article/us-sarepta-fd	149	0	149	541503	#fda	117	70	187	1087649
scientificamerican.com/article/fd	43	86	129	3989073	#eteplisen	70	104	174	677054
statnews.com/pharmalot/2016/0	48	73	121	624137	#sarepta	100	36	136	369678
accessdata.fda.gov/drugsatfda_	18	94	112	943512	#pharma	28	67	95	659703
cnbc.com/2016/09/19/sarepta-th	85	2	87	315545	#health	53	1	54	242579
bloomberg.com/news/articles/20	65	16	81	241147	#biotech	40	11	51	174725
webmd.com/children/news/2016	71	5	76	563827	#news	46	3	49	172660
statnews.com/pharmalot/2016/0	23	21	44	158628	#muscular/strophy	18	23	41	651109

Top Tweeters

Duchenne (DMD) Sep 16, 2016 - Sep 20, 2016

USERNAME FOLLOWERS

FT Financial Times (@FinancialTimes)	5360296
CNBC (@CNBC)	2422065
SA Scientific American (@SciAm)	1675271
BI Business Insider (@BusinessInsider)	1635460
WebMD (@WebMD)	1333200
ABC News (@ABCNews)	1163010
Clay Matthe... (@ClayMatthe...	994064
NYT Health (@NYTHealth)	941163
WSJ Health (@WSJHealth)	555682
The Boston (@TheBoston)	527092

FT Financial Times @FinancialTimes
 Headlines from the FT Follow us on @FT for news stories features and updates. Our customer service team is @FTcare.
 Follow @FinancialTimes

Location Greater London, United Kingdom

Latest mention of: Duchenne (DMD)

Financial Times @FinancialTimes
 Sarepta shares surge 90% on FDA approval on ft.com/2cLhRdJ

Top News Authors

Duchenne (DMD) Sep 16, 2016 - Sep 20, 2016

AUTHOR NAME SITE

Reuters	www.dailymail.co.uk
Associated Press	www.dailymail.co.uk
Rachel Wong	www.smh.com.au
Chronicle News Services	www.sfgate.com
newsfeeds@nzherald.co.nz	www.nzherald.co.nz
By The Associated Press	www.chron.com
Rachel Wong	www.theage.com.au
newsfeedback@fool.com (Todd Campbell)	www.fool.com
Associated Press	www.bostonherald.com
Todd Campbell	www.foxbusiness.com
Total for top authors	

Columns

MENTIONS IMPACT

MENTIONS TOTAL

2	64
4	64
1	60
1	59
3	59
1	58
1	58
2	58
1	56
1	56
17	

DMD Social Media 9/19 P.M. report

15M+ reach for topic (FDA/DMD) on Twitter

Key Insights Duchenne (DMD) Sep 19, 2016

Total Mentions: 1066
 Unique Authors: 761

Trending Topics

- How to treat Duchenne muscular dystrophy
- real life issues in genetic counseling
- Sarepta drug

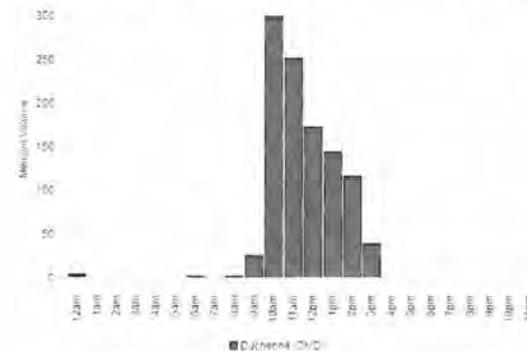
Top News Stories

- FDA tentatively approves 1st drug for
- Twitter to lay off some employees as it
- BRCA1 mutation associated with lung cancer

Mentions Over Time by Day
 Duchenne (DMD) Sep 19, 2016



Mentions by Hour of Day Duchenne (DMD) Sep 19, 2016



DMD Social Meida 9/19 A.M. report

14M+ reach for topic (FDA/DMD) on Twitter

Total Mentions up 7550%

Unique Authors up 6786%

Key Insights Duchenne (DMD) Sep 19, 2016

Filters

Total Mentions

612

▲ 7550%
Previous Period: 6

Unique Authors

482

▲ 6786%
Previous Period: 7

Trending Topics

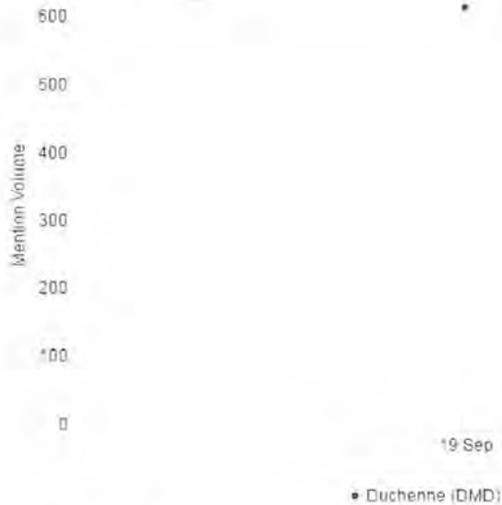
1. Duchenne Muscular Dystrophy drug
2. Sarepta's keenly watched muscle
3. 13 percent

Top News Stories

1. FDA grants accelerated approval to con
2. BRIEF-Monte dei Paschi ends session
3. Phone game Pokemon GO distracts dri

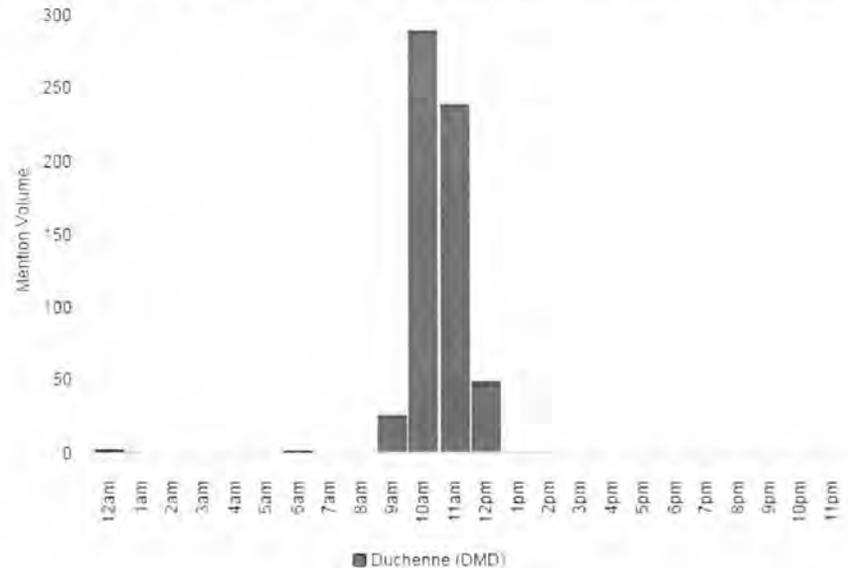
Mentions Over Time by Day

Duchenne (DMD) Sep 19, 2016



Mentions by Hour of Day

Duchenne (DMD) Sep 19, 2016



Tweets from the Hill



Dan Donovan RepDanDonovan Em

Happy to hear @US_FDA approved #DuchenneMuscularDystrophy treatment!
@PietrosFight



Rep. Erik Paulsen RepErikPaulsen Em

Glad @US_FDA approved first drug treatment for Duchenne muscular dystrophy. I sent them letter in July urging an expedited approval process

Additional Tweets of Note

The Boston Globe @BostonGlobe 13 minutes ago

As condition of FDA's approval of Sarepta drug, company will conduct two-year randomized controlled trial bos.gl/XLARdII

Kimberly Leonard @leonardkl 2h2 hours ago

FDA has fast-tracked a drug to treat Duchenne muscular dystrophy: [http://www.usnews.com/news/articles/2016-09-19/fda-fast-tracks-drug-for-duchenne-muscular-dystrophy?src=usn_tw ...](http://www.usnews.com/news/articles/2016-09-19/fda-fast-tracks-drug-for-duchenne-muscular-dystrophy?src=usn_tw...) #DMD

Medscape @Medscape 1h1 hour ago

NEWS ALERT: FDA grants accelerated approval for eteplirsen, first drug approved for DMD patients.

Forbes @Forbes 38 minutes ago

Sarepta has won a long-sought-after approval for its drug to treat DMD, but with a catch: on.forbes.com/6015B7d0F <https://t.co/MXz1gxzC3O>

Laura Helbling @Laura_H 2m2 minutes ago

Per Sarepta **eteplirsen** summary review, Commissioner Califf deferred to CDER Director Woodcock's judgment. - http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf ...

C. Michael Gibson MD @CMichaelGibson 7m7 minutes ago

Wow #Eteplirsen approved by FDA http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/206488Orig1s000ltr.pdf ...

Adam Feuerstein Verified account @adamfeuerstein 14m14 minutes ago

And there it is.... \$SRPT **eteplirsen** approved. FDA letter → http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/206488Orig1s000ltr.pdf ...

Donna Young @DonnaYoungDC 8m8 minutes ago

Donna Young Retweeted Donna Young
#FDA PR & letter for \$SRPT **eteplirsen** <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm> ...
http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/206488Orig1s000ltr.pdf ... #Duchenne #DMD #biotech

Michael McCaughan @BPMReporterMike 12m12 minutes ago

Eteplirsen approval letter signed by CDER Director Woodcock. Decision was appealed to Califf, who deferred to Woodcock. Unger appealed.

David Maizenberg @biologypartners 43s44 seconds ago

FDA approves Sarepta's **Eteplirsen**. Stock skyrockets. DMD families celebrate. Statisticians frown. Many essays will b written about this saga

Marilynn Marchione Verified account @MMarchioneAP 1m17 minute ago

A win for rare disease advocates: #FDA approves 1st Duchenne #muscular dystrophy drug, \$SRPT Sarepta's **eteplirsen** <http://tinyurl.com/zboal5z>

Kim McCleary @KimTweetsDC 10m19 minutes ago

#FDA will require #Sarepta to conduct addl study to confirm clinical benefit of **#eteplirsen**.

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm> ... #Duchenne #DMD

From: [Conover, Katie](#)
To: [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#); [Sherman, Rachel](#)
Cc: [Young, Jason](#); [Rodriguez, Jennifer](#); [Kraus, Tom](#)
Subject: RE: Annals of Neurology & An Eteplirsen Question
Date: Thursday, September 22, 2016 5:36:22 PM
Attachments: [image001.png](#)

To clarify – In the memos, while you don't literally call for a retraction, you do note that the data in the study was misleading and has not been retracted -- and Dr. Califf, you note that a dialogue that may lead to correction or retraction would be appropriate... The story has been picked up by RetractionWatch (blog), STAT and BioCentury (picked up by SeekingAlpha).

Katie

From: Conover, Katie
Sent: Thursday, September 22, 2016 5:32 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Young, Jason; Rodriguez, Jennifer; Kraus, Tom
Subject: Annals of Neurology & An Eteplirsen Question

Hello –

Flagging a question which has come from some STAT reporting today. While they did not contact us, they did quote directly from Dr. Califf and Dr. Borio's eteplirsen decisional memos.

<https://www.statnews.com/pharmalot/2016/09/22/fda-sarepta-duchenne-study-retraction/>

Dr. Califf and Dr. Borio both mention seeking a retraction of a misleading published article about eteplirsen in the Annals of Neurology from 2013. In Dr. Califf's DMD decisional memo, he does say that the Annals article was touted by the company and it greatly overstated the degree of protein expression. He said that "blinded experts assembled by the FDA fundamentally debunked this study, which has yet to be retracted and continues to be cited." In a footnote on page 10 of the posted documents, Dr. Califf says "In view of the scientific deficiencies identified in this analysis, I believe it would be appropriate to initiate a dialogue that would lead to a formal correction or retraction of the published report."

Stat reports that the journal editor has said, *"It takes more than a call by a politician for retraction of a paper. It takes actual evidence. It is the policy of Annals of Neurology, and every other responsible journal, to consider scientific evidence that one of its papers may be inaccurate. "If the FDA commissioner has, or knows of someone who has, evidence for an error in a paper published in Annals of Neurology, I encourage him to send that evidence to me and a copy to the authors of the article, for their reply. At that point we will engage in a scientific review of the evidence and make appropriate responses."*

The question now is whether Dr. Califf and/or Dr. Borio want to initiate a discussion with the Annals of Neurology since both of them mentioned a retraction of that study in their memos?

While we have no open media inquiries, we may be asked if that is happening.

Let us know your thoughts.

Best,

Katie and team

Katie Conover

Acting Associate Commissioner

Office of External Affairs

U.S. Food and Drug Administration

Tel: 240-402-2402 / Cell: 301-512-9120

priscilla.conover@fda.hhs.gov



From: [Evans, Dana](#)
To: [Califf, Robert](#)
Cc: [Palmer, Kelly](#)
Subject: Rose/Pink
Date: Thursday, September 22, 2016 9:57:51 AM
Attachments: [Rose Sheet Today's News Analysis.msg](#)
[Pink Sheet Today's News Analysis.msg](#)

Dr. Califf,

I've also printed these down for your review.

Thank you,

Dana

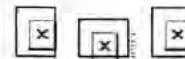
Smith, Celeste

From: Pink Sheet <info@pharmamedtechbi.net>
Sent: Thursday, September 22, 2016 6:17 AM
To: Commissioner FDA
Subject: Pink Sheet | Today's News & Analysis

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House Oversight Committee's diatribe against Mylan has been fueled by the company's efforts to engage lawmakers to advance its business...

ANALYSIS

EpiPen Generics: Woodcock Explains Injector Studies

In response to Congressional questions about whether FDA is a barrier to competition for the epinephrine product, CDER Director lays...

NEWS

China Regulatory Watch: New Fast-Track Designations, CTAs

China Regulatory Watch is our new snapshot of product-specific regulatory developments at the China FDA.



ANALYSIS

Formalizing 'Name And Shame': New Strategy To Rein In Price Increases

A bipartisan bill would require pharmaceutical manufacturers to provide notice and justification of any price increase over 10%. That formula...

ANALYSIS

Alzheimer's Drugs and Medicare: A Case For Pre-Approval Discussions

Medicare's Part D plan bidding schedule and uncertainty over the Alzheimer's drug pipeline is putting plan sponsors in a difficult...

ANALYSIS

Eteplirsen Review Offers Lessons For FDA, Advocacy Groups, Industry

Agency reviewers believed the line between patient input and external intimidation had been crossed; early data from the Sarepta muscular...

ANALYSIS

FDA's Beleaguered Criminal Investigations Unit Now Facing Congressional Scrutiny

After staff complain about becoming the 'Botox police,' a House committee is asking FDA for an update on two previous...

NEWS

€20m Action Tackles Poor Uptake Of Joint HTAs Across Europe; Commission Consultation Nears

Europe's EUnetHTA collaboration is working on producing a raft of new joint HTA reports for drug and medical device developers...

NEWS

UN Countries Make Bold Pledges On AMR, Including Funding For R&D Into New Drugs and Diagnostics

During the high-level UN meeting on Sept. 21, all 193 member countries will sign a declaration in which they pledge...

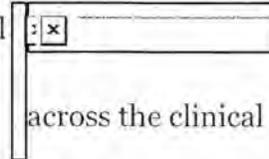
NEWS

Sarepta Wins Exon 51 Composition Patent Rights Over BioMarin

Patent Trial and Appeal Board rules against BioMarin in proceeding to determine who has rights to a composition of matter...

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From: [Evans, Dana](#)
To: [Califf, Robert](#); [Palmer, Kelly](#)
Cc: [Branch, Christina](#)
Subject: RE: Pink Sheet | Today's News & Analysis
Date: Thursday, September 22, 2016 2:00:01 PM

Hi Dr. Califf,

Will do!

Dana Evans, M.P.H.

Program Support Specialist to the Commissioner
Office of the Commissioner Immediate Office
U.S. Food and Drug Administration
Phone: 301-796-2021
BB: 301-467-8987
Email: dana.evans@fda.hhs.gov

From: Califf, Robert
Sent: Thursday, September 22, 2016 7:53 AM
To: Palmer, Kelly
Cc: Evans, Dana; Branch, Christina
Subject: FW: Pink Sheet | Today's News & Analysis

I'm just realizing that I used to get the all the sheets (pink , gray, etc.). can you make sure they start coming to me again?

Thx

rmc

From: Kux, Leslie
Sent: Wednesday, September 21, 2016 8:02 AM
To: Sharp, Jeremy; Califf, Robert
Cc: Kraus, Tom
Subject: FW: Pink Sheet | Today's News & Analysis

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Cancer Trial Endpoints: Minimal Residual Disease Eyed As Surrogate

More work needs to be done to validate MRD as predictive of clinical outcomes in hematological malignancies before it can...

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Merck KGaA Previews Cladribine Regulatory Revival Story At ECTRIMS

With the EMA's review of the latest MAA for cladribine ongoing, Merck KGaA uses ECTRIMS 2016 to showcase longer-term efficacy...

NEWS

Liquid Dosing Accuracy Four-Times Better With Oral Syringes – Study

Pediatric OTC and Rx dosage errors reach 43% for parents using a dosing cup but 16.7% with a 0.2 mL...

NEWS

Tom's Of Maine Ingredients' Efficacy Weighed Against 'Natural' Claim In NAD Review

Tom's of Maine's Naturally Dry Antiperspirant complies with FDA requirement that antiperspirants contain an aluminum salt-based active ingredient, but NAD...

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From: [Palmer, Kelly](#)
To: [Califf, Robert](#)
Cc: [Evans, Dana](#); [Branch, Christina](#)
Subject: RE: Pink Sheet | Today's News & Analysis
Date: Thursday, September 22, 2016 2:03:40 PM

I signed you up for the Pink and Rose Sheets. Apparently as of July 11, The Pink Sheet will subsume the content of the Pink Sheet Daily, Gold, RPM, and Tan Sheets. Let me know if it works! I set up your account as:

(b) (6)
[REDACTED]

From: Califf, Robert
Sent: Thursday, September 22, 2016 7:53 AM
To: Palmer, Kelly
Cc: Evans, Dana; Branch, Christina
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FDAOC0002329

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FDAOC0002331

From: [Misia Landau](#)
To: [Califf, Robert](#)
Subject: Re: Note for Dr. Califf—please forward
Date: Saturday, September 24, 2016 3:55:54 PM

Thank you so much. You've been playing that kind of sport for so long and so well--and yes, it's an amazing mission!

A wonderful weekend to you.

Misia

> On Sep 24, 2016, at 8:11 AM, Califf, Robert <RMC1@fda.hhs.gov> wrote:

>

> Misia,

>

> Thanks for your kind note. FDA Commissioner is a contact sport, but the mission is fantastic.

>

> Have a great weekend.

>

> rmc

>

> Robert M Califf MD

> Commissioner of Food and Drugs

>

>

> -----Original Message-----

> From: Pennington, Caitlin

> Sent: Wednesday, September 21, 2016 12:45 PM

> To: Califf, Robert

> Subject: FW: Note for Dr. Califf—please forward

>

> Hi Dr. Califf,

>

> Please see the below note.

>

> Thanks!

>

> Caitlin

>

> -----Original Message-----

> From: Misia Landau [[\(b\) \(6\) \(b\) \(6\)](mailto:(b) (6) (b) (6))]

> Sent: Wednesday, September 21, 2016 12:08 PM

> To: Rebello, Heidi

> Subject: Note for Dr. Califf—please forward

>

> Dear Dr. Califf,

>

> Thank you for taking the time during your extremely busy day to go back over the interview and make corrections (so sorry about the Holter monitors!). Also the photos are wonderful, thank you so much. My editor, Nader Rifai, loves the piece and was so impressed by the range and depth of our conversation. I think it's clear to him—as it will be to many readers—why you are where you are.

>

> I also wanted to say that yesterday I opened my local paper, The Boston Globe, and there on the front page was an

article about the FDA decision on the Sarepta drug. I felt a connection to the process that I would not have experienced prior to speaking with you. I was reminded of the last thing you said, about the Teddy Roosevelt speech. It brought home to me the real challenges that you face every day. I have no doubt that the FDA decision was based on a careful consideration of the evidence but for me, as for many others I'm sure, it also seemed to show heart: it brought to light the ethical aspects of all that you do.

>

> With warm wishes and appreciation,

>

> Misia

From: [Conover, Katie](#)
To: [McCall, Jonathan *](#); [Sherman, Rachel](#); [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#)
Cc: [Rodriguez, Jennifer](#); [Young, Jason](#); [Kraus, Tom](#); [Quinn, Kathleen](#)
Subject: RE: Annals of Neurology & An Eteplirsen Question
Date: Friday, September 23, 2016 9:07:02 AM

+ Kathleen.

From: McCall, Jonathan *
Sent: Friday, September 23, 2016 8:45 AM
To: Sherman, Rachel; Conover, Katie; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: Rodriguez, Jennifer; Young, Jason; Kraus, Tom
Subject: RE: Annals of Neurology & An Eteplirsen Question

Hello all –

I'm afraid I don't have any specific information as to what kind of action is in contemplation, although Rachel's thought below seems likely. The journal editor's specific remarks are quoted below in the excerpt from the STAT news report.

Best,

--

Jonathan

From: Sherman, Rachel
Sent: Thursday, September 22, 2016 6:07 PM
To: Conover, Katie; Califf, Robert; Dickinson, Elizabeth (FDA)
Cc: McCall, Jonathan *; Rodriguez, Jennifer; Young, Jason; Kraus, Tom
Subject: RE: Annals of Neurology & An Eteplirsen Question

Hi,

Truthfully I am not sure what Rob had in mind (I thought an email to the editor perhaps) but it might be a good idea to ask him tomorrow am.

I am copying Jonathan who has been follow this exchange and may have comments. Apparently the editor had particular words in response to this part of the memo.

Rachel

From: Conover, Katie <Priscilla.Conover@fda.hhs.gov>
Date: September 22, 2016 at 5:36:22 PM EDT

FDAOC0002334

To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>, Califf, Robert <RMC1@fda.hhs.gov>
Cc: Kraus, Tom <Tom.Kraus@fda.hhs.gov>, Young, Jason <Jason.Young@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>
Subject: RE: Annals of Neurology & An Eteplirsen Question

To clarify – In the memos, while you don't literally call for a retraction, you do note that the data in the study was misleading and has not been retracted -- and Dr. Califf, you note that a dialogue that may lead to correction or retraction would be appropriate... The story has been picked up by RetractionWatch (blog), STAT and BioCentury (picked up by SeekingAlpha).

Katie

From: Conover, Katie
Sent: Thursday, September 22, 2016 5:32 PM
To: Califf, Robert; Dickinson, Elizabeth (FDA); Sherman, Rachel
Cc: Young, Jason; Rodriguez, Jennifer; Kraus, Tom
Subject: Annals of Neurology & An Eteplirsen Question

Hello –

Flagging a question which has come from some STAT reporting today. While they did not contact us, they did quote directly from Dr. Califf and Dr. Borio's eteplirsen decisional memos.

<https://www.statnews.com/pharmalot/2016/09/22/fda-sarepta-duchenne-study-retraction/>

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The question now is whether Dr. Califf and/or Dr. Borio want to initiate a discussion with the Annals of Neurology since both of them mentioned a retraction of that study in their memos?

While we have no open media inquiries, we may be asked if that is happening.

Let us know your thoughts.

Best,

Katie and team

Katie Conover

Acting Associate Commissioner

Office of External Affairs

U.S. Food and Drug Administration

Tel: 240-402-2402 / Cell: 301-512-9120

priscilla.conover@fda.hhs.gov



From: [Sherman, Rachel](#)
To: [Califf, Robert](#)
Subject: RE: Congratulations
Date: Friday, September 23, 2016 9:10:00 PM

Ouch! I had to grovel Thursday am.

Nov 4th is not on my calendar but Cole is a reasonable person (except that he thinks I talk fast).

Want me to handle or refer?

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 23, 2016 at 7:50:47 PM EDT
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: RE: Congratulations

You and Ellen--it's a FOIC event?

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Friday, September 23, 2016 4:38 PM
To: Califf, Robert
Subject: Fwd: Congratulations

Who do I send him to?

From: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Date: September 23, 2016 at 4:35:53 PM EDT
To: Cole Werble <Cole.Werble@previsionpolicy.com>
Subject: Re: Congratulations

Hi,

Thanks and Rob is always thoughtful and nicely expressed!

He has a team that thinks about his discussions. Let me check and see who is the most

appropriate contact.

Best,
Rachel

From: Cole Werble <Cole.Werble@previsionpolicy.com>

Date: September 23, 2016 at 4:05:17 PM EDT

To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>

Subject: Congratulations

Congratulations on the new title; I assume the post and responsibilities are about the same as pre-title. Did I sense some counsel or ghost-writing from you on the *Exondys 51* scientific dispute resolution. Califf's part of that impressive package was thoughtful and nicely expressed.

I had been meaning to write. I will be introducing Califf at our meeting co-sponsored with Friends of Cancer Research on Nov. 4 and moderating an hour session with the center directors, Woodcock and Marks. I was going to ask for your help with some themes.

One idea that I would like to suggest to Califf as a potential topic would be some reflections on the old adage (frequently attributed to Kissinger) on the vehemence of academic politics because of the lack of stakes involved. I thought it might be interesting for the commissioner to reflect on the difference between his experience with academic politics and inter and intra-agency politics. I noticed he referred to the topic yesterday in some comments to a workshop on cardiovascular toxicity trials in oncology. If you think that is an interesting angle, could you point me to the right person around Califf to whom to suggest it?

Congrats again.

Cole

From: "Rachel.Sherman@fda.hhs.gov" <Rachel.Sherman@fda.hhs.gov>

Date: Tuesday, May 3, 2016 at 1:50 PM

To: Cole Werble <Cole.Werble@previsionpolicy.com>

Subject: RE: Glad to see you are writing/working on "EvGen"

Thanks Cole!

From: Cole Werble [<mailto:Cole.Werble@previsionpolicy.com>]

Sent: Tuesday, May 03, 2016 1:47 PM

To: Sherman, Rachel

Subject: Glad to see you are writing/working on "EvGen"

Rachel:

It is great that you are working on this topic; the short-form name seems very au courant. I hoped that would be one of your top assignments when returning to the agency. No policy is really more important in the long-run to the agency; you have the perfect background for taking it on.

Under a separate email, I am going to send two notes that I did over recent months from think tank discussions of the next steps in broadening the type of evidence that can be of use to the agency. I thought these were good practical suggestions by senior CDER people on the next steps: (1) looking at how Sentinel could help identify under-prescribing of blood thinners and (2) urging the drug companies to try to match data from some randomized controlled trials from real world evidence sources.

On the strange coincidences front, I think that Greenleaf is moving up the block in Georgetown to our office space: not just the same building; the actual offices that we now occupy. We are moving to a new suite (down to two choices) in the same area. We were part of a sublet on this space; the main tenant is letting it go.

I hope the return to the agency is going well.

Cole

Cole Werble
Prevision Policy, LLC

From: [Sherman, Rachel](#)
To: [Califf, Robert](#)
Subject: RE: Congratulations
Date: Sunday, September 25, 2016 8:19:20 AM

Okay, will do.

I'll try to speak slowly.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: September 25, 2016 at 8:17:17 AM EDT
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: RE: Congratulations

I think you should just talk with him.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Saturday, September 24, 2016 7:14 PM
To: Califf, Robert
Subject: RE: Congratulations

Okay, are you thinking or ignoring me?

Cole is reasonable and doesn't set people up. I've done several meetings with him – one was on promotion and first amendment; I basically filibustered (it was me and three lawyers, I had no choice). He was very gracious about it.

He thinks I talk fast – not sure why.

I can talk to him or send him to whomever you want. Just let me know.

From: Califf, Robert
Sent: Friday, September 23, 2016 7:51 PM
To: Sherman, Rachel
Subject: RE: Congratulations

You and Ellen==it's a FOQR event?

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Friday, September 23, 2016 4:38 PM
To: Califf, Robert
Subject: Fwd: Congratulations

Who do I send him to?

From: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Date: September 23, 2016 at 4:35:53 PM EDT
To: Cole Werble <Cole.Werble@previsionpolicy.com>
Subject: Re: Congratulations

Hi,

Thanks and Rob is always thoughtful and nicely expressed!

He has a team that thinks about his discussions. Let me check and see who is the most appropriate contact.

Best,
Rachel

From: Cole Werble <Cole.Werble@previsionpolicy.com>
Date: September 23, 2016 at 4:05:17 PM EDT
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: Congratulations

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Cole

Cole Werble
Prevision Policy, LLC

From: [Evans, Dana](#)
To: [Califf, Robert](#)
Subject: Reading Material
Date: Friday, September 30, 2016 7:43:22 AM
Attachments: [The FDA News Summary for Friday September 30 2016.msg](#)
[Center for Tobacco Products News Briefing for Friday September 30 2016.msg](#)
[HHS Secretary's News Briefing for Friday September 30 2016.msg](#)

Smith, Celeste

From: Bulletin Intelligence <FDA@BulletinIntelligence.com>
Sent: Friday, September 30, 2016 6:11 AM
To: FDA@bulletinintelligence.com
Subject: The FDA News Summary for Friday, September 30, 2016
Attachments: FDA160930.doc; FDA160930.pdf

This morning's FDA News Summary is attached.

Website: You can also read today's briefing, including searchable archive of past editions, at <http://FDA.BulletinIntelligence.com/>.

Full-text Links: Clicking the hypertext links in our write-ups will take you to the newspapers' original full-text articles.

Interactive Table of Contents: Clicking a page number on the table of contents page will take you directly to that story.

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NEWS BRIEFING

ONLINE VERSION AVAILABLE AT [HTTP://FDA.BULLETININTELLIGENCE.COM/](http://FDA.BULLETININTELLIGENCE.COM/)

TO: THE COMMISSIONER AND SENIOR OFFICIALS

DATE: FRIDAY, SEPTEMBER 30, 2016 6:00 AM EDT

TODAY'S EDITION

FDA In The News

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Medical Product Safety

CDC Concerned About Declining Flu Vaccination Rate,
Particularly Among The Elderly..... 1

Senate Majority Leader Says 21st Century Cures Bill Will Be A
"Top Priority" During Lame Duck Session..... 2

Kaiser Poll Finds 78% In US Want New Restrictions On
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FDA Places Hold On Experimental ADHD Drug..... 2

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Lupin Expects FDA Approvals For New Products From Goa
Facility In Two Months..... 2

Former US Senate Majority Leader Calls For Steps To Curb
Over-Prescription Of Opioids. 3

App For Diabetes Patients Expected To Generate "Predictive
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Food Safety

CDC Concludes Investigation Of Multistate E. Coli Outbreak
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FDA Issues Warning To Maker Of Stiff Bull Coffee Over
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Canadian Bakery Recalls Turkey, Chicken Products Due To
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FDA Credits Mexican Cilantro Monitoring Program With Drop In
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FDA IN THE NEWS

FDA Officials Question Priority Voucher Program.

Kaiser Health News (9/29, Tribble, 2K) reports that Sarepta Therapeutics received a rare pediatric disease priority review voucher upon approval of its Duchenne muscular dystrophy drug, eteplirsen. The voucher awards fast-track review of a drug and can be sold to other companies. In 2015, "a voucher sold for a record \$350 million when AbbVie Inc. bought one from United Therapeutics." However, Dr. John Jenkins, director of the office of new drugs in the FDA's Center for Drug Evaluation and Research, said the vouchers can raise safety concerns because they commit the agency to a fixed timeframe, even if the drug to be approved is complex. "We're not making pizza here," he said. According to FDA spokesperson Sandy Walsh, "FDA has not seen evidence that the program is effective" and it "adversely affects the agency's ability to set its public health priorities."

In a letter to the editor in the *Boston Globe* (9/30, 1.14M), Dr. Julie Kaufmann writes that "with the help of intense public and political pressure on the FDA over several months," Sarepta's DMD treatment got approval despite the

lack of evidence of its effectiveness and the quality of the design of the clinical trials meant to test the treatment. On the role the FDA plays in regulating drugs, she states that "our politicians and agencies abandoned this protection of the ill and vulnerable in favor of a misguided so-called public good, while a company's shares surge."

MEDICAL PRODUCT SAFETY

CDC Concerned About Declining Flu Vaccination Rate, Particularly Among The Elderly.

On its website, the *NPR* (9/29, Stein, 1.83M) "Shots" blog reports that Dr. Thomas Frieden, the director of the Centers for Disease Control and Prevention, is urging all Americans to obtain a flu shot as soon as possible. Frieden told reporters, "Flu is serious. Flu is unpredictable." Frieden is particularly concerned about a recent decline in the number of elderly people getting vaccinated.

On its website, *CNBC* (9/29, 2.52M) reports that over the past two flu seasons, the number of people age 50 to 64 getting vaccinated fell by 3.4% and the number of people age 65 and over getting vaccinated fell by 3.3%, according to the CDC. Frieden said, "Get a flu shot, no excuse not to get

Former US Senate Majority Leader Calls For Steps To Curb Over-Prescription Of Opioids.

In an opinion piece for Forbes (9/29, Frist, 14.92M), heart and lung transplant surgeon and former US Senate Majority Leader Bill Frist (R-TN) writes that each year, some 27,000 US infants are diagnosed with Neonatal Abstinence Syndrome (NAS). The condition has quadrupled "nationally from 1.5 per 1,000 hospital births in 1999 to 6.0 in 2013." In certain states, "such as Vermont, West Virginia, and Maine, children are twice as likely to be born with NAS than autism." Frist calls for steps "to curb over-prescription of opioids," including convincing "states, insurers, and providers of the importance of making a front-end investment to tackle opioid addiction." National Institute of Drug Abuse statistics reveal that "every dollar invested in addiction treatment programs yields a return of between \$4 and \$7 in reduced drug-related crime, criminal justice costs, and theft. When savings related to healthcare are included, total savings can exceed costs by a ratio of 12 to 1."

App For Diabetes Patients Expected To Generate "Predictive Insights."

In more reporting on the FDA's approval of Medtronic's artificial pancreas system, MobiHealthNews (9/29, Comstock, 1K) reports that a related app, Sugar. IQ, is ready to begin field-testing with some 100 diabetes patients. The app integrates data from Medtronic's MiniMed Connect and an upcoming, related app. Then, "as users record data about what they eat, when they use insulin, and their blood glucose levels, [IBM] Watson machine learning generates predictive insights. So if a user enters tuna salad in the log, the app might respond with an observation that four of the last five times they ate tuna salad, their blood glucose ended up going low." The app will need FDA "clearance," the report points out.

FOOD SAFETY

CDC Concludes Investigation Of Multistate E. Coli Outbreak Linked To Flour.

Reuters (9/29, Ajmera) reports the Centers for Disease Control and Prevention announced on Thursday that it had completed an investigation of a multistate E. coli outbreak "linked to flour produced at a General Mills Inc plant in Kansas City, Missouri." The CDC released a report (9/29, 315K) on the outbreak that affected 63 people in 24 states, but officials said that more cases are expected because flour products have long shelf lives. Food Safety News (9/30, 4K) provides coverage.

FDA Issues Warning To Maker Of Stiff Bull Coffee Over Unlisted Ingredient.

Fox News (9/29,

10.99M) reports that the Food and Drug Administration issued a warning to Stiff Bull Coffee for including desmethyl carbodenafil as an unlisted ingredient. According to Fox News, desmethyl carbodenafil is similar to sildenafil and "can have adverse interactions when consumed with nitrates." Stiff Bull "has since disputed the FDA's claim, saying that there was a mix-up of ingredients."

Canadian Bakery Recalls Turkey, Chicken Products Due To Listeria Contamination.

Food Safety News (9/29, 4K) reports sliced turkey and chicken products sold at a Canadian bakery have been connected to at least one illness as the result of a possible Listeria monocytogenes contamination. As a result, Tre Rose Bakery is recalling the products, as the Canadian Food Inspection Agency (CFIA) conducts a food safety investigation/

FDA Credits Mexican Cilantro Monitoring Program With Drop In Cyclospora Cases.

Food Safety News (9/30, 4K) reports the Food and Drug Administration is crediting its Mexican cilantro monitoring program with "a drop in domestically acquired Cyclospora cayetanensis infections." According to data from the Centers for Disease Control and Prevention, there were 134 confirmed cases of cyclosporiasis "with illness onset on or after May 1, compared with 319 for the same period last year."

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Smith, Celeste

From: CTP-Editors-BulletinNews
Sent: Friday, September 30, 2016 6:05 AM
To: CTP-Editors-BulletinNews
Subject: Center for Tobacco Products News Briefing for Friday, September 30, 2016

Mobile version and searchable archives available at ctp.bulletinintelligence.com.



DATE: FRIDAY, SEPTEMBER 30, 2016 6:00 AM EDT

TODAY'S EDITION

TOBACCO POLICY NEWS

- Health Organizations Form Coalition To Push Indiana Legislature To Raise Tobacco Taxes
- Lehigh Valley, Pennsylvania Vape Shops Brace For 40 Percent Wholesale Tax
- Campaign To Increase Tobacco Purchase Age To 21 Finds Success In 200 Counties, Municipalities

TOBACCO INDUSTRY NEWS

- PMI Feature: Philip Morris Expects \$1.2 Billion Boost From Cigarette Alternative

INTERNATIONAL NEWS

- Commentary Criticizes Tobacco Industry's Campaign Against Mandated Cigarette Plain Packaging In Canada

TOBACCO POLICY NEWS

Health Organizations Form Coalition To Push Indiana Legislature To Raise Tobacco Taxes.

The [Indianapolis Business Journal](#) (9/29, Russell, 80K) reports "the Indiana Hospital Association, the Indiana Chamber of Commerce, the Indiana State Medical Association, the Indiana University School of Public Health," and others have formed a coalition to lobby the Indiana General Assembly to raise taxes on cigarette packs "by at least \$1.50 each, raise the legal age of smoking from 18 to 21, and repeal the smoker's bill of rights." Indiana Hospital Association chair Bryan Mills said, "The healthiness of our state just keeps getting worse and worse," and advocates are combating smoking rates as a means of driving down the state's rising healthcare costs.

Lehigh Valley, Pennsylvania Vape Shops Brace For 40 Percent Wholesale Tax.

The [Allentown \(PA\) Morning Call](#) (9/29, Kraus, 307K) reports vape shop owners in Lehigh Valley, Pennsylvania are bracing for the state's new 40 percent wholesale tax on e-cigarette volume, part of Governor Tom Wolf's plan to generate \$13.3 million to balance the state budget. With the tax taking effect this Saturday, vape shop owner Bonnie Butz warns, "Most shops will close. ... There are over 300 vape stores in the state of Pennsylvania. I believe 70 of them have closed already."

Butz herself plans to stay in business, but warns she will be cutting staff and raising prices somewhat to compensate for the increased costs of doing business.

Campaign To Increase Tobacco Purchase Age To 21 Finds Success In 200 Counties, Municipalities.

Convenience Store News (9/29, 212K) reports the vote by Liberty, Missouri's city council to raise the legal age for purchasing tobacco to 21, means that at least 200 municipalities and counties in the US have passed similar laws. Meanwhile, Massachusetts, New Jersey, Washington, and Washington, DC are all considering similar legislation on a broader scale

TOBACCO INDUSTRY NEWS

PMI Feature: Philip Morris Expects \$1.2 Billion Boost From Cigarette Alternative.

Bloomberg News (9/29, Chambers, 2.49M) reports Philip Morris International said the company is "boosting investment in cigarette alternatives to expand sales to as many as 35 countries next year" – aiming to be the top industry leader in developing reduced-risk products that it "says will eventually replace traditional smokes." PMI has "'increasing confidence' that it will reach the upper end of its forecast for that business to add \$700 million to \$1.2 billion to earnings by 2020," according to Chief Executive Officer Andre Calantzopoulos, speaking at an investor presentation in Lausanne, Switzerland on Thursday. Bloomberg says Philip Morris "is throwing more money behind its iQOS heat-not-burn tobacco device to outdistance its rivals, British American Tobacco Plc and Japan Tobacco Inc."

INTERNATIONAL NEWS

Commentary Criticizes Tobacco Industry's Campaign Against Mandated Cigarette Plain Packaging In Canada.

The Huffington Post (CAN) (9/29, 63K) features commentary from writer Kevin Elliott in its "Living" blog concerning the tobacco industry's advertising campaign against the proposed law to mandate plain-packaged cigarettes in Canada. Elliott focuses on JTI-Macdonald Corp.'s website entitled "Both Side of the Argument," which he accuses of targeting poorly educated Canadians to get them to oppose the government's proposed changes. Elliott concludes, "The logical conclusion I have deduced, Big Tobacco, is that you are insulting the intelligence of Canadians with your sleazy website and its Critical Thinking Test."

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Smith, Celeste

From: Bulletin Intelligence <HHS@BulletinIntelligence.com>
Sent: Friday, September 30, 2016 5:59 AM
To: HHS@BulletinIntelligence.com
Subject: HHS Secretary's News Briefing for Friday, September 30, 2016

HHS SECRETARY'S NEWS BRIEFING

FRIDAY, SEPTEMBER 30, 2016 6:00 AM EDT

Zika Virus News:

U.S. SPENDING BILL FREES UP \$1.1 BILLION TO FIGHT ZIKA

Wall Street Journal (9/29, Stephanie Armour)

In continuing coverage, the Wall Street Journal reports that Congress passed legislation allocating \$1.1 billion to fund Zika vaccine development and mosquito control efforts. The Centers for Disease Control and Prevention had warned that existing funds for Zika would run out by the end of this month. CDC spokesperson Erin Sykes added that funds will also support mosquito surveillance, research into the long-term effects of Zika, and new diagnostic tests.

More Coverage. [Gov. Scott Relieved To Get Zika Funds, But Slams Federal Response \(Orlando \(FL\) Sentinel, 9/29\)](#), [Sylvia Matthews Burwell: What Happened While America Waited For Zika Funding \(The Atlantic, 9/29\)](#), [Congress Finally Approves Funding To Fight Zika \(Kaiser Health News, 9/29\)](#), [Congress Finally Passes Zika Funding Bill; Provides \\$1.1 Billion \(NBC News, 9/29\)](#), [Zika Fight Funding Delay May Have Affected Research On Alzheimer's And Diabetes \(Modern Healthcare, 9/29\)](#), [Congress Acts To Fight Zika Virus After Eight Months, Murray Condemns Delay \(Seattle Post-Intelligencer, 9/29\)](#)

4 NEW ZIKA CASES IN DELAWARE, INCLUDING INFANT

Wilmington (DE) News Journal (9/29, Jen Rini)

The Wilmington (DE) News Journal reports that four Delaware residents "tested positive for the Zika virus, including an infant who got the illness while traveling abroad, state health officials said Thursday." The new cases bring the state's total number of confirmed cases to 15.

More Coverage. [Zika Virus: Testing Backlog Wait Times Improve For Pregnant Women Florida, Jackson Memorial Doctor \(Miami Herald, 9/29\)](#), [3 More Travel-related Zika Cases In Polk \(Lakeland \(FL\) Ledger, 9/29\)](#)

ZIKA-RELATED BIRTH DEFECTS LIKELY HIGHER THAN ANTICIPATED: PANEL

Reuters (9/29)

Reuters reports that earlier this year, an analysis "estimated the risk of microcephaly following a mother's infection with the virus during the first trimester of pregnancy at between 1 percent and 13 percent." However, during a panel discussion presented by Harvard T.H. Chan School of Public Health in collaboration with Reuters on the Zika Thursday, National Institute of Allergy and Infectious Diseases Director Dr. Anthony Fauci said that the estimate doesn't include overall risk of birth defects. Fauci said, "If you're talking about any congenital defect I think it's going to be much higher than 13 percent," adding, "I think we're going to see something very disturbing." Fauci also stressed, "Puerto Rico is going through a terrible situation and we have to help them right now."

THAILAND CONFIRMS TWO CASES OF ZIKA-LINKED MICROCEPHALY, FIRST IN REGION

Reuters (9/30)

Reuters reports Thailand on Friday confirmed two Zika-related cases of microcephaly, the first in Southeast Asia, according to the World Health Organization. The U.S. Centers for Disease Control and Prevention on Thursday recommended "pregnant women postpone nonessential travel to 11 Southeast Asian countries, including Thailand," due to concerns about Zika. Thailand has had 349 confirmed cases of Zika this year.

More Coverage. [Study Finds Zika Infects Neural Cells Related To Skull Formation \(Reuters, 9/29\)](#), [Scientists ID Key Fetal Cells Vulnerable To Zika \(HealthDay, 9/29\)](#), [Zika Travel Advisory Issued For 11 Southeast Asia Countries \(Associated Press, 9/29, Mike Stobbe\)](#), [U.S. CDC Issues Zika Travel Advisory For 11 Southeast Asian Countries \(Reuters, 9/29\)](#), [CDC Issues Zika Travel Notice For 11 Southeast Asian Countries \(Washington Post, 9/29, Lena H. Sun\)](#),

CDC Warns Of Zika Outbreaks In 11 Southeast Asian Countries (Washington Examiner, 9/29), Pregnant Women Should Consider Not Traveling To Southeast Asia : The Two-Way : NPR (NPR, 9/29), C.D.C. Advises Against Travel To Zika-Affected Countries In Southeast Asia (New York Times, 9/29, Donald G. McNeil Jr.), Zika Prompts Southeast Asia Travel Warning (STAT, 9/29)

Top National Stories:

REPORT SAYS OBAMA ADMINISTRATION FAILED TO FOLLOW HEALTH LAW

Associated Press (9/29, Ricardo Alonso-Zaldivar)

The AP reports the Government Accountability Office has found that the Administration violated the ACA's provisions regarding "transitional reinsurance." Under the program, the government was to collect \$25 billion over the years 2014 to 2016 and submit \$5 billion to the Treasury. The Department of Health and Human Services did not submit the money to the Treasury because the fees charged to health insurance plans did not bring in sufficient funds. GAO general counsel Susan Poling wrote, "HHS lacks authority to ignore the statute's directive to deposit amounts (collected under the program) in the Treasury."

More Coverage. Watchdog Says Treasury Shortchanged In Affordable Care Program (Wall Street Journal, 9/29, Louise Radnofsky), U.S. Paid Insurers Funds Meant For Treasury, Auditors Say (New York Times, 9/29, Robert Pear), Watchdog Knocks Administration For Misusing Obamacare Funds (Politico, 9/29, By Paul Demko), Watchdog: HHS Can't Divert Billions From Treasury To Obamacare Insurers (Washington Examiner, 9/29), Insurer Payments Flouted Plain Text Of Obamacare: Gov't Report

Health Insurance Marketplaces:

REGULATORS APPROVE NEW D.C. HEALTH LINK PLAN RATES

Washington Business Journal (9/29, Tina Reed)

The Washington Business Journal reports the Washington, DC Department of Insurance, Securities and Banking announced Wednesday that premiums for policies sold on the DC Health Link marketplace would rise "a little more than 7 percent on average next year." CareFirst HMO plans will have a 22.8 percent increase.

BCBST SHAKEUP BRINGS UNCERTAINTY TO MANY IN TENNESSEE

Tennessean (9/29)

The Tennessean in continuing coverage profiles several Tennesseans who will be affected by BlueCross BlueShield of Tennessee's recent announcement that it will not offer 2017 plans through the state's exchange in the Nashville, Memphis, and Knoxville markets. According to the article, "Many people on individual plans moved to the exchange to take advantage of subsidies, but now the exchange options and the benefits or networks are limited."

More Coverage. BCBST Marketplace Policyholders In Knoxville Waiting To Learn Options (Knoxville (TN) News Sentinel, 9/29)

HARKEN EXITS OBAMACARE MARKETS AS UNITEDHEALTH STARTUP STRUGGLES

Bloomberg News (9/29, Zachary Tracer)

Bloomberg News reports UnitedHealth Group Inc.'s Harken Health Insurance Co. startup is withdrawing "from the two exchanges where it was selling plans," in Georgia and in Chicago. It will no longer offer individual plans in those exchanges, though it will do so in the regular market. The decision indicates that UnitedHealth's attempt "to develop a profitable model for selling plans" in the exchanges has not worked.

More Coverage. Harken To Exit Illinois Obamacare Exchange (Chicago Tribune, 9/29, Lisa Schencker), UnitedHealth Subsidiary Ditches ACA Exchange After Posting Losses (Modern Healthcare, 9/29)

ARKANSAS AGENCY BACKS HEALTH INSURER'S BID FOR SMALLER RATE RISE

Arkansas Democrat Gazette (9/29)

The Arkansas Democrat Gazette reports the Arkansas Insurance Department is recommending that the proposal by QualChoice Health Insurance for premium increases "less than the amount the department approved last month" should be approved. The new proposal is for an 11 percent average increase, down from 13.5 percent. The increase must be approved by the Centers for Medicare and Medicaid Services.

STATE OF MINNESOTA ASKED 45,000 TO REAPPLY FOR COVERAGE

Minneapolis Star Tribune (9/29)

The Minneapolis Star Tribune reports Minnesota's Department of Human Services has requested 45,000 people to

"reapply by the end of September" for public health policies in order to "fix data mismatches between two computer systems." In the notice, the department said there was a "system problem" preventing them from being able to determine whether those notified "were eligible for benefits in either the MinnesotaCare or Medical Assistance [Medicaid] programs." The mismatch appears to be due to the department shifting the public insurance enrollees to a new computer system, called METS, separate from the MNsure system that serves those purchasing private insurance on the state ACA marketplace. While the two system are supposed to "automatically sync with one another," in a number of cases that did not happen.

Health Reform & Healthcare:

HHS CHIEF: EPIPEN COST SURGE SHOWS NEED FOR NEGOTIATING POWER

The Hill (9/29, Sarah Ferris)

The Hill reports Health and Human Services Secretary Sylvia Mathews Burwell on Thursday, speaking at The Atlantic's Washington Ideas Forum, in response to the "uproar over EpiPen pricing," said, "One of the most important tools that we could gain would be an ability to negotiate." She added, "Access to drugs, and affordable access to drugs, we think is a priority. We need to take steps as a nation to make sure we do that."

More Coverage. [Burwell Calls For HHS To Negotiate Drug Prices \(Morning Consult, 9/29\)](#)

HHS NAMES WINNERS OF CHALLENGE TO BUILD A BETTER MEDICAL BILL

Healthcare IT News (9/29)

Several specialized sources carried continuing coverage on the Department of Health and Human Services "A Bill You Can Understand" competition sponsored by AARP. All sources quoted Secretary Burwell saying, "One of our priorities is to put patients at the center of their own health care," and adding, "Helping Americans understand their medical bills empowers them to take more control of their health, and that's a step in the right direction for our entire health care system."

More Coverage. [Blog: Designers Achieve The Improbable: A Clear And Readable Explanation Of Benefits \(Modern Healthcare, 9/29\)](#), [Healthcare Comes One Step Closer To An Easy-to-understand Medical Bill \(Fierce Healthcare, 9/29\)](#), [HHS Unveils Simpler Medical Billing Process Challenge Winners \(RevCycle Intelligence, 9/29\)](#)

OBAMA ADMINISTRATION MAY USE OBSCURE FUND TO PAY BILLIONS TO ACA INSURERS

Washington Post (9/29, Amy Goldstein)

The Washington Post reports the Administration "is maneuvering to pay billions of dollars" in a settlement with health insurers, suing under the ACA, and may use "an obscure Treasury Department fund" to do so. The Post says Justice Department officials "have told several health plans" involved in suits that the government is "eager to negotiate a broad settlement" so that the government can "compensate about 170 other insurers" as well as those that filed suit. This is described as an effort to "bypass congressional Republicans" who have "blocked" HHS "from paying health plans what they are owed." Andy Slavitt, acting administrator for the CMS, has told the Congress that the payments are "an obligation of the federal government." The lack of these payments "contributed to the collapse" of co-ops.

OBAMACARE LED TO SIMILAR DROPS IN UNINSURED RATE ACROSS ALL INCOME GROUPS

CNBC (9/29)

CNBC reports the Health and Human Services Department issued a report finding that under the ACA "every income group 'experienced significant and similar drops' in the rate of uninsured people." Overall, HHS found that there was a 40 percent decline in uninsured Americans, "in all income groups for 2010 through 2015, including individuals with incomes above 400 percent of the federal poverty level." In addition, among Americans 18 to 25 years old there was a 52 percent decline in the uninsured, while among 26- to 34-year-olds the decline was 36 percent. Among those living in urban or metropolitan areas, there was a 42 percent decline, while in rural areas it was 39 percent. There were also significant drops in uninsured people among Asians (59 percent), blacks (47 percent), whites (46 percent), and Hispanics (35 percent). HHS Secretary Sylvia Burwell commented, "Regardless of your income, age, geography, or race, everyone is gaining access to coverage or better coverage under the Affordable Care Act."

More Coverage. [HHS Says Obamacare Lowering Uninsured Rates Across All Groups \(Washington Examiner, 9/29\)](#)

MOST AMERICANS UNAWARE OF ACA'S EFFECT ON UNINSURED RATE, POLL FINDS

Morning Consult (9/29)

Morning Consult reports a Kaiser Family Foundation poll found that 26 percent of adults "knew that the rate of uninsured people in the US is at a historic low of 9.1 percent," while 21 percent believe it to be "at an all-time high," and 46 percent think "it has remained even."

More Coverage. [Obamacare Cut The Uninsured Rate To An All-time Low. Most Americans Have No Idea.](#) (Vox, 9/29)

THE HEALTH CARE 'PUBLIC OPTION' IS BACK. CAN IT HELP OBAMACARE?

New York Times (9/29, Reed Abelson And Margot Sanger-Katz)

In "The Upshot," the New York Times carries a discussion between New York Times reporters Reed Abelson and Margot Sanger-Katz on the "public option" in healthcare, partially in response to Hillary Clinton's recent article in the New England Journal of Medicine in which she "reiterated her support" for the idea. Sanger-Katz notes the increasing popularity of the idea with support from Clinton, Obama and 33 Democratic Senators, as well as California's insurance commissioner, Dave Jones. Abelson explains that it is being presented as "a possible fallback" in areas where private insurers have withdrawn from marketplaces and co-ops have closed. Sanger-Katz points out that the "public option" is not a single idea, but different supporters mean different things whether allowing a "buy in" to Medicare or Medicaid, or an actual insurance plan "run by the government." Abelson asks whether it is intended as "a fallback" or if it is a plan "to use the government's negotiating clout to introduce lower-cost plans?"

More Coverage. [Clinton Touts ObamaCare Improvements In Journal Article](#) (The Hill, 9/29, Peter Sullivan)

UTAHNS LIKELY WON'T BE ABLE TO SIGN UP FOR MEDICAID EXPANSION ON JAN. 1

Salt Lake (UT) Tribune (9/29)

The Salt Lake (UT) Tribune reports that even if Utah's Medicaid expansion plan is approved by the Federal government, it is unlikely that residents will be able to enroll in the program on the estimated Jan. 1 start date. The plan "recently underwent public comment." Nate Checketts, the Utah Department of Health's deputy director, "said Thursday that the state was hoping to receive an 'early nod' from the federal Centers for Medicare and Medicaid Services, indicating that the plan was 'on a good path' by September."

MEDICAID EXPANSION WILL DRIVE AFFORDABILITY, INSURANCE LEADER SAYS

Bloomberg BNA (9/28)

Bloomberg BNA reports former CMS administrator Marilyn Tavenner, president and CEO of America's Health Insurance Plans, speaking at the McKesson Health Solutions Conference in Orlando, Florida, said that the remaining states should expand Medicaid, which would "likely grow to about 130 million enrollees." She also said that "the troubled health insurance exchanges will need to be fixed," and that the current price of health insurance with "premiums for family plans, averaging about \$20,000 a year" is "not affordable, nor is it sustainable." After the elections, Tavenner said that AHIP will seek changes to "anti-kickback prohibitions" in order to make it easier for physicians to be part of accountable care organizations. It will also work for "interoperability of data systems."

WITH DRUG PRICES SPIKING, AMERICANS WANT MORE GOVERNMENT ACTION, NEW POLL FINDS

Los Angeles Times (9/29)

The Los Angeles Times reports that a survey by the Kaiser Family Foundation suggests that over three out of four Americans "believe that prescription drug prices are unreasonable." According to the survey, 78 percent support "new restrictions on how much pharmaceutical companies can charge for high-cost drugs for illnesses such as hepatitis or cancer" and 86 percent "support new requirements on drug companies to release information on how they set prices."

More Coverage. [Most Americans Want Stronger Action To Lower Drug Prices](#) (McClatchy, 9/29), [Poll Finds Majority Of Americans Want Restraints On Drug Prices](#) (Kaiser Health News, 9/29), [Did Landmark Laws From Congress Enable High Drug Prices?](#) (Associated Press, 9/29, Ricardo Alonso-Zaldivar), [Big Majorities Say Government Should Work To Curb Prescription Drug Price Hikes](#) (CNBC, 9/29), [More Americans Say They're Unreasonable: Kaiser](#) (Money, 9/29), [Americans Favor Policies To Lower Drug Prices](#) (Washington Examiner, 9/29).

THE NEW IRS EMAIL SCAM COMING TO YOUR INBOX

Wall Street Journal (9/29, Laura Saunders)

The Wall Street Journal reports on an email scam in which the targets are told they owe tax under the ACA. In addition to email, some warnings are coming through the mail. Targets are told to pay a balance because they have insufficient health insurance coverage under the ACA. The IRS urges people who receive such notices to call them at 800-829-1040 if they wish to be certain of their status.

MEDICARE SETS NEW PATIENT SAFETY GOALS FOR HOSPITALS

Associated Press (9/29)

The AP reports that Medicare on Thursday announced "new goals for greater improvement" in its effort at "keeping hospitalized patients safe and reducing readmissions." It also announced \$347 million for "hospital associations and other health organizations" in order to reach the goals that include reducing "preventable medical problems in hospitals from 121 per 1,000 patients discharged, to 97 per 1,000 by 2019."

More Coverage. CMS Awards \$347 Million To Healthcare Groups To Improve Patient Safety (Modern Healthcare, 9/29)

CDC URGES AMERICANS TO GET A FLU SHOT AS SOON AS POSSIBLE

NPR (9/29)

On its website, the NPR "Shots" blog reports that Dr. Thomas Frieden, the director of the Centers for Disease Control and Prevention, is urging all Americans to obtain a flu shot as soon as possible. Frieden told reporters, "Flu is serious. Flu is unpredictable." Frieden is particularly concerned about a recent decline in the number of elderly people getting vaccinated.

More Coverage: *Print and Online.* CDC Officials Worry That New Flu Vaccine Recommendations Could Reduce Use (Washington Post, 9/29, Lena H. Sun), Federal Officials Encourage Flu Shots, Not FluMist Spray (San Francisco Chronicle, 9/29), 'Concerning' Drop Seen In The Number Of Older Adults Getting Flu Vaccinations (CNBC, 9/29), Time To Get A Flu Shot, Health Officials Say (Pittsburgh Tribune-Review, 9/29), What To Know About The 2016-2017 Flu Vaccine (TIME, 9/29), With No Nasal Option, Flu Immunization May Fall (U.S. News & World Report, 9/29), With FluMist Deemed Ineffective This Year, Patients Have To Roll Up Their Sleeves (Chicago Tribune, 9/29), Flu Season: How Bad Will It Be? (USA Today, 9/29, Karen Weintraub), CDC Urges Adults To Get The Flu Shot Amid Declining Vaccination Rates (Fox News, 9/29), Health Officials Make It Clear: Get A Flu Shot (Pittsburgh Post-Gazette, 9/30)

MILITARY COULD SPEND UP TO \$8.4M ANNUALLY ON GENDER REASSIGNMENT TREATMENTS

USA Today (9/29, Ashley May)

USA Today reports that on October 3, the Department of Defense will begin paying for gender reassignment treatment and surgery for eligible soldiers, which is estimated to cost between \$2.4 million and \$8.4 million per year. RAND Corp. "estimates that between 30 and 140" soldiers "would like hormone treatment, and 25 to 130 would seek surgery" under the new policy.

Blogs:

UNITEDHEALTHCARE HARKEN HEALTH QUITTING OBAMACARE EXCHANGES ACA

Business Insider (9/29)

In a blog entry for the Business Insider, Bob Bryan writes, "Harken Health Insurance, a startup and part of UnitedHealthcare that offered low-cost health plans through the Affordable Care Act (ACA) exchanges, is leaving the marketplace." The company "said it will continue to offer plans in various states to individuals outside of" ACA exchanges. According to Bryan, "The move by Harken is the second Obamacare-focused startup that has rolled back ACA plans."

WHY GREAT IDEAS IN HEALTH CARE DON'T THRIVE EVERYWHERE

Health Affairs (9/29)

In a blog entry for Health Affairs, Jeff Goldsmith, National Advisor to Navigant Healthcare and Associate Professor, Public Health Sciences University of Virginia, and Lawton R. Burns, PhD, MBA, he James Joo-Jin Kim Professor in the Wharton School at the University of Pennsylvania, write, "A failure to understand and respect the role that local culture and market conditions for health system innovation profoundly limits the effectiveness of 'single bullet' policy solutions." Goldsmith and Burns posit, "Perhaps a healthy respect for non-economic factors in health system behavior – often rooted in local and regional circumstances and in institutional culture – might be a corrective for those who see sweeping 'national' solutions to complex problems."

OUR PROGRESS IN DIGITIZING HEALTH CARE

Health Affairs (9/29)

In a blog entry for Health Affairs, Dr. Karen DeSalvo, Acting Assistant Secretary for Health in the U.S. Department of Health and Human Services, and Dr. Vindell Washington, National Coordinator for Health Information Technology, write that due to 2009's Health Information Technology for Economic and Clinical Health (HITECH) Act, "nearly all hospitals (96 percent) and nearly eight in 10 (78 percent) physicians use certified" electronic health records (EHRs). According to Drs. DeSalvo and Washington, "The Office of the National Coordinator for Health Information Technology (ONC) and our public and private partners have accelerated interoperability efforts by focusing on three key drivers of success." Those three drivers are "the use of common, federally recognized, national standards; changing the culture around access to information – including combating data blocking; and, building the business case for interoperability."

Opinion:

DISCREDITED 'PUBLIC OPTION' WILL FAIL: SEN. HATCH AND REP. UPTON

USA Today (9/29, Orrin Hatch And Fred Upton)

Sen. Orrin Hatch (R-UT) and Rep. Fred Upton (R-MI) write in USA Today against the ACA's "fundamental failure to tackle

costs and embrace" competition, and against the idea of a "public option" which they say "simply doesn't work." They cite the failure of co-ops as their chief exhibit.

INSURE CALIFORNIA'S UNDOCUMENTED IMMIGRANTS: RAUL REYES

USA Today (9/29, Raul Reyes)

Raul A. Reyes, an attorney, and an NBCNews.com and CNN Opinion contributor, writes for USA Today in favor of a proposal to allow "up to 30%" of California's "2 million undocumented residents" to buy health insurance coverage through the state's insurance exchange. He argues that the policy would improve the health and possibly reduce costs to the state.

DENYING POOR PATIENTS HEALTH CARE COVERAGE WON'T FIX OBAMACARE

U.S. News & World Report (9/29)

Former Rep. Ronnie Shows writes for . News & World ReportU.S against a recent proposal by the CMS "that would prevent patients with end-stage renal disease from receiving charitable assistance to help pay the premiums for health plans purchased on the health care law's exchanges." Shows argues that CMS appears to want "these patients out of the exchanges," but these plans may "offer distinct benefits over Medicare" chiefly that some "offer care coordination services," and all "limit patient out-of-pocket costs."

THE CRITICAL ISSUE THE FIRST DEBATE MISSED

CNN (9/29, Lynn O'Connor Vos)

Lynn O'Connor Vos, chief executive officer of Greyhealth Group, writes on CNN in favor of the presidential candidates covering their healthcare proposals in a future debate. In order to help in that effort, she says that Hillary Clinton plans to "build on the Democrats' success and implement steps to improve on what we have, making the good even better." Meanwhile, Donald Trump "intends to immediately scrap Obamacare," yet, this cannot be done "without creating complete chaos."

THIS IS THE SCARIEST THING ABOUT HEALTH CARE IN AMERICA TODAY

Huffington Post (9/29)

Ann Brenoff writes in her column in the Huffington Post on the experience of her husband being hospitalized and having a "parade" of physicians who "stayed for all of about 90 seconds" and were "out-of-network." She points out that he and she really had no choice about these physicians and did not "hire" them or choose to receive their services and yet they are billed just as if they did. She also points out that he was in the in-network hospital and yet that appears to have made no difference.

COLUMN: IN-PATIENT OR NOT? MEDICARE REQUIRES HOSPITALS TO TELL YOU

Reuters (9/29)

Mark Miller writes in his column for Reuters about the difference between "observation status" and admitted patient under Medicare, namely that "observation status can result in thousands of dollars in higher costs." He explains that under a recent law, the hospital must "notify patients if they stay in the hospital more than 24 hours without being formally admitted." Advocates say the hospitals should also provide a means for patients to appeal their status.

WHY HEALTH INSURANCE INDUSTRY CONSOLIDATION IS BAD FOR YOUR HEALTH

Huffington Post (9/29)

Wendell Potter, author of "Nation on the Take, How Big Money Corrupts Our Democracy and What We Can Do About It," writes for "The Blog" in the Huffington Post against proposed mergers of health insurance companies that will affect "tens of millions" who will have "health plans with much worse patient satisfaction and customer complaint scores." In both cases, Potter says, the purchasers – Anthem and Aetna – "have higher customer complaint ratios and lower patient satisfaction scores" than do the companies they are acquiring – Cigna and Humana.

National Front Page News:

HEADLINES FROM TODAY'S FRONT PAGES.

New York Times:

Hoboken Train Crash Leaves At Least One Dead And Dozens Injured

Ohio, Long A Bellwether, Is Fading On The Electoral Map

Claims Of Saudi Role In 9/11 Appear Headed For Manhattan Court

Ex-Marine Describes Violent Hazing And The Lies That Covered It Up

Torn Over Donald Trump And Cut Off By Culture Wars, Evangelicals Despair

It's No Cold War, But Vladimir Putin Relishes His Role As Disrupter

Wall Street Journal:

Qualcomm In Talks To Acquire NXP Semiconductors

Portman May Provide Reverse Coattails For Trump In Ohio

Deutsche Bank Clients Take Steps To Cut Exposure

A CBS-Viacom Merger? It Depends On The Redstone-Moonves Dance

Washington Post:

She Tried To Stop Deportations. Now She's Fighting Her Own.

Payouts In Works To Shore Up ACA

Trump's Foundation May Lack NY Status

Women In India Often Must Fight For Property Rights.

Obama Is Mourning Peres — And A Dormant Peace Process

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From: [Unger, Ellis](#)
To: [Califf, Robert](#)
Subject: RE: any progress on that letter to the neuro journal?
Date: Friday, September 30, 2016 3:45:55 PM
Attachments: [Saper_2.doc](#)

Thanks! She's starting to move in the right direction.

Here's a draft letter. Feel free to comment/revise, and I'm more than happy for you to sign it if you wish.

Ellis

From: Califf, Robert
Sent: Friday, September 30, 2016 8:10 AM
To: Unger, Ellis
Subject: RE: any progress on that letter to the neuro journal?

No problem. I'm happy to look at a draft over weekend.
Hope all is well with (b) (6).

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Unger, Ellis
Sent: Thursday, September 29, 2016 6:19 PM
To: Califf, Robert
Subject: RE: any progress on that letter to the neuro journal?

Sorry – I've been wrestling this week with (b) (6) illness, but will get on it now

From: Califf, Robert
Sent: Thursday, September 29, 2016 5:44 PM
To: Unger, Ellis
Subject: any progress on that letter to the neuro journal?

Robert M Califf MD
Commissioner of Food and Drugs



Clifford B. Saper, M.D., Ph.D.
Editor-in-Chief
Annals of Neurology

c/o Managing Editor
330 Brookline Avenue
Boston, MA 02215
email: aon@bidmc.harvard.edu

Dear Dr. Saper:

This letter is in reference to the paper “Eteplirsen for the treatment of Duchenne muscular dystrophy,” by Jerry R. Mendell, Louise R. Rodino-Klapac, Zarife Sahenk, Kandice Roush, Loren Bird, Linda P. Lowes, Lindsay Alfano, Ann Maria Gomez, Sarah Lewis, Janaiah Kota, Vinod Malik, Kim Shontz, Christopher M. Walker, Kevin M. Flanigan, Marco Corridore MD, John R. Kean, Hugh D. Allen, Chris Shilling, Kathleen R. Melia, Peter Sazani, Jay B. Saoud, and Edward M. Kaye, published in the *Annals of Neurology* (*Ann Neurol* 2013;74:637–647).

The principal conclusion of the study was: “Eteplirsen restored dystrophin in the 30 and 50 mg/kg/wk cohorts, and in subsequently treated, placebo-controlled subjects.”

We believe that the reported findings are clearly incorrect, and that the conclusions, based on these erroneous findings, are misleading. We therefore urge that the paper be corrected or retracted from the *Annals of Neurology*.

In the course of FDA’s review of a New Drug Application for eteplirsen for the treatment of Duchenne muscular dystrophy in patients with a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, FDA inspected the Columbus, Ohio facility where the study had been conducted. As noted in documents posted on the internet subsequent to our September 19, 2016, approval,¹ a number of significant methodological problems were found that importantly affect the study results.

The Patients and Methods section of the original publication states:

“To evaluate dystrophin-positive fiber levels, immunohistochemical staining was done on 10 µm frozen sections of 3 separate blocks of biopsy tissue separated by at least 200 µm and evaluated by blinded expert muscle pathologists. For dystrophin localization, sections were stained with MANDYS106 NCL, a mouse monoclonal antibody to amino acids 1749–2248,[15, 16] using standard immunofluorescence methodology.[9, 14] Dystrophin-positive fibers and total fibers were counted, and the percentage of dystrophin-positive fibers was calculated across all samples.”

¹ Downloaded 9/29/16 from
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf

Note that the first sentence states that the tissues were evaluated by “blinded expert muscle pathologists,” implying more than one such evaluator. The third sentence explains that dystrophin-positive and total muscle fibers were counted, and because this sentence closely follows the first sentence and is in the same paragraph, there is the implication that the fiber counting was also performed by “blinded expert muscle pathologists.” In fact, the counting was performed by a single histotechnician.

The FDA inspectional findings pertinent to the fiber counting are reprinted from pp. 12 to 15 of the Office Director Decisional Memo.¹

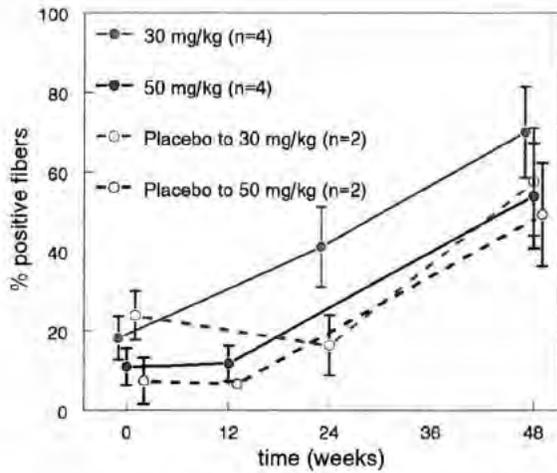
“Although the technician had been blinded to treatment group, access to the treatment code was not protected with the kinds of safeguards and firewalls that one would ordinarily put in place for an adequate and well controlled trial. The immunohistochemistry images were only faintly stained, and had been read by a single technician using an older liquid crystal display (LCD) computer monitor in a windowed room where lighting was not controlled. (The technician had to suspend reading around mid-day, when brighter light began to fill the room and reading became impossible.) These issues are well described in a summary of inspectional findings in Dr. Breder’s clinical review (page 27). There was also concern that the reader, although masked to treatment assignment, was not masked to sequence/time (see below). Importantly, in a trial where all patients eventually received the active drug, knowledge of sequence could lead to the false appearance of a treatment effect, i.e., the appearance of increasing dystrophin expression with time, simply by having a lower threshold for calling fibers “positive” at later time points in the study.

Having uncovered numerous technical and operational shortcomings in Columbus, our team worked collaboratively with the applicant to develop improved methods for a reassessment of the stored images. We suggested a re-read of all images by 3 independent masked readers, such that blinding could be assured and inter- and intra-observer variability could be characterized. We also suggested the use of better equipment, specifically, high-quality light-emitting diode (LED) computer monitors, in darkened rooms.

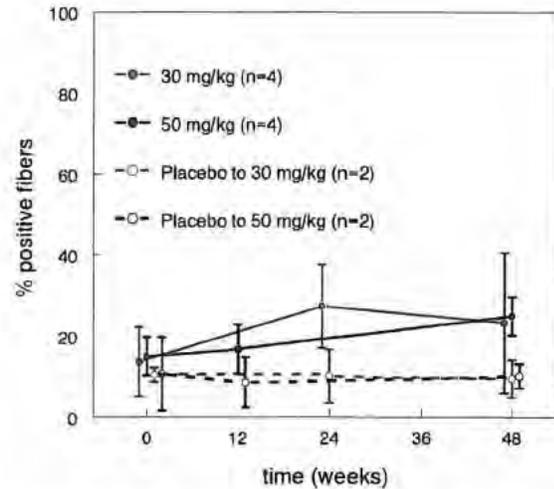
The applicant undertook a blinded re-analysis of the images on the server as FDA suggested. Unfortunately, the re-analyses failed to show a significant increase in dystrophin-positive fiber counts in eteplirsen treated patients (Figure 3). Note also that for patients who switched from placebo to eteplirsen at Week 24 (dashed red and black lines), there was no response between Weeks 24 and 48.”

The results of the original analysis (left) and the blinded re-analysis by 3 readers (right) are shown graphically below. These show actual percent positive fiber counts, without baseline subtraction. Note the marked differences between readings in the left and right plots, particularly at later time points.

**Original reading at
Nationwide Children's Hospital**



Blinded re-read by 3 pathologists



The original results were shown in Table 2 of the paper as percent positive fibers; absolute change from baseline, reprinted below:

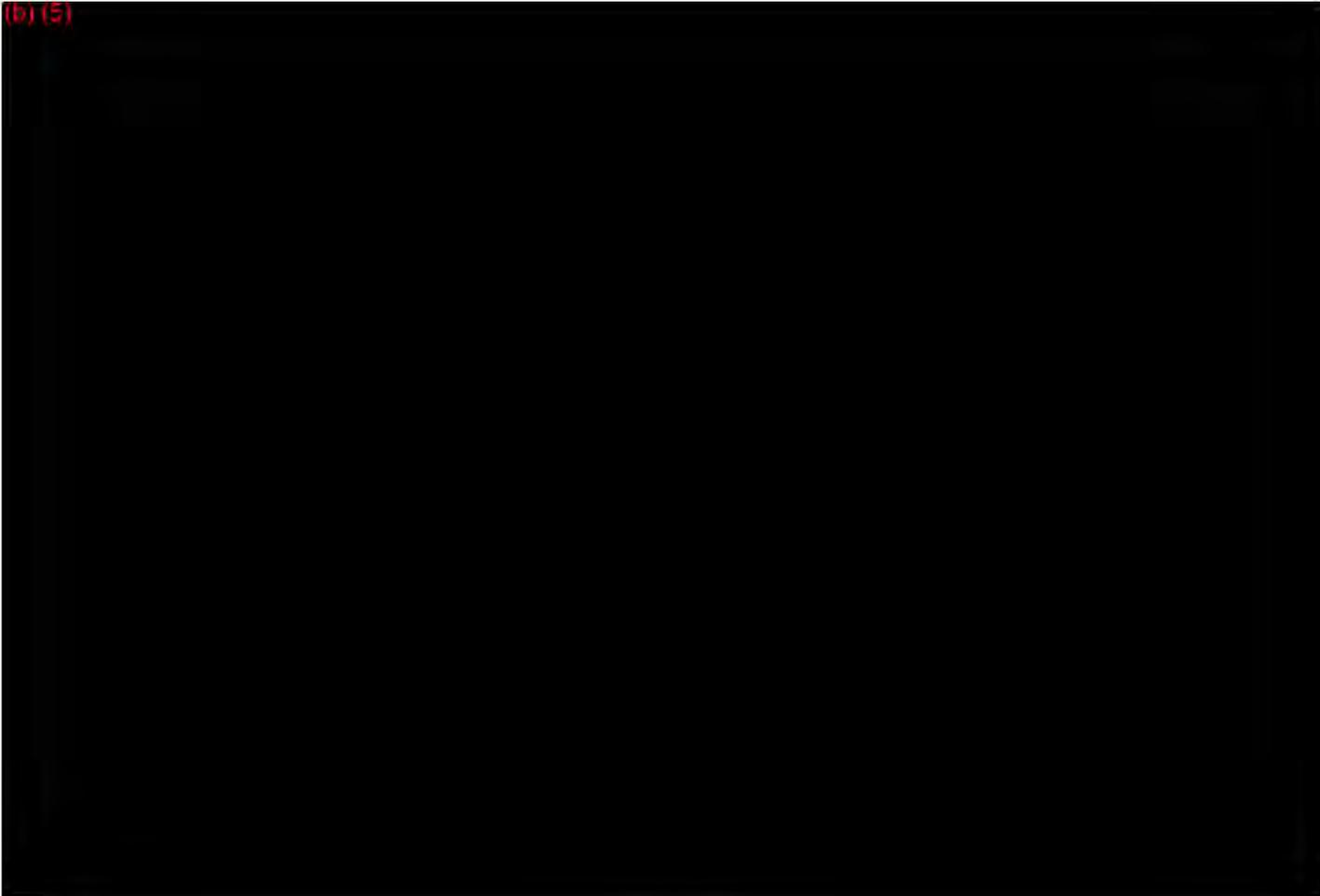
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Cohort (n)	Week 12 Mean Change from BL, SE (p-value) *	Week 24 Mean Change from BL, SE (p-value) *	Week 48 Mean Change from BL, SE (p-value) *
All Eteplirsen (8)	NA	NA	47.3, 3.89 (≤0.001)
Eteplirsen 30mg/kg (4)	ND	22.9, 2.90 (≤0.002)	51.7, 3.54 (≤0.001)
Eteplirsen 50 mg/kg (4)	0.8, 3.55 (NS)	ND	42.9, 6.72 (≤0.008)
Placebo/Delayed Eteplirsen (4) †	-4.0, 2.92	-4.0, 2.92	37.7, 6.30 (≤0.009) †
Eteplirsen 30 mg/kg (2)	ND	-7.48, 1.00	33.6, 5.23
Eteplirsen 50 mg/kg (2)	-0.6, 5.16	ND	41.8, 13.30

Based on data received by FDA, the revised and markedly different results from the blinded re-read of 3 pathologists are shown using the same format:

	Week 12 Mean Change from BL (SE)	Week 24 Mean Change from BL (SE)	Week 48 Mean Change from BL (SE)
All Eteplirsen (8)	NA	NA	9.8, 2.38
Eteplirsen 30 mg/kg (4)		13.7, 2.04	9.6, 4.54
Eteplirsen 50 mg/kg (4)	1.8, 3.57	ND	10, 2.41
Placebo - delayed Eteplirsen (4)	-1.2, 1.69	-1.2, 1.69	-0.8, 1.96
Eteplirsen 30 mg/kg (2)	ND	-0.4, 3.4	-1, 2.02
Eteplirsen 50 mg/kg (2)	-2.1, 2.05	ND	-0.6, 4.34

(b) (5)



Sincerely,

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

From: [Califf, Robert](#)
To: [Unger, Ellis](#)
Cc: [Woodcock, Janet](#); [jenkins, John K \(John.Jenkins@fda.hhs.gov\)](mailto:jenkins, John K (John.Jenkins@fda.hhs.gov))
Subject: RE: any progress on that letter to the neuro journal?
Date: Saturday, October 01, 2016 11:28:00 AM
Attachments: [Saper 2 rmc.doc](#)

Ellis,

A few edits. Let me know what you think. Yes, I'd like to be a coauthor, as there are policy implications for our NIH efforts here. I'm interested in Janet and John's views also.

It may be that the best course would be for the journal to publish the letter with a reply from the authors.

rmc
Robert M Califf MD
Commissioner of Food and Drugs

From: Unger, Ellis
Sent: Friday, September 30, 2016 3:46 PM
To: Califf, Robert
Subject: RE: any progress on that letter to the neuro journal?

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

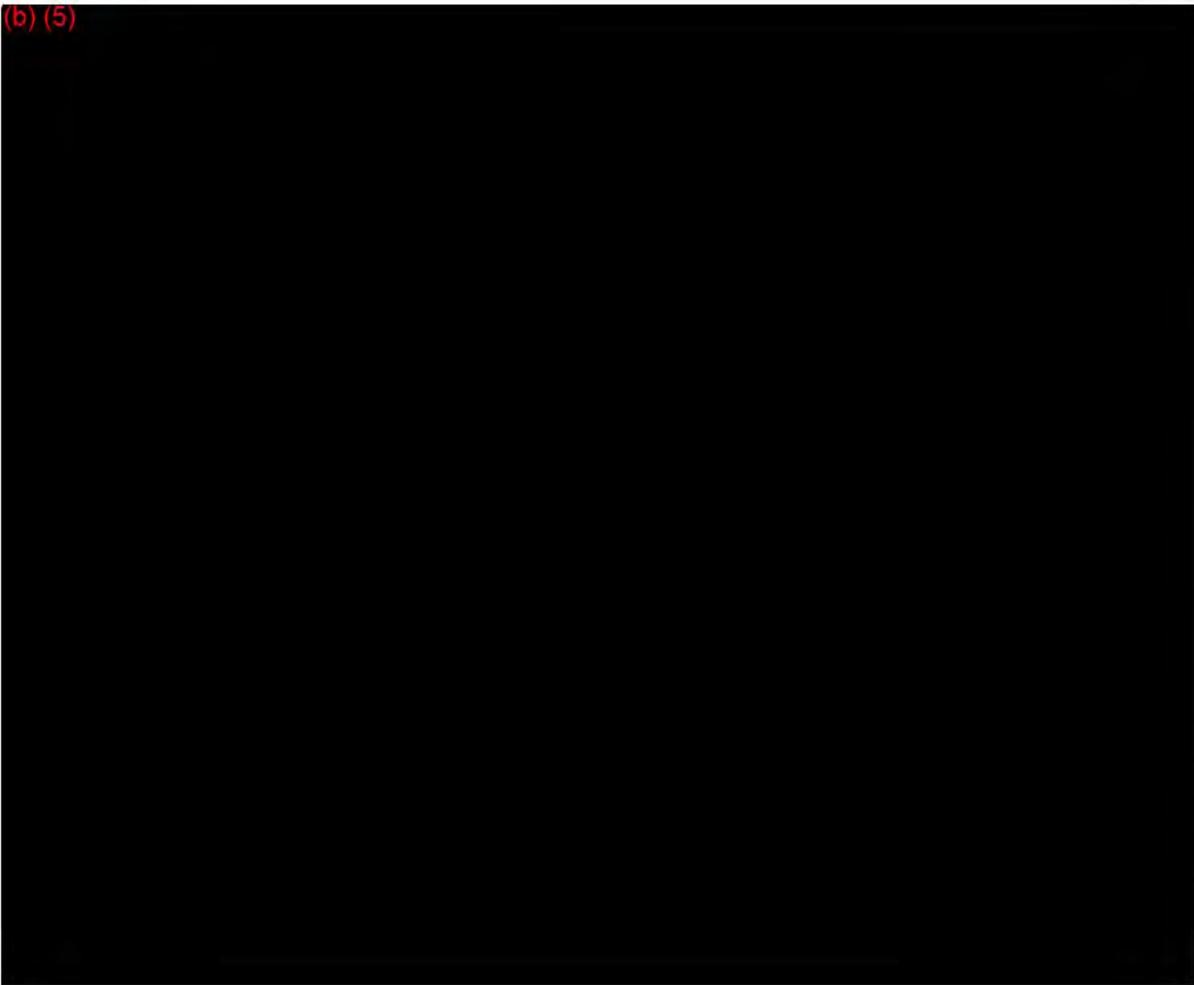
Food and Drug Administration
Silver Spring MD 20993

Clifford B. Saper, M.D., Ph.D.
Editor-in-Chief
Annals of Neurology

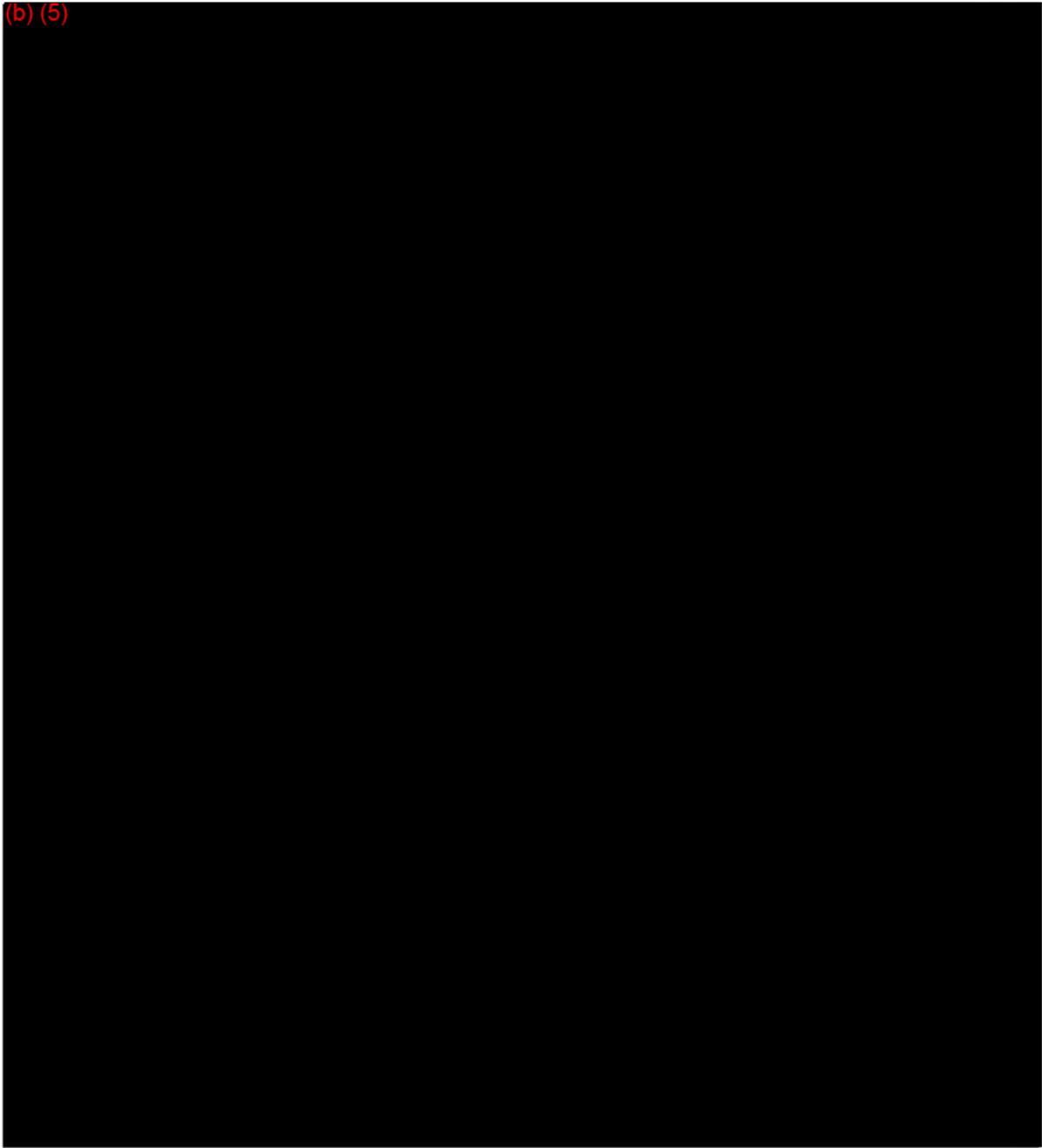
c/o Managing Editor
330 Brookline Avenue
Boston, MA 02215
email: aon@bidmc.harvard.edu

Dear Dr. Saper:

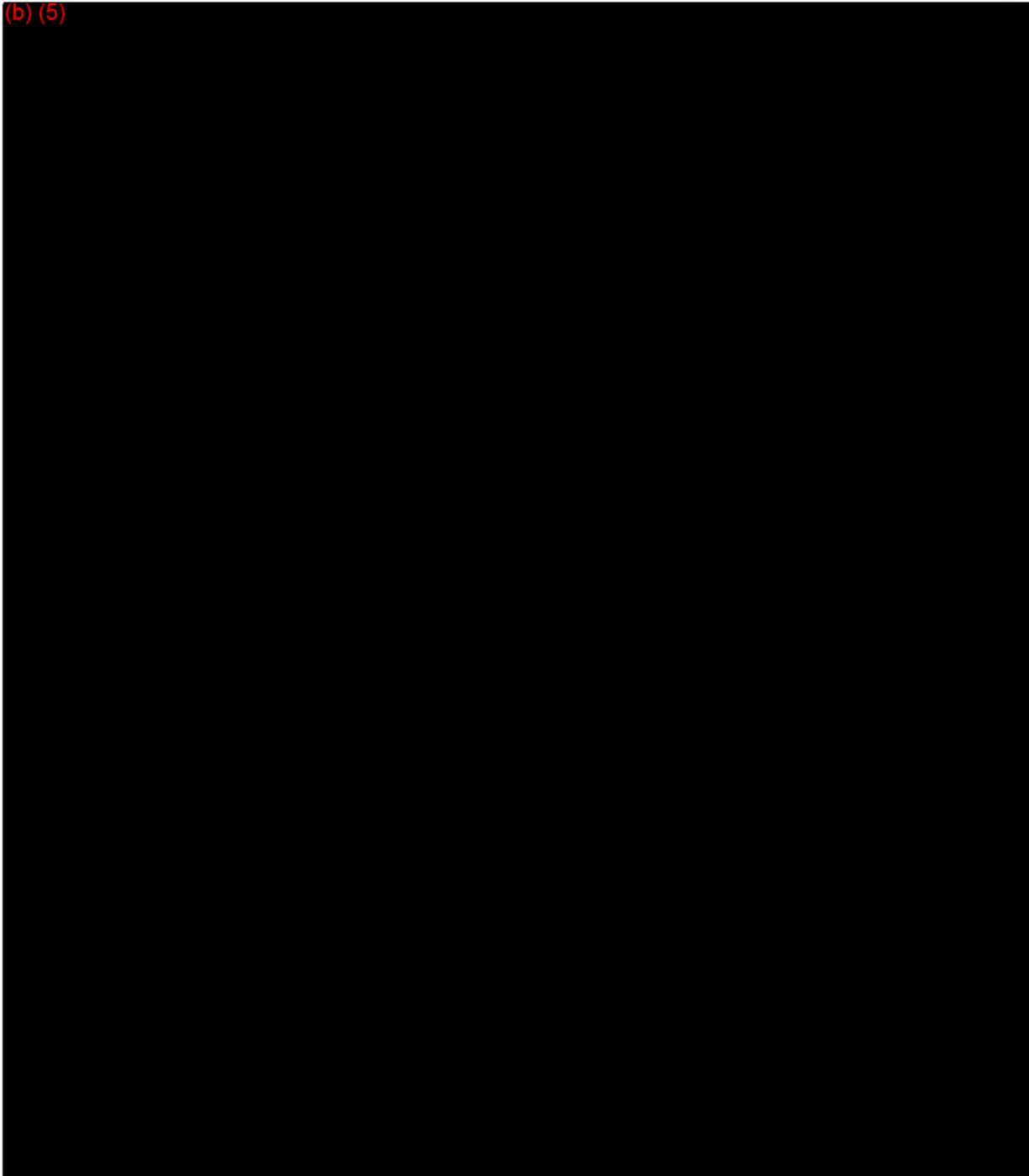
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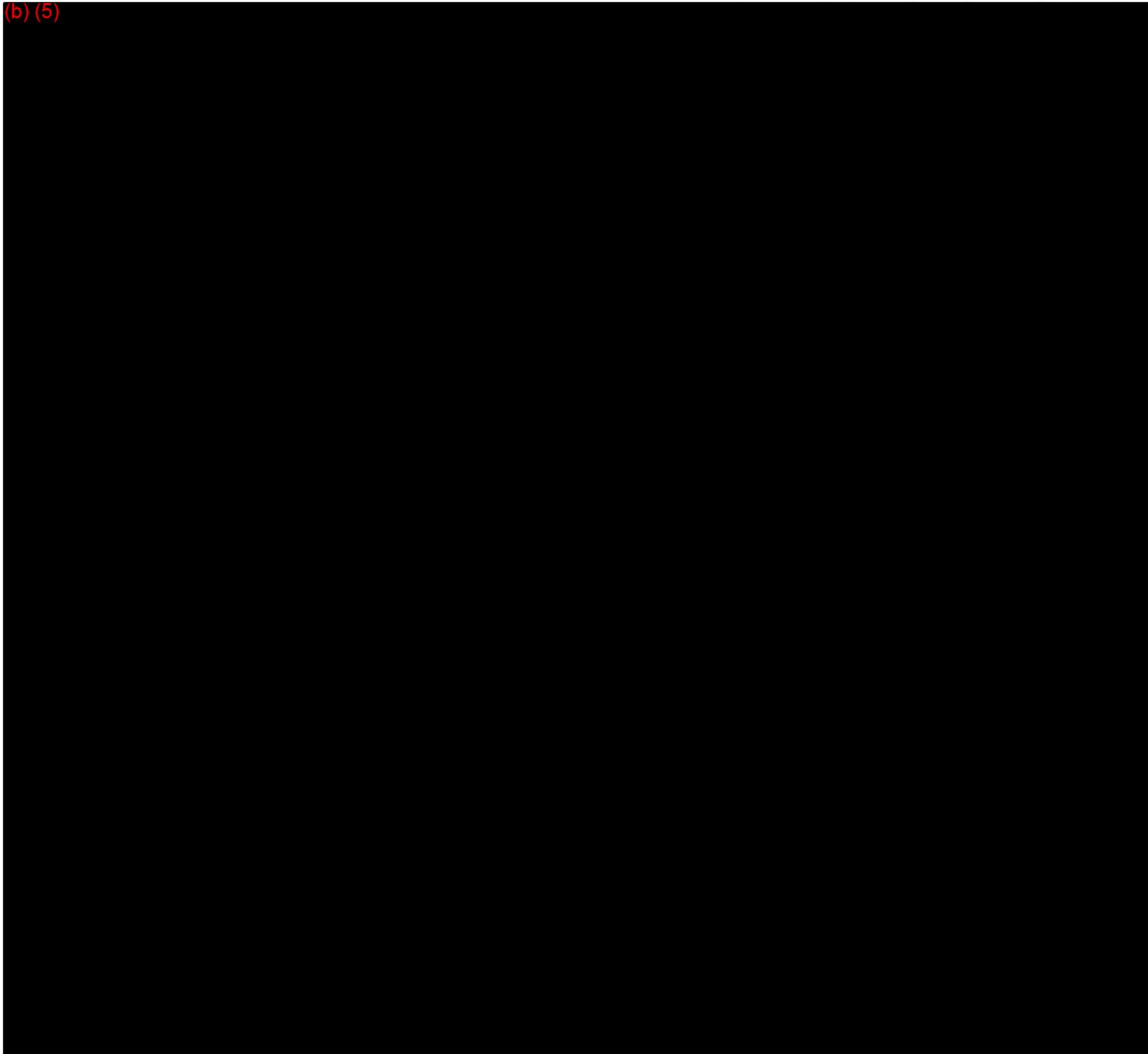
(b) (5)



(b) (5)



(b) (5)



From: [Conover, Katie](#)
To: [Califf, Robert](#); [Kraus, Tom](#); [Woodcock, Janet](#); [Sharp, Jeremy](#)
Subject: RE: prv's
Date: Monday, October 03, 2016 9:31:13 AM

As promised, here are the PRV talking points that we have been using with media.

While we are supportive of incentivizing research and development into products that treat rare pediatric diseases, the Priority Review Voucher (PRV) programs require the FDA to provide a service (i.e., priority review) that would not otherwise be warranted on the merits for the application for which the voucher is redeemed. This approach is not consistent with FDA's usual approach to determine priorities for its public health work based on the merits of the application under review. In effect, these programs allow sponsors to "purchase" a priority review at the expense of other important public health work in FDA's portfolio. The FDA has very limited resources and the more we are mandated to provide special attention to products that do not warrant such special attention, the less any application can be treated as a priority. The special user fee for redemption of a PRV, while calculated to compensate the FDA for the extra work involved in conducting a priority review on a standard application, does not in practice provide additional review resources to the team responsible for reviewing the application that is the subject of the redeemed voucher.

The FDA has expressed to the Government Accountability Office (as captured in [GAO's report](#)) and in discussions with congressional offices our concerns about the rare pediatric diseases priority review voucher program. FDA supports the goal of incentivizing drug development for rare pediatric diseases, however has expressed concern that the program adversely affects the agency's ability to set its public health priorities by requiring the FDA to provide priority reviews for new drug applications that would not otherwise qualify for priority review as the product covered is not intended to treat a serious condition or provide a significant improvement in safety or effectiveness over existing products.

A few other talk points:

The authorization for the Rare Pediatric Disease Priority Review Voucher program was set to terminate on Oct. 1, 2016. [It has just been extended by Congress.]

Seven vouchers under this program have been issued. Rare Pediatric Disease Priority Review Vouchers have been awarded to the following:

- Vimizim (elosulfase alfa) for the treatment of Mucopolysaccharidosis Type IV A (Morquio A syndrome) (BioMarin) 2014
- Cholbam (cholic acid) for the treatment of bile acid synthesis disorders due to single

enzyme defects and as adjunctive treatment of peroxisomal disorders, including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease or steatorrhea or complications from decreased fat soluble vitamin absorption (Asklepion) 2015

- Unituxin (dinutuximab) for use in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy (United Therapeutics) 2015
- Xuriden (uridine triacetate) for patients with hereditary orotic aciduria (Wellstat) 2015
- Strensiq (asfotase alfa) for perinatal, infantile and juvenile-onset hypophosphatasia (Alexion) 2015
- Kanuma (sebelipase alfa) for lysosomal acid lipase (LAL) deficiency. (Alexion) 2015
- Exondys 51 (eteplirsen) for Duchenne muscular dystrophy (Sarepta) 2016

Vouchers are awarded at the time an application is approved for marketing, per the guidance - <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf> (Q.16 – “Under section 529(a)(2) of the FD&C Act, a priority review voucher is a voucher that FDA issues to the sponsor of a rare pediatric disease product application at the time of the marketing application approval.”

From: Califf, Robert
Sent: Friday, September 30, 2016 9:50 AM
To: Conover, Katie; Kraus, Tom; Woodcock, Janet; Sharp, Jeremy
Subject: RE: prv's

Yes, of course

Thx

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Conover, Katie
Sent: Friday, September 30, 2016 9:49 AM
To: Califf, Robert; Kraus, Tom; Woodcock, Janet; Sharp, Jeremy

Subject: RE: prv's

And the answer is yes – there is some good language in the GAO report on the rare pediatric PRV and some talking points in the KMQA from DMD. Will send some material as soon as possible. Our press officer on this is out today – so it may be Monday, if that's okay...

From: Conover, Katie
Sent: Friday, September 30, 2016 9:36 AM
To: Califf, Robert; Kraus, Tom; Woodcock, Janet; Sharp, Jeremy
Subject: RE: prv's

I am sure we have some good language. I'll look and get back to you.

From: Califf, Robert
Sent: Friday, September 30, 2016 9:33 AM
To: Conover, Katie; Kraus, Tom; Woodcock, Janet; Sharp, Jeremy
Subject: prv's

Do we have a succinct summary of our prv position? I was surprised to see the level of interest in Congress. I guess they all want to be seen as helping one constituency or another!

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: [Pink Sheet](#)
To: [Califf, Robert](#)
Subject: Pink Sheet | Highlights Of The Week
Date: Monday, October 03, 2016 11:54:08 AM

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03 Oct 2016

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WEEKLY HIGHLIGHTS

Look below for key developments and intriguing perspectives from the past week to inform your strategic decision-making. And check out our new hot topic pages on the drug pricing debate and US elections.



THIS WEEK'S TOP STORIES

23 Sep 2016 | **NEWS**

Amgen's Amjevita Approved As First Biosimilar To AbbVie's Humira

By Sue Sutter

Adalimumab-atto is approved for seven indications on the reference product label but lacks four others that are protected by orphan product exclusivity; launch timing is unclear due 'patent dance' litigation.

29 Sep 2016 | **OPINION**

The Eteplirsen Approval: Former FDA Officials Weigh In On The Science

By Ramsey Baghdadi

A former CDER director, office director, division director, and supervisory reviewer

agreed to comment for the record on the merits of the science that formed the basis of FDA's accelerated approval of the Duchenne Muscular Dystrophy therapy Exondys 51.



23 Sep 2016 | **ANALYSIS**

Patient Advocacy With FDA Review Staff Will Be Tougher Post-Sarepta

By Cole Werble

Efforts by CDER management to encourage more interaction between patients and FDA reviewers may be part of the collateral damage from the difficult FDA review of Sarepta's Exondys 51. The hopes of parents of boys with DMD pushed the regulatory flexibility by CDER management on this application – but may end up limiting the willingness of FDA reviewers to engage with patients in the future.



26 Sep 2016 | **NEWS**

Lilly's Sarcoma Drug Lartruvo Latest To Test EU Conditional Approval System

By Ian Schofield

Lartruvo, Lilly's new drug for the rare condition soft tissue sarcoma, has been recommended for conditional marketing authorization in the EU pending the results of an ongoing Phase III study. The conditional approval system itself is under scrutiny regarding the fulfilment of obligations.



23 Sep 2016 | **NEWS**

Dublin The Odds: Ireland Plays On Strengths As It Prepares EMA Bid

By Ian Schofield

Ireland's health minister says the country is preparing to launch a formal bid to host the European Medicines Agency following the UK's decision to quit the EU, claiming it can offer an "excellent track record" in regulating medicines and medical devices, a proactive drugs agency, and a "thriving" pharmaceutical sector.

26 Sep 2016 | **NEWS**

Pfizer Keeps Hands On Consumer Product Wheel In Opting Against Split

By Malcolm Spicer

Pfizer didn't cite its consumer health business in announcing it will retain current structure, but best-selling Lipitor's cholesterol treatment indication is the most coveted indication yet to be available OTC.

27 Sep 2016 | **ANALYSIS**

Novartis Tests Global Manufacturing Process For CAR-T Therapy

By Bowman Cox

Rather than wait for regulatory approval prior to commercial-scale manufacturing, Novartis is proving out its global commercial manufacturing process for a CAR-T cell therapy in a Phase II clinical trial as questions remain on how to translate the manufacturing process from the research laboratory to the factory.

27 Sep 2016 | **ANALYSIS**

A Tale Of Two Committees: Which Probed EpiPen Better?

By Derrick Gingery

If you were an FDA official, would you prefer to be a sideshow at a contentious House committee hearing or the focus of a cordial Senate one?



27 Sep 2016 | **OPINION**

Big Pharma's Big Debate Win

By Michael McCaughan

Sometimes silence is golden. The first Presidential debate had lots of noise – but no discussion of health care, much less drug pricing. And, as an added bonus, both candidates agreed that tax repatriation is a good idea.

28 Sep 2016 | **ANALYSIS**

Duke's McClellan: Changing Drug Development Policy From Outside FDA

By Sue Sutter

In an interview, Margolis Center for Health Policy's Mark McClellan and Gregory Daniel talk about their recent move from Brookings to Duke, the breadth and impact of their work with FDA on drug development issues, and opportunities for potential future collaborations under PDUFA VI.

28 Sep 2016 | **NEWS**

FDA's Drug Promotion Advisory Reviews Taking Longer

By Sue Sutter

FDA is having trouble meeting its internal goal of 45-day reviews for core launch materials due to complex issues that have required medical review division consultations, Office of Prescription Drug Promotion Director Abrams says.



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From: [Marchand, Heidi](#)
To: [Riley, Karen](#)
Subject: FW: Stakeholder Listening Session with the FDA Commissioner on Neurology, Aging, Alzheimer's and Parkinson's Diseases
Date: Thursday, October 06, 2016 4:44:19 PM
Attachments: [Elderly Clinical Trial Participants in NMEs approved in 2015.pdf](#)
[RE Stakeholder Listening Session with the FDA Commissioner on Neurology Aging Alzheimer's and Parkinson's Diseases.msg](#)
[Neuro Listening Session--Briefing Doc 9-30-16.docx](#)

Karen,

We'll be in 32/1243 from 9-12:30 tomorrow! Join if you'd like to. Heidi

From: Marchand, Heidi
Sent: Thursday, October 06, 2016 3:12 PM
To: Califf, Robert; Sherman, Rachel; Fiuzat, Mona; Conover, Katie; Shuren, Jeff; Maisel, William; Como, Peter; Heetderks, William; Gutierrez, Alberto; Pena, Carlos L; Schwartz, Suzanne; O'Callaghan, Kathryn; Tenenbaum, Cara; Marks, Peter; Witten, Celia (CBER); Maloney, Diane; Bryan, Wilson; Woodcock, Janet; Unger, Ellis; Dunn, Billy; Bastings, Eric; Kozauer, Nicholas; Temple, Robert; Whyte, John; Hoffmann, Michael; Pretti, Jeffery
Subject: RE: Stakeholder Listening Session with the FDA Commissioner on Neurology, Aging, Alzheimer's and Parkinson's Diseases

Hi, In 2015, FDA's Center for Drug Evaluation and Research (CDER) approved 47 New Molecular Entities and

published the demographic data of the pivotal trials online in the Drug Trial Snapshots. Below are the demographics for age. Regards, Heidi

Of **all approved NMEs** from 2015 (Table 1):

- 6229 (6%) participants were 80 years old and above.
- 16069 (15%) participants were 75 years old and above

Of all approved NMEs with **Cardiovascular Indications** from 2015 (Table 2):

- 5807 (9%) participants were 80 years old and above.
- 14348 (22%) participants were 75 years old and above

Of all approved NMEs with **Oncology Indications** from 2015 (Table

3):

- 225 (4%) participants were 80 years old and above.
- 643 (10%) participants were 75 years old and above

From: Marchand, Heidi

Sent: Thursday, October 06, 2016 11:36 AM

To: Califf, Robert; Sherman, Rachel; Fiuzat, Mona; Conover, Katie; Shuren, Jeff; Maisel, William; Como, Peter; Heetderks, William; Gutierrez, Alberto; Pena, Carlos L; Schwartz, Suzanne; O'Callaghan, Kathryn; Tenenbaum, Cara; Marks, Peter; Witten, Celia (CBER); Maloney, Diane; Bryan, Wilson; Woodcock, Janet; Unger, Ellis; Dunn, Billy; Bastings, Eric; Brown, Heather (CDER-OEP); Kozauer, Nicholas; Temple, Robert; Whyte, John; Hoffmann, Michael

Subject: RE: Stakeholder Listening Session with the FDA Commissioner on Neurology, Aging, Alzheimer's and Parkinson's Diseases

Dear All, << File: PR_Hearing Aid Sale Guidance_9 30 2016.doc >> << File: Hearing Aids KMQA 09 28 2016.docx >> << File: BRAIN Initiative FY17 Fact Sheet 03-02.pdf >> << File: FDA BRAIN Initiative Announcements and Accomplishments 082516.pdf >> << File: OHOP_approvals_2015_demographics.xlsx >>

Included are updates for the backgrounder for tomorrow's Listening Session that were discussed at our briefing on Monday, October 3. Thanks to all who provided the additional materials.

Regards, Heidi

Conditions for Sale- Hearing Aids

FDA is taking steps to support consumer access to certain hearing aids by no longer enforcing the requirement that patients 18 and up receive a medical exam or waive such an exam prior to purchasing low-risk, air conduction hearing aids. The guidance is expected to publish the week of October 10 and FDA will implement the guidance immediately to assist in addressing a significant public health issue.

Two reports on hearing Aids recently were published:

In 2015, the President's Council on Science and Technology (PCAST) report recommended that the FDA should "approve a class of hearing aids for over-the-counter sale, without the requirement for consultation with a credentialed dispenser," and that "the requirement for a medical examination (or a written waiver of such examination) provides little patient benefit."

A subsequent June 2016 report from National Academies of Sciences, Engineering and Medicine (NAS) concluded that the medical evaluation requirement should be removed for adults as a majority of consumers are already signing the waiver in lieu of a medical

evaluation.

Eteplirsen Approval Standards

The agency reviewed eteplirsen using the appropriate standards for products granted an accelerated approval. Studies conducted to support an accelerated approval must meet the traditional standard of substantial evidence based on adequate and well-controlled clinical investigations. However, what is different for such an approval is that instead of a clinical endpoint, the investigations can rely on an unvalidated surrogate endpoint and the reasonable likelihood that the effect on the surrogate endpoint will predict clinical benefit.

Determining whether an effect on an unvalidated surrogate endpoint is reasonably likely to predict clinical benefit is a matter of judgment based on the biological plausibility of the relationship between the disease, the endpoint, the desired effect and the empirical evidence to support that relationship. In making the determination of whether an effect is reasonably likely to predict clinical benefit, the FDA statute and regulations provide that the agency may consider a broad range of evidence (e.g., epidemiologic, pathophysiologic, pharmacologic).

BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative

FDA's main focus in support of the White House BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative has been to enhance the transparency and predictability of the regulatory landscape for neurological devices (and neurotechnologies) and assisting developers and innovators of medical devices, to bring safe and effective products to patients and consumers.

FDA accomplishments to date include:

- FDA Regulatory Webinar Series: Moving Devices to Market
- Finalizing New Guidance on Neurological Devices Targeting Disease Progression and Clinical Outcomes
- Marketing of first-of-kind computerized cognitive tests to help assess cognitive skills after a head injury

Demographic Data –Age Greater than 80 years

CDER analyzed information by age for NMEs and BLAs approved in 2015 for hematology and oncology medical products. For 14 approvals, data show the following: 54.9% were <65, 17.7% were 65-69, 14.4% were 70-74, 8.2% were 75-79 and 4.8% were 80+.

CDER is also reviewing the data for cardiovascular diseases and hope to have them available for discussion at the October 7 Listening Session.



Memorandum

TO: Robert M. Califf, M.D., Commissioner of Food and Drugs
Janet Woodcock, M.D., Director, CDER

FROM: John J. Whyte, M.D., M.P.H., Director of Professional Affairs and Stakeholder Engagement (PASE)

RE: Elderly Clinical Trial Participants in NMEs approved in 2015

DATE: October 6, 2016

In 2015, FDA's Center for Drug Evaluation and Research (CDER) approved 47 New Molecular Entities and published the demographic data of the pivotal trials online in the Drug Trial Snapshots.

Of **all approved NMEs** from 2015 (Table 1):

- 6229 (6%) participants were 80 years old and above.
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Of all approved NMEs with **Oncology Indications** from 2015 (Table 3):

- 225 (4%) participants were 80 years old and above.
- 643 (10%) participants were 75 years old and above

Elderly Participants in Pivotal Trials | CDER Approved NMEs for 2015

	Brand	Generic	Indication	≥ 65		≥ 75		≥ 80		TOTAL N
1	ADDYI	flibanserin	Treatment of acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women	0	0%	0	0%	0	0%	3099
2	ALECENSA	alectinib	For the treatment of metastatic non-small cell lung cancer	36	14%	10	4%	2	1%	253
3	ARISTADA	aripiprazole laurixil	Treatment of schizophrenia	0	0%	0	0%	0	0%	623
4	AVYCAZ	ceftazidime-avibactam	Treatment of complicated urinary tract infection (abbreviated as cUTI)	23	11%	16	8%	8	4%	203
5	AVYCAZ	ceftazidime-avibactam	Treatment of complicated intra-abdominal infection (abbreviated as cIAI)	23	17%	5	4%	4	3%	135
6	BRIDION	sugammadex	For the reversal of the effects of certain neuromuscular blocking agents	70	14%	14	3%	5	1%	495
7	CHOLBAM	cholic acid	For treatment of bile acid synthesis disorders due to single enzyme defects	0	0%	0	0%	0	0%	44
8	CHOLBAM	cholic acid	For treatment of peroxisomal disorders, including Zellweger spectrum disorders	0	0%	0	0%	0	0%	24
9	CORLANOR	ivabradine	To reduce hospitalization from worsening heart failure.	2474	38%	722	11%	207	3%	6505
10	COSENTYX	secukinumab	Treatment of moderate to severe plaque psoriasis in adults who do not respond well to medication applied directly to the skin	167	8%	29	1%	4	0%	2044
11	COTELLIC	cobimetinib	Part of combination treatment melanoma	133	27%	43	9%	14	3%	495
12	CRESEMBA	isavuconazonium sulfate	Treatment of invasive aspergillosis	125	24%	24	5%	5	1%	516
13	CRESEMBA	isavuconazonium sulfate	Treatment of invasive mucormycosis	5	14%	3	8%	0	0%	37
14	DAKLINZA	daclatasvir	Treatment of chronic Hepatitis C genotype 3 infection	10	7%	0	0%	0	0%	152
15	DARZALEX	daratumumab	Treatment of multiple myeloma	70	45%	16	10%	5	3%	156
16	EMPLICITI	elotuzumab	Treatment of multiple myeloma	370	57%	129	20%	45	7%	646
17	ENTRESTO	secubitril/valsartan	Treatment of heart failure	4120	49%	1563	19%	587	7%	8399
18	FARYDAK	panobinostat	Treatment of multiple myeloma	67	35%	9	5%	0	0%	193
19	GENVOYA†	elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide	Complete regimen for the treatment of HIV-1 in adults and children 12 years of age and older.	0	0%	0	0%	0	0%	23
20	GENVOYA‡	elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide	Complete regimen for the treatment of HIV-1 in adults and children 12 years of age and older.	91	3%	7	0%	1	0%	3171
21	IBRANCE	palbociclib	Treatment of a specific form of advanced breast cancer called ER-positive, HER2-negative (ER+/HER-) breast cancer in women who have gone through menopause (post-menopausal)	76	46%	15	9%	5	3%	165
22	KANUMA(i)	sebelipase alfa	Treatment of Lysosomal Acid Lipase (LAL) deficiency	0	0%	0	0%	0	0%	9
23	KANUMA(ii)	sebelipase alfa	Treatment of Lysosomal Acid Lipase (LAL) deficiency	0	0%	0	0%	0	0%	66
24	KENGREAL	cangrelor	For prevention of coronary artery blood clot formation in patients undergoing PCI	5351	48%	2033	18%	864	8%	11145
25	KYBELLA	deoxycholic acid	Treatment for double chin	14	1%	0	0%	0	0%	1022
26	LENVIMA	lenvatinib	Treatment of progressive, differentiated thyroid cancer (DTC) that can no longer be treated with radioactive iodine	156	40%	38	10%	14	4%	392
27	LONSURF	trifluridine and tipiracil	Treatment of advanced colorectal cancer	352	44%	60	8%	10	1%	800
28	NATPARA	parathyroid hormone	For control of hypocalcemia along with calcium and vitamin D in adults with hypoparathyroidism	8	6%	1	1%	1	1%	124
29	NINLARO	ixazomib citrate	Treatment of multiple myeloma	418	58%	129	18%	45	6%	722
30	ODOMZO	sonidegib	Treatment of locally advanced basal cell carcinoma	125	54%	78	34%	54	23%	230
31	ORKAMBI	lumacaftor/ivacaftor	Treatment of cystic fibrosis	0	0%	0	0%	0	0%	1108
32	PORTRAZZA	necitumumab	For the treatment of metastatic squamous non-small cell lung cancer	421	39%	45	4%	11	1%	1093
33	PRALUENT	alirocumab	Treatment of certain patients with high cholesterol	1203	32%	239	6%	4	0%	3752
34	PRAXBIND	idarucizumab	Reversal of the anticoagulant effects of Pradaxa during emergency situations or when there is a need to reverse its blood-thinning effects.	113	92%	74	60%	54	44%	123
35	REPATHA††	evolocumab	Treatment of certain patients with high cholesterol	1160	28%	138	3%	4	0%	4177
36	REPATHA‡‡	evolocumab	Treatment of certain patients with high cholesterol	0	0%	0	0%	0	0%	49
37	REXULTI	brexpiprazole	Treatment of schizophrenia	3	0%	0	0%	0	0%	1220
38	REXULTI	brexpiprazole	Treatment of major depressive disorder	7	1%	0	0%	0	0%	1054
39	RYZODEG*	insulin degludec and insulin aspart injection	Improves blood sugar control in adults with diabetes mellitus (DM)	25	5%	6	1%	1	0%	548
40	RYZODEG**	insulin degludec and insulin aspart injection	Improves blood sugar control in adults with diabetes mellitus (DM)	486	26%	59	3%	5	0%	1860

Elderly Participants in Pivotal Trials | CDER Approved NMEs for 2015

	Brand	Generic	Indication	≥ 65		≥ 75		≥ 80		TOTAL N
41	SAVAYSA	edoxaban	Prevention of stroke in patients with atrial fibrillation	15543	74%	8462	40%	3569	17%	21026
42	SAVAYSA	edoxaban	Reduction of risk of venous thromboembolism (VTE) in patients with previous VTE	2704	33%	1104	13%	517	6%	8240
43	STIOLTO RESPIMAT	tiotropium bromide and olodaterol	Long-term treatment of COPD	1515	49%	317	10%	65	2%	3100
44	STRENSIQ(^)	trabectedin	Treatment of perinatal, infantile and juvenile-onset hypophosphatasia (HPP)	0	0%	0	0%	0	0%	79
45	STRENSIQ(^)	trabectedin	Treatment of perinatal, infantile and juvenile-onset hypophosphatasia (HPP)	0	0%	0	0%	0	0%	20
46	TAGRISSO	osimertinib mesylate	Treatment of patients with advanced non-small cell lung cancer (NSCLC)	187	45%	54	13%	18	4%	411
47	TRESIBA*	insulin degludec injection	To improve glucose control in adults with diabetes mellitus	107	7%	14	1%	3	0%	1577
48	TRESIBA**	insulin degludec injection	To improve glucose control in adults with diabetes mellitus	969	24%	118	3%	23	1%	4048
49	UNITUXIN	dinutuximab	Treatment of children with high-risk neuroblastoma	0	0%	0	0%	0	0%	226
50	UPTRAVI	selexipag	For the treatment of adults with pulmonary artery hypertension	206	18%	13	1%	1	0%	1152
51	VARUBI	ralapitant	To prevent delayed phase chemotherapy-induced nausea and vomiting	684	26%	124	5%	34	1%	2595
52	VELTASSA	patiromer	Treatment of hyperkalemia	433	61%	150	21%	26	4%	715
53	VIBERZI	eluxadoline	Treatment of irritable bowel syndrome with diarrhea	241	10%	146	6%	1	0%	2425
54	VISTOGARD	uridine triacetate	For the emergency treatment of an overdose with fluorouracil or capecitabine	43	32%	16	12%	3	2%	135
55	VRAYLAR	cariprazine	Treatment of bipolar disorder	2	0%	0	0%	0	0%	1065
56	VRAYLAR	cariprazine	Treatment of schizophrenia	1	0%	0	0%	0	0%	1901
57	XURIDEN	uridine triacetate	Treatment of patients with hereditary orotic aciduria	0	0%	0	0%	0	0%	4
58	YONDELIS	trabectedin	Treatment of certain types of advanced tissue sarcoma	115	22%	17	3%	2	0%	518
59	ZURAMPIC	lesinurad	For lowering uric acid levels in the blood of adult patients with gout	130	13%	29	3%	8	1%	1027
Average				38%		15%		6%		
Totals				40582		16069		6229		107136

Of the 47 NMEs, six had two indications and another six contained two distinct clinical trial populations (e.g., a clinical trial of Type 1 Diabetes and a clinical trial for Type 2 Diabetes within one NME for the same indication) for a total of 59 distinct trial populations that were in the pivotal trials upon which approval of the drug was based.

*Clinical Trial of Type 1 DM patients only

**Clinical Trial of Type 2 DM patients only

† Clinical Trial of Children Only

Clinical Trial of Adults Only

(i) Clinical Trial of Infants Only

(ii) Clinical Trial of Children and Adults

†† Clinical Trial of HeFH Patients

‡‡ Clinical Trial of HoFH Patients

(^) Clinical Trial of Perinatal/Infantile-Onset HPP patients only

(^^) Clinical Trial of Juvenile-Onset HPP patients only

Elderly Participants in Pivotal Trials | Cardiovascular NMEs for 2015

	Brand	Generic	Indication	≥ 65		≥ 75		≥ 80		TOTAL N
1	CORLANOR	ivabradine	To reduce hospitalization from worsening heart failure.	2474	38%	722	11%	207	3%	6505
2	ENTRESTO	secubitril/valsartan	Treatment of heart failure	4120	49%	1563	19%	587	7%	8399
3	KENGREAL	cangrelor	For prevention of coronary artery blood clot formation in patients undergoing PCI	5351	48%	2033	18%	864	8%	11145
4	PRALUENT	alirocumab	Treatment of certain patients with high cholesterol	1203	32%	239	6%	4	0%	3752
5	PRAXBIND	idarucizumab	Reversal of the anticoagulant effects of Pradaxa during emergency situations or when there is a need to reverse its blood-thinning effects.	113	92%	74	60%	54	44%	123
6	REPATHA††	evolocumab	Treatment of certain patients with high cholesterol	1160	28%	138	3%	4	0%	4177
7	REPATHA‡‡	evolocumab	Treatment of certain patients with high cholesterol	0	0%	0	0%	0	0%	49
8	SAVAYSA	edoxaban	Prevention of stroke in patients with atrial fibrillation	15543	74%	8462	40%	3569	17%	21026
9	SAVAYSA	edoxaban	Reduction of risk of venous thromboembolism (VTE) in patients with previous VTE	2704	33%	1104	13%	517	6%	8240
10	UPTRAVI	selexipag	For the treatment of adults with pulmonary artery hypertension	206	18%	13	1%	1	0%	1152
Average				51%		22%		9%		
Totals				32874		14348		5807		64568

†† Clinical Trial of heterozygous familial hypercholesterolemia (HeFH) Patients

‡‡ Clinical Trial of homozygous familial hypercholesterolemia (HoFH) Patients

Elderly Participants in Pivotal Trials | Oncology NMEs for 2015

	Brand	Generic	Indication	≥ 65		≥ 75		≥ 80		TOTAL N
1	ALECENSA	alectinib	For the treatment of metastatic non-small cell lung cancer	36	14%	10	4%	2	1%	253
2	COTELLIC	cobimetinib	Part of combination treatment melanoma	133	27%	43	9%	14	3%	495
3	DARZALEX	daratumumab	Treatment of multiple myeloma	70	45%	16	10%	5	3%	156
4	EMPLICITI	elotuzumab	Treatment of multiple myeloma	370	57%	129	20%	45	7%	646
5	FARYDAK	panobinostat	Treatment of multiple myeloma	67	35%	9	5%	0	0%	193
6	IBRANCE	palbociclib	Treatment of a specific form of advanced breast cancer called ER-positive, HER2-negative (ER+/HER-) breast cancer in women who have gone through menopause (post-menopausal)	76	46%	15	9%	5	3%	165
7	LENVIMA	lenvatinib	Treatment of progressive, differentiated thyroid cancer (DTC) that can no longer be treated with radioactive iodine	156	40%	38	10%	14	4%	392
8	LONSURF	trifluridine and tipiracil	Treatment of advanced colorectal cancer	352	44%	60	8%	10	1%	800
9	NINLARO	ixazomib citrate	Treatment of multiple myeloma	418	58%	129	18%	45	6%	722
10	ODOMZO	sonidegib	Treatment of locally advanced basal cell carcinoma	125	54%	78	34%	54	23%	230
11	PORTRAZZA	necitumumab	For the treatment of metastatic squamous non-small cell lung cancer	421	39%	45	4%	11	1%	1093
12	TAGRISSO	osimertinib mesylate	Treatment of patients with advanced non-small cell lung cancer (NSCLC)	187	45%	54	13%	18	4%	411
13	UNITUXIN	dinutuximab	Treatment of children with high-risk neuroblastoma	0	0%	0	0%	0	0%	226
14	YONDELIS	trabectedin	Treatment of certain types of advanced tissue sarcoma	115	22%	17	3%	2	0%	518
Average				40%		10%		4%		
Totals				2526		643		225		6300

Smith, Celeste

From: Marchand, Heidi
Sent: Thursday, October 06, 2016 11:36 AM
To: Califf, Robert; Sherman, Rachel; Fiuzat, Mona; Conover, Katie; Shuren, Jeff; Maisel, William; Como, Peter; Heetderks, William; Gutierrez, Alberto; Pena, Carlos L; Schwartz, Suzanne; O'Callaghan, Kathryn; Tenenbaum, Cara; Marks, Peter; Witten, Celia (CBER); Maloney, Diane; Bryan, Wilson; Woodcock, Janet; Unger, Ellis; Dunn, Billy; Bastings, Eric; Brown, Heather (CDER-OEP); Kozauer, Nicholas; Temple, Robert; Whyte, John; Hoffmann, Michael
Subject: RE: Stakeholder Listening Session with the FDA Commissioner on Neurology, Aging, Alzheimer's and Parkinson's Diseases



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Hearing Aids



BRAIN Initiative
FY17 Fact She...



FDA BRAIN
Initiative Annou...



OHOP_approval...

Dear All,

Included are updates for the backgrounder for tomorrow's Listening Session that were discussed at our briefing on Monday, October 3. Thanks to all who provided the additional materials.

Regards, Heidi

Conditions for Sale- Hearing Aids

FDA is taking steps to support consumer access to certain hearing aids by no longer enforcing the requirement that patients 18 and up receive a medical exam or waive such an exam prior to purchasing low-risk, air conduction hearing aids. The guidance is expected to publish the week of October 10 and FDA will implement the guidance immediately to assist in addressing a significant public health issue.

Two reports on hearing Aids recently were published:

In 2015, the [President's Council on Science and Technology \(PCAST\) report](#) recommended that the FDA should "approve a class of hearing aids for over-the-counter sale, without the requirement for consultation with a credentialed dispenser," and that "the requirement for a medical examination (or a written waiver of such examination) provides little patient benefit."

A subsequent June 2016 [report from National Academies of Sciences, Engineering and Medicine \(NAS\)](#) concluded that the medical evaluation requirement should be removed for adults as a majority of consumers are already signing the waiver in lieu of a medical evaluation.

Eteplirsen Approval Standards

The agency reviewed eteplirsen using the appropriate standards for products granted an accelerated approval. Studies conducted to support an accelerated approval must meet the traditional standard of substantial evidence based on adequate and well-controlled clinical investigations. However, what is different for such an approval is that instead of a clinical endpoint, the investigations can rely on an unvalidated surrogate endpoint and the reasonable likelihood that the effect on the surrogate endpoint will predict clinical benefit.

Determining whether an effect on an unvalidated surrogate endpoint is reasonably likely to predict clinical benefit is a matter of judgment based on the biological plausibility of the relationship between the disease, the endpoint, the desired effect and the empirical evidence to support that relationship. In making the determination of whether an effect is reasonably likely to predict clinical benefit, the FDA statute and regulations provide that the agency may consider a broad range of evidence (e.g., epidemiologic, pathophysiologic, pharmacologic).

BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative

FDA's main focus in support of the White House BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative has been to enhance the transparency and predictability of the regulatory landscape for neurological devices (and neurotechnologies) and assisting developers and innovators of medical devices, to bring safe and effective products to patients and consumers.

FDA accomplishments to date include:

- FDA Regulatory Webinar Series: Moving Devices to Market

- Finalizing New Guidance on Neurological Devices Targeting Disease Progression and Clinical Outcomes

- Marketing of first-of-kind computerized cognitive tests to help assess cognitive skills after a head injury

Demographic Data –Age Greater than 80 years

CDER analyzed information by age for NMEs and BLAs approved in 2015 for hematology and oncology medical products. For 14 approvals, data show the following: 54.9% were <65, 17.7% were 65-69, 14.4% were 70-74, 8.2% were 75-79 and 4.8% were 80+.

CDER is also reviewing the data for cardiovascular diseases and hope to have them available for discussion at the October 7 Listening Session.

Key Messages & Responsive QA: Immediately in Effect Guidance Document: Conditions for Sale for Hearing Aids

Updated: 9/28/16

SECTION I: TOP LINE MESSAGES

1. The FDA is taking steps to better support consumer access to certain hearing aids by no longer enforcing the requirement that patients 18 and up receive a medical exam or waive such an exam prior to purchasing certain low-risk, air conduction hearing aids. This guidance is being released as “immediately-in-effect” to ease reported barriers to access for current and prospective hearing aid users 18 years of age and older.
2. The FDA will be changing the regulation for such medical exams through its public rule making process, so that the exams will no longer be required. However, the FDA continues to recommend that all prospective hearing aid users with suspected or known hearing loss have a medical evaluation to rule out any treatable medical conditions for their hearing loss.
3. While the FDA is working on modifying the “conditions for sale” regulations for hearing aids, the FDA will not enforce the medical evaluation or waiver, and recordkeeping requirements for users 18 years of age and older, and will work to eventually remove the requirement.

SECTION II: KEY MESSAGES

The FDA is taking steps to better support consumer access to certain hearing aids by no longer enforcing the requirement that patients 18 and up receive a medical exam or waive such an exam prior to purchasing certain low-risk, air conduction hearing aids. This guidance is being released as “immediately-in-effect” to ease reported barriers to access for current and prospective hearing aid users 18 years of age and older.

- FDA regulations requiring medical evaluations as a condition for sale for hearing aids have been cited as presenting barriers to availability and accessibility of hearing aids for users 18 years of age or older.
- An October 2015 President's Council on Science and Technology (PCAST) report recommended that the FDA should “approve a class of hearing aids for over-the-counter sale, without the requirement for consultation with a credentialed dispenser,” and that “the requirement for a medical examination (or a written waiver of such examination) provides little patient benefit.”
- A subsequent June 2016 report from National Academies of Sciences, Engineering and Medicine (NAS) concluded that the medical evaluation requirement should be removed for adults as a majority of consumers are already signing the waiver in lieu of a medical evaluation.

Key Message #2: The FDA will be changing the regulation for such medical exams through its public rule making process, so that the exams will no longer be required. However, the FDA continues to recommend that all prospective hearing aid users with suspected or known hearing loss have a medical evaluation to rule out any treatable medical conditions for their hearing loss.

- Despite the high prevalence and public health impact of hearing loss, only about one-fifth of people that could benefit from a hearing aid seek intervention.
- A medical evaluation can be a useful tool in diagnosing a medical or surgically treatable cause of hearing loss, such as infection, autoimmune disease, injury or deformity, ear wax in the ear canal, and in rare cases, tumors.
- Early diagnosis of the cause of hearing loss may lead to a better outcome, such as preserving your hearing or preventing the progression of hearing loss.
- Children with hearing loss have specific needs and health concerns that make medical evaluation important, therefore, they are still required to have a medical evaluation prior to being sold and fitted with a hearing aid.

Key Message #3: While the FDA is working on modifying the “conditions for sale” regulations for hearing aids, the FDA will not enforce the medical evaluation or waiver, and recordkeeping requirements for users 18 years of age and older, and will work to eventually remove the requirement.

- Hearing aid dispensers are still required to make available, and provide prospective users an opportunity to review the User Instructional Brochure containing specific labeling requirements, before the sale of a hearing aid device. Only users 18 years of age and older may purchase hearing aids without a medical evaluation or waiver.

Current and prospective hearing aid users can also find more information by visiting the [FDA’s website on Hearing Aids](#).

SECTION III: RESPONSIVE QA

Q1: What rulemaking is being proposed in relation to this issue? When can we expect that?

The FDA intends to revise regulation 21 CFR 801.421 to remove the requirement for medical evaluation, or waiver of medical evaluation, for users over 18 years of age. In the meantime, this guidance will address NAS’ recommendations as we do not intend to enforce the medical evaluation requirement for users aged 18 and older in order to help increase accessibility and use of hearing aids.

The FDA does not have a timeframe as to when a revised regulation will be issued.

Q2: Is this guidance a move towards the FDA regulating hearing aids in the same way that other over-the-counter (OTC) medical devices are regulated?

Yes, to the extent that consumers do not need to undergo a medical examination prior to the purchase of other OTC medical devices. The FDA is also considering additional regulatory actions to promote access to hearing aids for adult consumers with mild to moderate hearing loss.

Q3: How is this new guidance likely to affect the dispensing of hearing aids?

The FDA expects that this guidance will ease the burden on sales for both hearing aid dispenser and users. Previous recordkeeping requirements which mandated completion of a medical evaluation or a waiver will no longer apply to users 18 years of age or older.

These changes also provide an opportunity for consumers to become more informed about the benefits, risks and other important information regarding hearing aid use, as dispensers are required to provide all prospective users with an opportunity to review the *User Instructional Brochure* prior to the sale of a hearing aid device.

Q4: Why is this guidance immediately-in-effect? What has spurred the rush to implementation? Will this guidance be open for public comments?

The FDA believes that immediate implementation of the guidance is needed to assist in addressing a significant public health issue; furthermore, this guidance document presents a position that is more consistent with protecting and promoting public health.

The policy changes indicated in this guidance are the result of feedback we gathered from public workshops, consumers, healthcare professionals and the medical device industry, as well as reports from the National Academies of Sciences, Engineering and Medicine (NAS), and the President's Council of Advisors on Science and Technology (PCAST). We also gathered information from many groups of stakeholders who could be affected, and we believe this guidance exemplifies the FDA's commitment to partnering with consumers and industry on policy changes.

This guidance is final and immediately in effect, and there is not a specific timeframe for comments. The public can still comment at anytime at: <https://www.regulations.gov/>, and the FDA will consider all comments received and revise the guidance document as appropriate.

SECTION IV: ADDITIONAL RESOURCES

- [21 CFR 801.420 \(Hearing aid devices; professional and patient labeling\)](#)
- [Previous Guidance \(11/7/13\): Regulatory Requirements for Hearing Aid Devices and Personal Sound Amplification Products - Draft Guidance for Industry and Food and Drug Administration Staff](#)
- [PCAST Report on Hearing Aids \(Oct. 2015\): Aging America & Hearing Loss: Imperative of Improved Hearing Technologies](#)
- [Public Workshop \(4/21/16\): Streamlining Good Manufacturing Practices \(GMPs\) for Hearing Aids](#)
- [National Academies of Sciences, Engineering and Medicine \(NAS\) Report \(6/2/16\): Hearing Health Care for Adults: Priorities for Improving Access and Affordability](#)

SECTION V: POINTS OF CONTACT

Eric Mann, Srinivas Nandkumar – ODE Subject Matter Experts
Aisha Coffey – OCE Communications Project Manager
Theresa Eisenman – OMA Press Officer

Close Hold - Draft - Deliberative

FDA NEWS RELEASE

For Immediate Release: Oct. XX, 2016

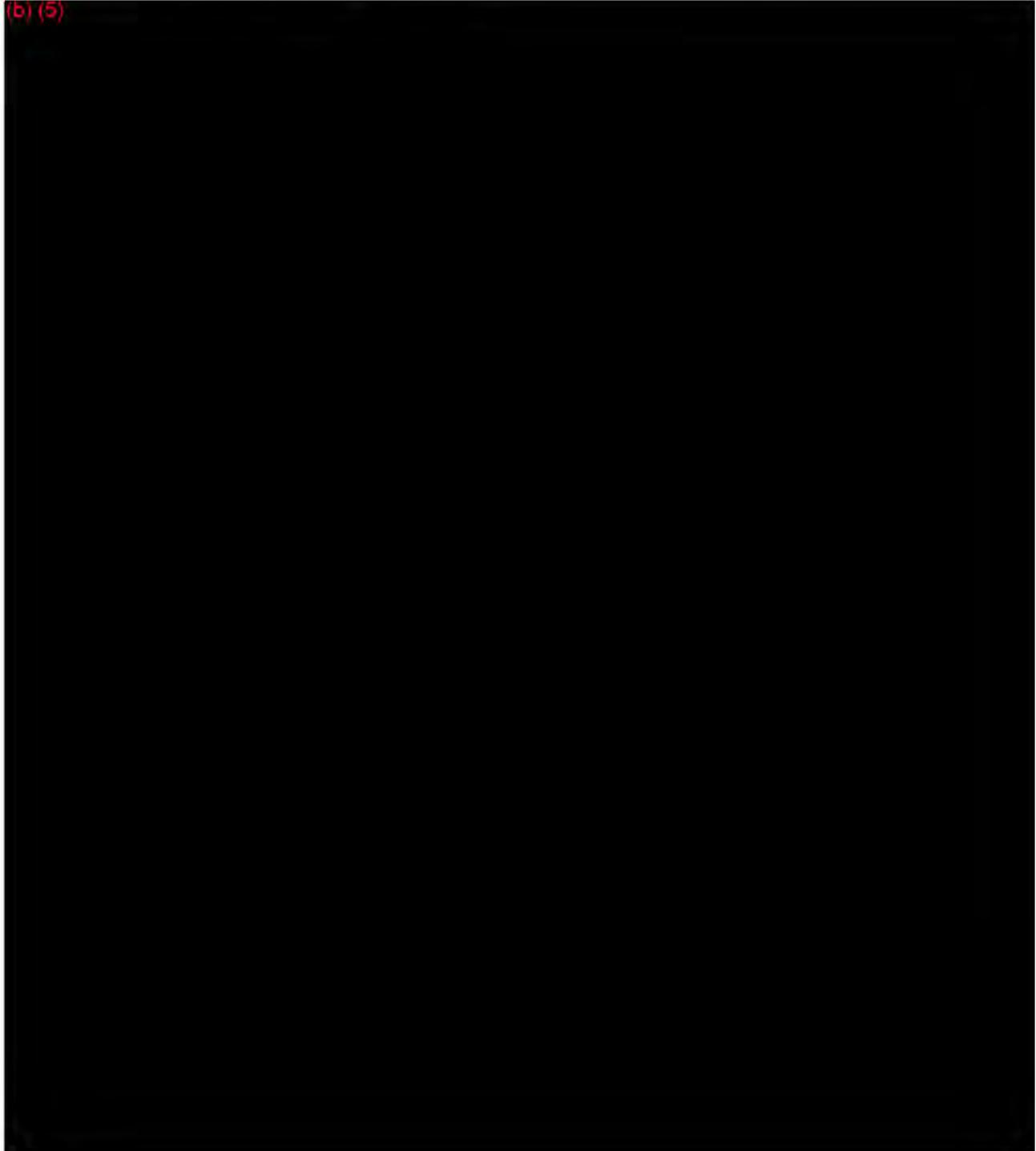
Media Inquiries: Theresa Eisenman, 301-796-2969, theresa.eisenman@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

FDA issues guidance to make hearing aids more accessible

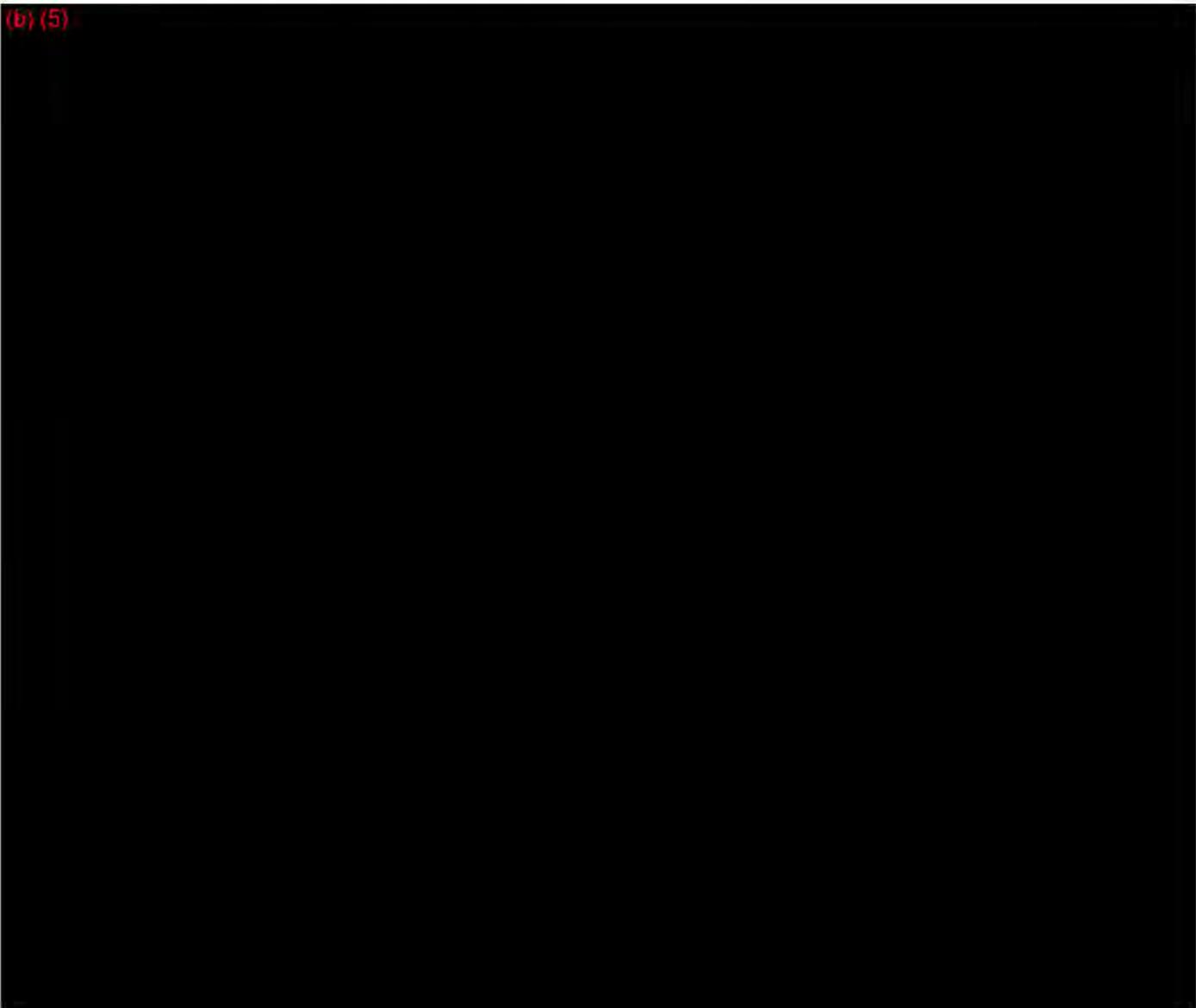
Guidance "Immediately in Effect"

(b) (5)



Close Hold - Draft - Deliberative

(b) (5)





Obama Administration Proposes Over \$434 Million in Funding for the BRAIN Initiative

“Last year, I launched the BRAIN Initiative to help unlock the mysteries of the brain, to improve our treatment of conditions like Alzheimer’s and autism and to deepen our understanding of how we think, learn and remember. I’m pleased to announce new steps that my Administration is taking to support this critical research, and I’m heartened to see so many private, philanthropic, and academic institutions joining this effort.”

- President Barack Obama
September 2014

Since its launch in April 2013, the President’s BRAIN Initiative[®] - Brain Research through Advancing Innovative Neurotechnologies – has grown to include investments from five Federal agencies: the Defense Advanced Research Projects Agency (DARPA), the National Institutes of Health (NIH), the National Science Foundation (NSF), Intelligence Advanced Research Projects Activity (IARPA), and the Food and Drug Administration (FDA). Federal agencies are supporting the initiative by investing in promising research projects aimed at revolutionizing our understanding of the human brain, developing novel technologies, and supporting further research and development in neurotechnology. The President’s 2017 Budget also proposes funding for the Department of Energy (DOE) to join DARPA, NIH, NSF, IARPA, and FDA in advancing the goals of the BRAIN Initiative.

Major foundations, private research institutions, and companies including the Howard Hughes Medical Institute, Allen Institute for Brain Science, the Kavli Foundation, GE, GlaxoSmithKline, as well as patient advocacy organizations and universities, have committed over \$500 million to the BRAIN Initiative. There are many opportunities for others across sectors to play a role in this historic initiative through new and expanded commitments to advance the BRAIN Initiative.

The President’s 2017 Budget proposes to increase the Federal investment in the BRAIN Initiative from about \$300 million in FY 2016 to more than \$434 million in FY 2017. Proposed investments by the NIH, NSF, DARPA, DOE, IARPA, and FDA are described below.

National Institutes of Health (NIH): In FY 2017, the President’s budget calls for NIH to provide an estimated \$190 million in funding for the BRAIN Initiative. This investment will support a diverse set of projects with ambitious goals, including efforts towards creating a complete accounting of the cellular components of brain circuits in various vertebrate species; creation of tools and infrastructure to address big data from these cell census projects; developing breakthrough neuroimaging technologies to study human brain function; and support for broad research teams to understand how patterns of neural activity at multiple spatial and temporal scales that span from local circuits to complex interconnected networks give rise to mental experience and behavior. Together these efforts aim to create a dynamic picture of the brain in action, providing the critical knowledge base for researchers seeking new ways to treat, cure, and even prevent brain disorders.

The BRAIN Initiative at NIH is guided by *BRAIN 2025: A Scientific Vision*, a multi-year scientific plan developed by a working group of the Advisory Committee to the NIH Director and informed by broad input from the scientific community, patient advocates, and the general public. Additionally, NIH investment in the initiative is informed by a BRAIN Multi-Council Working Group of esteemed experts in numerous disciplines who assist in ensuring a coordinated and focused effort across the agency. NIH is also working in close collaboration with other government agencies and private partners to ensure the success of the BRAIN Initiative investments. NIH issued 67 new awards in FY 2015, totaling more than \$38 million, to support 131 investigators working at 125 institutions in the United States and eight other countries. These awards expand NIH's efforts to develop new tools and technologies to understand neural circuit function and capture a dynamic view of the brain in action. Projects include proposals to develop soft self-powered brain electrodes, ultrasound methods for measuring brain activity, and the use of deep brain stimulation to improve the level of consciousness in persons suffering from severe traumatic brain injuries. For FY 2016 and beyond, NIH awards will continue to support critical objectives of *BRAIN 2025*, including development of tools to analyze cells and circuits and technologies for large-scale neuronal recording and modulation. The initiative will also expand to encompass new areas of emphasis. Of particular note are new efforts towards understanding human brain function and treating human brain disorders. These include new tools and more sophisticated understanding of non-invasive neuromodulation techniques, and studies to understand the signals underlying non-invasive imaging modalities. NIH is also expanding its portfolio of research with implantable neuromodulation devices, including a new BRAIN Public Private Partnership Program, which connects academic researchers with manufacturers of next-generation invasive devices for recording and modulation in the human central nervous system. To understand the unique properties and functions of human neural circuits, NIH is supporting research opportunities for studies with neurosurgical patients. Finally, separate announcements will fund development of new theories, models, and methods to analyze complex neural data, and technology dissemination grants for researchers to learn new techniques and take advantage of the technologies developed under the BRAIN Initiative. NIH is also engaging investigators to explore important neuro-ethical issues in modern brain science.

Defense Advanced Research Projects Agency (DARPA): In FY 2017, DARPA plans to invest an estimated \$118 million to support the BRAIN Initiative. DARPA's investments aim to leverage nervous system research to alleviate the burden of illness and injury and provide novel, neurotechnology-based capabilities for military personnel and civilians alike. In addition, DARPA is fostering advances in neural interfaces, data handling, imaging and advanced analytics to improve researchers' understanding of interactions across the entire nervous system.

In FY 2017, the Restoring Active Memory (RAM) effort will continue research to develop quantitative models of the neurobiological mechanisms underlying knowledge and skill-based memory encoding and recall in people. These models will be integrated into neural interface systems that operate in real time to restore a patient's ability to encode new memories and learn new skills with the goal of accelerating warfighter recovery after traumatic brain injury. DARPA's Systems-Based Neurotechnology for Emerging Therapies (SUBNETS) program will continue to develop the first set of prototype closed-loop medical devices able to measure and

modulate networks of neurons in research participants with intractable psychiatric illness and alleviate severe symptoms of diseases such as post-traumatic stress disorder, major depression and general anxiety disorder. In 2017, SUBNETS will build upon current research to further reduce key symptoms such as anxiety in clinical populations. DARPA-funded researchers are developing new methods to analyze large datasets of neural signals, allowing investigators to rapidly and transparently solve complex problems of computation, generate new models and model the brain in multiple dimensions and spatiotemporal scales. In 2017, the Neuro-Function, Activity, Structure and Technology (Neuro-FAST) program will use optical and photonic techniques to continue developing state-of-the-art imaging and discovery tools to build upon its demonstrated ability to sense the structure and activity of thousands of neurons simultaneously in the active brain. Achieving stable, high-resolution imagery over multiple experiments promises new insights into brain function and clues to treat injury. The Hand Proprioception and Touch Interfaces (HAPTIX) program is developing implantable medical devices for amputees to enable natural sensation from and control of prosthetic hands. HAPTIX investigators have demonstrated that peripheral nerve stimulation allows amputees to feel vivid sensations of touch and proprioception. Additionally, HAPTIX has enabled the first take-home trial of a prosthetic hand outfitted with the sense of touch, achieving an important milestone in DARPA's efforts to move this technology out of the lab and into the real world. The Electrical Prescriptions (ElectRx) program is developing novel technology for diagnosing, monitoring and treating inflammatory disease and mental health disorders by modulating the peripheral nerve circuits that maintain physical and mental health. In 2017, ElectRx will leverage new technologies for achieving precise, peripheral nerve stimulation and initial mapping of the neural circuits to modulate peripheral nerves implicated in target diseases, such as immunological dysfunction and post-traumatic stress disorder. The Neural Engineering System Design (NESD) program is a new DARPA effort that aims to develop an implantable neural interface able to provide unprecedented signal resolution and data-transfer bandwidth between the brain and the digital world. FY17 goals are to develop algorithms and initial prototype hardware devices and neural transducers to read and write to individual neurons with a spatial resolution beyond the state of the art.

National Science Foundation (NSF): In FY 2017, NSF plans to invest \$74 million to support the BRAIN Initiative. To attain a fundamental scientific understanding of the complexity of the brain, in context and in action, NSF investments in the BRAIN Initiative will generate an array of physical and conceptual tools needed to determine how healthy brains function across the lifespan. NSF will also focus on the development and use of these tools to produce a comprehensive understanding of how thoughts, memories, and actions emerge from the dynamic actions of the brain. NSF prioritizes research in three areas where the agency's capacities are uniquely strong: integrative and interdisciplinary research; new theories, computational models, and analytical tools that will guide research questions and analyze experimental data; and the development of innovative technologies and data infrastructure required to handle the large-scale datasets resulting from this research. NSF has made significant investments in FY 2015 to support the BRAIN Initiative including \$13 million for 16 new awards in Integrated Strategies for Understanding Neural and Cognitive Systems and \$15 million for three collaborative projects designed to crack the olfactory code. In FY 2017, NSF will further the plans to create a National Brain Observatory and to coordinate large-scale brain research projects internationally to leverage global investments to maximize advancement of this complex area of science.

Department of Energy (DOE): The DOE plans to invest \$9 million to the BRAIN Initiative focused on the development of enabling technologies, with respect to three major themes: developing the specialized, high-resolution tools for measuring key neurological processes, developing the capabilities for obtaining a dynamic, real-time read-out of these measurements, and developing the integrated computational framework for analyzing and interpreting this dynamic multi-modal data. Developing the tools to integrate and synthesize multimodal data on the brain and nervous system would be unprecedented and would inform other analyses of complex systems. A workshop will be held in FY 2016 to inform the priority requirements for developing novel biosensors and probes that can measure key molecular components or processes relevant to neuroscience.

Intelligence Advanced Research Projects Activity (IARPA): In FY17, the Intelligence Advanced Research Projects Activity (IARPA) is proposing \$43 million to continue investing in applied neuroscience research programs focused in three areas: (1) advancing understanding of cognition and computation in the brain; (2) developing non-invasive neural interventions that have the potential to significantly improve adaptive reasoning and problem solving; and (3) building novel computing systems that employ neurally-inspired components and architectures.

Food and Drug Administration (FDA): FDA supports the BRAIN Initiative by enhancing the transparency and predictability of the regulatory landscape for neurological devices and assisting developers and innovators of medical devices, which is critical to realizing the investments made in the research and development technology sectors. In FY 2017, FDA's Center for Devices and Radiological Health intends to facilitate the timely development of high quality, safe and effective novel neurological medical products by issuing new guidance on innovative neurostimulation and neurointerventional medical devices, leading BRAIN Initiative related public workshops on topics such as Traumatic Brain Injury, and hosting publicly accessible webinars introducing developers and innovators on how to efficiently move a product to market. FDA also plans to rely on postmarket data collection to support new product approvals or in lieu of some premarket evidence generation, where appropriate. FDA will continue to engage all stakeholders, including patients, to assist developers and innovators in moving safe and effective products to the market. FDA remains committed to continuing its role under the BRAIN Initiative in making as transparent as possible the regulatory framework applicable to neurological devices and thereby helping to bring safe and effective products to patients and consumers.

FDA BRAIN Initiative Announcements & Accomplishments for a Fall White House Event (Date TBD)

Current FDA Events and Announcements

New FDA Regulatory Webinar Series: Moving Devices to Market

As part of the FDA's ongoing effort to assure patients and providers have timely and continued access to safe, effective, and high-quality medical devices, the FDA is hosting a regulatory webinar series for medical device clinical investigators and sponsors on how to participate in bringing innovative medical devices to the United States marketplace. This webinar series is part of the FDA's continuing support of the White House Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative focused on understanding the human brain and uncovering new ways to treat, cure, and prevent brain disorders. The Fall webinar, scheduled for September 14, 2016 (10am-12pm) and hosted by the FDA will focus on: Neurological Devices, Initiating a Medical Device Study, and Investigational Device Exemptions (IDEs); First in Human Studies, Early Feasibility Studies, and Traditional Feasibility Studies; and FDA Engagement and the Pre-Submission process. Winter and spring webinars are also planned.

FDA Fall Flier attached

Finalizing New Guidance on Neurological Devices Targeting Disease Progression and Clinical Outcomes

On March 7, 2016, the U.S. Food and Drug Administration (FDA) issued the draft guidance for public comment, Clinical Considerations for Investigational Device Exemptions (IDEs) for Neurological Devices Targeting Disease Progression and Clinical Outcomes. The FDA recognizes the value of medical device innovation to address unmet clinical needs and improve patient care, particularly when novel treatments may revolutionize how we treat neurological diseases or conditions. The FDA developed the draft guidance to assist sponsors, who intend to submit investigational device exemption (IDE) applications to the FDA to conduct clinical trials on medical devices targeting neurological disease progression and clinically meaningful patient-centered outcomes. Medical devices intended to slow, stop, or reverse the effects of neurological disease (neurological devices) face challenges with regard to collecting safety and efficacy data in a clinical study, when less invasive pharmacotherapy approaches may be better understood or more accepted in the clinical community. The FDA's Center for Devices and Radiological Health (CDRH) is issuing this draft guidance for industry and FDA staff to assist in considering the benefits and risks of medical devices that target either the cause or progression of the neurological disorder or condition such as Alzheimer's disease, Parkinson's Disease, or Primary Dystonia, rather than their symptoms, and importantly, address unmet

medical needs of patients. The public comment period closed June 6, 2016. The FDA received and is currently reviewing the comments in an effort to finalize the guidance before the end of 2016.

Link to Draft Guidance:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM489111.pdf>

FDA allows marketing of first-of-kind computerized cognitive tests to help assess cognitive skills after a head injury

The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) and ImPACT Pediatric are the first medical devices that are intended to assess cognitive function following a possible concussion. They are intended as part of the medical evaluation that doctors perform to assess signs and symptoms of a head injury. ImPACT software runs on a desktop or laptop and is intended for those ages 12 to 59, while the ImPACT Pediatric runs on an iPad and is designed for children ages 5 to 11. Only licensed health care professionals should perform the test analysis and interpret the results.

The device is manufactured by ImPACT Applications, located in Pittsburgh, PA.

Press Release- <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm517526.htm>

Additional Noteworthy Past Announcements and Accomplishments (2014-2016)

FDA unveils Expedited Access Pathway Program to Address Unmet Medical Needs (2016)

The FDA's Center for Devices and Radiological Health has proposed a new Expedited Access Pathway (EAP) voluntary program for certain medical devices, including devices applicable to The BRAIN Initiative, that demonstrate the potential to address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions. This new program provides an expedited pathway to market for qualified devices. Under EAP, the FDA works with device sponsors to try to reduce the time and cost from development to marketing decision without changing the FDA's premarket approval (PMA) statutory standard of reasonable assurance of safety and effectiveness, the standards for granting *de novo* classification requests, or our standard of valid scientific evidence. Components of the program include priority review, more interactive review, senior management involvement, and assignment of a case manager. The extent to which the FDA provides these features depends on the availability of resources. Participation in the EAP program is only at the request of the sponsor and with the FDA's agreement. If the FDA determines that a device may be eligible for this program and the sponsor has not yet submitted a pre-submission (please see the [guidance](#) on CDRH's pre-submission program) requesting EAP Designation, the FDA intends to inform the sponsor of the program.

Link to more information:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm441467.htm>

DARPA and FDA sign Memorandum of Understanding to move products faster to the military personnel and the American public (2016)

This year, the Defense Advanced Research Projects Agency (DARPA) and the FDA signed a new memorandum of understanding to move products from research to market faster, especially for military service personnel and American patients and consumers. The DARPA creates breakthrough technologies for national security and the FDA reviews data supporting the safety and effectiveness of medical devices and decides whether they may be approved, licensed, cleared, or authorized for use. The DARPA and the FDA realize that open communication and close coordination is essential if the investments made in the latest technologies emerging from the biological sciences are to be realized. Under this new agreement, the DARPA and the FDA plan to partner and facilitate innovation of medical products, including neurosensing, neuromodulation, and neurostimulation devices for the treatment of neurologic and psychiatric deficits and other neurological and physical medicine devices.

Investing in Traumatic Brain Injury: FDA Holds Public Meeting to Advance Biomarker Development (2016)

Traumatic Brain Injury (TBI) remains a major public health problem in our society, and it is a contributing factor in a third of all injury-related US deaths. Among TBI, mild TBI (mTBI) is estimated to account for 80–90% of diagnoses. The importance of apparently mild injuries has been recognized as a major public health crisis¹. Growing concerns about the long-term sequelae of mild TBI in civilian populations, military personnel, and sports participants make this a clinically important topic. These concerns also give rise to a greater awareness of the need to find better ways to diagnose, treat, and prevent all forms of TBI, with a strong emphasis on mTBI. This FDA workshop held March 3, 2016 aimed to examine potential biomarkers, discuss the challenges and solutions related to biomarker development methodologies, and establish strategies for data standardization in, and sharing and analysis of big data sets for TBI. By convening the relevant stakeholders, the FDA sought input on the scientific, clinical, patient, and regulatory considerations associated with developing biomarkers for TBI to improve the clinical utility of these markers and the diagnosis of TBI. The FDA is currently reviewing the meeting proceedings to develop potential approaches to advance the development of biomarkers in TBI.

Link to Public Workshop:

<http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm483551.htm>

Understanding Cognition (2015)

The FDA held a public workshop, “Neurodiagnostics and Non-Invasive Brain Stimulation Medical Devices”, on November 19-20, 2015. The workshop focused on two primary topics, non-invasive medical devices to evaluate cognitive function and non-invasive brain stimulation devices to improve or influence cognitive function. Through this workshop, the FDA obtained public input on scientific, clinical, and regulatory considerations associated with medical devices for assessing and influencing cognitive function. At the workshop, the FDA also convened a panel of representatives from the Consumer Product Safety Commission, Defense Advanced Research Projects Agency, Federal Trade Commission, Intelligence Advanced Research Projects Agency, National Institutes of Health and National Science Foundation to discuss communication and coordination across the federal government for non-invasive brain stimulation.

¹ Control NCFIPa. Report to Congress on mild traumatic brain injury in the United States: steps to prevent a serious public health problem. Atlanta, GA: Centers for Disease Control and Prevention, 2003.

The panel also discussed the White House BRAIN Initiative and strategies for moving products to the marketplace.

Link to Public Workshop:

<http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm458018.htm>

FDA approves expanded indication for medical device to treat a form of brain cancer (2015)

The Novocure Inc. Optune System is intended to treat patients with newly-diagnosed glioblastoma multiforme (GBM), an aggressive form of brain cancer. The device delivers low-intensity, alternating electrical fields called tumor treatment fields. GBM tumor cells are especially susceptible to damage when exposed to these fields, which may halt tumor growth. The device is portable and can be powered with batteries or plugged into an electrical outlet. Patients can use the device at home or work, allowing them to continue their normal daily activities. Patients using the device with chemotherapy survived for an average of 19.4 months compared to an average of 16.6 months for those treated with only chemotherapy. The device was reviewed under the FDA's priority review program, which provides for an expedited review of certain devices to treat life-threatening conditions.

The Optune System is made by Novocure Inc. of Portsmouth, NH.

Press Release- <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm465744.htm>

FDA allows marketing of first prosthetic arm that translates signals from person's muscles to perform complex tasks (2014)

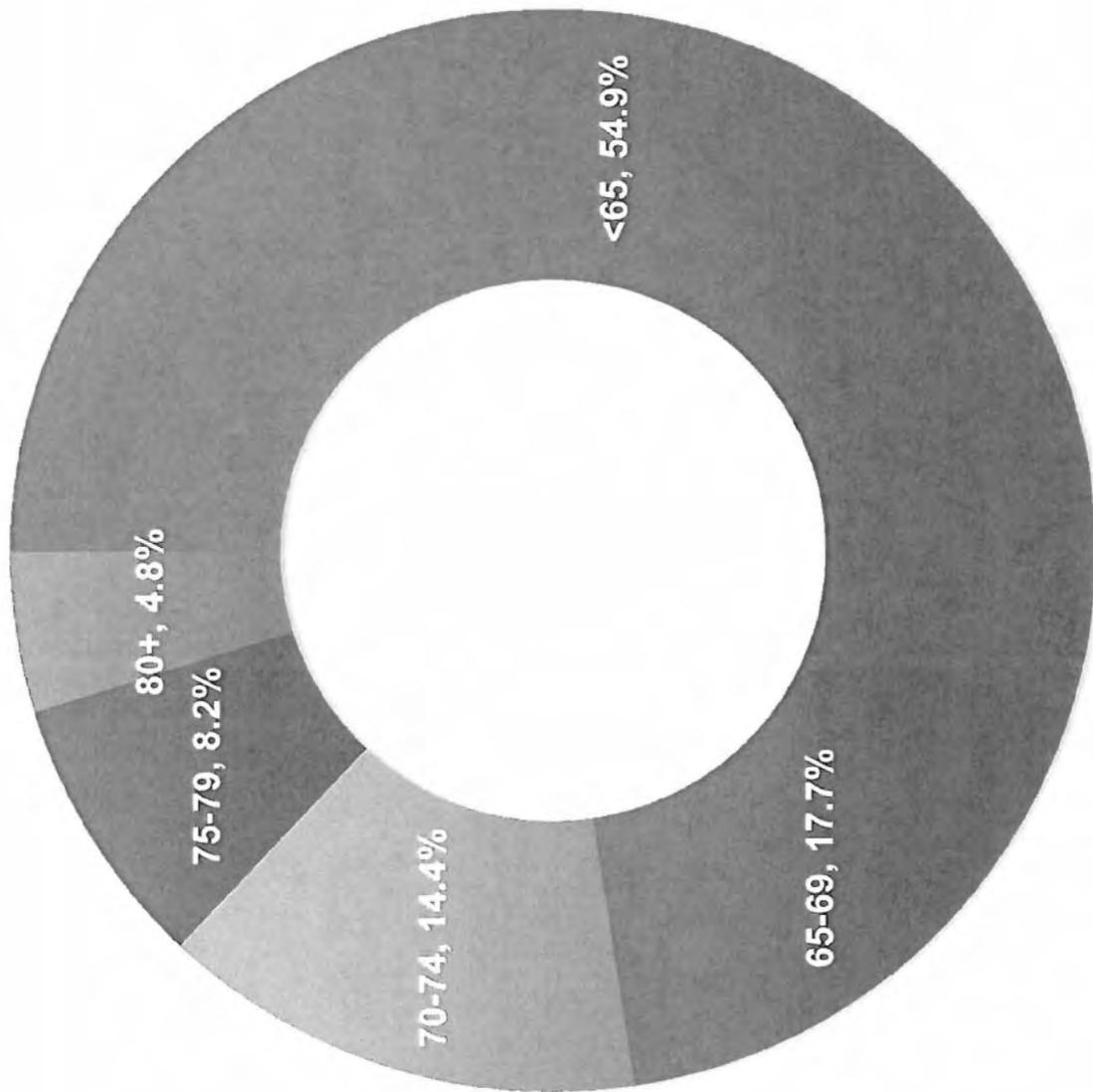
The DEKA Arm System, the first prosthetic arm that can perform multiple, simultaneous powered movements controlled by electrical signals from electromyogram (EMG) electrodes. The EMG electrodes in the DEKA Arm System convert electrical signals into up to 10 powered movements, and it is the same shape and weight as an adult arm. In addition to the EMG electrodes, the DEKA Arm System contains a combination of mechanisms including switches, movement sensors, and force sensors that cause the prosthesis to move.

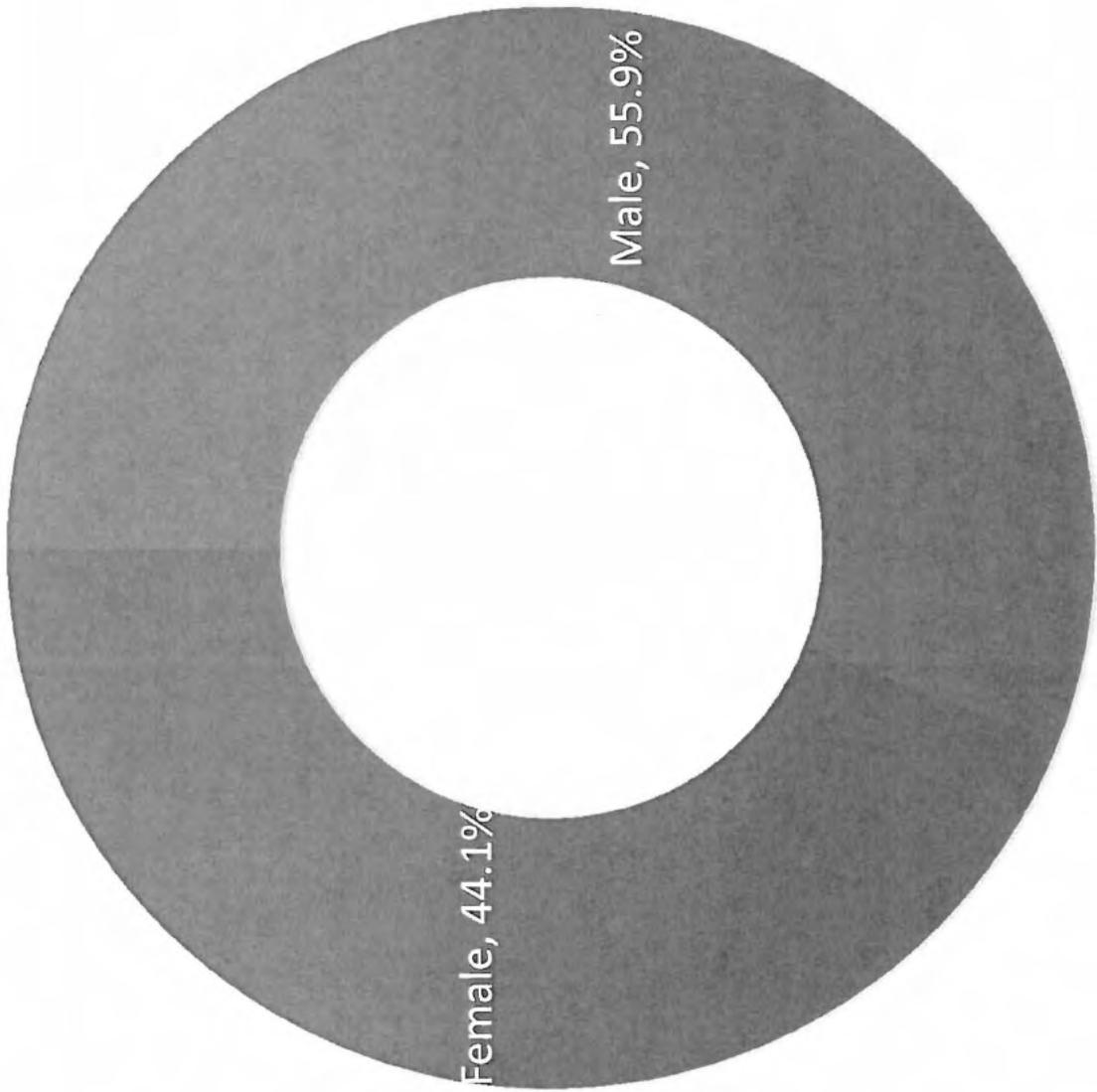
Mobius Bionics, LLC formed to begin commercial manufacturing of the DARPA-funded Luke Arm developed by DEKA Integrated Solutions Corporation of Manchester, NH.

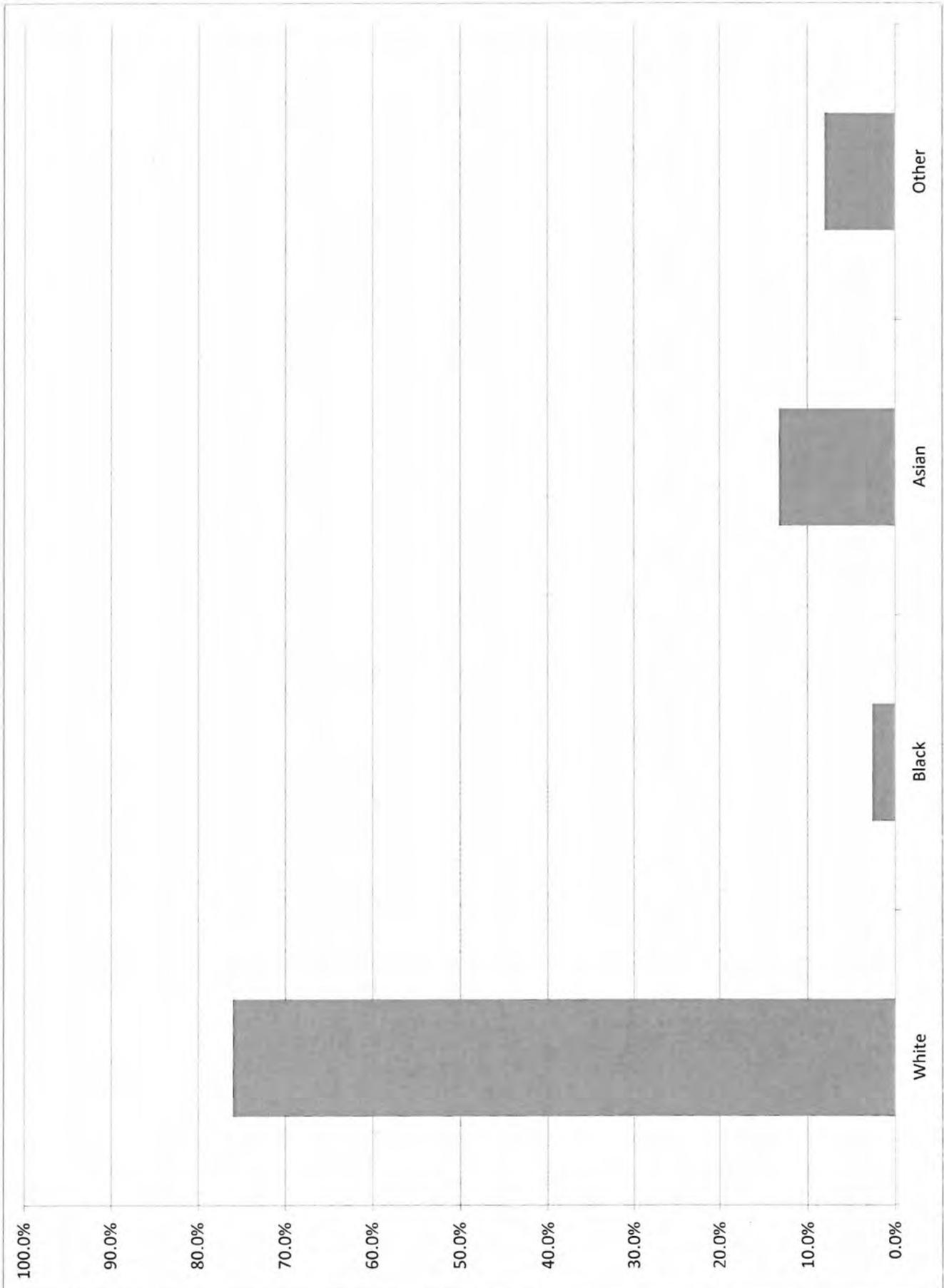
Press Release- <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm396688.htm>

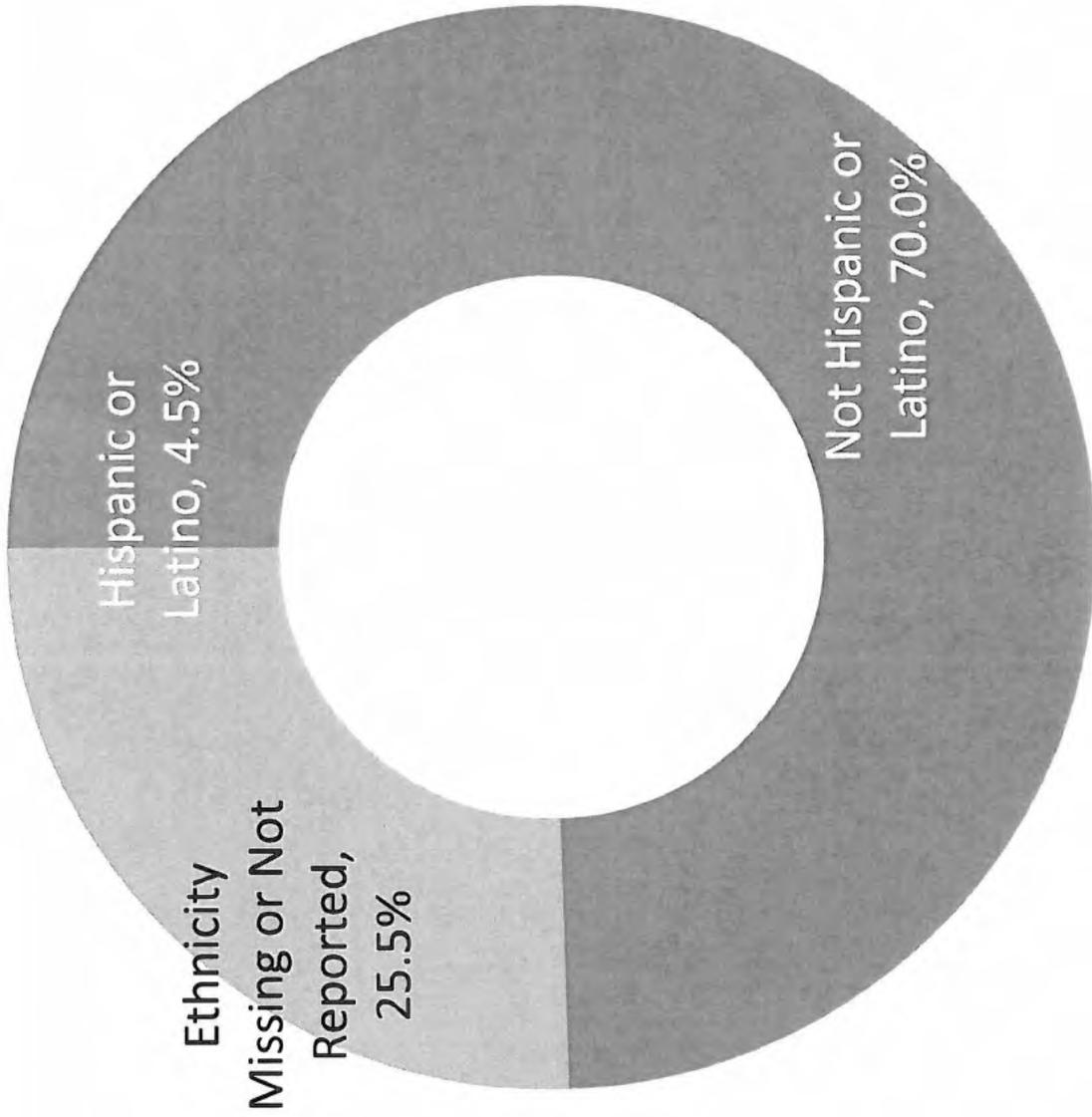
Name	Subname	Indication	NDA/BLA number	Study Name(s)	Total number of	
					participants	Dataset(s)?
Darzalex	daratumumab	multiple myeloma	BLA761036	MMY2002, GEN501	148	Y
Farydak	panobinostat	multiple myeloma	NDA205353	Trial D2308	768	Y
Praxbind	idarucizumab	reversal of anti coag effects of dabigatran	BLA761025	1321.3	123	
Alecensa	alectinib	ALK+ metastatic non-small cell lung cancer	NDA208434	NP28761, NP28673	285	Y
Cotellic	cobimetinib	BRAF V600E, V600K melanoma	NDA206192	GO28141	495	Y
Empliciti	elotuzumab	multiple myeloma, prior therapies	BLA761035	CA204004	646	Y
Ibrance	palbociclib	ER+, HER2- breast cancer	NDA207103	PALOMA-1	165	Y
Lenvima	lenvatinib	thyroid cancer	NDA206947	SELECT	392	Y
Lonsurf	trifluridine and tipiracil	metastatic colorectal cancer	NDA207981	TPU-TAS-102-301	800	Y
Ninlaro	ixazomib citrate	multiple myeloma	NDA208462	C16010	722	Y
Odomzo	sonidegib	locally advanced basal cell carcinoma	NDA205266	CLDE225A2201	269	Y
Portrazza	necitumumab	metastatic squamous non-small cell lung cancer	BLA125547	SQUIRE (I4X-IE-JFCC)	1093	Y
Tagrisso	osimertinib mesylate	EGFR T790M mutation+ non-small cell lung cancer	NDA208065	D5160C00001: AURA 1,	411	Y
Yondelis	trabectedin	liposarcoma or leiomyosarcoma	NDA207953	ET743-SAR-3007	518	Y
					6835	

Year	Appr. Name	Subname	Indication	NDA/BLA number	Male Sex_M	Female Sex_F	White Race_W	Black Race_B	Asian Race_A	Other Race_Oth	<65 Age_Unde	65-69 Age_65to69	70-74 Age_70to74	75-79 Age_75to79	80+ Age_80andover	65 or older Age_65andover	Hispanic HisLat	Not Hispanic NonHisLat	Ethnicity Missing or Not Reported	
2015	Darzalex	daratumumab	multiple myeloma	BLA761036	148	79	69	116	16	4	12	87	22	23	11	5	61	10	130	8
2015	Farydak	panobinostat	multiple myeloma	NDA205353	768	406	352	491	22		245	283	141	156	113	65	475			758
2015	Praxbind	idarucizumab	reversal of anti coag effects of dabigatran	BLA761025	123	65	58	105	1	8	9	12	17	18	37	37	111			123
2015	Alecensa	alelectinib	ALK+ metastatic non-small cell lung cancer	NDA208434	285	132	153	208	8	51	18	246	20	9	8	2	39	21	264	
2015	Cotellic	cobimetinib	BRAF V600E, V600K melanoma	NDA206192	495	286	209	462		1	32	362	52	38	29	14	133	26	434	35
2015	Empliciti	elotuzumab	multiple myeloma, prior therapy	BLA761035	646	385	261	544	23	64	15	275	126	116	84	45	371	6	61	579
2015	Ibrance	palbociclib	ER+, HER2- breast cancer	NDA207103	165	0	165	148	2	10	5	89	27	34	10	5	76	5	160	
2015	Lenvima	lenvatinib	thyroid cancer	NDA206947	392	200	192	311	8	70	3	220	81	53	24	14	172	19	373	
2015	Lonsurf	trifluridine and tipiracine	metastatic colorectal cancer	NDA207981	800	491	309	461	9	278	52	448	168	124	50	10	352	16	724	60
2015	Ninlaro	ixazomib citrate	multiple myeloma	NDA208462	722	409	313	611	13	64	12	305	165	123	84	45	417	21	672	29
2015	Odomzo	sonidegib	locally advanced basal cell carcinoma	NDA205266	269	169	100	254	1		14	122	38	31	24	54	147	6	225	38
2015	Portrazza	necitumumab	metastatic squamous non-small cell lung cancer	BLA125547	1093	909	185	914	11	85	84	669	218	162	34	11	425	111	980	3
2015	Tagrisso	osimertinib mesylate	EGFR T790M mutation+ non-small cell lung cancer	NDA208065	411	132	279	151	4	247	7	224	74	59	36	18	187	21	316	74
2015	Yondelis	trabectedin	liposarcoma or leiomyosarcoma	NDA207953	518	154	364	394	63	19	42	403	61	37	15	2	115	46	439	33
					55.9%	44.1%	76.0%	7.7%	13.2%	8.1%	54.9%	17.7%	14.4%	8.2%	4.8%	45.1%	4.5%	70.0%	25.5%	



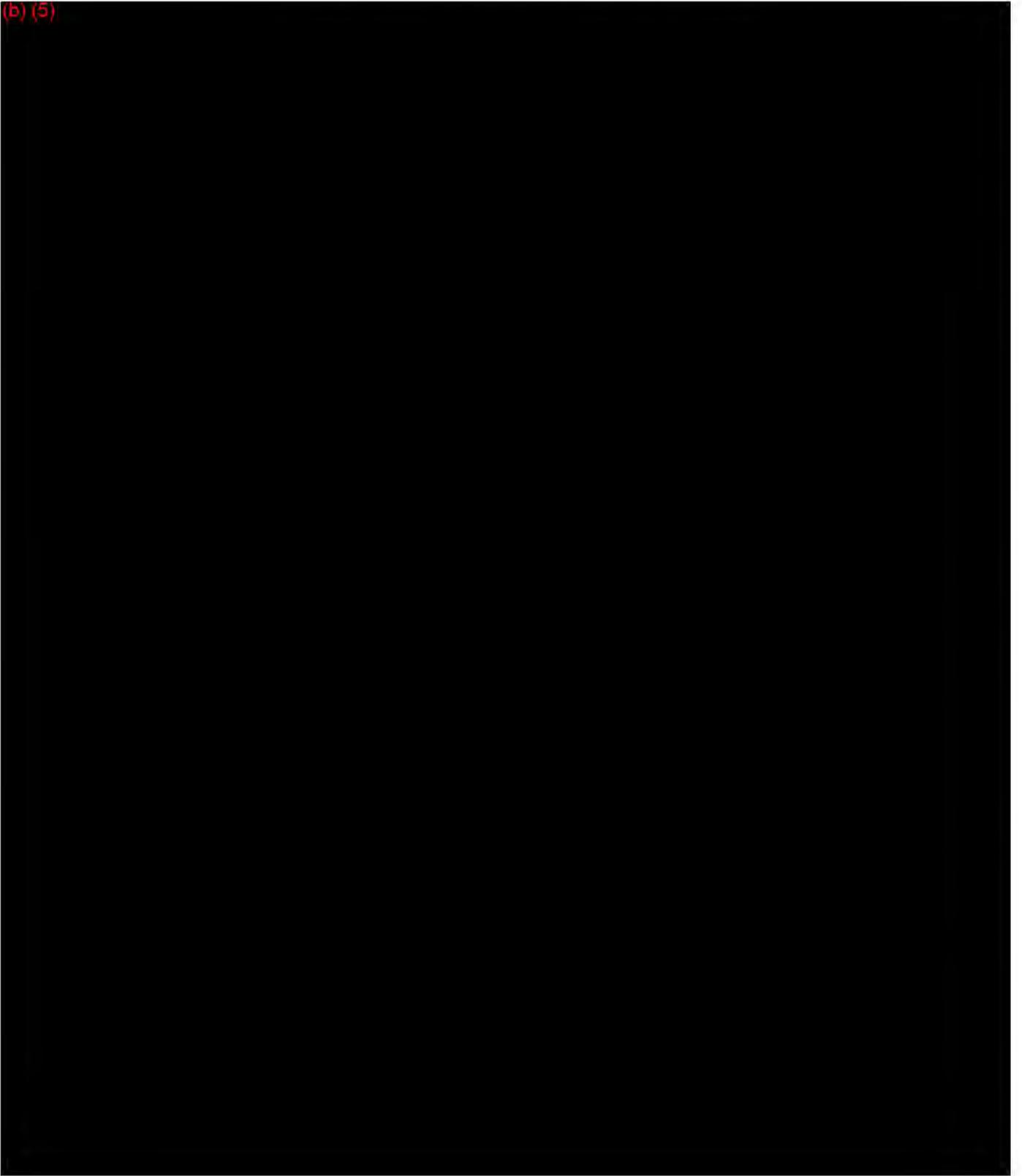






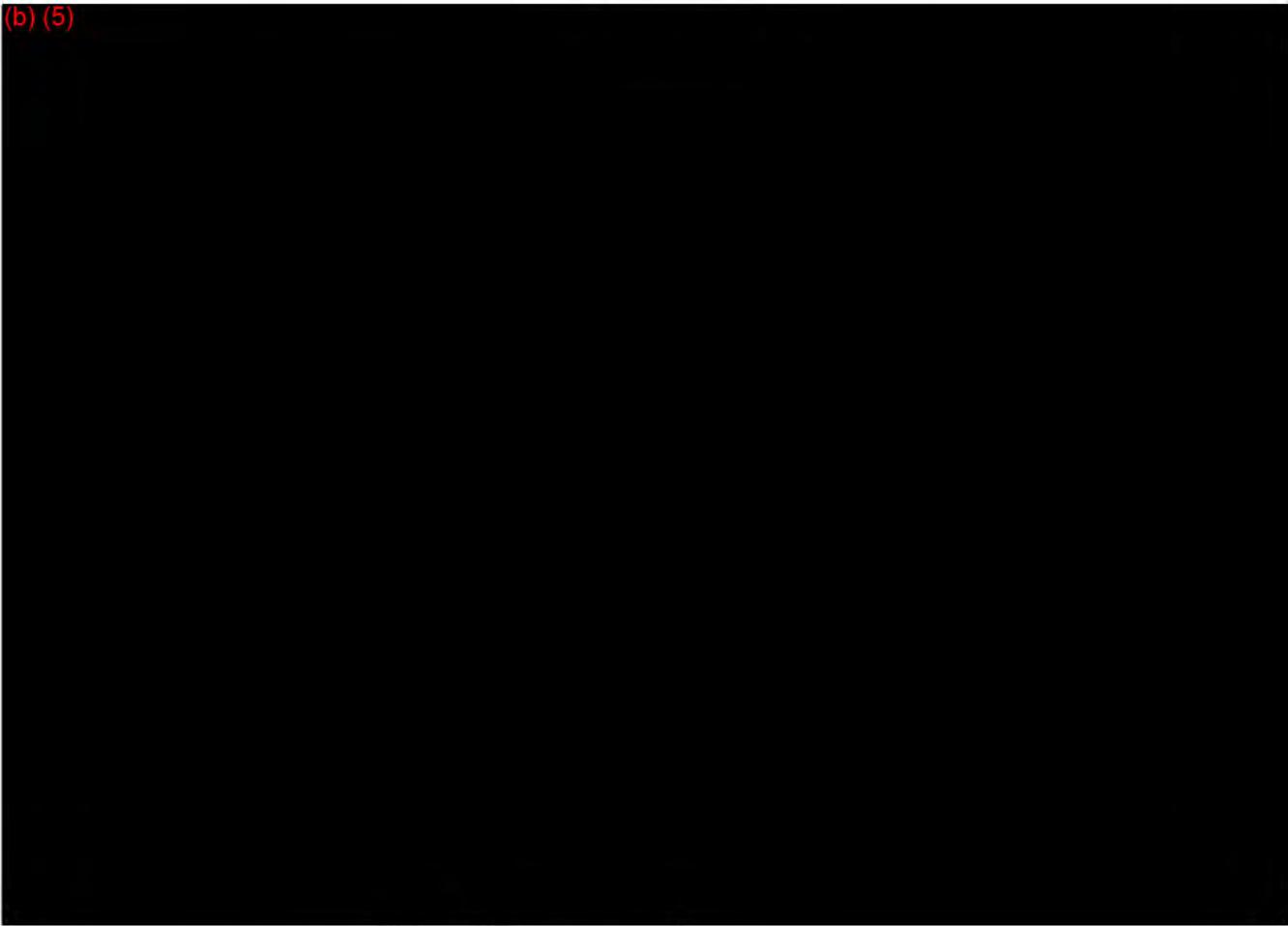
**Stakeholder Listening Session with the FDA Commissioner:
Neurology, Aging, Alzheimer's and Parkinson's
AGENDA**

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Organizations

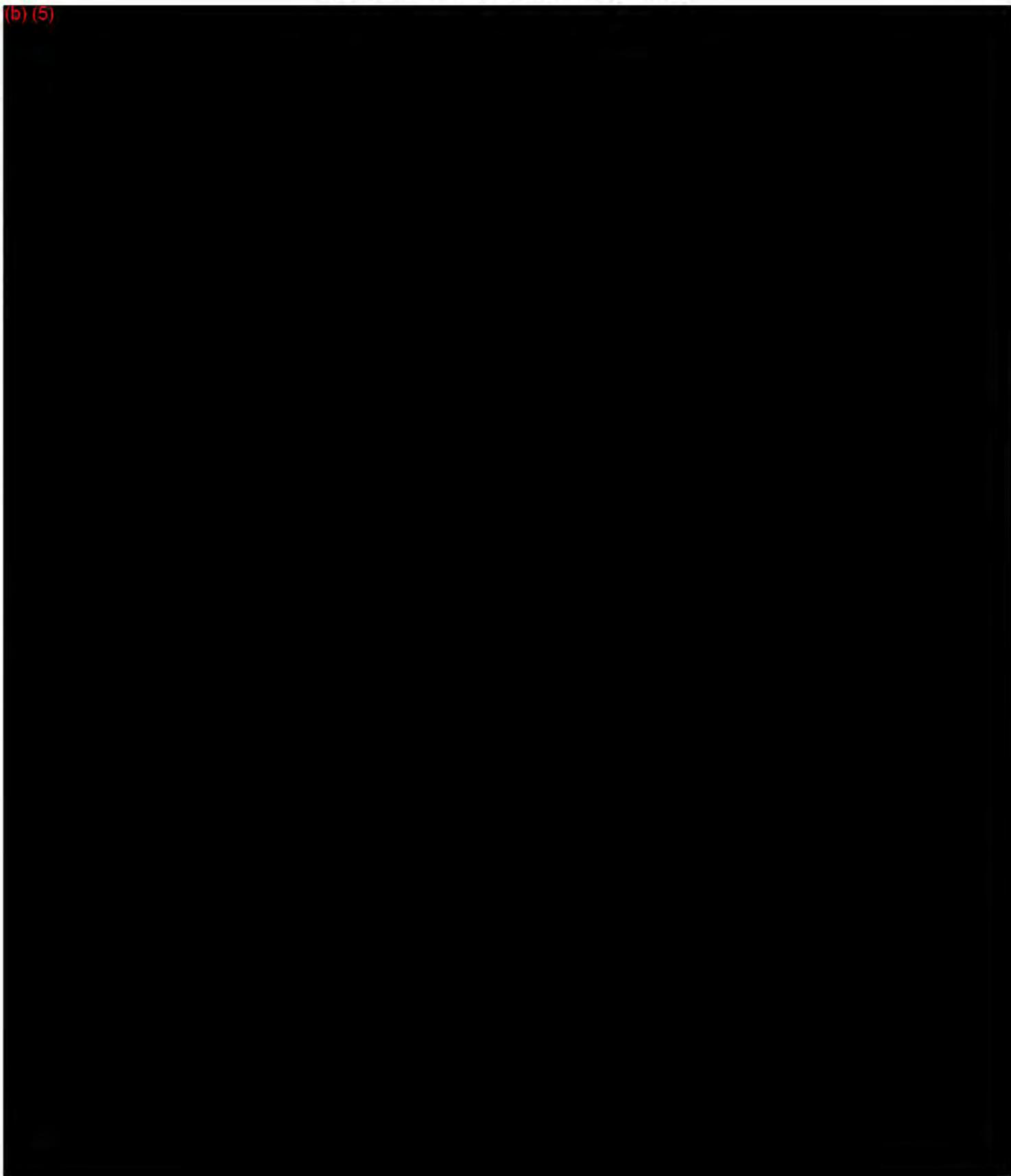
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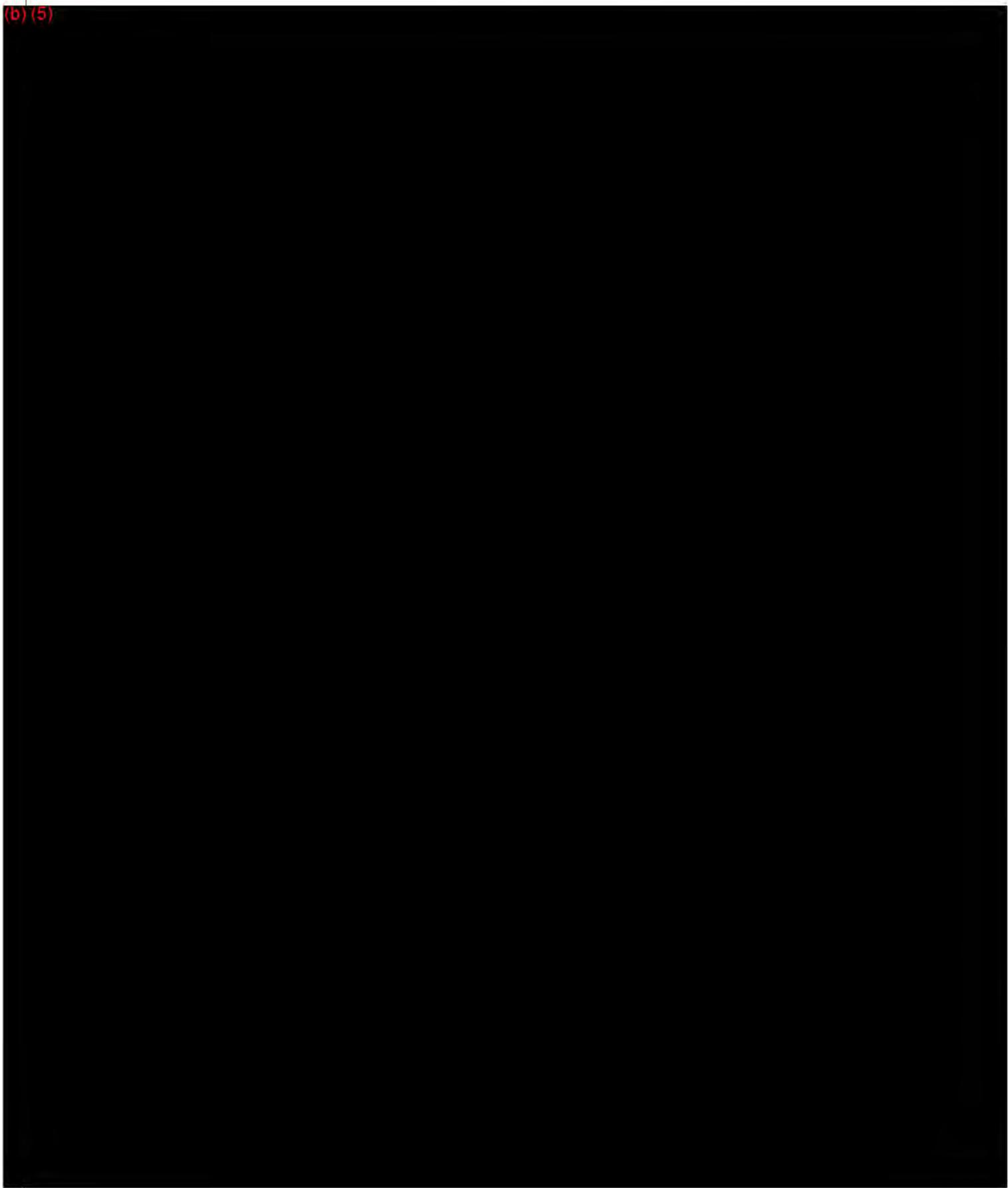
Day-of-Event (Detailed Agenda)

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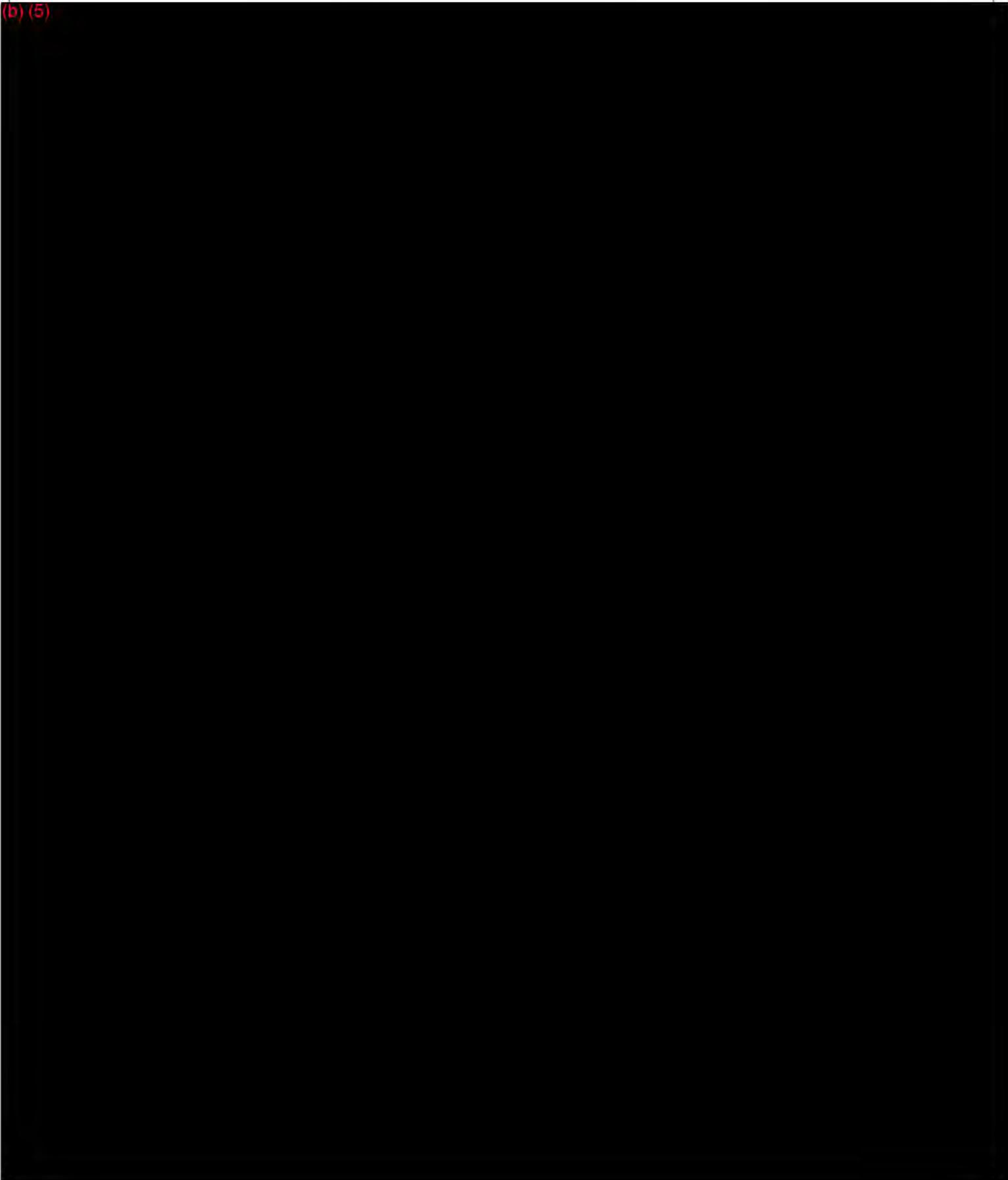


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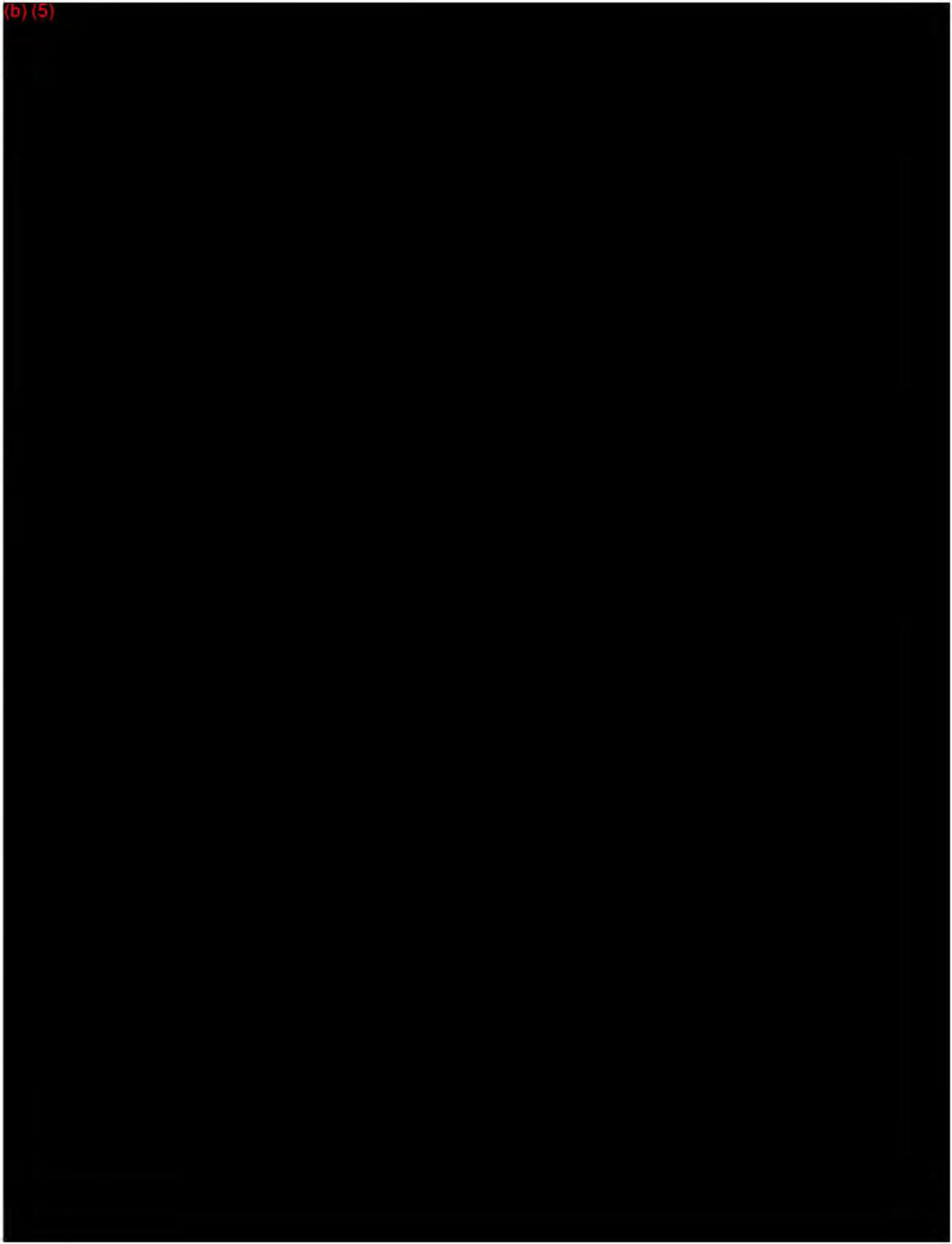
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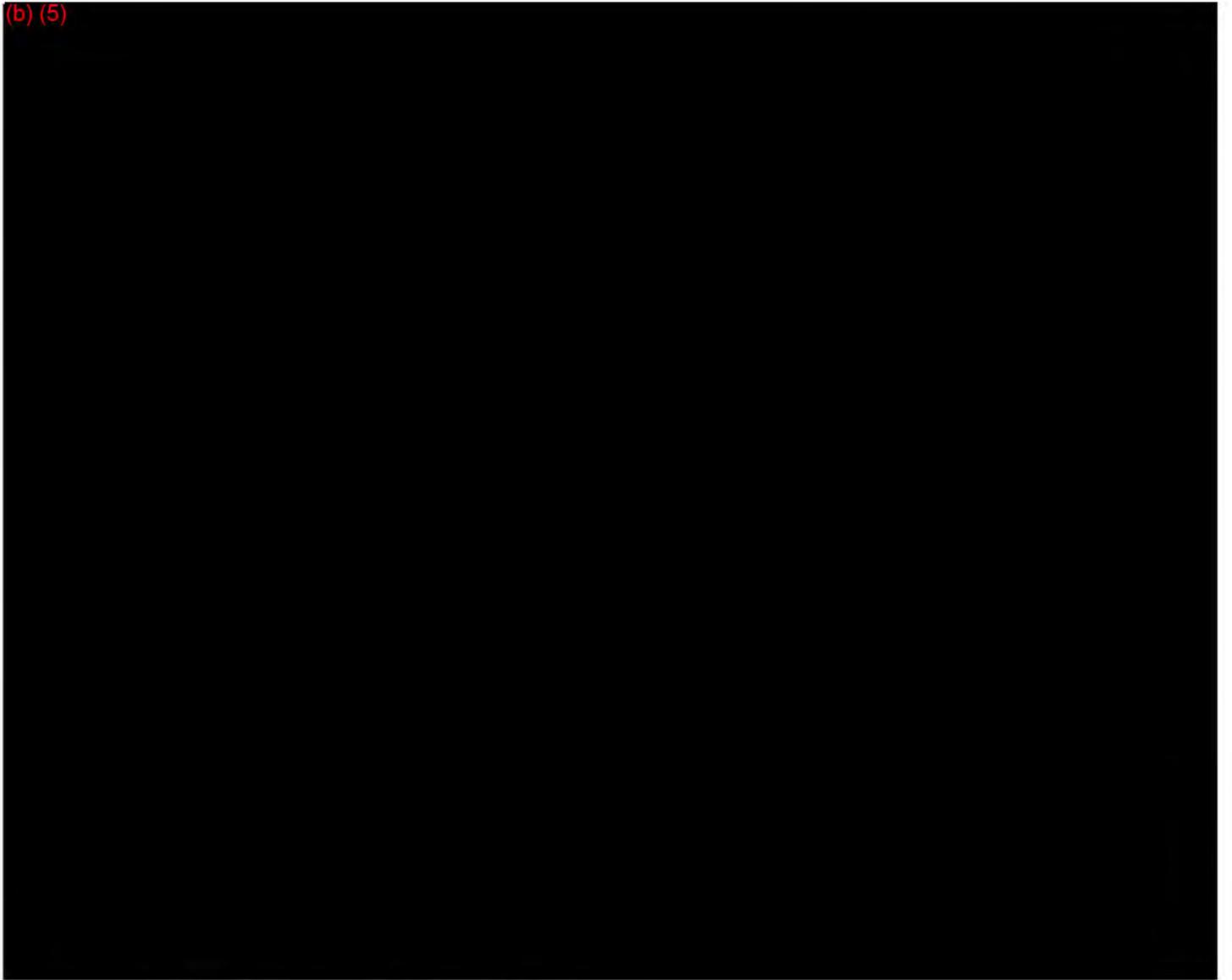
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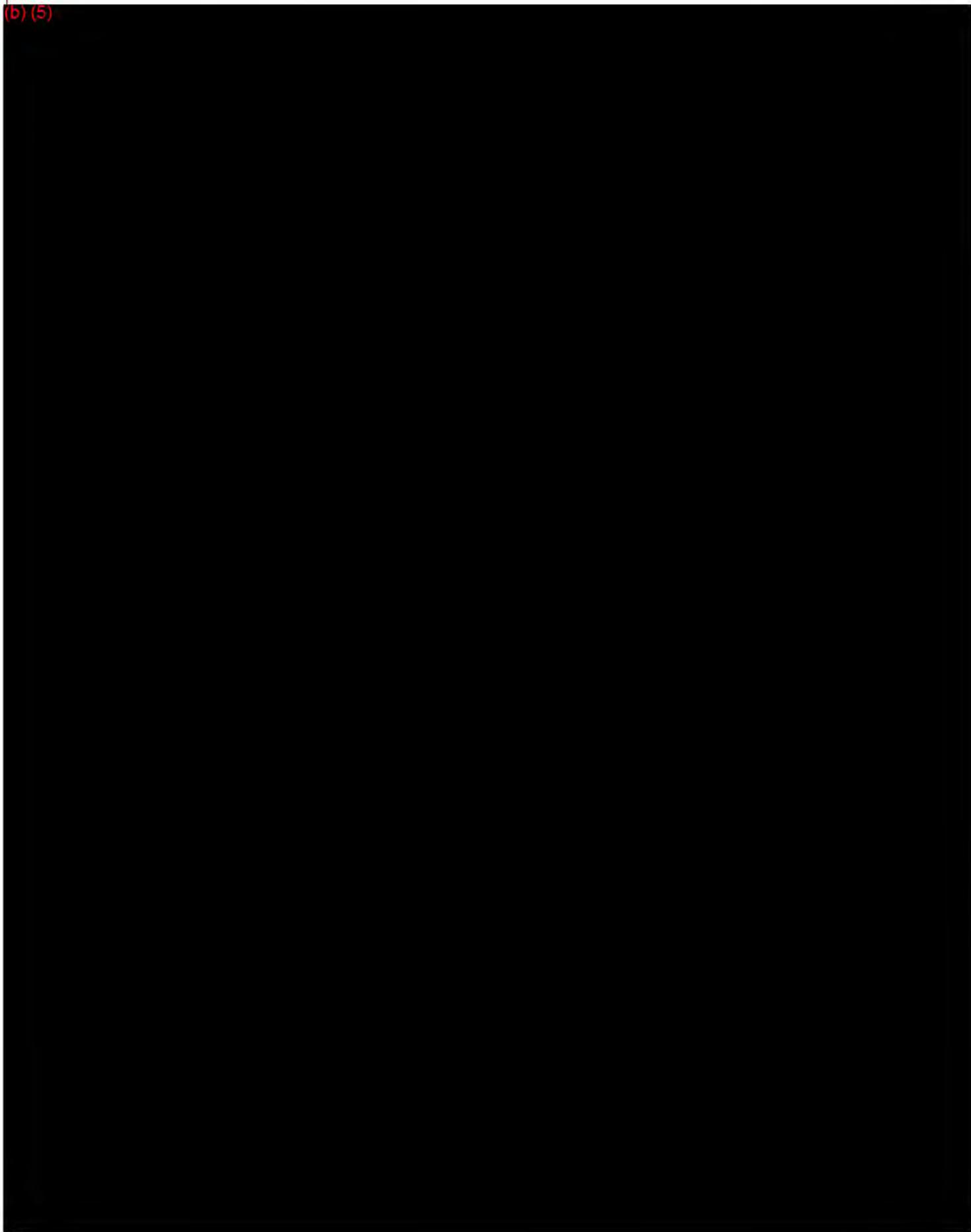
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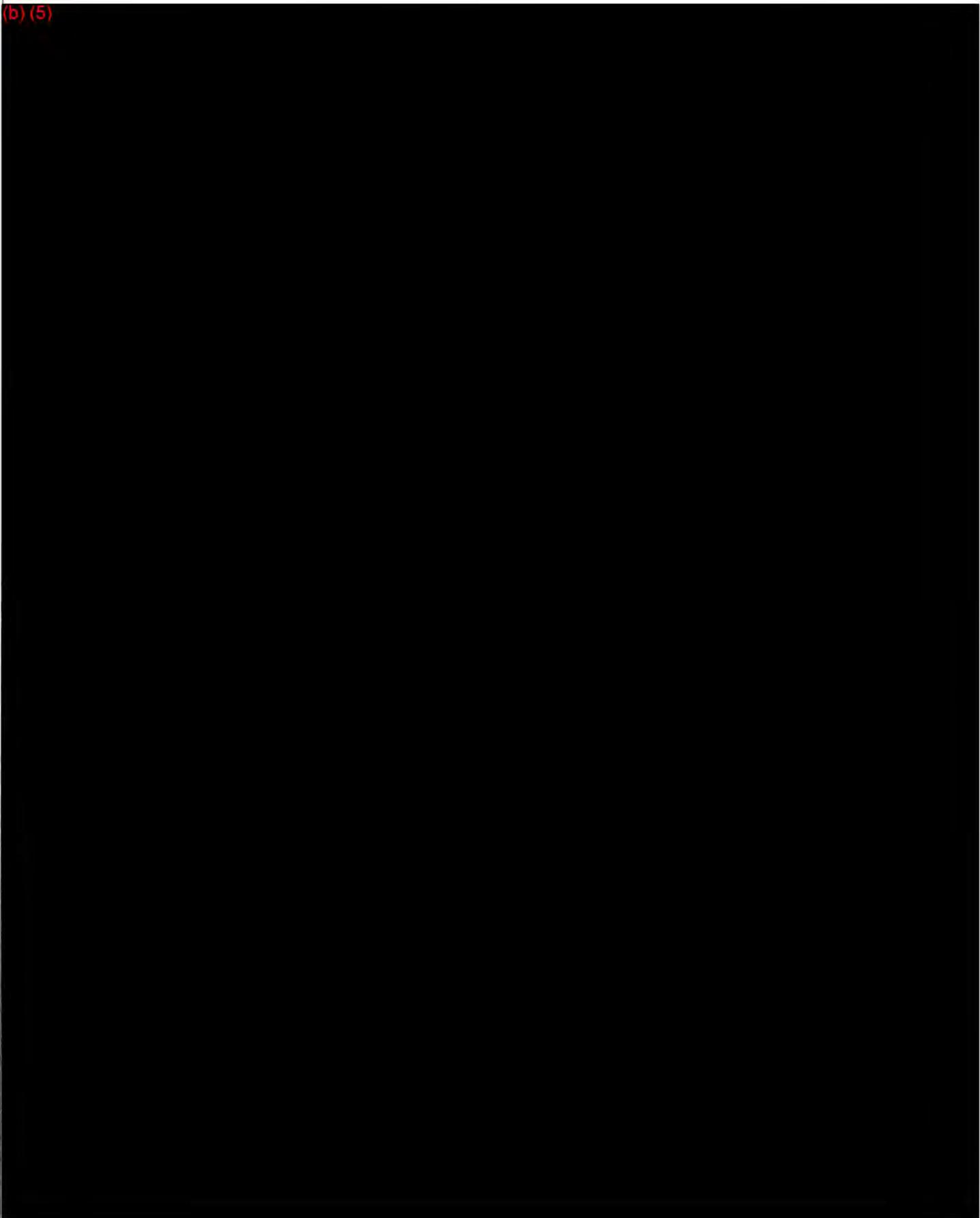
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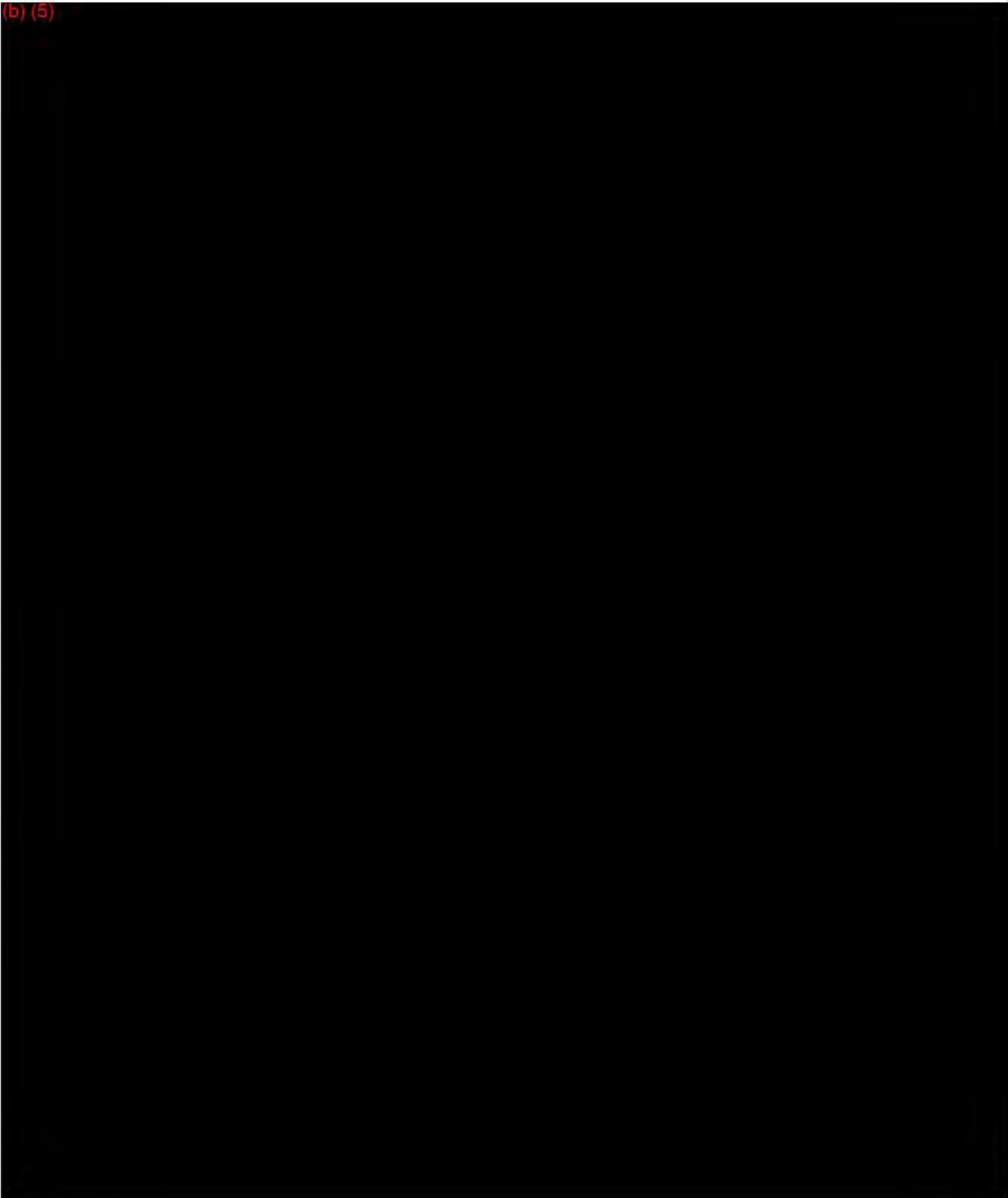


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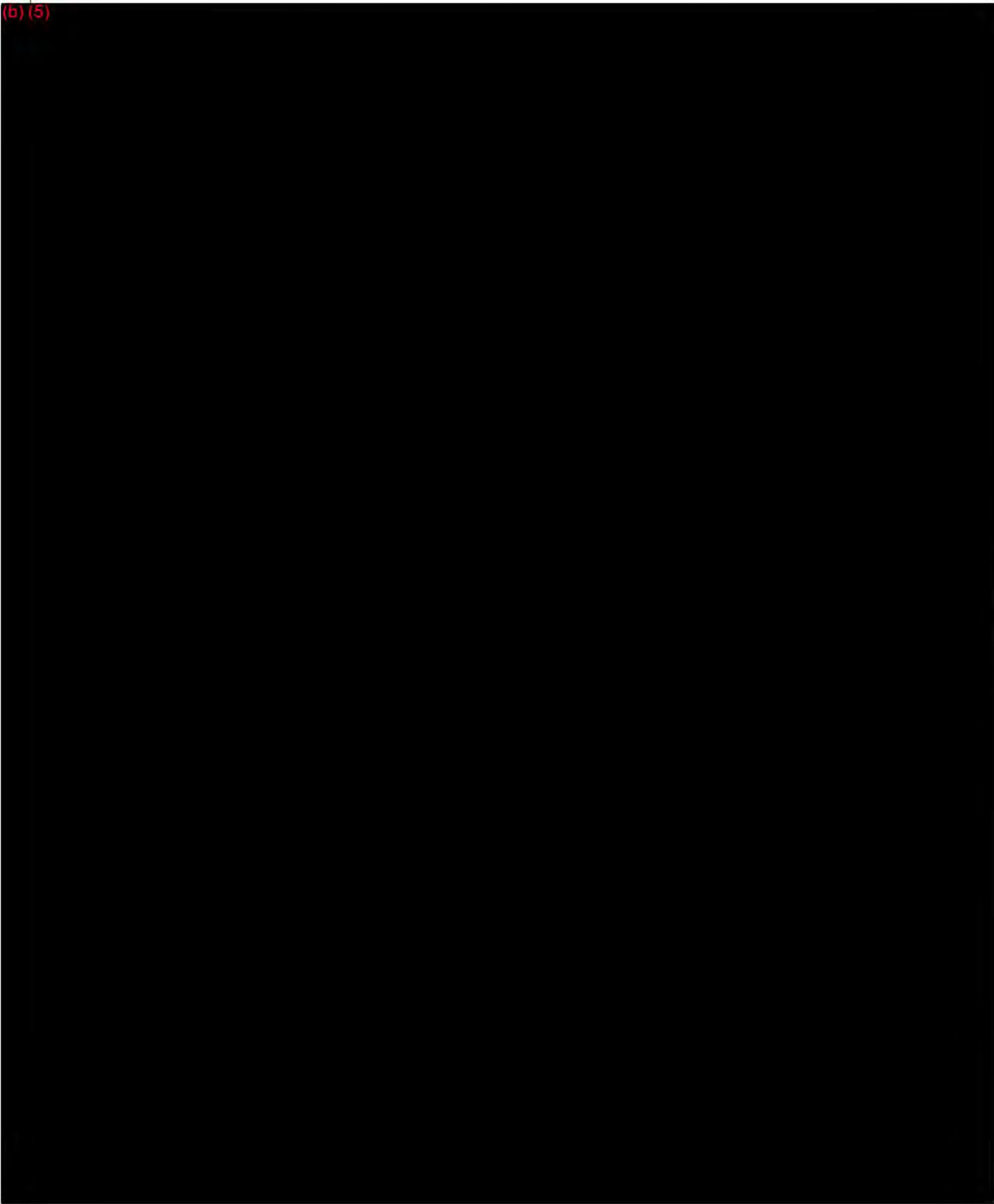


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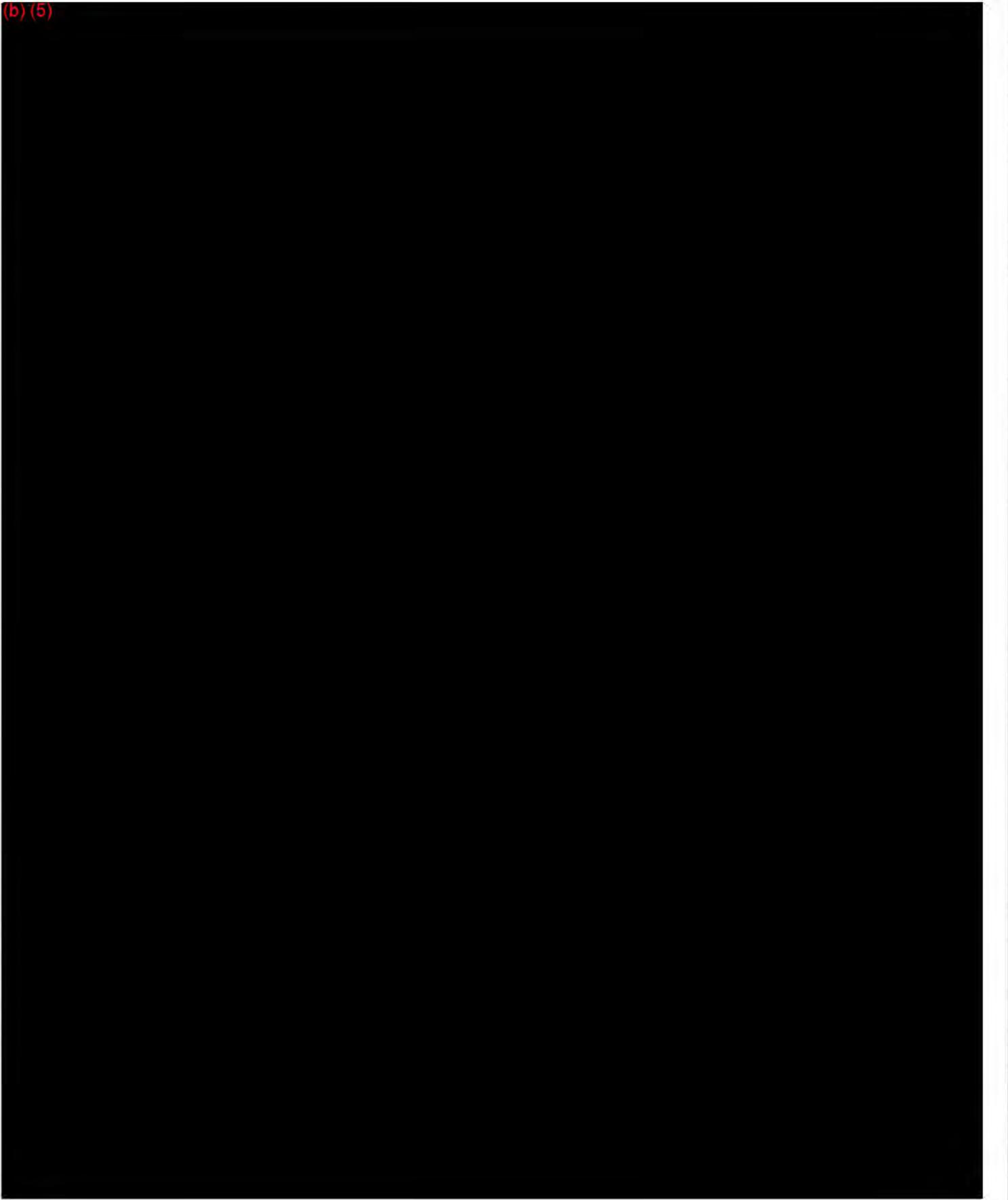
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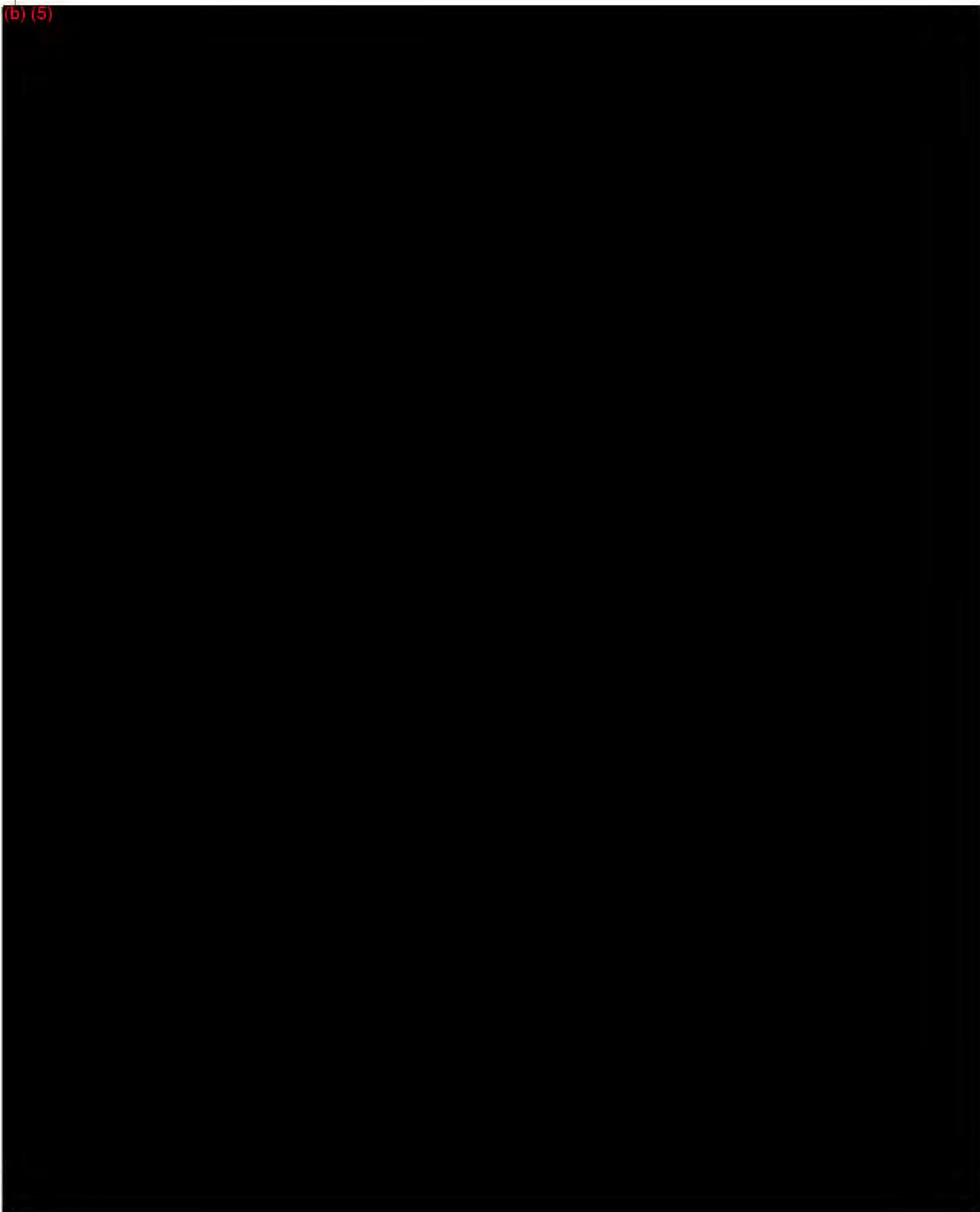
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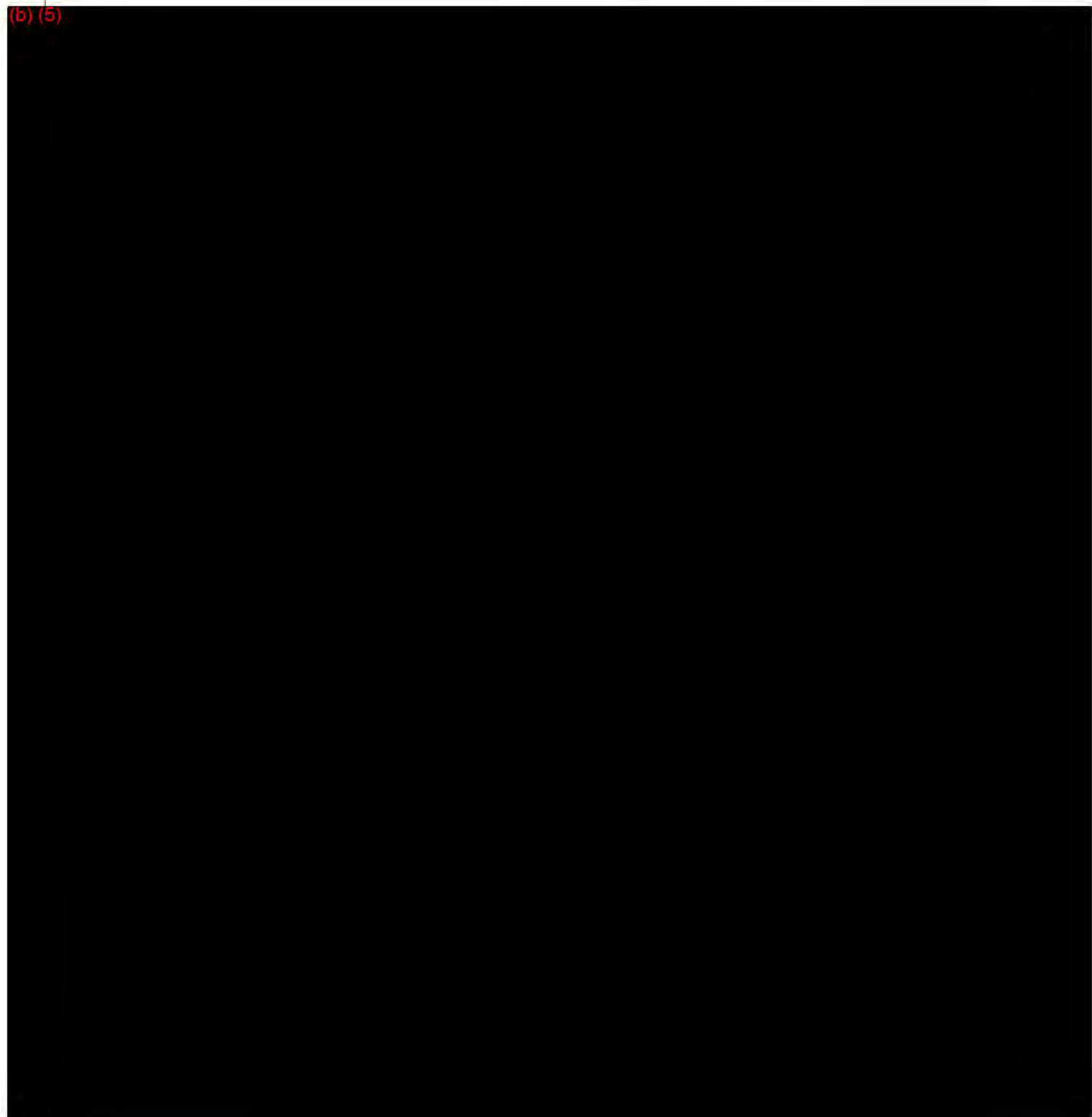
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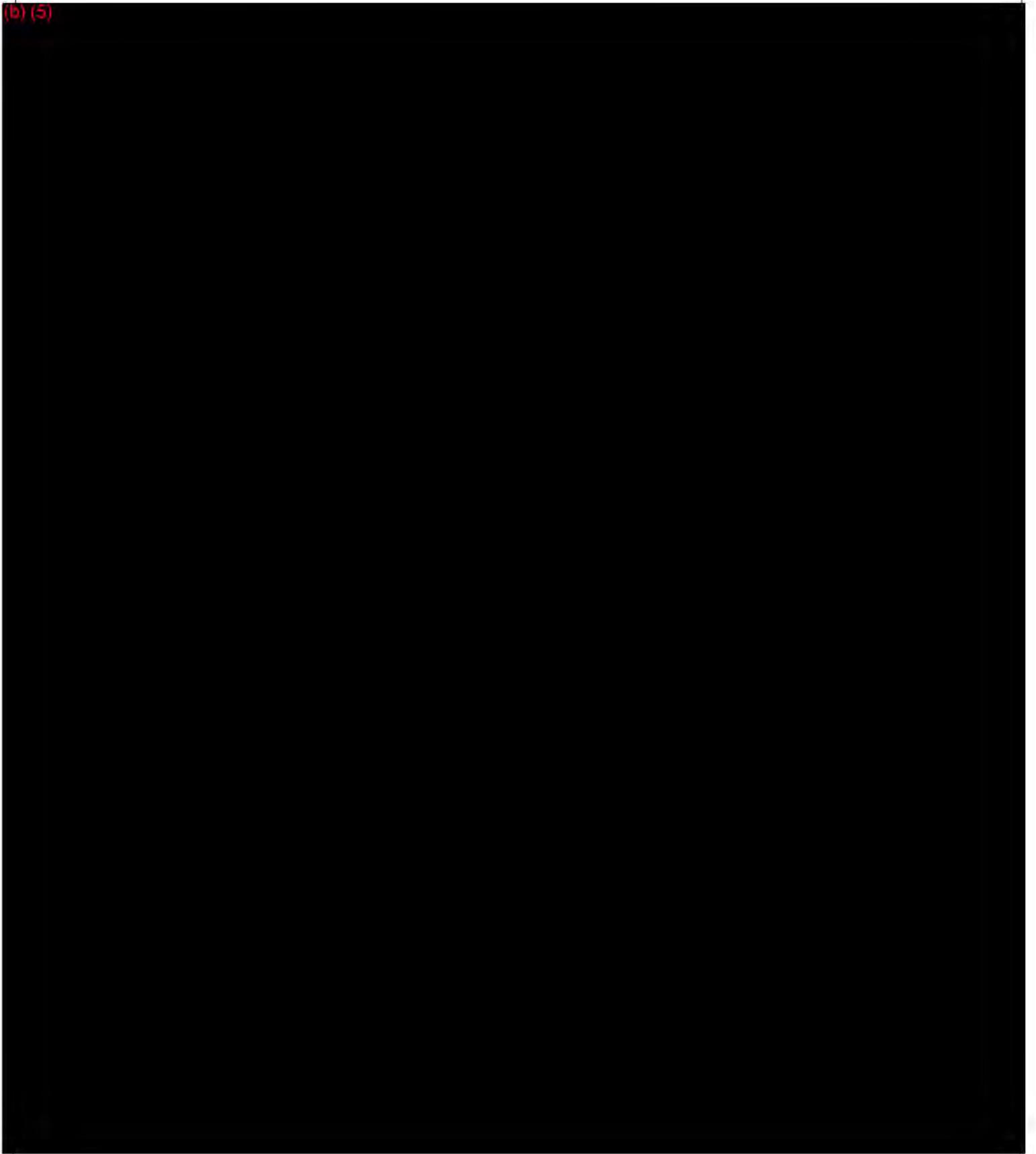


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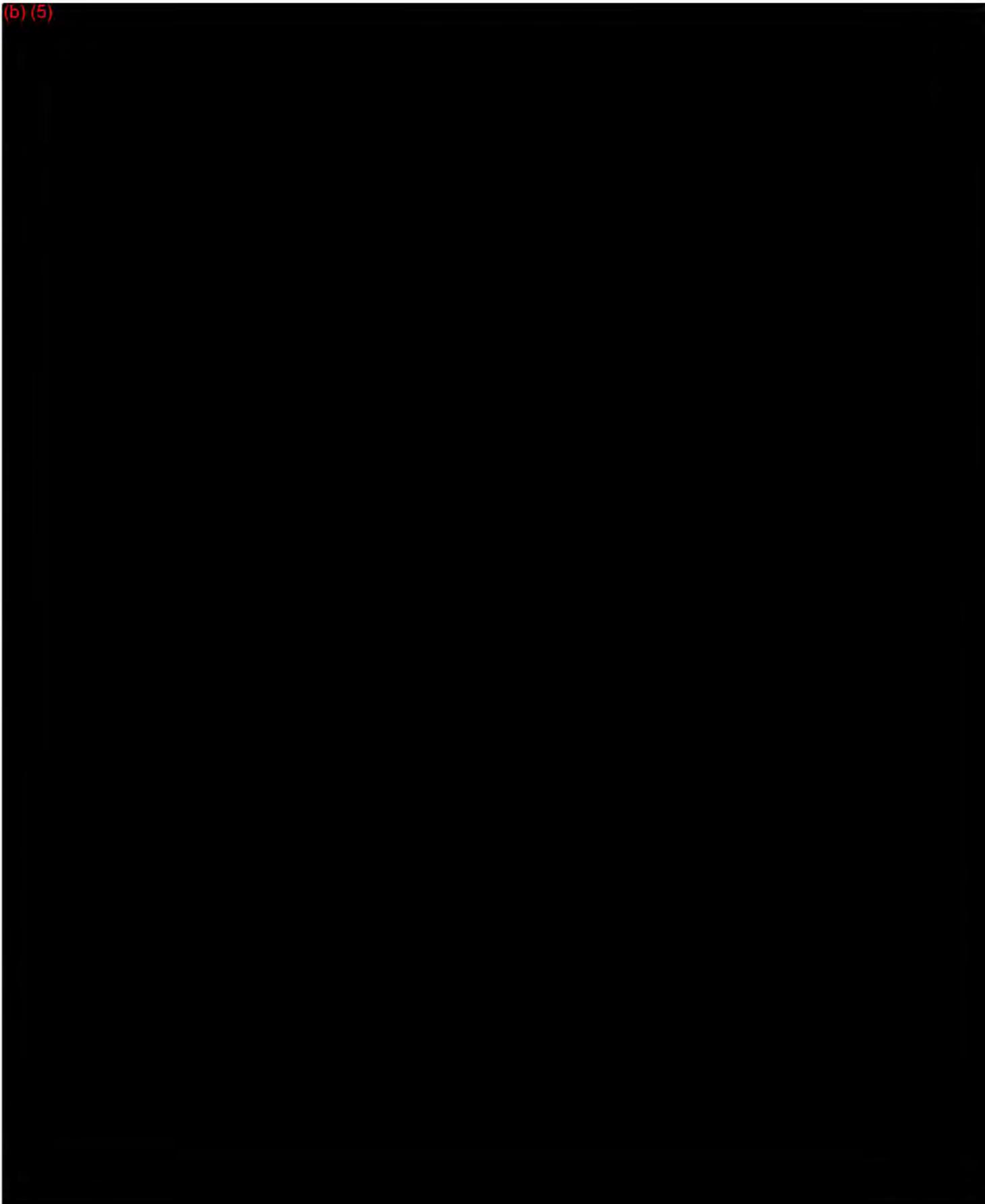
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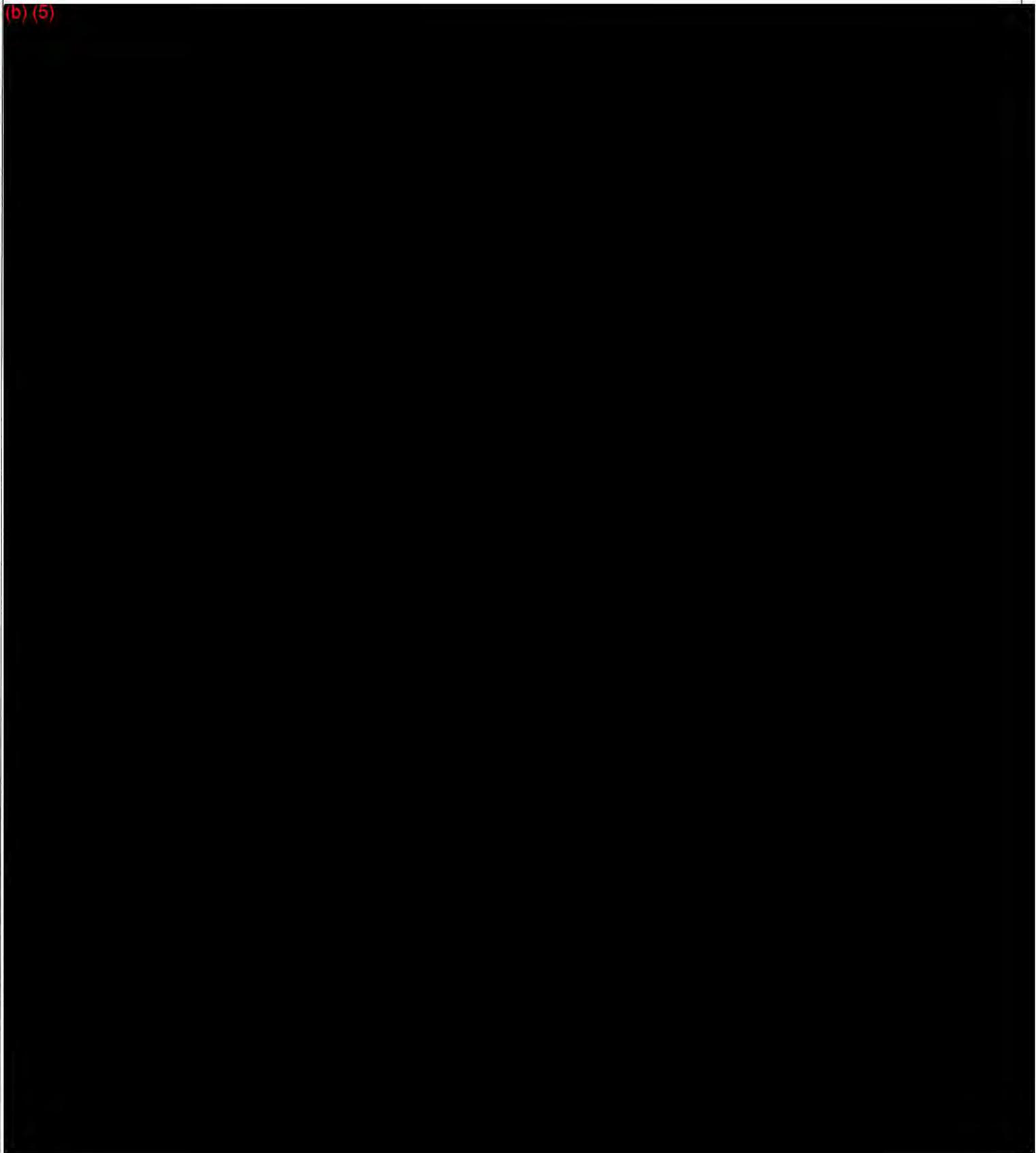
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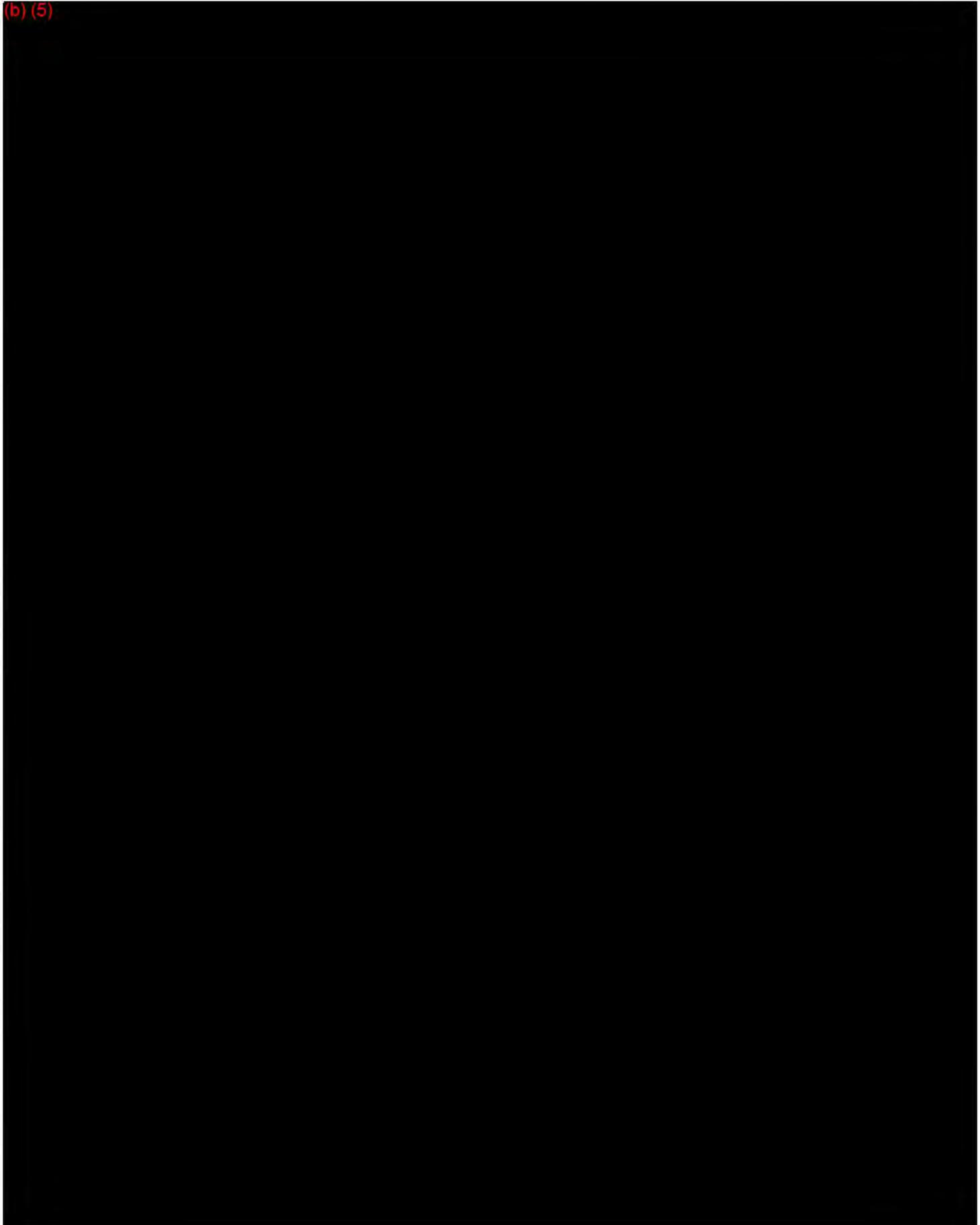
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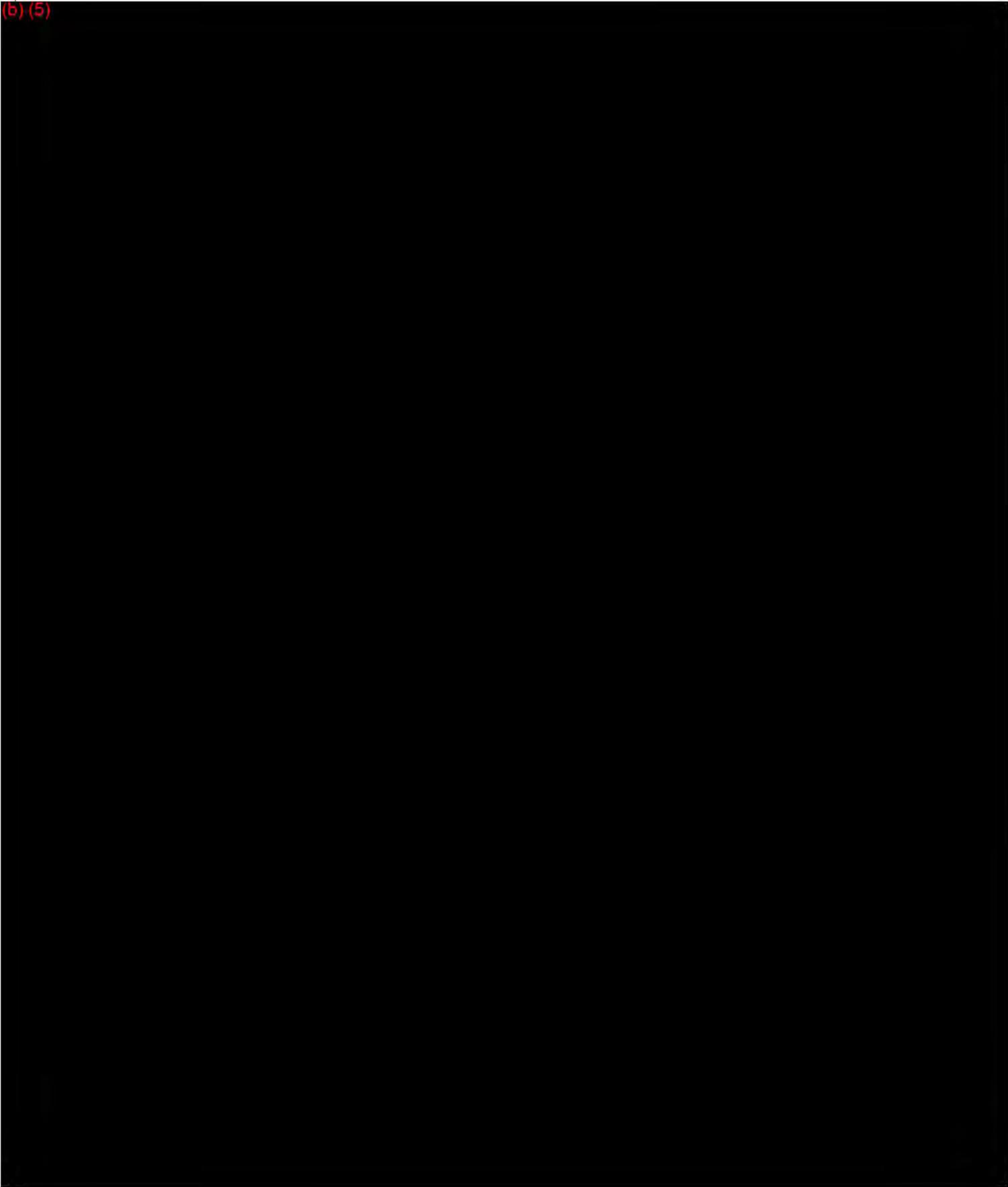
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From: [Wohl, Alexander](#)
To: [Califf, Robert](#)
Cc: [Rao, Gayatri](#); [Moscicki, Richard](#); [Pennington, Caitlin](#); [Branch, Christina](#)
Subject: [NORD 2016.doc](#)
Date: Thursday, October 06, 2016 9:29:04 PM
Attachments: [NORD 2016.doc](#)

Dr. Califf,

Here's a draft outline for the NORD speech, for discussion in our meeting tomorrow morning.

Thanks,

Alex

Speech to the 2016 National Organization for Rare Disorders (NORD) Summit
October 17, 2016
Washington, D.C.
DRAFT OUTLINE

I. (b) (5)

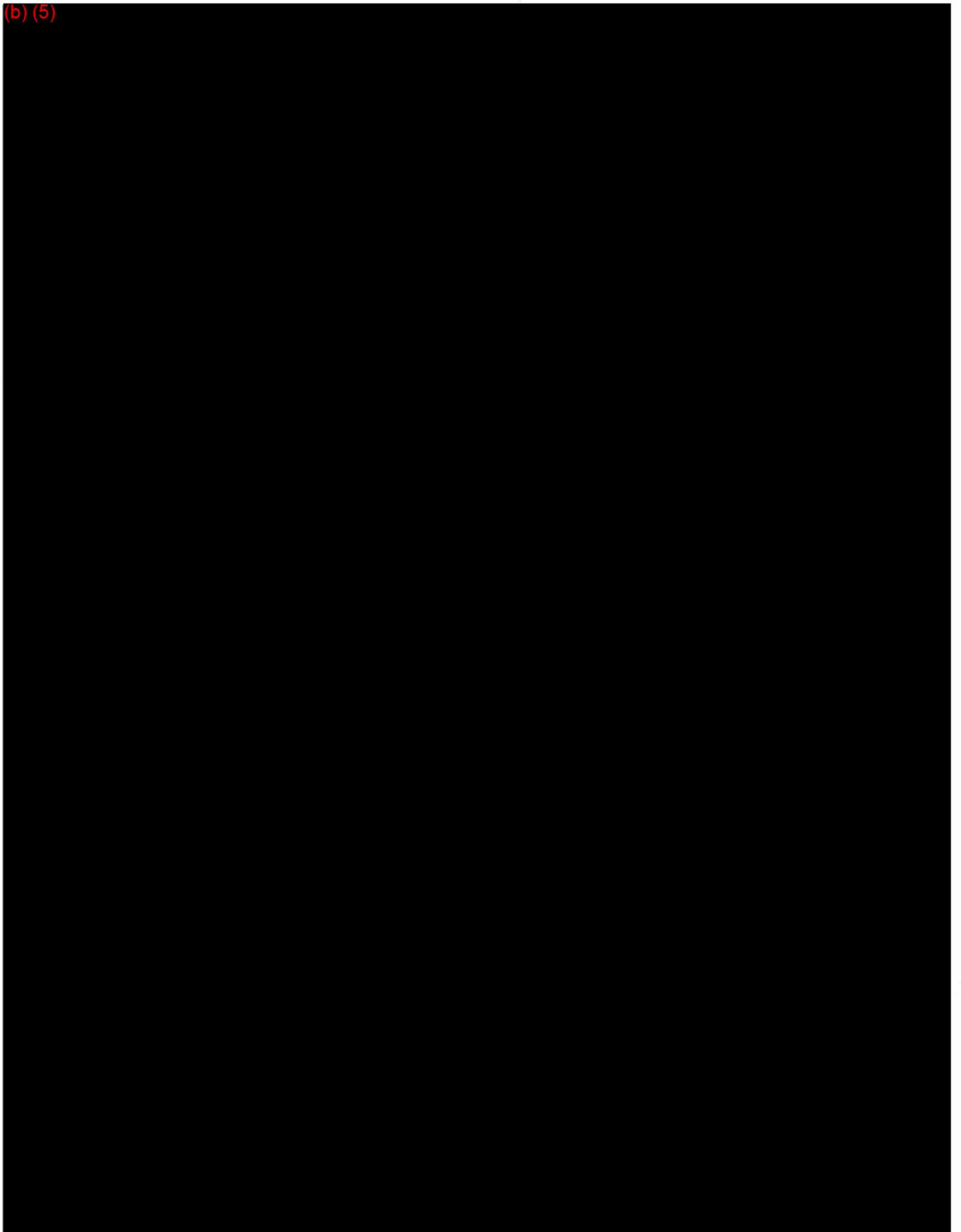


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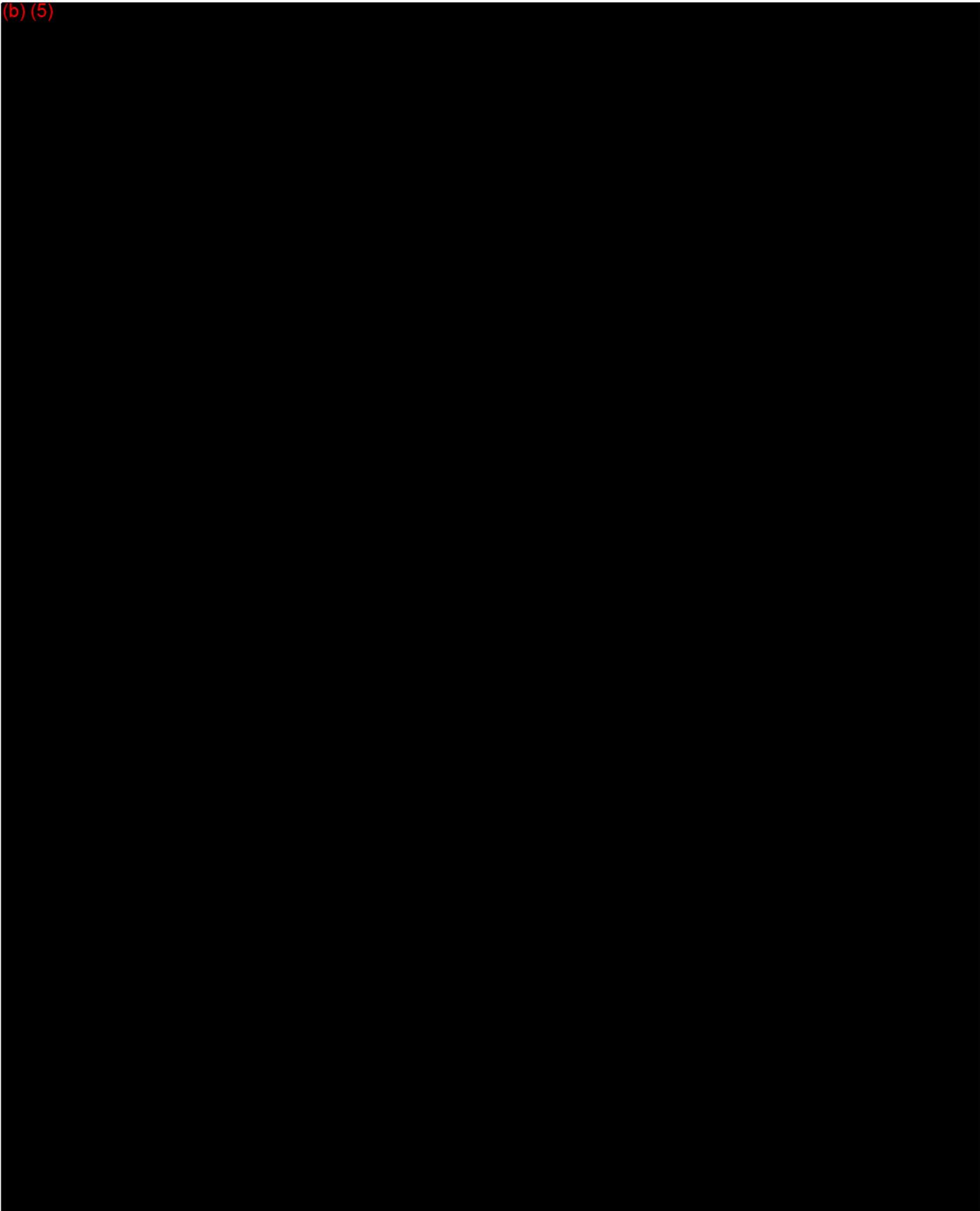


III.

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From: Marchand, Heidi
To: [Califf, Robert](#); [Sherman, Rachel](#); [Fluzat, Mona](#); [Conover, Katie](#); [Shuren, Jeff](#); [Maisel, William](#); [Como, Peter](#); [Heetderks, William](#); [Gutierrez, Alberto](#); [Pena, Carlos L](#); [Schwartz, Suzanne](#); [O'Callaghan, Kathryn](#); [Tenenbaum, Cara](#); [Marks, Peter](#); [Witten, Celia \(CBFR\)](#); [Maloney, Diane](#); [Bryan, Wilson](#); [Woodcock, Janet](#); [Unger, Ellis](#); [Dunn, Billy](#); [Bastings, Eric](#); [Brown, Heather \(CDER-OEP\)](#); [Kozauer, Nicholas](#); [Temple, Robert](#); [Whyte, John](#); [Hoffmann, Michael](#)
Subject: RE: Stakeholder Listening Session with the FDA Commissioner on Neurology, Aging, Alzheimer's and Parkinson's Diseases
Date: Thursday, October 06, 2016 11:35:00 AM
Attachments: [PR_Hearing Aid Sale Guidance_9_30_2016.doc](#)
[Hearing Aids KMOA 09 28 2016.docx](#)
[BRAIN Initiative FY17 Fact Sheet 03-02.pdf](#)
[FDA BRAIN Initiative Announcements and Accomplishments 082516.pdf](#)
[OHOP_approvals_2015_demographics.xlsx](#)

Dear All,

Included are updates for the backgrounder for tomorrow's Listening Session that were discussed at our briefing on Monday, October 3. Thanks to all who provided the additional materials.

Regards, Heidi

Conditions for Sale- Hearing Aids

FDA is taking steps to support consumer access to certain hearing aids by no longer enforcing the requirement that patients 18 and up receive a medical exam or waive such an exam prior to purchasing low-risk, air conduction hearing aids. The guidance is expected to publish the week of October 10 and FDA will implement the guidance immediately to assist in addressing a significant public health issue.

Two reports on hearing Aids recently were published:

In 2015, the [President's Council on Science and Technology \(PCAST\) report](#) recommended that the FDA should "approve a class of hearing aids for over-the-counter sale, without the requirement for consultation with a credentialed dispenser," and that "the requirement for a medical examination (or a written waiver of such examination) provides little patient benefit."

A subsequent June 2016 [report from National Academies of Sciences, Engineering and Medicine \(NAS\)](#) concluded that the medical evaluation requirement should be removed for adults as a majority of consumers are already signing the waiver in lieu of a medical evaluation.

Eteplirsen Approval Standards

The agency reviewed eteplirsen using the appropriate standards for products granted an accelerated approval. Studies conducted to support an accelerated approval must meet the traditional standard of substantial evidence based on adequate and well-controlled clinical

investigations. However, what is different for such an approval is that instead of a clinical endpoint, the investigations can rely on an unvalidated surrogate endpoint and the reasonable likelihood that the effect on the surrogate endpoint will predict clinical benefit.

Determining whether an effect on an unvalidated surrogate endpoint is reasonably likely to predict clinical benefit is a matter of judgment based on the biological plausibility of the relationship between the disease, the endpoint, the desired effect and the empirical evidence to support that relationship. In making the determination of whether an effect is reasonably likely to predict clinical benefit, the FDA statute and regulations provide that the agency may consider a broad range of evidence (e.g., epidemiologic, pathophysiologic, pharmacologic).

BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative

FDA's main focus in support of the White House BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative has been to enhance the transparency and predictability of the regulatory landscape for neurological devices (and neurotechnologies) and assisting developers and innovators of medical devices, to bring safe and effective products to patients and consumers.

FDA accomplishments to date include:

- FDA Regulatory Webinar Series: Moving Devices to Market
- Finalizing New Guidance on Neurological Devices Targeting Disease Progression and Clinical Outcomes
- Marketing of first-of-kind computerized cognitive tests to help assess cognitive skills after a head injury

Demographic Data –Age Greater than 80 years

CDER analyzed information by age for NMEs and BLAs approved in 2015 for hematology and oncology medical products. For 14 approvals, data show the following: 54.9% were <65, 17.7% were 65-69, 14.4% were 70-74, 8.2% were 75-79 and 4.8% were 80+.

CDER is also reviewing the data for cardiovascular diseases and hope to have them available for discussion at the October 7 Listening Session.

Key Messages & Responsive QA: Immediately in Effect Guidance Document: Conditions for Sale for Hearing Aids

Updated: 9/28/16

SECTION I: TOP LINE MESSAGES

1. The FDA is taking steps to better support consumer access to certain hearing aids by no longer enforcing the requirement that patients 18 and up receive a medical exam or waive such an exam prior to purchasing certain low-risk, air conduction hearing aids. This guidance is being released as “immediately-in-effect” to ease reported barriers to access for current and prospective hearing aid users 18 years of age and older.
2. The FDA will be changing the regulation for such medical exams through its public rule making process, so that the exams will no longer be required. However, the FDA continues to recommend that all prospective hearing aid users with suspected or known hearing loss have a medical evaluation to rule out any treatable medical conditions for their hearing loss.
3. While the FDA is working on modifying the “conditions for sale” regulations for hearing aids, the FDA will not enforce the medical evaluation or waiver, and recordkeeping requirements for users 18 years of age and older, and will work to eventually remove the requirement.

SECTION II: KEY MESSAGES

The FDA is taking steps to better support consumer access to certain hearing aids by no longer enforcing the requirement that patients 18 and up receive a medical exam or waive such an exam prior to purchasing certain low-risk, air conduction hearing aids. This guidance is being released as “immediately-in-effect” to ease reported barriers to access for current and prospective hearing aid users 18 years of age and older.

- FDA regulations requiring medical evaluations as a condition for sale for hearing aids have been cited as presenting barriers to availability and accessibility of hearing aids for users 18 years of age or older.
- An October 2015 President's Council on Science and Technology (PCAST) report recommended that the FDA should “approve a class of hearing aids for over-the-counter sale, without the requirement for consultation with a credentialed dispenser,” and that “the requirement for a medical examination (or a written waiver of such examination) provides little patient benefit.”
- A subsequent June 2016 report from National Academies of Sciences, Engineering and Medicine (NAS) concluded that the medical evaluation requirement should be removed for adults as a majority of consumers are already signing the waiver in lieu of a medical evaluation.

Key Message #2: The FDA will be changing the regulation for such medical exams through its public rule making process, so that the exams will no longer be required. However, the FDA continues to recommend that all prospective hearing aid users with suspected or known hearing loss have a medical evaluation to rule out any treatable medical conditions for their hearing loss.

- Despite the high prevalence and public health impact of hearing loss, only about one-fifth of people that could benefit from a hearing aid seek intervention.
- A medical evaluation can be a useful tool in diagnosing a medical or surgically treatable cause of hearing loss, such as infection, autoimmune disease, injury or deformity, ear wax in the ear canal, and in rare cases, tumors.
- Early diagnosis of the cause of hearing loss may lead to a better outcome, such as preserving your hearing or preventing the progression of hearing loss.
- Children with hearing loss have specific needs and health concerns that make medical evaluation important, therefore, they are still required to have a medical evaluation prior to being sold and fitted with a hearing aid.

Key Message #3: While the FDA is working on modifying the “conditions for sale” regulations for hearing aids, the FDA will not enforce the medical evaluation or waiver, and recordkeeping requirements for users 18 years of age and older, and will work to eventually remove the requirement.

- Hearing aid dispensers are still required to make available, and provide prospective users an opportunity to review the User Instructional Brochure containing specific labeling requirements, before the sale of a hearing aid device. Only users 18 years of age and older may purchase hearing aids without a medical evaluation or waiver.

Current and prospective hearing aid users can also find more information by visiting the [FDA’s website on Hearing Aids](#).

SECTION III: RESPONSIVE QA

Q1: What rulemaking is being proposed in relation to this issue? When can we expect that?

The FDA intends to revise regulation 21 CFR 801.421 to remove the requirement for medical evaluation, or waiver of medical evaluation, for users over 18 years of age. In the meantime, this guidance will address NAS’ recommendations as we do not intend to enforce the medical evaluation requirement for users aged 18 and older in order to help increase accessibility and use of hearing aids.

The FDA does not have a timeframe as to when a revised regulation will be issued.

Q2: Is this guidance a move towards the FDA regulating hearing aids in the same way that other over-the-counter (OTC) medical devices are regulated?

Yes, to the extent that consumers do not need to undergo a medical examination prior to the purchase of other OTC medical devices. The FDA is also considering additional regulatory actions to promote access to hearing aids for adult consumers with mild to moderate hearing loss.

Q3: How is this new guidance likely to affect the dispensing of hearing aids?

The FDA expects that this guidance will ease the burden on sales for both hearing aid dispenser and users. Previous recordkeeping requirements which mandated completion of a medical evaluation or a waiver will no longer apply to users 18 years of age or older.

These changes also provide an opportunity for consumers to become more informed about the benefits, risks and other important information regarding hearing aid use, as dispensers are required to provide all prospective users with an opportunity to review the *User Instructional Brochure* prior to the sale of a hearing aid device.

Q4: Why is this guidance immediately-in-effect? What has spurred the rush to implementation? Will this guidance be open for public comments?

The FDA believes that immediate implementation of the guidance is needed to assist in addressing a significant public health issue; furthermore, this guidance document presents a position that is more consistent with protecting and promoting public health.

The policy changes indicated in this guidance are the result of feedback we gathered from public workshops, consumers, healthcare professionals and the medical device industry, as well as reports from the National Academies of Sciences, Engineering and Medicine (NAS), and the President's Council of Advisors on Science and Technology (PCAST). We also gathered information from many groups of stakeholders who could be affected, and we believe this guidance exemplifies the FDA's commitment to partnering with consumers and industry on policy changes.

This guidance is final and immediately in effect, and there is not a specific timeframe for comments. The public can still comment at anytime at: <https://www.regulations.gov/>, and the FDA will consider all comments received and revise the guidance document as appropriate.

SECTION IV: ADDITIONAL RESOURCES

- [21 CFR 801.420 \(Hearing aid devices; professional and patient labeling\)](#)
- [Previous Guidance \(11/7/13\): Regulatory Requirements for Hearing Aid Devices and Personal Sound Amplification Products - Draft Guidance for Industry and Food and Drug Administration Staff](#)
- [PCAST Report on Hearing Aids \(Oct. 2015\): Aging America & Hearing Loss: Imperative of Improved Hearing Technologies](#)
- [Public Workshop \(4/21/16\): Streamlining Good Manufacturing Practices \(GMPs\) for Hearing Aids](#)
- [National Academies of Sciences, Engineering and Medicine \(NAS\) Report \(6/2/16\): Hearing Health Care for Adults: Priorities for Improving Access and Affordability](#)

SECTION V: POINTS OF CONTACT

Eric Mann, Srinivas Nandkumar – ODE Subject Matter Experts
Aisha Coffey – OCE Communications Project Manager
Theresa Eisenman – OMA Press Officer

Close Hold - Draft - Deliberative

FDA NEWS RELEASE

For Immediate Release: Oct. XX, 2016

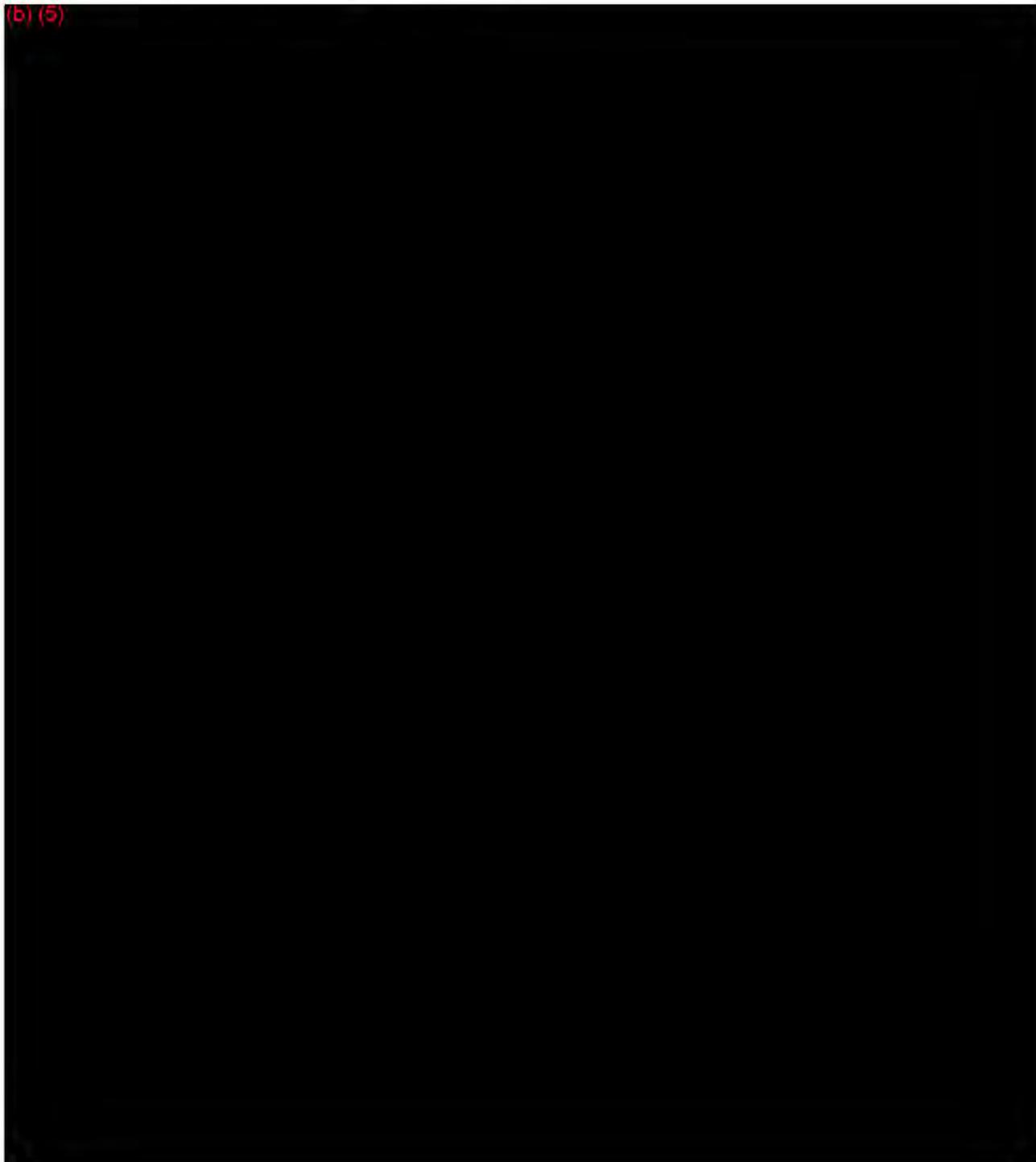
Media Inquiries: Theresa Eisenman, 301-796-2969, theresa.eisenman@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

FDA issues guidance to make hearing aids more accessible

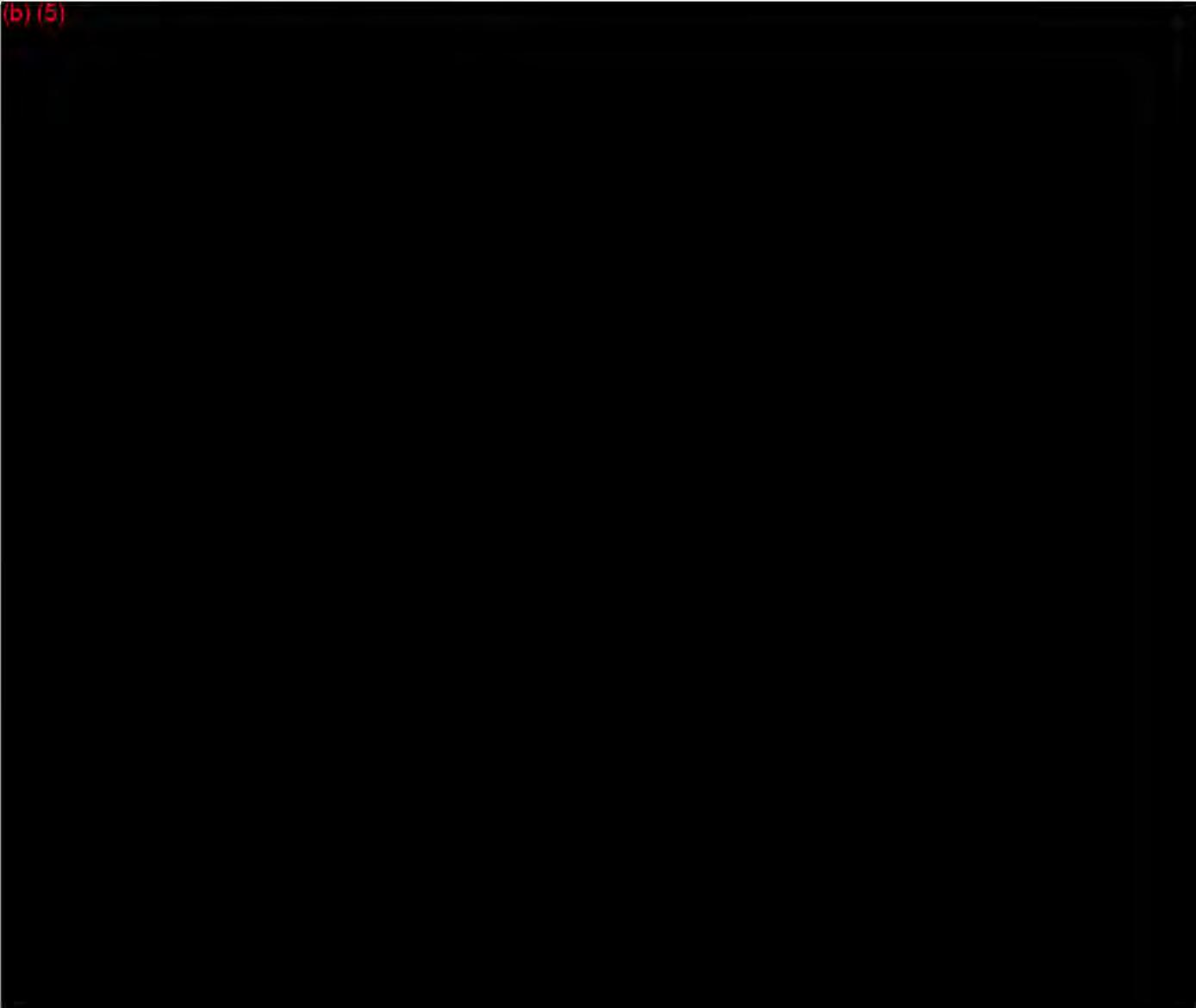
Guidance "Immediately in Effect"

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Close Hold - Draft - Deliberative

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Obama Administration Proposes Over \$434 Million in Funding for the BRAIN Initiative

“Last year, I launched the BRAIN Initiative to help unlock the mysteries of the brain, to improve our treatment of conditions like Alzheimer’s and autism and to deepen our understanding of how we think, learn and remember. I’m pleased to announce new steps that my Administration is taking to support this critical research, and I’m heartened to see so many private, philanthropic, and academic institutions joining this effort.”

- President Barack Obama
September 2014

Since its launch in April 2013, the President’s BRAIN Initiative[®] - Brain Research through Advancing Innovative Neurotechnologies – has grown to include investments from five Federal agencies: the Defense Advanced Research Projects Agency (DARPA), the National Institutes of Health (NIH), the National Science Foundation (NSF), Intelligence Advanced Research Projects Activity (IARPA), and the Food and Drug Administration (FDA). Federal agencies are supporting the initiative by investing in promising research projects aimed at revolutionizing our understanding of the human brain, developing novel technologies, and supporting further research and development in neurotechnology. The President’s 2017 Budget also proposes funding for the Department of Energy (DOE) to join DARPA, NIH, NSF, IARPA, and FDA in advancing the goals of the BRAIN Initiative.

Major foundations, private research institutions, and companies including the Howard Hughes Medical Institute, Allen Institute for Brain Science, the Kavli Foundation, GE, GlaxoSmithKline, as well as patient advocacy organizations and universities, have committed over \$500 million to the BRAIN Initiative. There are many opportunities for others across sectors to play a role in this historic initiative through new and expanded commitments to advance the BRAIN Initiative.

The President’s 2017 Budget proposes to increase the Federal investment in the BRAIN Initiative from about \$300 million in FY 2016 to more than \$434 million in FY 2017. Proposed investments by the NIH, NSF, DARPA, DOE, IARPA, and FDA are described below.

National Institutes of Health (NIH): In FY 2017, the President’s budget calls for NIH to provide an estimated \$190 million in funding for the BRAIN Initiative. This investment will support a diverse set of projects with ambitious goals, including efforts towards creating a complete accounting of the cellular components of brain circuits in various vertebrate species; creation of tools and infrastructure to address big data from these cell census projects; developing breakthrough neuroimaging technologies to study human brain function; and support for broad research teams to understand how patterns of neural activity at multiple spatial and temporal scales that span from local circuits to complex interconnected networks give rise to mental experience and behavior. Together these efforts aim to create a dynamic picture of the brain in action, providing the critical knowledge base for researchers seeking new ways to treat, cure, and even prevent brain disorders.

The BRAIN Initiative at NIH is guided by *BRAIN 2025: A Scientific Vision*, a multi-year scientific plan developed by a working group of the Advisory Committee to the NIH Director and informed by broad input from the scientific community, patient advocates, and the general public. Additionally, NIH investment in the initiative is informed by a BRAIN Multi-Council Working Group of esteemed experts in numerous disciplines who assist in ensuring a coordinated and focused effort across the agency. NIH is also working in close collaboration with other government agencies and private partners to ensure the success of the BRAIN Initiative investments. NIH issued 67 new awards in FY 2015, totaling more than \$38 million, to support 131 investigators working at 125 institutions in the United States and eight other countries. These awards expand NIH's efforts to develop new tools and technologies to understand neural circuit function and capture a dynamic view of the brain in action. Projects include proposals to develop soft self-powered brain electrodes, ultrasound methods for measuring brain activity, and the use of deep brain stimulation to improve the level of consciousness in persons suffering from severe traumatic brain injuries. For FY 2016 and beyond, NIH awards will continue to support critical objectives of *BRAIN 2025*, including development of tools to analyze cells and circuits and technologies for large-scale neuronal recording and modulation. The initiative will also expand to encompass new areas of emphasis. Of particular note are new efforts towards understanding human brain function and treating human brain disorders. These include new tools and more sophisticated understanding of non-invasive neuromodulation techniques, and studies to understand the signals underlying non-invasive imaging modalities. NIH is also expanding its portfolio of research with implantable neuromodulation devices, including a new BRAIN Public Private Partnership Program, which connects academic researchers with manufacturers of next-generation invasive devices for recording and modulation in the human central nervous system. To understand the unique properties and functions of human neural circuits, NIH is supporting research opportunities for studies with neurosurgical patients. Finally, separate announcements will fund development of new theories, models, and methods to analyze complex neural data, and technology dissemination grants for researchers to learn new techniques and take advantage of the technologies developed under the BRAIN Initiative. NIH is also engaging investigators to explore important neuro-ethical issues in modern brain science.

Defense Advanced Research Projects Agency (DARPA): In FY 2017, DARPA plans to invest an estimated \$118 million to support the BRAIN Initiative. DARPA's investments aim to leverage nervous system research to alleviate the burden of illness and injury and provide novel, neurotechnology-based capabilities for military personnel and civilians alike. In addition, DARPA is fostering advances in neural interfaces, data handling, imaging and advanced analytics to improve researchers' understanding of interactions across the entire nervous system.

In FY 2017, the Restoring Active Memory (RAM) effort will continue research to develop quantitative models of the neurobiological mechanisms underlying knowledge and skill-based memory encoding and recall in people. These models will be integrated into neural interface systems that operate in real time to restore a patient's ability to encode new memories and learn new skills with the goal of accelerating warfighter recovery after traumatic brain injury. DARPA's Systems-Based Neurotechnology for Emerging Therapies (SUBNETS) program will continue to develop the first set of prototype closed-loop medical devices able to measure and

modulate networks of neurons in research participants with intractable psychiatric illness and alleviate severe symptoms of diseases such as post-traumatic stress disorder, major depression and general anxiety disorder. In 2017, SUBNETS will build upon current research to further reduce key symptoms such as anxiety in clinical populations. DARPA-funded researchers are developing new methods to analyze large datasets of neural signals, allowing investigators to rapidly and transparently solve complex problems of computation, generate new models and model the brain in multiple dimensions and spatiotemporal scales. In 2017, the Neuro-Function, Activity, Structure and Technology (Neuro-FAST) program will use optical and photonic techniques to continue developing state-of-the-art imaging and discovery tools to build upon its demonstrated ability to sense the structure and activity of thousands of neurons simultaneously in the active brain. Achieving stable, high-resolution imagery over multiple experiments promises new insights into brain function and clues to treat injury. The Hand Proprioception and Touch Interfaces (HAPTIX) program is developing implantable medical devices for amputees to enable natural sensation from and control of prosthetic hands. HAPTIX investigators have demonstrated that peripheral nerve stimulation allows amputees to feel vivid sensations of touch and proprioception. Additionally, HAPTIX has enabled the first take-home trial of a prosthetic hand outfitted with the sense of touch, achieving an important milestone in DARPA's efforts to move this technology out of the lab and into the real world. The Electrical Prescriptions (ElectRx) program is developing novel technology for diagnosing, monitoring and treating inflammatory disease and mental health disorders by modulating the peripheral nerve circuits that maintain physical and mental health. In 2017, ElectRx will leverage new technologies for achieving precise, peripheral nerve stimulation and initial mapping of the neural circuits to modulate peripheral nerves implicated in target diseases, such as immunological dysfunction and post-traumatic stress disorder. The Neural Engineering System Design (NESD) program is a new DARPA effort that aims to develop an implantable neural interface able to provide unprecedented signal resolution and data-transfer bandwidth between the brain and the digital world. FY17 goals are to develop algorithms and initial prototype hardware devices and neural transducers to read and write to individual neurons with a spatial resolution beyond the state of the art.

National Science Foundation (NSF): In FY 2017, NSF plans to invest \$74 million to support the BRAIN Initiative. To attain a fundamental scientific understanding of the complexity of the brain, in context and in action, NSF investments in the BRAIN Initiative will generate an array of physical and conceptual tools needed to determine how healthy brains function across the lifespan. NSF will also focus on the development and use of these tools to produce a comprehensive understanding of how thoughts, memories, and actions emerge from the dynamic actions of the brain. NSF prioritizes research in three areas where the agency's capacities are uniquely strong: integrative and interdisciplinary research; new theories, computational models, and analytical tools that will guide research questions and analyze experimental data; and the development of innovative technologies and data infrastructure required to handle the large-scale datasets resulting from this research. NSF has made significant investments in FY 2015 to support the BRAIN Initiative including \$13 million for 16 new awards in Integrated Strategies for Understanding Neural and Cognitive Systems and \$15 million for three collaborative projects designed to crack the olfactory code. In FY 2017, NSF will further the plans to create a National Brain Observatory and to coordinate large-scale brain research projects internationally to leverage global investments to maximize advancement of this complex area of science.

Department of Energy (DOE): The DOE plans to invest \$9 million to the BRAIN Initiative focused on the development of enabling technologies, with respect to three major themes: developing the specialized, high-resolution tools for measuring key neurological processes, developing the capabilities for obtaining a dynamic, real-time read-out of these measurements, and developing the integrated computational framework for analyzing and interpreting this dynamic multi-modal data. Developing the tools to integrate and synthesize multimodal data on the brain and nervous system would be unprecedented and would inform other analyses of complex systems. A workshop will be held in FY 2016 to inform the priority requirements for developing novel biosensors and probes that can measure key molecular components or processes relevant to neuroscience.

Intelligence Advanced Research Projects Activity (IARPA): In FY17, the Intelligence Advanced Research Projects Activity (IARPA) is proposing \$43 million to continue investing in applied neuroscience research programs focused in three areas: (1) advancing understanding of cognition and computation in the brain; (2) developing non-invasive neural interventions that have the potential to significantly improve adaptive reasoning and problem solving; and (3) building novel computing systems that employ neurally-inspired components and architectures.

Food and Drug Administration (FDA): FDA supports the BRAIN Initiative by enhancing the transparency and predictability of the regulatory landscape for neurological devices and assisting developers and innovators of medical devices, which is critical to realizing the investments made in the research and development technology sectors. In FY 2017, FDA's Center for Devices and Radiological Health intends to facilitate the timely development of high quality, safe and effective novel neurological medical products by issuing new guidance on innovative neurostimulation and neurointerventional medical devices, leading BRAIN Initiative related public workshops on topics such as Traumatic Brain Injury, and hosting publicly accessible webinars introducing developers and innovators on how to efficiently move a product to market. FDA also plans to rely on postmarket data collection to support new product approvals or in lieu of some premarket evidence generation, where appropriate. FDA will continue to engage all stakeholders, including patients, to assist developers and innovators in moving safe and effective products to the market. FDA remains committed to continuing its role under the BRAIN Initiative in making as transparent as possible the regulatory framework applicable to neurological devices and thereby helping to bring safe and effective products to patients and consumers.

FDA BRAIN Initiative Announcements & Accomplishments for a Fall White House Event (Date TBD)

Current FDA Events and Announcements

New FDA Regulatory Webinar Series: Moving Devices to Market

As part of the FDA's ongoing effort to assure patients and providers have timely and continued access to safe, effective, and high-quality medical devices, the FDA is hosting a regulatory webinar series for medical device clinical investigators and sponsors on how to participate in bringing innovative medical devices to the United States marketplace. This webinar series is part of the FDA's continuing support of the White House Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative focused on understanding the human brain and uncovering new ways to treat, cure, and prevent brain disorders. The Fall webinar, scheduled for September 14, 2016 (10am-12pm) and hosted by the FDA will focus on: Neurological Devices, Initiating a Medical Device Study, and Investigational Device Exemptions (IDEs); First in Human Studies, Early Feasibility Studies, and Traditional Feasibility Studies; and FDA Engagement and the Pre-Submission process. Winter and spring webinars are also planned.

FDA Fall Flier attached

Finalizing New Guidance on Neurological Devices Targeting Disease Progression and Clinical Outcomes

On March 7, 2016, the U.S. Food and Drug Administration (FDA) issued the draft guidance for public comment, Clinical Considerations for Investigational Device Exemptions (IDEs) for Neurological Devices Targeting Disease Progression and Clinical Outcomes. The FDA recognizes the value of medical device innovation to address unmet clinical needs and improve patient care, particularly when novel treatments may revolutionize how we treat neurological diseases or conditions. The FDA developed the draft guidance to assist sponsors, who intend to submit investigational device exemption (IDE) applications to the FDA to conduct clinical trials on medical devices targeting neurological disease progression and clinically meaningful patient-centered outcomes. Medical devices intended to slow, stop, or reverse the effects of neurological disease (neurological devices) face challenges with regard to collecting safety and efficacy data in a clinical study, when less invasive pharmacotherapy approaches may be better understood or more accepted in the clinical community. The FDA's Center for Devices and Radiological Health (CDRH) is issuing this draft guidance for industry and FDA staff to assist in considering the benefits and risks of medical devices that target either the cause or progression of the neurological disorder or condition such as Alzheimer's disease, Parkinson's Disease, or Primary Dystonia, rather than their symptoms, and importantly, address unmet

medical needs of patients. The public comment period closed June 6, 2016. The FDA received and is currently reviewing the comments in an effort to finalize the guidance before the end of 2016.

Link to Draft Guidance:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM489111.pdf>

FDA allows marketing of first-of-kind computerized cognitive tests to help assess cognitive skills after a head injury

The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) and ImPACT Pediatric are the first medical devices that are intended to assess cognitive function following a possible concussion. They are intended as part of the medical evaluation that doctors perform to assess signs and symptoms of a head injury. ImPACT software runs on a desktop or laptop and is intended for those ages 12 to 59, while the ImPACT Pediatric runs on an iPad and is designed for children ages 5 to 11. Only licensed health care professionals should perform the test analysis and interpret the results.

The device is manufactured by ImPACT Applications, located in Pittsburgh, PA.

Press Release- <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm517526.htm>

Additional Noteworthy Past Announcements and Accomplishments (2014-2016)

FDA unveils Expedited Access Pathway Program to Address Unmet Medical Needs (2016)

The FDA's Center for Devices and Radiological Health has proposed a new Expedited Access Pathway (EAP) voluntary program for certain medical devices, including devices applicable to The BRAIN Initiative, that demonstrate the potential to address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions. This new program provides an expedited pathway to market for qualified devices. Under EAP, the FDA works with device sponsors to try to reduce the time and cost from development to marketing decision without changing the FDA's premarket approval (PMA) statutory standard of reasonable assurance of safety and effectiveness, the standards for granting *de novo* classification requests, or our standard of valid scientific evidence. Components of the program include priority review, more interactive review, senior management involvement, and assignment of a case manager. The extent to which the FDA provides these features depends on the availability of resources. Participation in the EAP program is only at the request of the sponsor and with the FDA's agreement. If the FDA determines that a device may be eligible for this program and the sponsor has not yet submitted a pre-submission (please see the [guidance](#) on CDRH's pre-submission program) requesting EAP Designation, the FDA intends to inform the sponsor of the program.

Link to more information:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm441467.htm>

DARPA and FDA sign Memorandum of Understanding to move products faster to the military personnel and the American public (2016)

This year, the Defense Advanced Research Projects Agency (DARPA) and the FDA signed a new memorandum of understanding to move products from research to market faster, especially for military service personnel and American patients and consumers. The DARPA creates breakthrough technologies for national security and the FDA reviews data supporting the safety and effectiveness of medical devices and decides whether they may be approved, licensed, cleared, or authorized for use. The DARPA and the FDA realize that open communication and close coordination is essential if the investments made in the latest technologies emerging from the biological sciences are to be realized. Under this new agreement, the DARPA and the FDA plan to partner and facilitate innovation of medical products, including neurosensing, neuromodulation, and neurostimulation devices for the treatment of neurologic and psychiatric deficits and other neurological and physical medicine devices.

Investing in Traumatic Brain Injury: FDA Holds Public Meeting to Advance Biomarker Development (2016)

Traumatic Brain Injury (TBI) remains a major public health problem in our society, and it is a contributing factor in a third of all injury-related US deaths. Among TBI, mild TBI (mTBI) is estimated to account for 80–90% of diagnoses. The importance of apparently mild injuries has been recognized as a major public health crisis¹. Growing concerns about the long-term sequelae of mild TBI in civilian populations, military personnel, and sports participants make this a clinically important topic. These concerns also give rise to a greater awareness of the need to find better ways to diagnose, treat, and prevent all forms of TBI, with a strong emphasis on mTBI. This FDA workshop held March 3, 2016 aimed to examine potential biomarkers, discuss the challenges and solutions related to biomarker development methodologies, and establish strategies for data standardization in, and sharing and analysis of big data sets for TBI. By convening the relevant stakeholders, the FDA sought input on the scientific, clinical, patient, and regulatory considerations associated with developing biomarkers for TBI to improve the clinical utility of these markers and the diagnosis of TBI. The FDA is currently reviewing the meeting proceedings to develop potential approaches to advance the development of biomarkers in TBI.

Link to Public Workshop:

<http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm483551.htm>

Understanding Cognition (2015)

The FDA held a public workshop, “Neurodiagnostics and Non-Invasive Brain Stimulation Medical Devices”, on November 19-20, 2015. The workshop focused on two primary topics, non-invasive medical devices to evaluate cognitive function and non-invasive brain stimulation devices to improve or influence cognitive function. Through this workshop, the FDA obtained public input on scientific, clinical, and regulatory considerations associated with medical devices for assessing and influencing cognitive function. At the workshop, the FDA also convened a panel of representatives from the Consumer Product Safety Commission, Defense Advanced Research Projects Agency, Federal Trade Commission, Intelligence Advanced Research Projects Agency, National Institutes of Health and National Science Foundation to discuss communication and coordination across the federal government for non-invasive brain stimulation.

¹ Control NCFIPa. Report to Congress on mild traumatic brain injury in the United States: steps to prevent a serious public health problem. Atlanta, GA: Centers for Disease Control and Prevention, 2003.

The panel also discussed the White House BRAIN Initiative and strategies for moving products to the marketplace.

Link to Public Workshop:

<http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm458018.htm>

FDA approves expanded indication for medical device to treat a form of brain cancer (2015)

The Novocure Inc. Optune System is intended to treat patients with newly-diagnosed glioblastoma multiforme (GBM), an aggressive form of brain cancer. The device delivers low-intensity, alternating electrical fields called tumor treatment fields. GBM tumor cells are especially susceptible to damage when exposed to these fields, which may halt tumor growth. The device is portable and can be powered with batteries or plugged into an electrical outlet. Patients can use the device at home or work, allowing them to continue their normal daily activities. Patients using the device with chemotherapy survived for an average of 19.4 months compared to an average of 16.6 months for those treated with only chemotherapy. The device was reviewed under the FDA's priority review program, which provides for an expedited review of certain devices to treat life-threatening conditions.

The Optune System is made by Novocure Inc. of Portsmouth, NH.

Press Release- <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm465744.htm>

FDA allows marketing of first prosthetic arm that translates signals from person's muscles to perform complex tasks (2014)

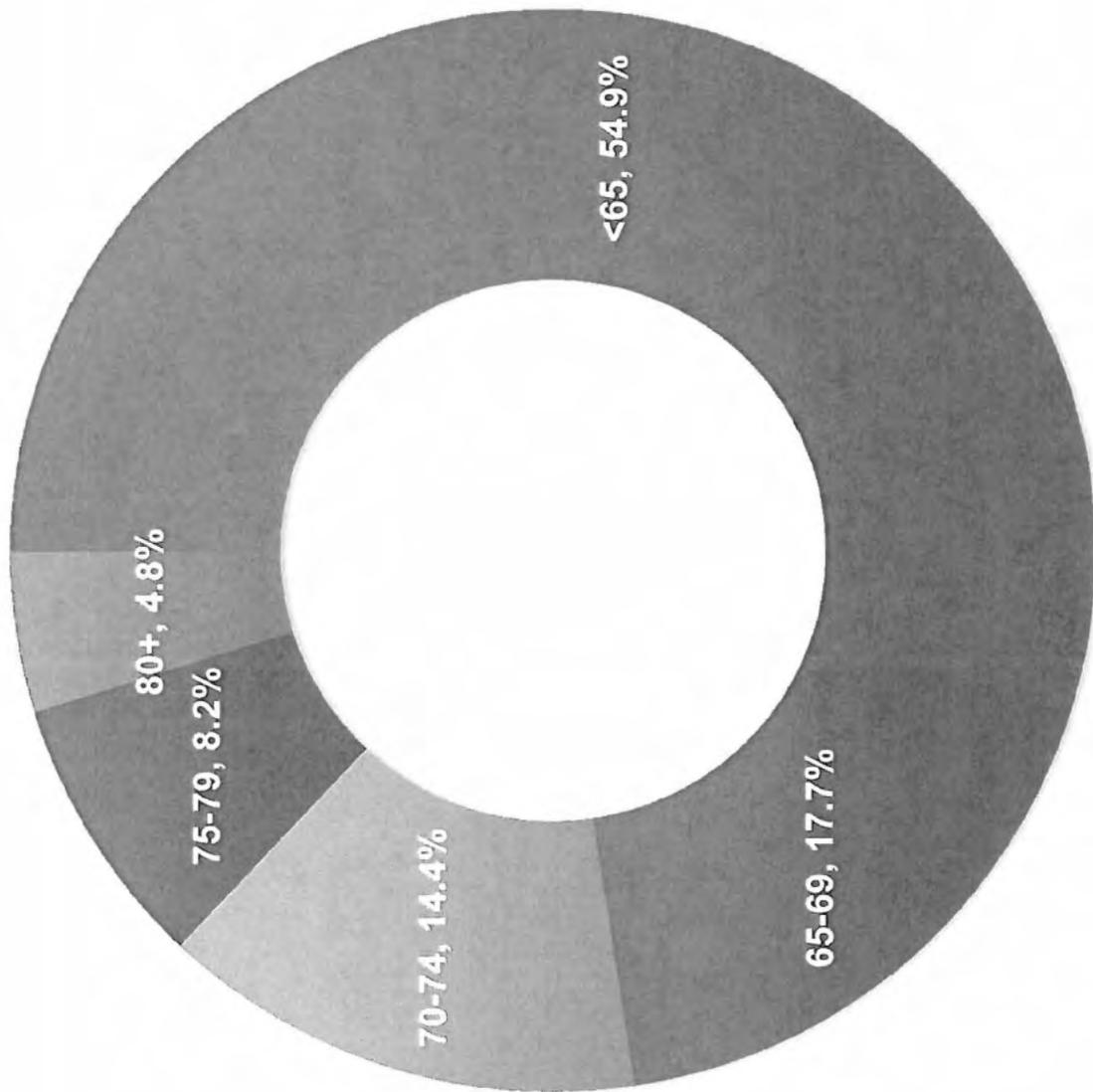
The DEKA Arm System, the first prosthetic arm that can perform multiple, simultaneous powered movements controlled by electrical signals from electromyogram (EMG) electrodes. The EMG electrodes in the DEKA Arm System convert electrical signals into up to 10 powered movements, and it is the same shape and weight as an adult arm. In addition to the EMG electrodes, the DEKA Arm System contains a combination of mechanisms including switches, movement sensors, and force sensors that cause the prosthesis to move.

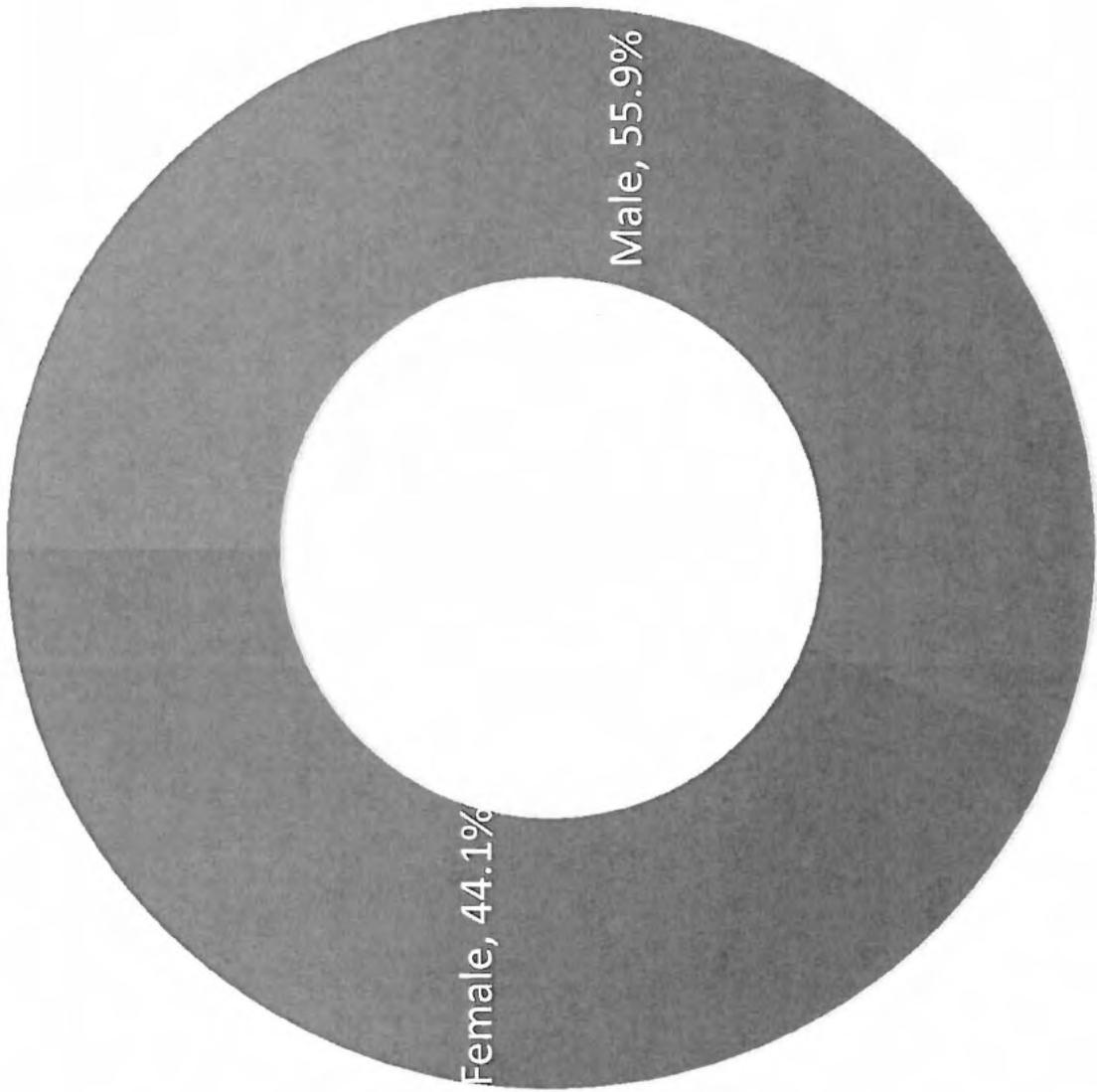
Mobius Bionics, LLC formed to begin commercial manufacturing of the DARPA-funded Luke Arm developed by DEKA Integrated Solutions Corporation of Manchester, NH.

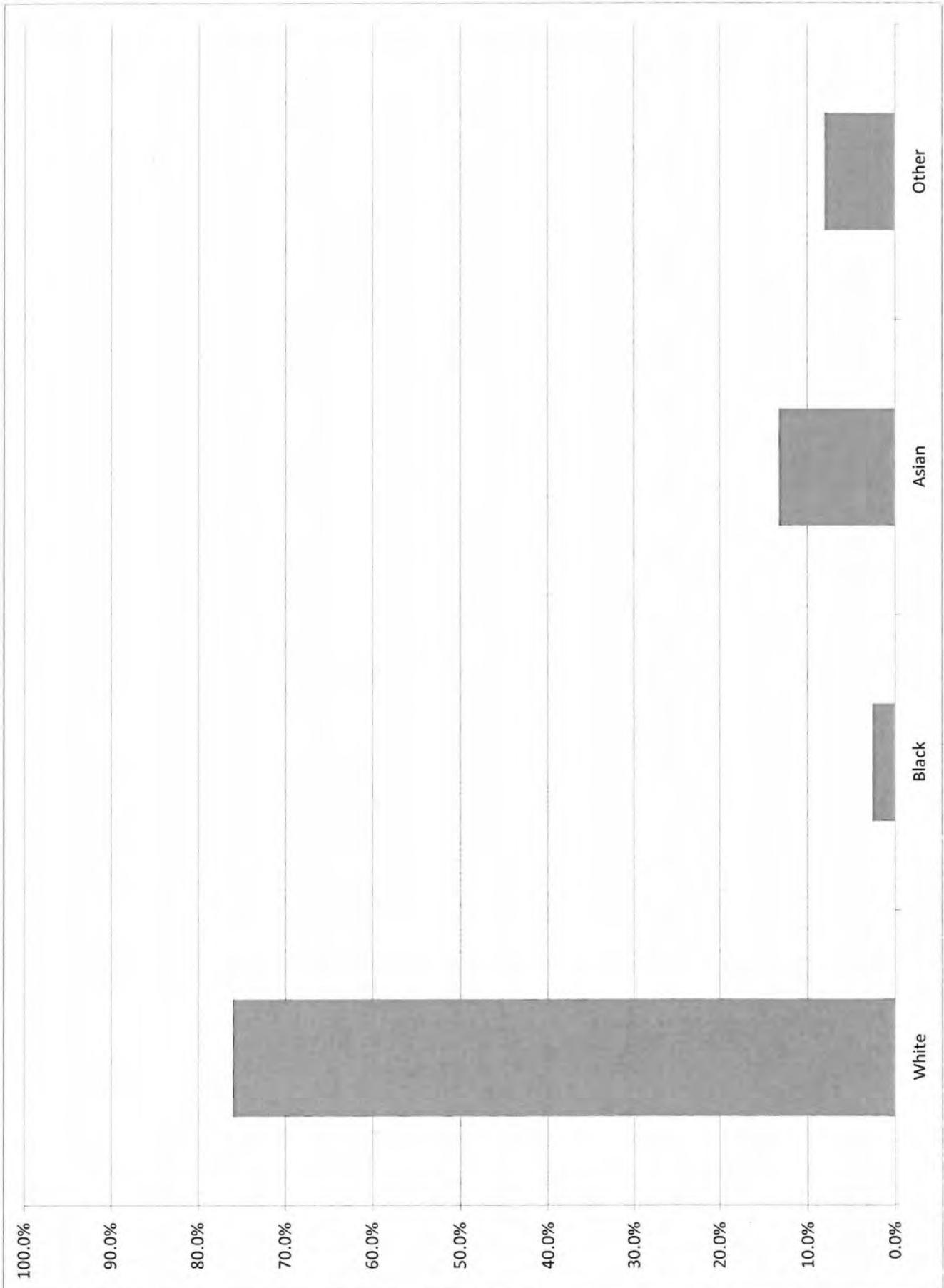
Press Release- <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm396688.htm>

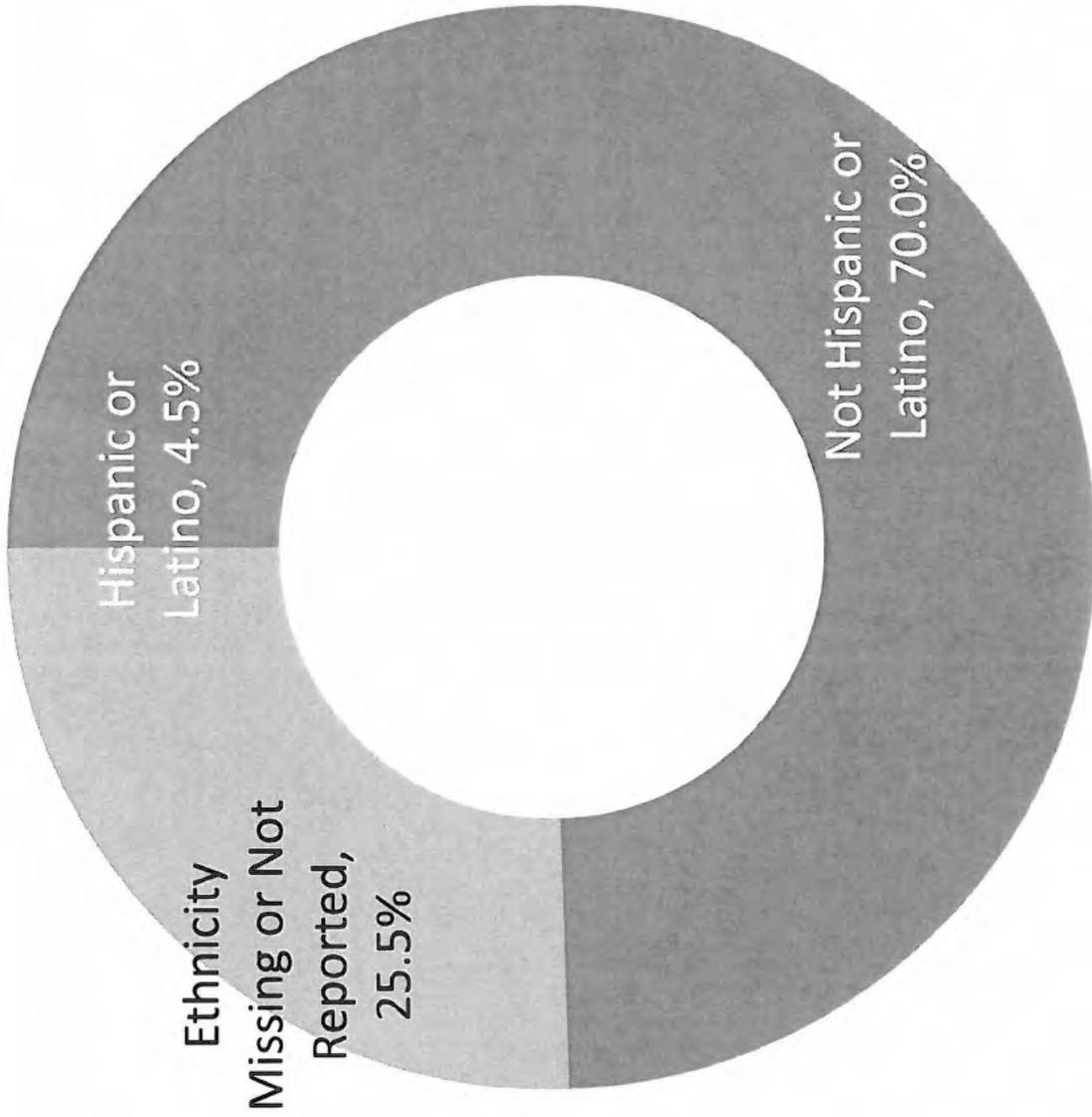
Name	Subname	Indication	NDA/BLA number	Study Name(s)	Total number of	
					participants	Dataset(s)?
Darzalex	daratumumab	multiple myeloma	BLA761036	MMY2002, GEN501	148	Y
Farydak	panobinostat	multiple myeloma	NDA205353	Trial D2308	768	Y
Praxbind	idarucizumab	reversal of anti coag effects of dabigatran	BLA761025	1321.3	123	
Alecensa	alectinib	ALK+ metastatic non-small cell lung cancer	NDA208434	NP28761, NP28673	285	Y
Cotellic	cobimetinib	BRAF V600E, V600K melanoma	NDA206192	GO28141	495	Y
Empliciti	elotuzumab	multiple myeloma, prior therapies	BLA761035	CA204004	646	Y
Ibrance	palbociclib	ER+, HER2- breast cancer	NDA207103	PALOMA-1	165	Y
Lenvima	lenvatinib	thyroid cancer	NDA206947	SELECT	392	Y
Lonsurf	trifluridine and tipiracil	metastatic colorectal cancer	NDA207981	TPU-TAS-102-301	800	Y
Ninlaro	ixazomib citrate	multiple myeloma	NDA208462	C16010	722	Y
Odomzo	sonidegib	locally advanced basal cell carcinoma	NDA205266	CLDE225A2201	269	Y
Portrazza	necitumumab	metastatic squamous non-small cell lung cancer	BLA125547	SQUIRE (I4X-IE-JFCC)	1093	Y
Tagrisso	osimertinib mesylate	EGFR T790M mutation+ non-small cell lung cancer	NDA208065	D5160C00001: AURA 1,	411	Y
Yondelis	trabectedin	liposarcoma or leiomyosarcoma	NDA207953	ET743-SAR-3007	518	Y
					6835	

Year	Appr. Name	Subname	Indication	NDA/BLA num	Male Sex_M	Female Sex_F	White Race_W	Black Race_B	Asian Race_A	Other Race_Oth	<65 Age_Unde	65-69 Age_65to69	70-74 Age_70to74	75-79 Age_75to79	80+ Age_80andover	65 or older Age_65andover	Hispanic Hispanic	Not Hispanic NonHispanic	Ethnicity Missing or Not Reported Missing	
2015	Darzalex	daratumumab	multiple myeloma	BLA761036	148	79	69	116	16	4	12	87	22	23	11	5	61	10	130	8
2015	Farydak	panobinostat	multiple myeloma	NDA205353	768	406	352	491	22		245	283	141	156	113	65	475			758
2015	Praxbind	idarucizumab	reversal of anti coag effects of	BLA761025	123	65	58	105	1	8	9	12	17	18	37	37	111			123
2015	Alecensa	alectinib	ALK+ metastatic non-small cell	NDA208434	285	132	153	208	8	51	18	246	20	9	8	2	39	21	264	
2015	Cotellic	cobimetinib	BRAF V600E, V600K melanoma	NDA206192	495	286	209	462		1	32	362	52	38	29	14	133	26	434	35
2015	Empliciti	elotuzumab	multiple myeloma, prior therapy	BLA761035	646	385	261	544	23	64	15	275	126	116	84	45	371	6	61	579
2015	Ibrance	palbociclib	ER+, HER2- breast cancer	NDA207103	165	0	165	148	2	10	5	89	27	34	10	5	76	5	160	
2015	Lenvima	lenvatinib	thyroid cancer	NDA206947	392	200	192	311	8	70	3	220	81	53	24	14	172	19	373	
2015	Lonsurf	trifluridine and tipiracine	metastatic colorectal cancer	NDA207981	800	491	309	461	9	278	52	448	168	124	50	10	352	16	724	60
2015	Ninlaro	ixazomib citrate	multiple myeloma	NDA208462	722	409	313	611	13	64	12	305	165	123	84	45	417	21	672	29
2015	Odomzo	sonidegib	locally advanced basal cell carcinoma	NDA205266	269	169	100	254	1		14	122	38	31	24	54	147	6	225	38
2015	Portrazza	necitumumab	metastatic squamous non-small cell lung cancer	BLA125547	1093	909	185	914	11	85	84	669	218	162	34	11	425	111	980	3
2015	Tagrisso	osimertinib mesylate	EGFR T790M mutation+ non-small cell lung cancer	NDA208065	411	132	279	151	4	247	7	224	74	59	36	18	187	21	316	74
2015	Yondelis	trabectedin	liposarcoma or leiomyosarcoma	NDA207953	518	154	364	394	63	19	42	403	61	37	15	2	115	46	439	33
					55.9%	44.1%	76.0%	7.7%	13.2%	8.1%	54.9%	17.7%	14.4%	8.2%	4.8%	45.1%	4.5%	70.0%	25.5%	









From: [Califf, Robert](#)
To: [Wohl, Alexander](#)
Subject: RE: talking points for MOU signing tomorrow morning
Date: Wednesday, October 12, 2016 5:29:00 PM
Attachments: [20161012_NORD_Draft.doc](#)

Here's where I am on NORD. Will be working on this and globalization this evening while waiting on planes.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Wohl, Alexander
Sent: Wednesday, October 12, 2016 3:41 PM
To: Califf, Robert
Cc: Branch, Christina; Palmer, Kelly; Evans, Dana; Pennington, Caitlin; Kraus, Tom; Conover, Katie
Subject: talking points for MOU signing tomorrow morning

Dr. Califf,

Hope you have had a productive trip on the west coast. Attached are talking points for your brief remarks tomorrow morning at the MOU signing. As you will see, you are there to welcome the parties and focus on the general collaborative effort, including with FDA, surrounding the development in the land adjacent to FDA and the creation of a Life-Sci village/Silicon Valley for healthcare. Please let me know if you have any questions.

Also, have you had any chance to further develop the NORD speech, and do you need anything from me at this stage?

Have a good trip back.

Alex

Critical Lessons about Rare Disease Drug Development

We are entering a remarkable time in which molecular biology, genetics and genomics and information technology are converging to open the possibilities for treatment of previously untreatable rare diseases. AS we celebrate this exciting new time, we need to take stock of lessons from the history of therapeutic development and recent experiences with rare diseases so that we optimize the efficiency of the development and evaluation of the plethora of potential treatments in the pipeline. We are excited at FDA about the number of previously untreatable diseases that could be cured or ameliorated, but we are also chastened by the history of unfulfilled promises.

Despite the remarkable progress, the latest data continue to indicate that the vast majority of drugs entered into early phase human testing will not make it to market. This is due to a complex combination of failure to demonstrate efficacy, unexpected toxicity and difficulty with manufacturing. Therefore, while speed to access is vital to suffering people, we also must continue to develop methods that rapidly discard therapies that are dangerous or ineffective and speed along therapies that truly provide clinical benefit. And we believe that all members of the ecosystem, FDA itself, patients and their advocates, industry, academia, practitioners and health systems all have a vital role to play to optimize the amazing opportunity before us.

Expedited pathways

The Congress and the FDA have worked together with advocacy groups and the clinical community to develop a series of expedited pathways for promising therapies for diseases without effective therapies and with dire prognoses. The fundamental concept is that for extraordinarily promising therapies FDA can assist in development to expedite the process and to provide rapid and frequent feedback so that developers move quickly with greater confidence that errors in development will not be made. The extreme ends of the spectrum are accelerated approval and expanded access.

Accelerated approval allows FDA to allow marketing for life threatening or disabling diseases based on substantial evidence that the therapy changes an unvalidated biomarker in a direction that is “reasonably likely” to lead to clinical benefit. The statute allows enormous latitude for FDA to consider the spectrum of evidence about biological plausibility, clinical epidemiology and fundamental knowledge that could link the biomarker of interest to the possibility of being a valid surrogate.

Expanded access has been the source of much controversy, but the situation is relatively straightforward. When patients and their doctors believe there is no effective alternative on the market and an experimental agent may be useful, they can request access through a form that has been streamlined so that a doctor with a deep knowledge of the patient can make the request with less than an hour’s work . FDA approves over 99% of such requests, but only after considering whether the patient is eligible for an ongoing clinical trial, as generating knowledge about new drugs is the top priority in the pre-market phase, and combining access with new knowledge is an extraordinarily positive contribution to relieving suffering. But when there is no possibility of enrolling in a trial, either

because of eligibility criteria or logistics (as in the patient lives far away from the nearest study site and cannot travel), it is up to the company to decide whether the drug can be made available. We are working on a navigator system to make it even easier to access the system and we are following with interest efforts to increase the transparency of the policies of companies about their experimental drugs and biologics.

One fascinating and critical example of the need to continue to work on the regulatory science issues involved in these pathways is the question of what “reasonably likely” actually means. It is not defined either in statute or guidance, and although scientifically the evaluation of the totality of evidence should lead one to a quantitative or probabilistic estimate,

Improving the Quality of Early Studies

The time from academic laboratory to startup and human clinical studies is becoming compressed. It is critical that the quality of these early studies improve as they will be the basis for regulatory decisions in many situations. Among many other considerations, careful attention to assay validation for biomarkers and the use of randomization early are critical.

We have made numerous advances in conjunction with NIH on this area including the passing of the final rule for ClinicalTrials.gov, the development of a standard template for protocol design and the initiation of a joint effort to provide a source of knowledge about biomarkers, named the Biomarkers, Endpoints and other Tools (BEsT).

Independence of FDA in Decision Making

The complex process of drug to make a decision about approval and labeling has a long history replete with precedents and accumulated wisdom. One of the most important issues is the preservation of independence of the FDA as a regulatory and public health agency from the vicissitudes of political influence. This was a critical part of my decision about eteplirsen—setting a precedent of political appointees intervening in decisions that belong in a scientific process opens the door to a potentially dangerous temptation for others to intervene more frequently. While it is true that FDA decision making is difficult and imperfect, political meddling would undermine confidence and introduce the type of bias that is not helpful.

Interaction with Patient Advocacy Groups

While independence of FDA in decision-making is a critical issue, interaction with the external “ecosystem” is critical for multiple reasons. In general a more outgoing FDA has been good for the efficient development and assessment of technologies. The more knowledgeable the cadre of FDA reviewers about the disciplinary (clinical medicine, pharmacology, biostatistics, engineering, etc.) and clinical medical (oncology, mental health, cardiology, etc.), the better the ability to assess the proper design of studies and interpretation of the evidence.

Within the ecosystem, patients and patient advocates are taking an increasingly prominent role.

Completion of Confirmatory Studies

While accelerated approval and other means of speeding drug development are welcome, their common use points to the need for high quality studies in the post-market to confirm or refute assumptions made based on less complete data.

Effectively Acting on Findings of Confirmatory Studies

Finally, if such studies do not confirm a positive benefit risk balance in the population intended for treatment, it will be important to assure that the product will either be removed from the market or its label changed to reflect the finding.

From: [Califf, Robert](#)
To: [Wohl, Alexander](#)
Subject: FW: talking points for MOU signing tomorrow morning
Date: Thursday, October 13, 2016 7:11:00 PM
Attachments: [20161012 NORD Draft.doc](#)

Just making sure you got this. I hope to send you something sort of near final early am.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Califf, Robert
Sent: Wednesday, October 12, 2016 5:29 PM
To: Wohl, Alexander
Subject: RE: talking points for MOU signing tomorrow morning

Here's where I am on NORD. Will be working on this and globalization this evening while waiting on planes.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Wohl, Alexander
Sent: Wednesday, October 12, 2016 3:41 PM
To: Califf, Robert
Cc: Branch, Christina; Palmer, Kelly; Evans, Dana; Pennington, Caitlin; Kraus, Tom; Conover, Katie
Subject: talking points for MOU signing tomorrow morning

Dr. Califf,

Hope you have had a productive trip on the west coast. Attached are talking points for your brief remarks tomorrow morning at the MOU signing. As you will see, you are there to welcome the parties and focus on the general collaborative effort, including with FDA, surrounding the development in the land adjacent to FDA and the creation of a Life-Sci village/Silicon Valley for healthcare. Please let me know if you have any questions.

Also, have you had any chance to further develop the NORD speech, and do you need anything from me at this stage?

Have a good trip back.

Alex

From: [Wohl, Alexander](#)
To: [Califf, Robert](#)
Cc: [Branch, Christina](#); [Pennington, Caitlin](#); [Evans, Dana](#); [Palmer, Kelly](#); [Kraus, Tom](#); [Conover, Katie](#); [Rao, Gayatri](#)
Subject: NORD 2016 draft updated
Date: Friday, October 14, 2016 4:47:05 PM
Attachments: [10-17-16 NORD 2016 with comments.doc](#)

Dr. Califf,

Attached is the current draft of NORD. As you will see, I added an introductory section, which I think flows nicely into the main piece. The places where you have noted you will add a paragraph or discussion are still in there. But I've broken up some of the paragraphs and added bullets for emphasis and ease of reading. I hope that's not counterproductive for you. In addition, Gayetri and OCC reviewed the speech and I've included their very good edits as well as a few of my own. Where significant, I've left in their comments and questions. Even though the speech is not complete, I think it reads quite well.

Please let me know if you have any questions or need anything additional over the weekend.

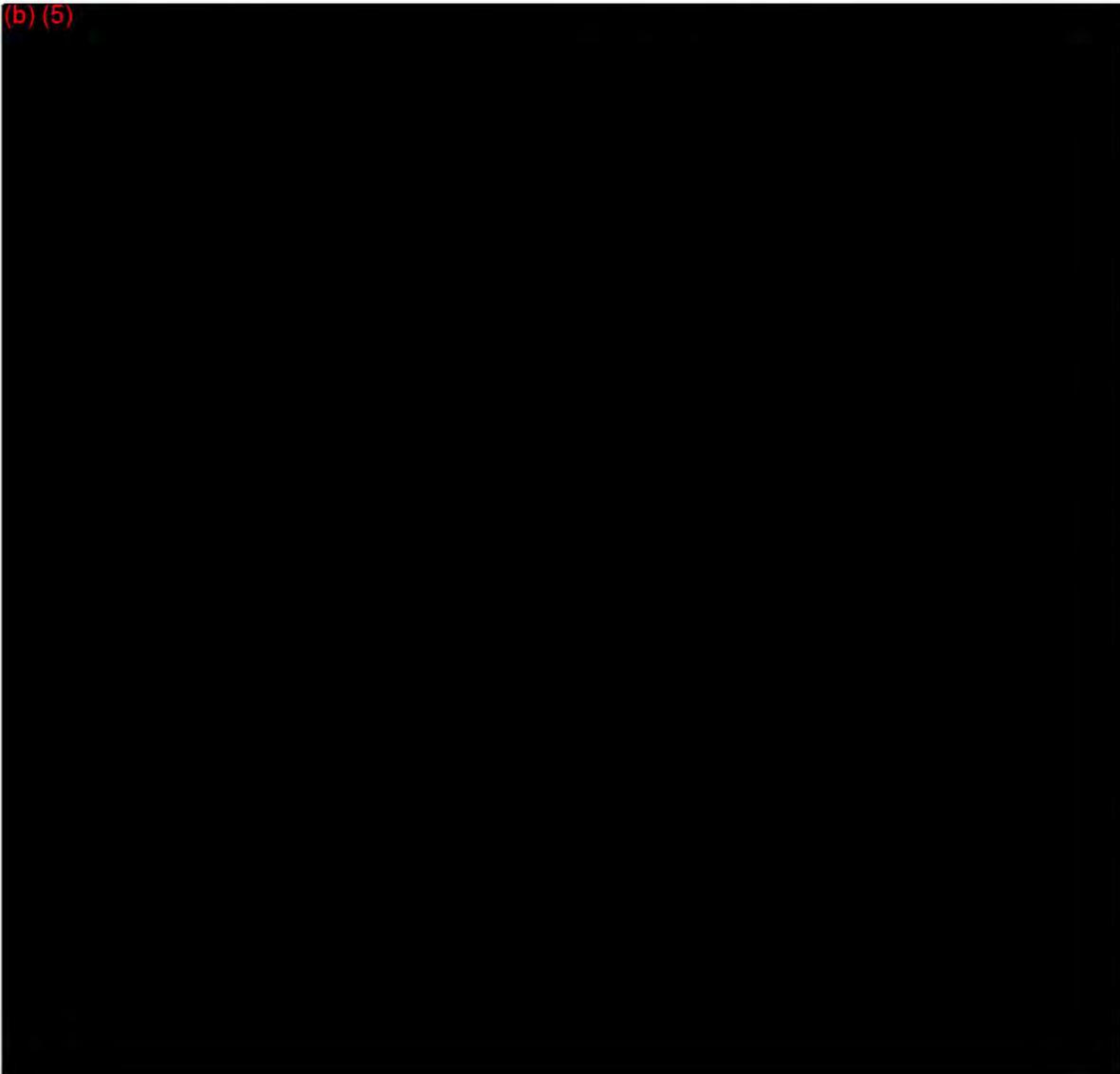
Thanks,

Alex

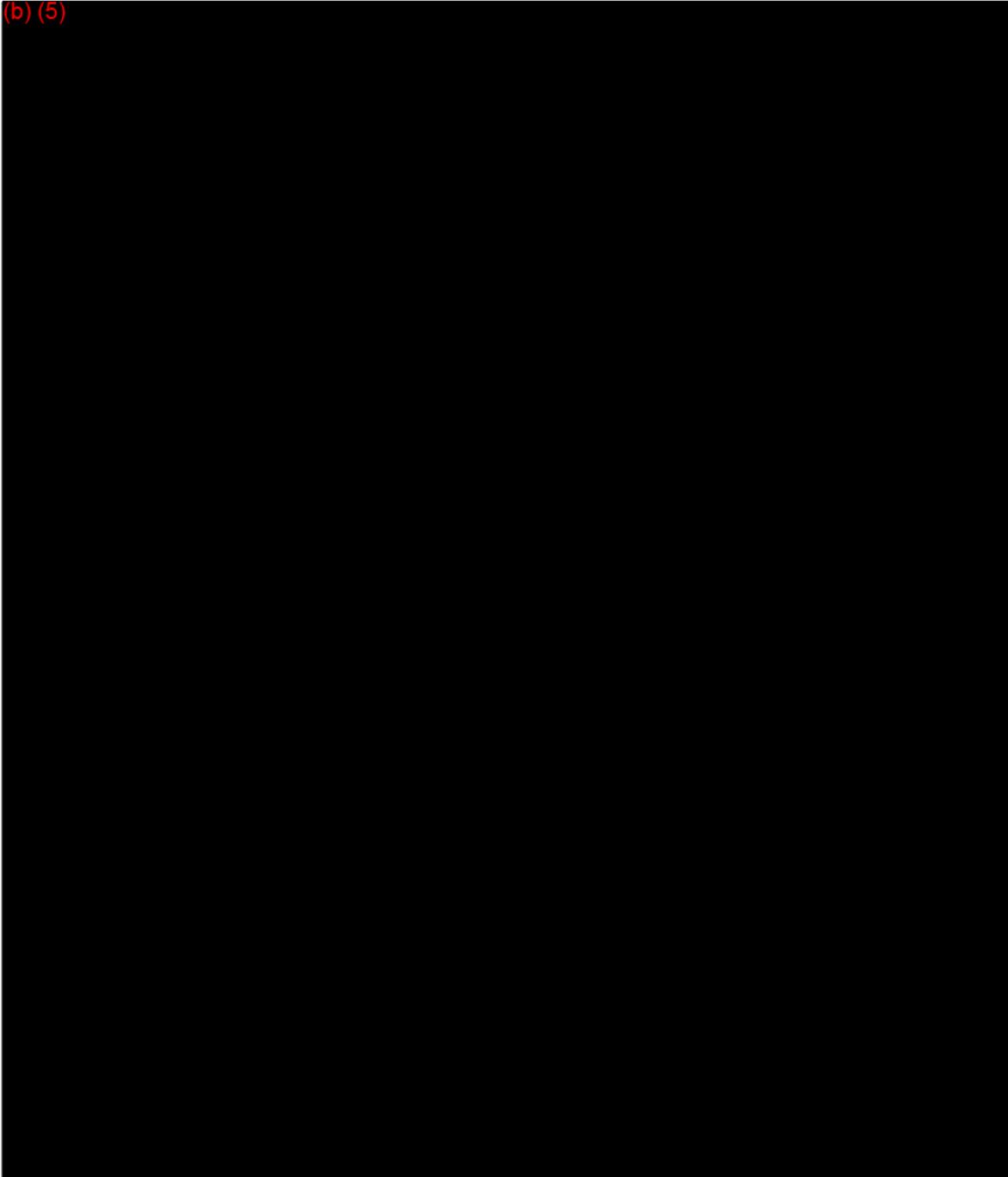
Speech by Robert M. Califf, M.D.
Commissioner of Food and Drugs
2016 National Organization for Rare Disorders (NORD) Summit
October 17, 2016
Washington, D.C.

“Critical Lessons about Rare Disease Drug Development”

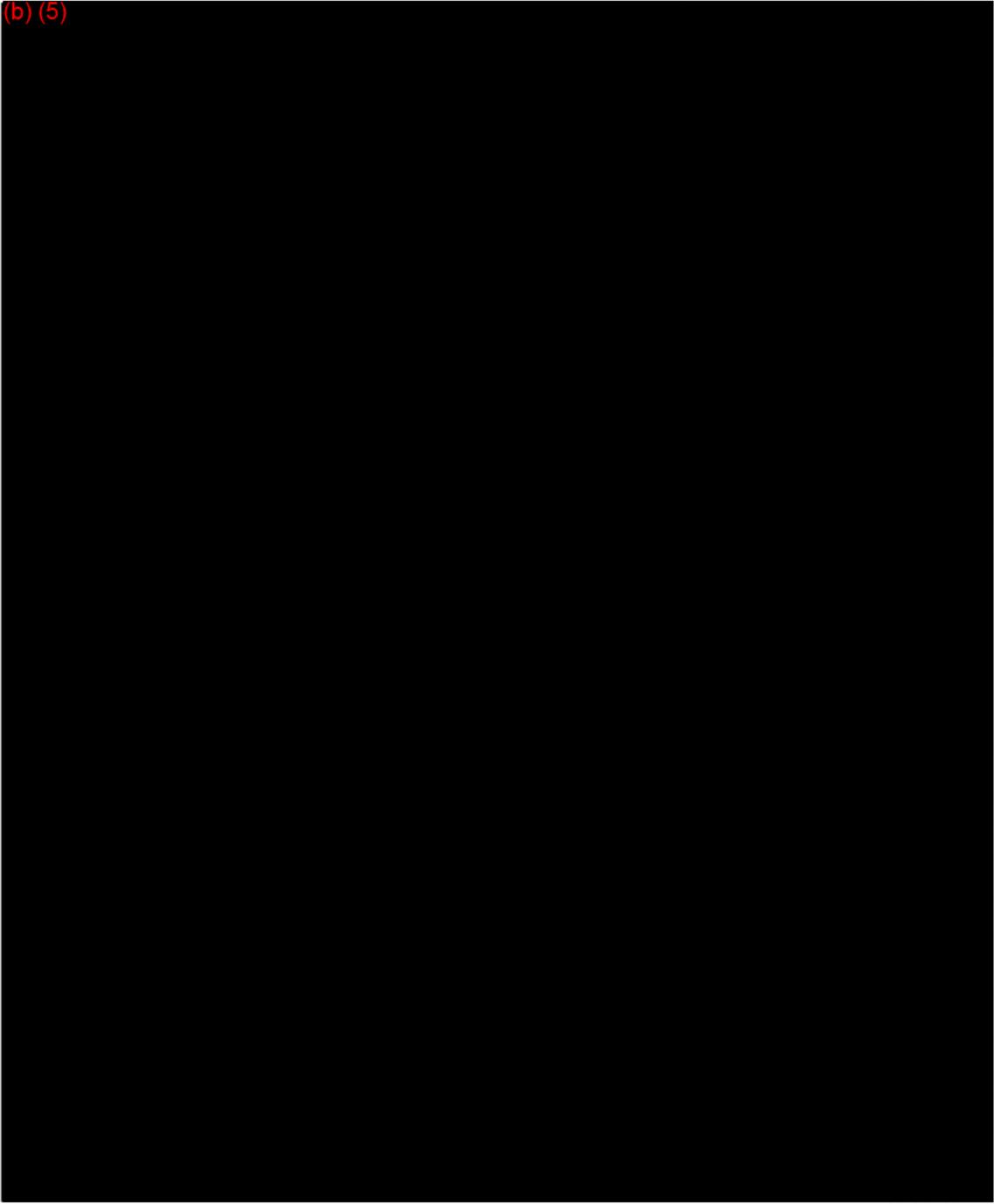
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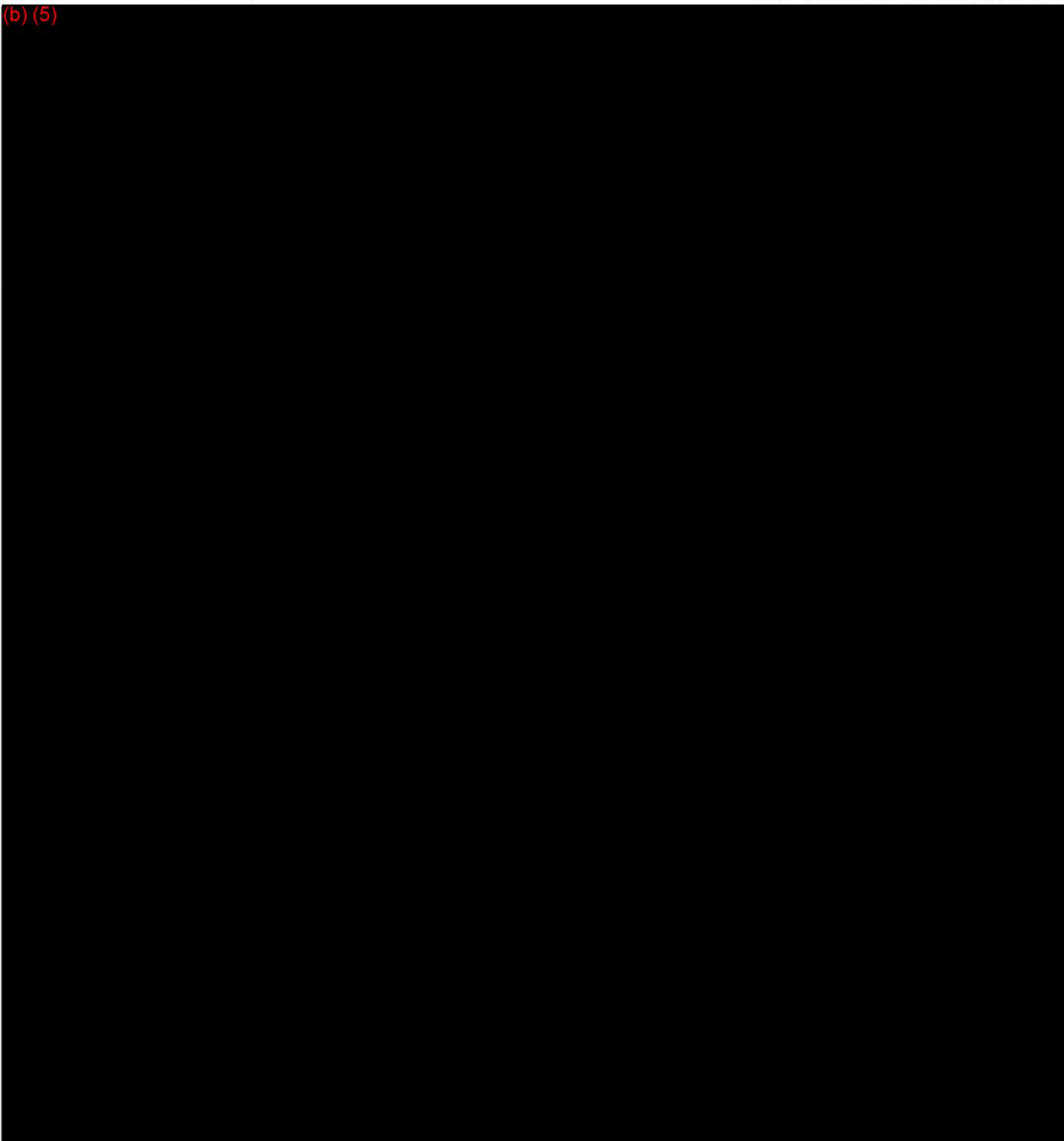
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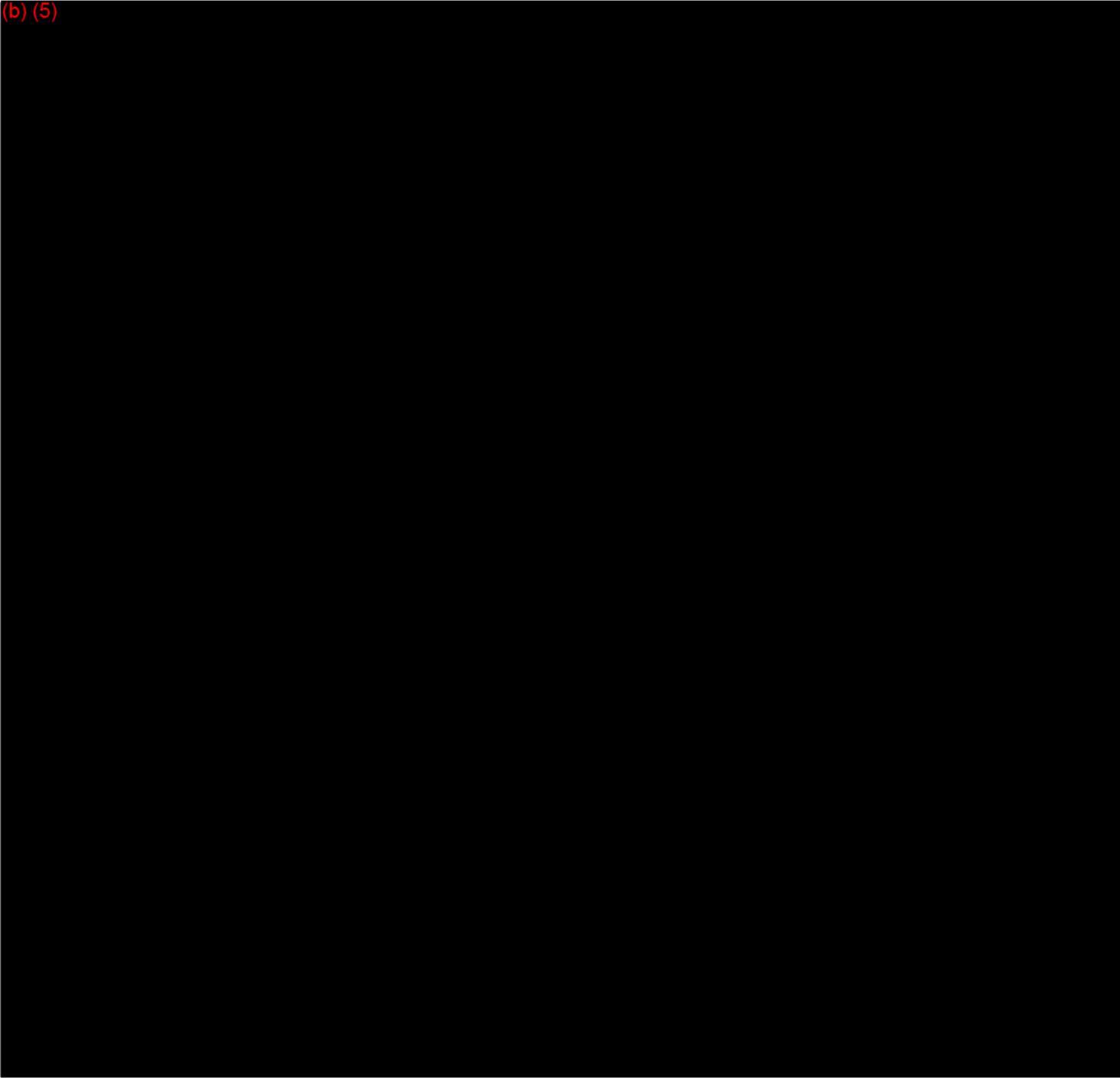
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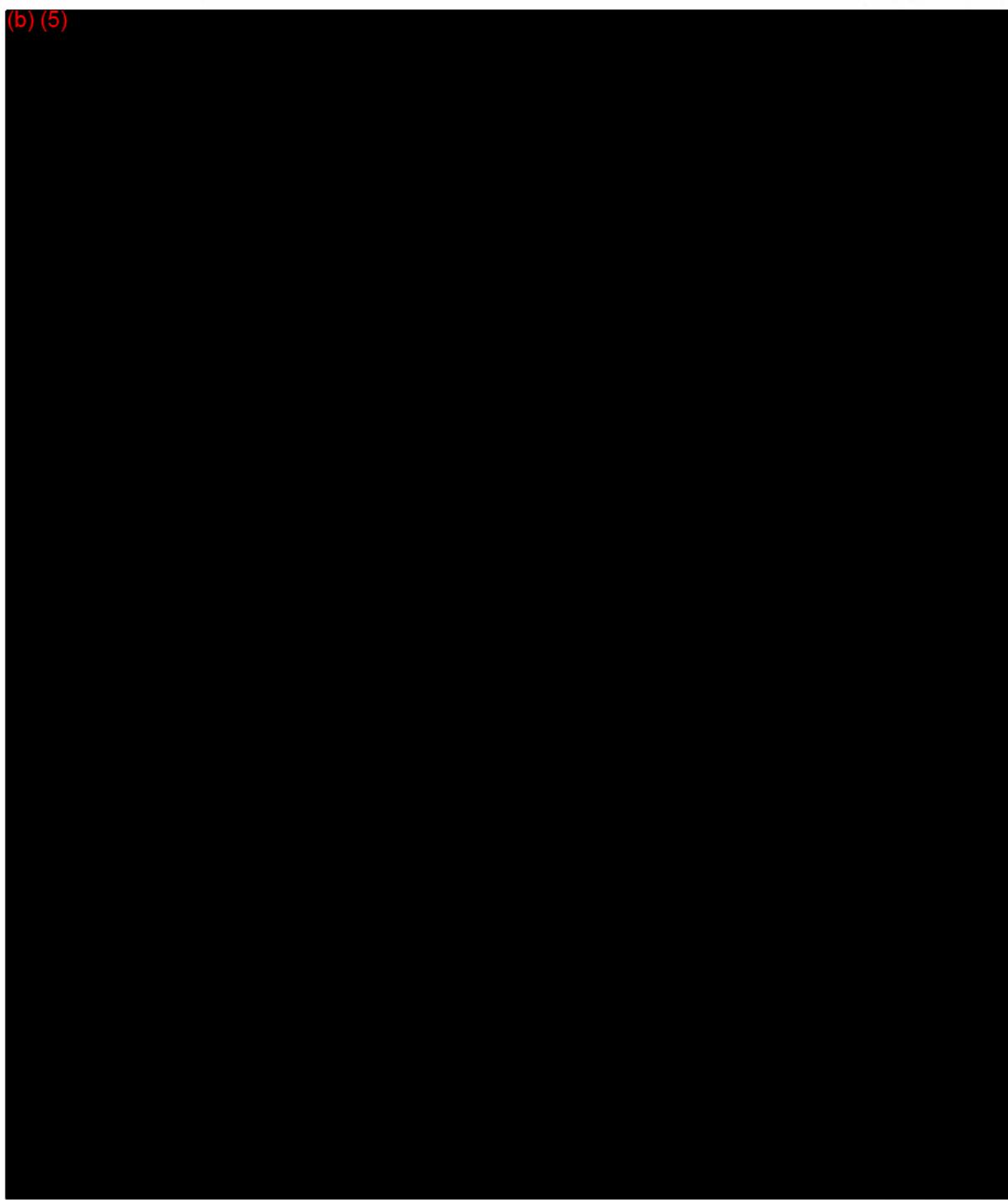
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From: [Califf, Robert](#)
To: [Wohl, Alexander](#)
Subject: Monday
Date: Friday, October 14, 2016 8:30:00 AM
Attachments: [20161014 FDA Globalization.pptx](#)
[20161013 NORD Draft.doc](#)

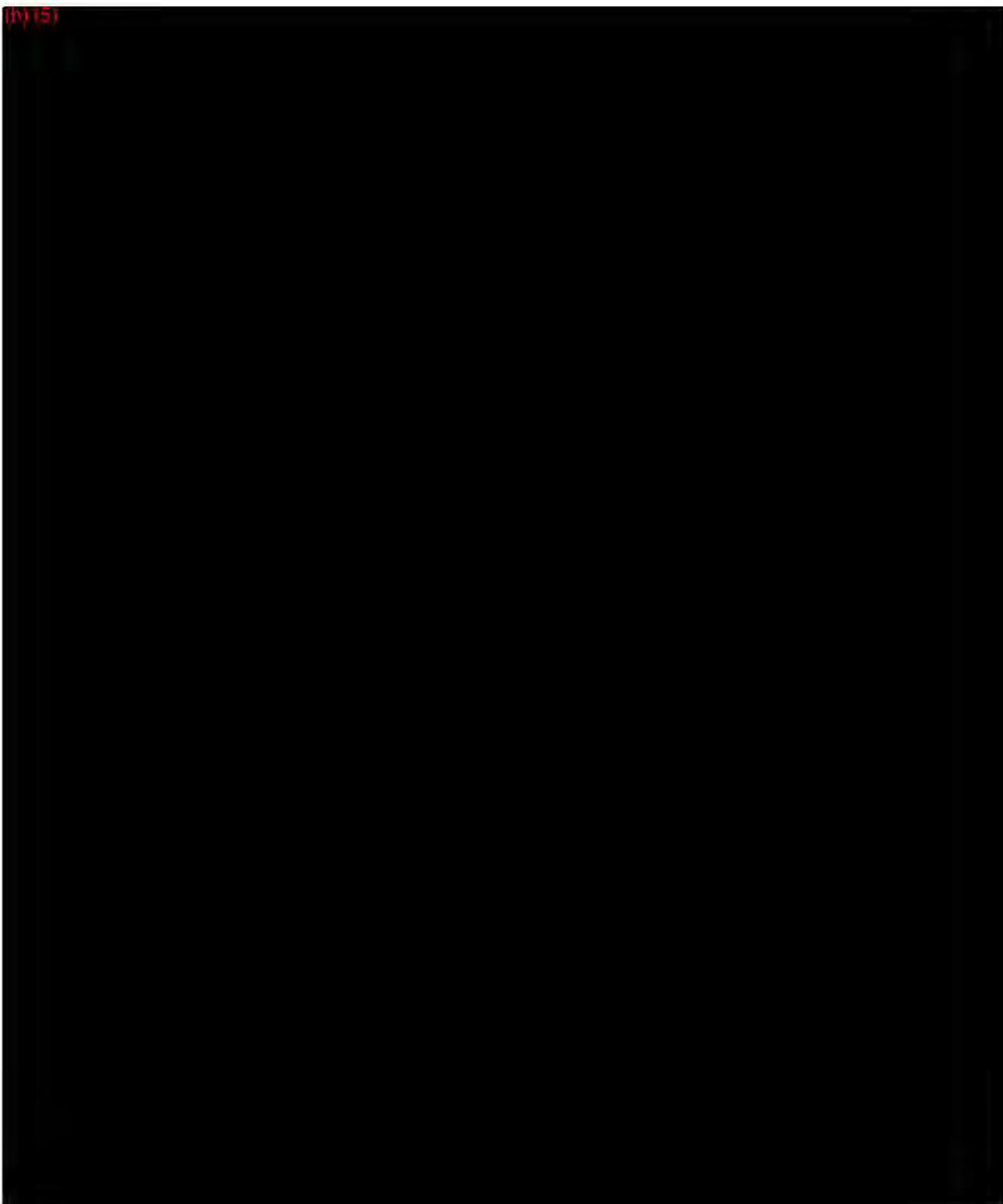
Well, here we go again. I keep running out of time. I'm not at all worried about the talks, but I won't be able to finalize till tomorrow and Sunday. Every day these days is jam packed and today is no exception. Too much to do and not enough time with 99 days to go.

1. The NORD talk will be fun. I need to finish the last parts, but I think I've got enough for you to work with. I'll need whatever you have when you knock off today. I plan to get up early tomorrow and do a good draft.
2. Also, will be alternating with finalizing the globalization slides. You can see where I'm going from what is attached.

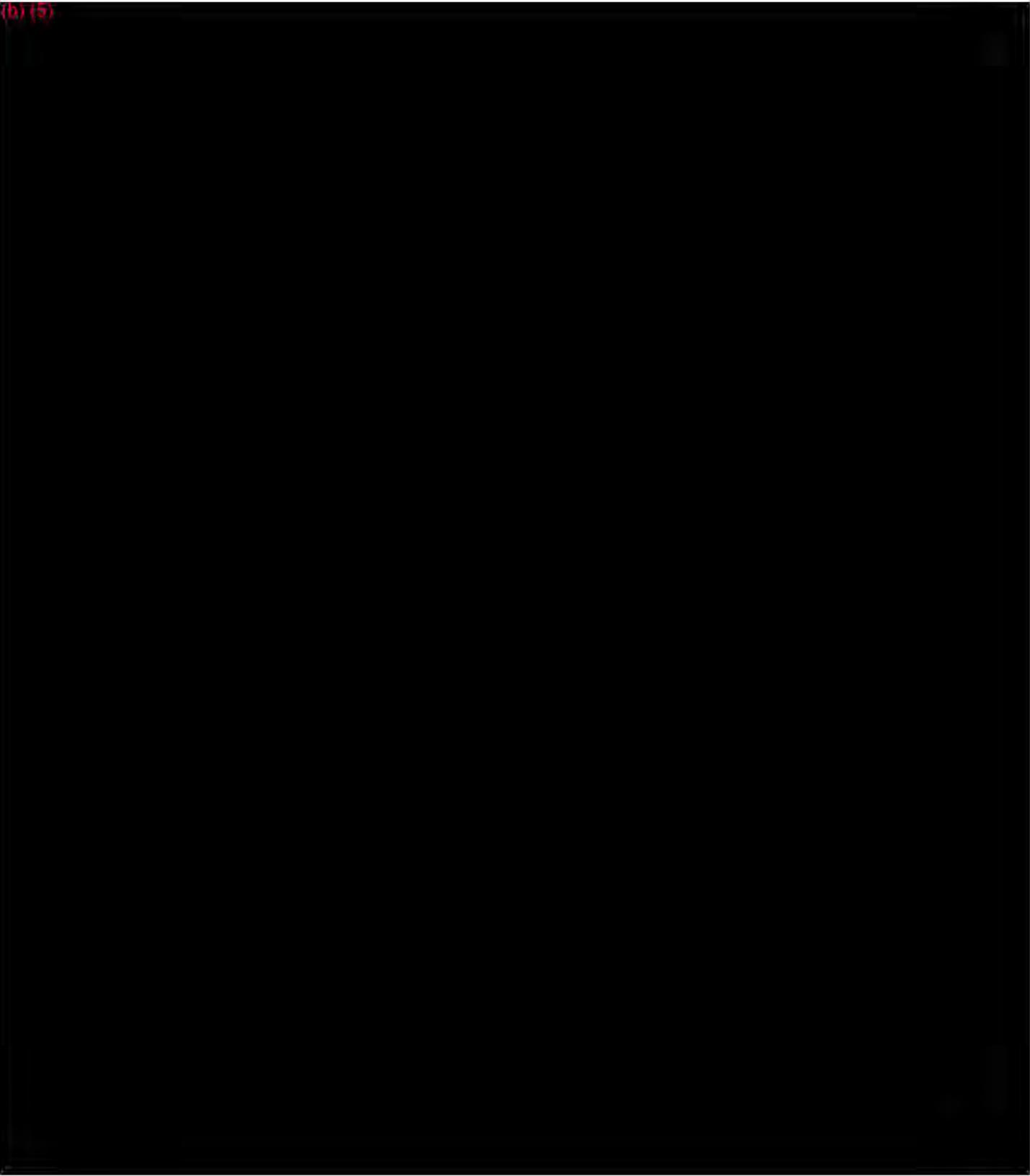
I feel good about where I am, but I'm sorry these things keep getting rushed. I don't think it will change till November, however. Sorry about that.

rmc

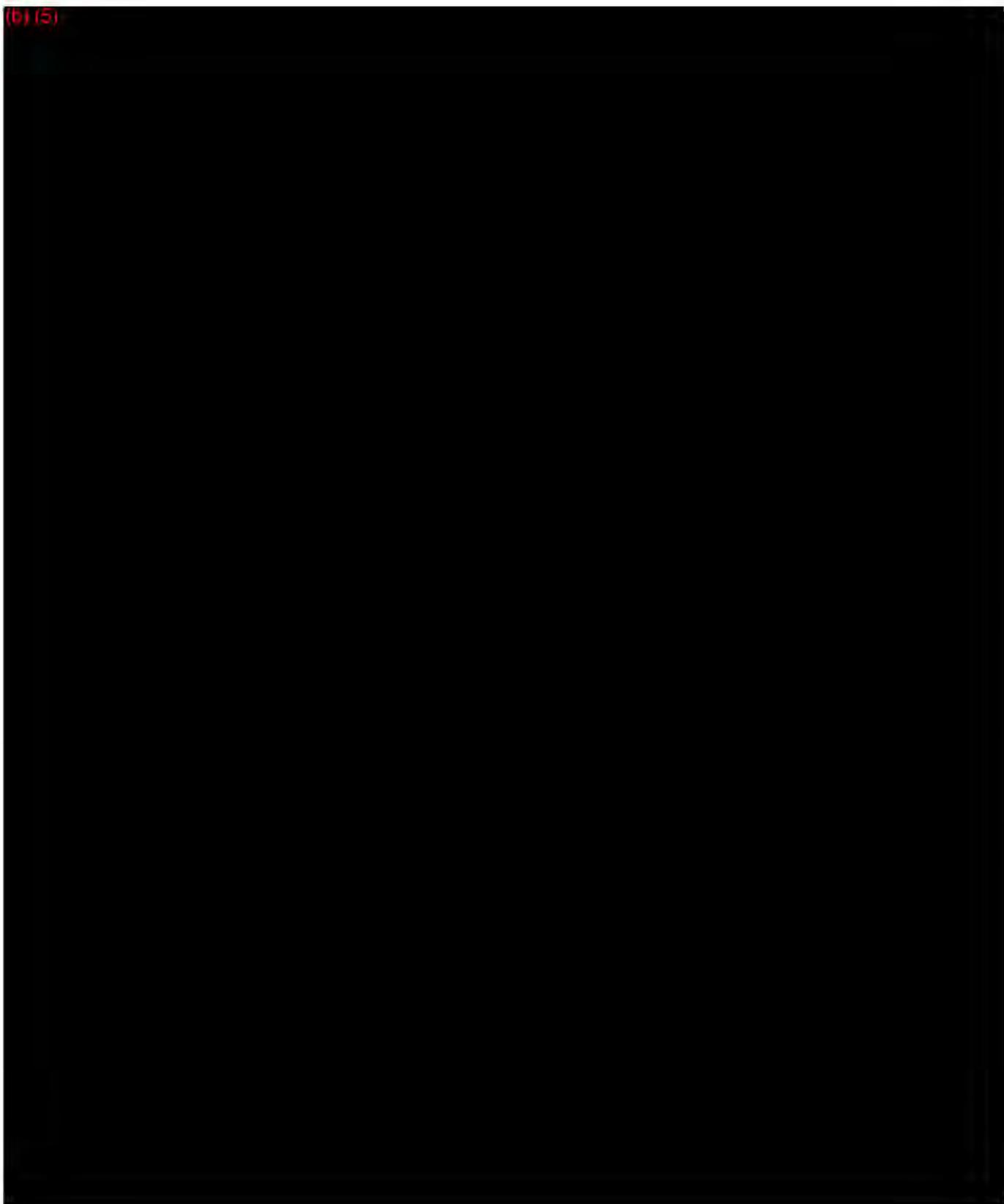
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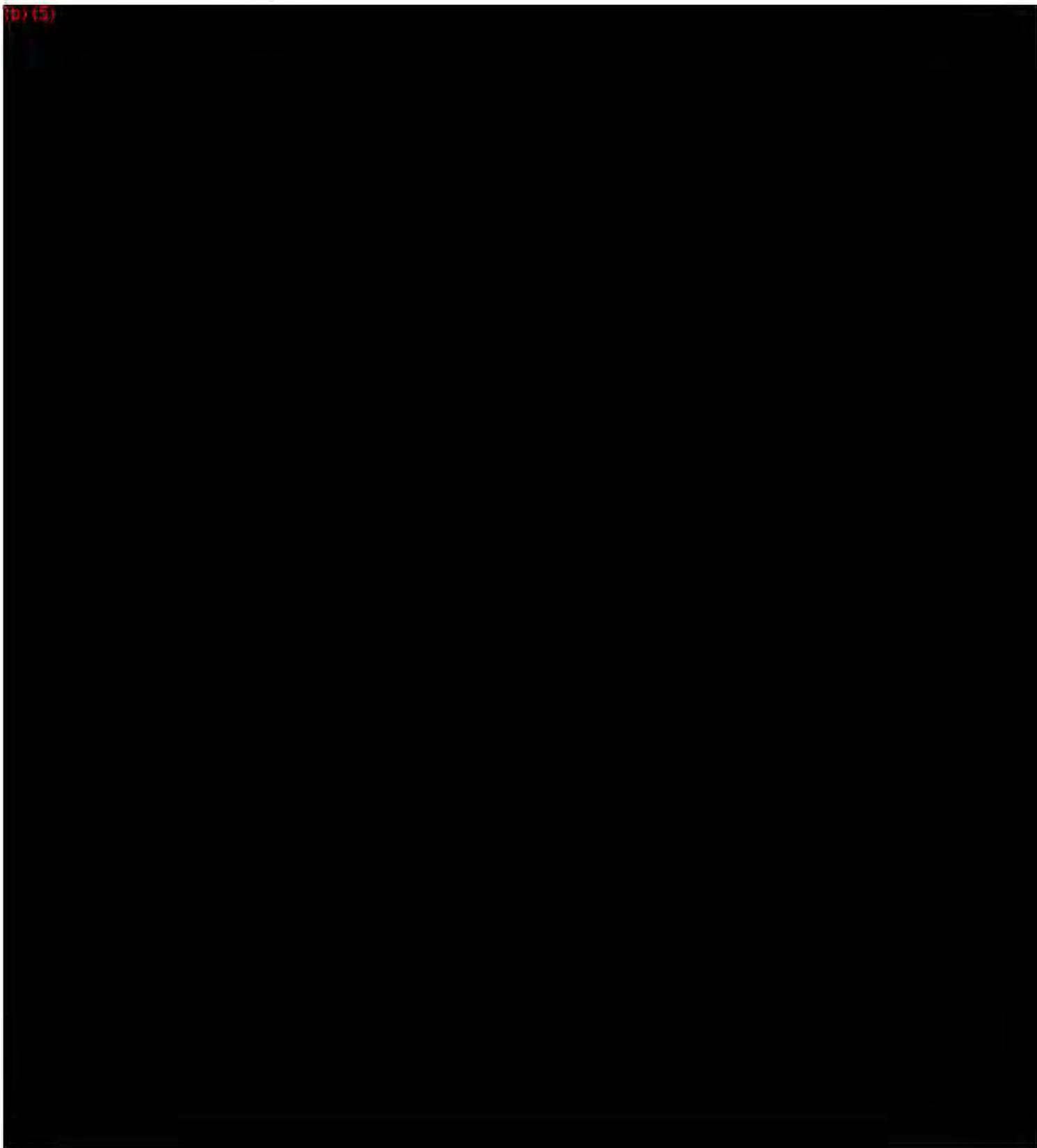
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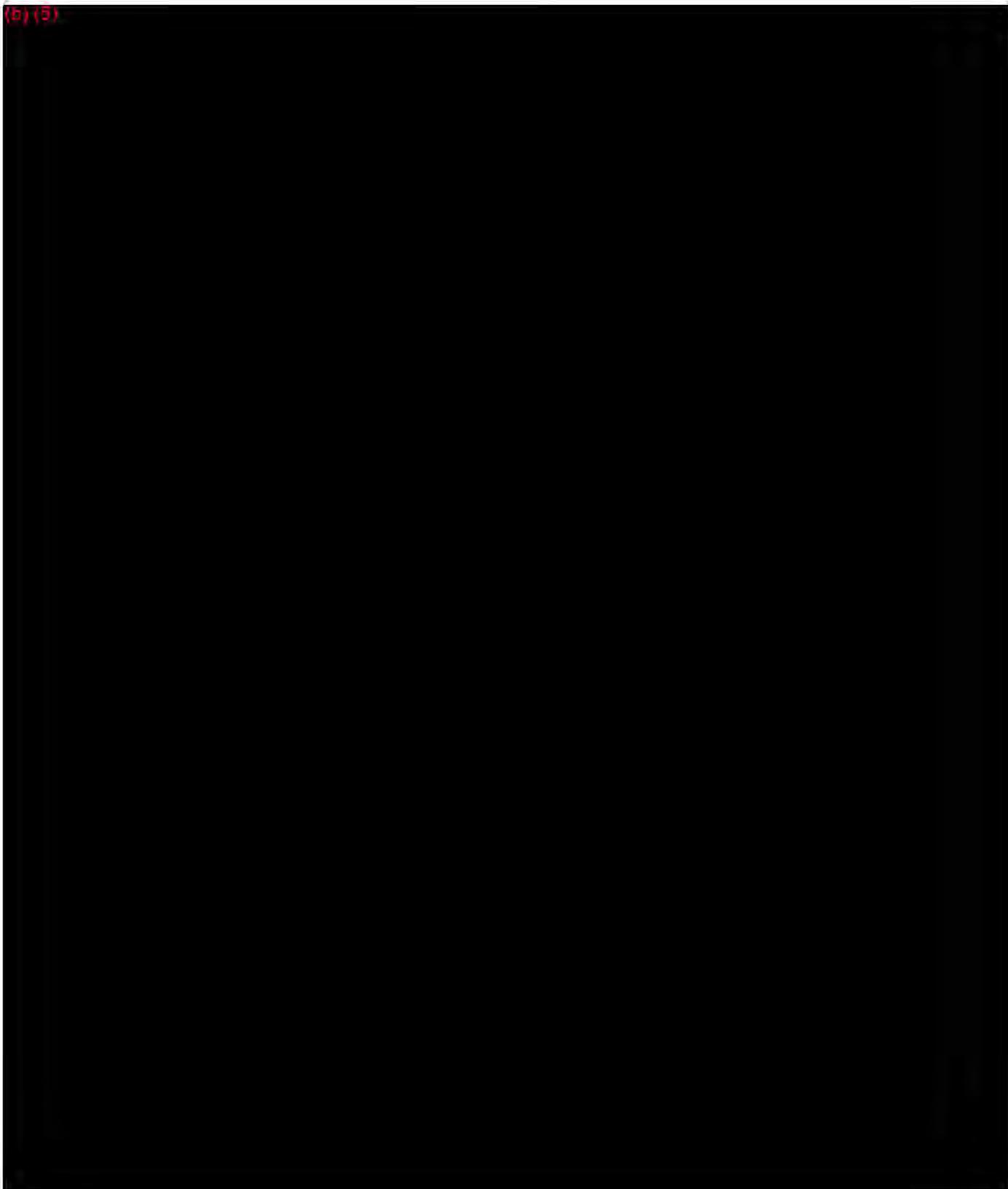
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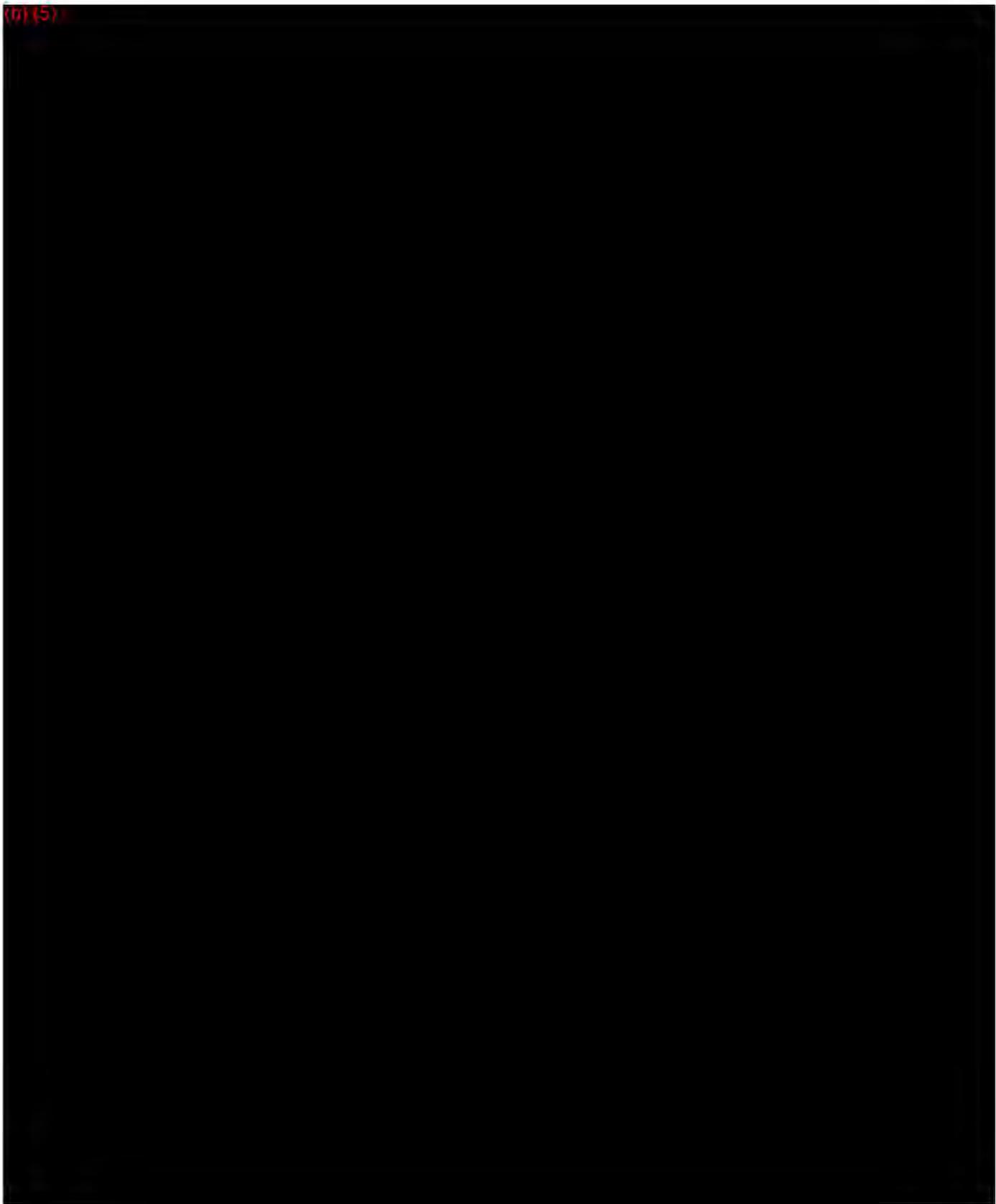
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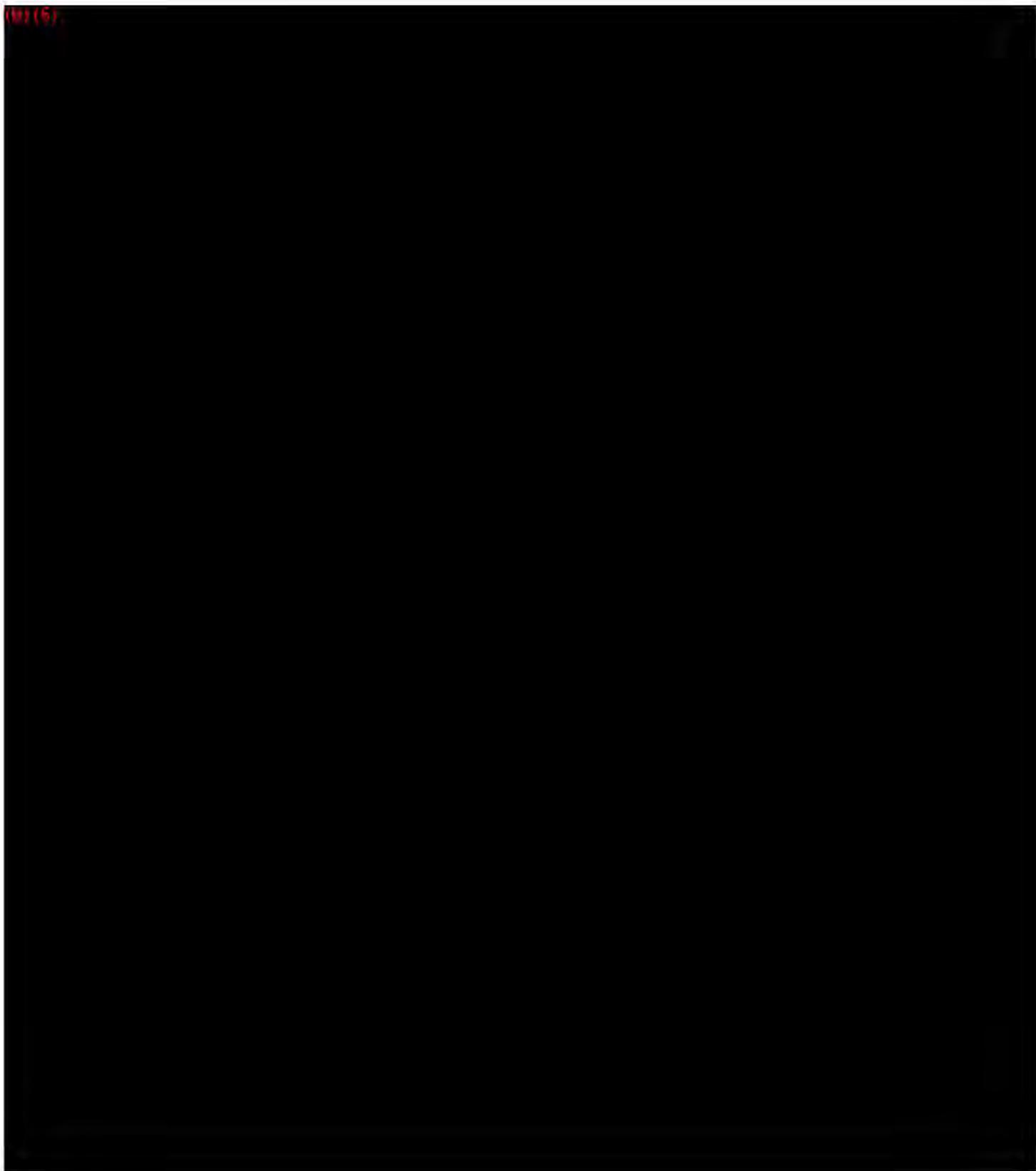
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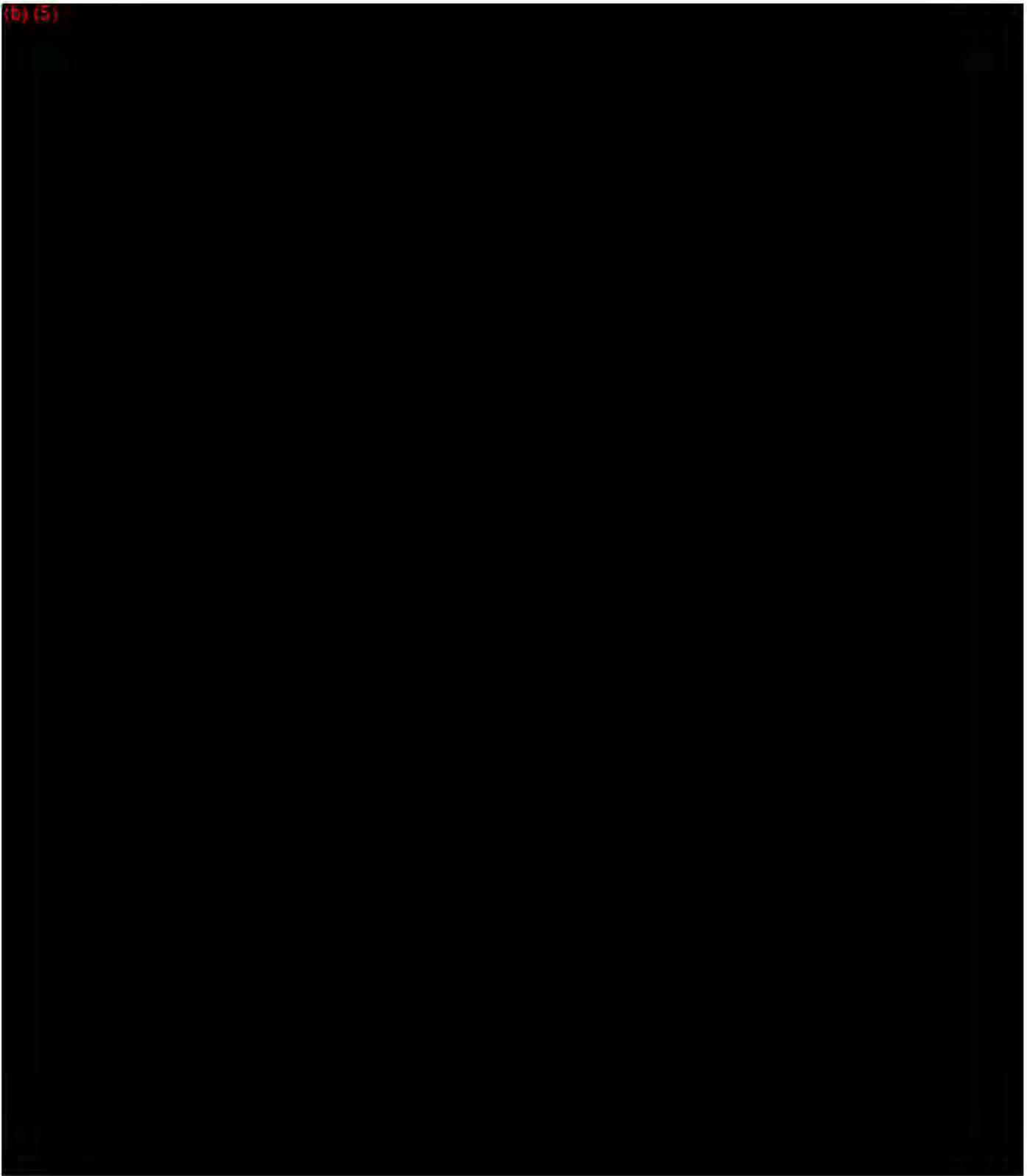
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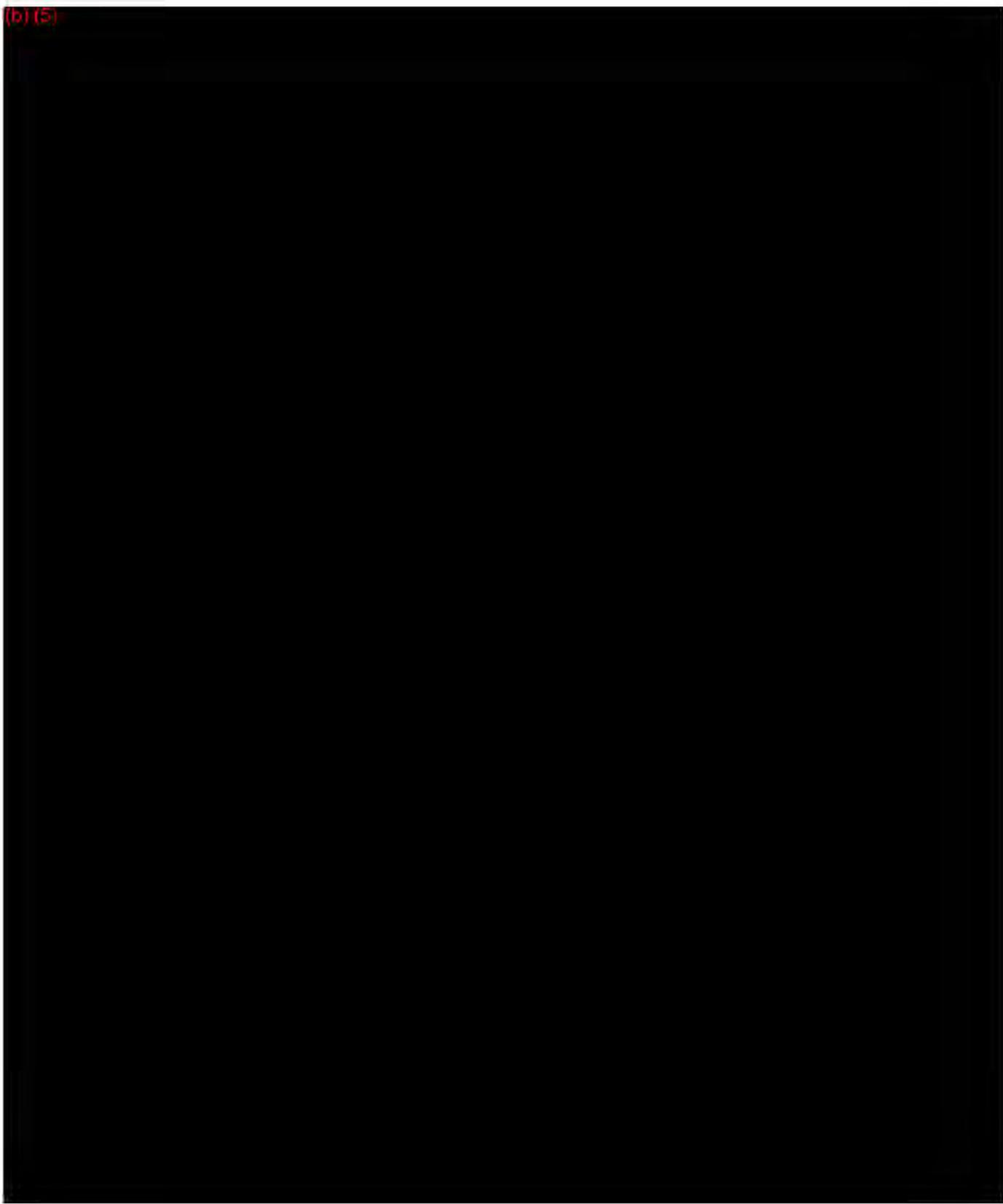
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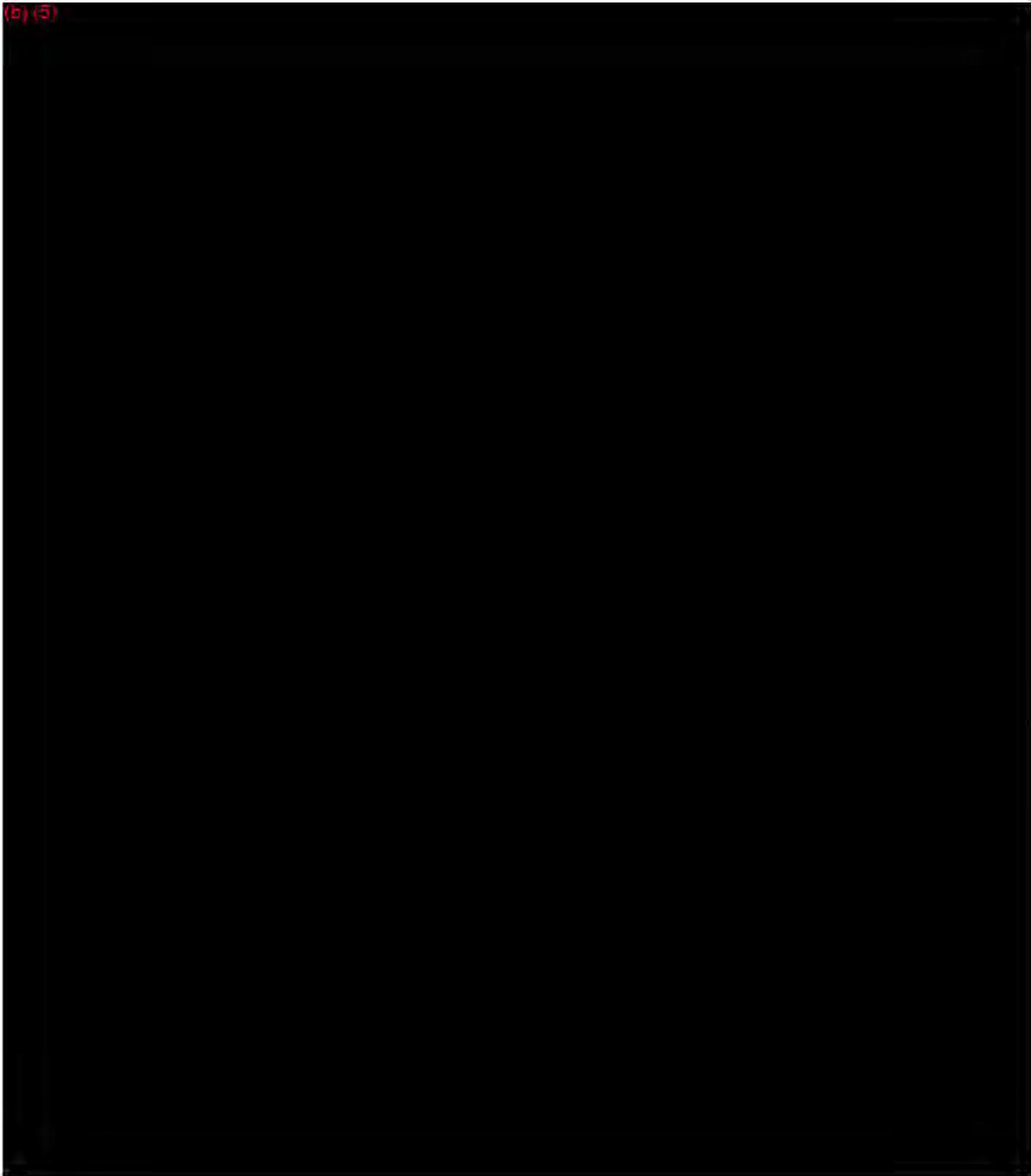
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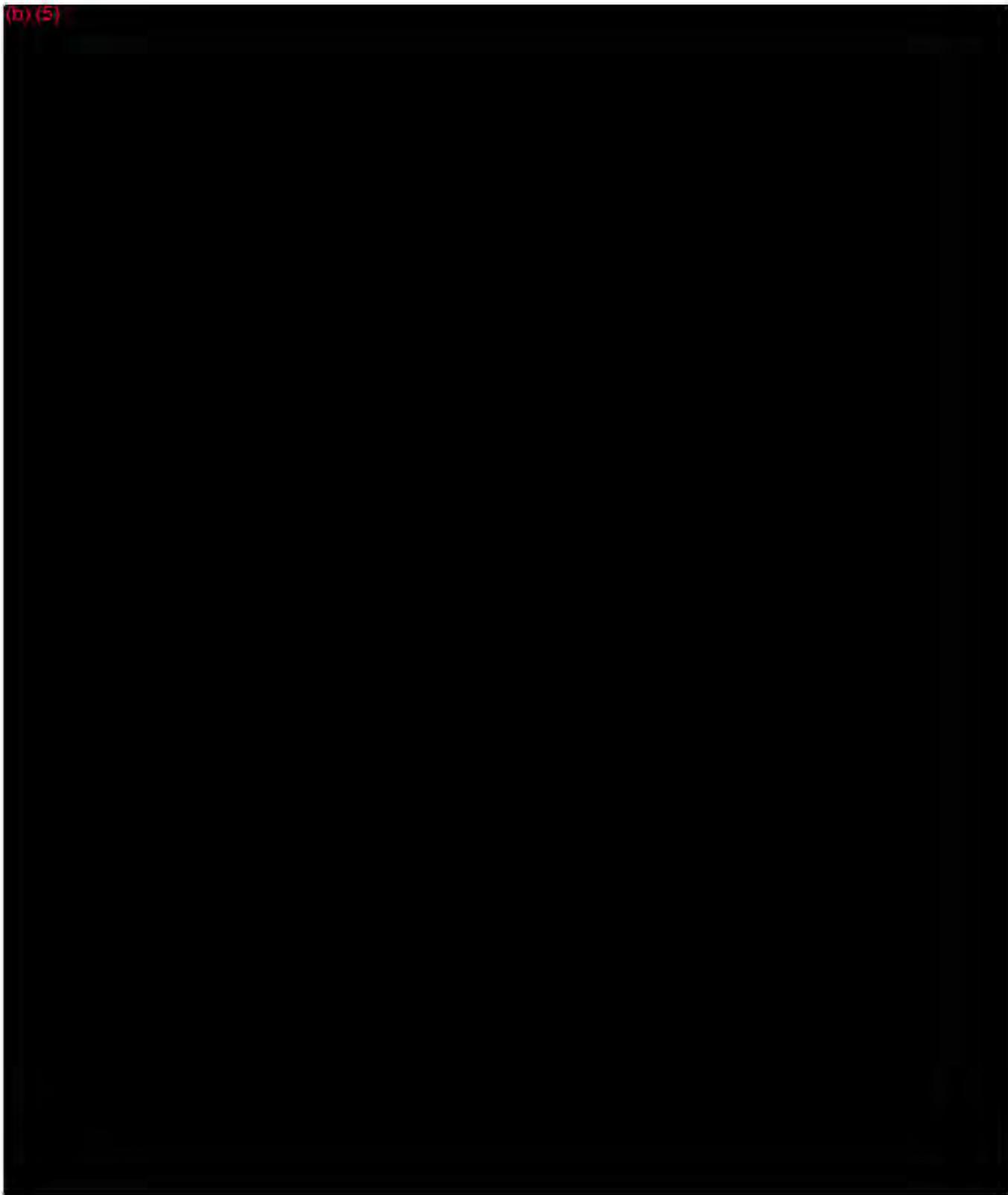
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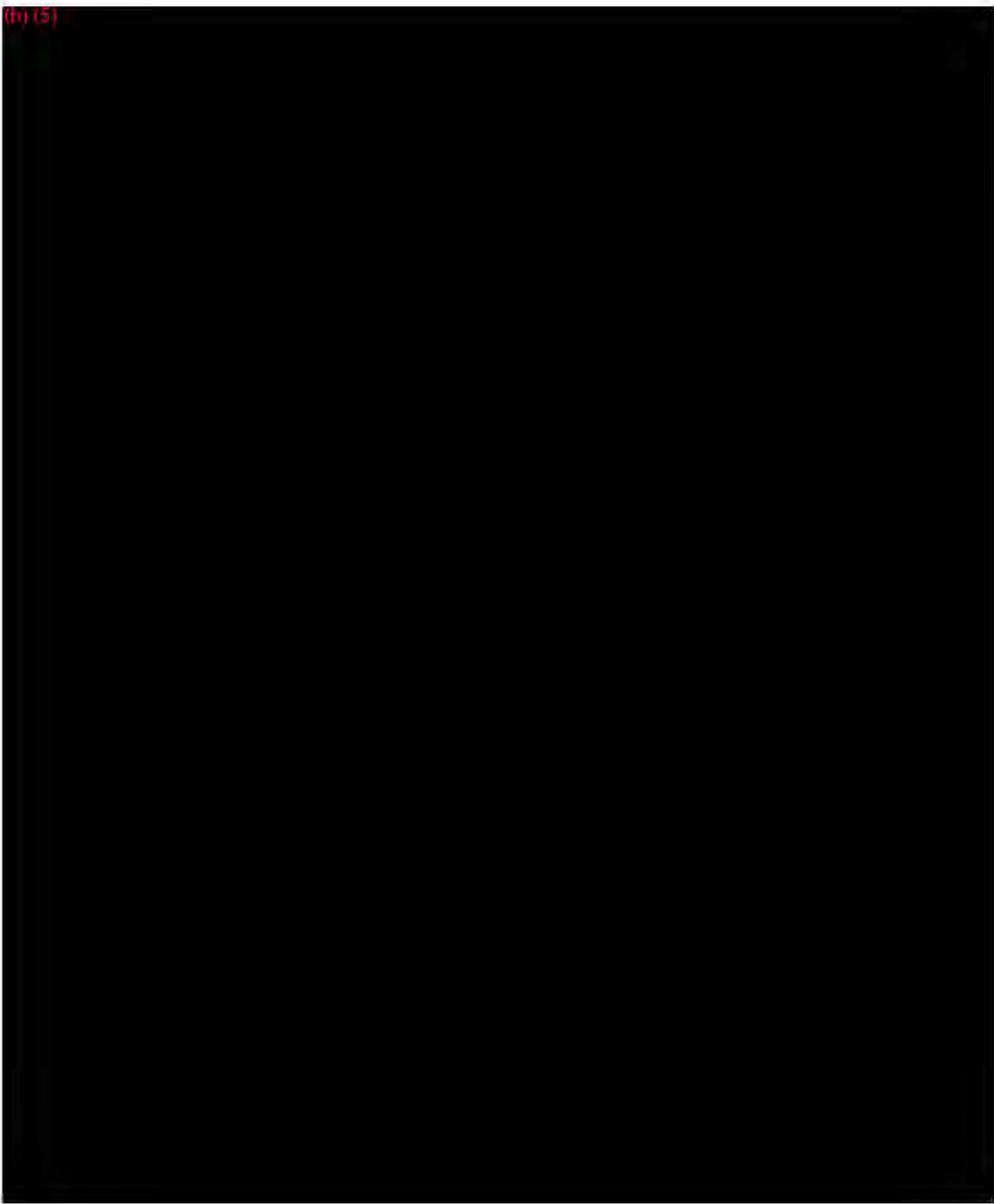
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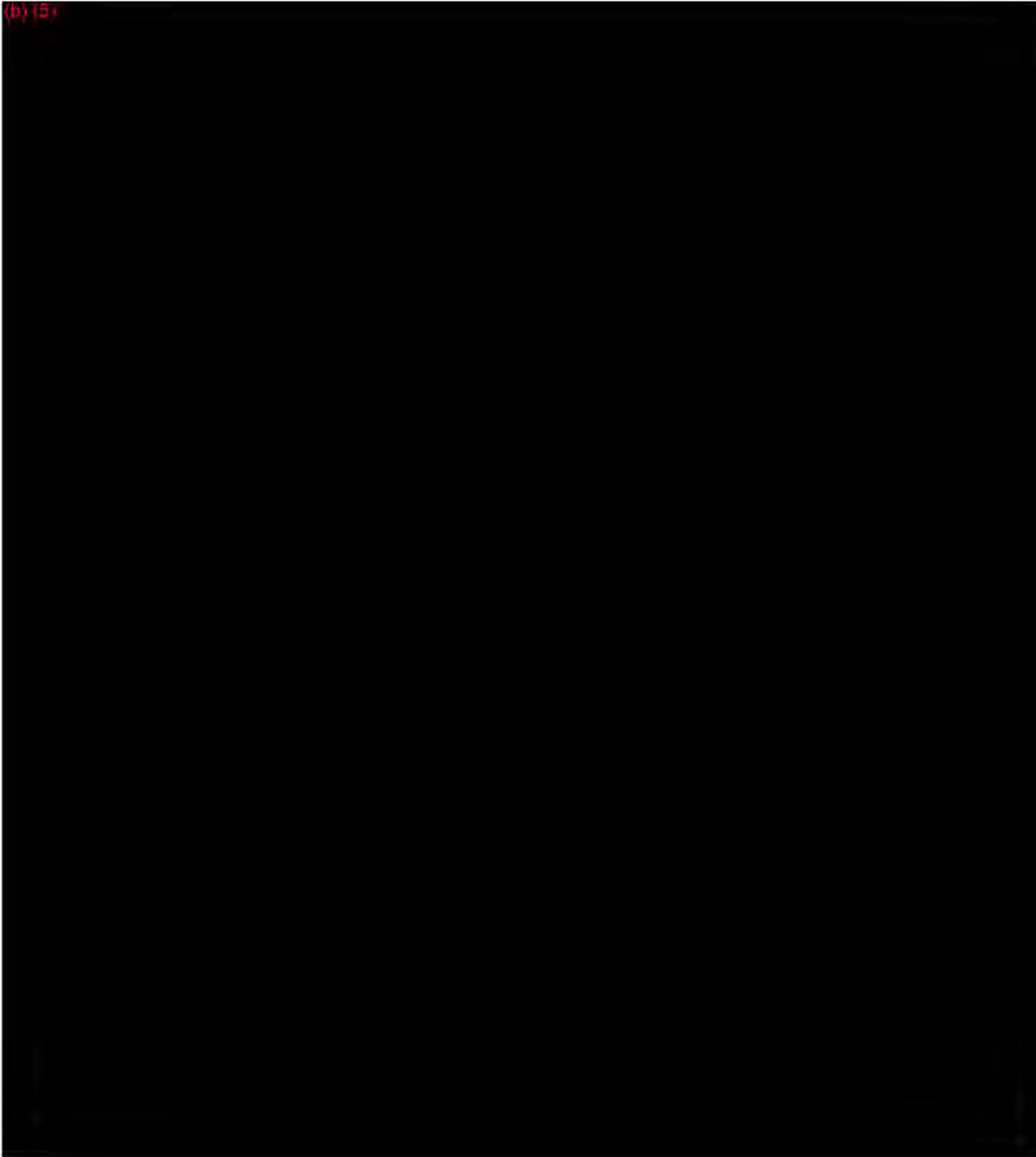
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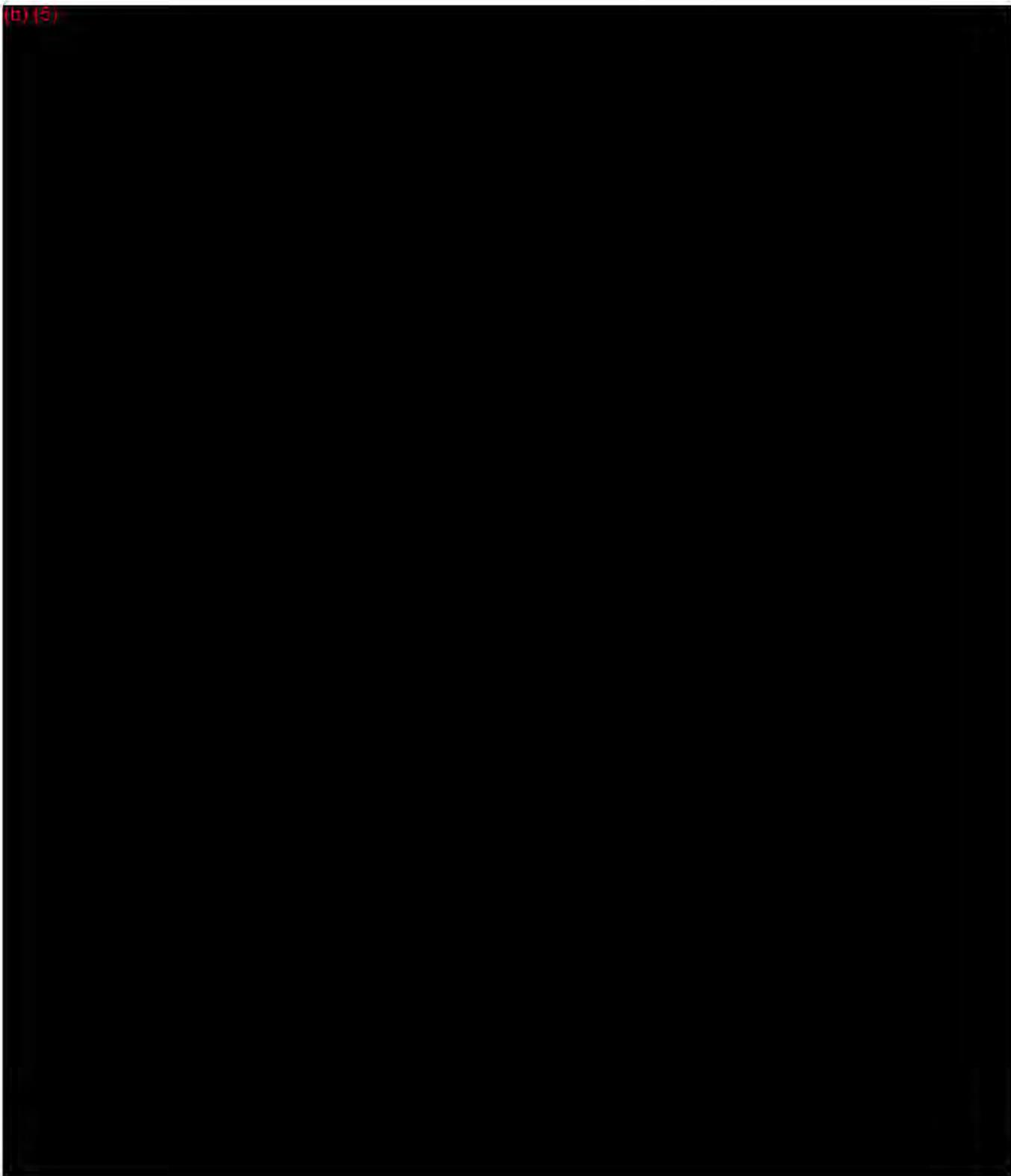
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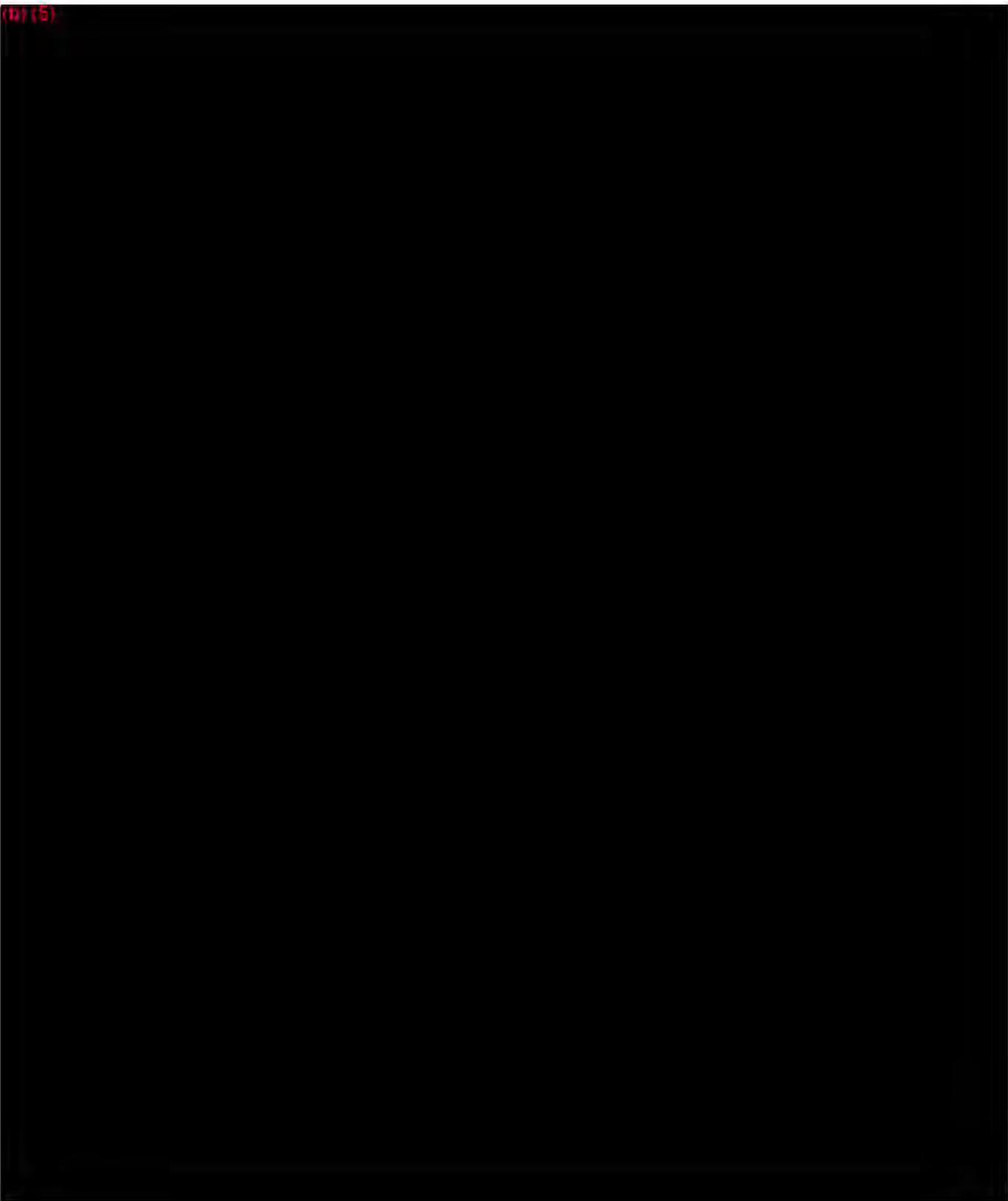
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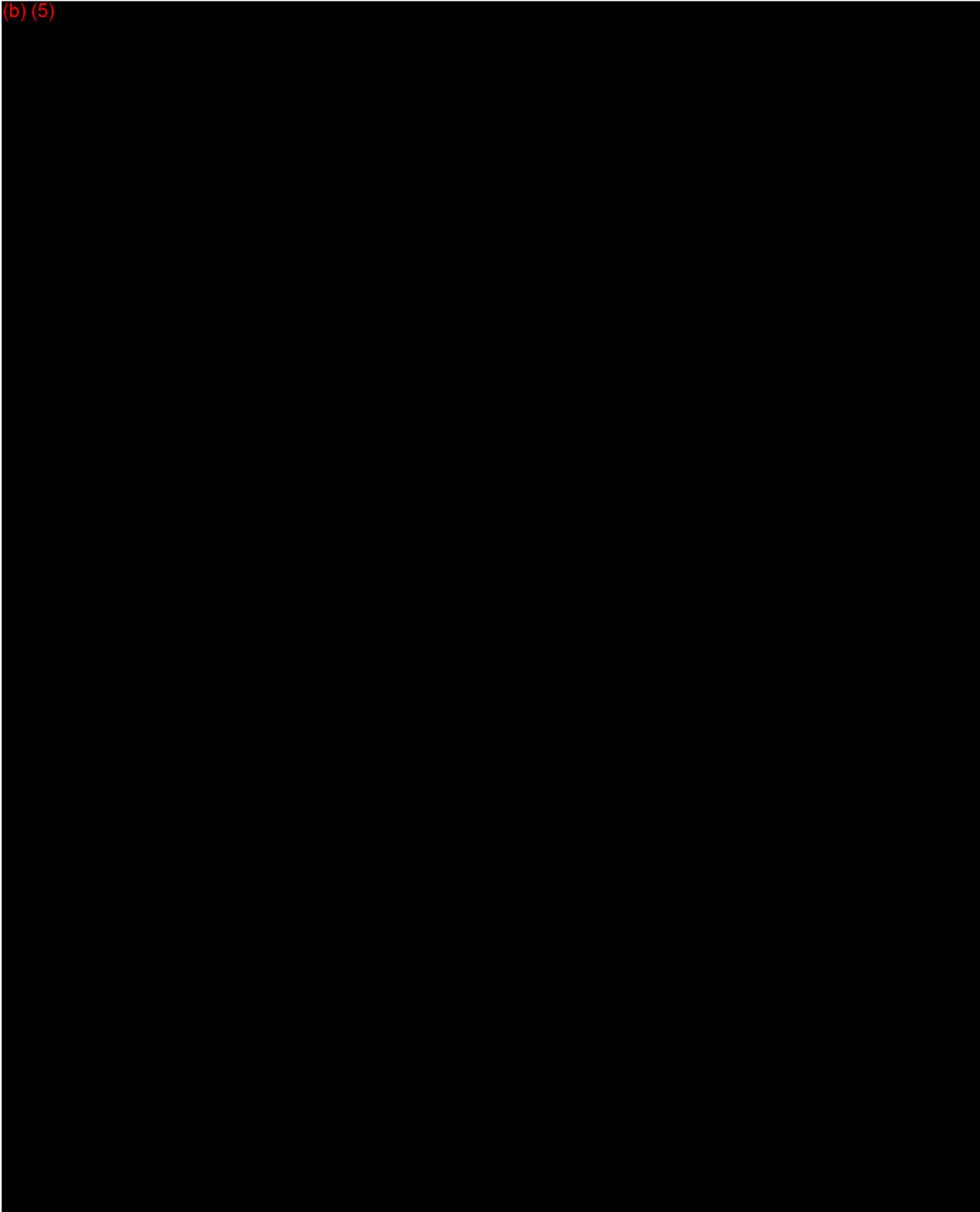
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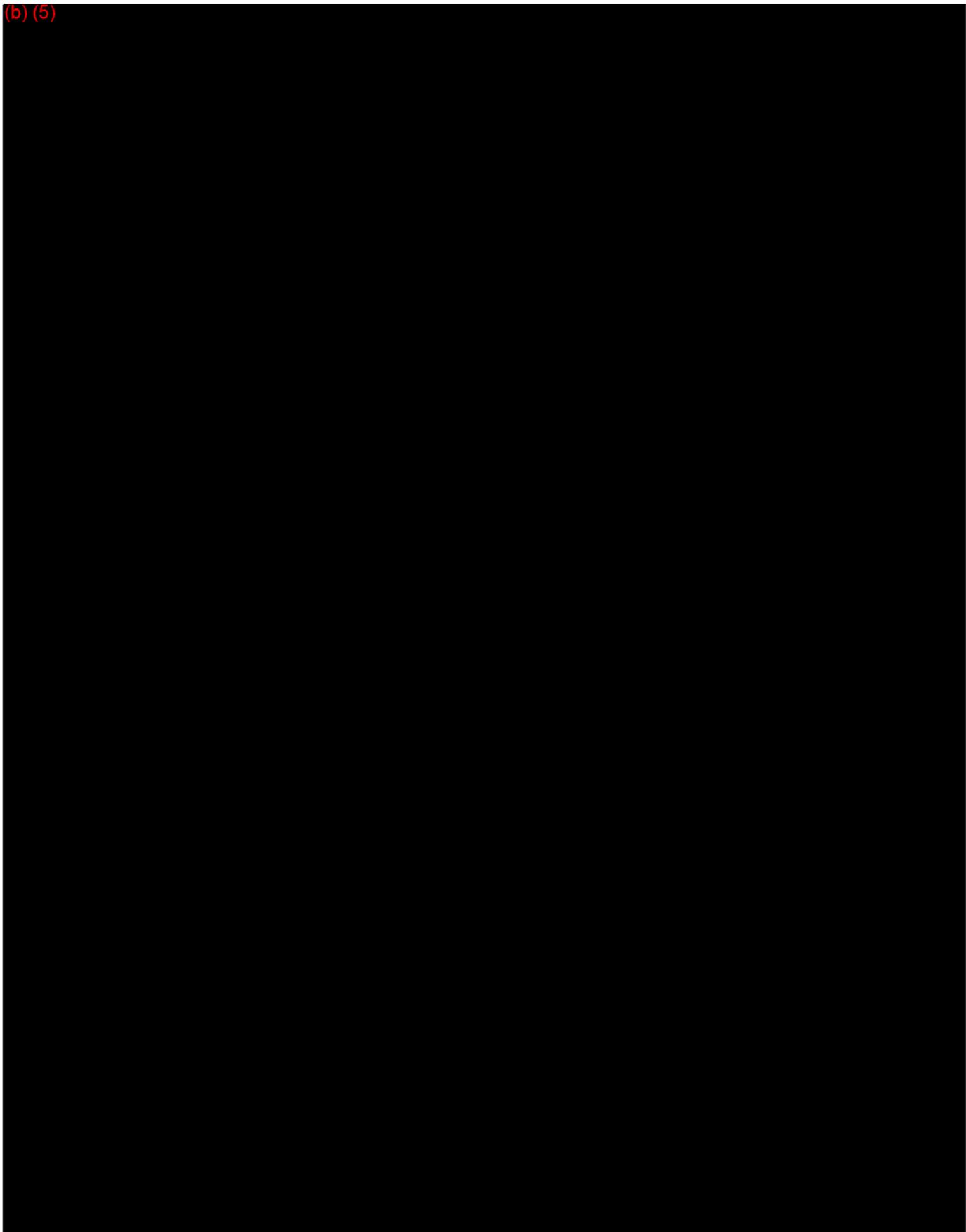
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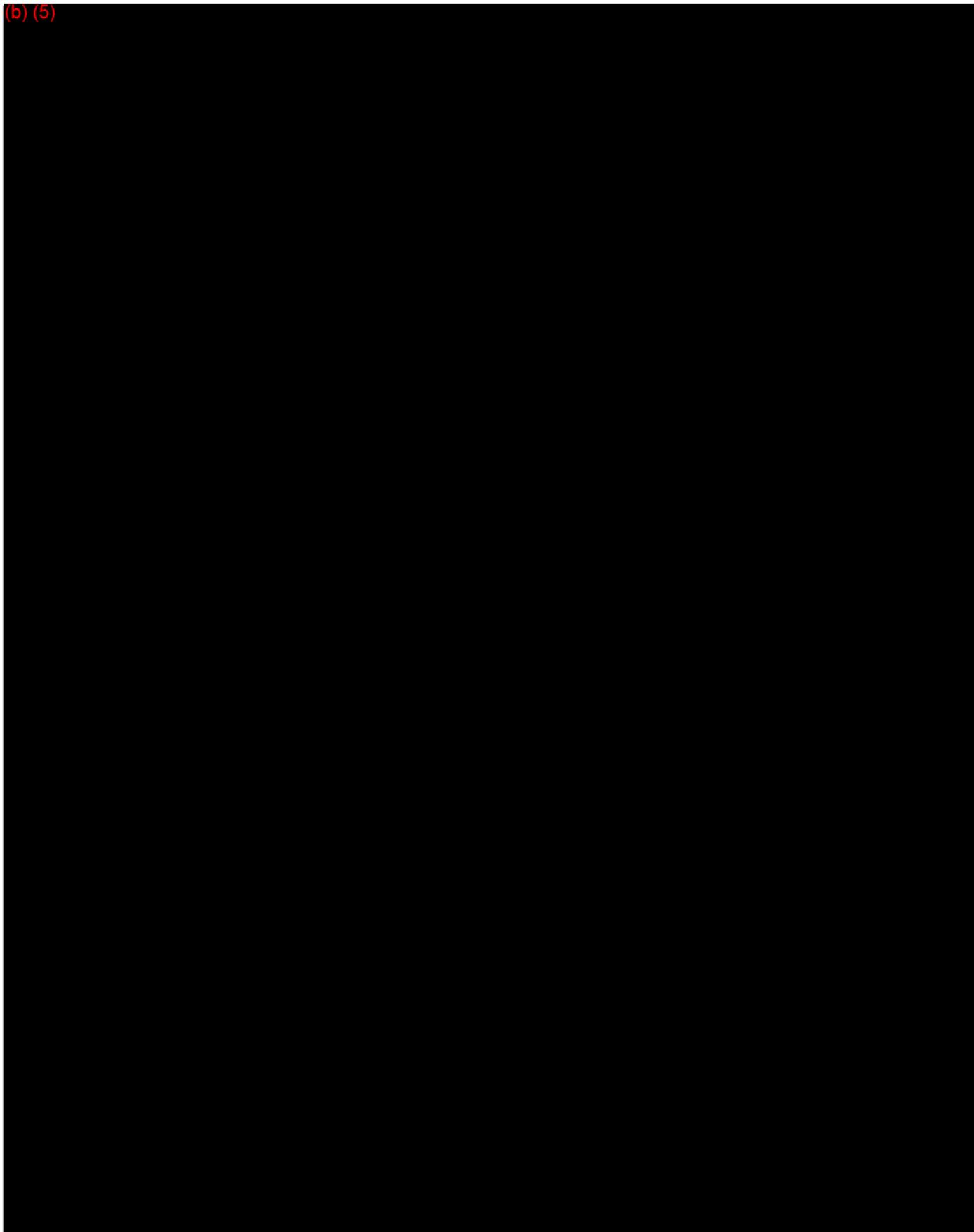
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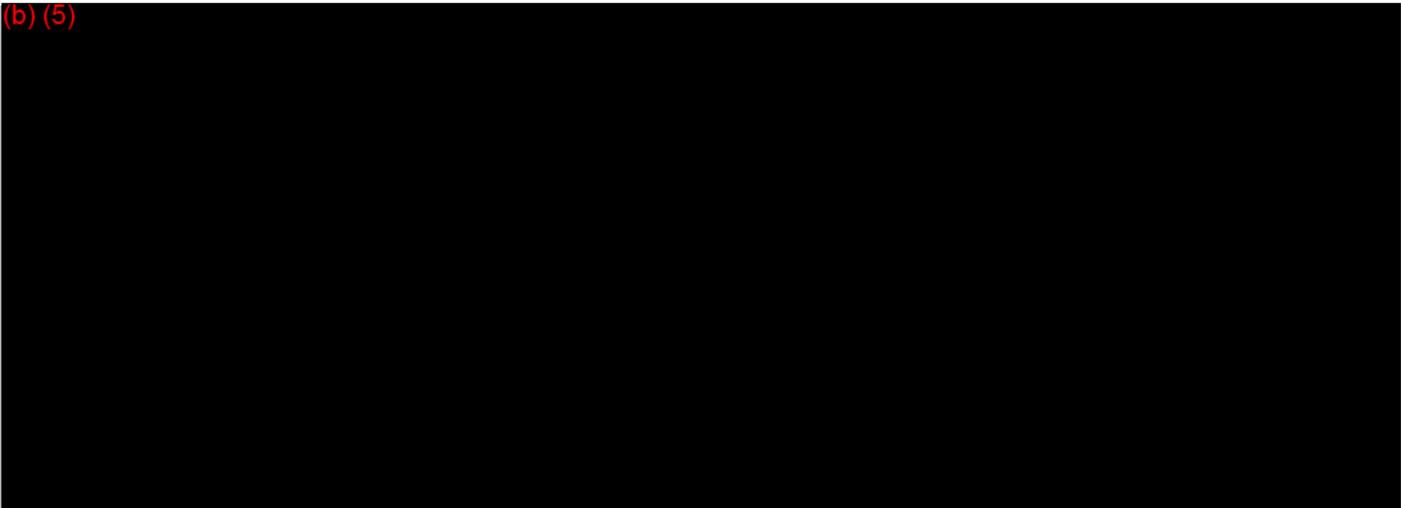
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From: [Califf, Robert](#)
To: [Sherman, Rachel](#)
Date: Sunday, October 16, 2016 2:19:00 PM
Attachments: [20161016_NORD_penultimate_clean.doc](#)

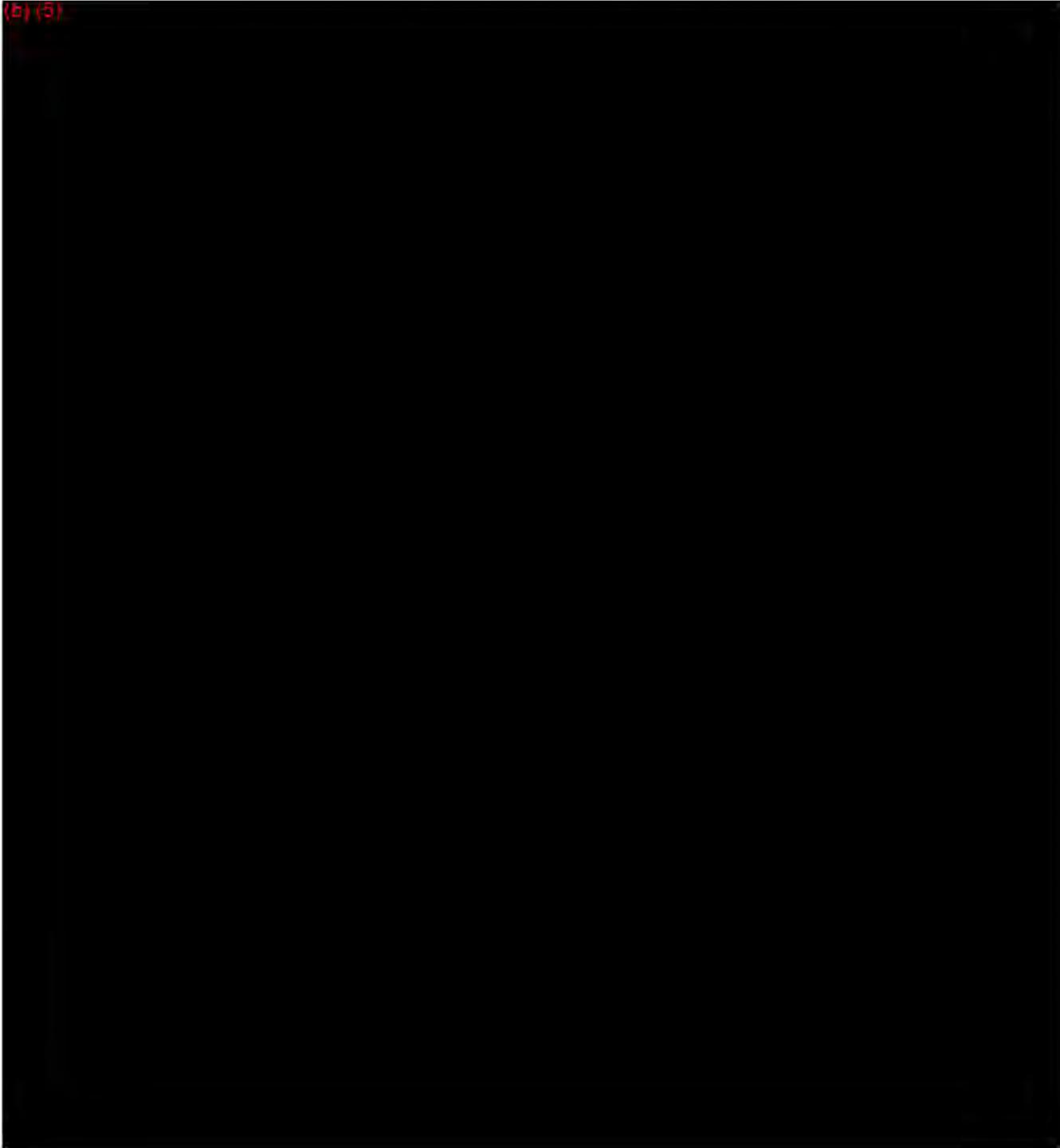
See what you think.

rmc

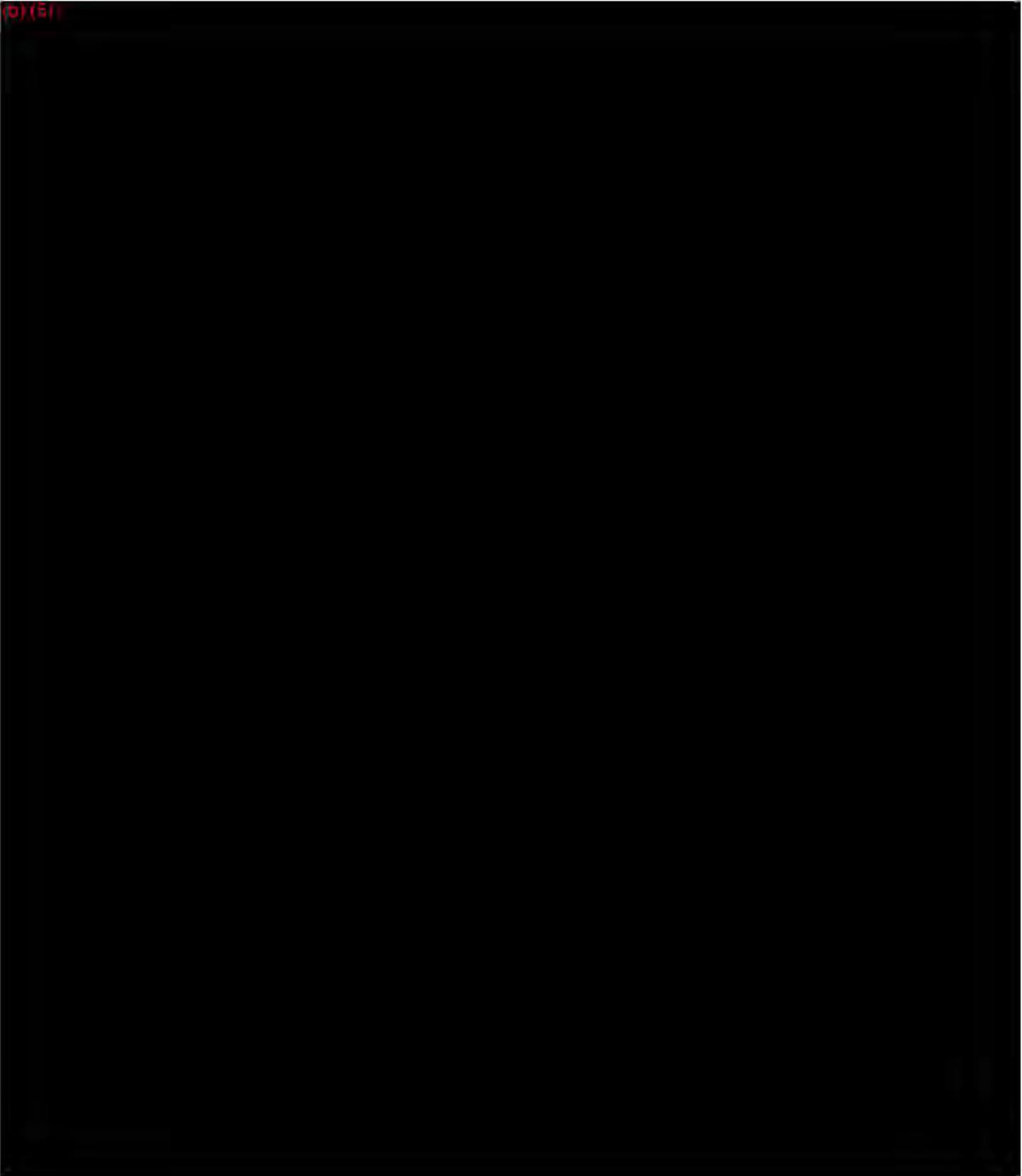
Speech by Robert M. Califf, M.D.
Commissioner of Food and Drugs
2016 National Organization for Rare Disorders (NORD) Summit
October 17, 2016
Washington, D.C.

“Critical Lessons about Rare Disease Drug Development”

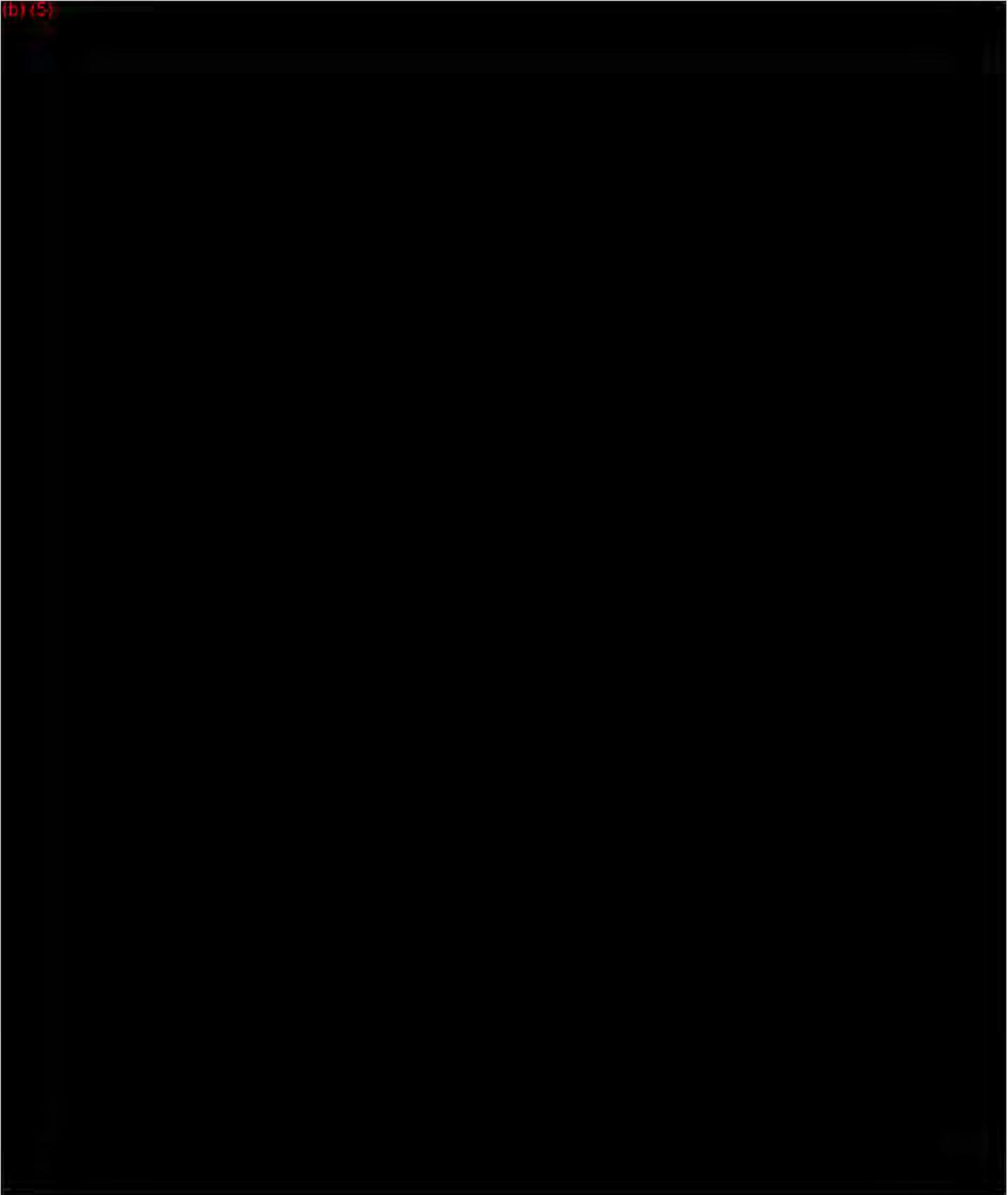
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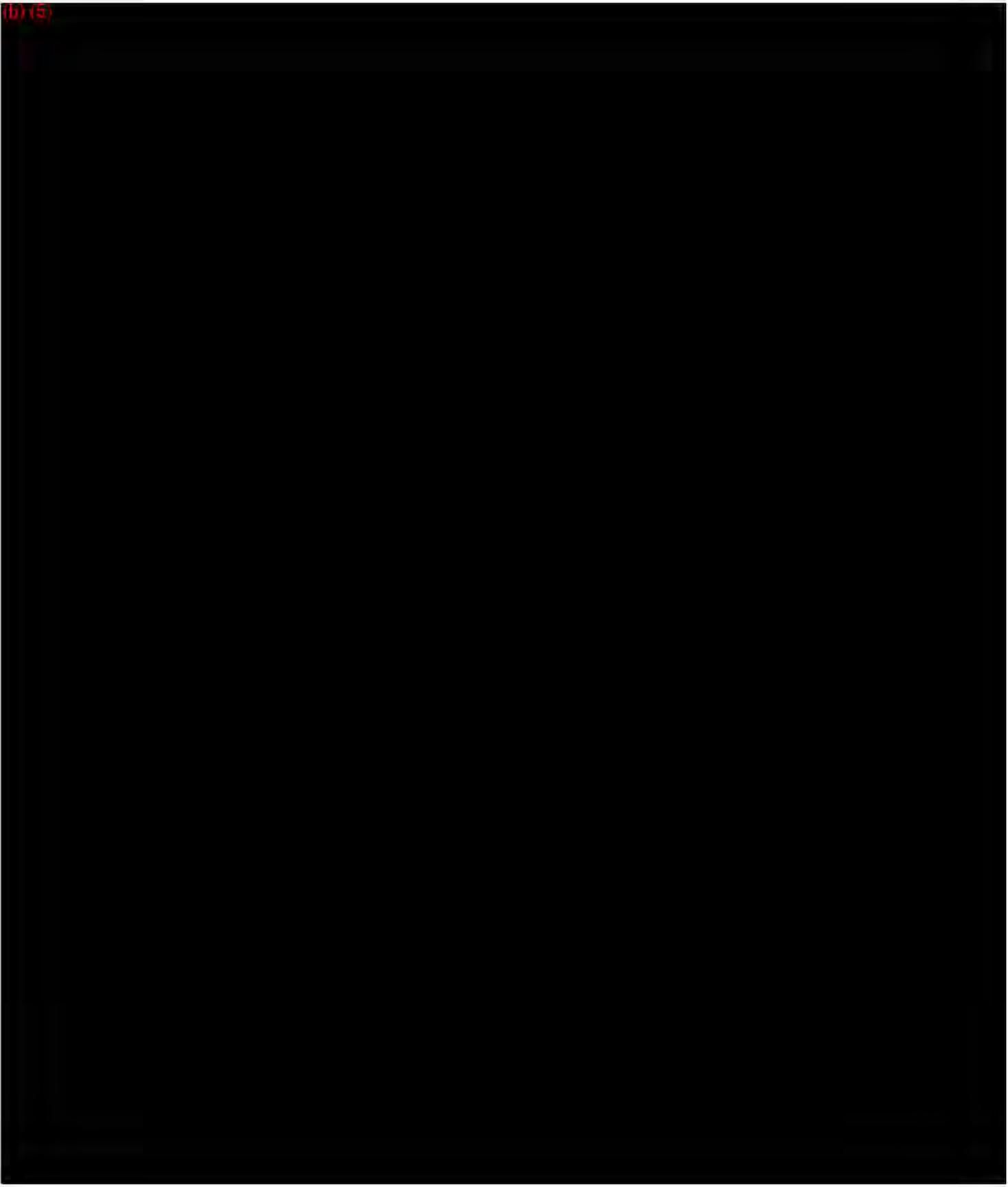
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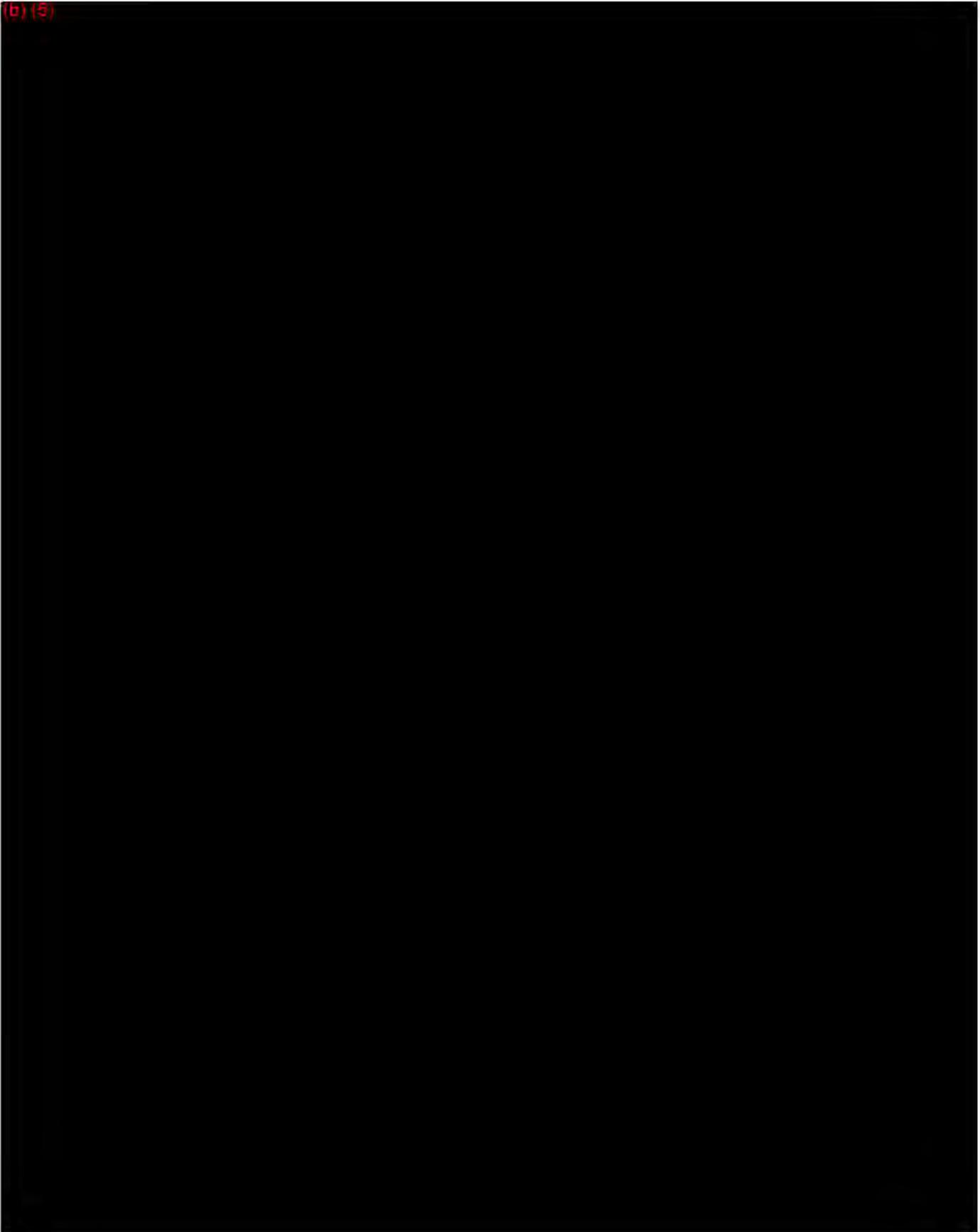
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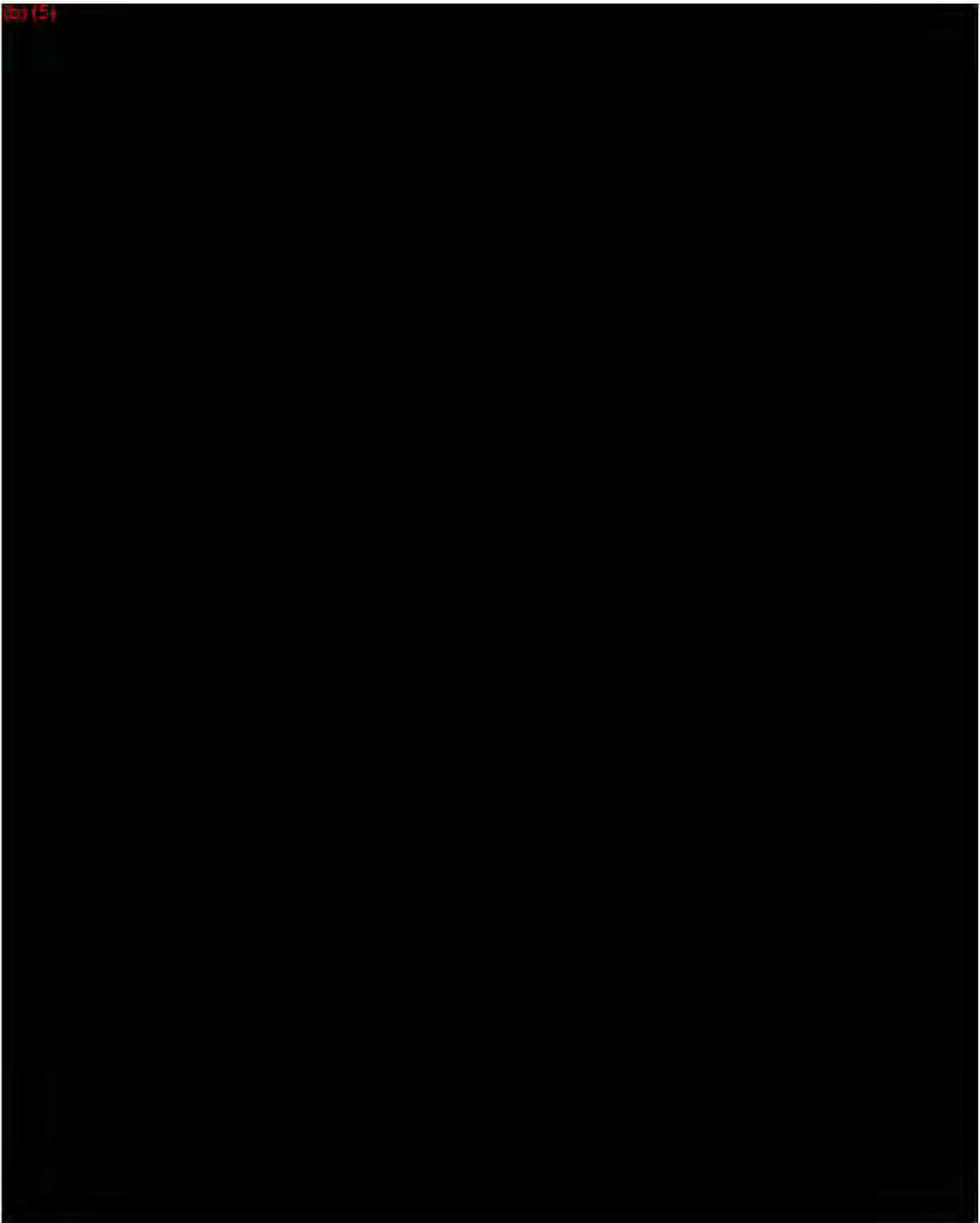
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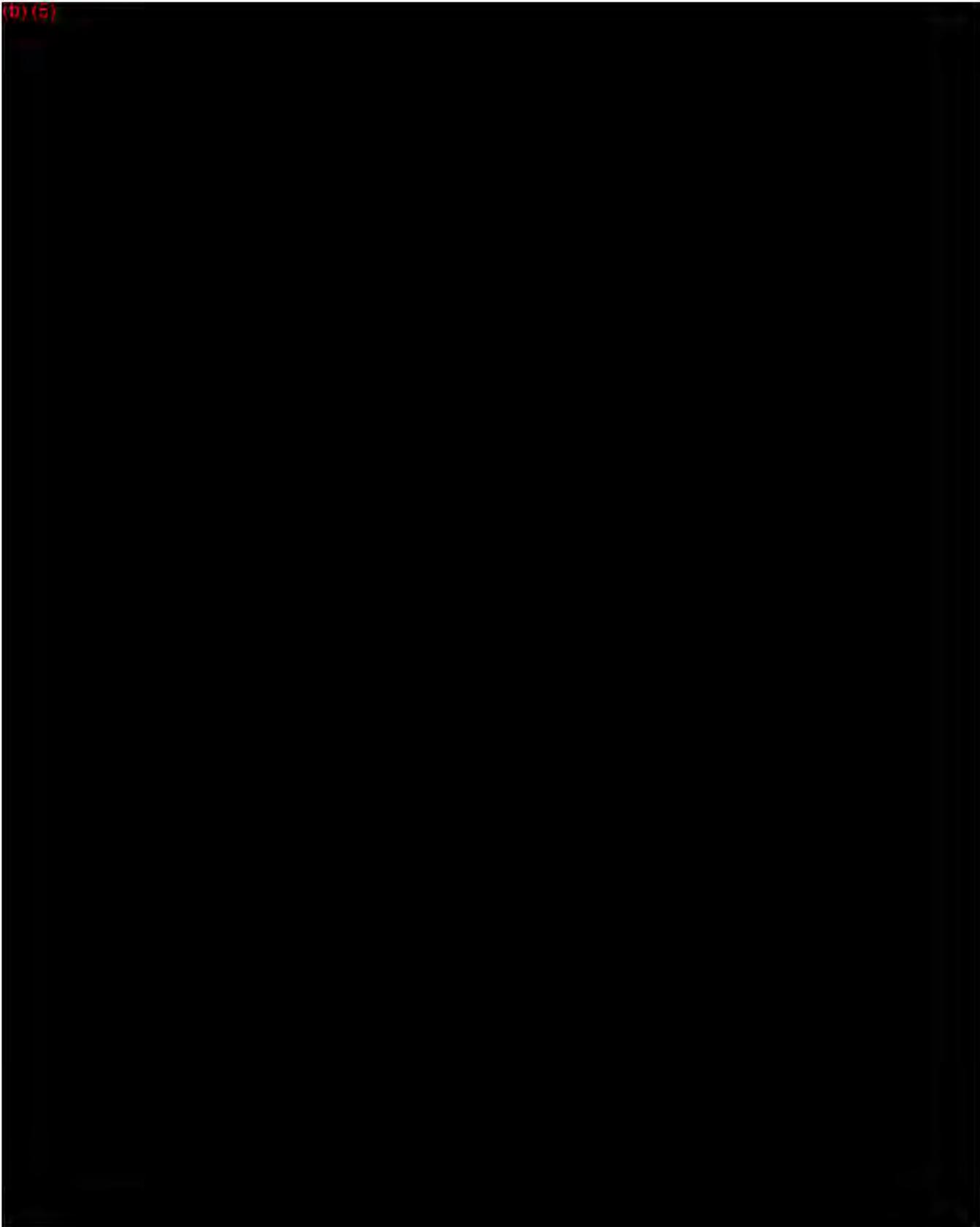
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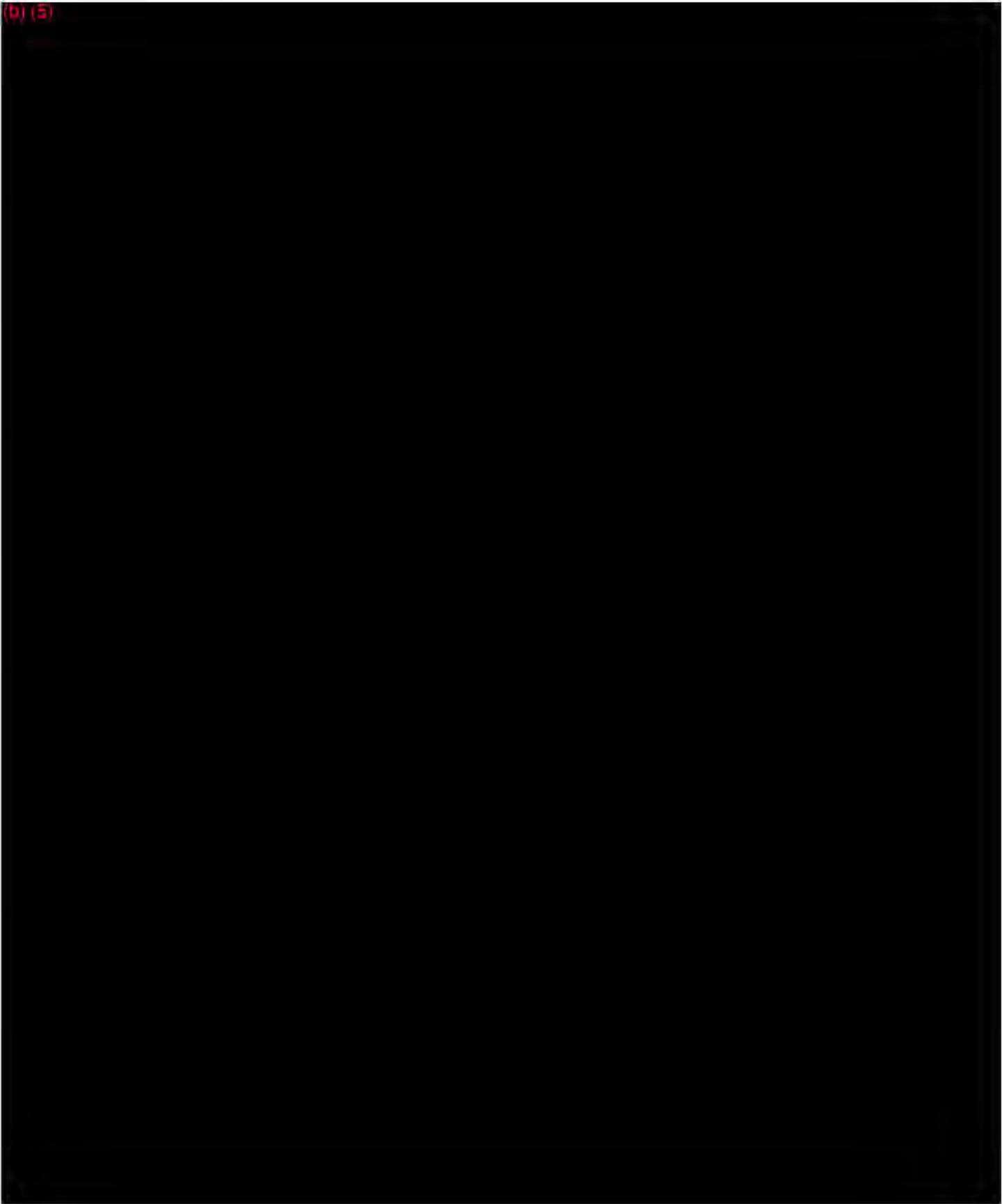
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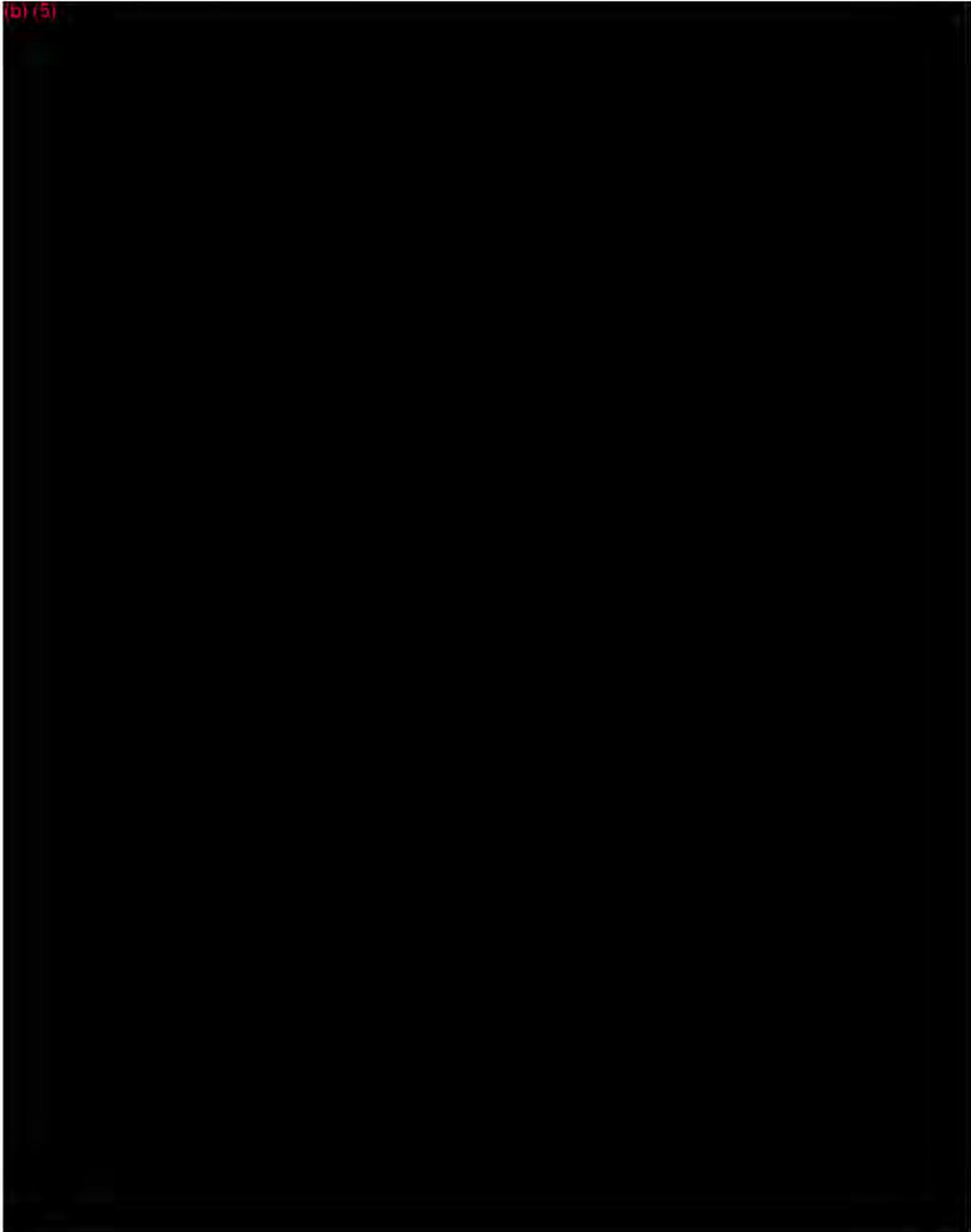
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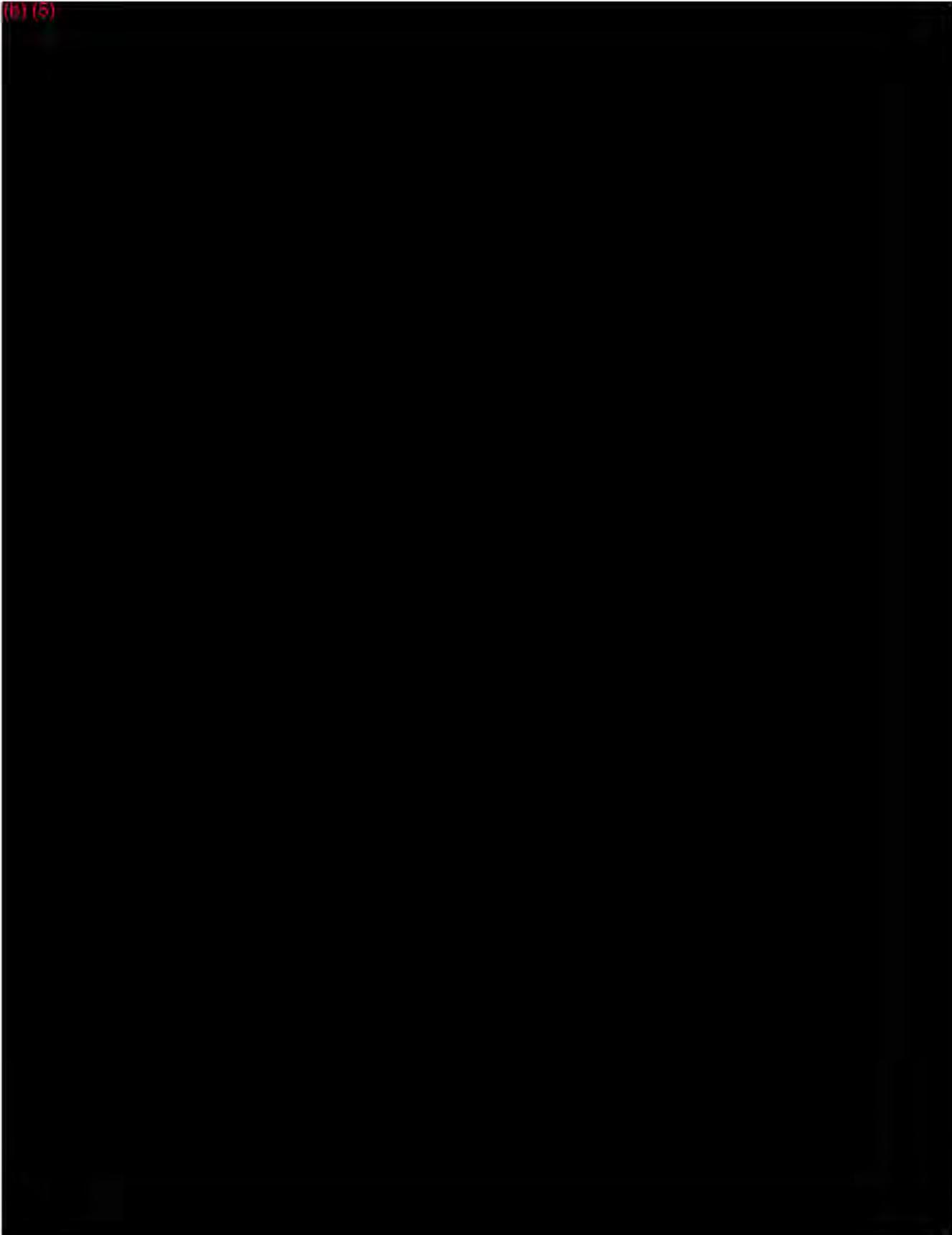
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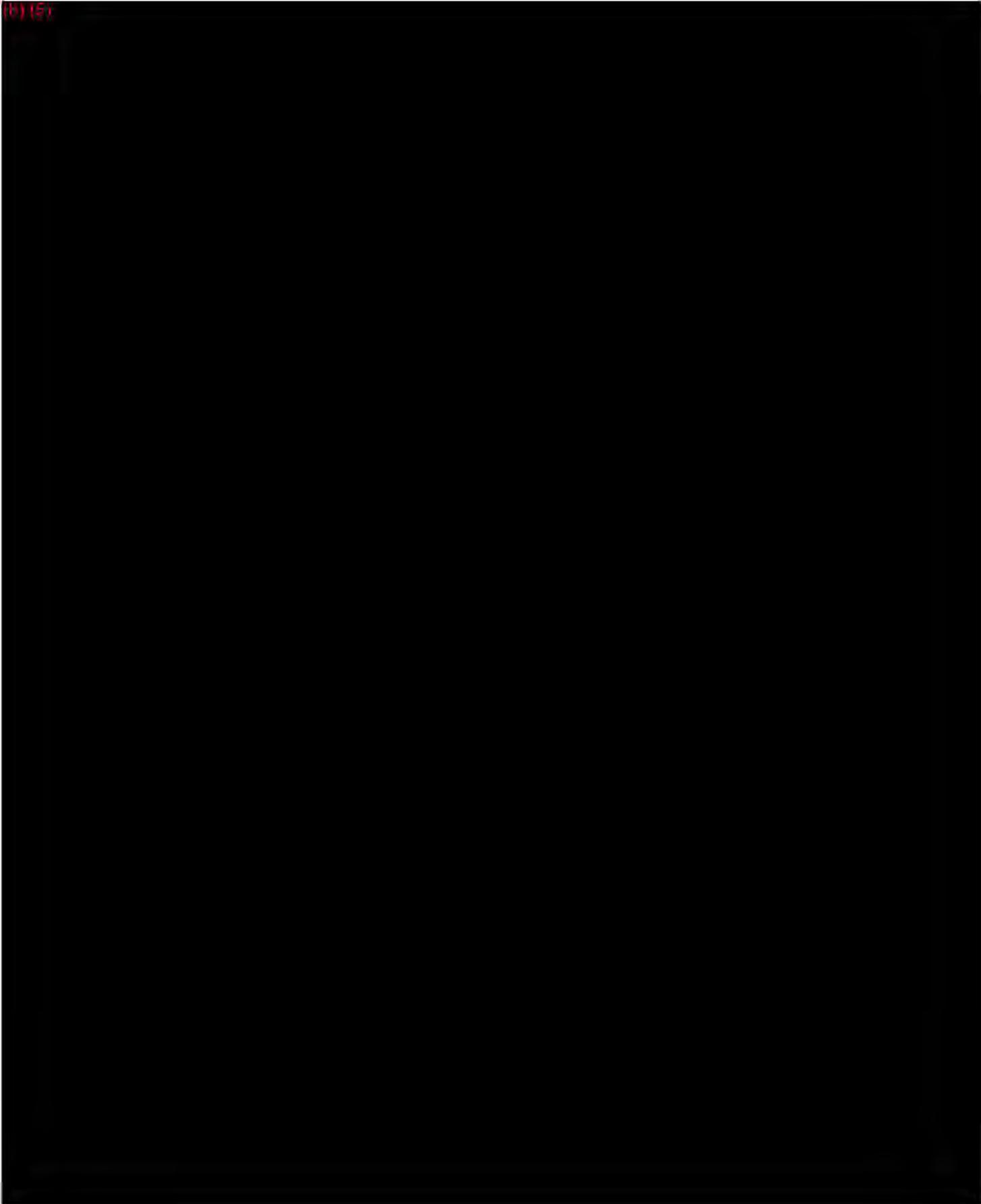
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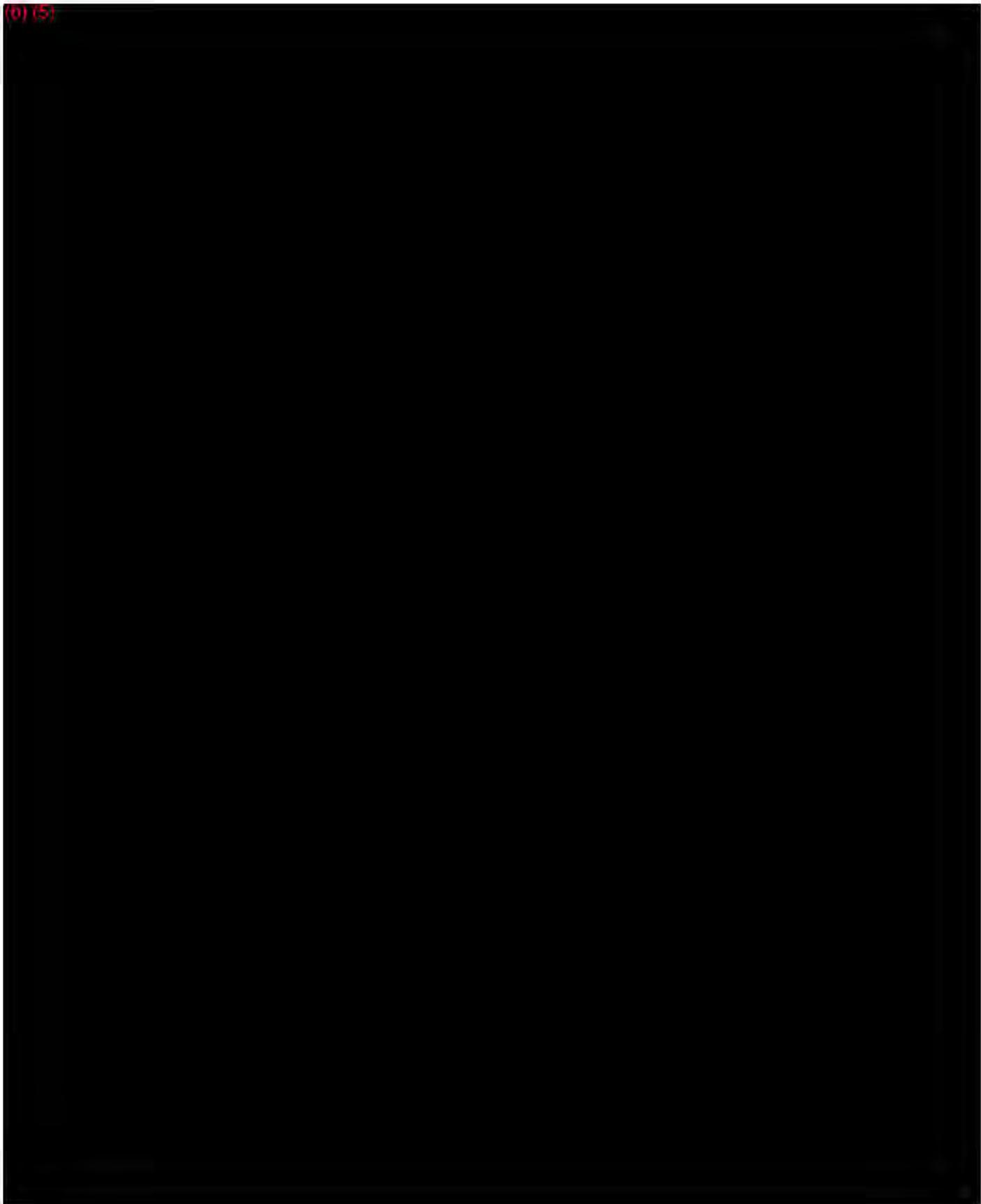
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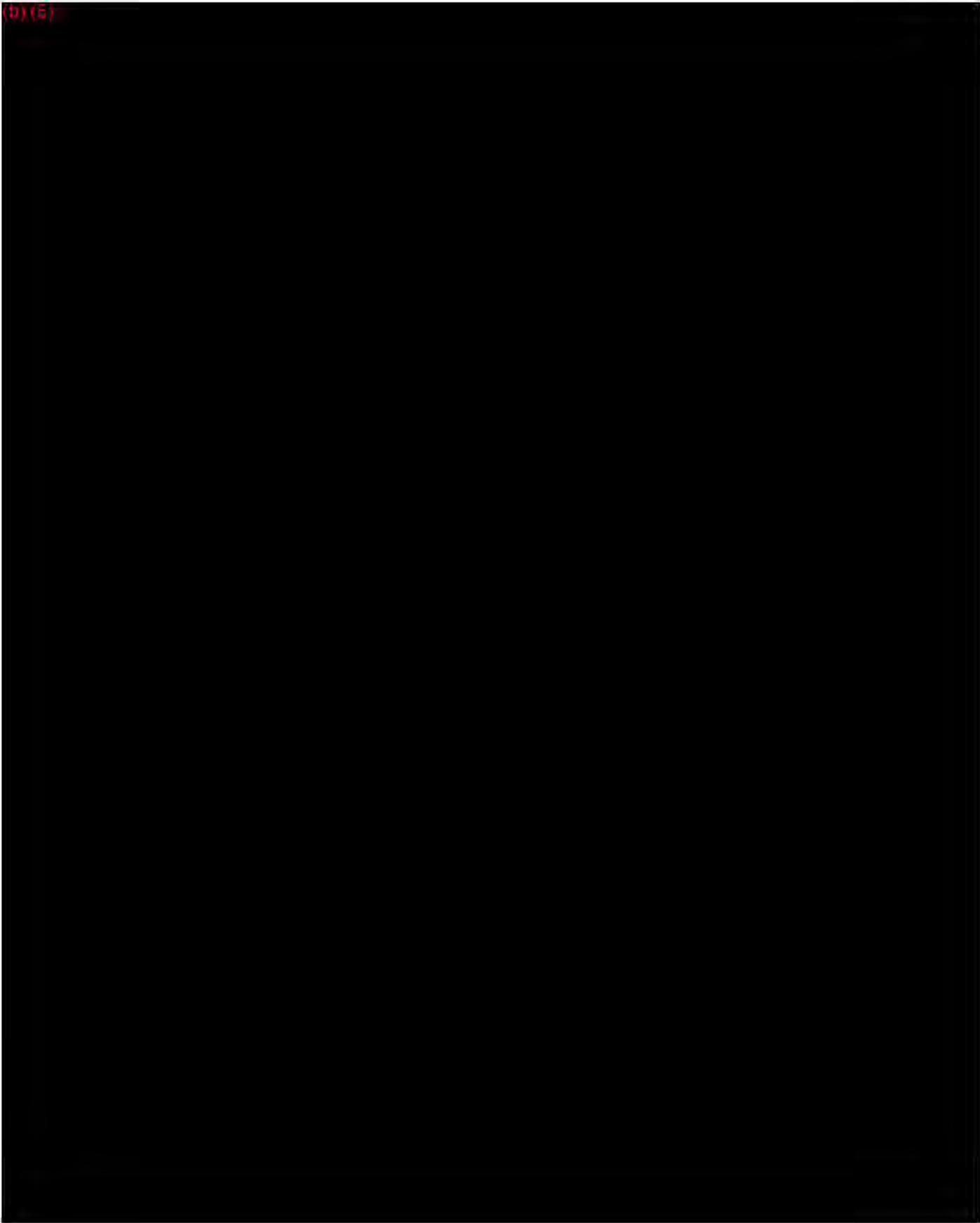
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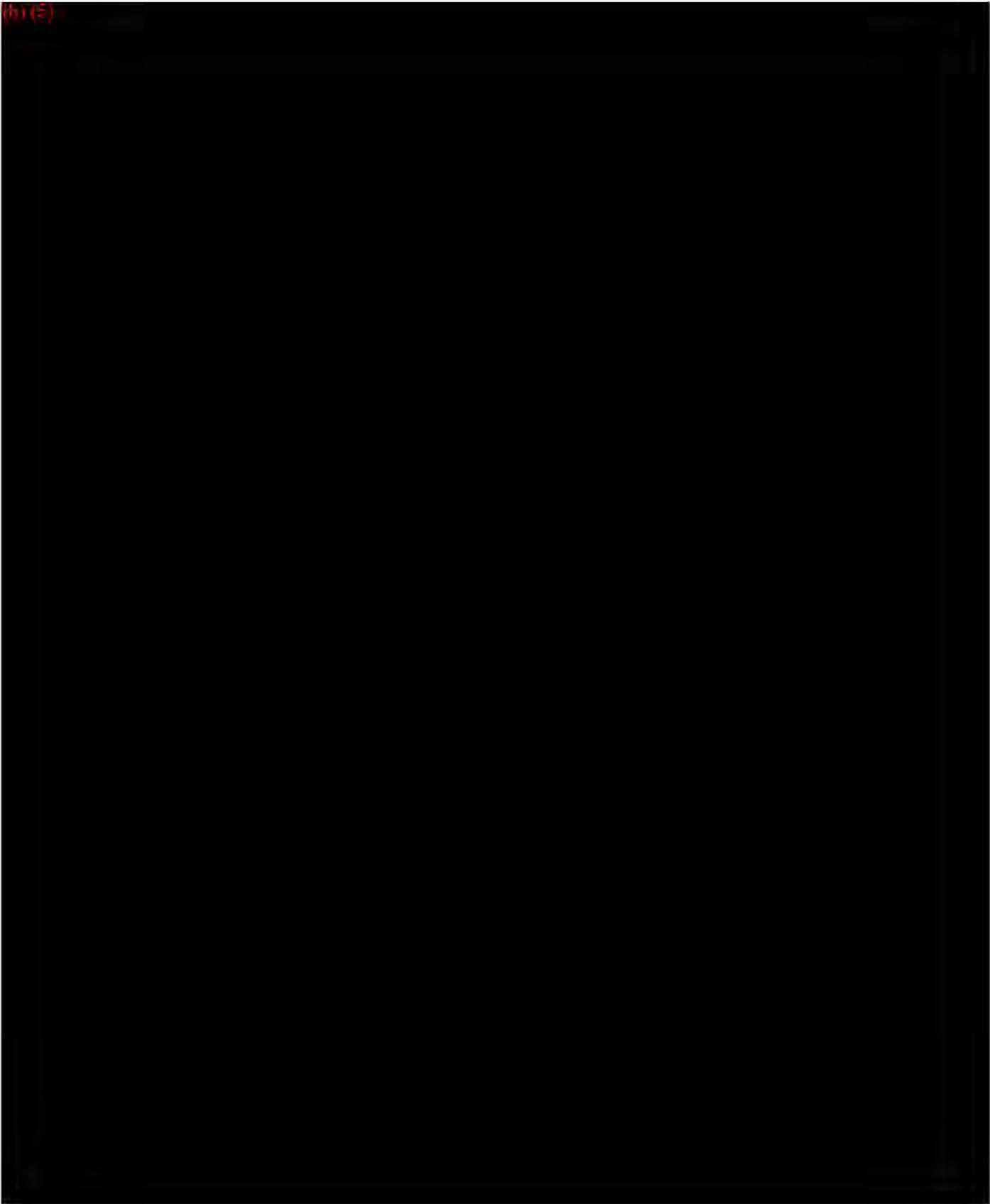
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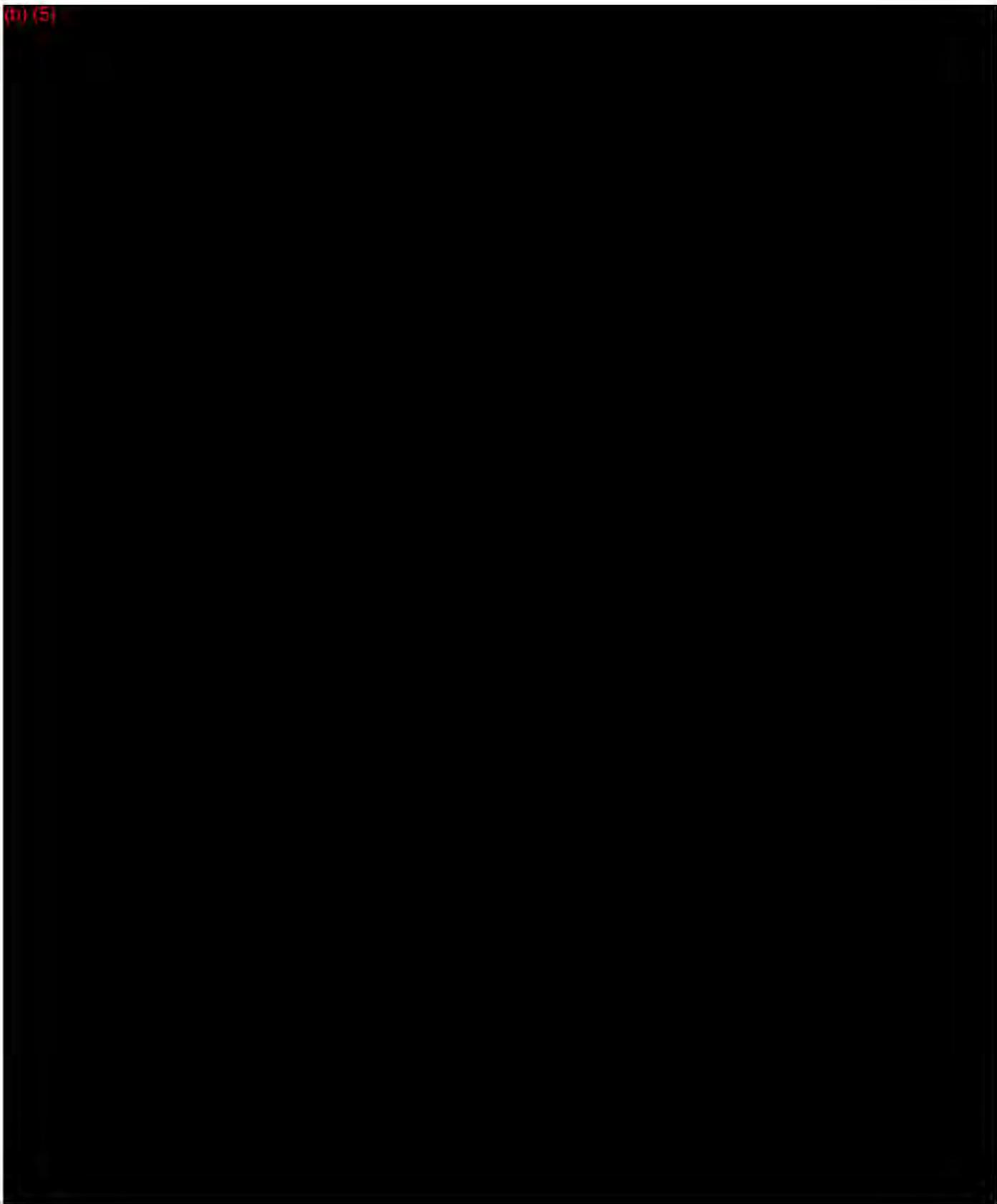
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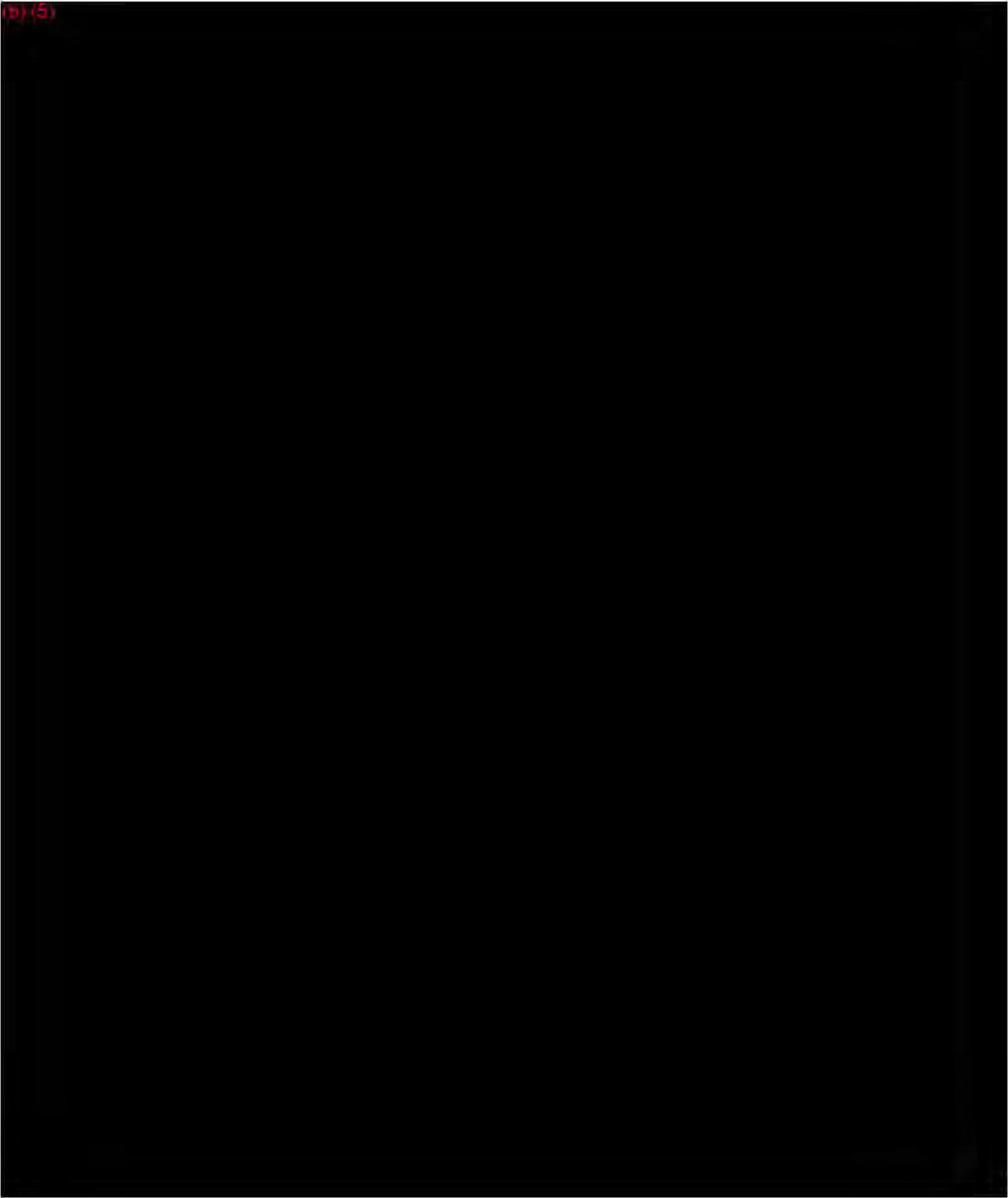
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From: [Rao, Gayatri](#)
To: [Califf, Robert](#); [Wohl, Alexander](#); [Riley, Karen](#)
Subject: RE: NORD
Date: Sunday, October 16, 2016 2:38:52 PM
Attachments: [20161016 NORD penultimate clean GRedits.doc](#)

Dr. Califf,

Thank for the opportunity to review the speech and for the kind words in the speech itself. I think you cover all the main areas that are salient to this audience. Attached are just a few minor edits/suggestions.

I look forward to hearing this speech tomorrow!

Gayatri

From: Califf, Robert
Sent: Sunday, October 16, 2016 12:00 PM
To: Wohl, Alexander; Rao, Gayatri; Riley, Karen
Subject: NORD

Here is a marked up and clean version for review. I'm personally very comfortable with the content but interested in any corrections/edits you might suggest.

Hope you're enjoying the day. Gayatri, note that you're now mentioned.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

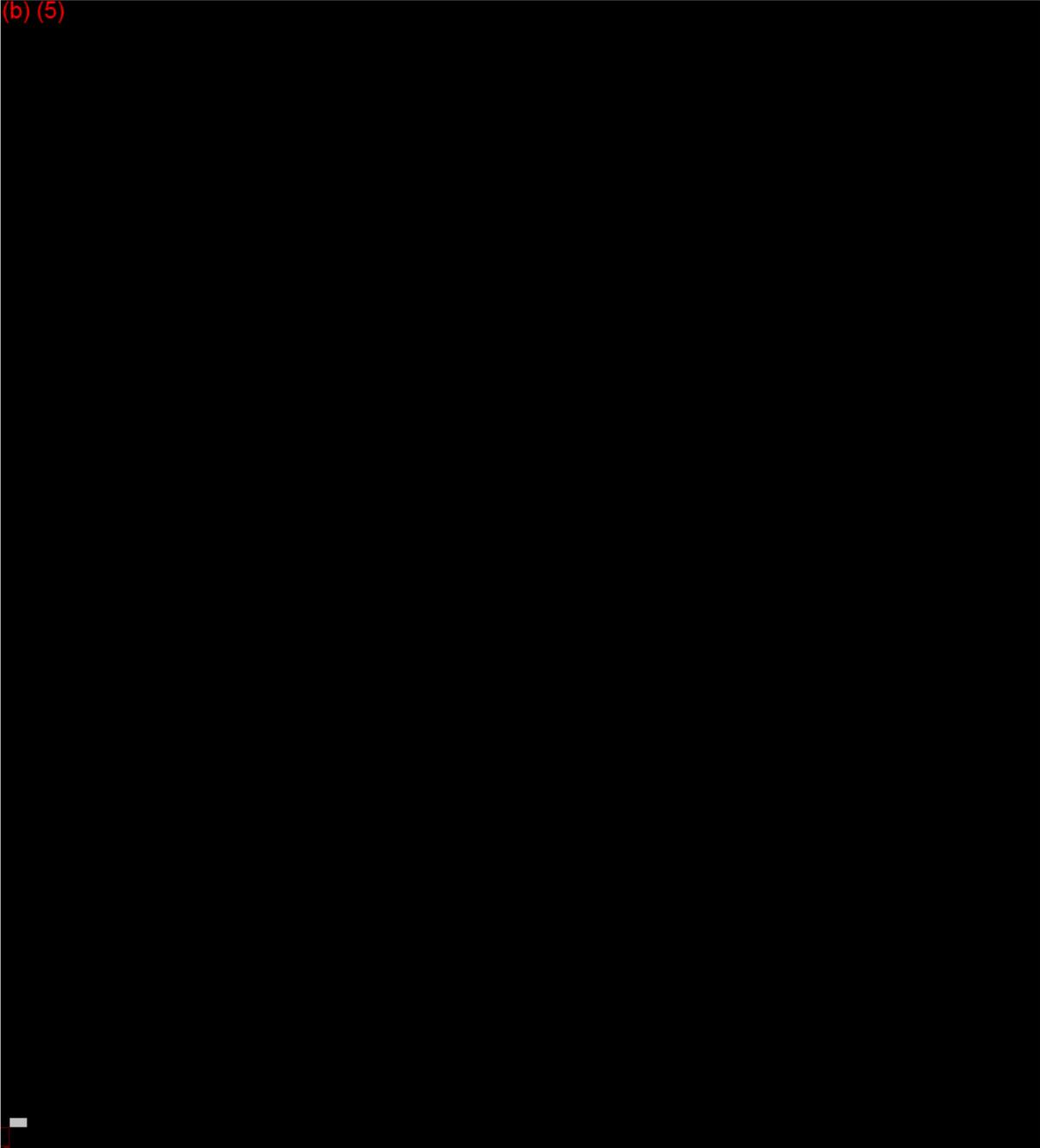
Speech by Robert M. Califf, M.D.
Commissioner of Food and Drugs
2016 National Organization for Rare Disorders (NORD) Summit
October 17, 2016
Washington, D.C.

“Critical Lessons about Rare Disease Drug Development”

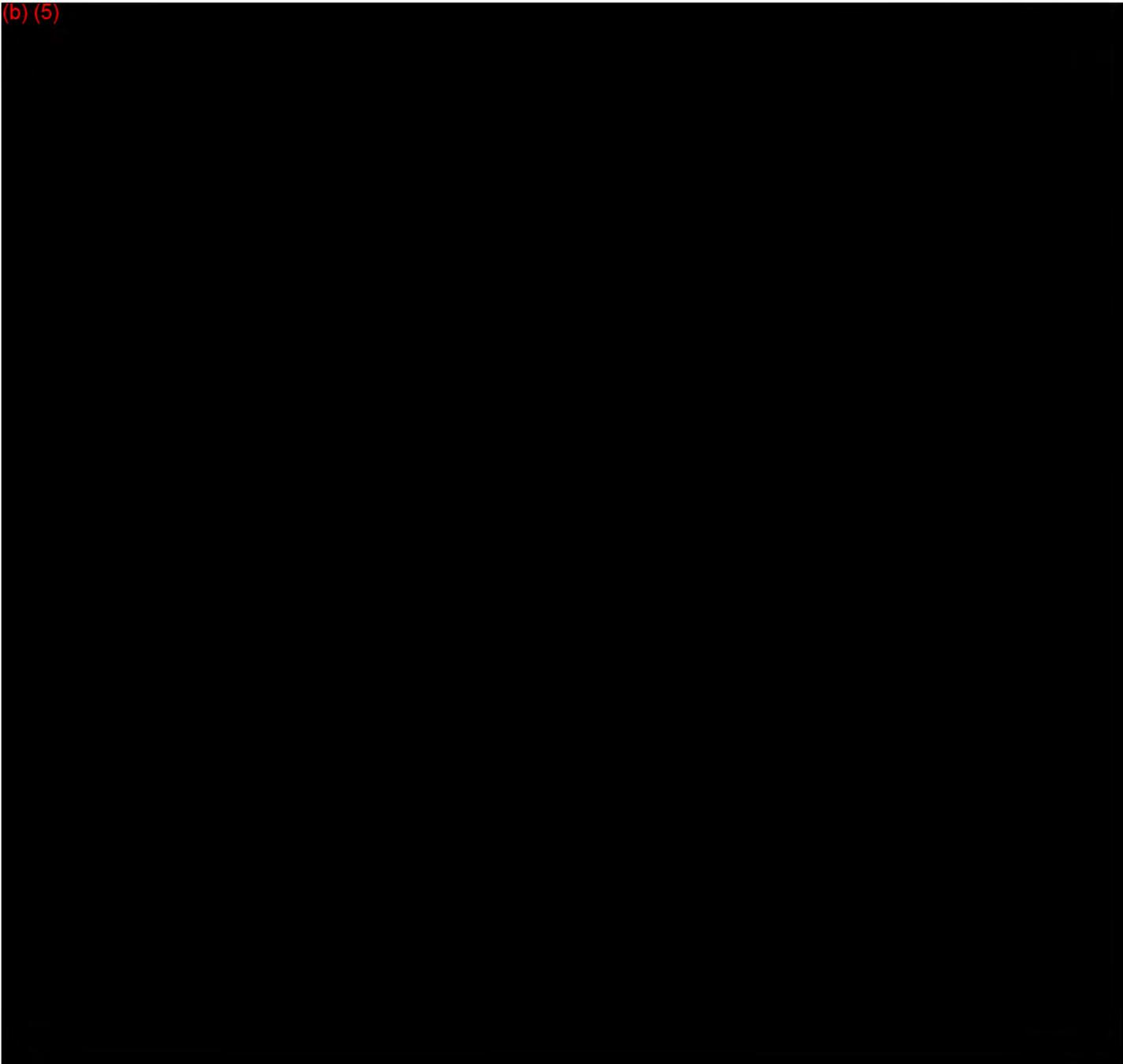
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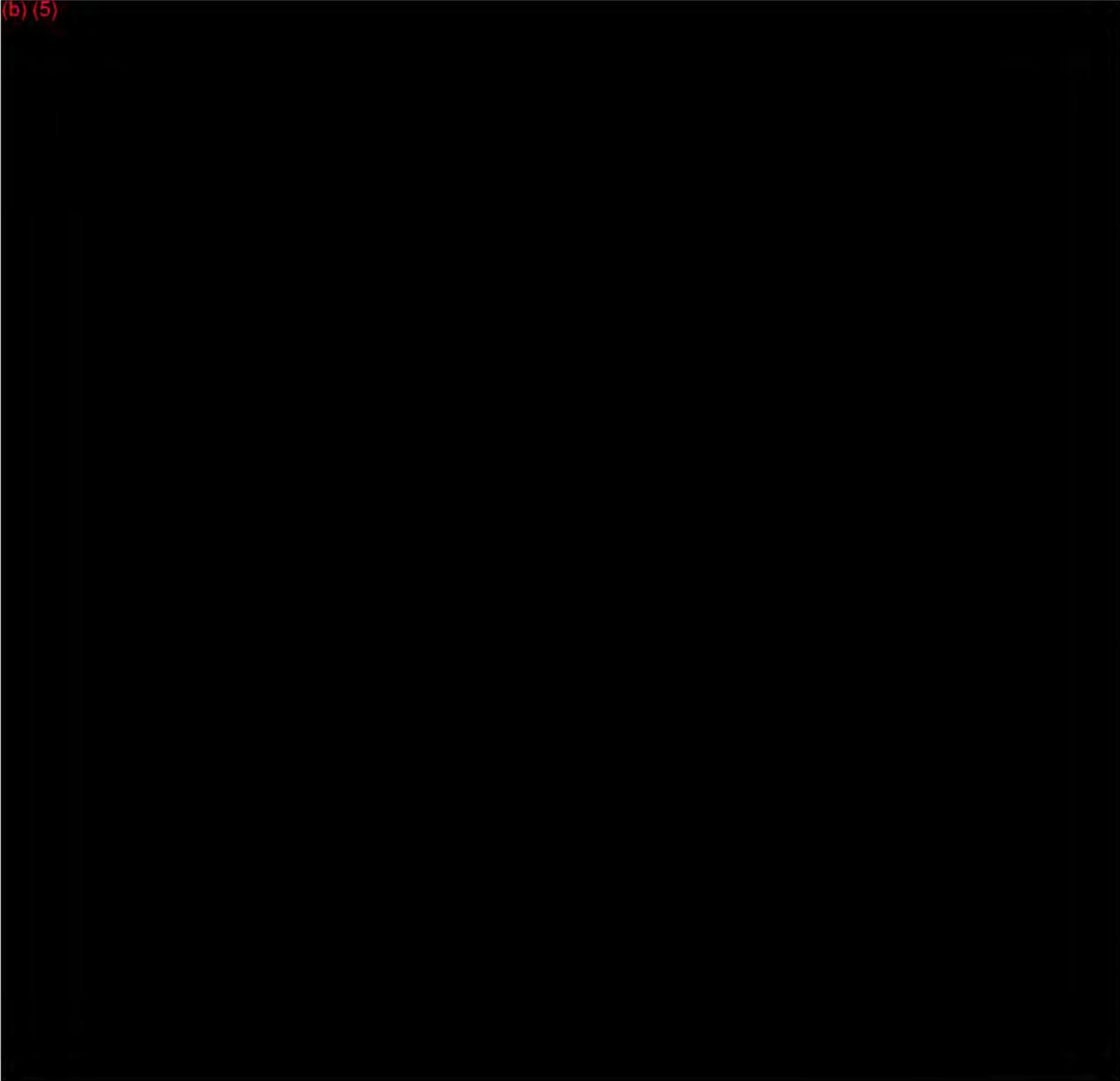
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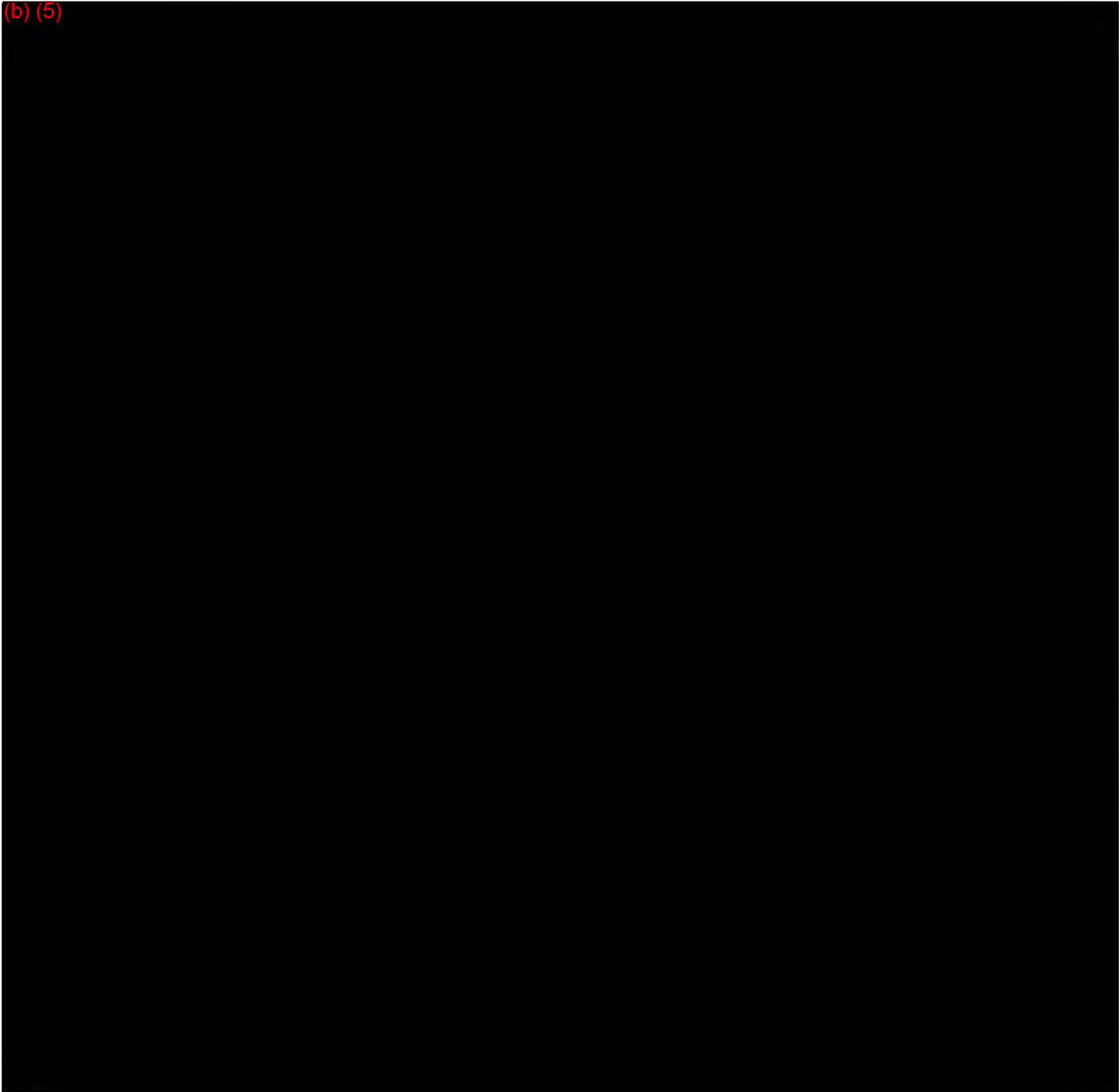
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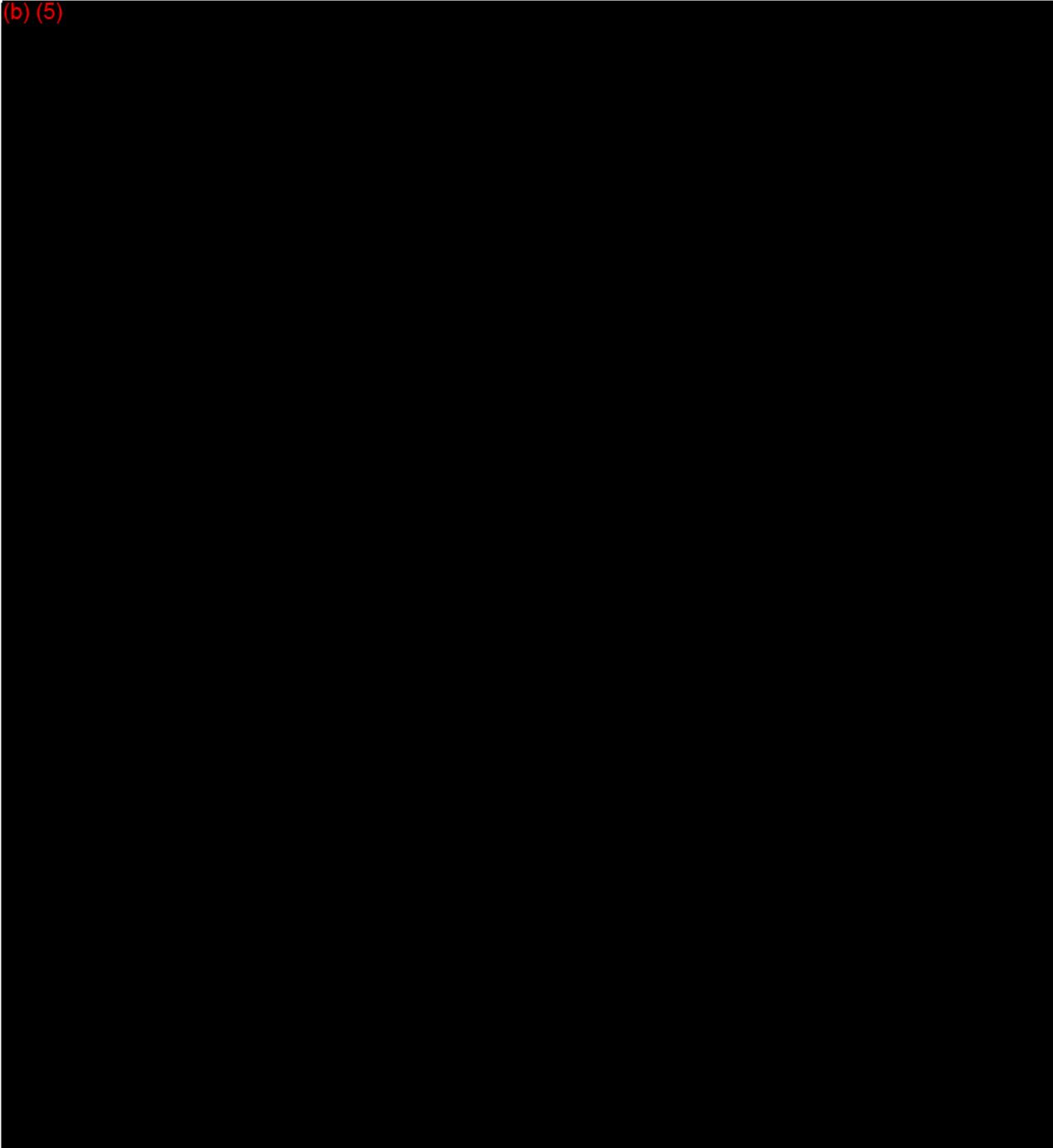
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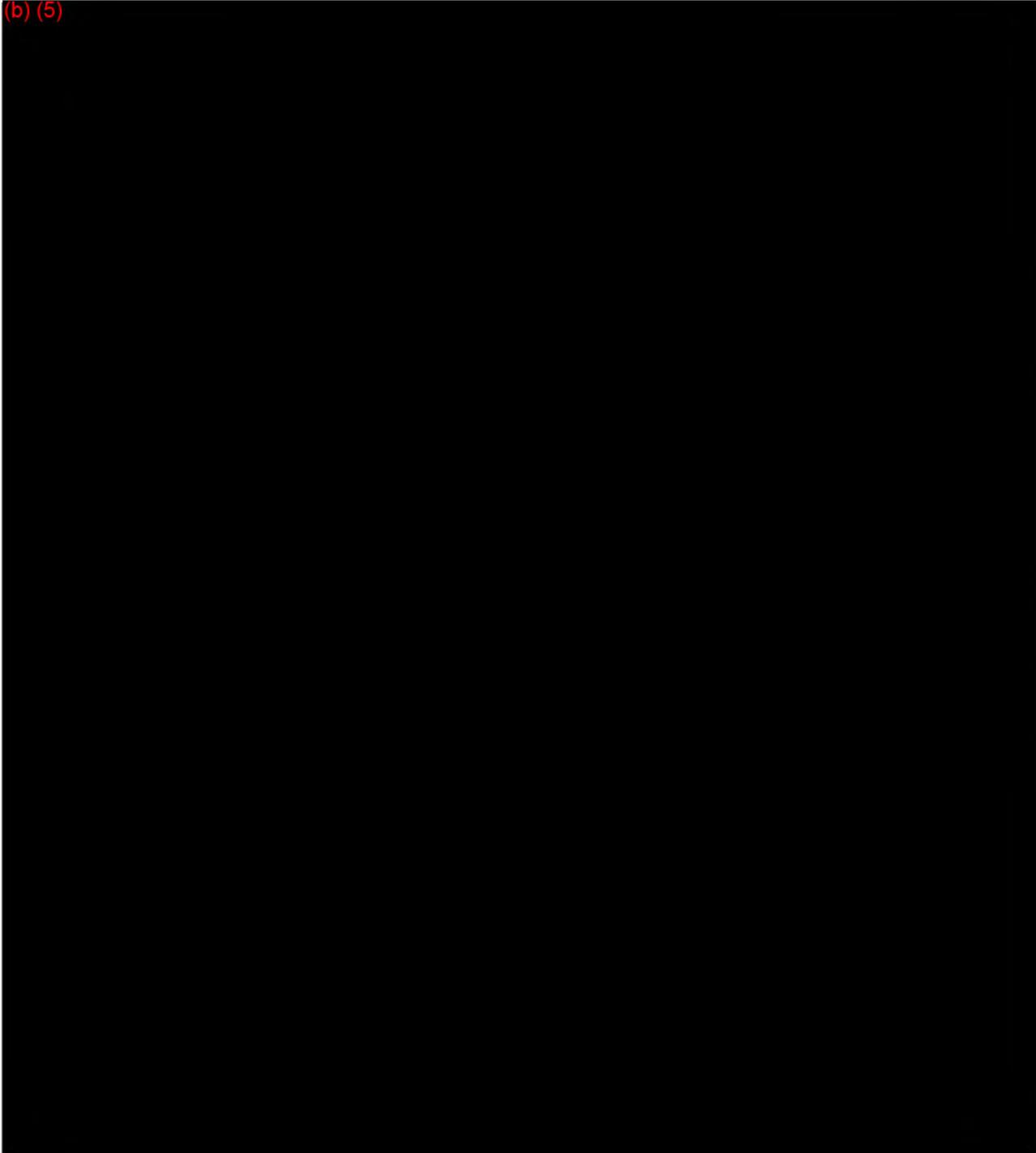
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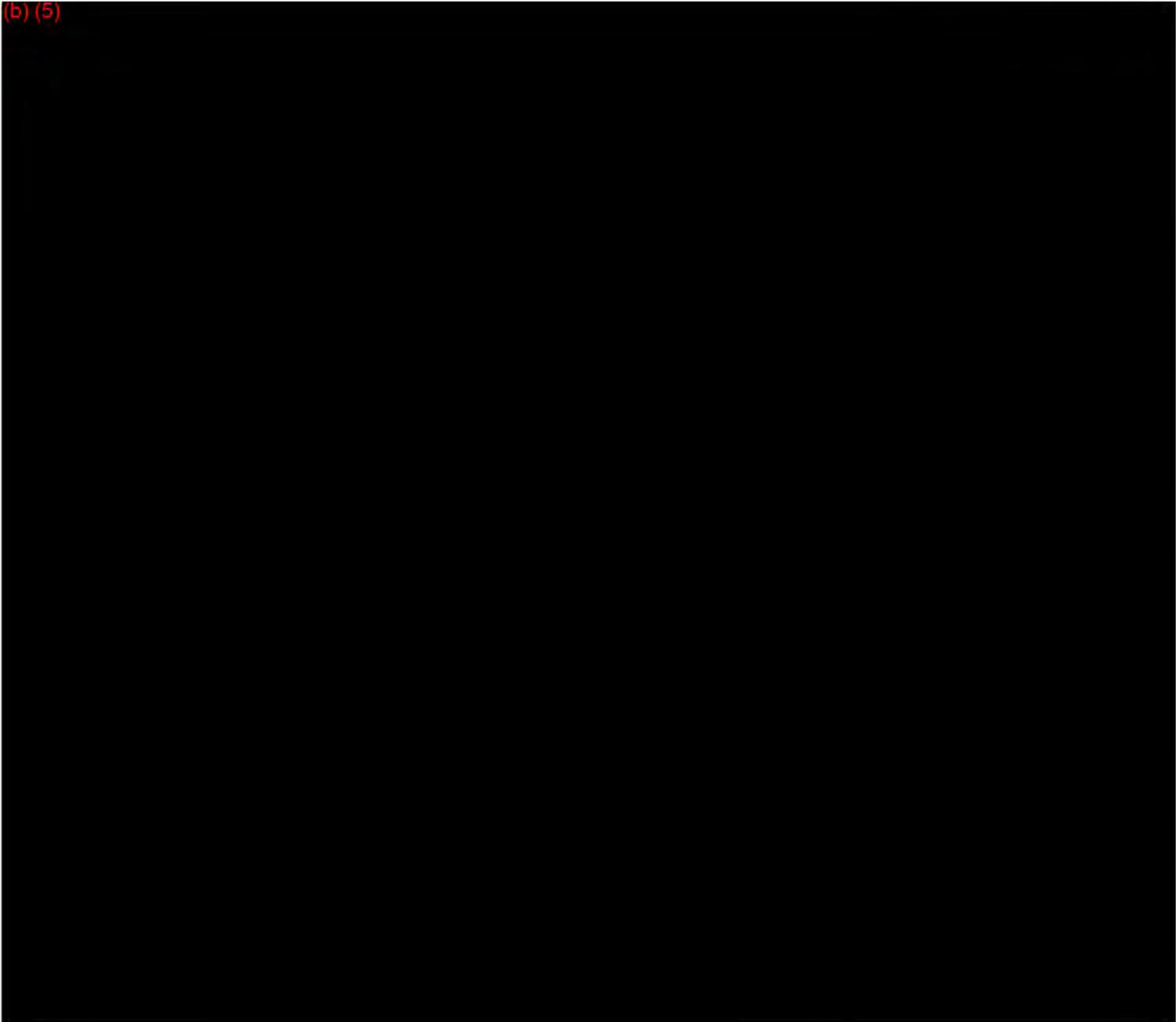
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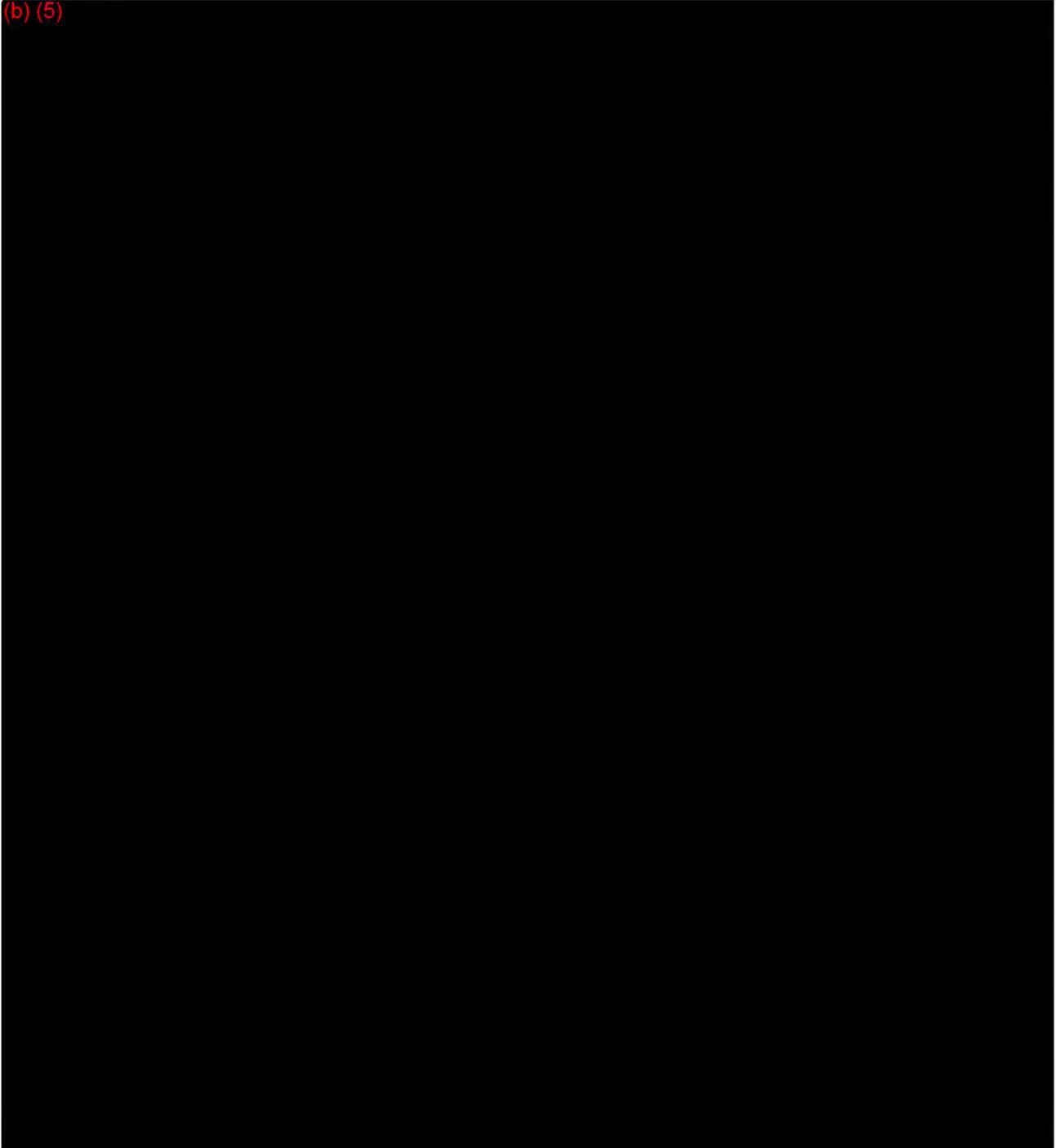
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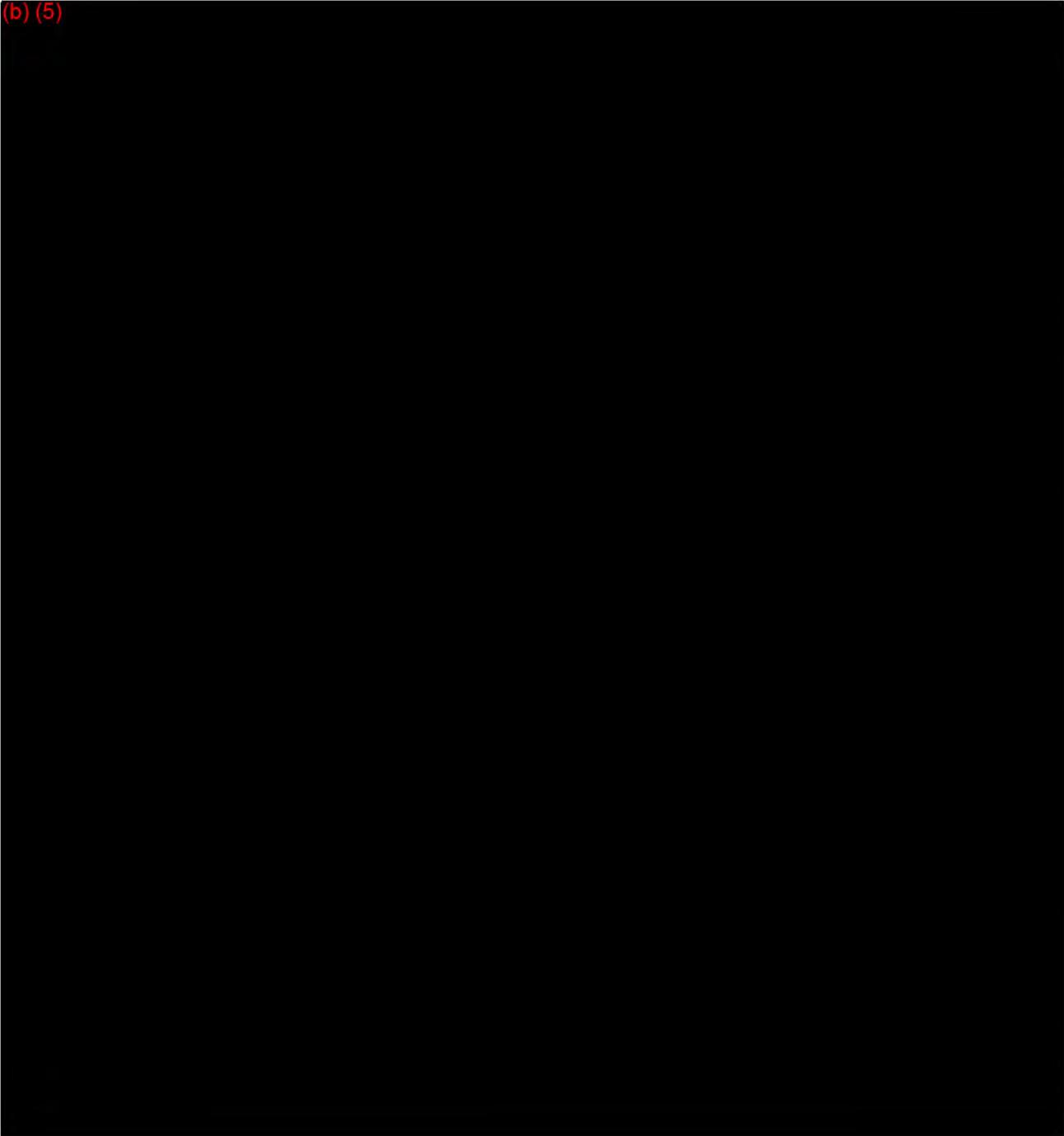
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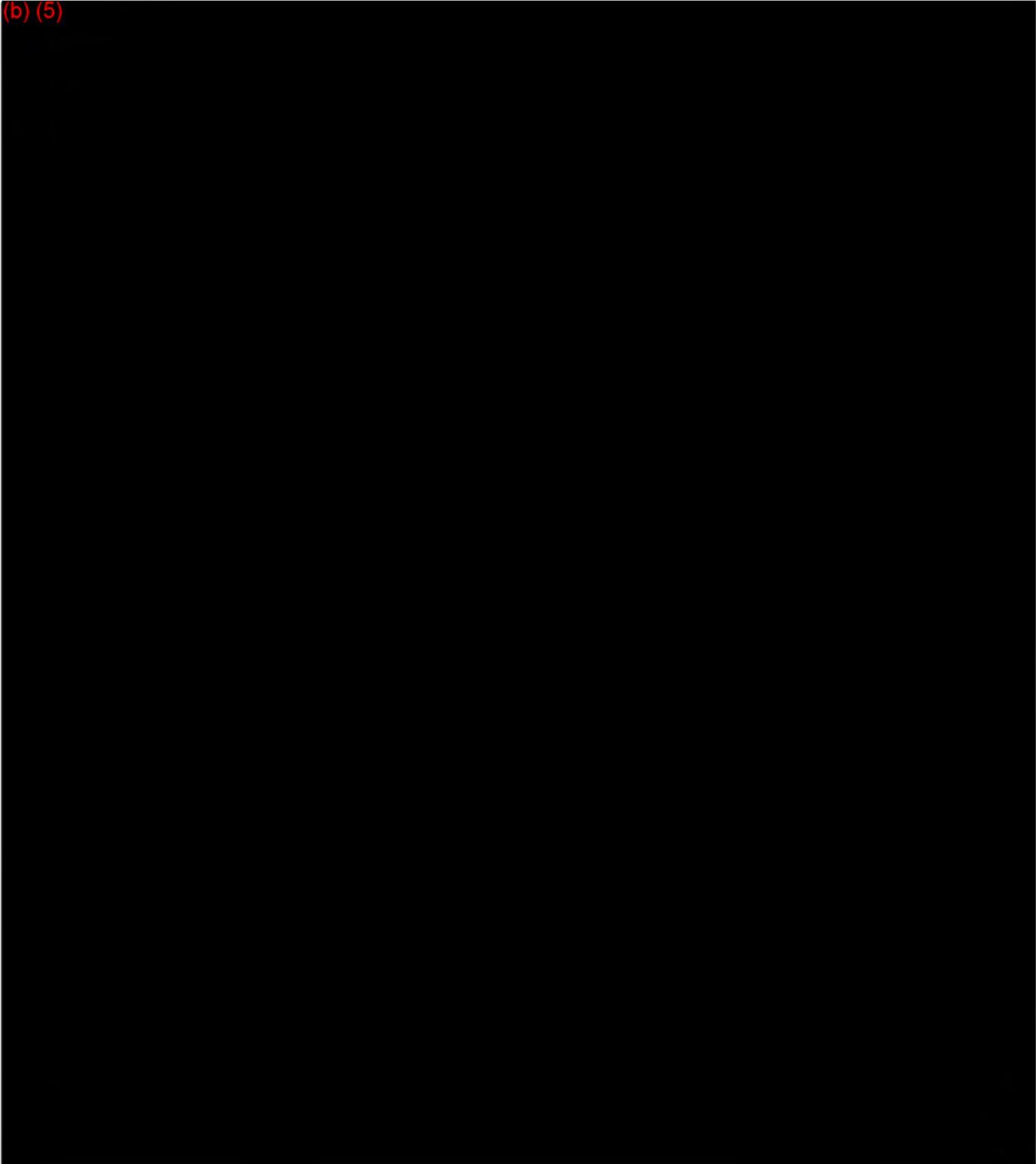
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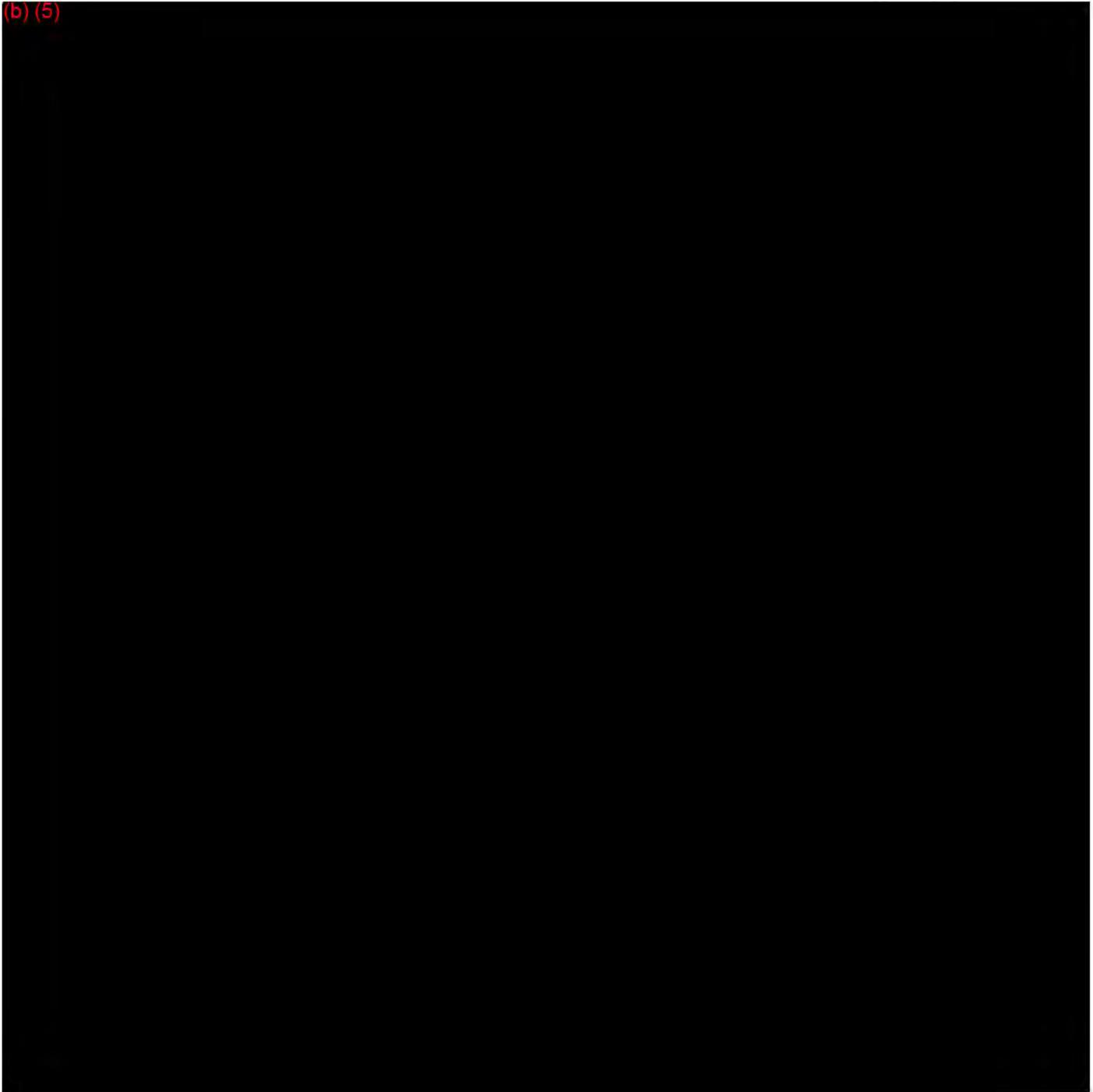
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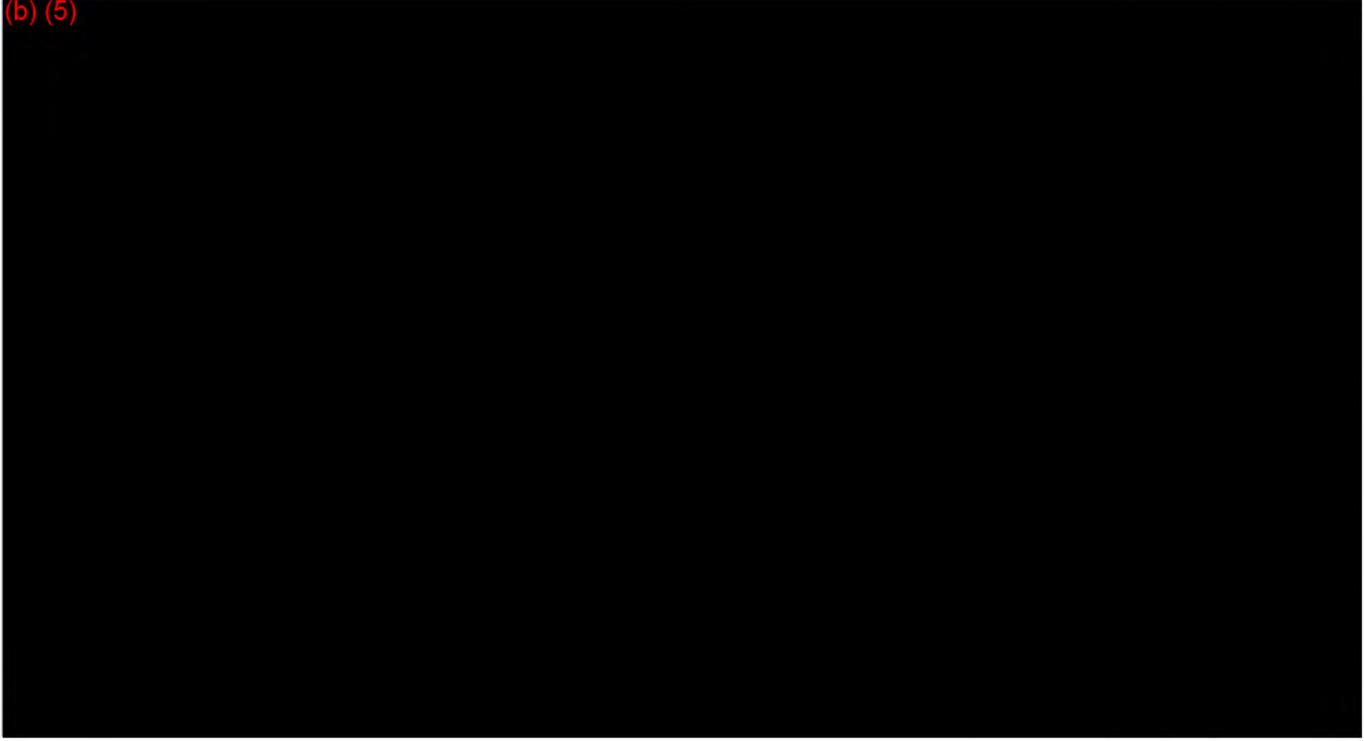
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From: [Wohl, Alexander](#)
To: [Califf, Robert](#); [Rao, Gayatri](#); [Riley, Karen](#)
Cc: [Evans, Dana](#)
Subject: RE: NORD
Date: Sunday, October 16, 2016 4:30:00 PM
Attachments: [20161016 NORD penultimate clean_GRAWedits.doc](#)

Sorry. Here it is.

From: Califf, Robert
Sent: Sunday, October 16, 2016 4:18 PM
To: Wohl, Alexander; Rao, Gayatri; Riley, Karen
Cc: Evans, Dana
Subject: RE: NORD

Did you have an attachment? I have a little more editing to do so no need to format.

Thx

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Wohl, Alexander
Sent: Sunday, October 16, 2016 4:16 PM
To: Rao, Gayatri; Califf, Robert; Riley, Karen
Cc: Evans, Dana
Subject: RE: NORD

Just a few small edits on top of Gayatri's.
Do you want me to do any additional formatting of this before the morning?

From: Rao, Gayatri
Sent: Sunday, October 16, 2016 2:39 PM
To: Califf, Robert; Wohl, Alexander; Riley, Karen
Subject: RE: NORD

Dr. Califf,

Thank for the opportunity to review the speech and for the kind words in the speech itself. I think you cover all the main areas that are salient to this audience. Attached are just a few minor edits/suggestions.

I look forward to hearing this speech tomorrow!

Gayatri

From: Califf, Robert

Sent: Sunday, October 16, 2016 12:00 PM
To: Wohl, Alexander; Rao, Gayatri; Riley, Karen
Subject: NORD

Here is a marked up and clean version for review. I'm personally very comfortable with the content but interested in any corrections/edits you might suggest.

Hope you're enjoying the day. Gayatri, note that you're now mentioned.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

Speech by Robert M. Califf, M.D.
Commissioner of Food and Drugs
2016 National Organization for Rare Disorders (NORD) Summit
October 17, 2016
Washington, D.C.

“Critical Lessons about Rare Disease Drug Development”

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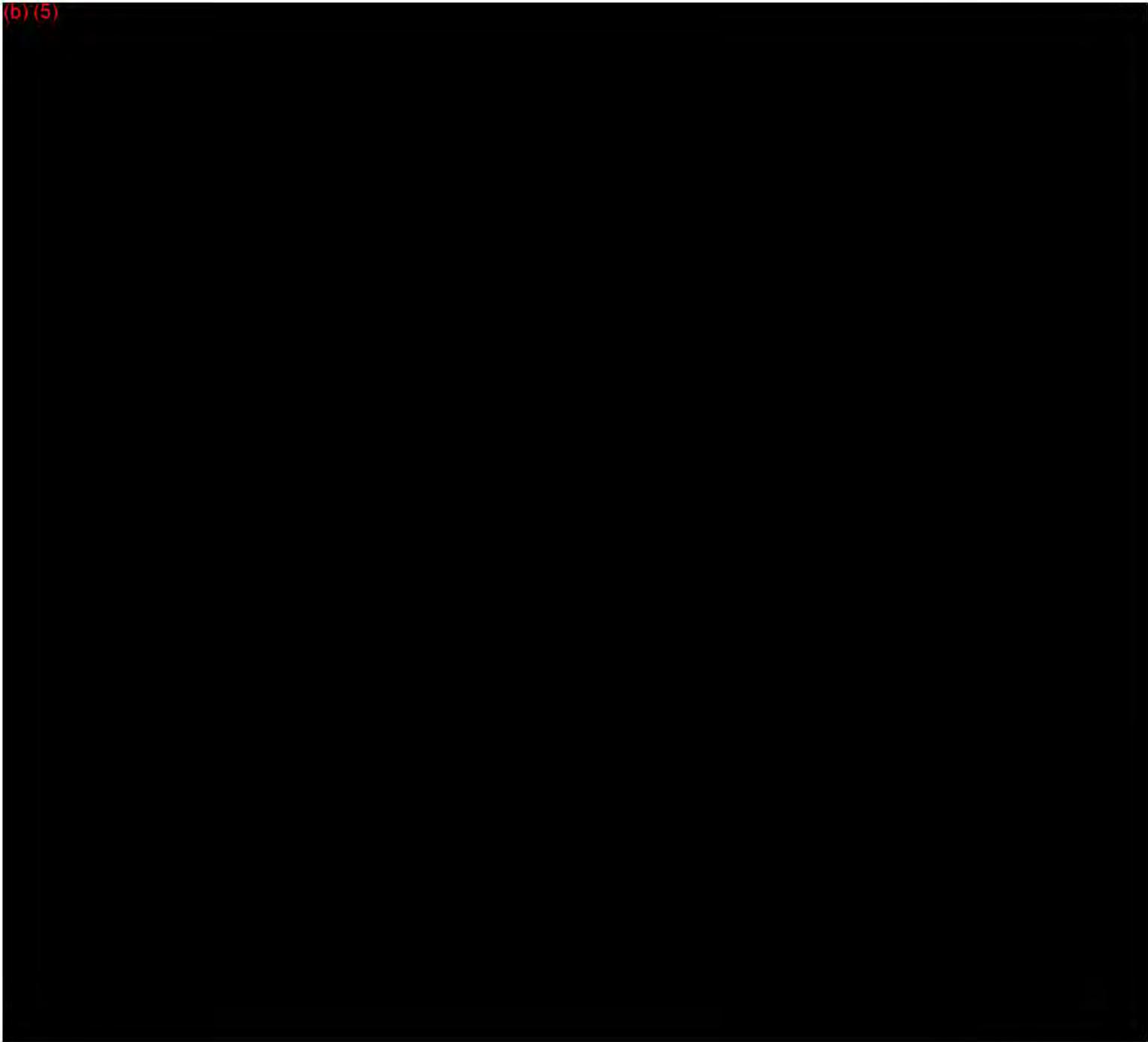
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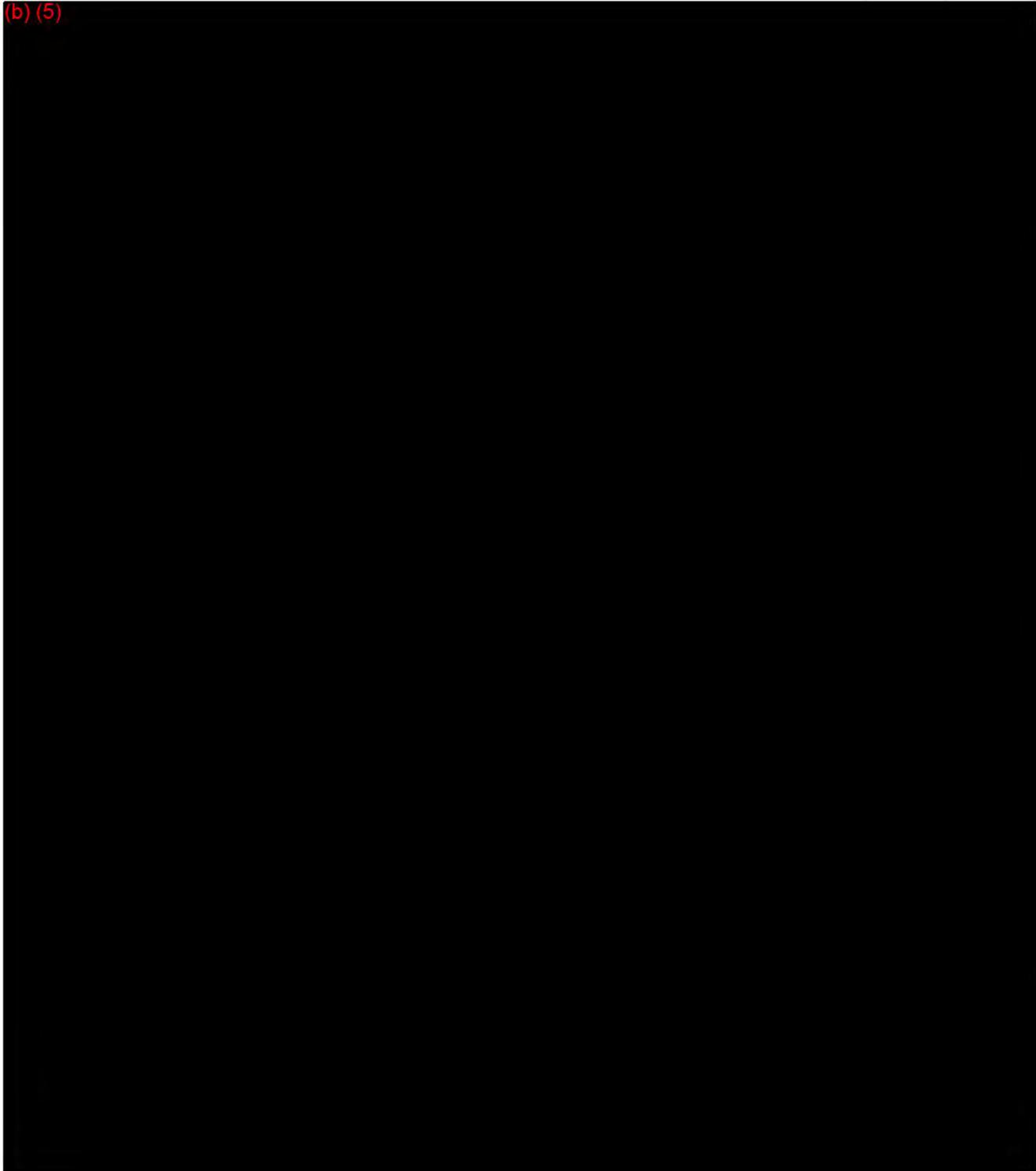
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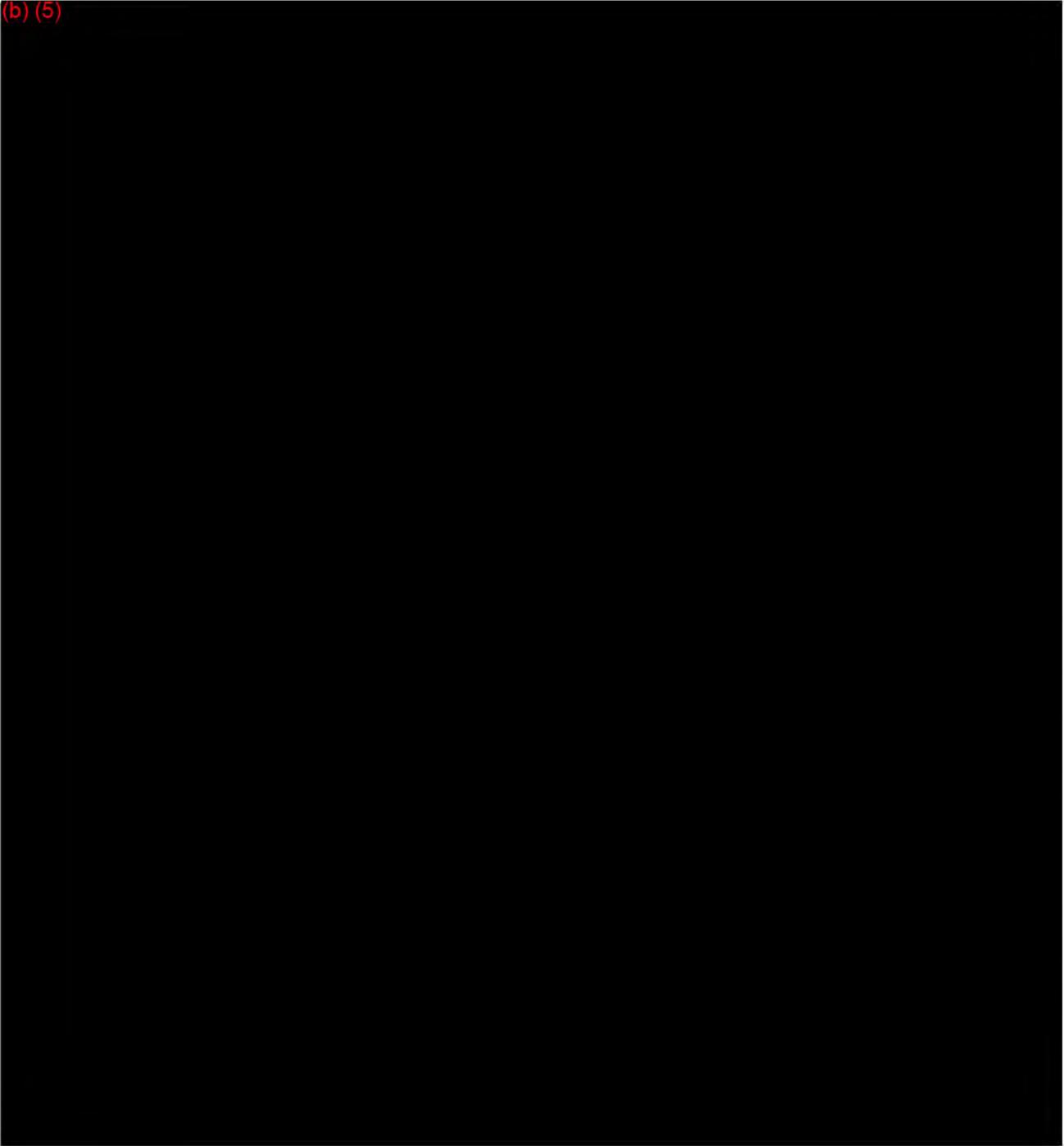
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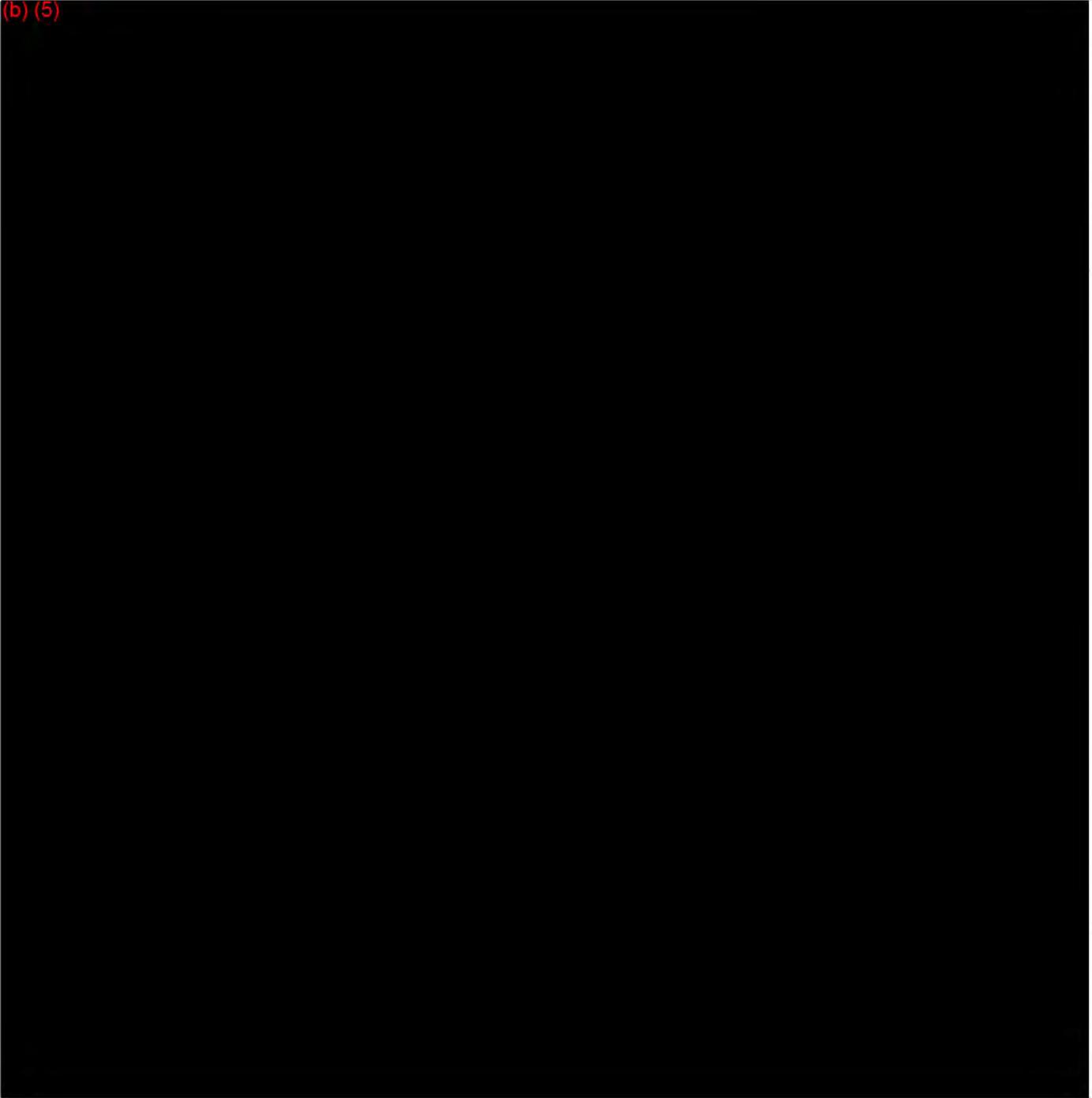
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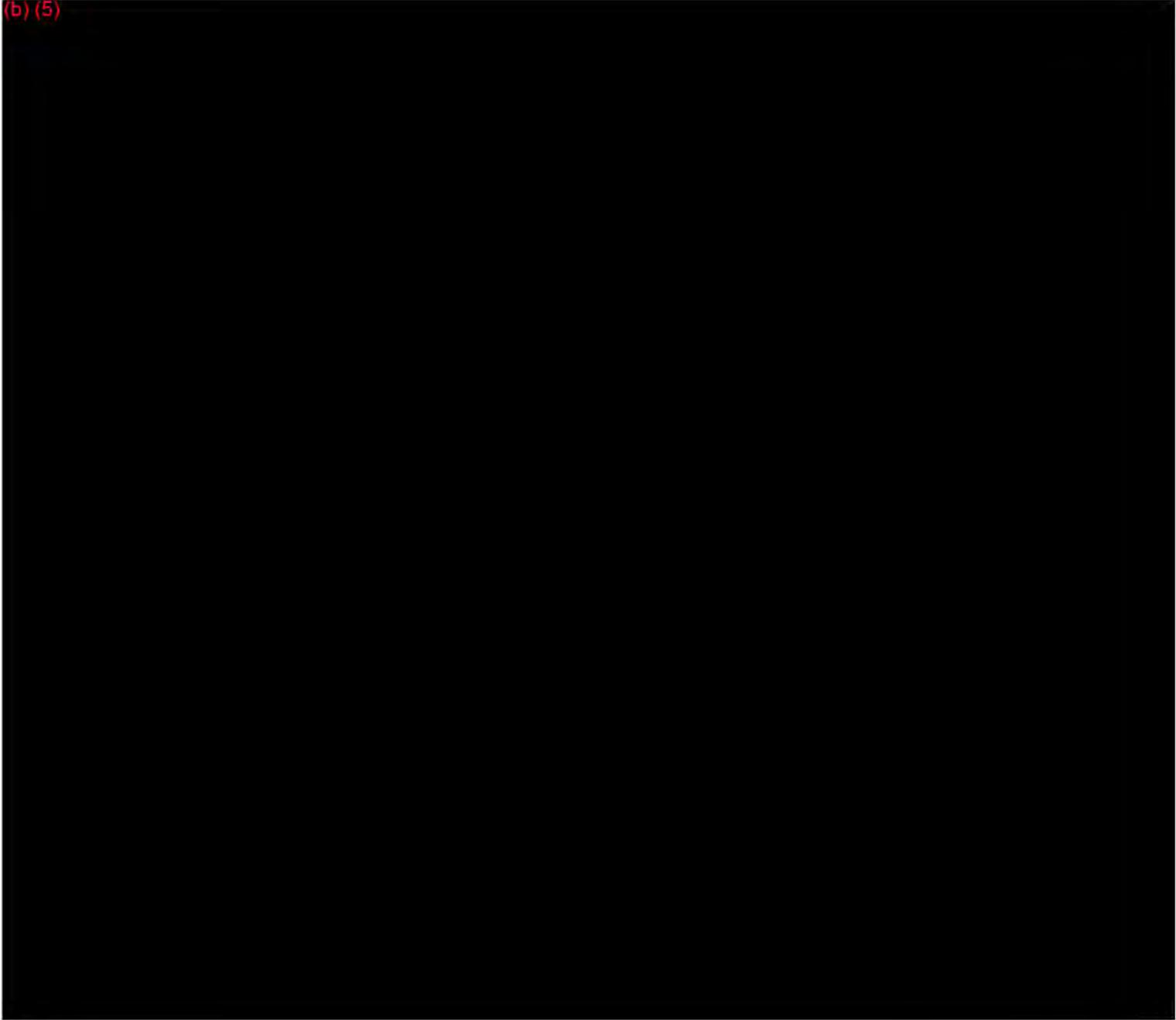
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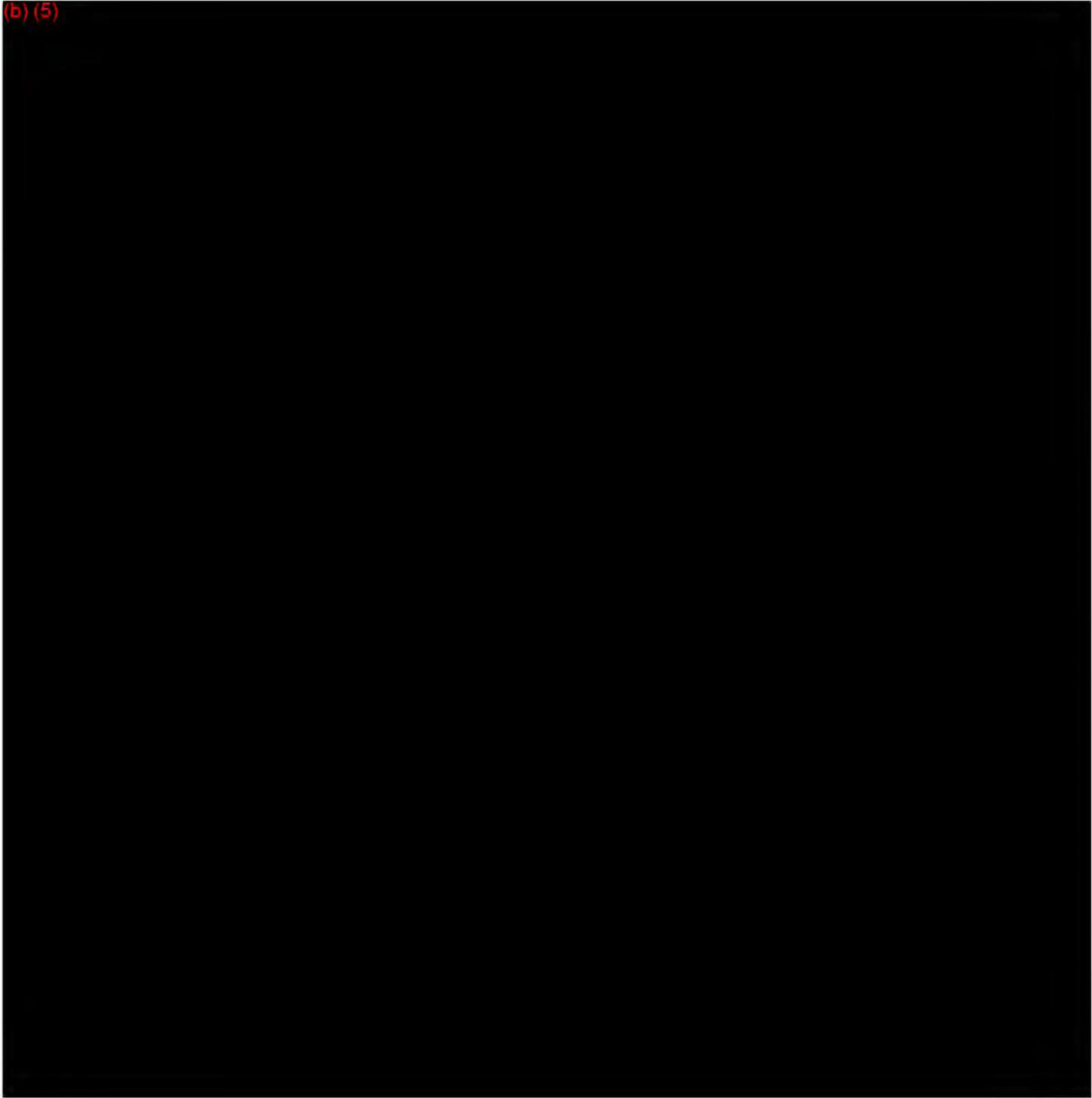
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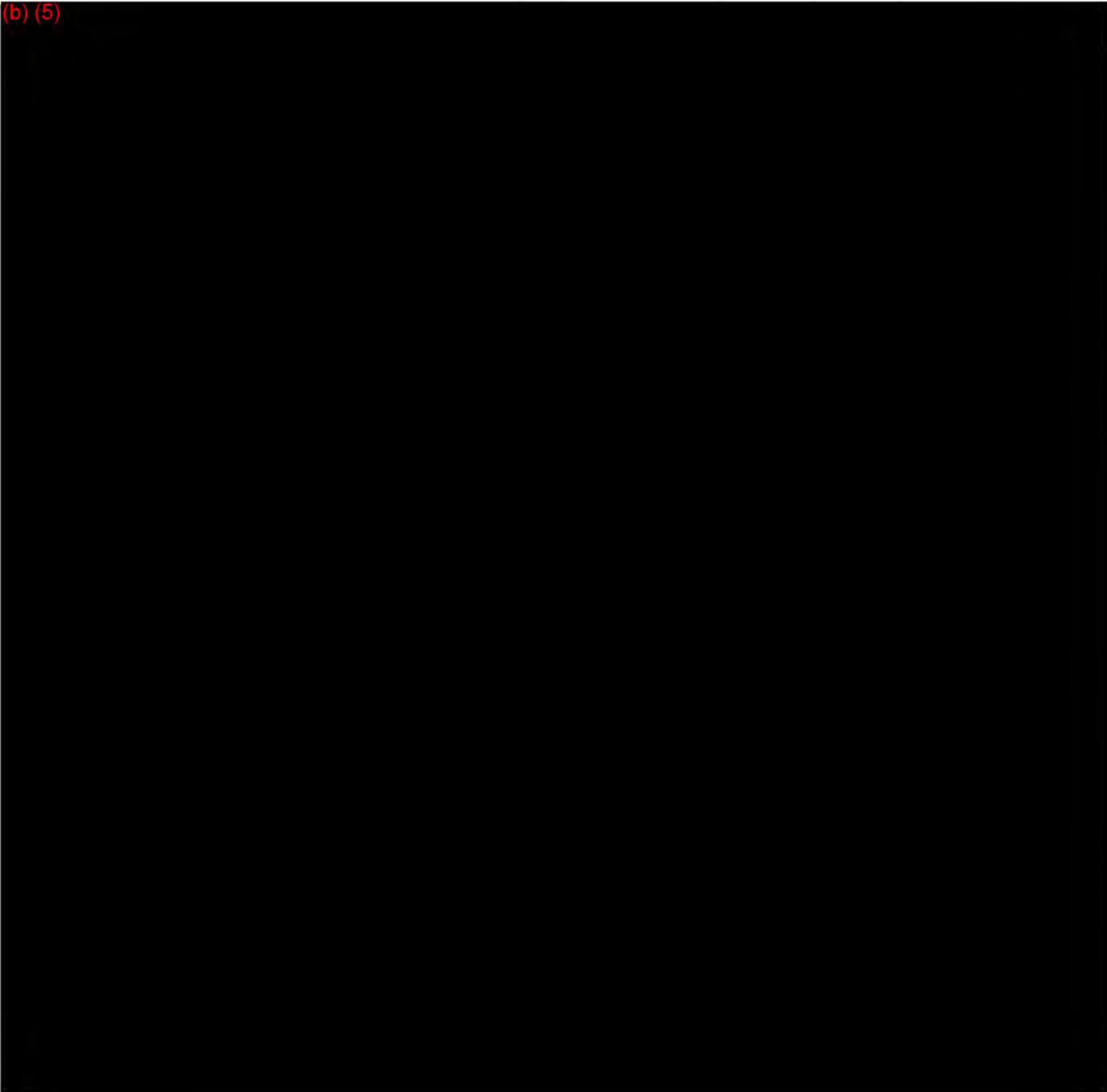
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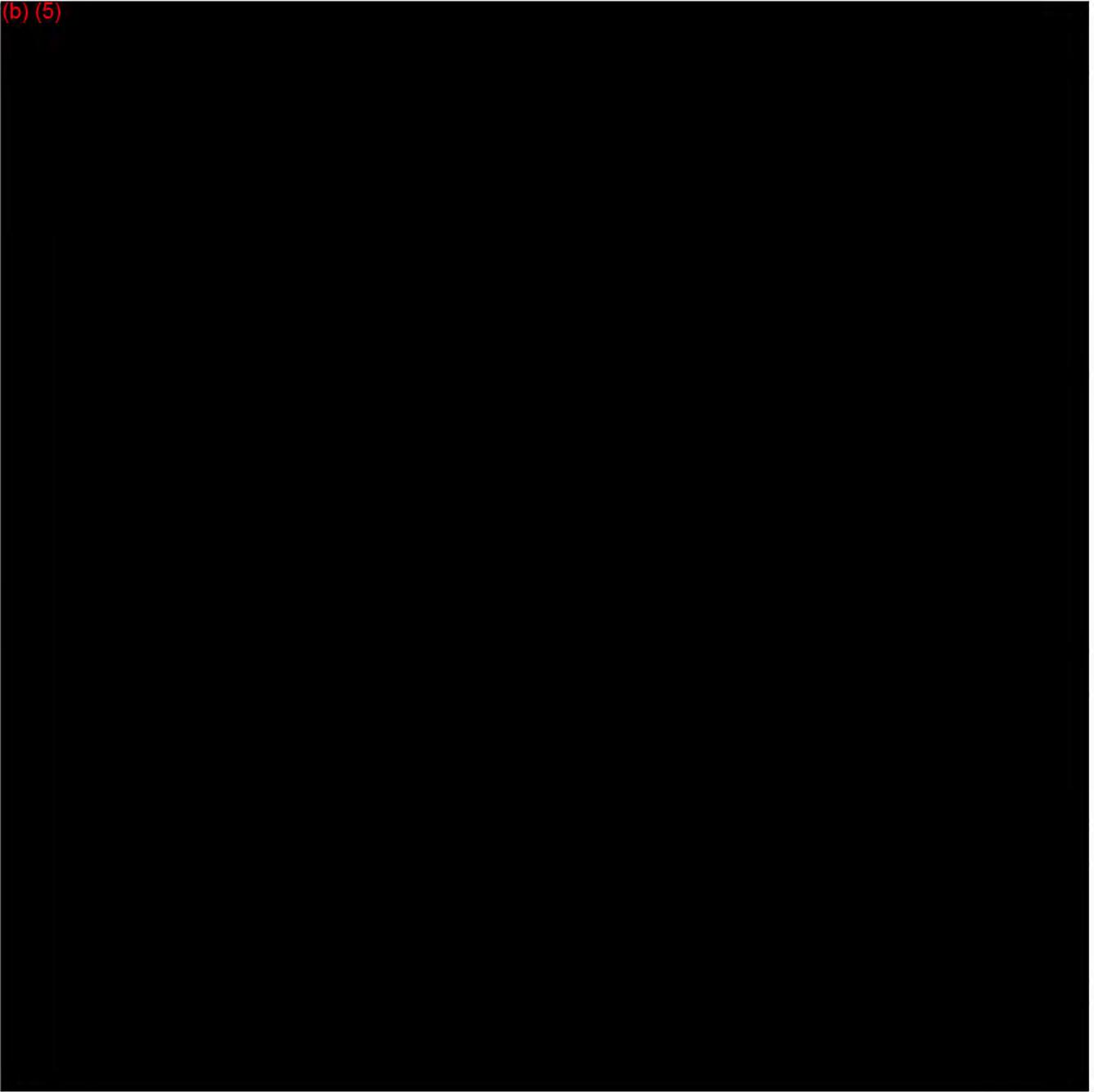
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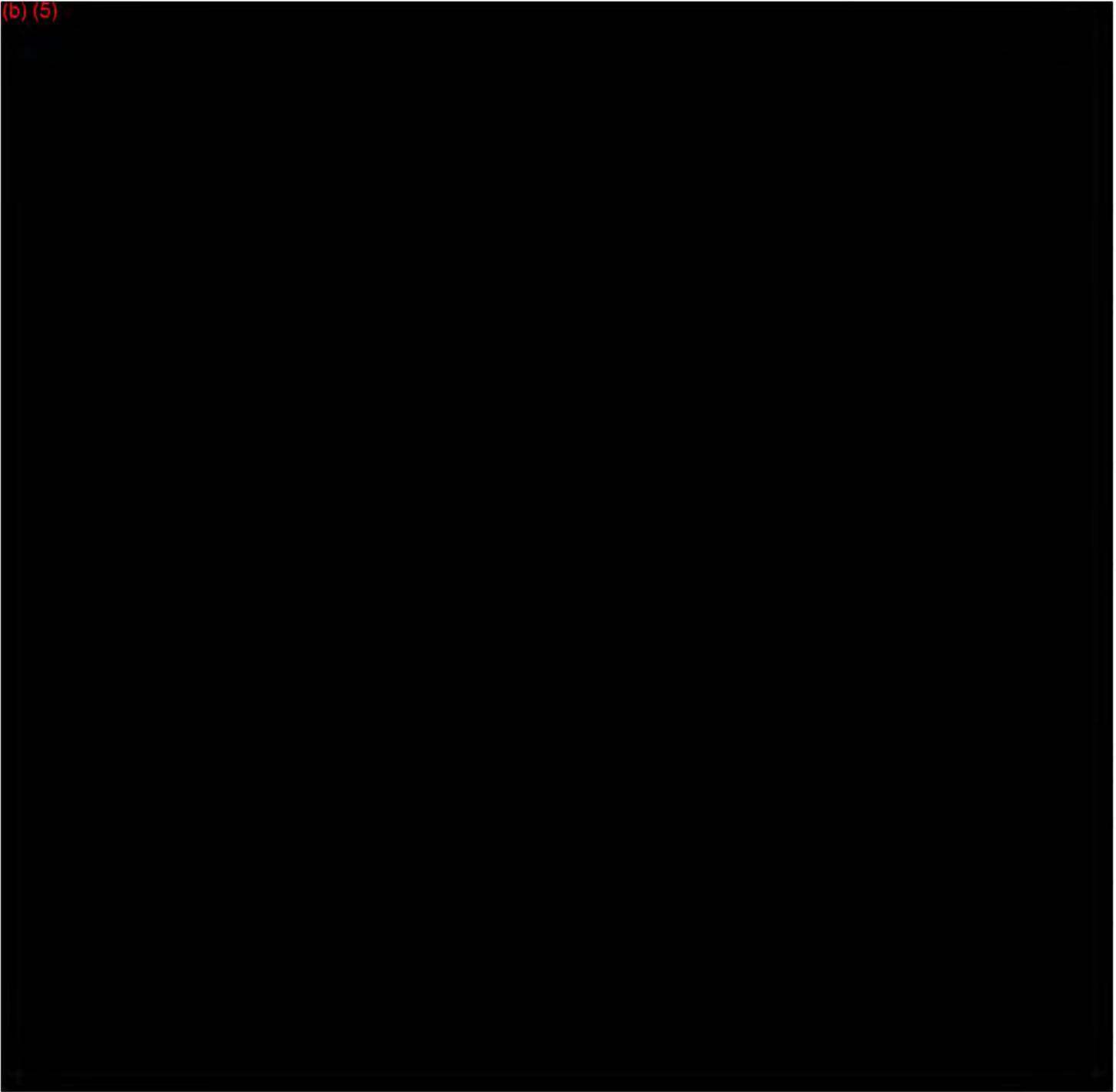
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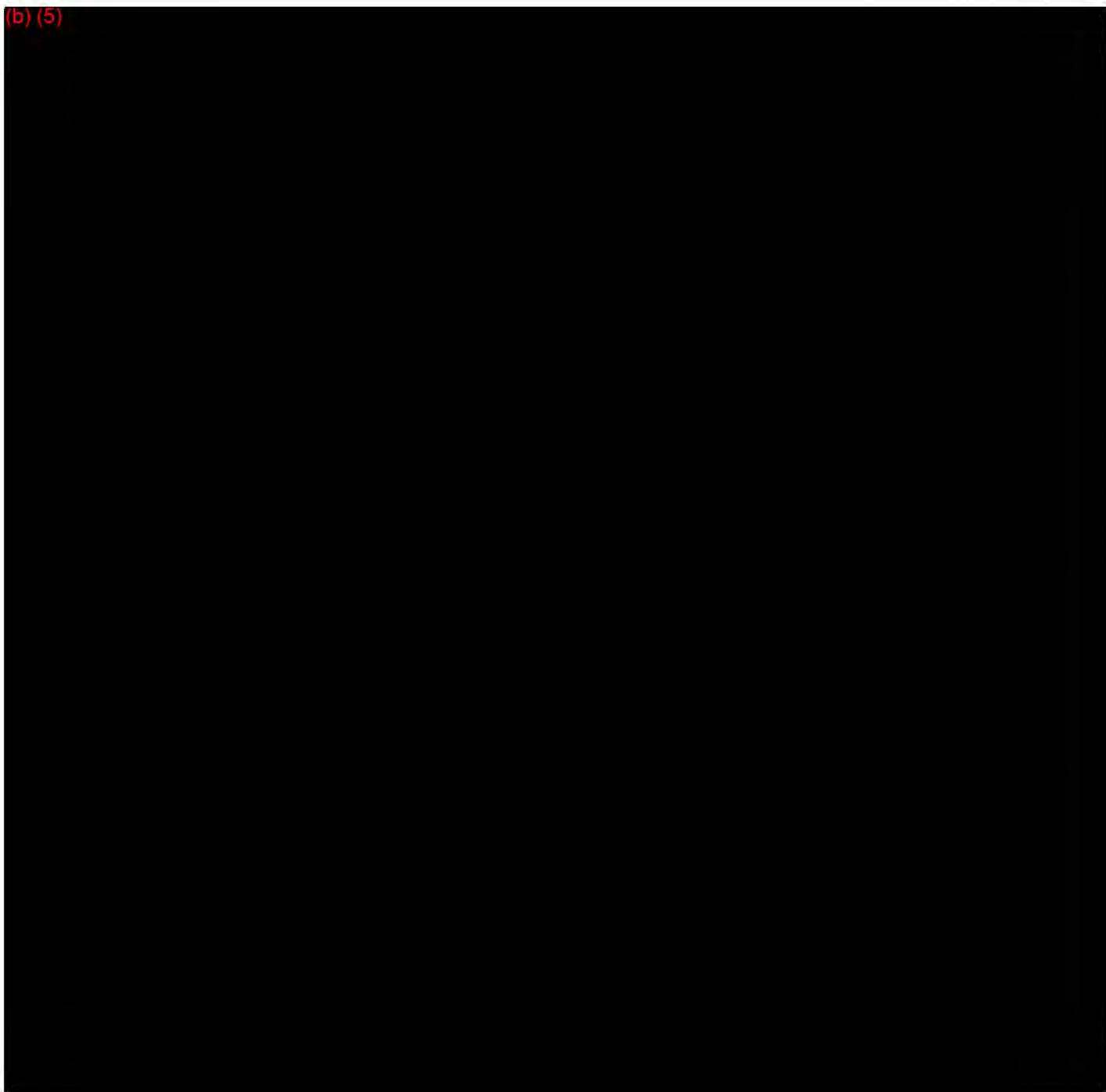
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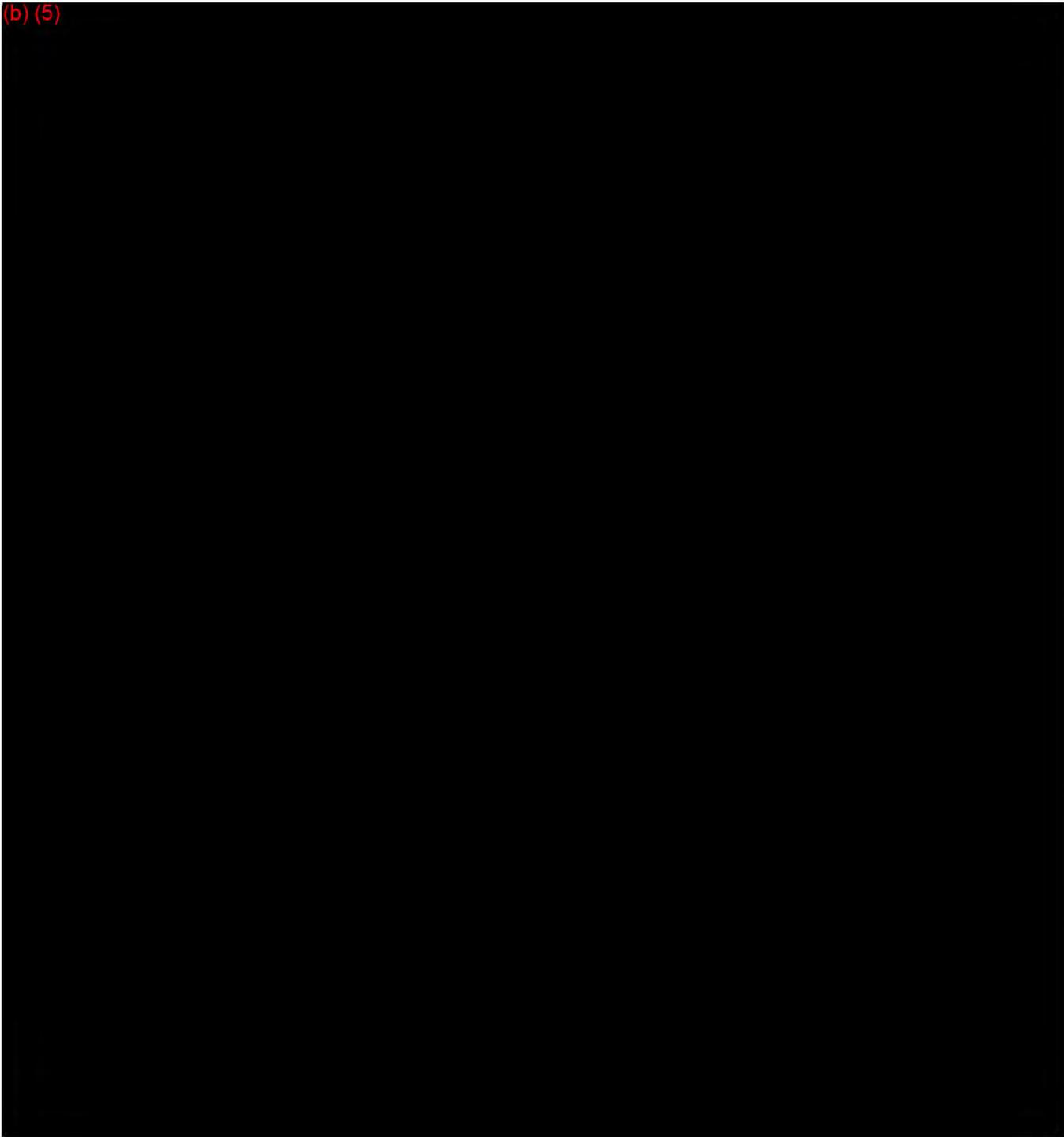
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(b) (5)



(b) (5)



From: [Rao, Gayatri](#)
To: [Riley, Karen](#); [Califf, Robert](#)
Cc: [Wohl, Alexander](#)
Subject: RE: NORD Speech
Date: Sunday, October 16, 2016 9:11:32 PM
Attachments: 20161016 NORD penultimate clean GRkredits-2.doc

Apologies again for the delay. Attached are a few additions in response to Karen's comments.

Gayatri

From: Rao, Gayatri
Sent: Sunday, October 16, 2016 8:08 PM
To: Riley, Karen; Califf, Robert
Cc: Wohl, Alexander
Subject: Re: NORD Speech

Apologies; I've been tied up with (b) (6) I can review in a bit if it's not too late.

From: Riley, Karen
Sent: Sunday, October 16, 2016 5:23 PM
To: Califf, Robert
Cc: Wohl, Alexander; Rao, Gayatri
Subject: Fw: NORD Speech

Here you are. Incorporates all. Gayatri, I asked a couple of questions. Can we include a sentence (b) (5)

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Karen Riley (b) (6) (b) (6)
Sent: Sunday, October 16, 2016 5:20 PM
To: Riley, Karen
Subject: NORD Speech

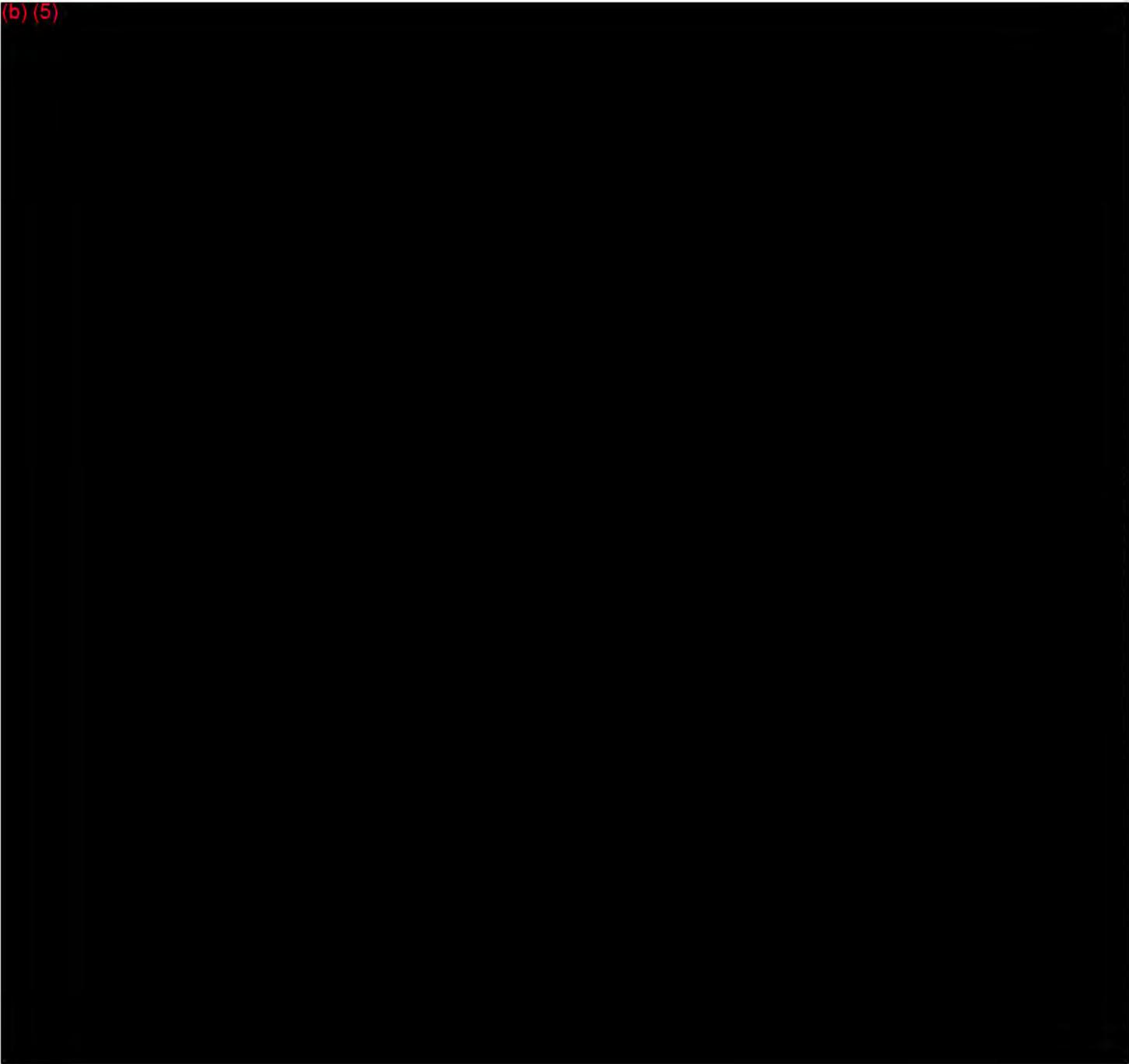
Speech by Robert M. Califf, M.D.
Commissioner of Food and Drugs
2016 National Organization for Rare Disorders (NORD) Summit
October 17, 2016
Washington, D.C.

“Critical Lessons about Rare Disease Drug Development”

(b) (5)



(b) (5)

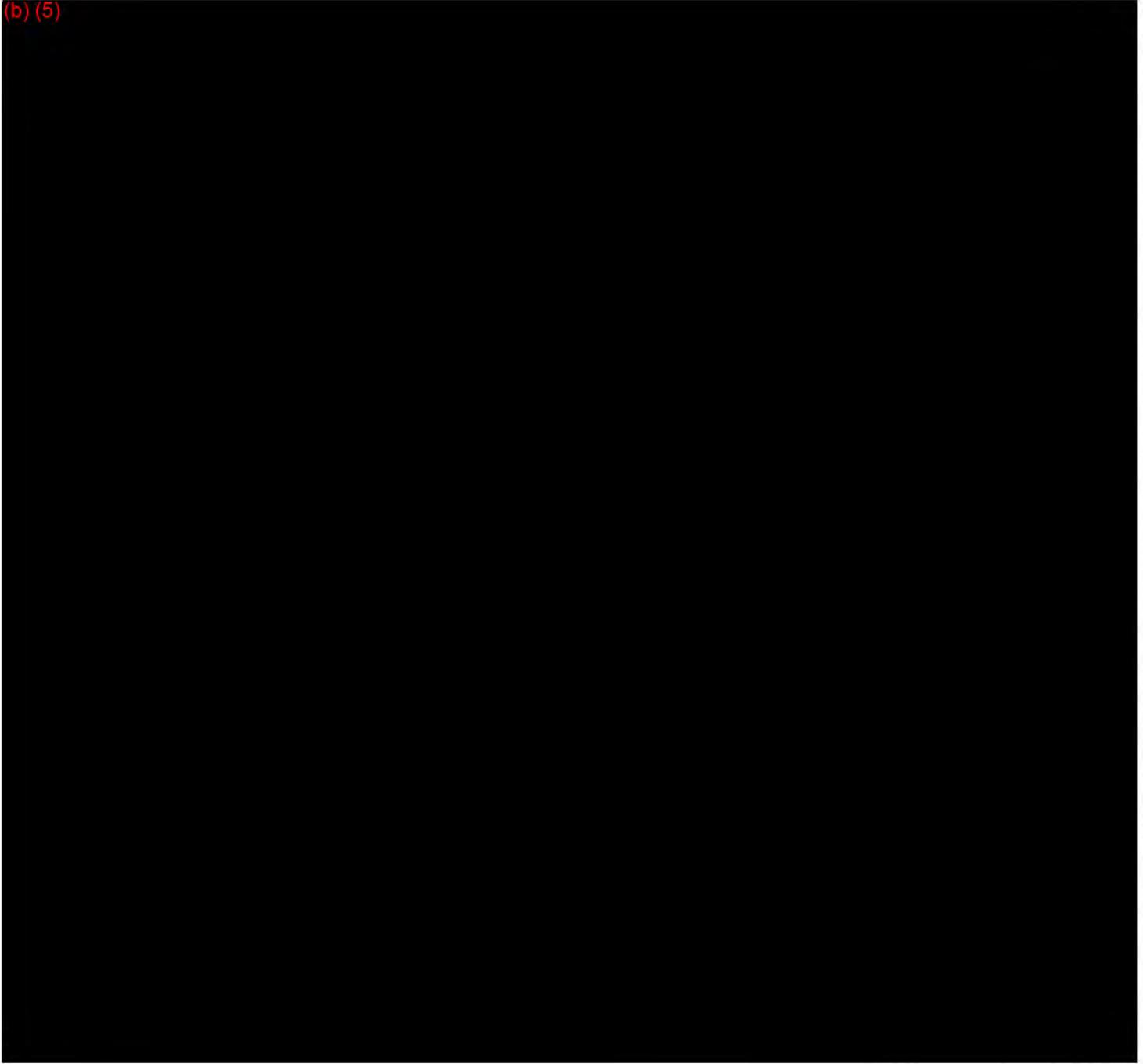


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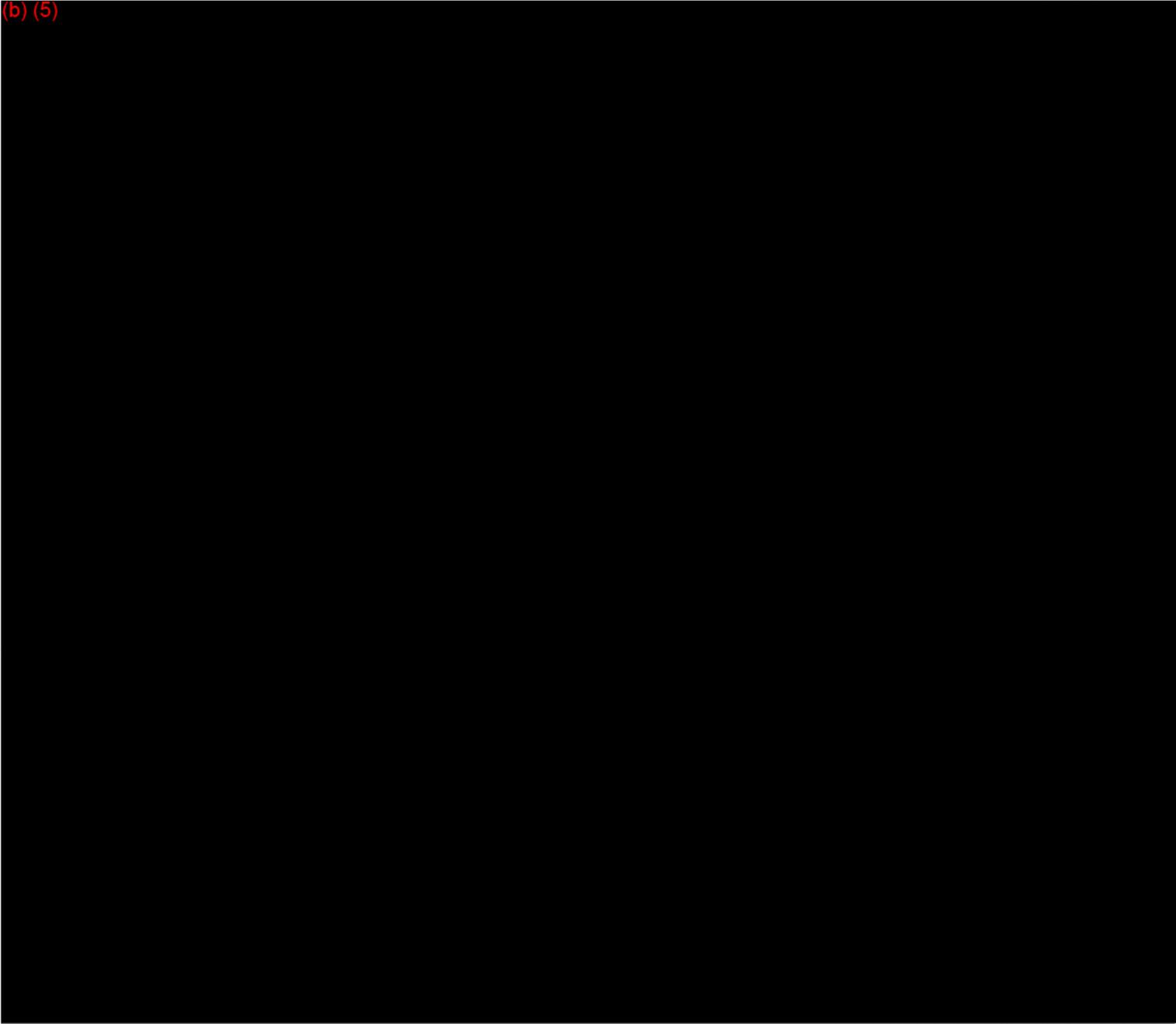
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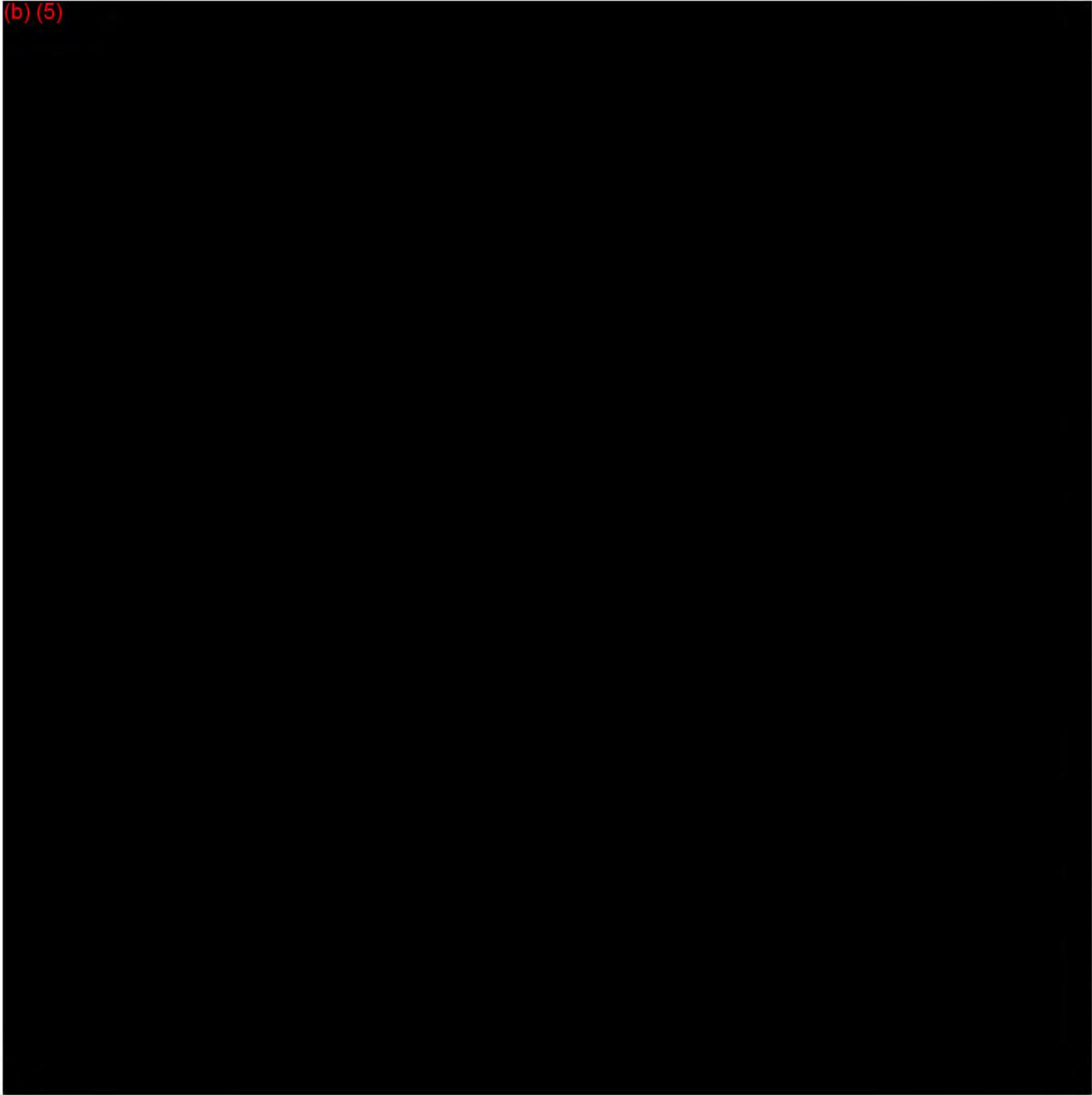
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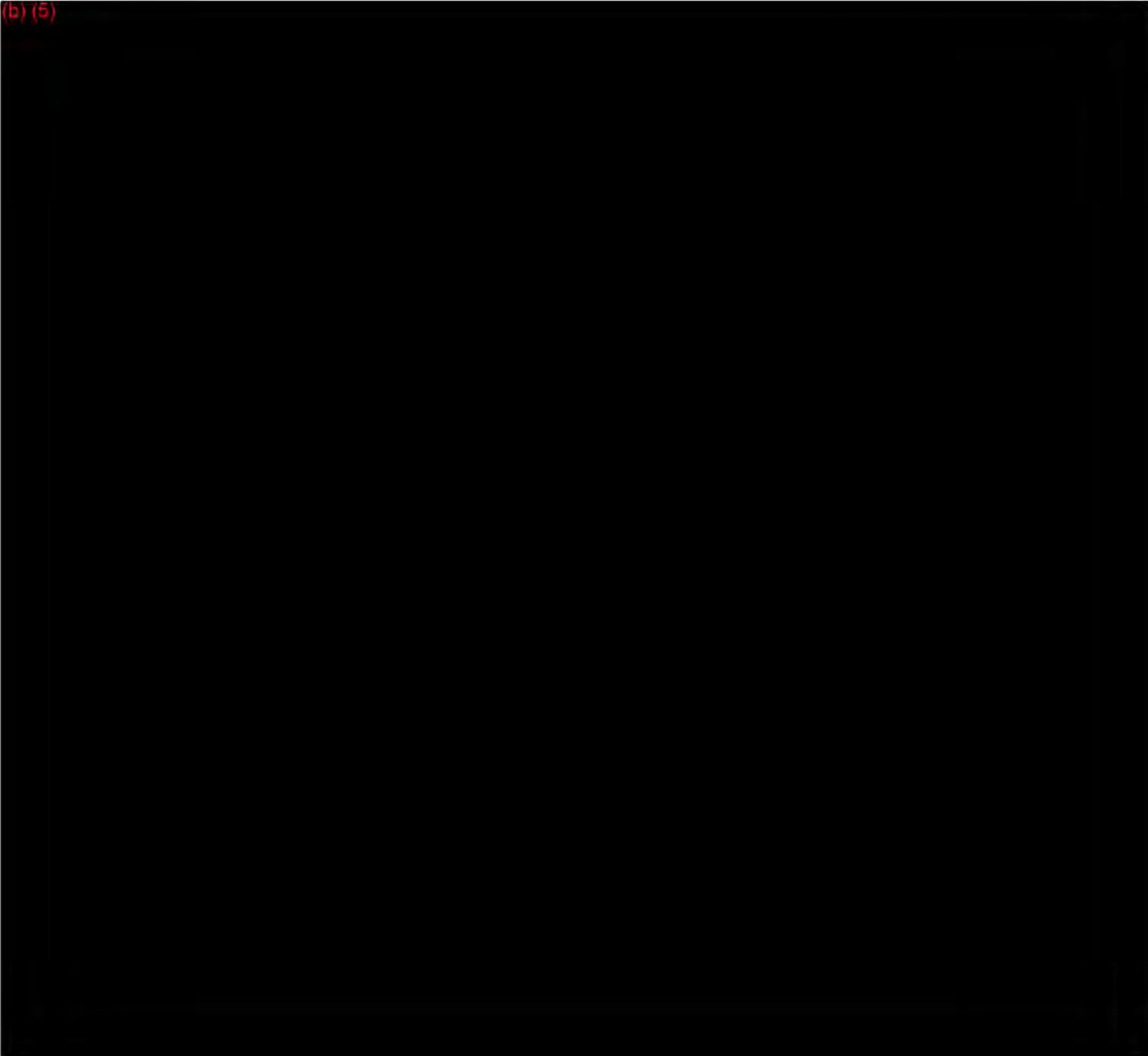
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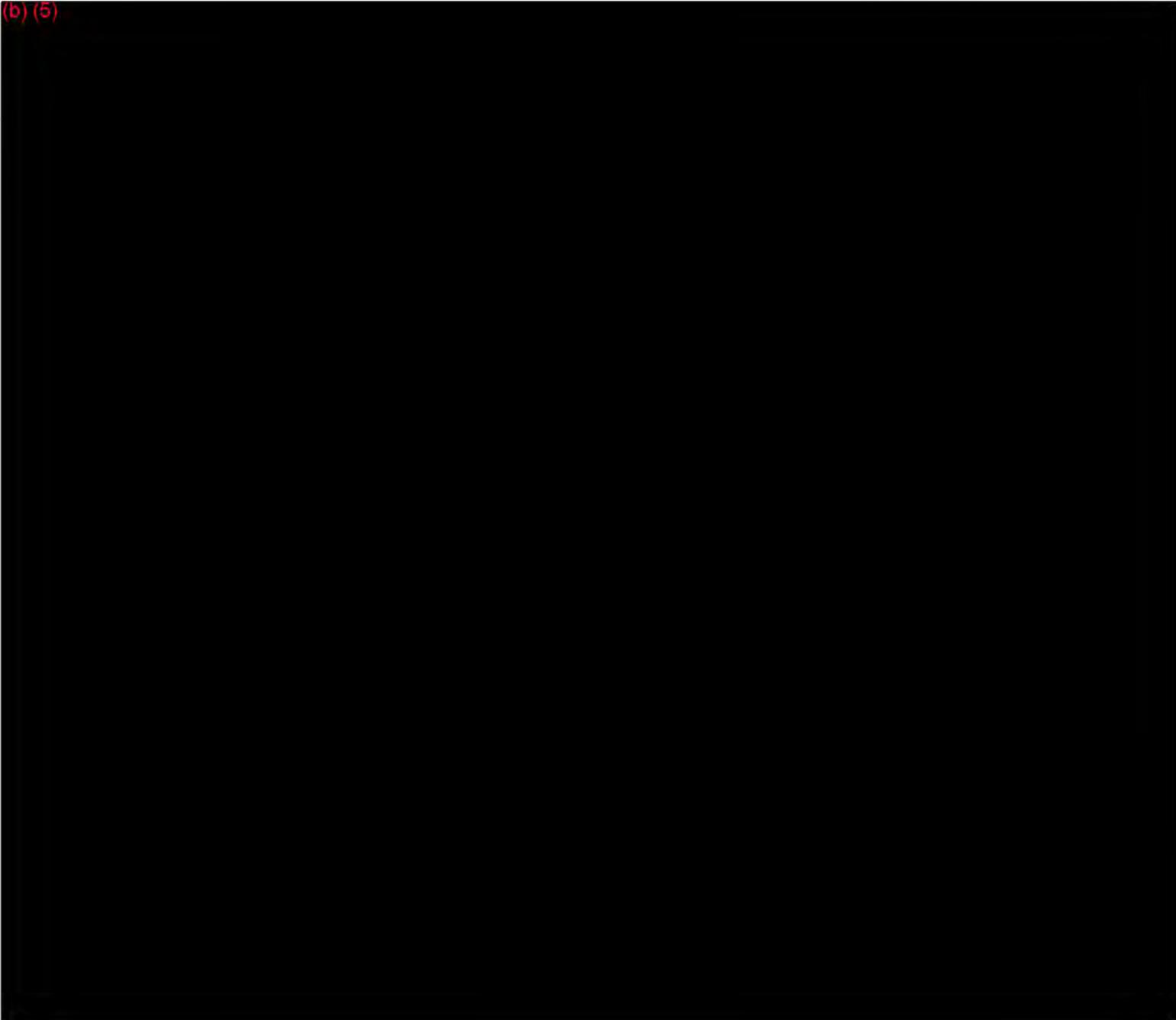
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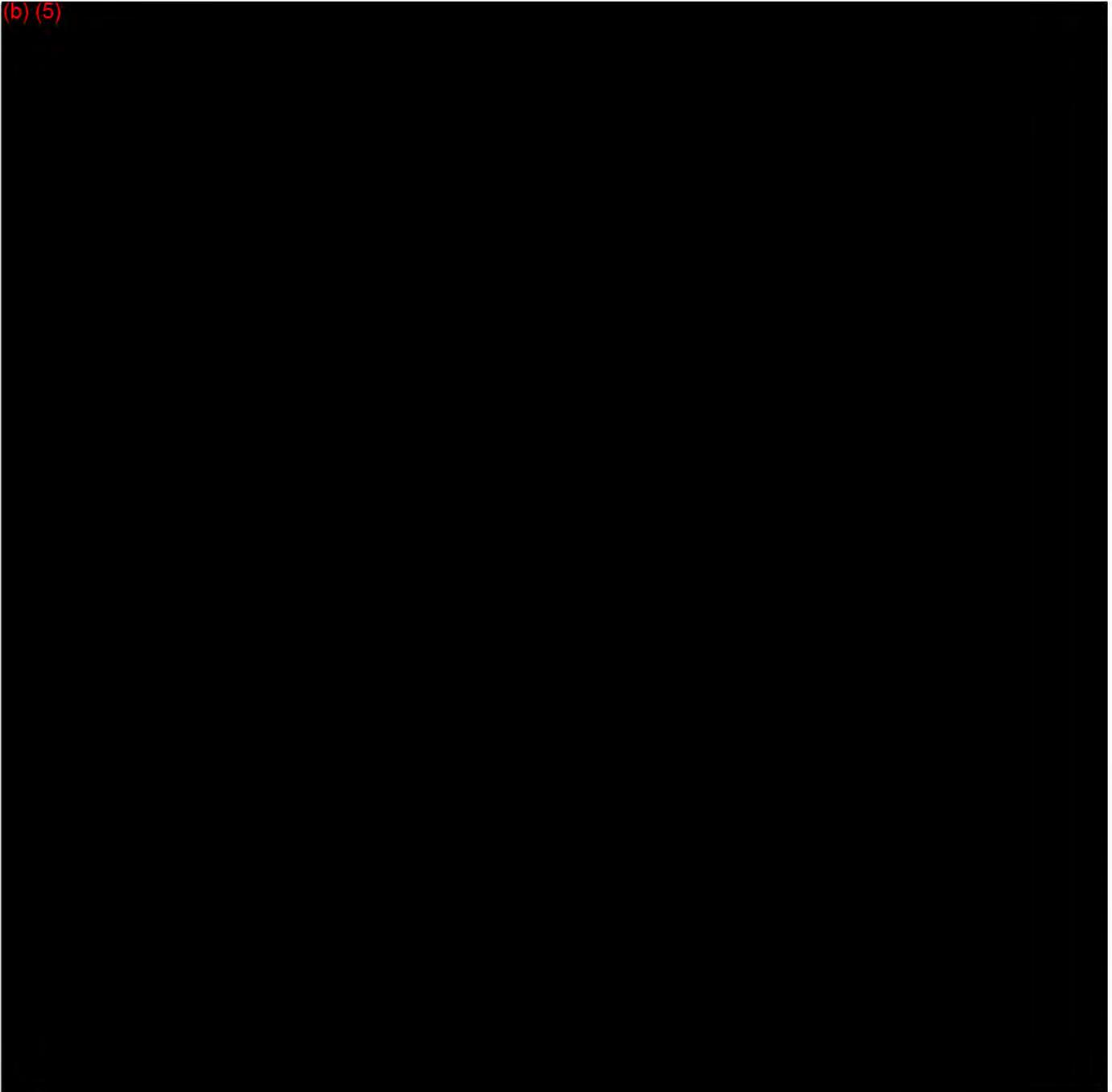
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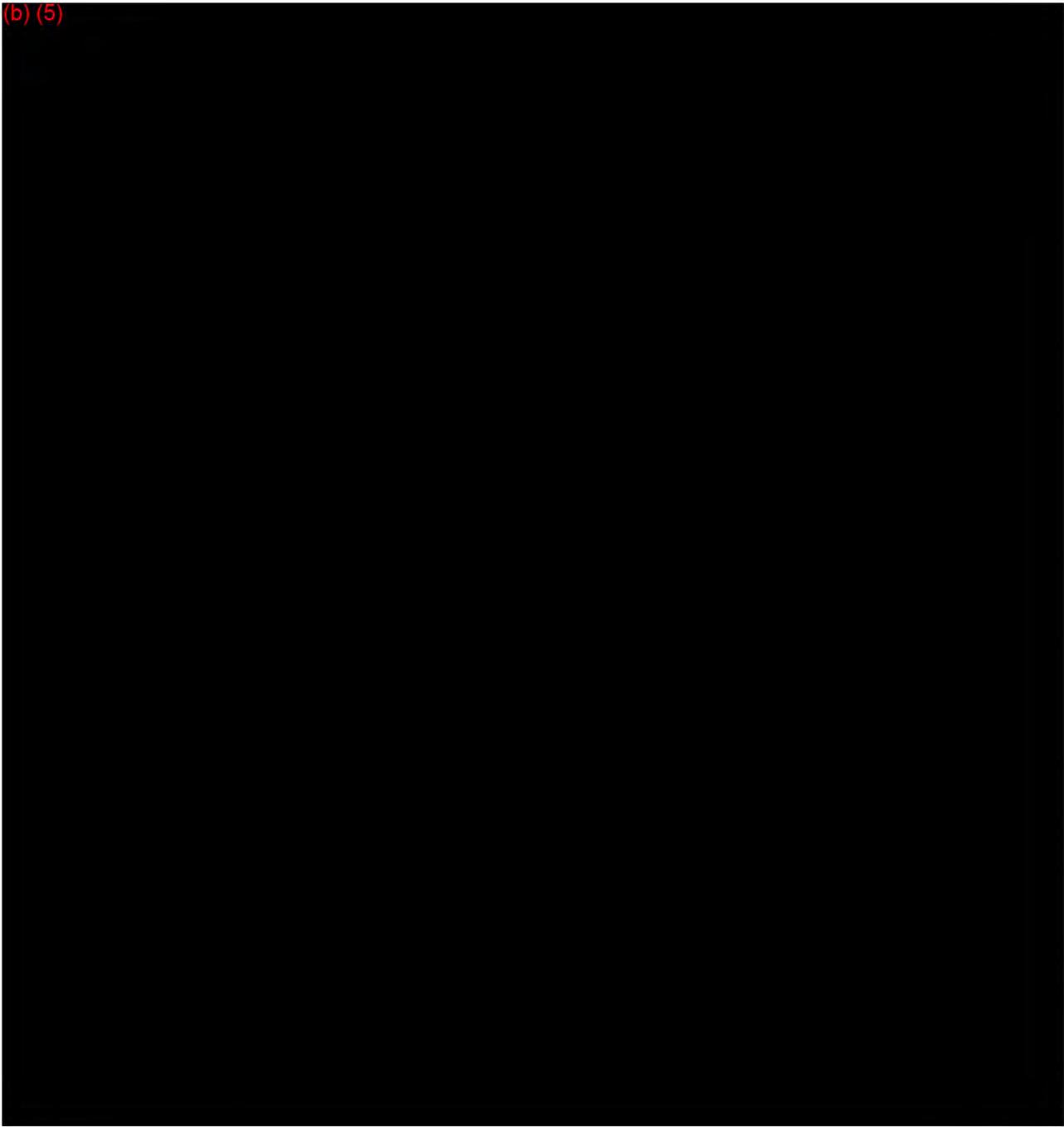
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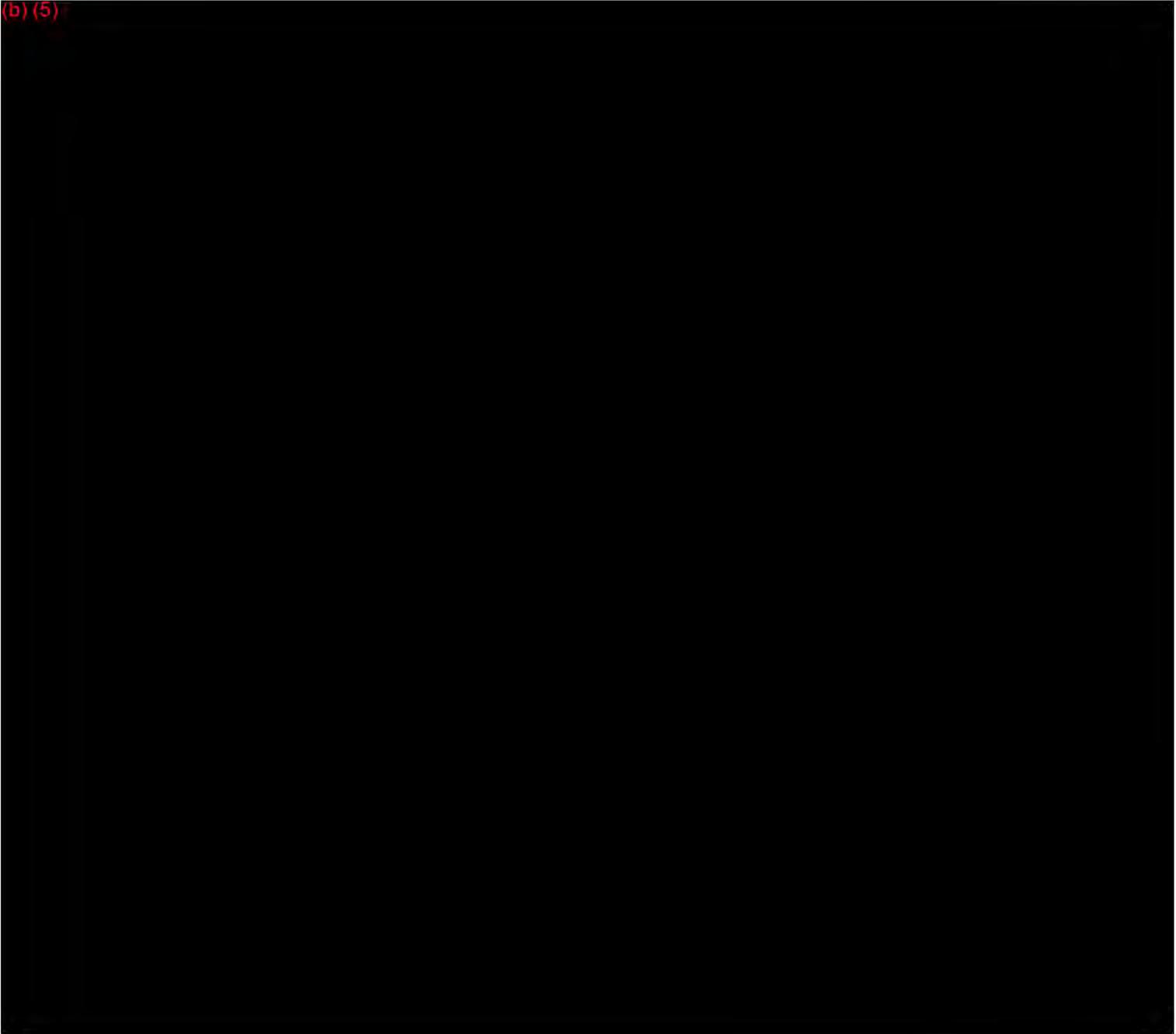
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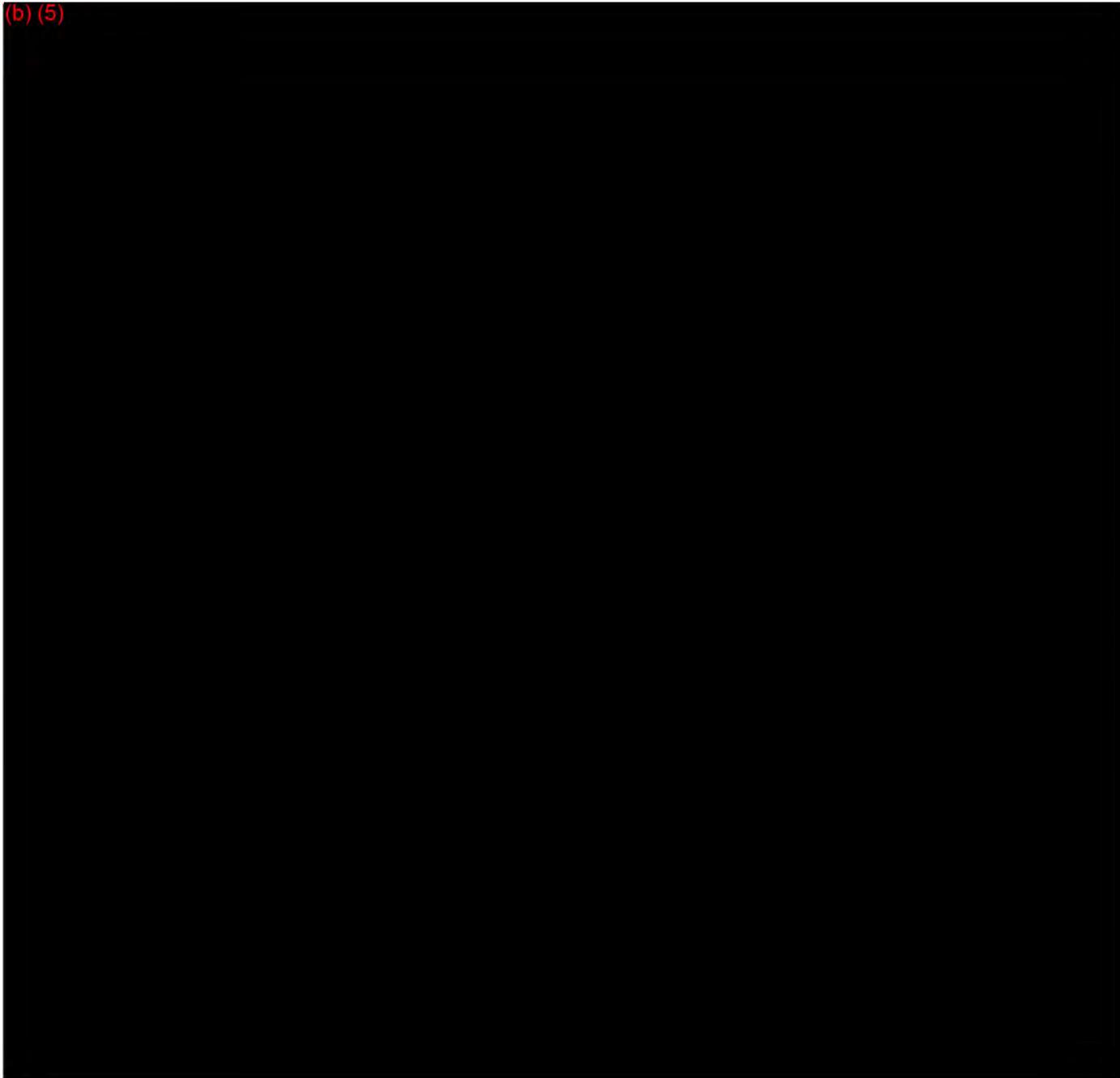
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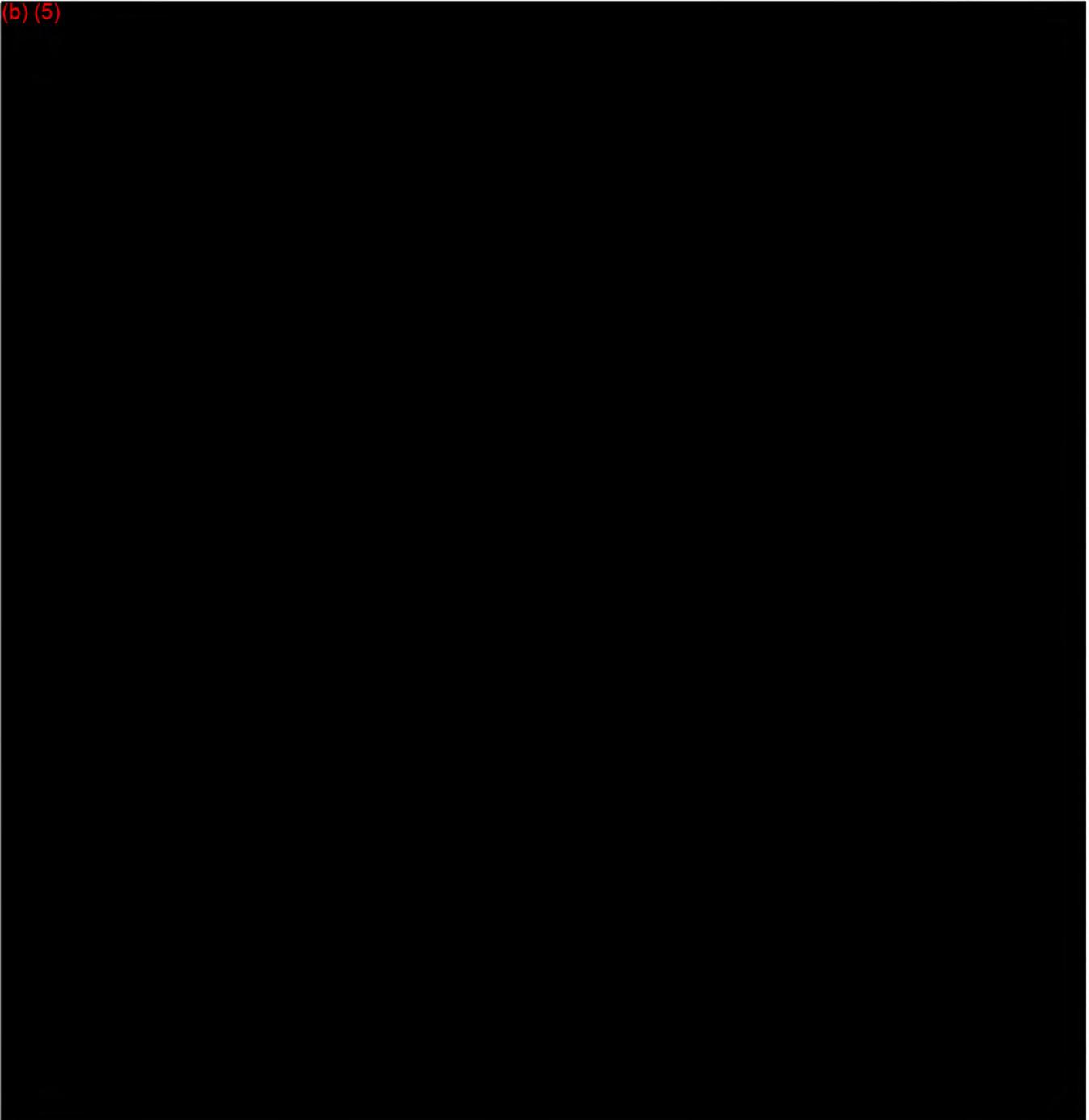
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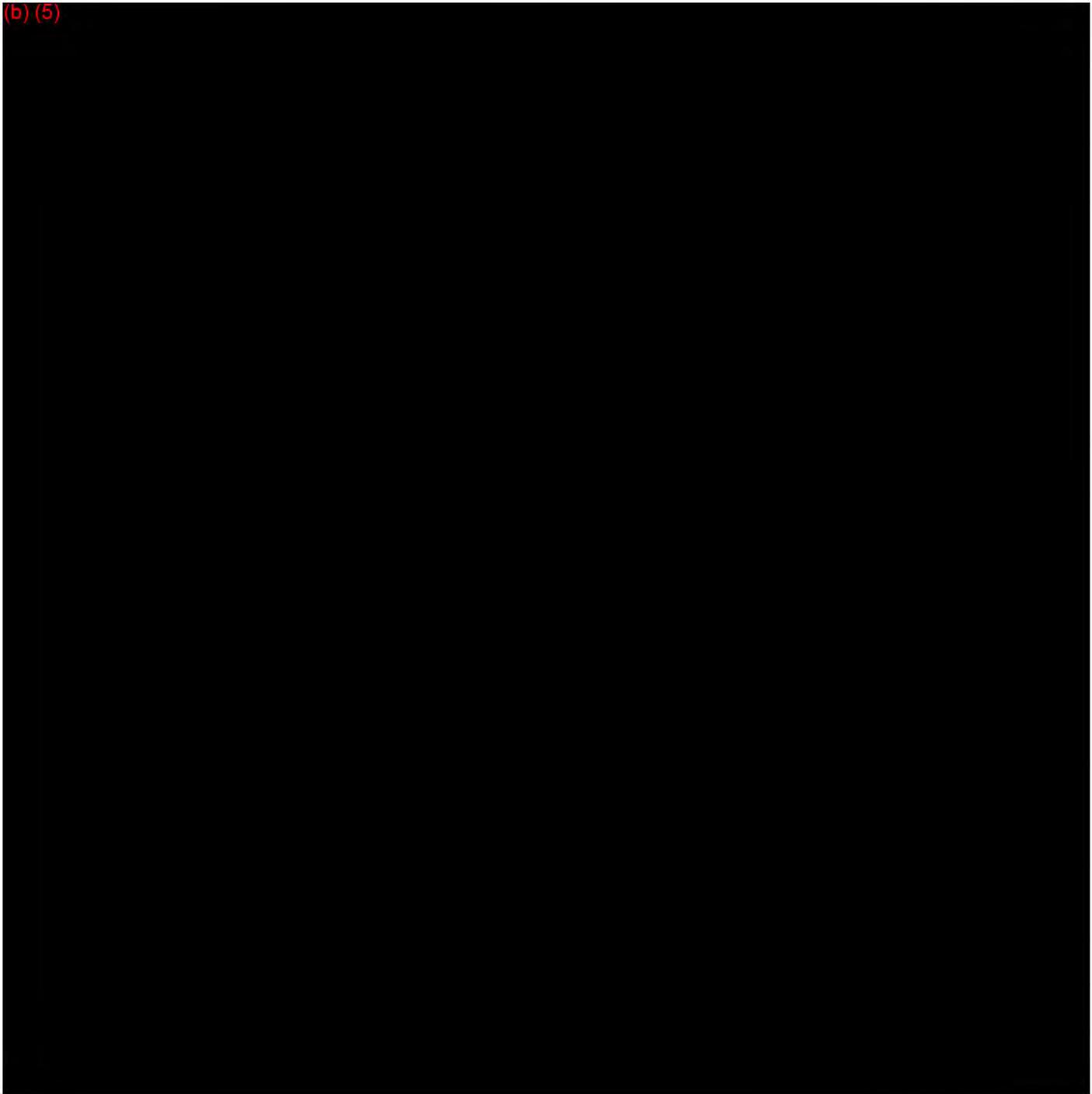
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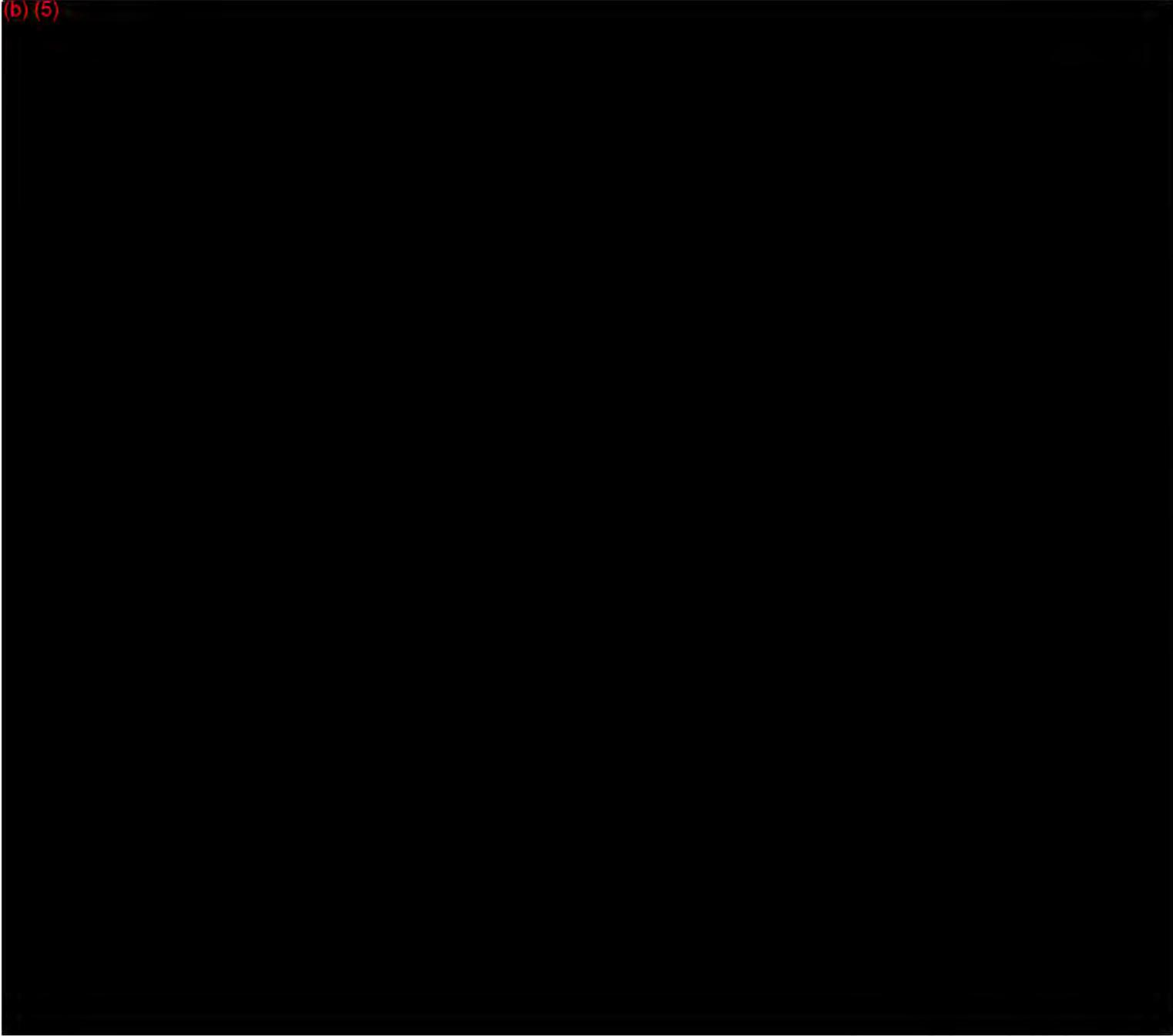
(b) (5)



(b) (5)



(b) (5)



(b) (5)



From: [Califf, Robert](#)
To: [Wohl, Alexander](#); [Rao, Gayatri](#); [Riley, Karen](#)
Subject: NORD
Date: Sunday, October 16, 2016 11:59:39 AM
Attachments: [20161016 NORD penultimate clean.doc](#)
[20161016 NORD penultimate.doc](#)

Here is a marked up and clean version for review. I'm personally very comfortable with the content but interested in any corrections/edits you might suggest.

Hope you're enjoying the day. Gayatri, note that you're now mentioned.

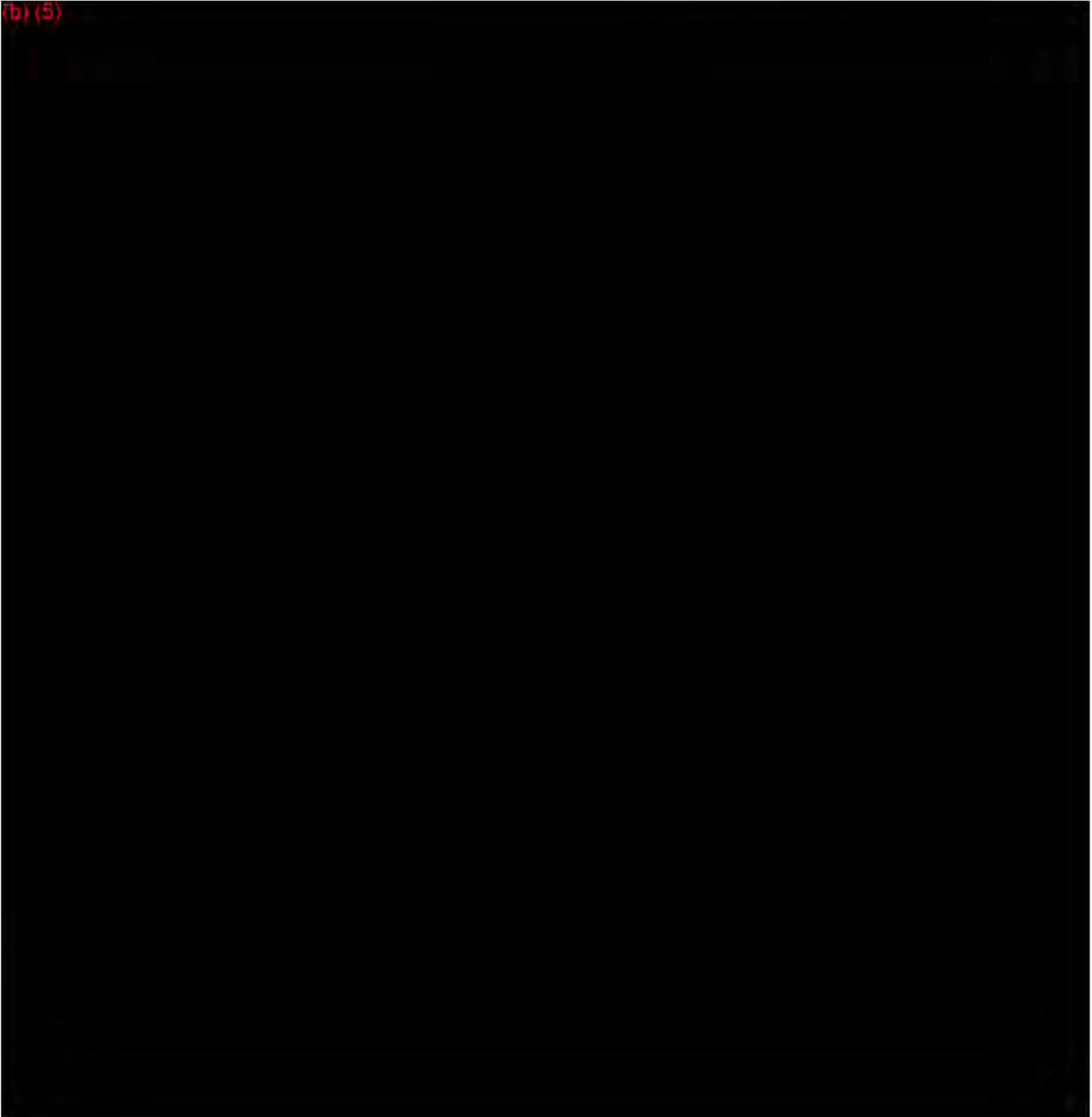
rmc

Robert M Califf MD
Commissioner of Food and Drugs

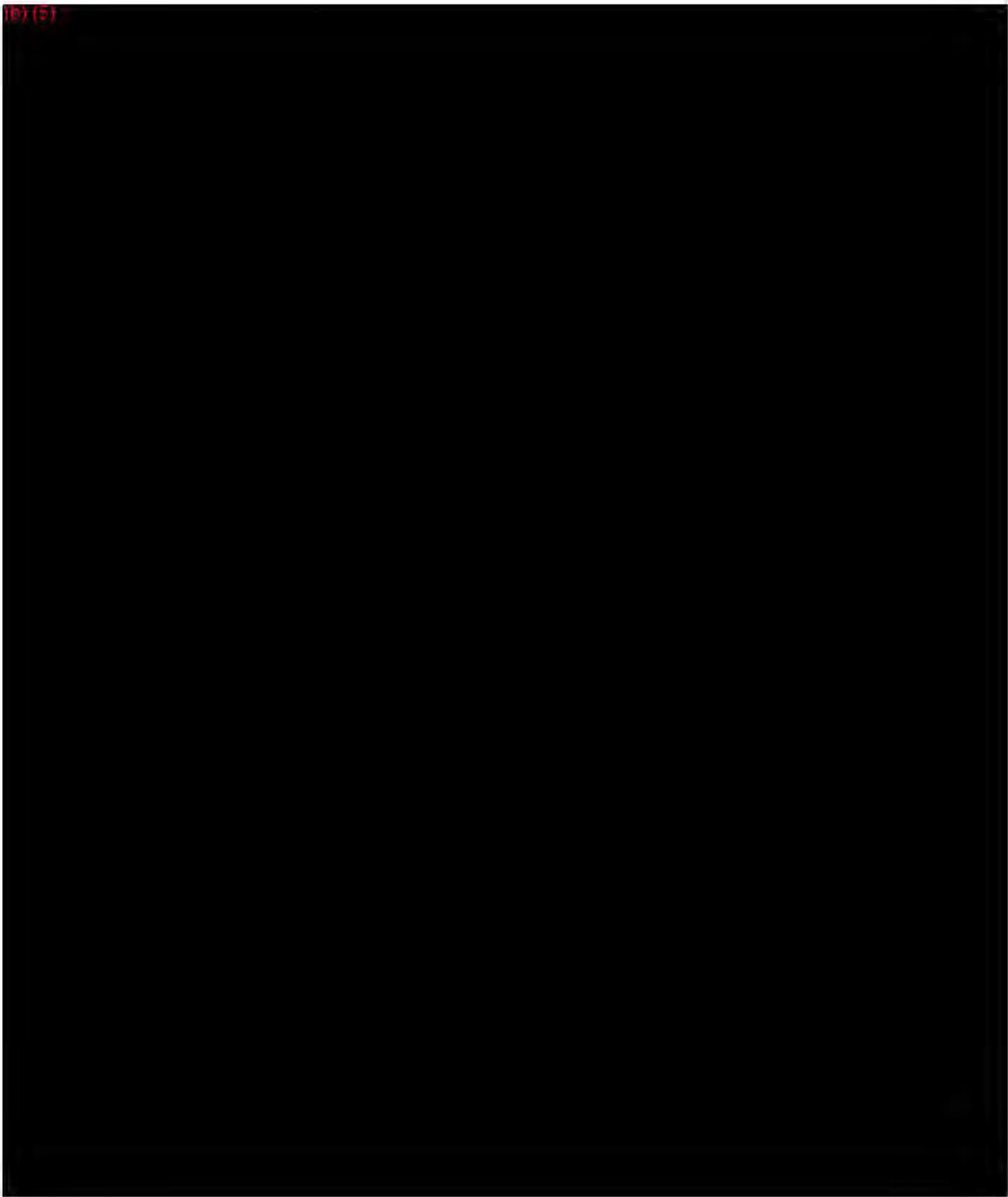
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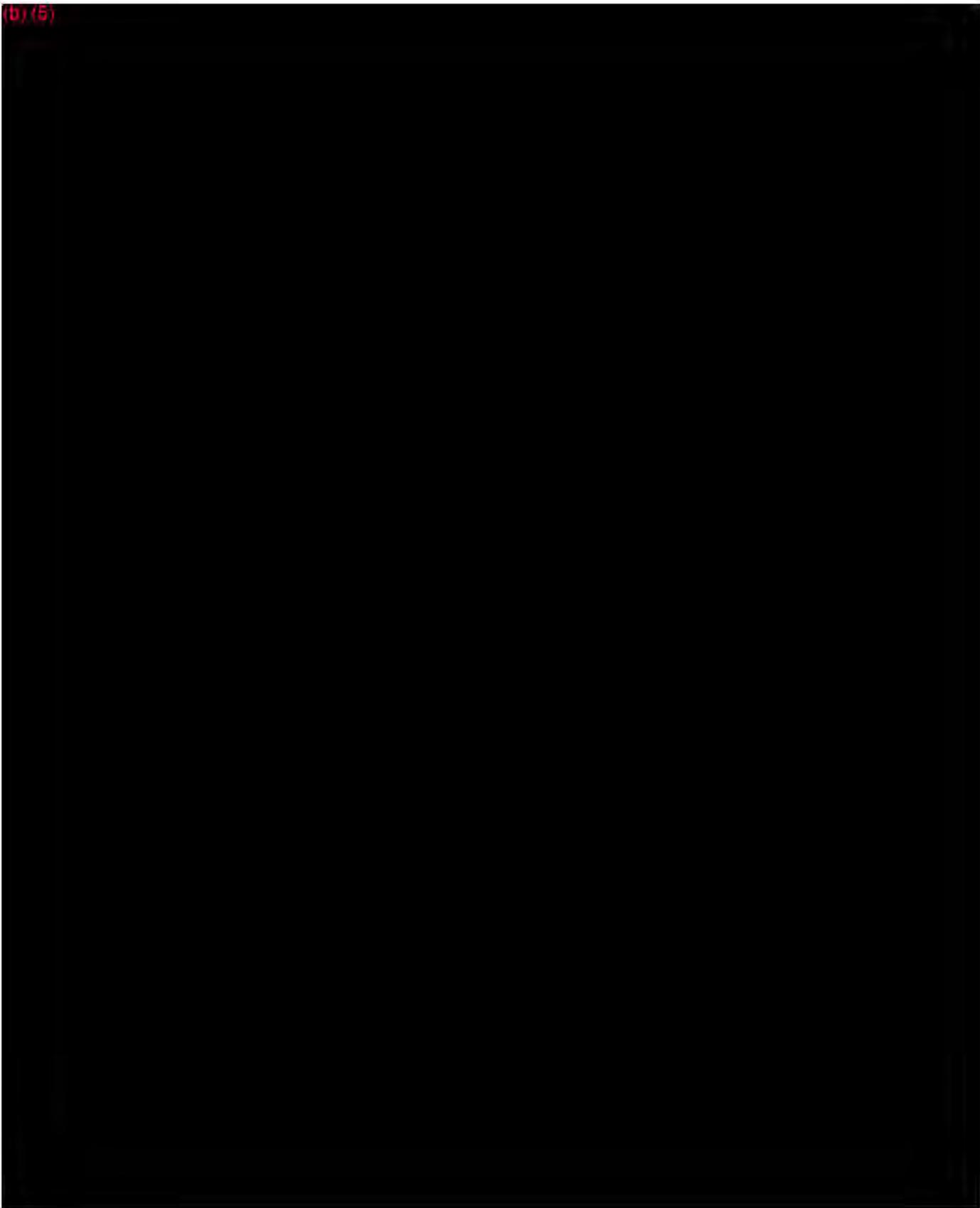
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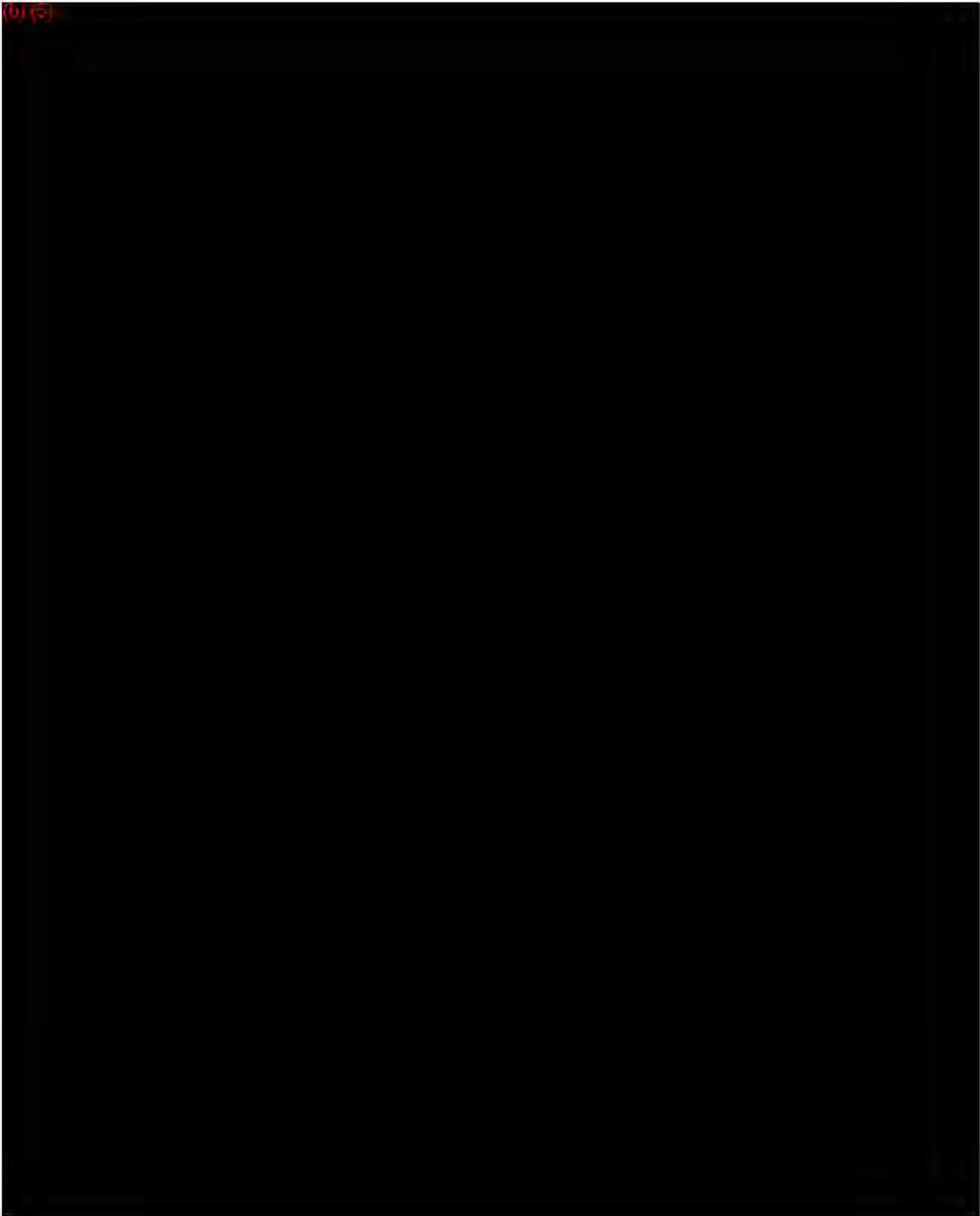
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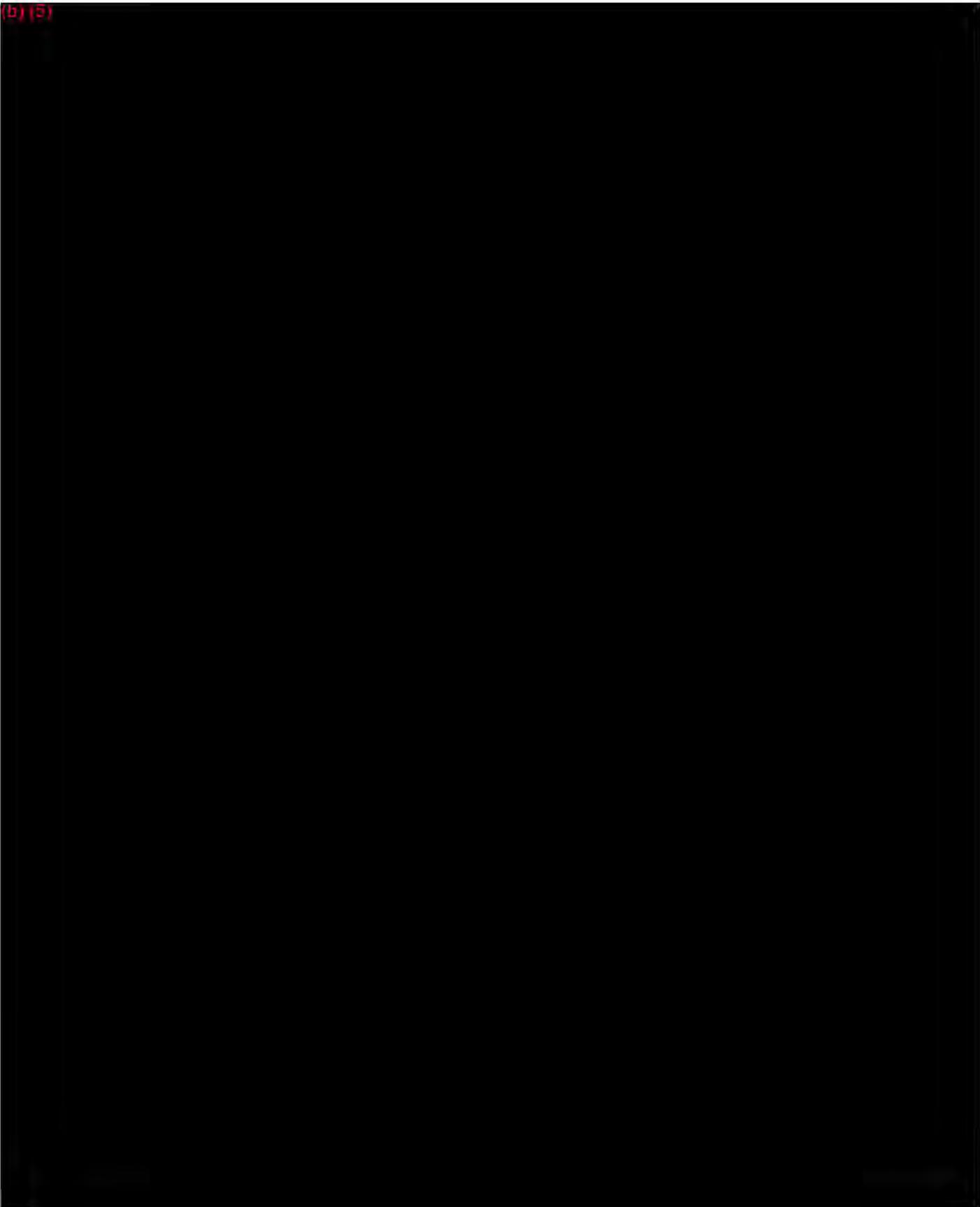
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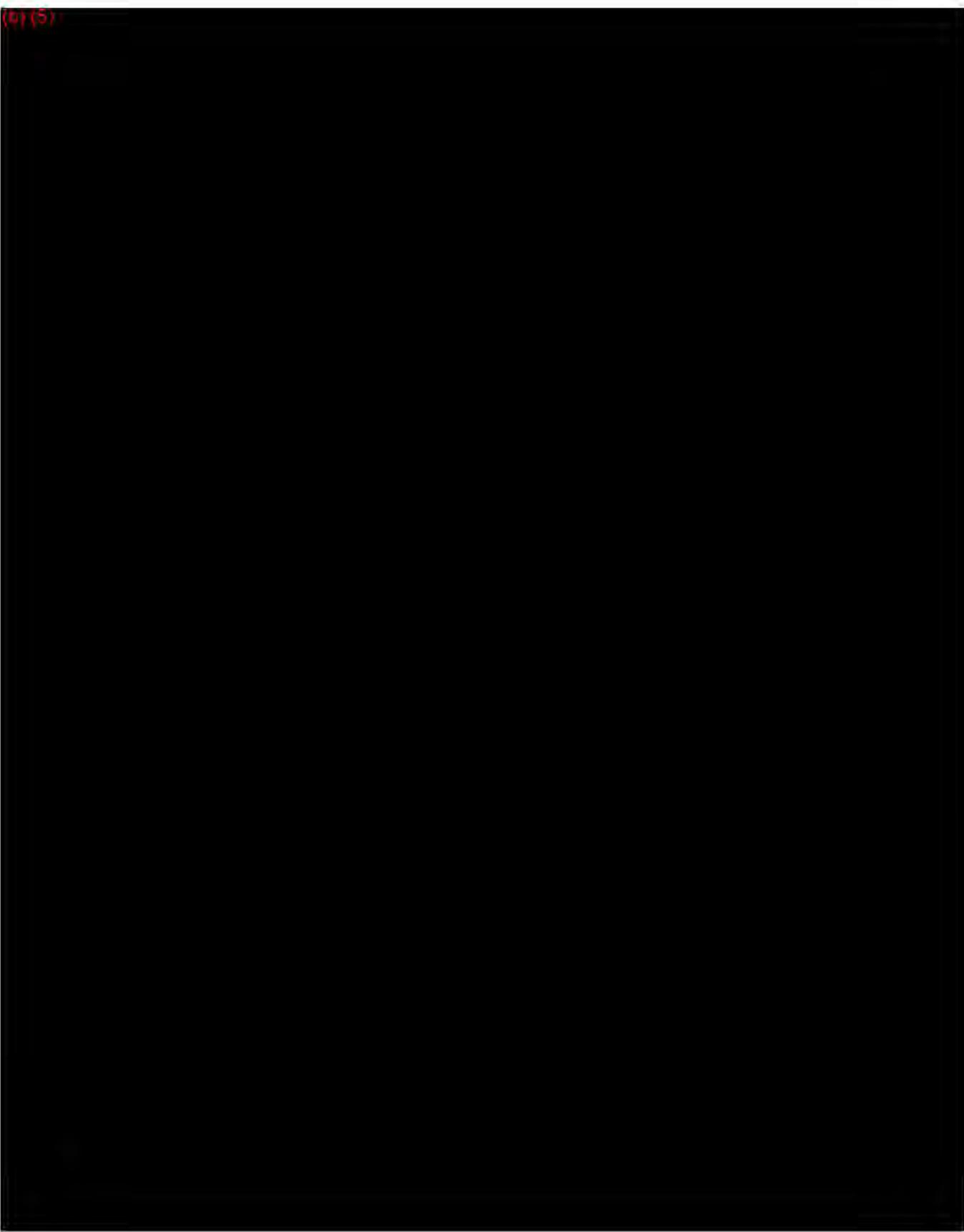
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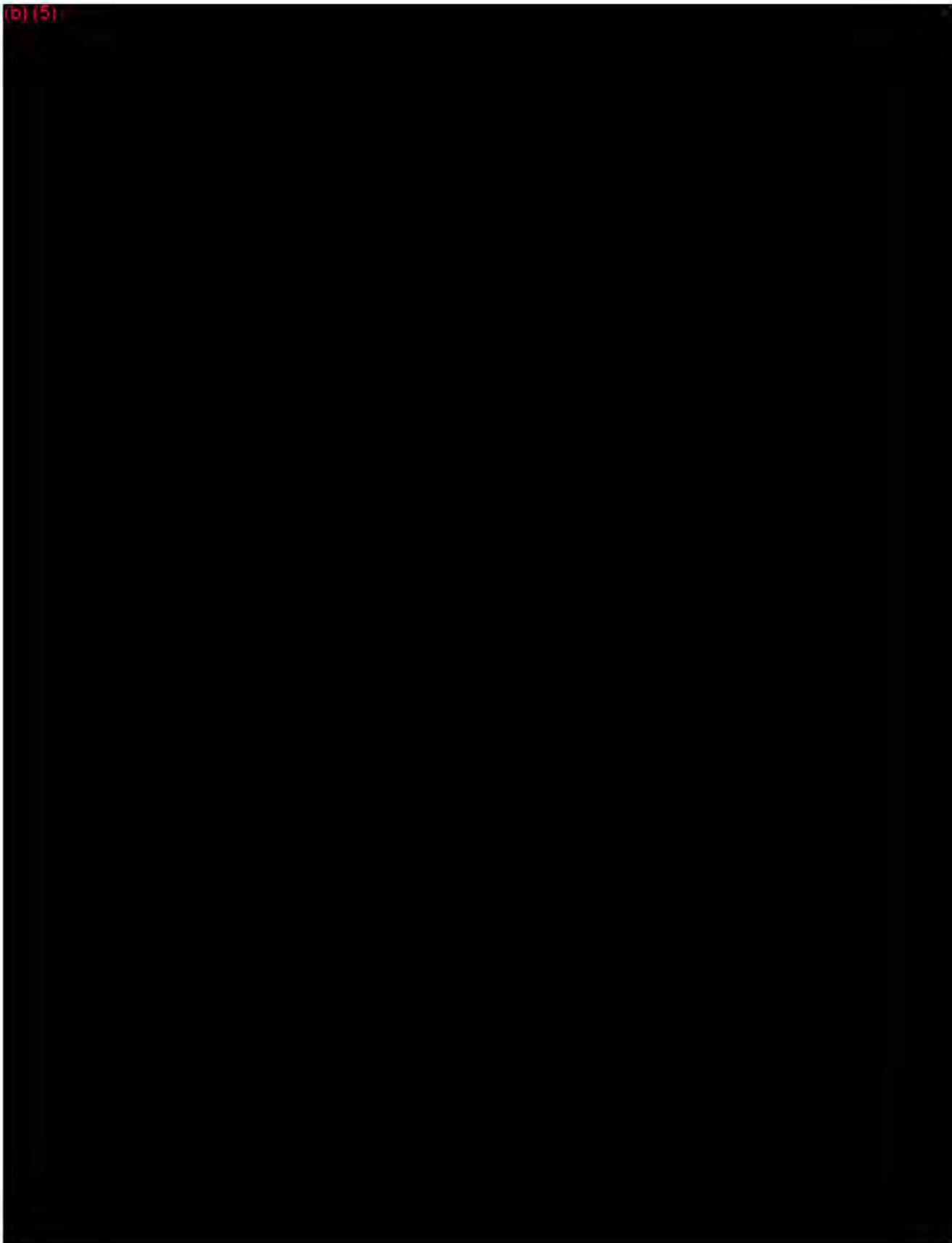
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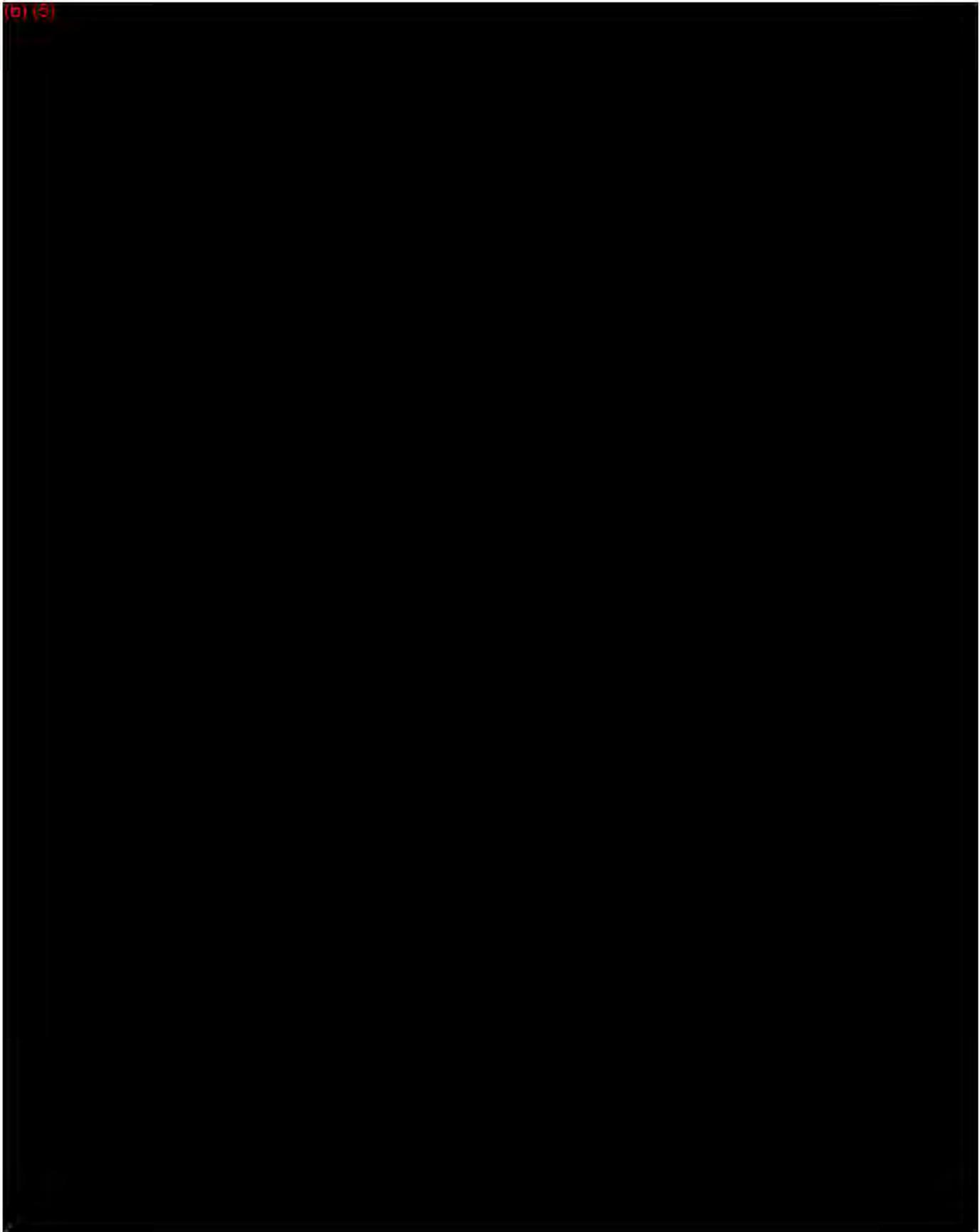
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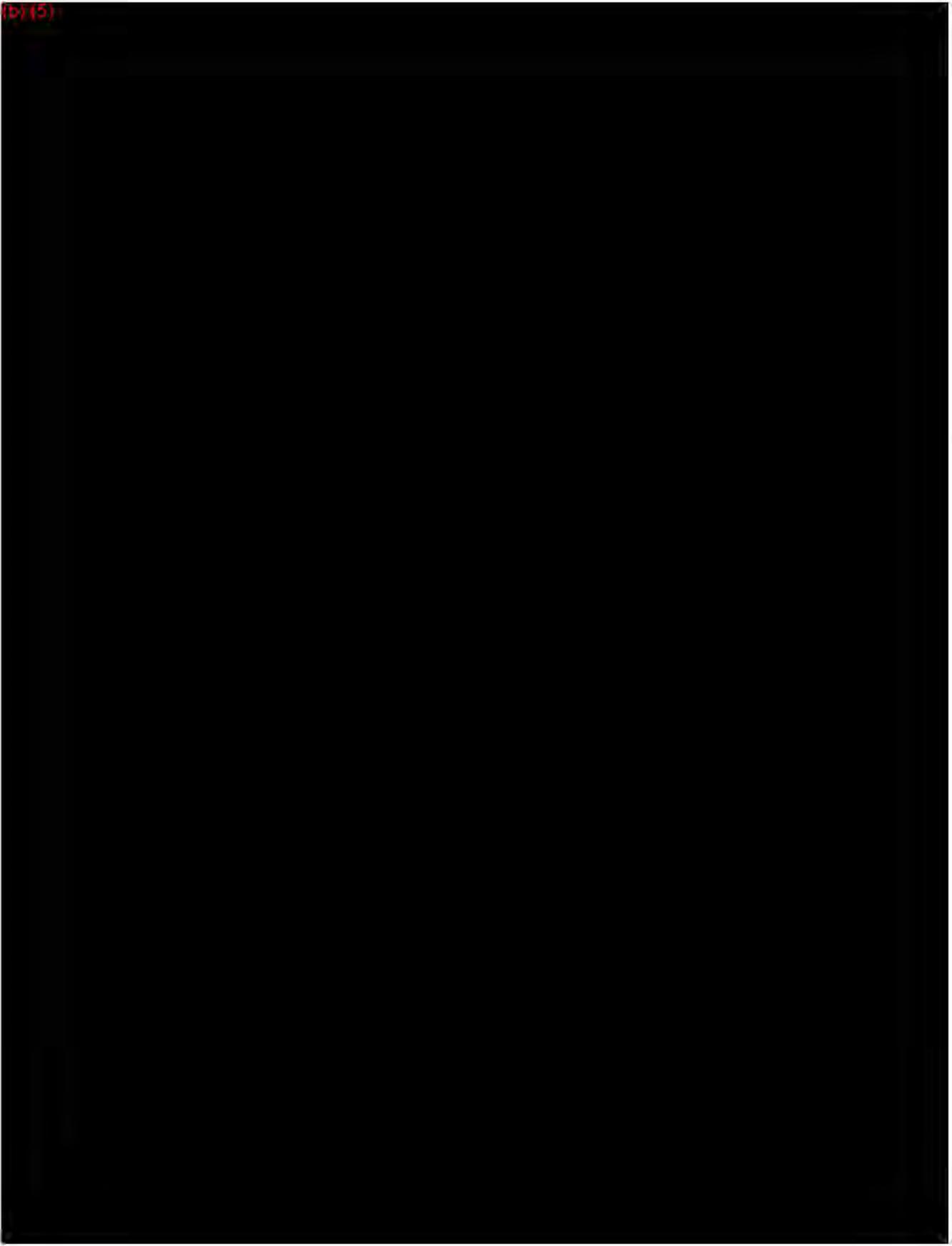
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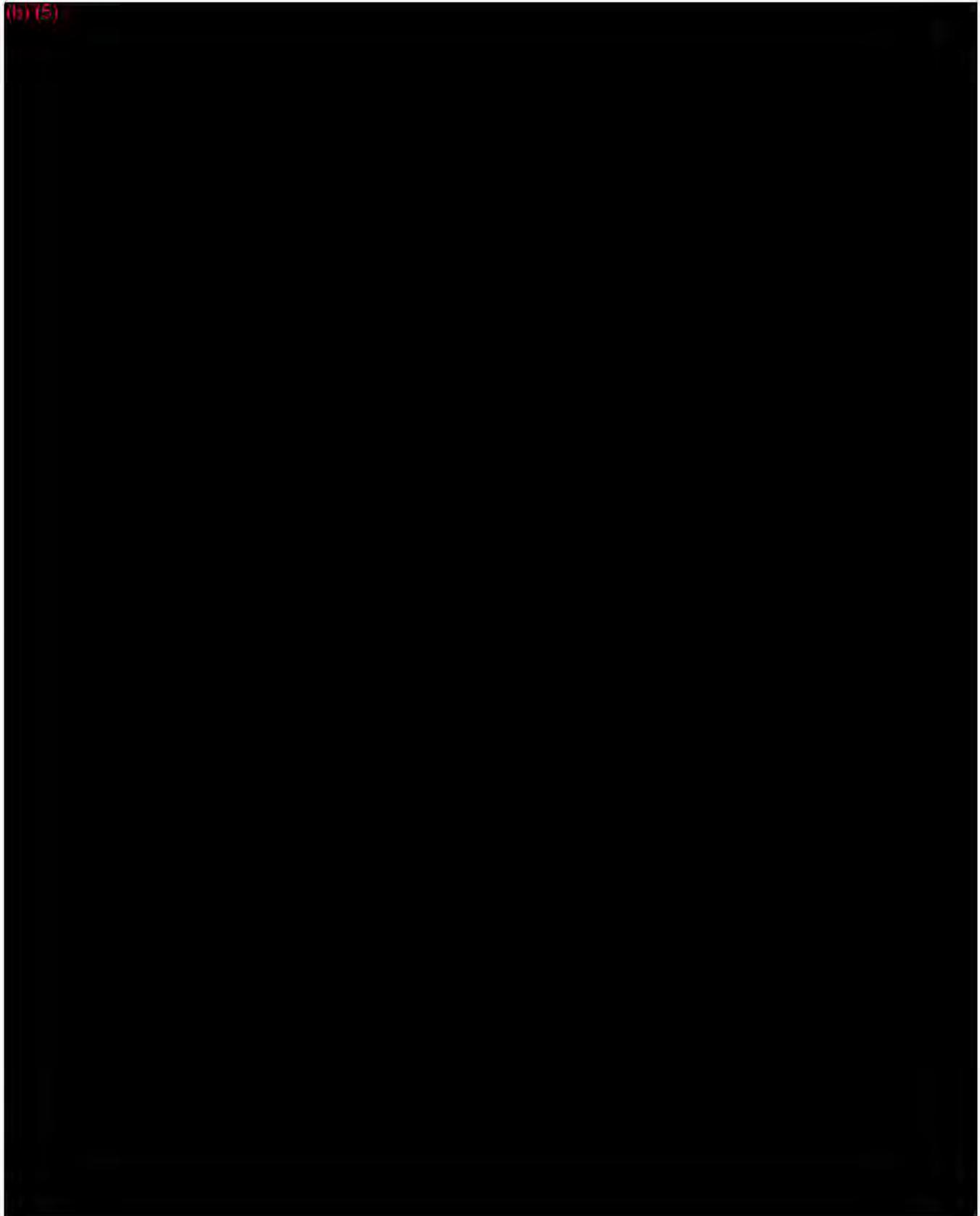
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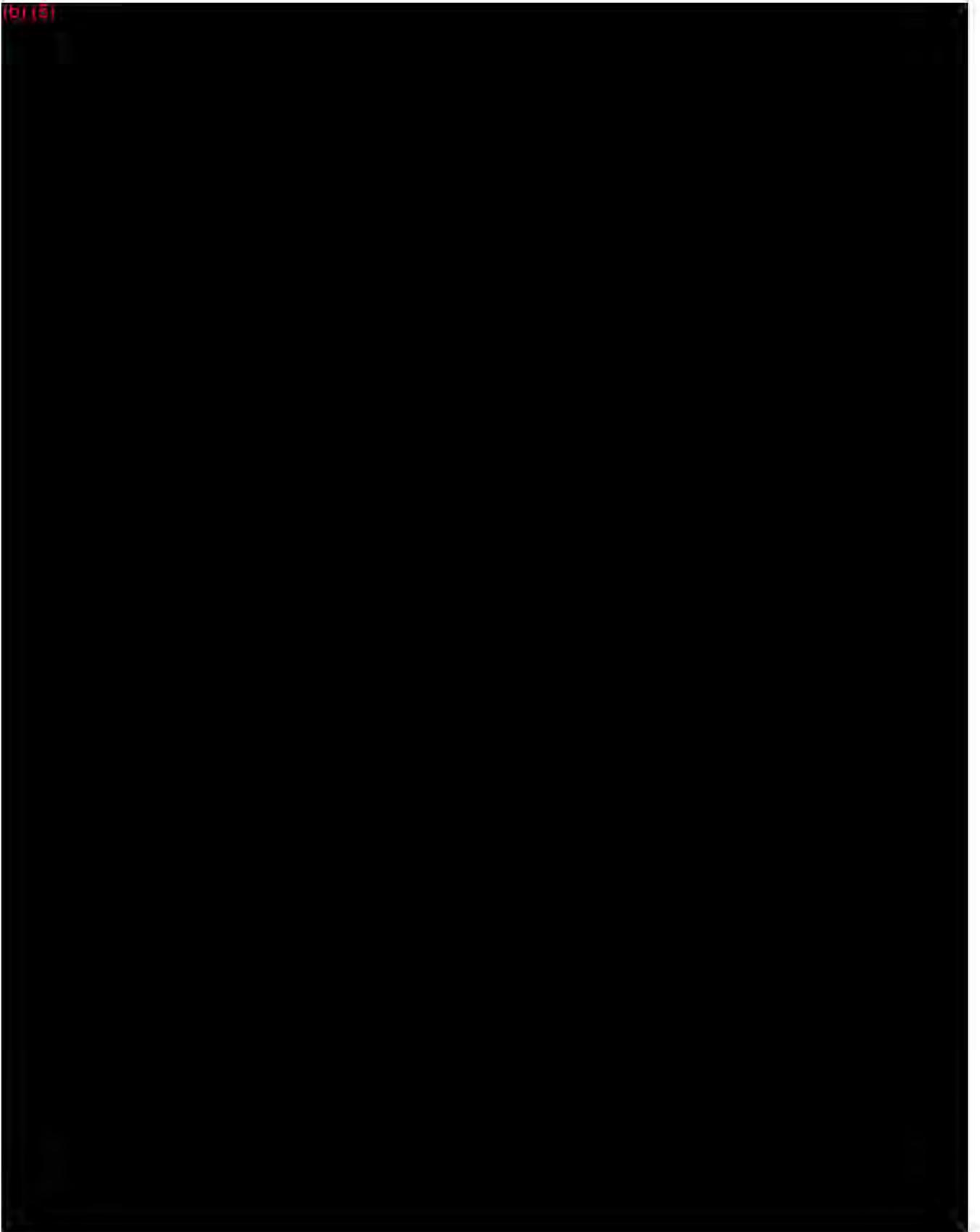
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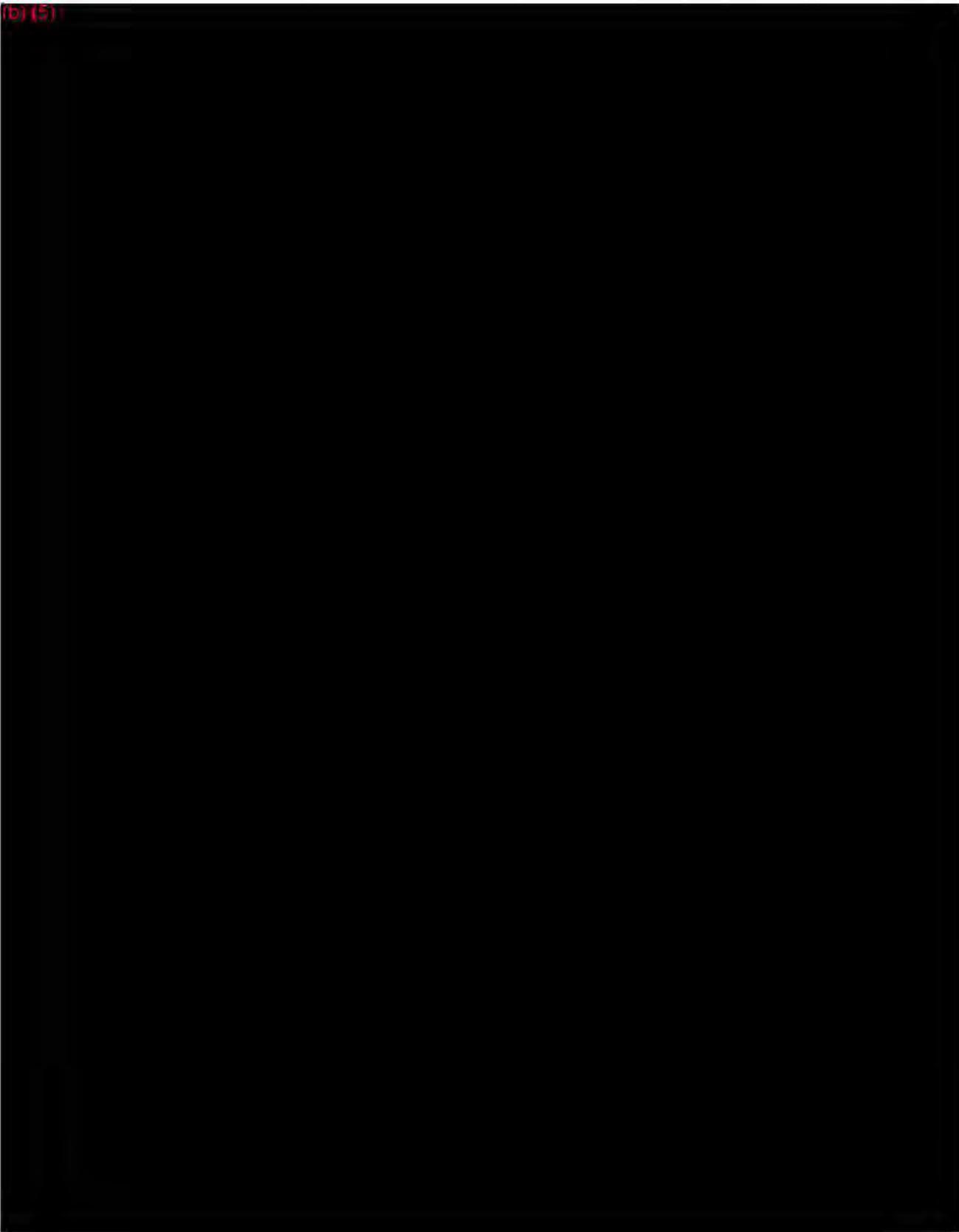
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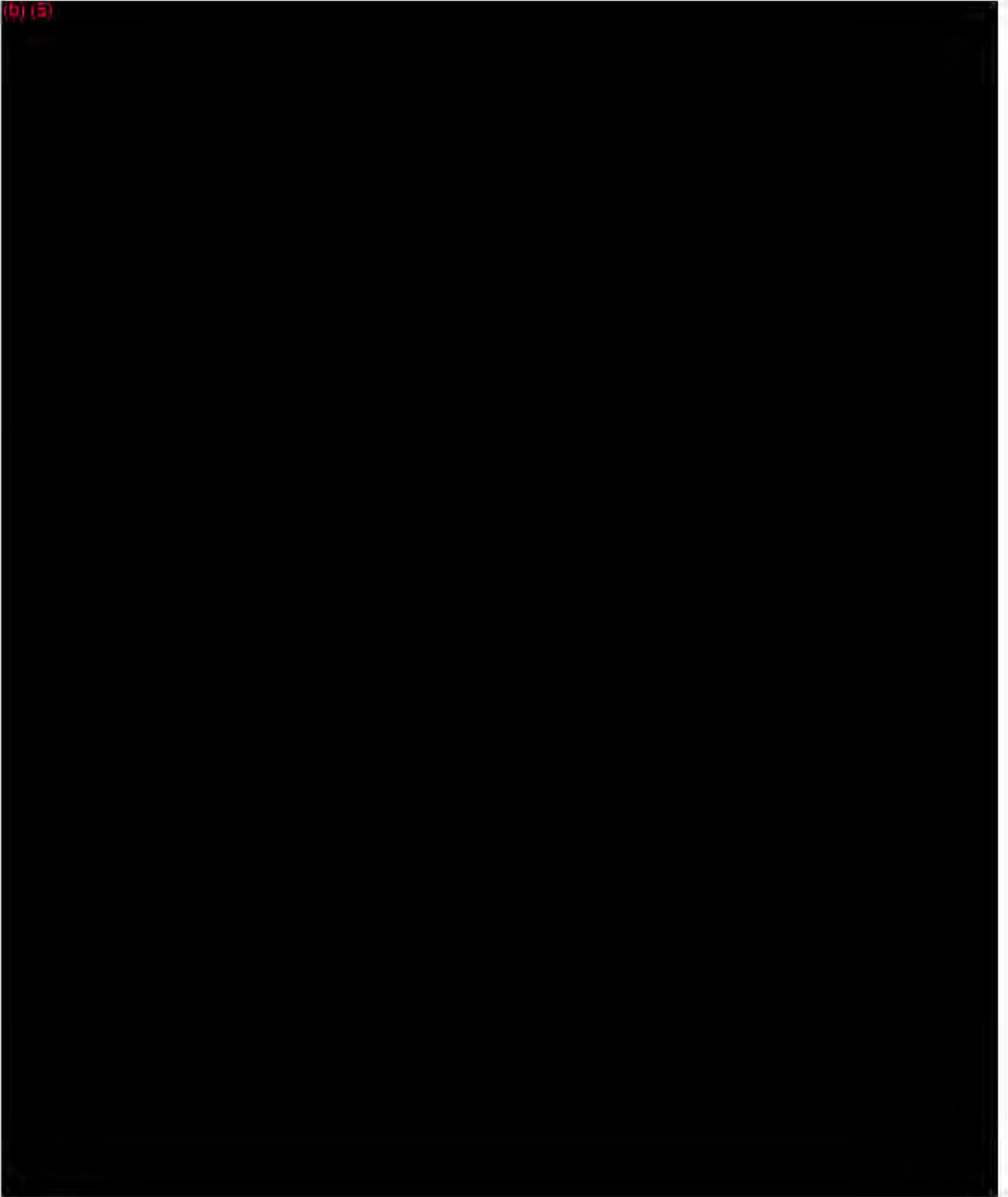
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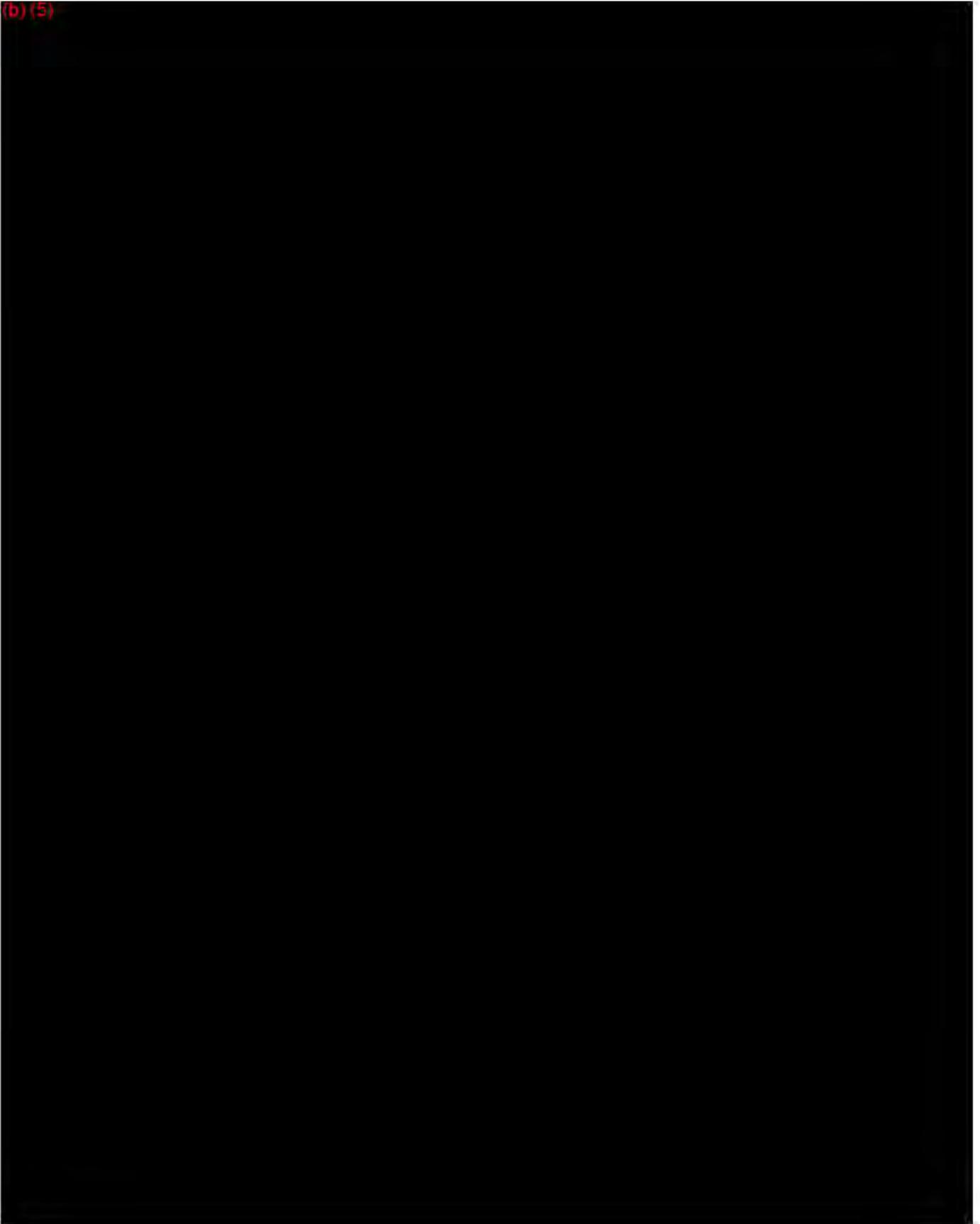
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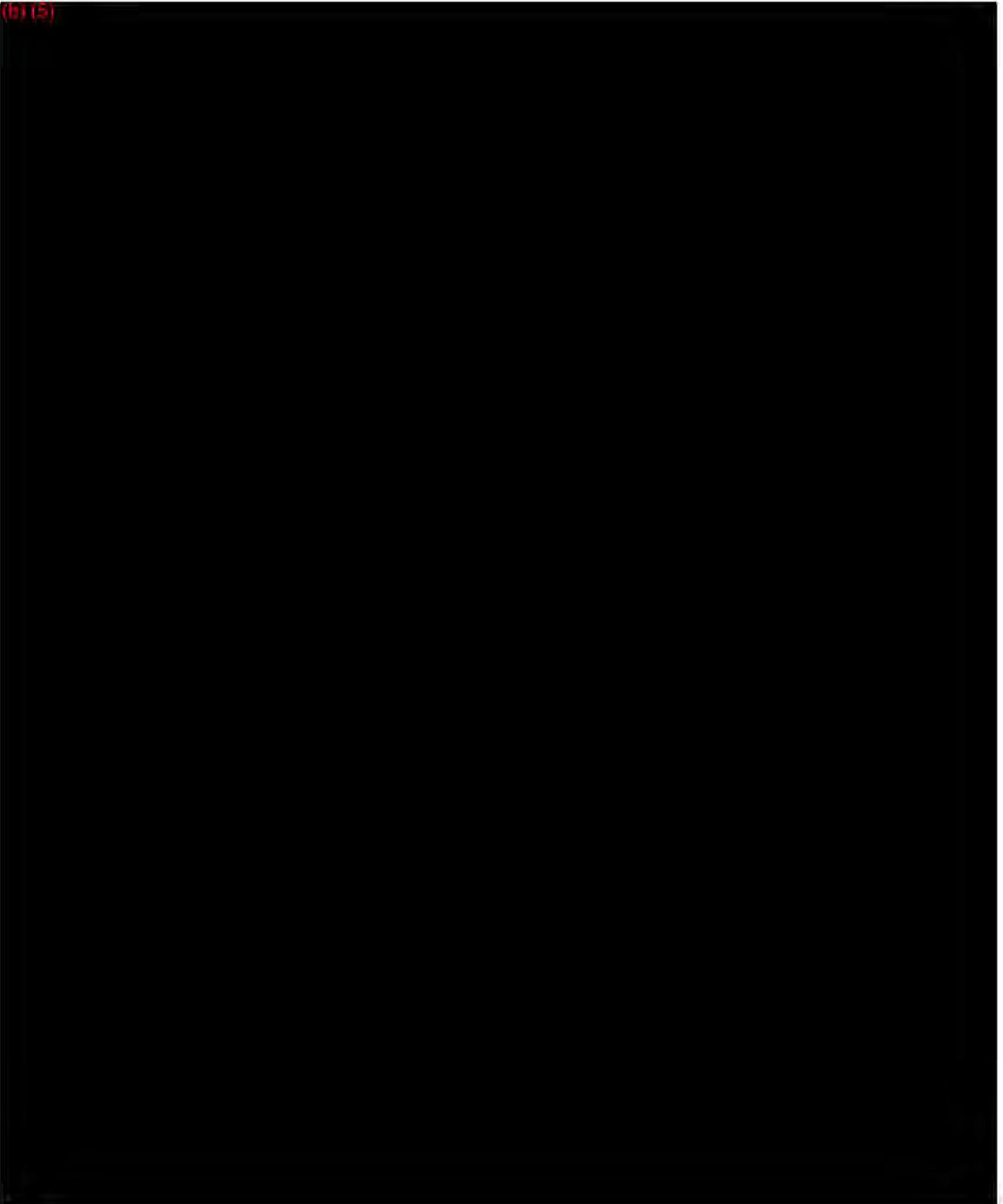
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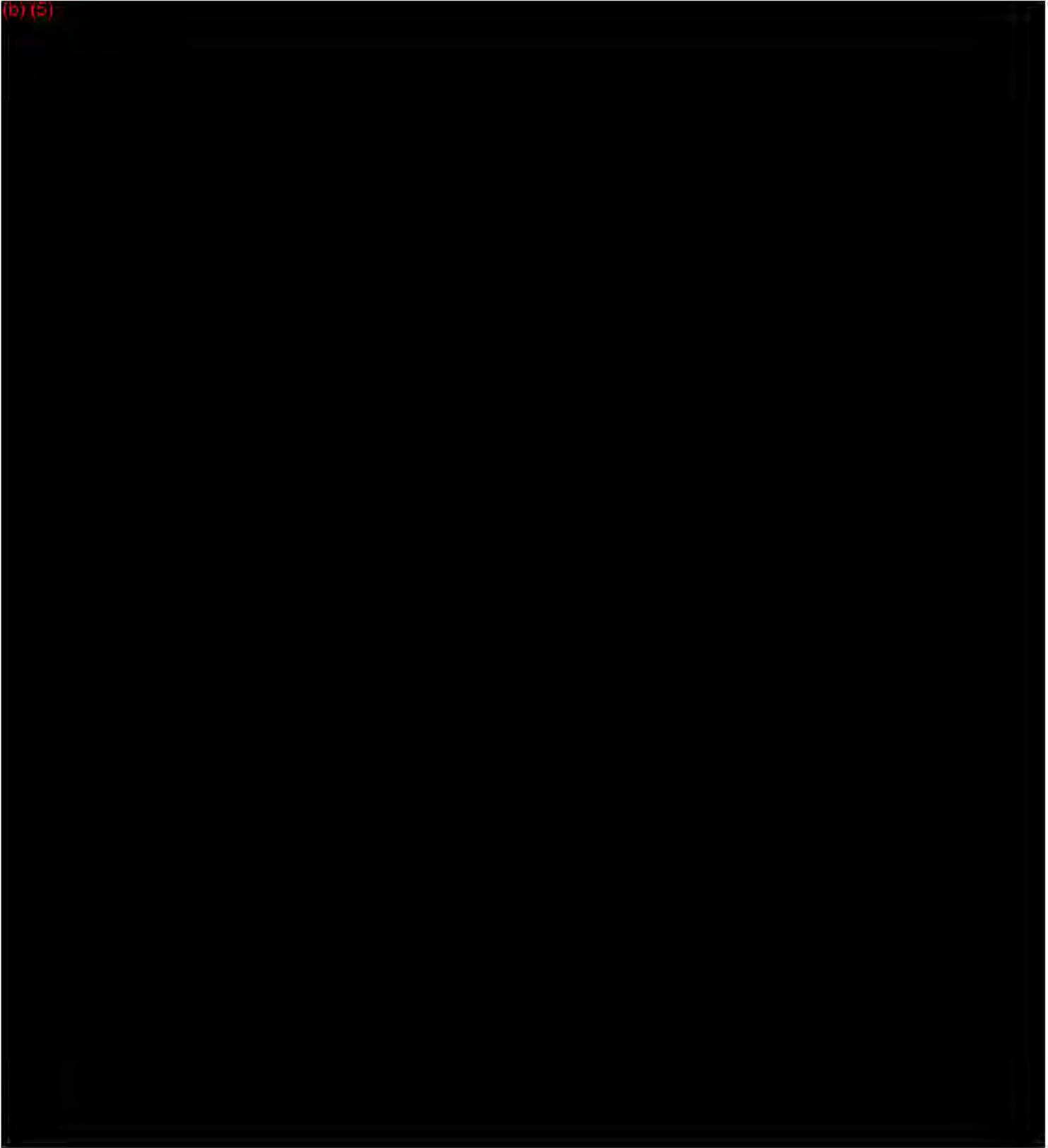
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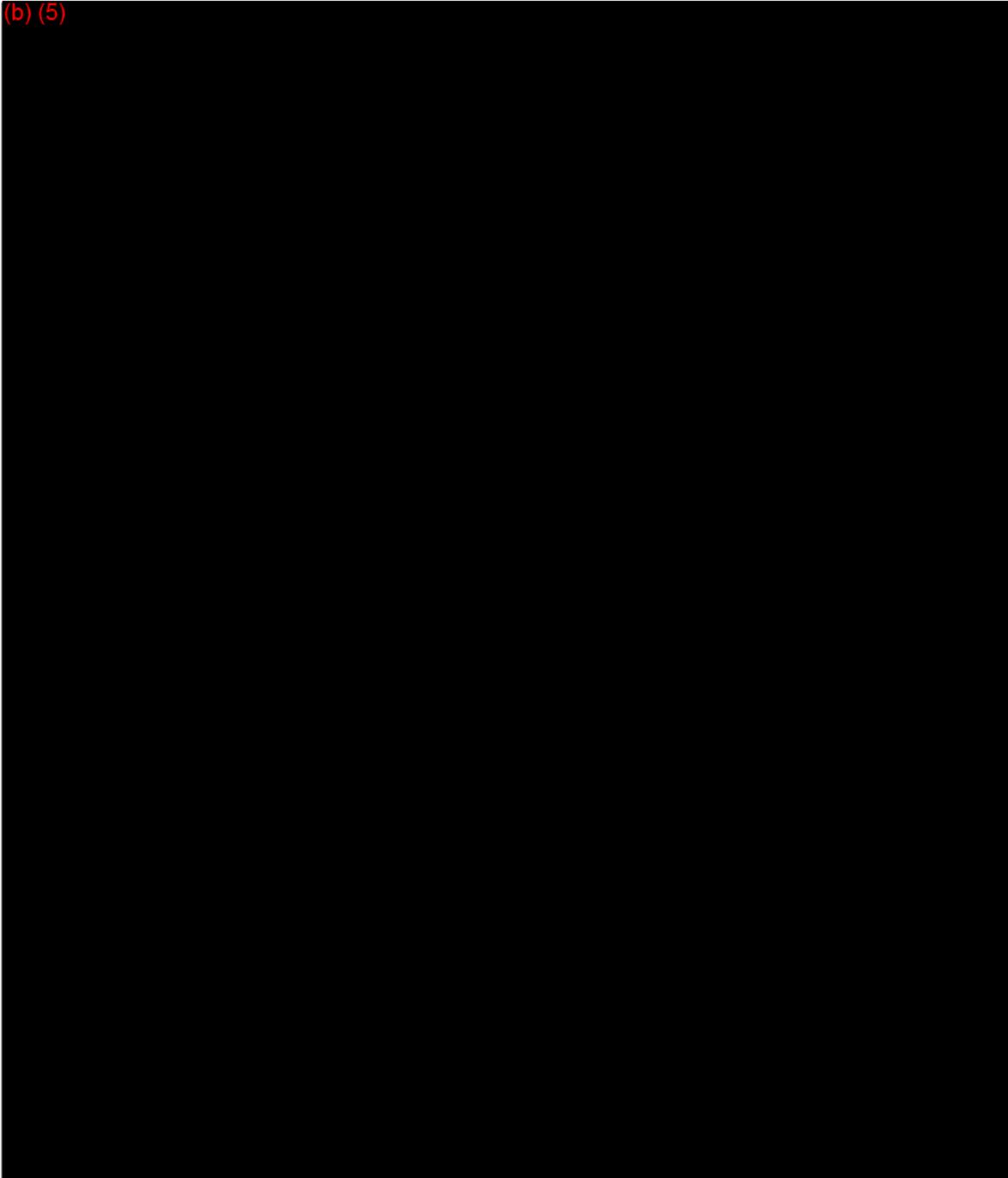
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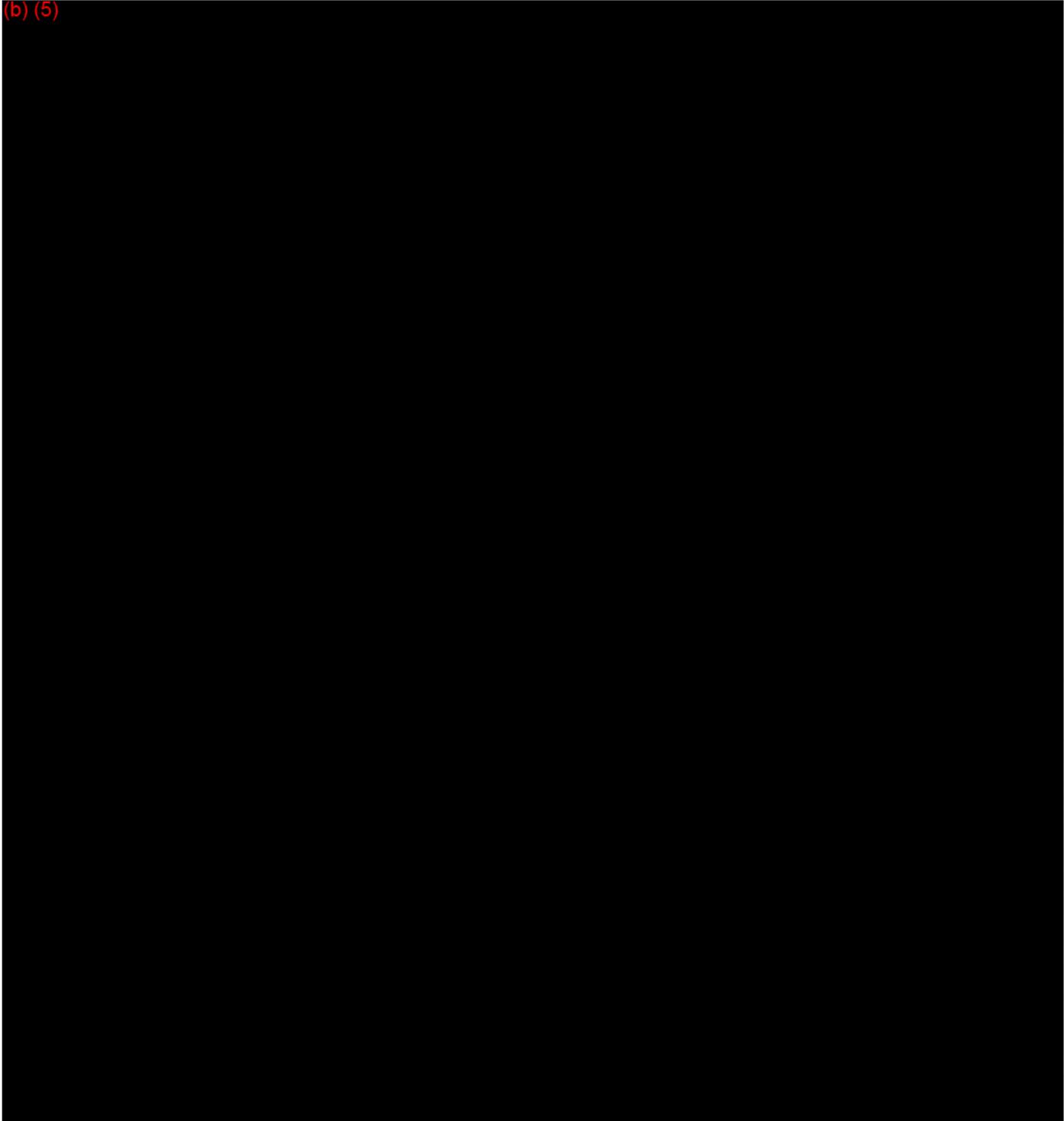
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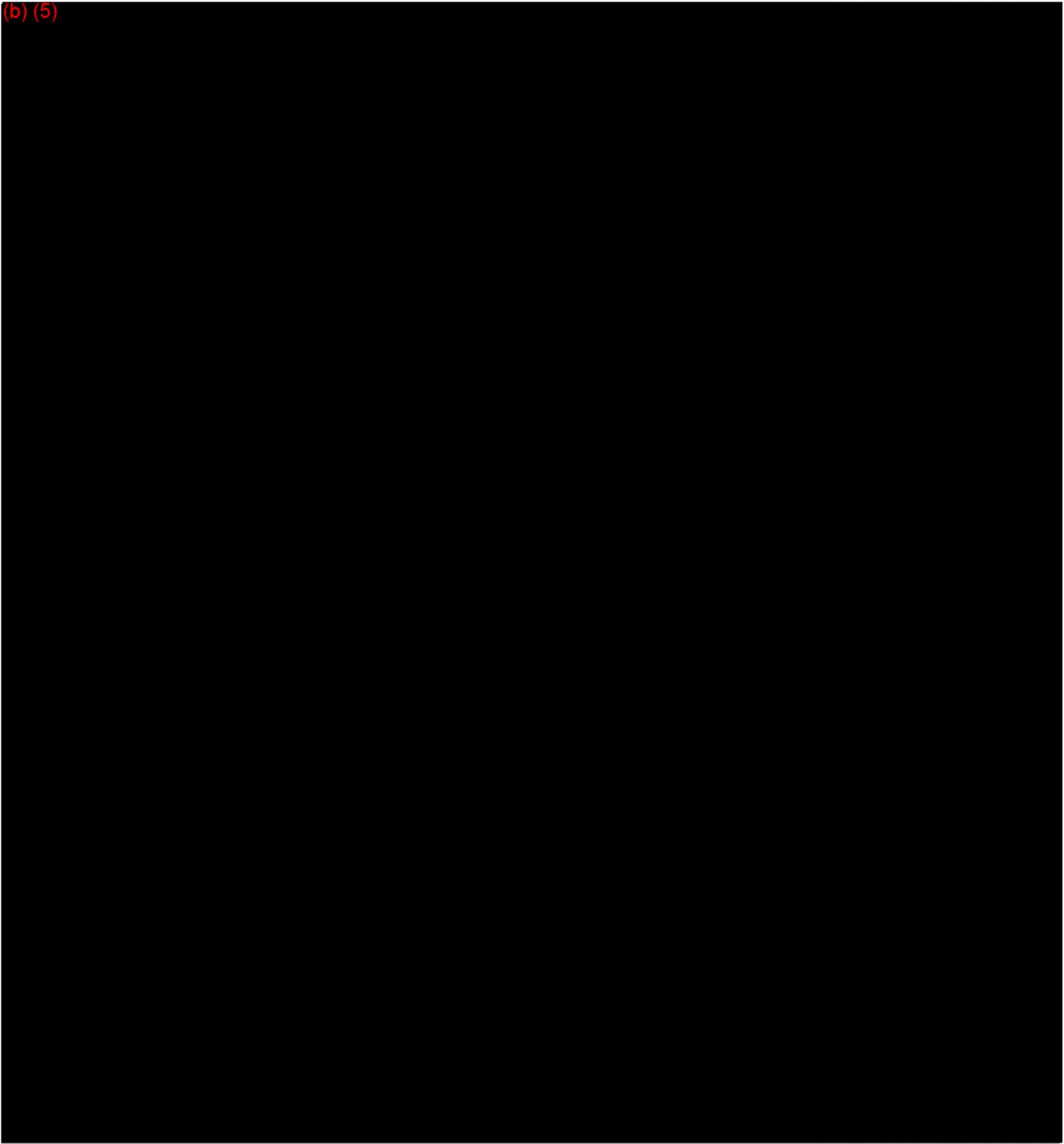
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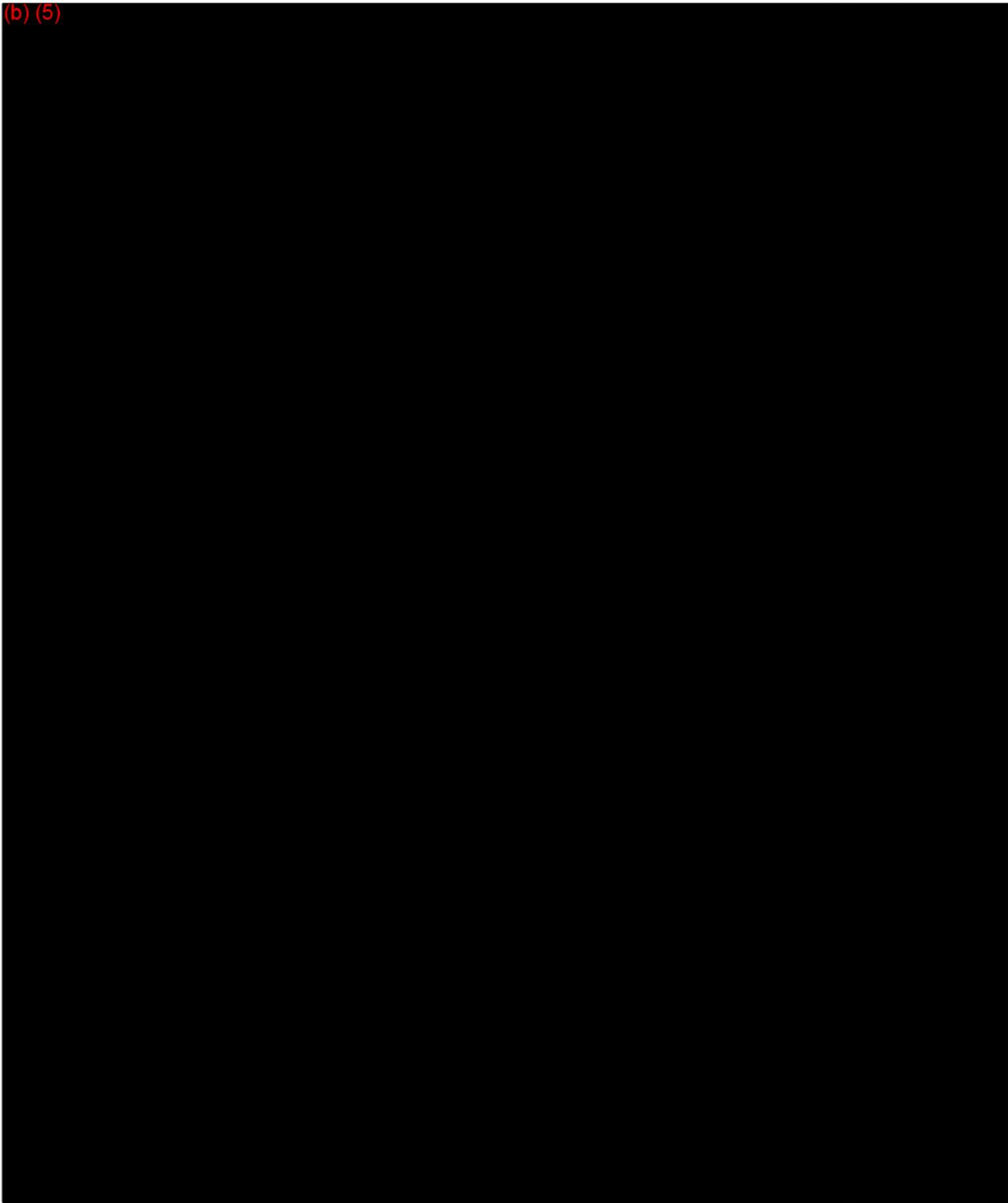
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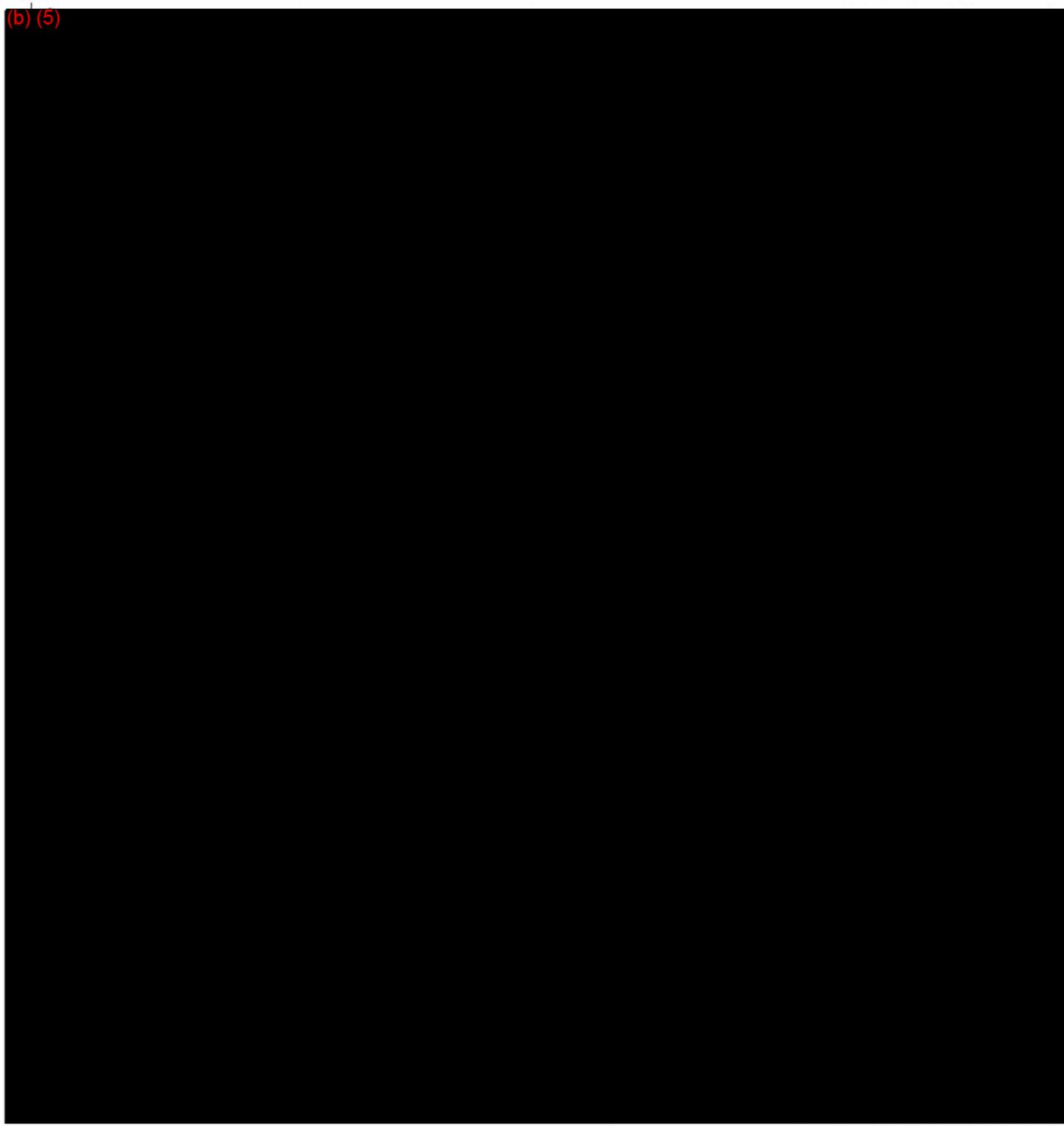
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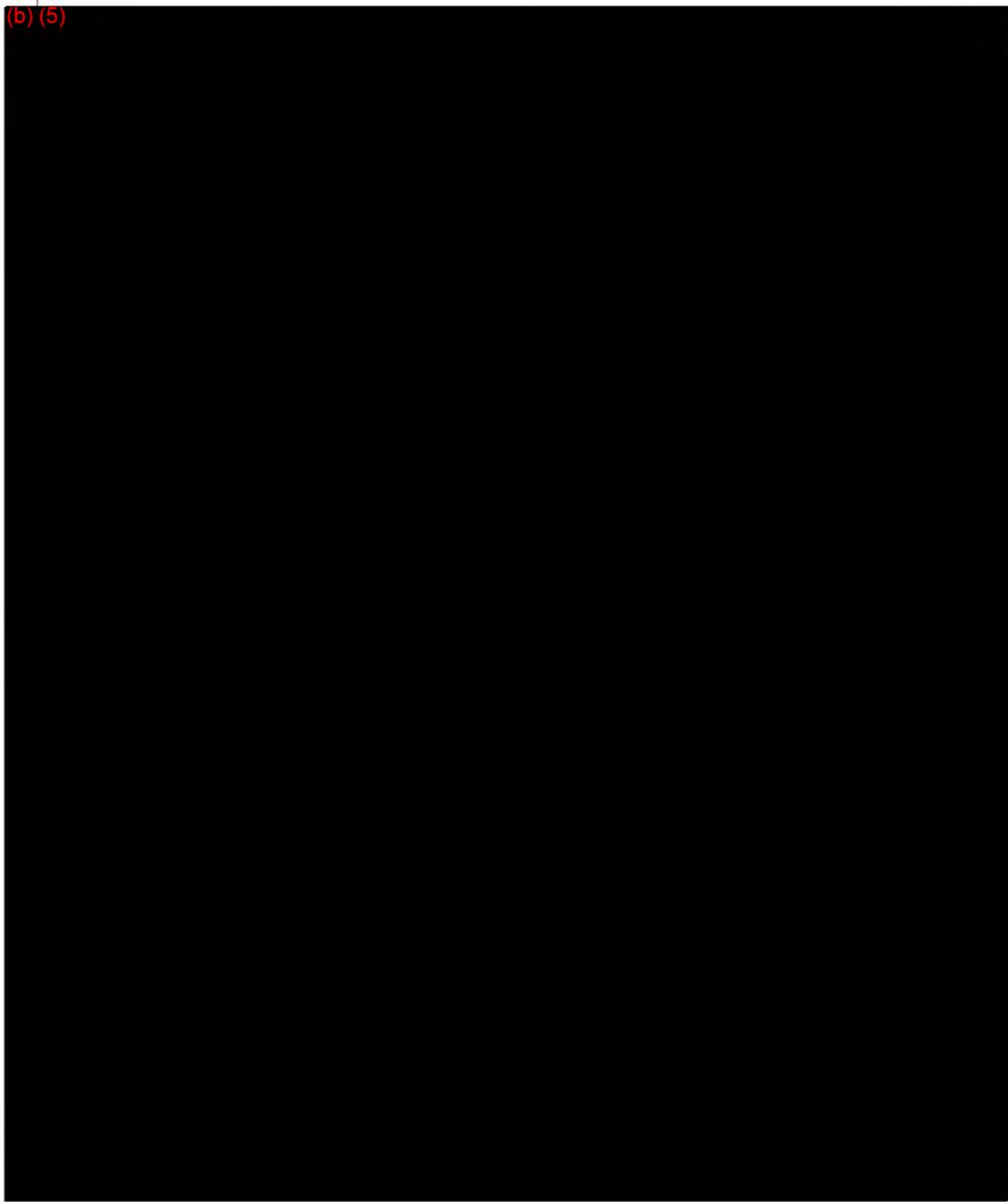
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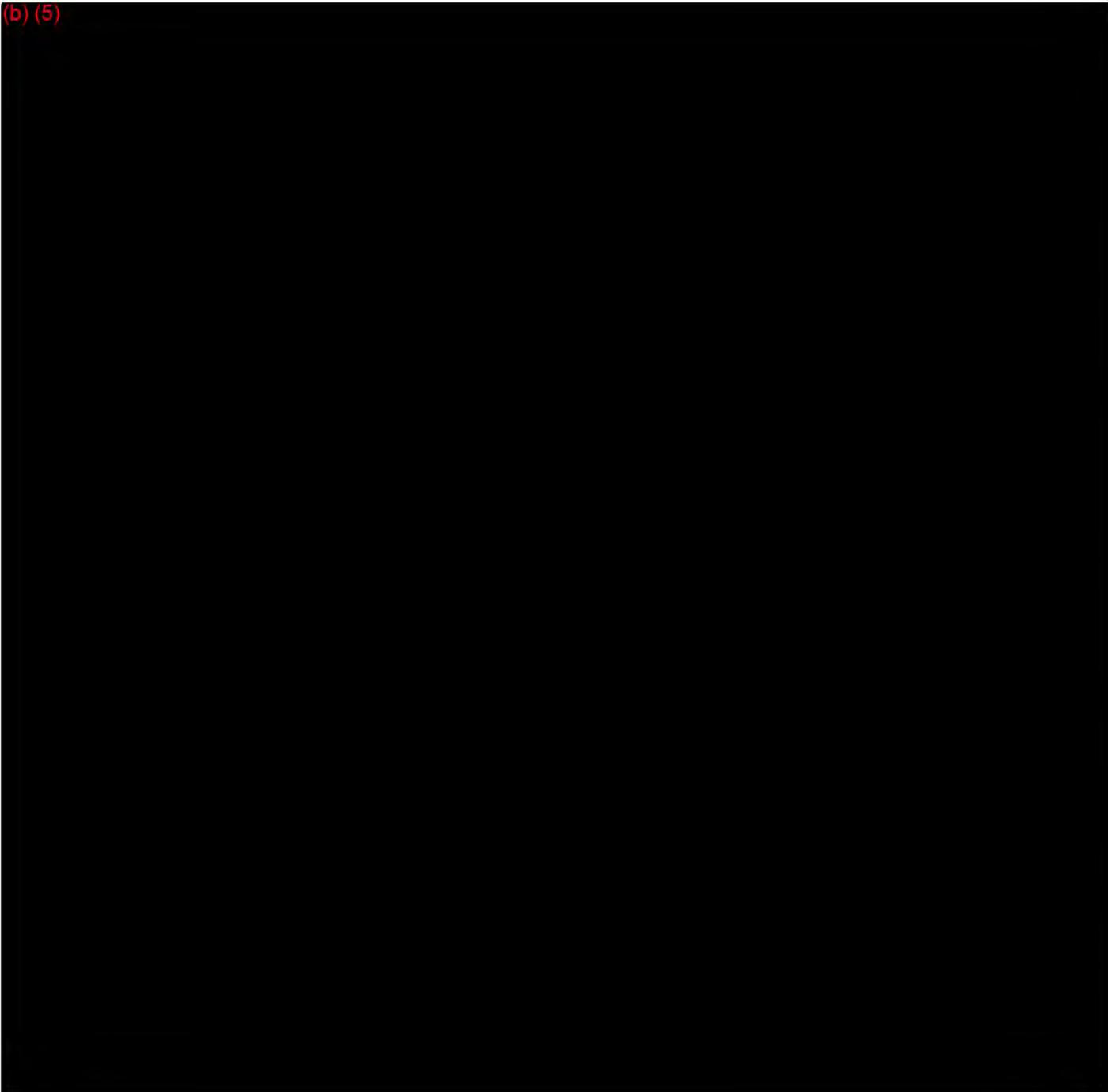
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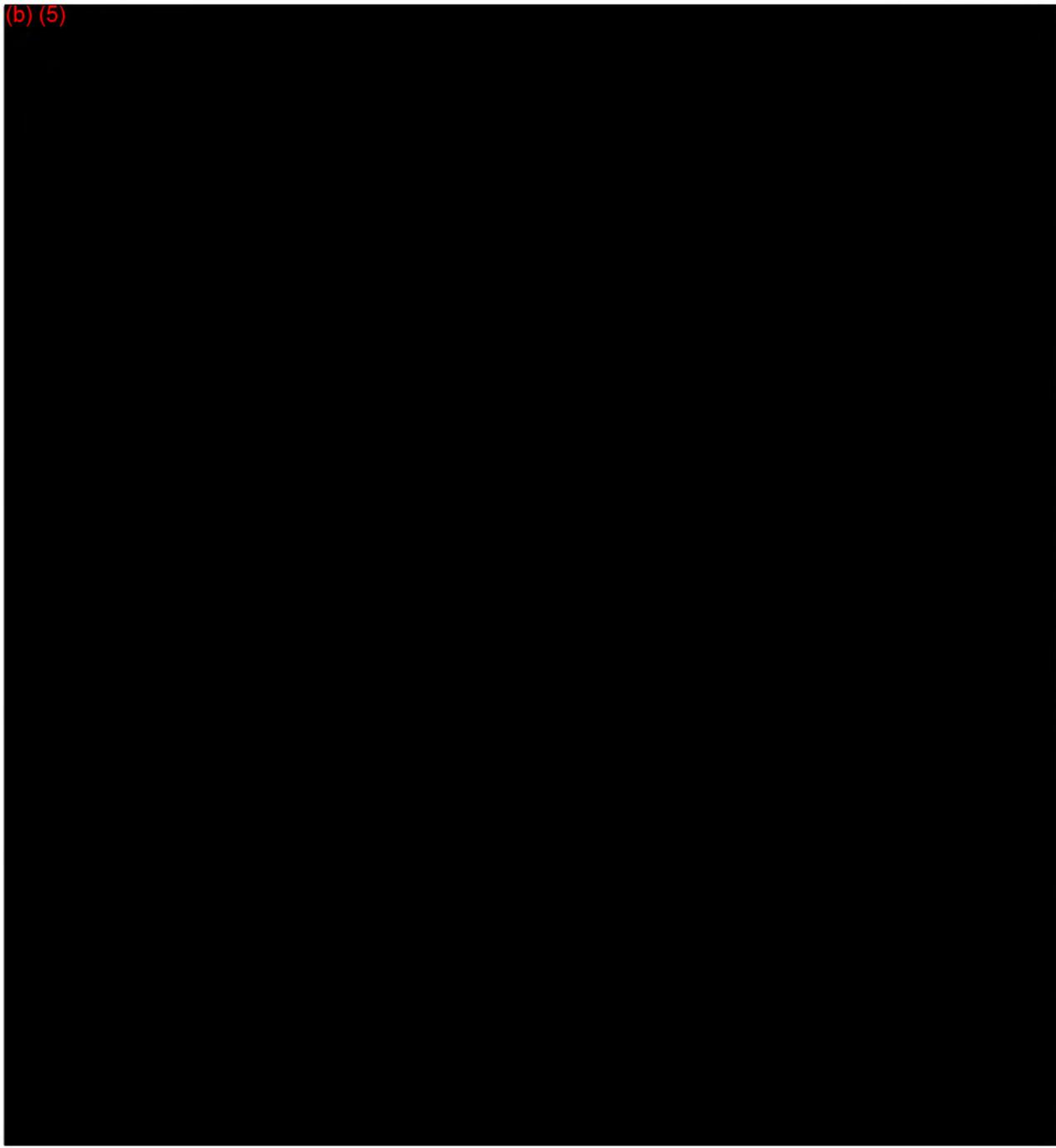
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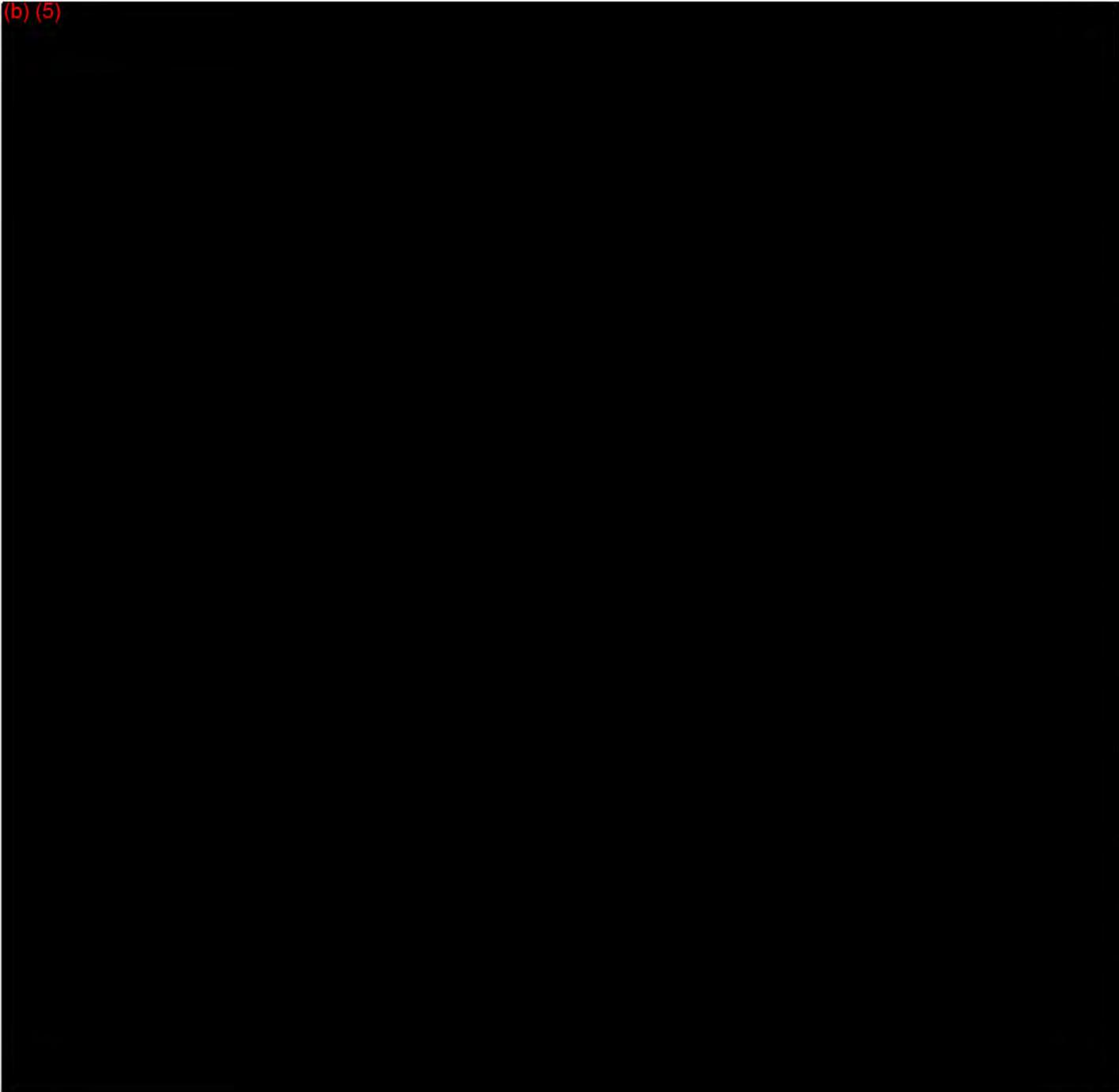
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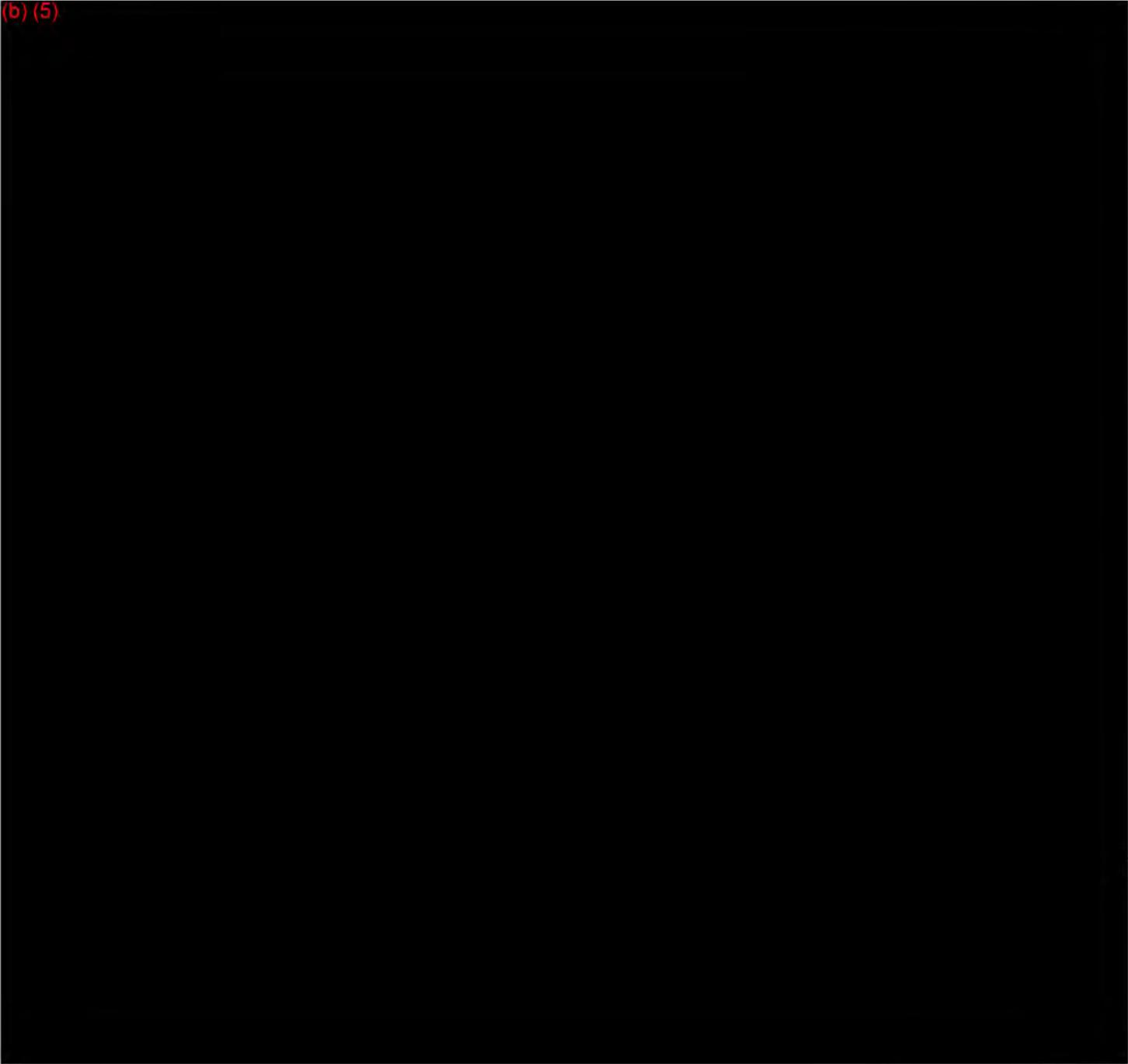
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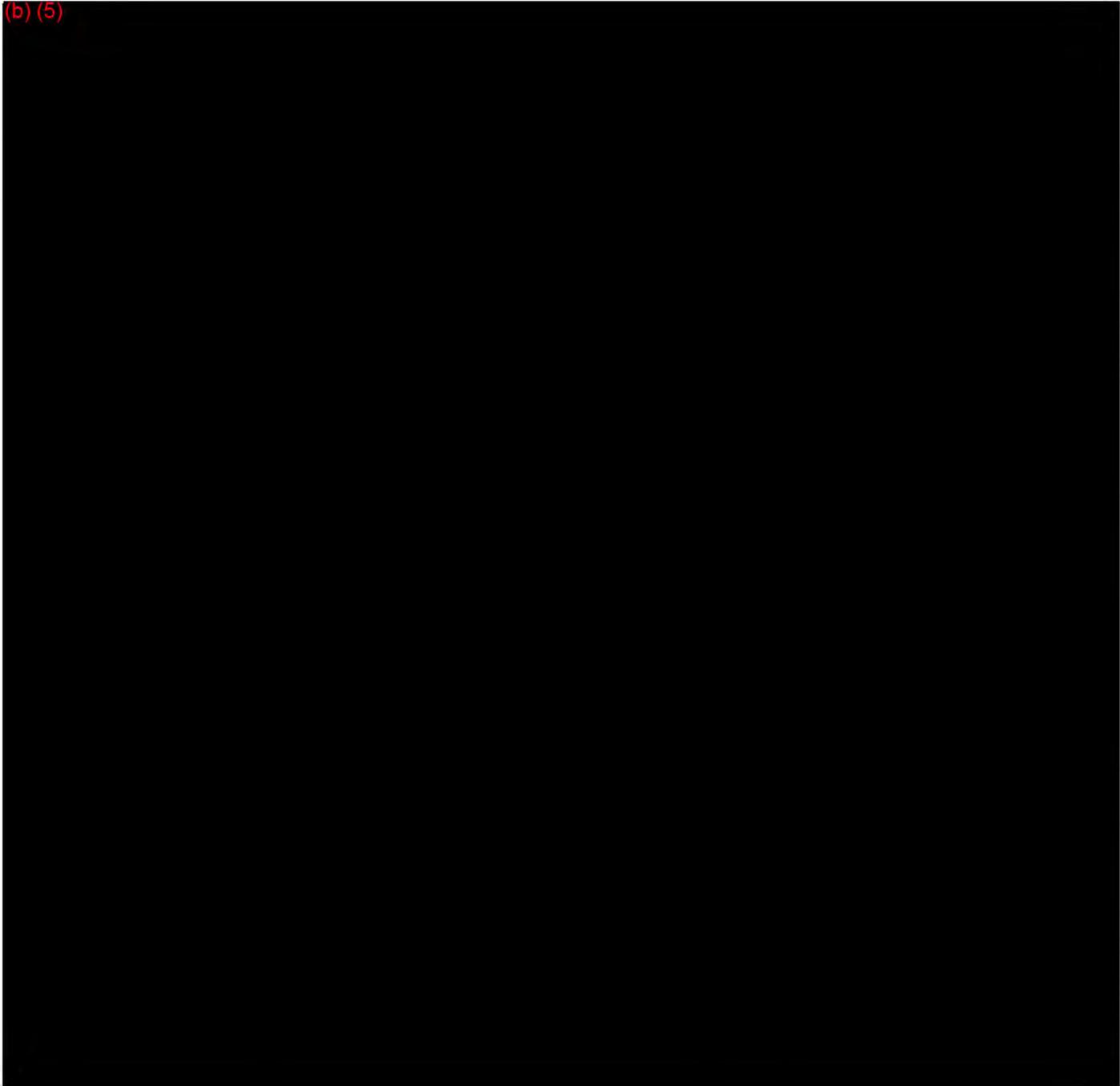
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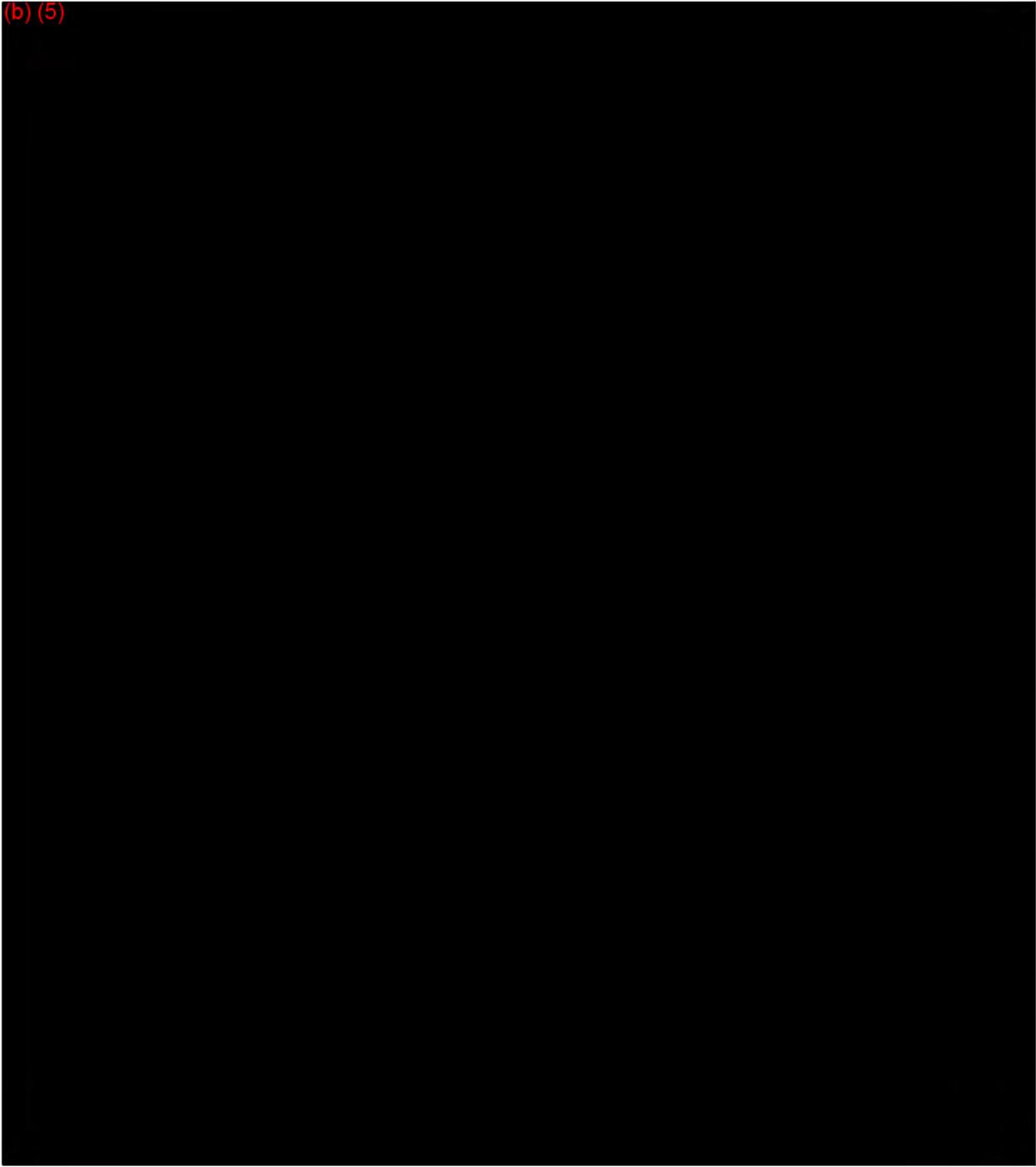
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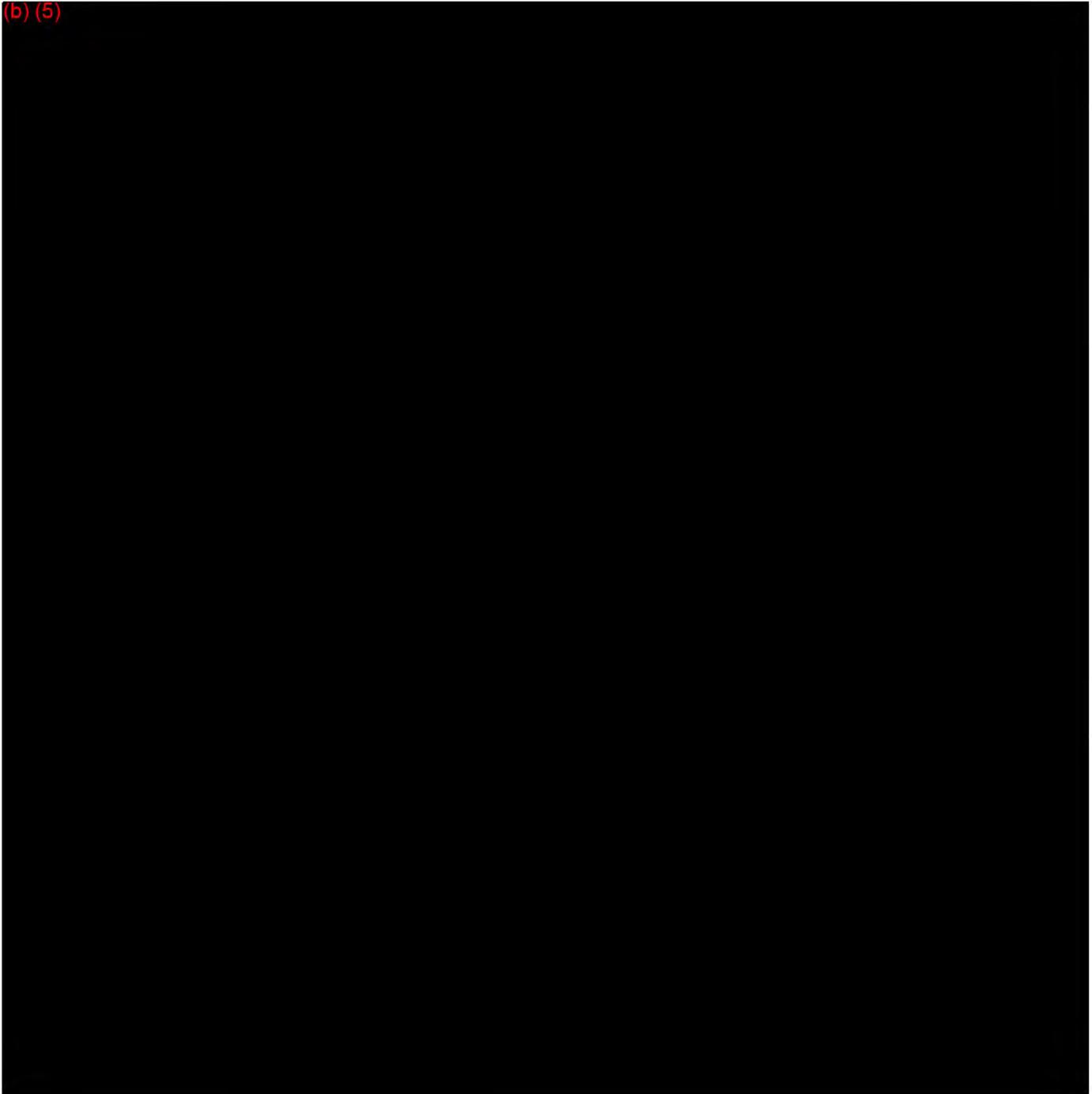
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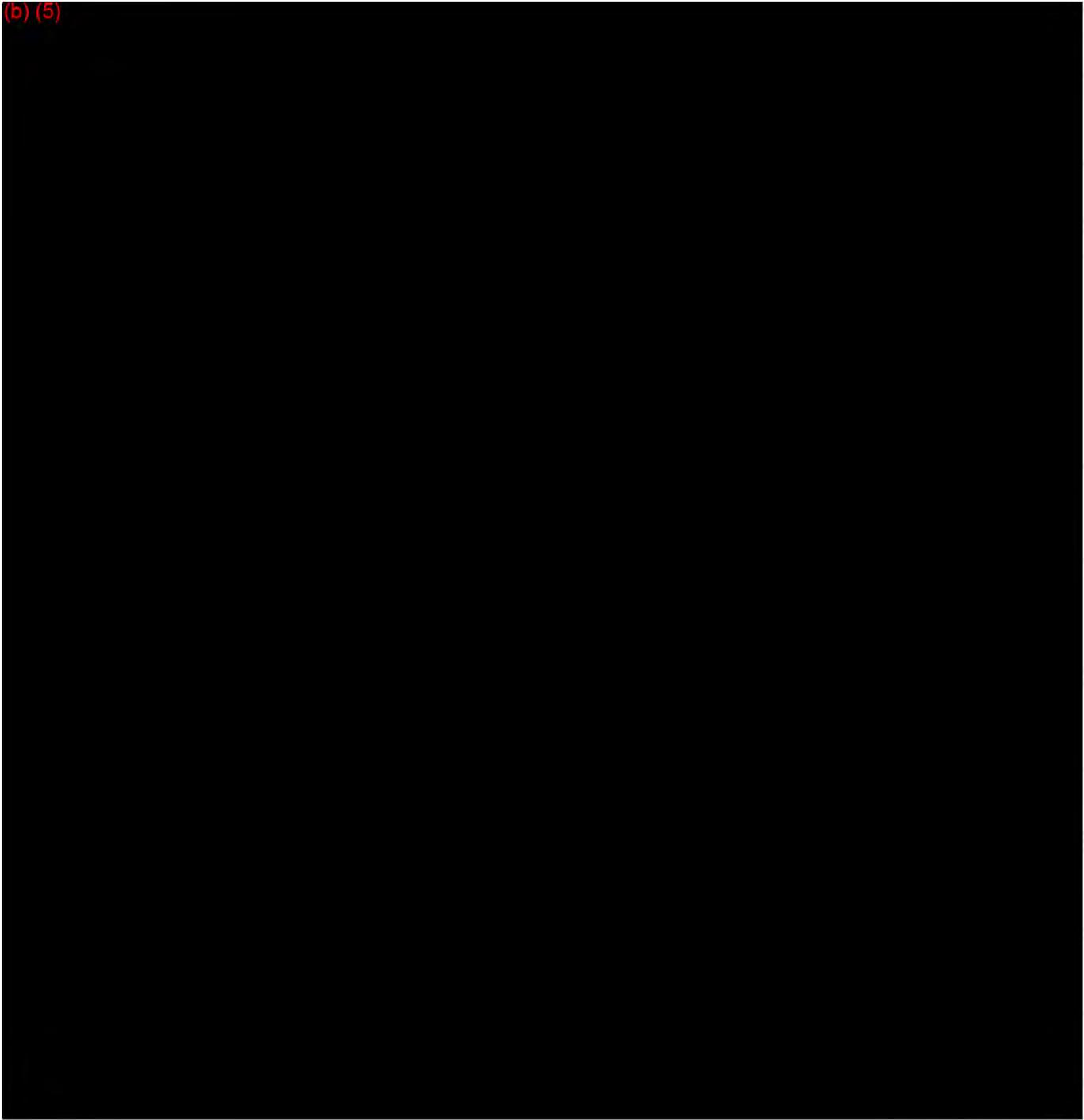
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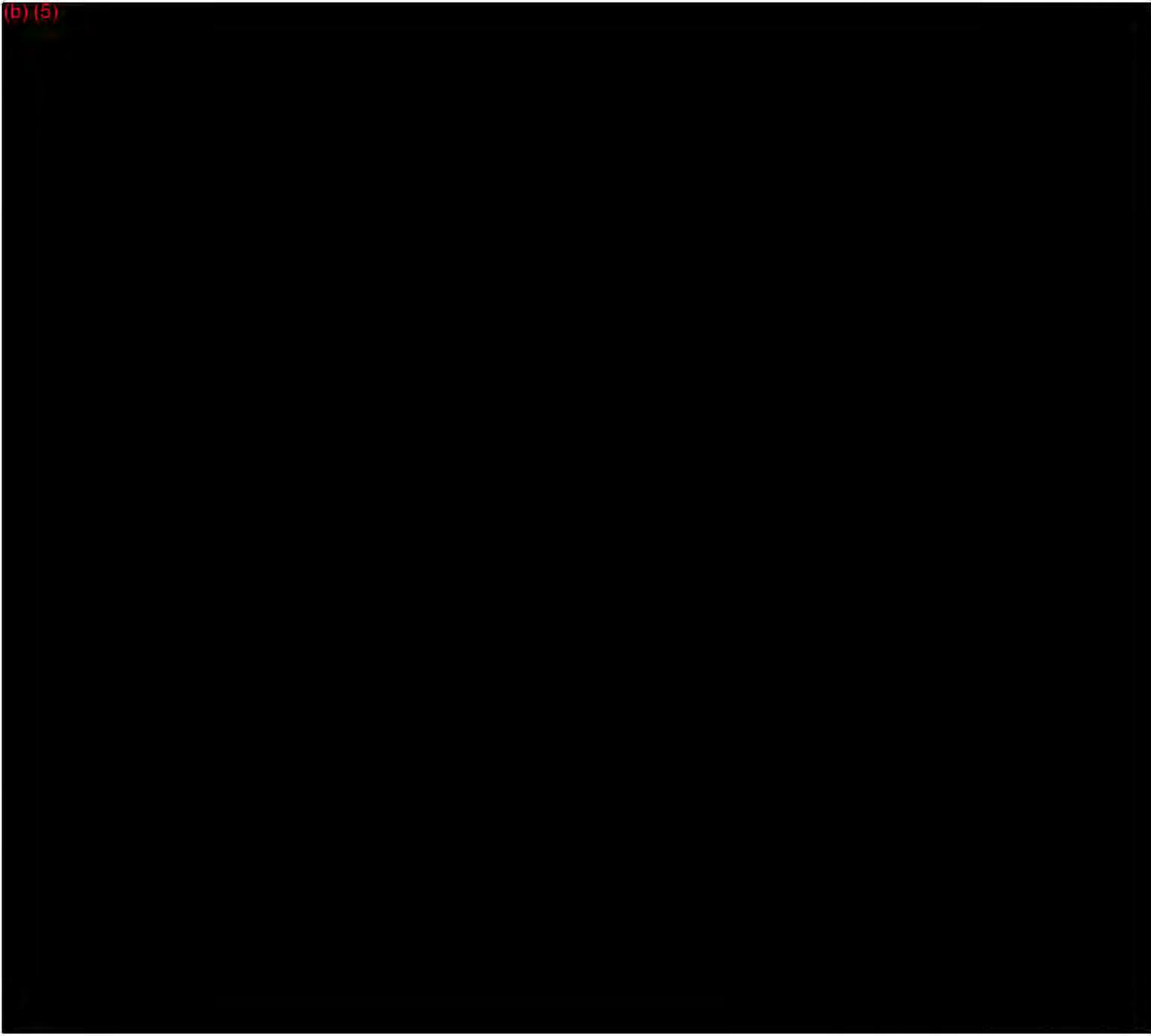
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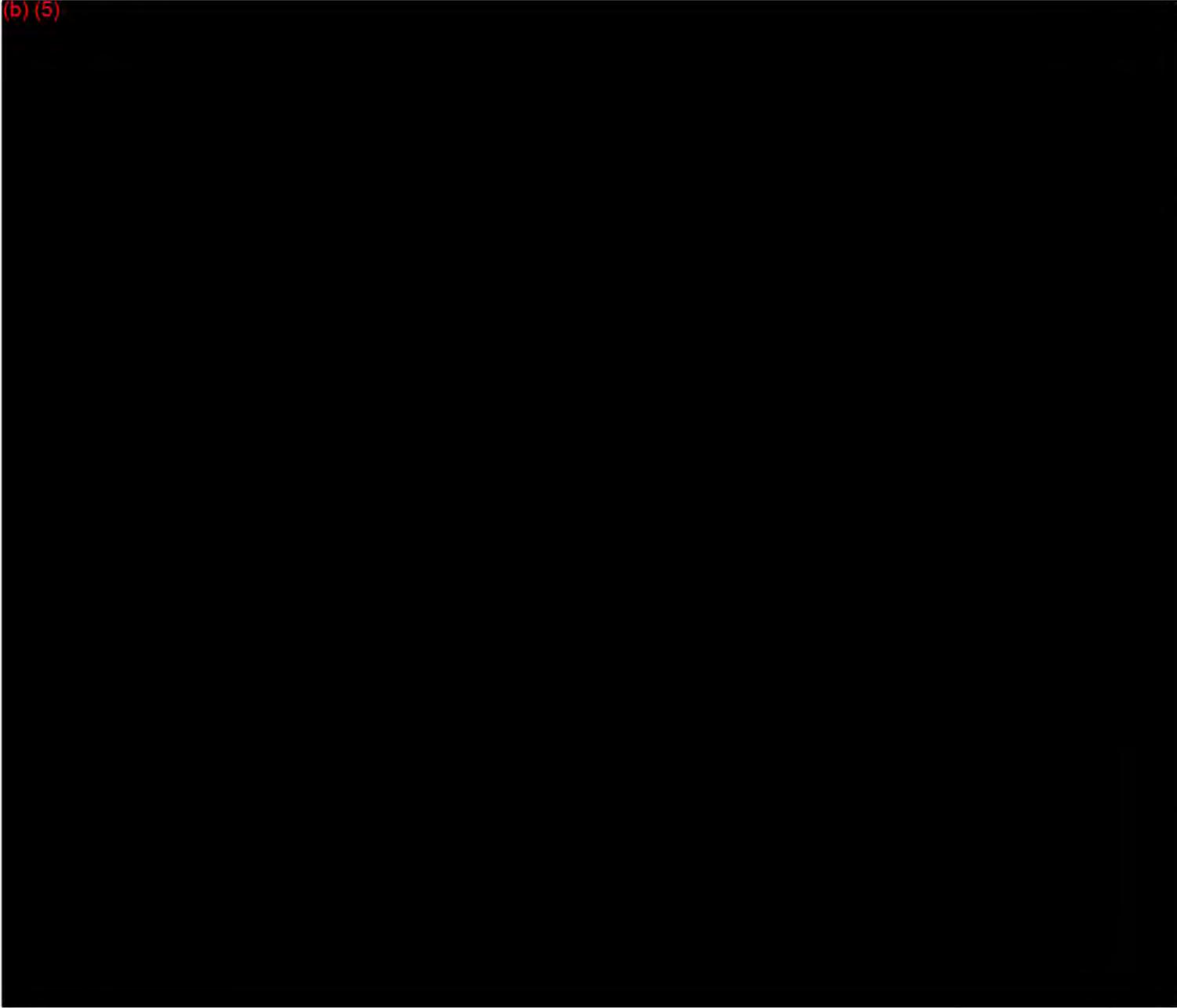
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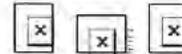
From: [Evans, Dana](#)
To: [Califf, Robert](#)
Subject: Rose/Pink
Date: Monday, October 17, 2016 9:59:28 AM
Attachments: [Rose Sheet Today's News Analysis.msg](#)
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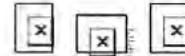
Smith, Celeste

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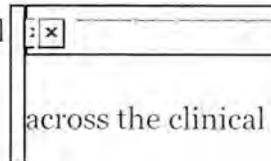
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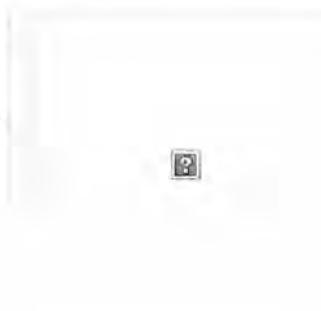
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To: [Califf, Robert](#)
Subject: Rose/Pink
Date: Monday, October 17, 2016 9:59:28 AM
Attachments: [Rose Sheet Today's News Analysis.msg](#)
[Pink Sheet Today's News Analysis.msg](#)

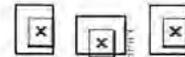
Smith, Celeste

From: Pink Sheet <info@pharmamedtechbi.net>
Sent: Monday, October 17, 2016 6:14 AM
To: Commissioner FDA
Subject: Pink Sheet | Today's News & Analysis

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CDER has published guidances, required by the 2014 Sunscreen Innovation Act, on FDA's process for advisory committees to consider firms'...

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Recent And Upcoming FDA Advisory Committees

Recent and upcoming FDA advisory committee meetings and a summary of topics covered.

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FDA's ANDA Approvals

Generic drug approvals and tentative approvals in early October.

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Below are FDA's original approvals of NDAs and BLAs issued in the past week. Please see key below chart for...

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From: [Auchincloss, Kalah](#)
To: [Califf, Robert](#)
Subject: RE: a nagging list of loose ends
Date: Monday, October 17, 2016 4:26:00 PM
Attachments: [Nicotine Replacement Therapy.msg](#)

My comments below. Happy to get Caitlin to try to block office time for you to do some of the writing/editing on there; and happy to have her schedule calls as needed.

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Sent: Monday, October 17, 2016 1:30 PM
To: Auchincloss, Kalah
Cc: Califf, Robert
Subject: a nagging list of loose ends

In no particular order:

1. (b) (5)

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21. Eteplirsen letter with Ellis Unger for neurology journal

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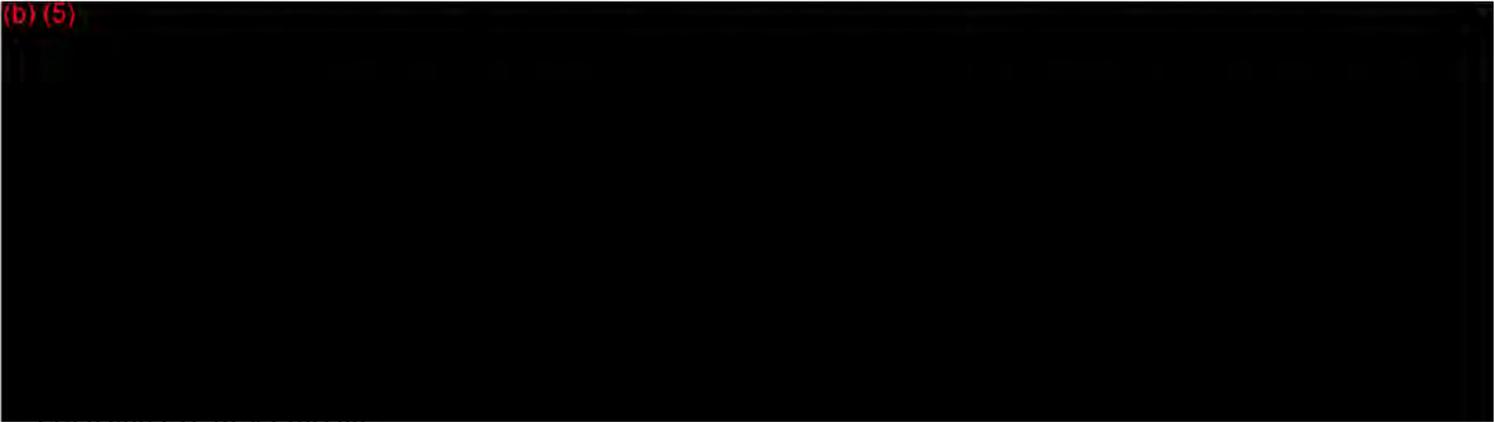
.rnc

Smith, Celeste

From: Sharp, Jeremy
Sent: Friday, October 14, 2016 3:28 PM
To: Califf, Robert
Cc: Auchincloss, Kalah; Bleicher, Esther
Subject: Nicotine Replacement Therapy
Attachments: NRT Draft Brainstorming Questions 10-14-16 .doc

Rob – you asked for a draft of an agenda or discussion questions for a meeting you want to have with CDER re: NRT. We put this together as a starting point. We haven't shared this with CDER or CTP. We wanted you to look first.

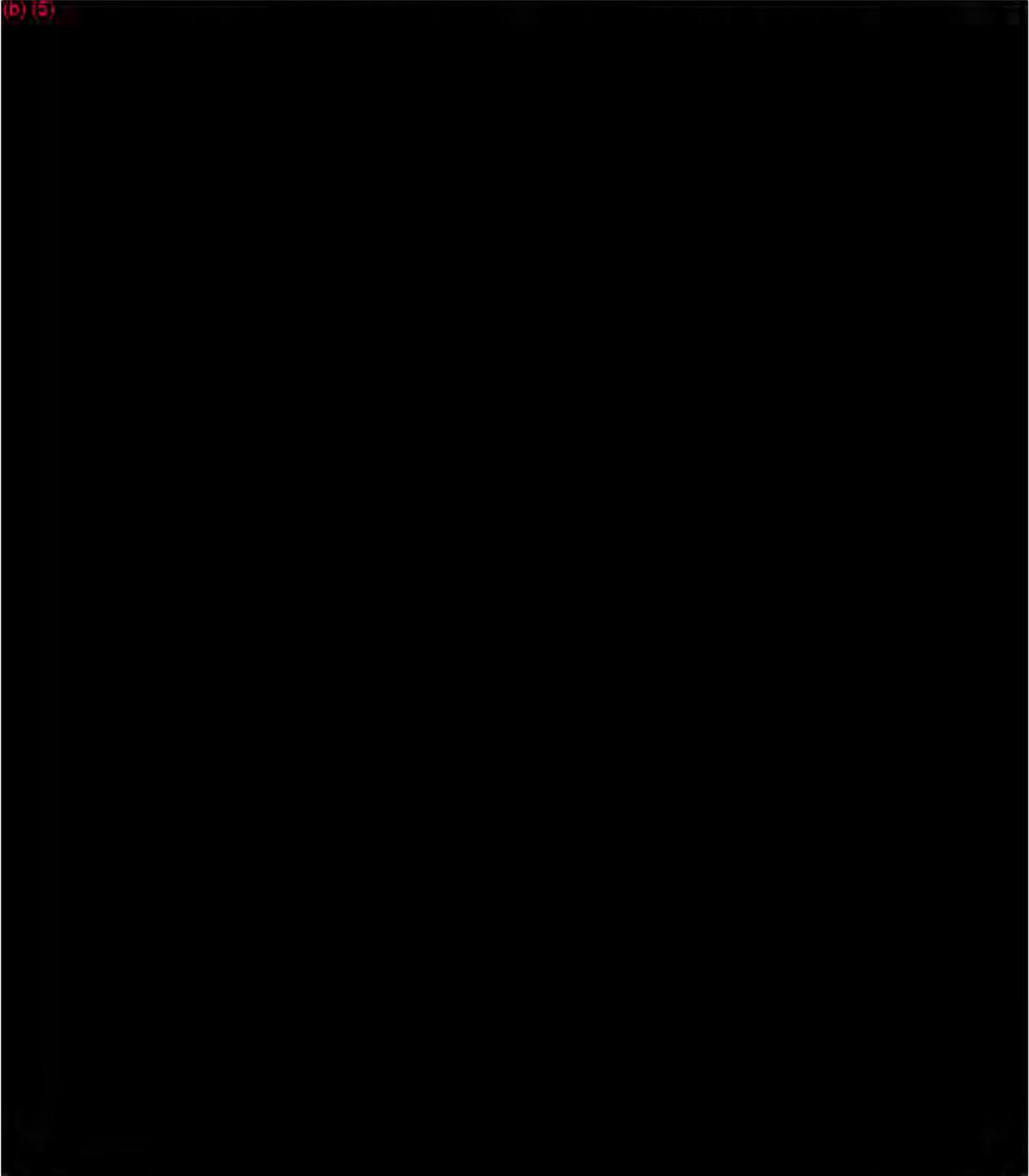
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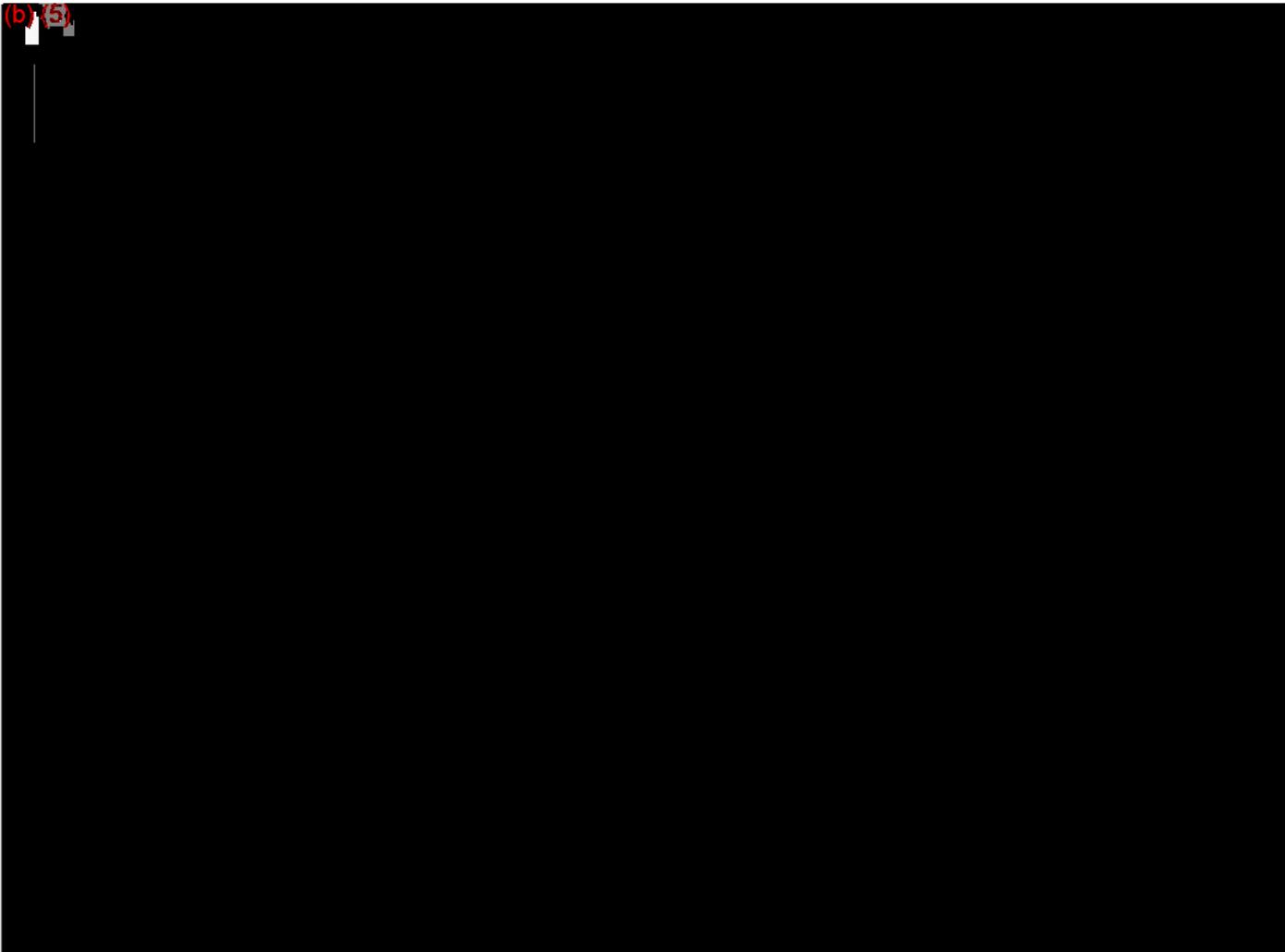
Jeremy Sharp
Deputy Commissioner
Policy, Planning, Legislation, and Analysis
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
301-796-8770

QUESTIONS FOR BRAINSTORMING SESSION WITH DR. CALIFF REGARDING NICOTINE REPLACEMENT THERAPY [AND AN FDA COMPREHENSIVE NICOTINE REGULATORY POLICY FOR THE AGENCY?]

(b) (5)



(b) (5)



From: [Califf, Robert](#)
To: [Conover, Katie](#)
Subject: FW: NORD Speech
Date: Tuesday, October 18, 2016 7:16:00 PM
Attachments: [20161917 NORD Califf.doc](#)

Stuff about expanded access is in here. good discussion today.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Califf, Robert
Sent: Tuesday, October 18, 2016 7:45 AM
To: Wohl, Alexander; Riley, Karen
Subject: RE: NORD Speech

Here's the version I gave. Feel free to clean it up.

Thx

rmc

From: Wohl, Alexander
Sent: Monday, October 17, 2016 8:37 PM
To: Califf, Robert
Subject: NORD Speech

Hi Dr. Califf,
Did you end up using the examples Gayatri added? Can you please send me the final version of your speech so that I can post on our web site, which NORD will then link to?
Thank you.
Alex

From: Rao, Gayatri
Sent: Sunday, October 16, 2016 9:12 PM
To: Riley, Karen; Califf, Robert
Cc: Wohl, Alexander
Subject: RE: NORD Speech

Apologies again for the delay. Attached are a few additions in response to Karen's comments.

Gayatri

From: Rao, Gayatri
Sent: Sunday, October 16, 2016 8:08 PM
To: Riley, Karen; Califf, Robert
Cc: Wohl, Alexander
Subject: Re: NORD Speech

Apologies; I've been tied up with (b) (6) can review in a bit if it's not too late.

From: Riley, Karen
Sent: Sunday, October 16, 2016 5:23 PM
To: Califf, Robert
Cc: Wohl, Alexander; Rao, Gayatri
Subject: Fw: NORD Speech

Here you are. Incorporates all. Gayatri, I asked a couple of questions. Can we include a sentence (b) (5)

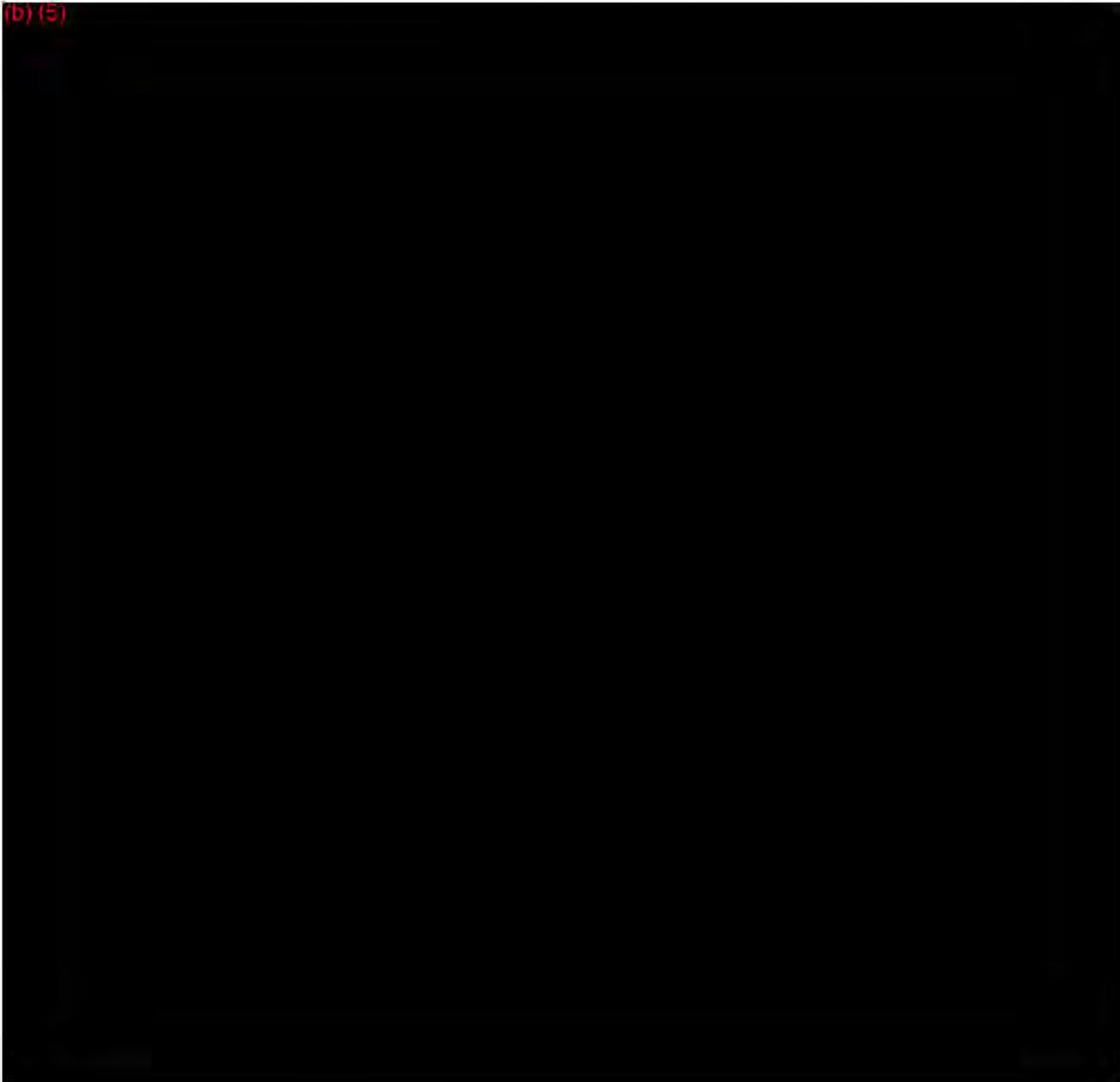
Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Karen Riley (b) (6)
Sent: Sunday, October 16, 2016 5:20 PM
To: Riley, Karen
Subject: NORD Speech

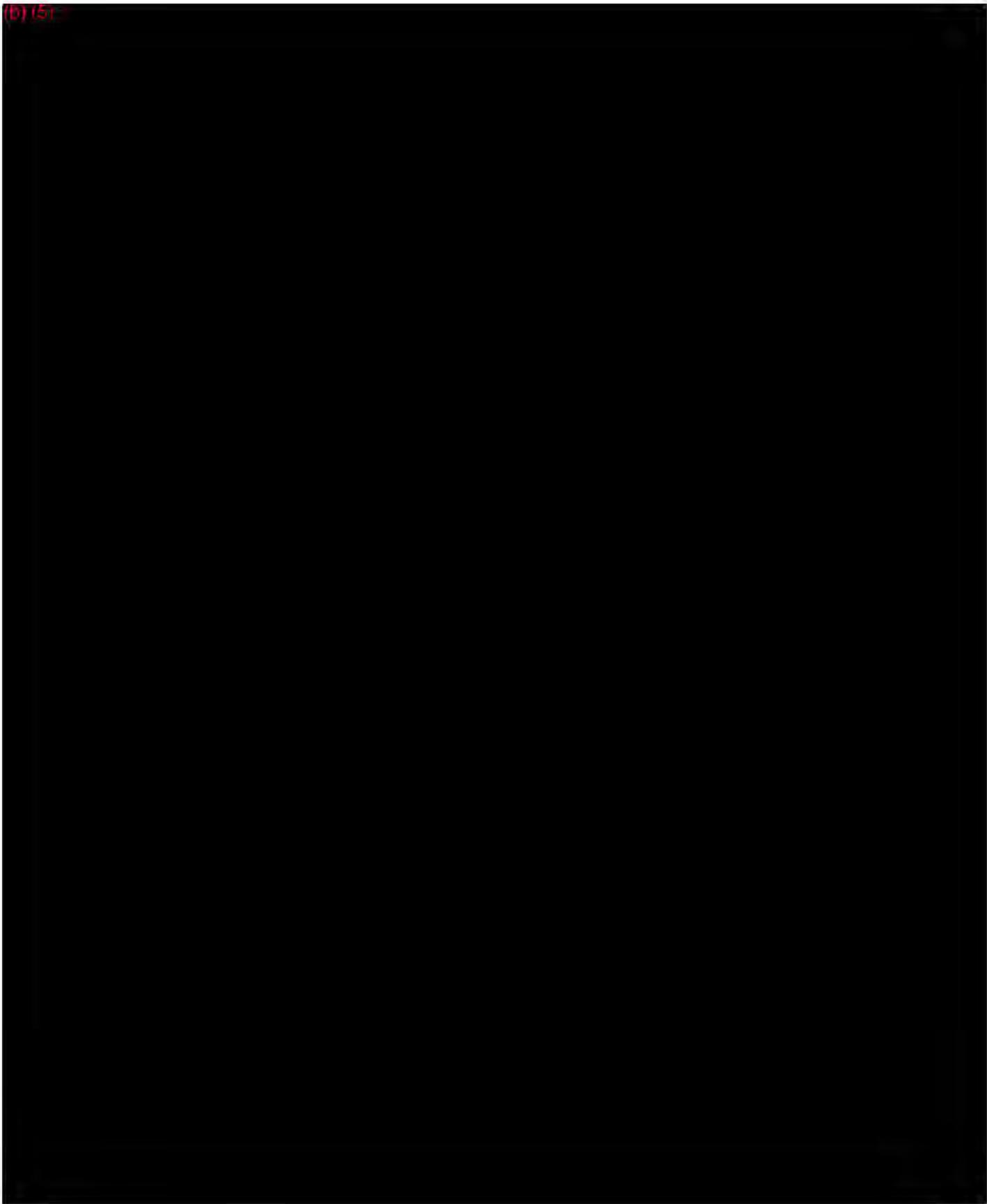
Speech by Robert M. Califf, M.D.
Commissioner of Food and Drugs
2016 National Organization for Rare Disorders (NORD) Summit
October 17, 2016
Washington, D.C.

“Critical Lessons about Rare Disease Drug Development”

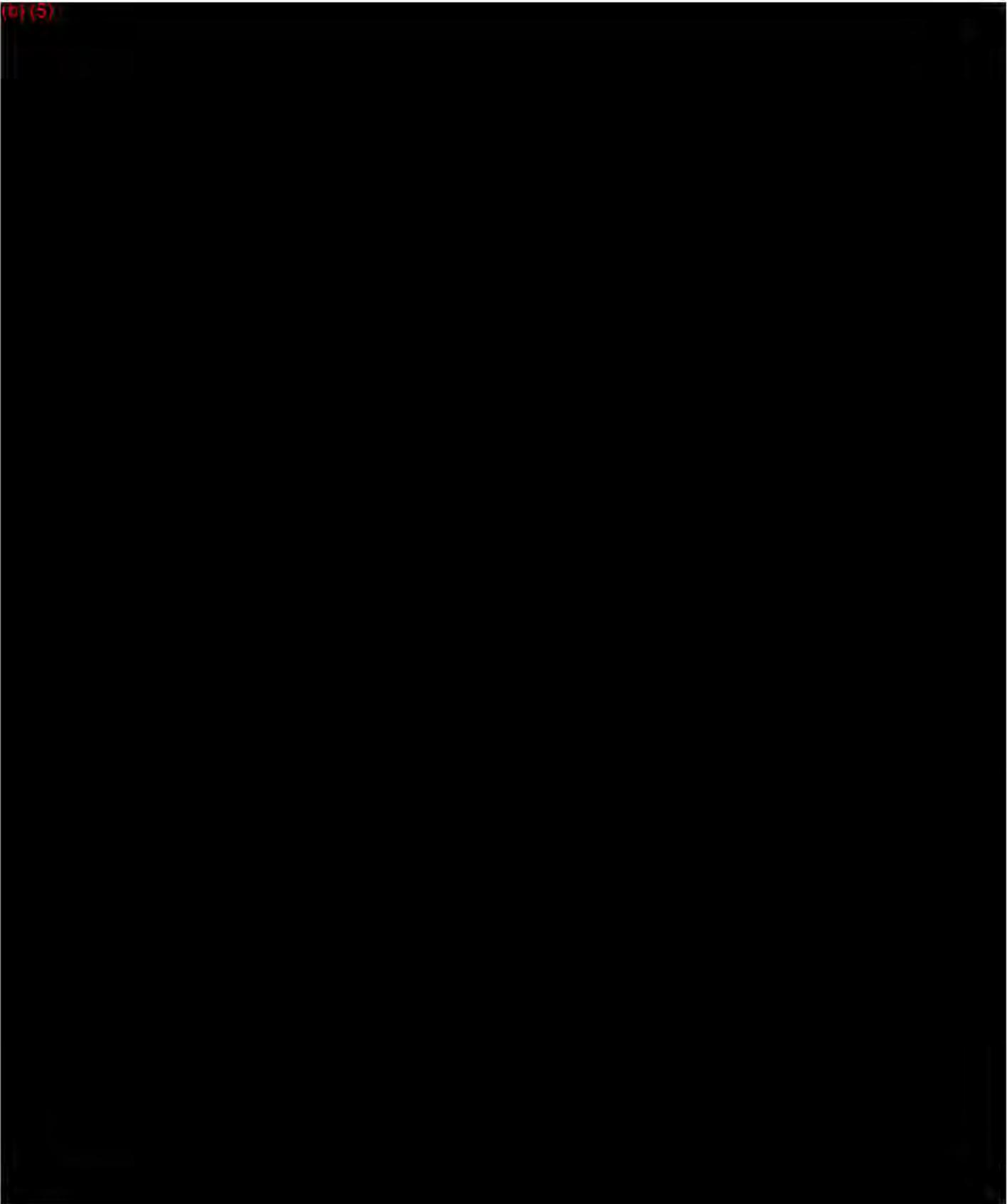
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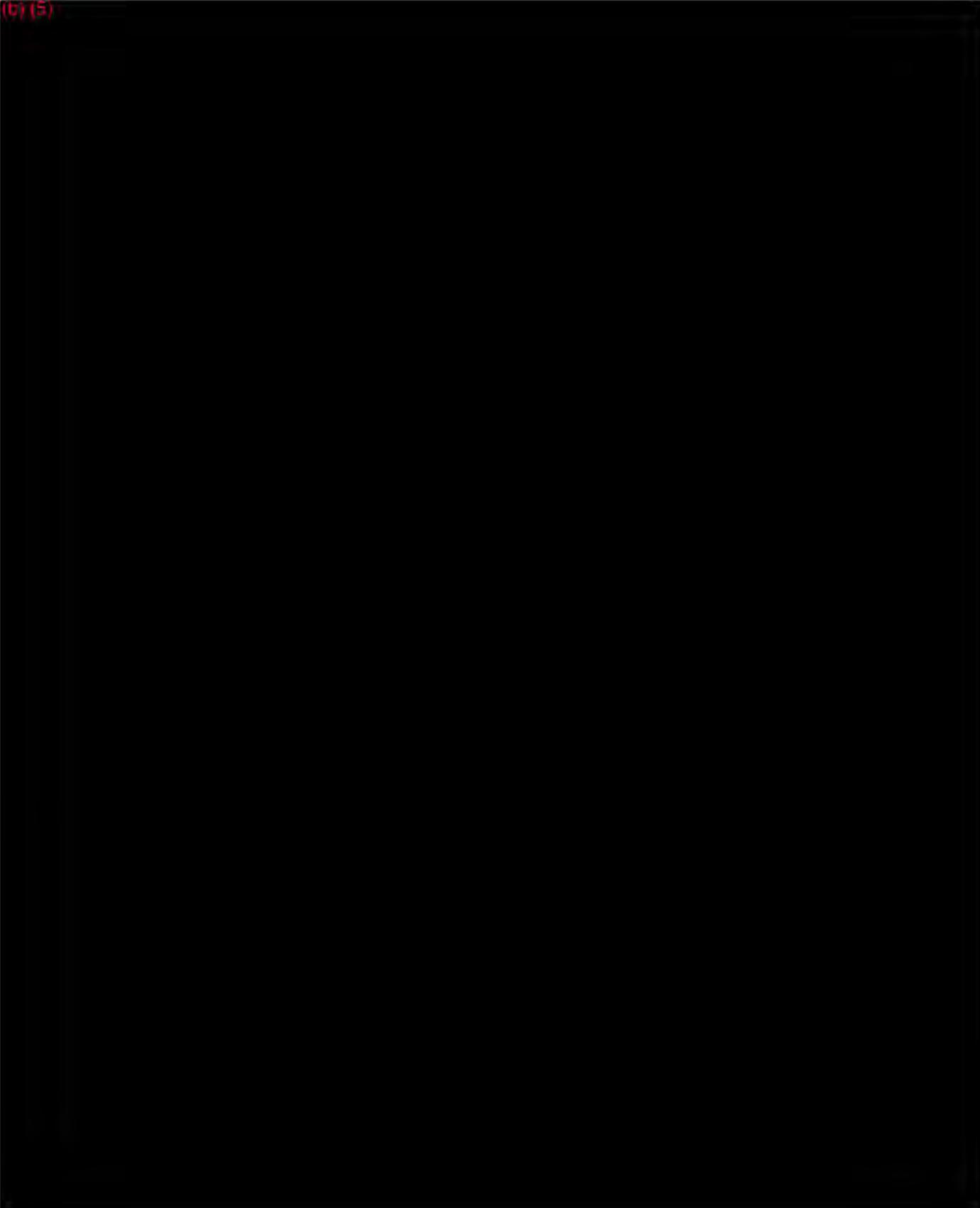
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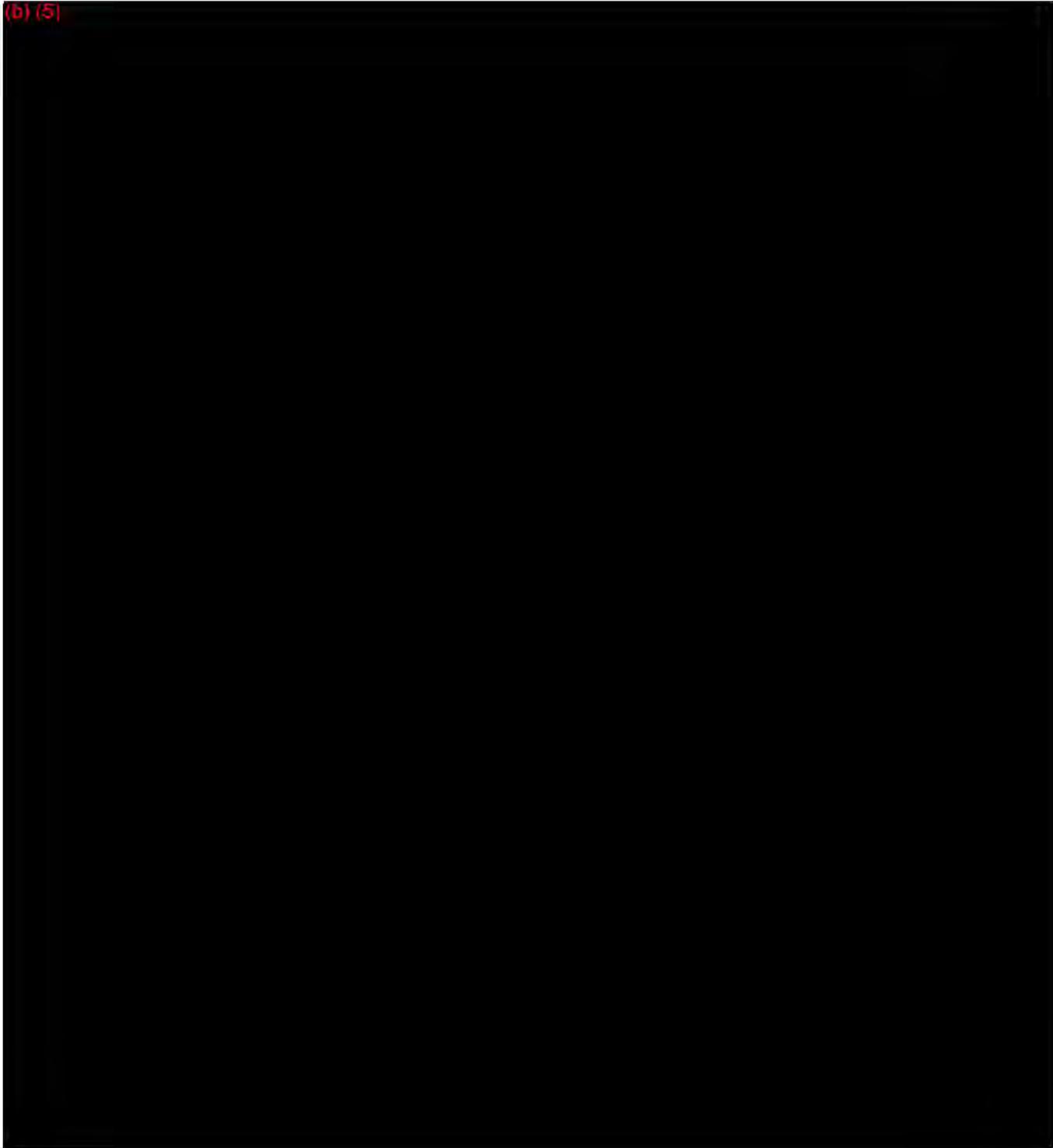
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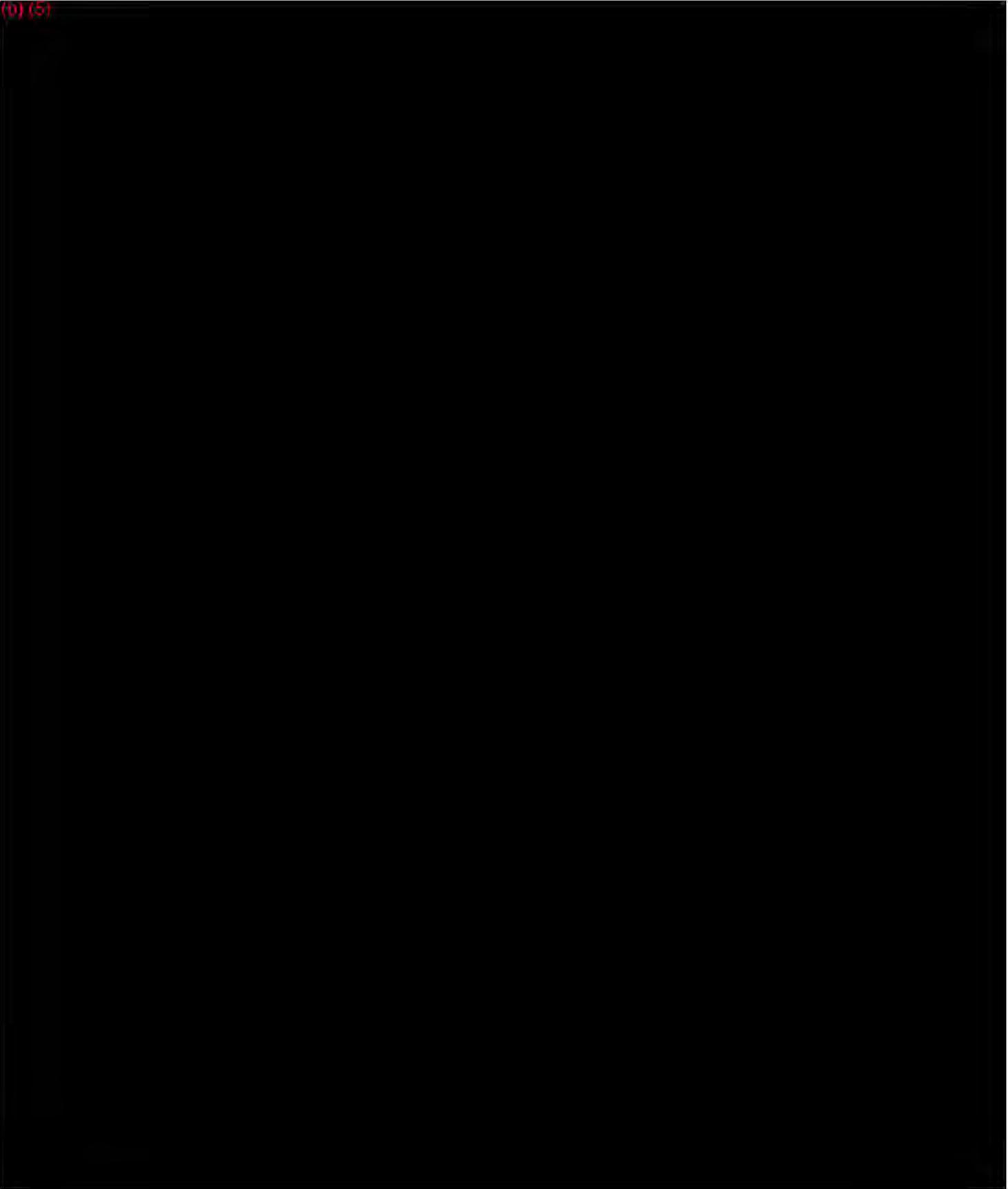
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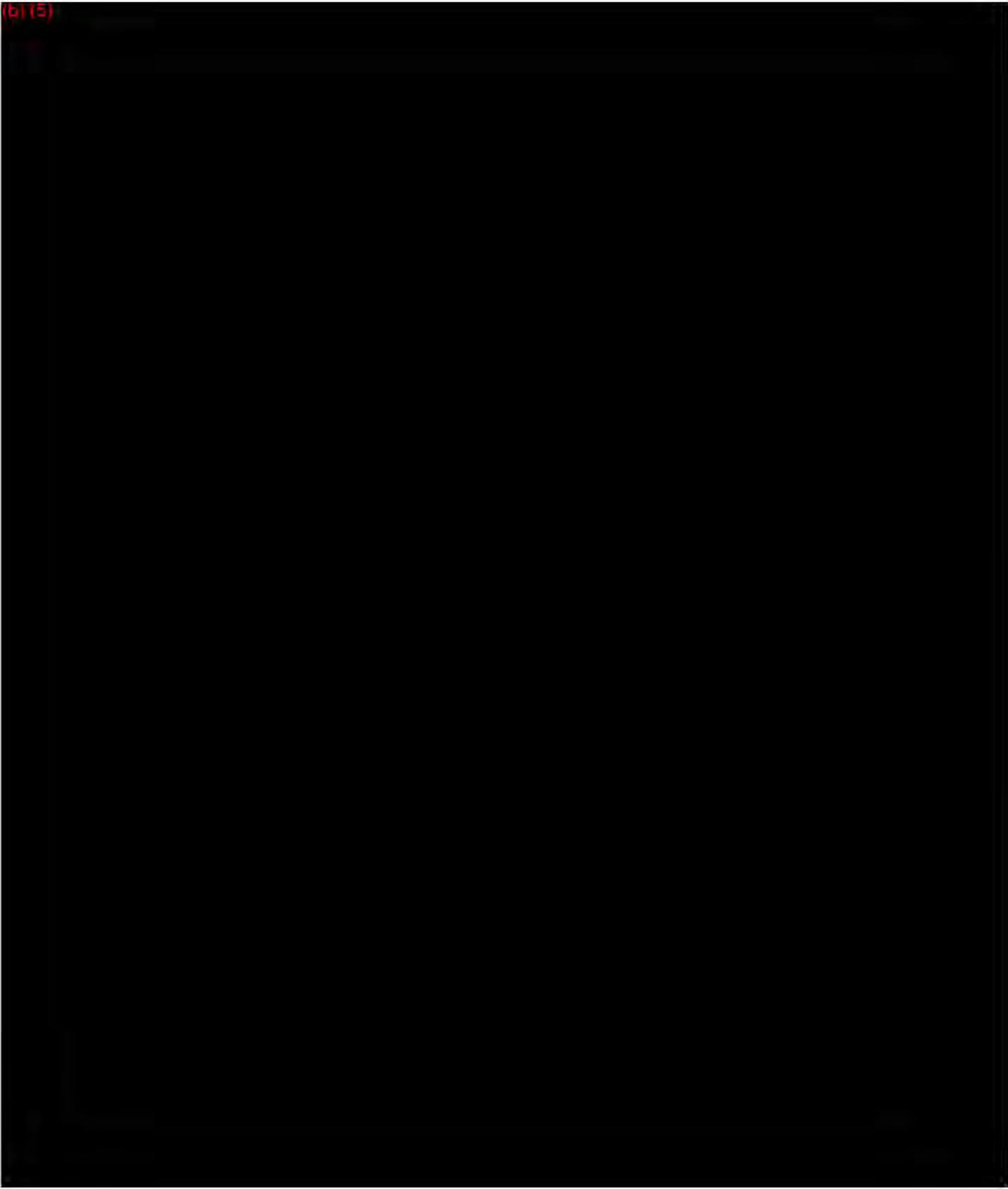
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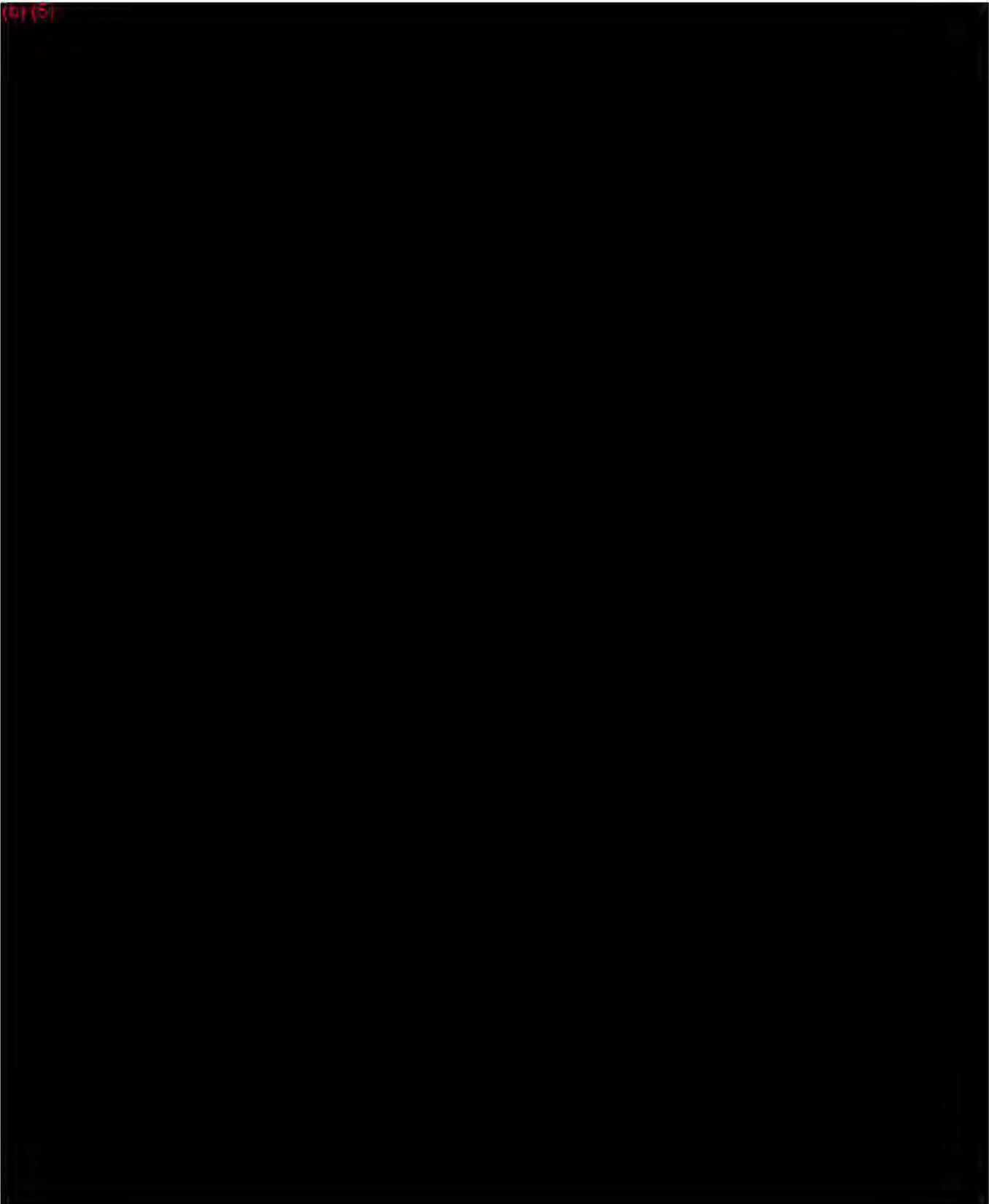
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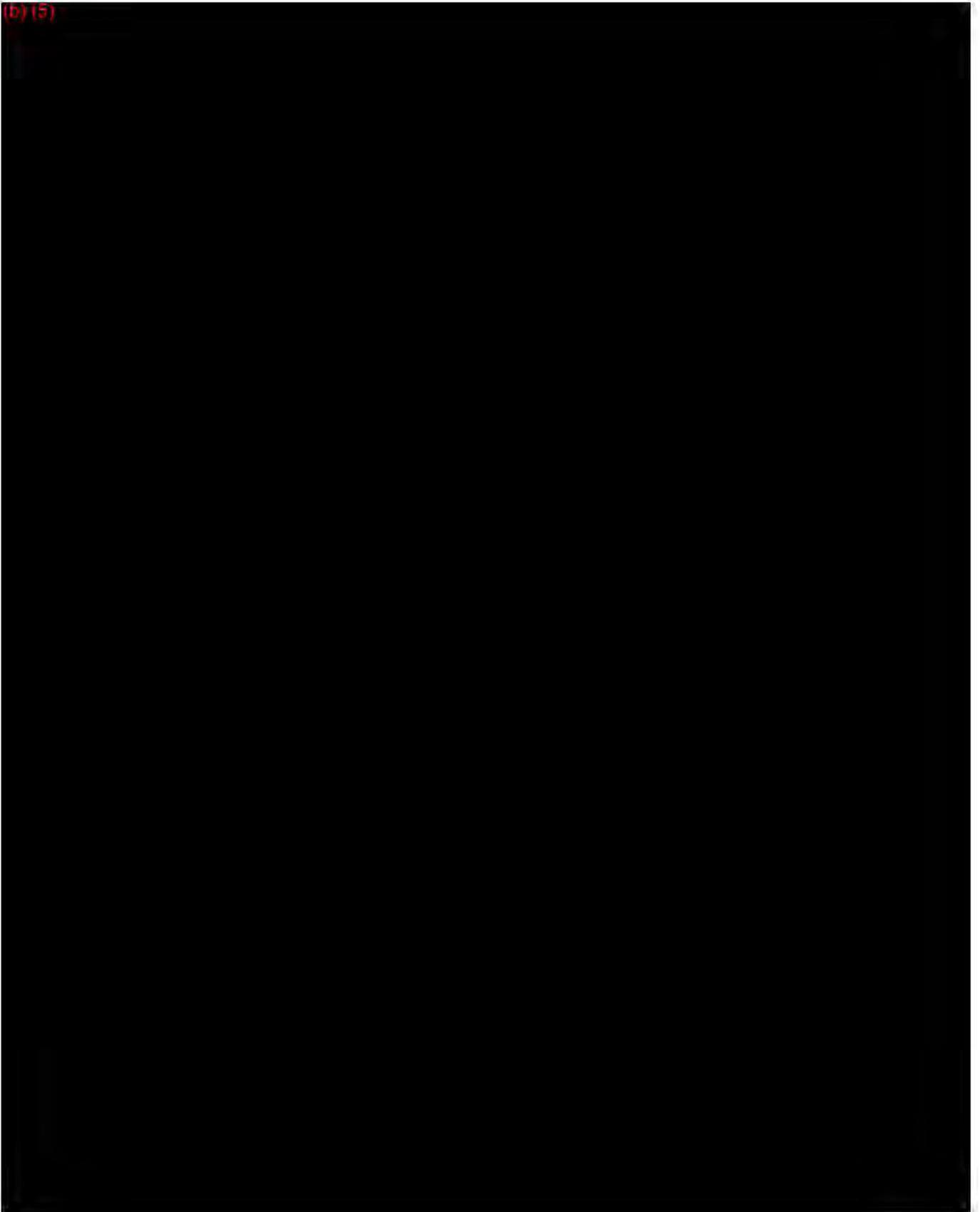
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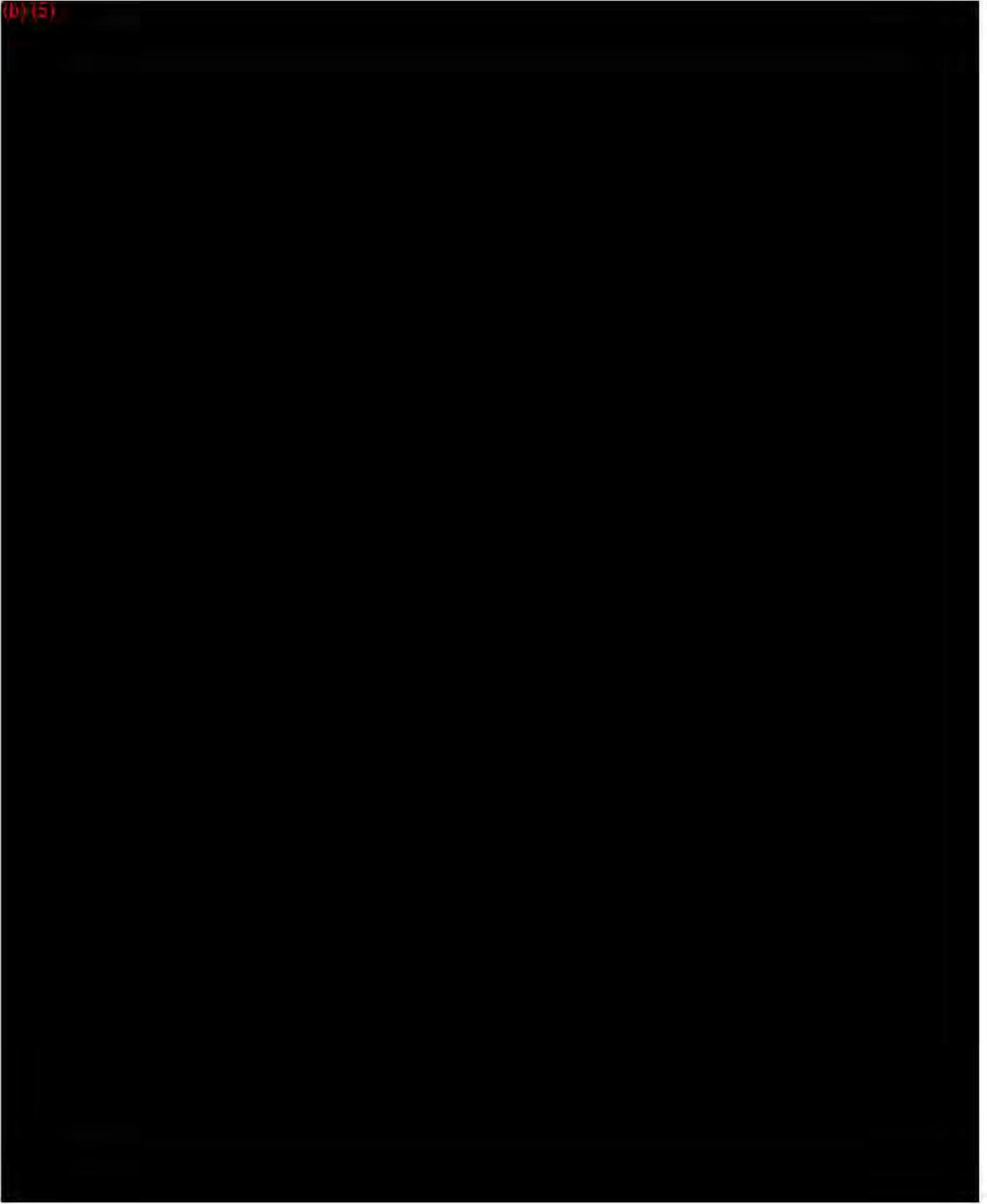
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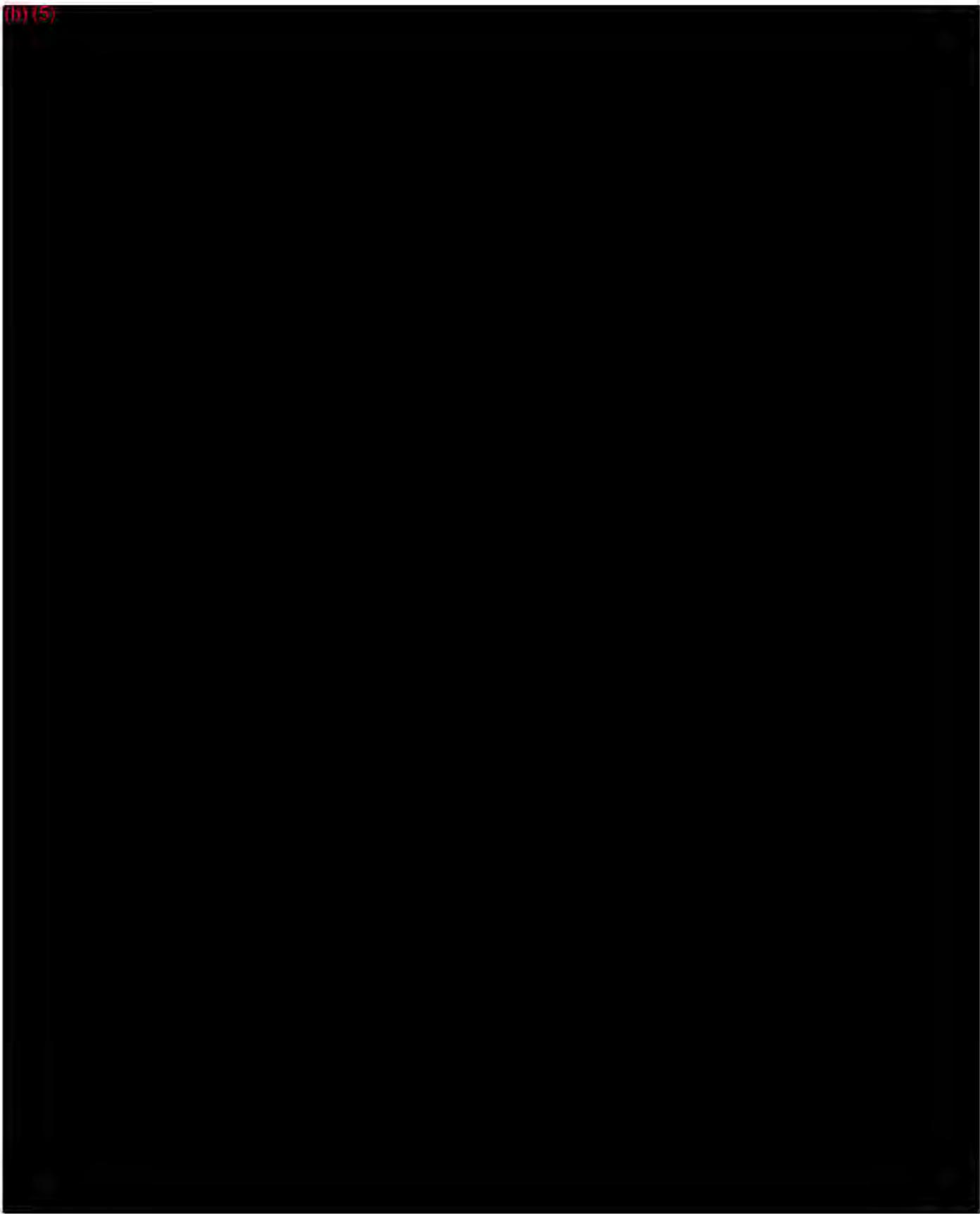
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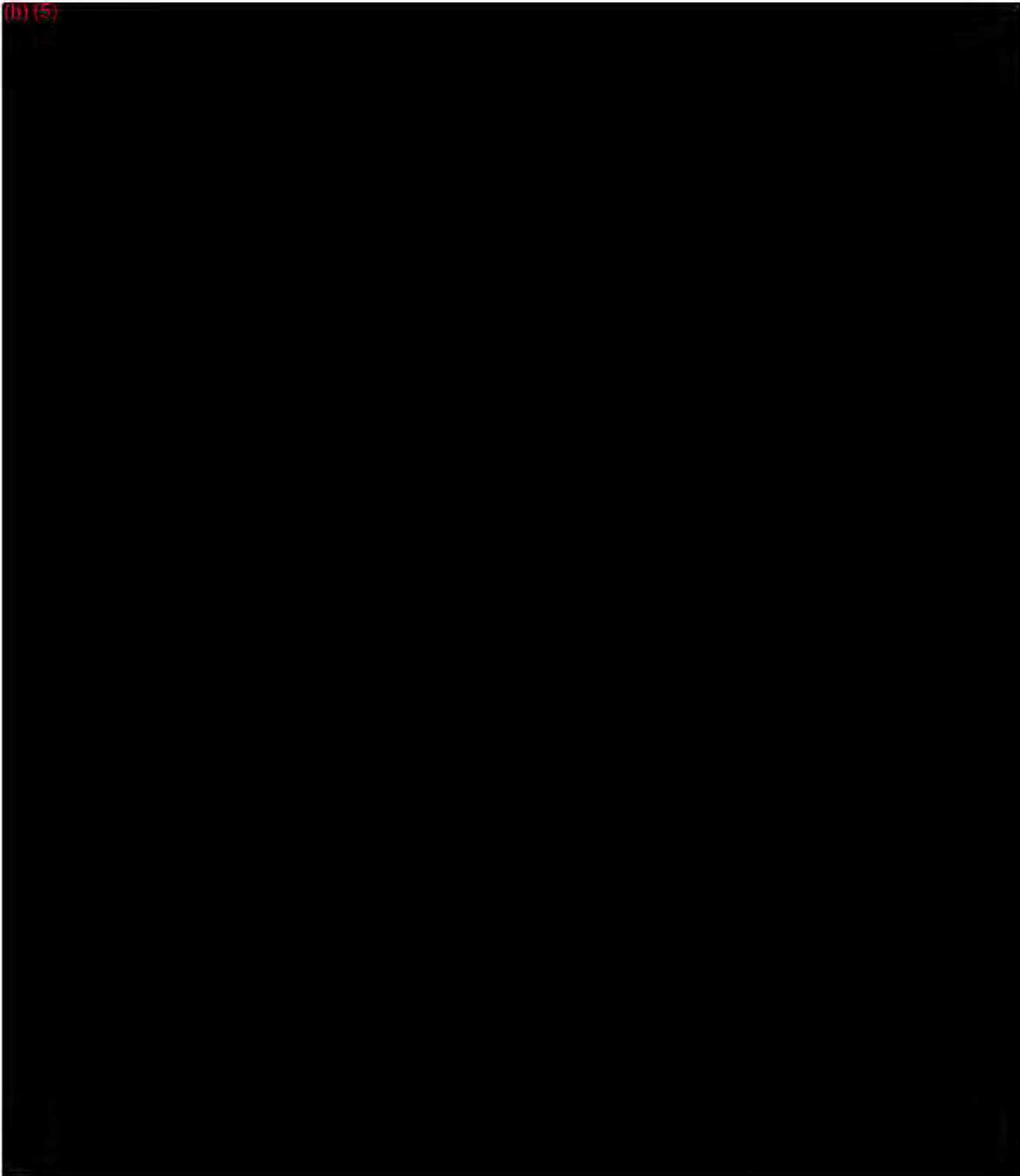
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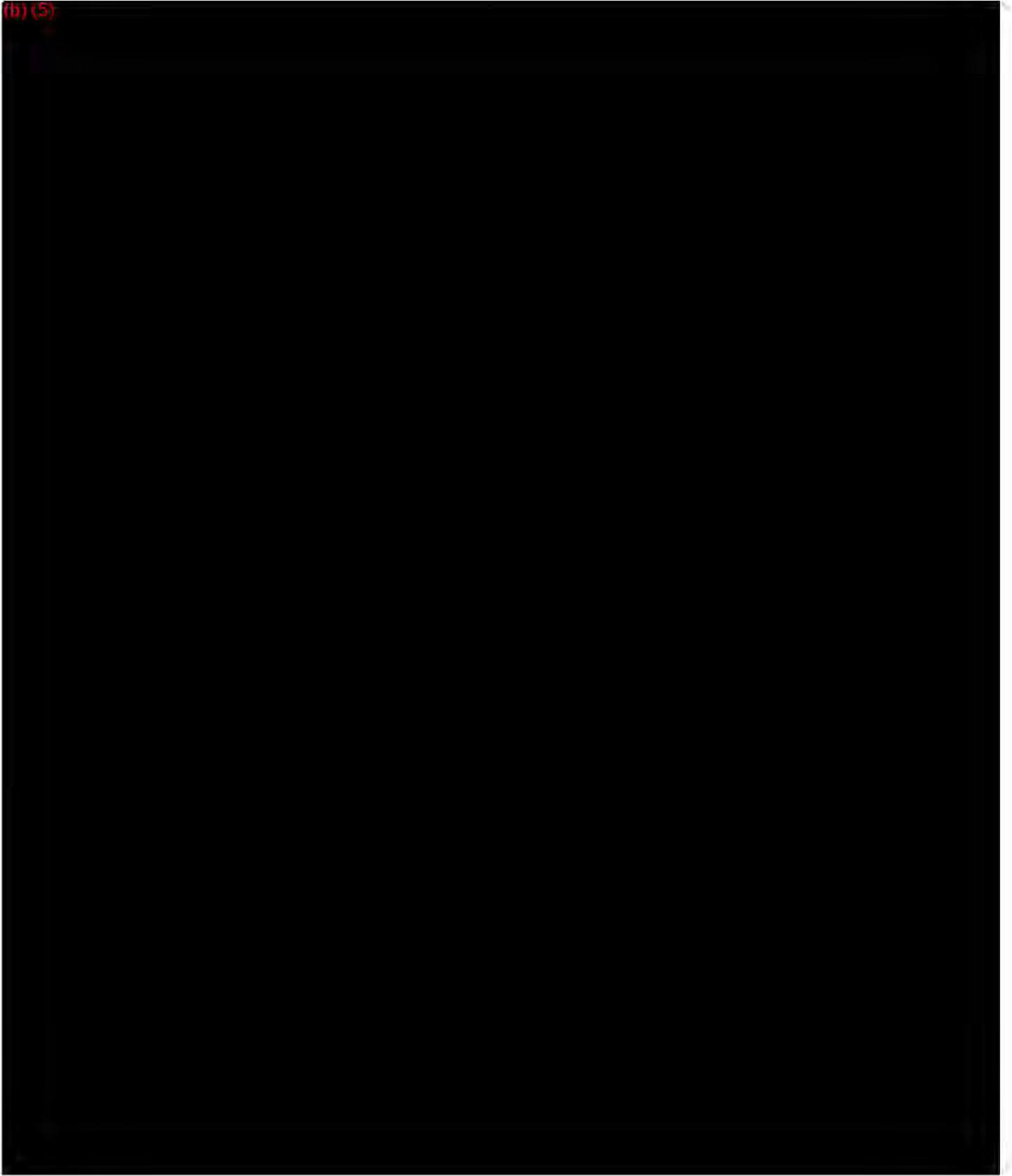
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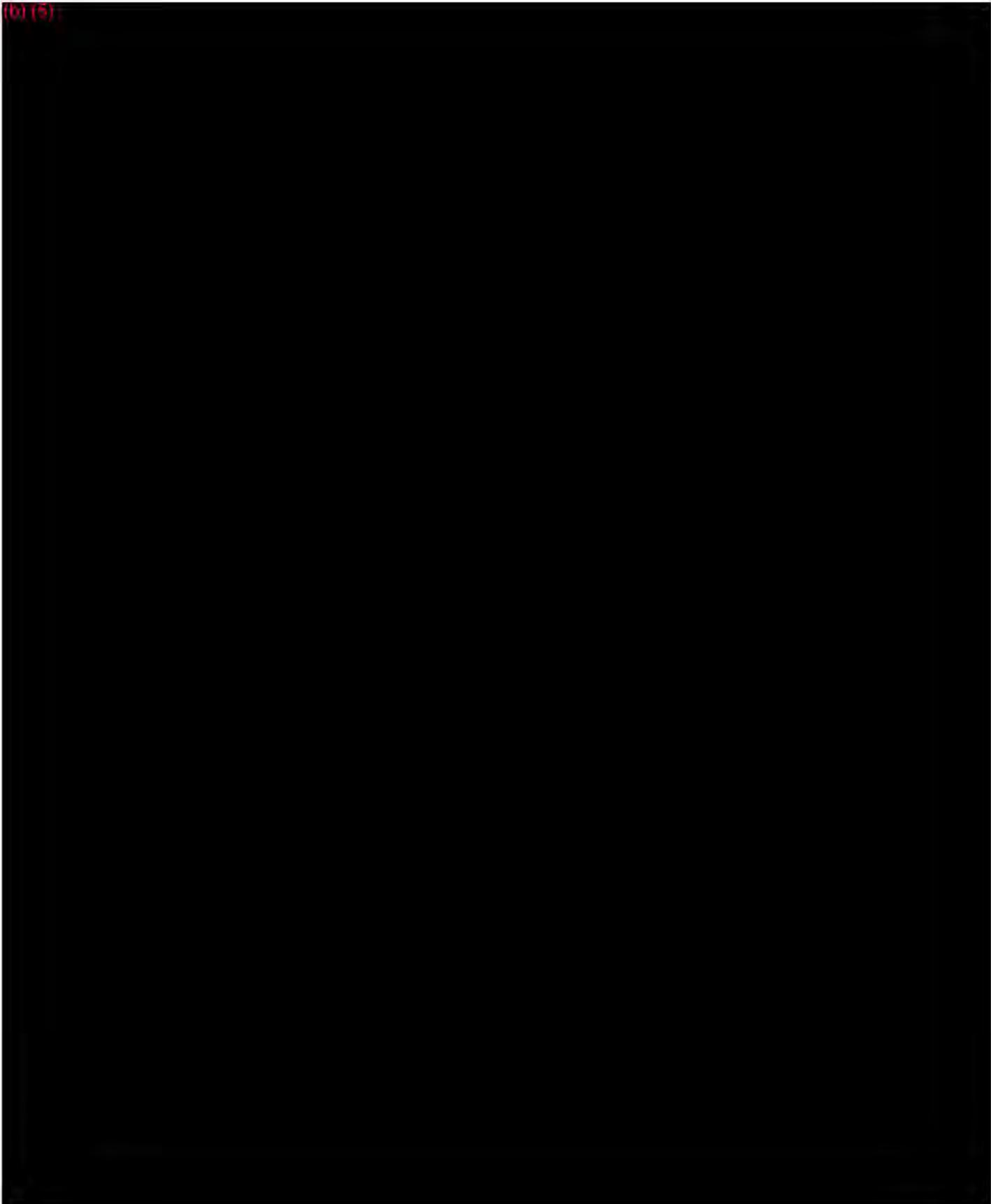
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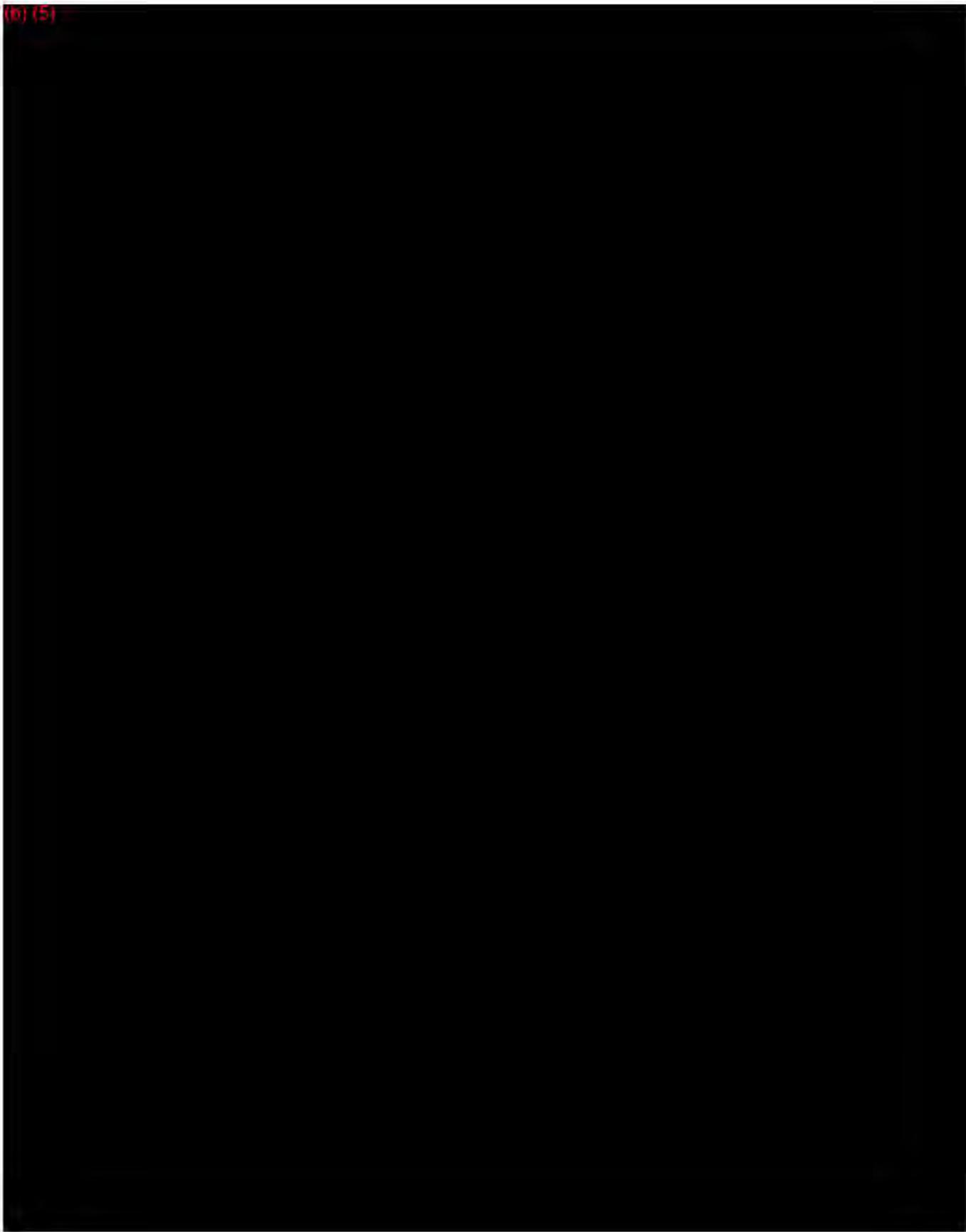
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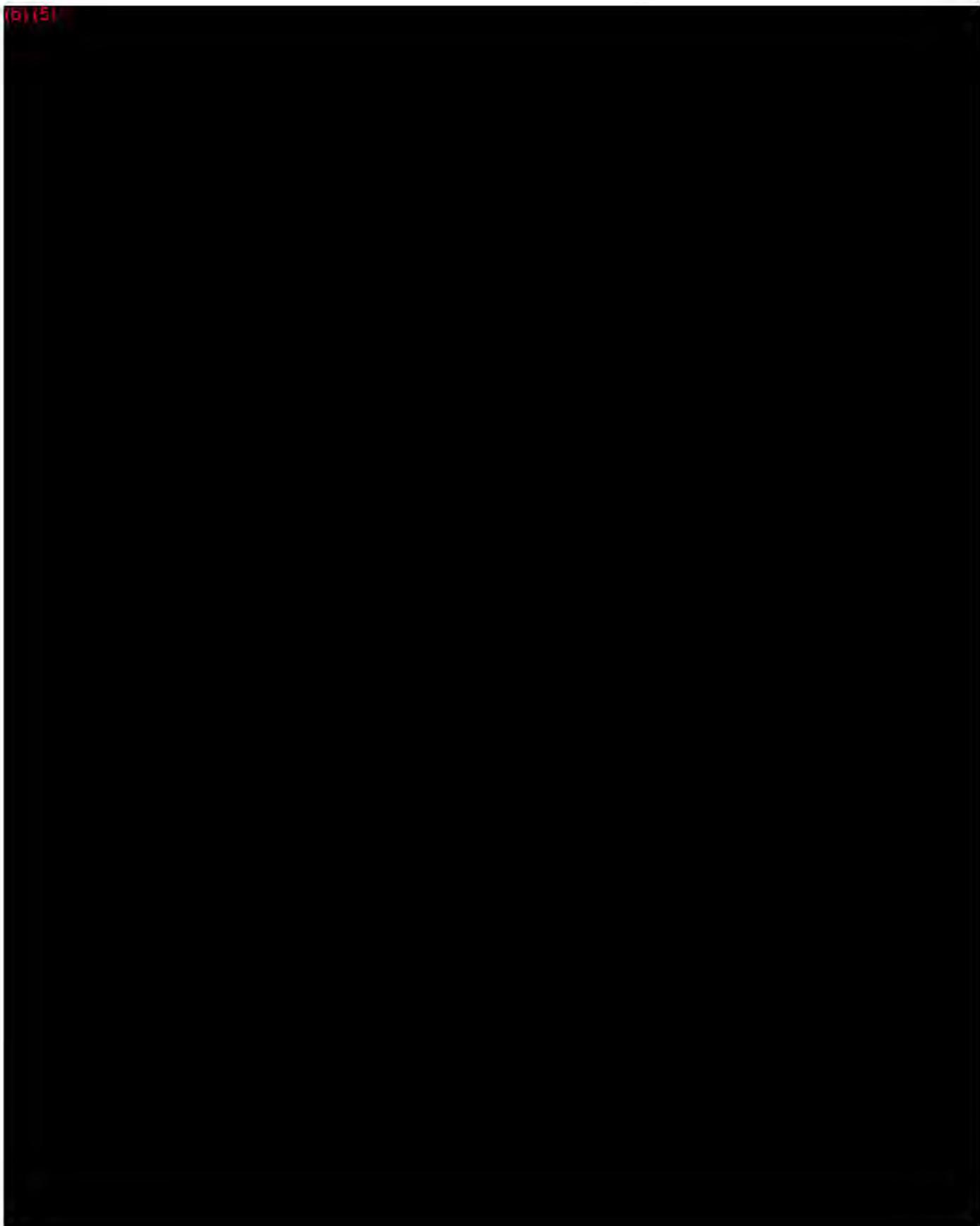
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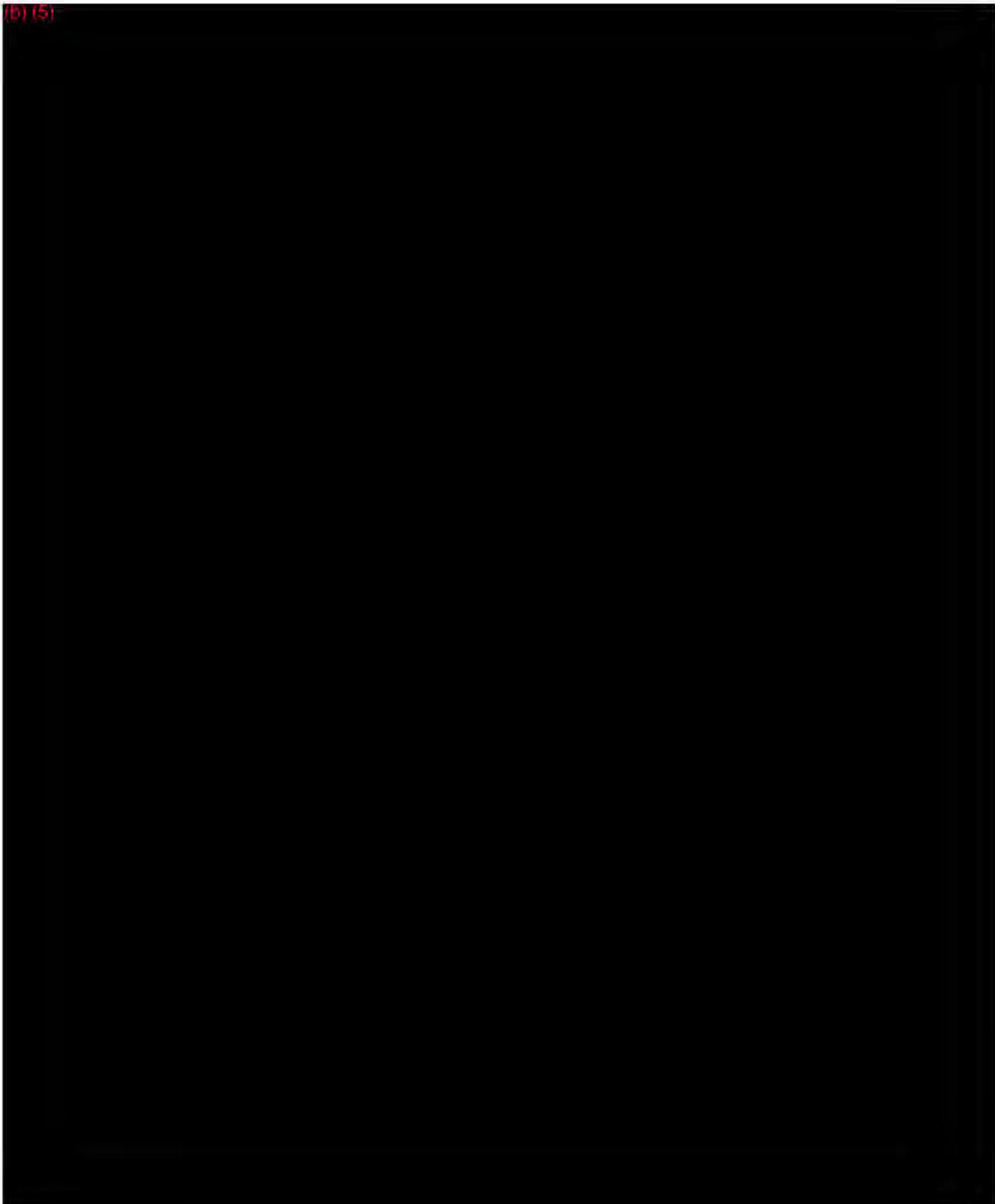
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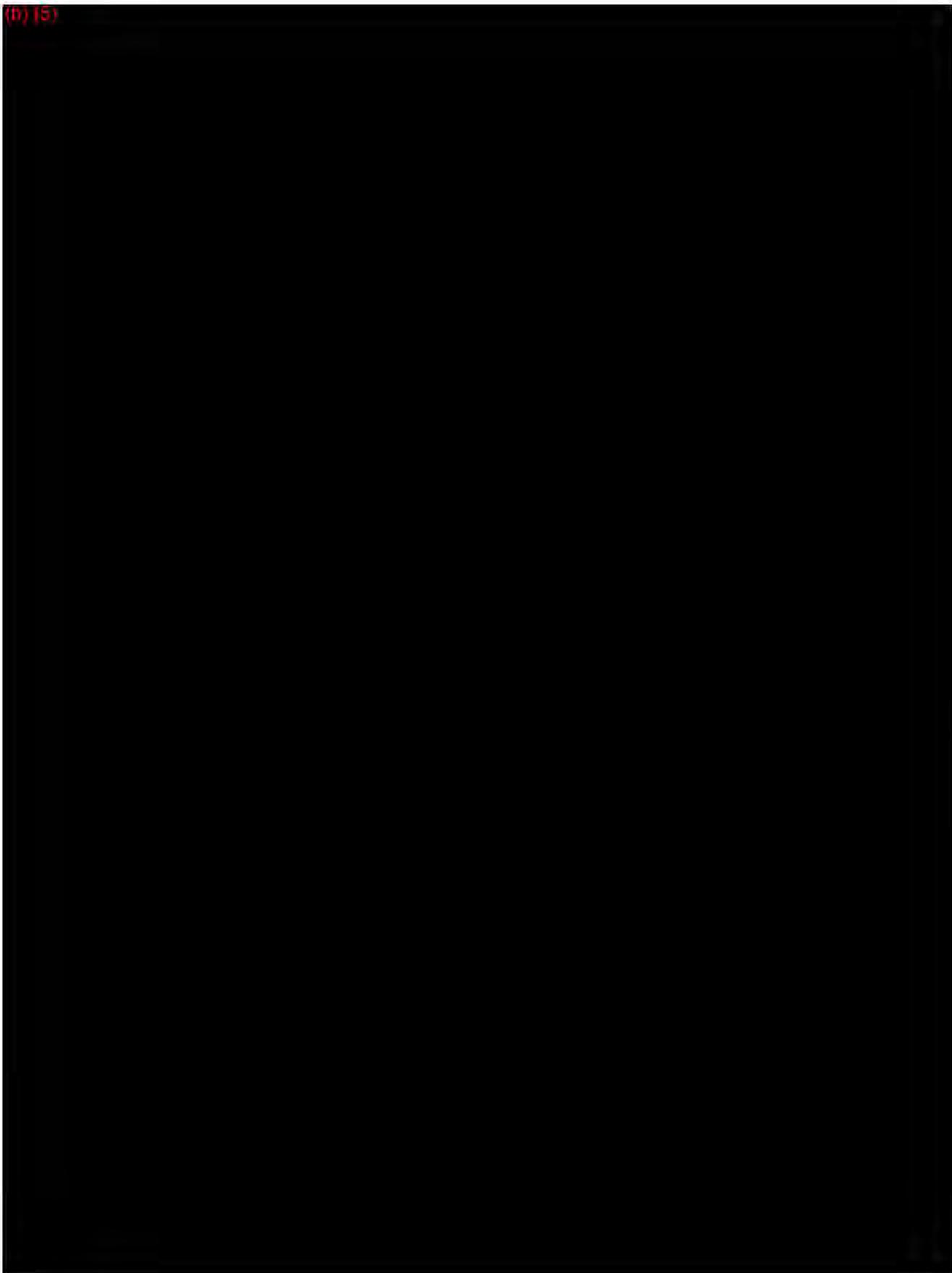
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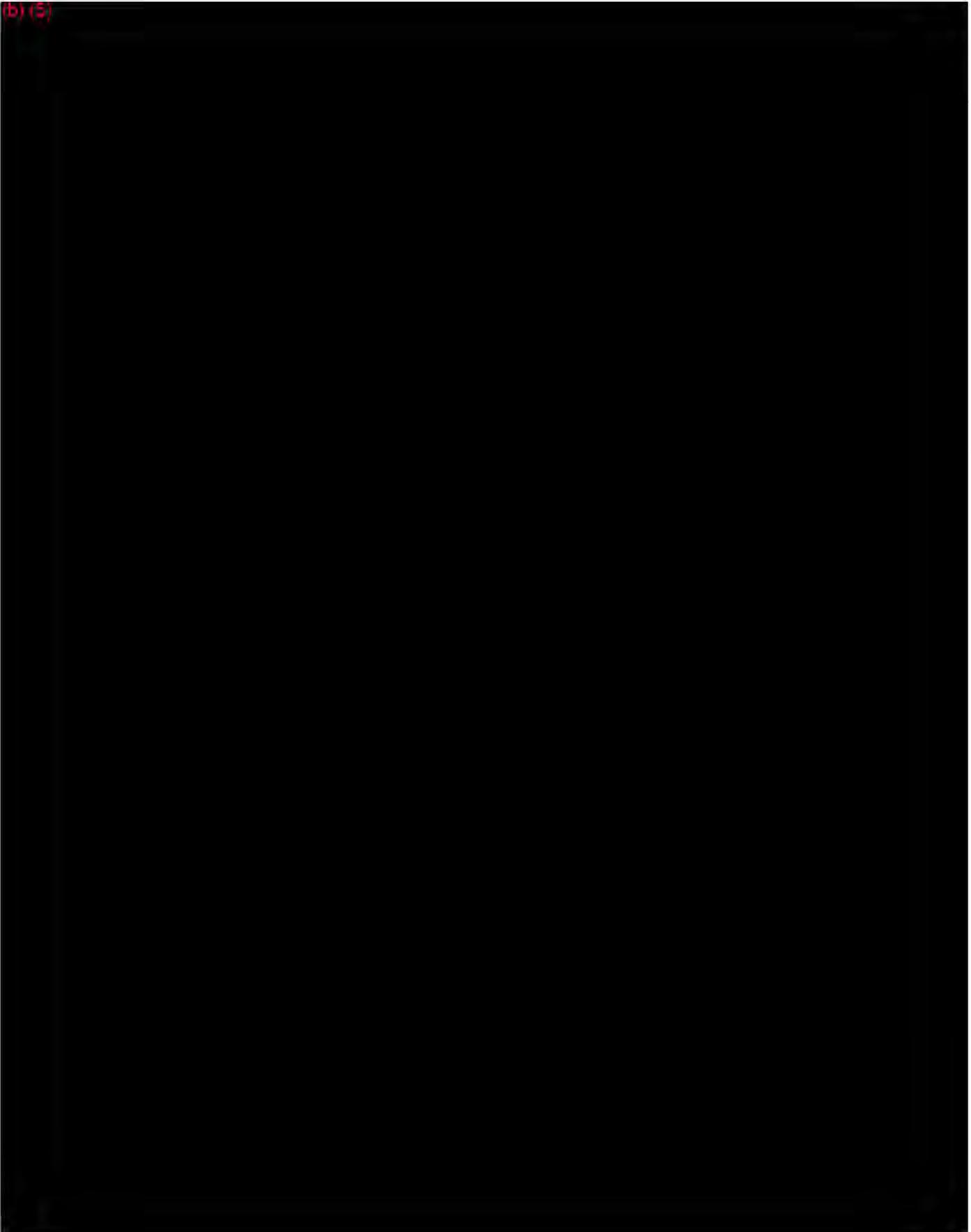
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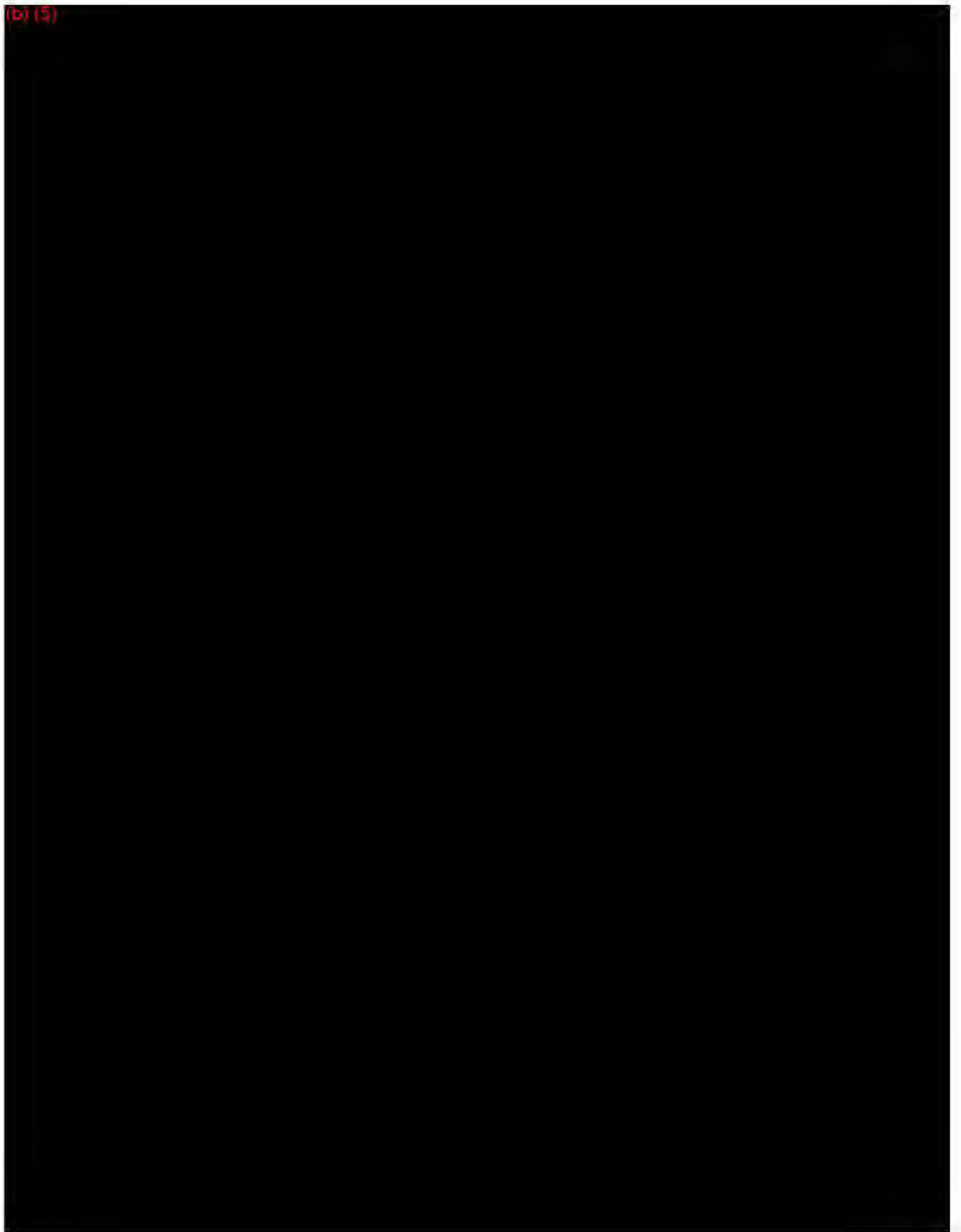
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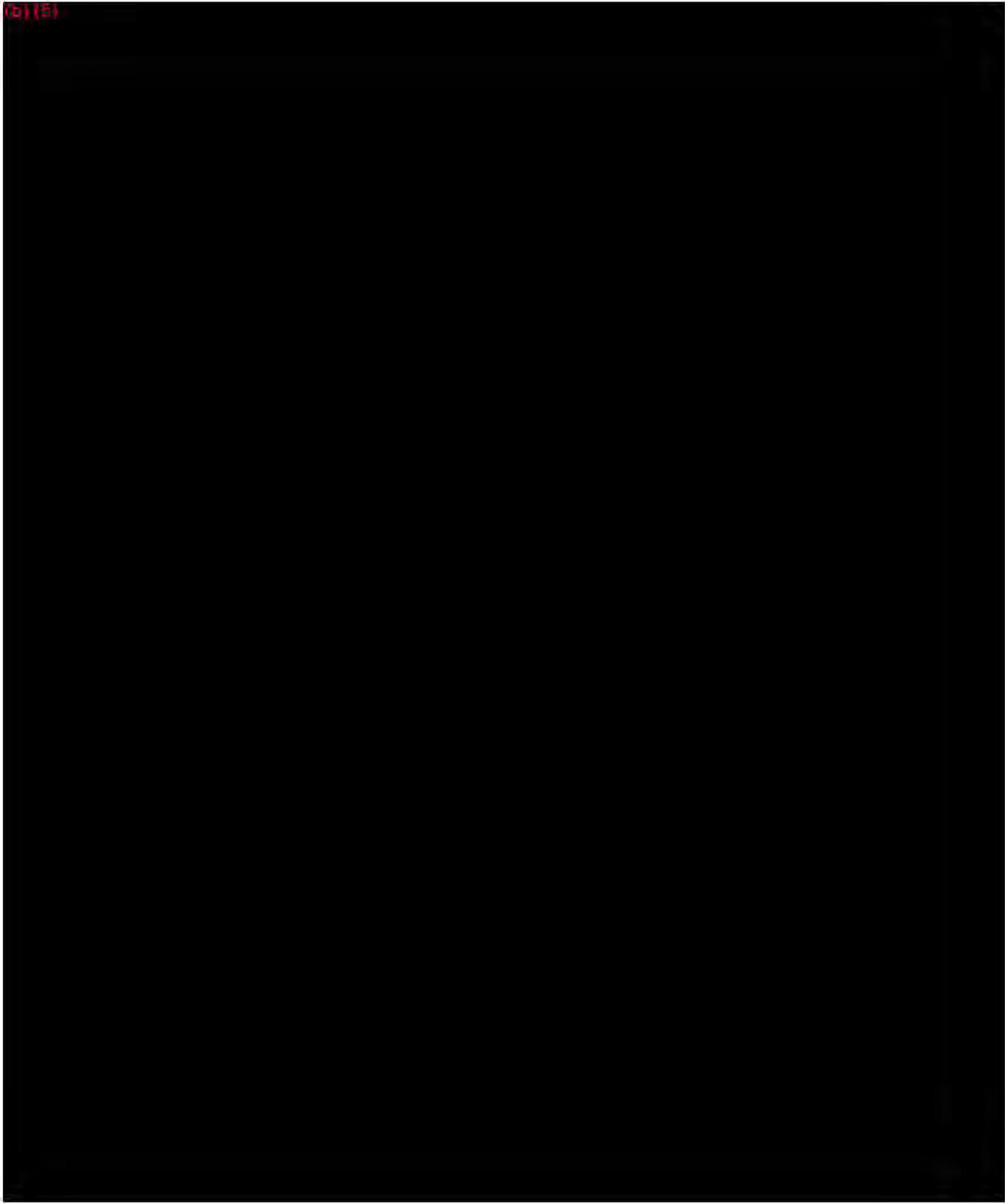
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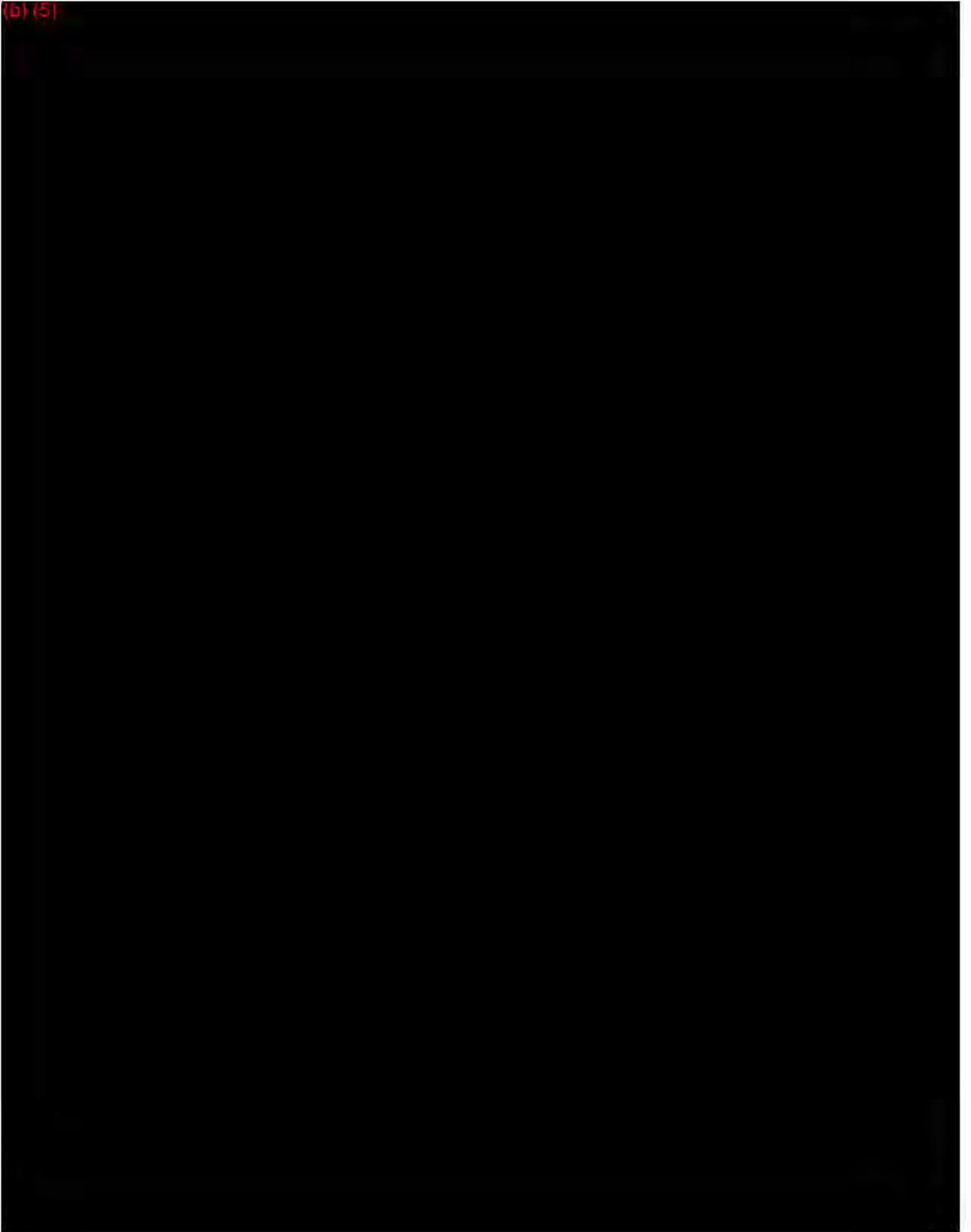
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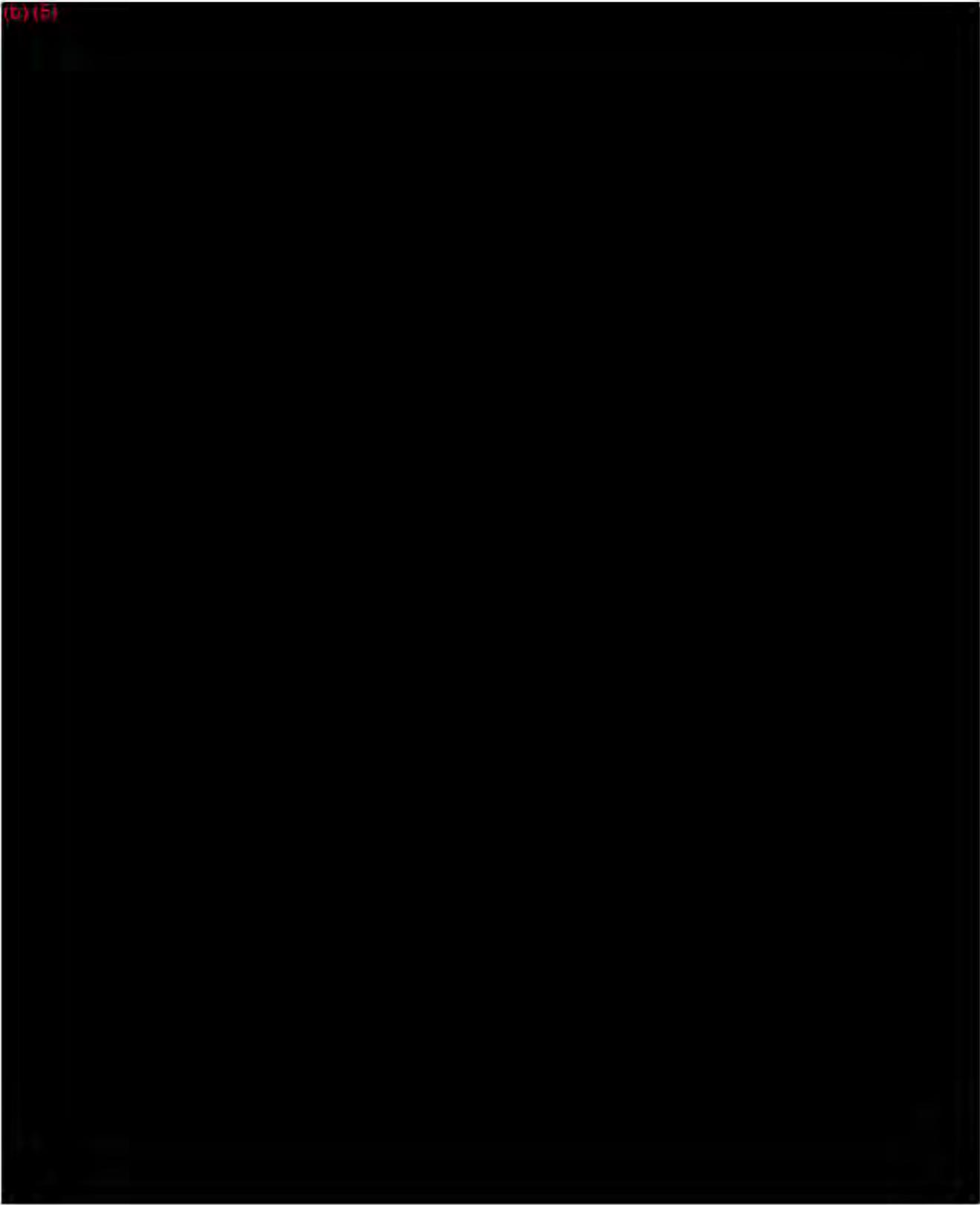
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(b) (5)



From: [Califf, Robert](#)
To: [Auchincloss, Kalah](#)
Subject: RE: a nagging list of loose ends
Date: Tuesday, October 18, 2016 7:54:00 AM

Can't find your "separate" SES plan e mail.

rnc

From: Auchincloss, Kalah
Sent: Monday, October 17, 2016 4:26 PM
To: Califf, Robert
Subject: RE: a nagging list of loose ends

My comments below. Happy to get Caitlin to try to block office time for you to do some of the writing/editing on there; and happy to have her schedule calls as needed.

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21. Eteplirsen letter with Ellis Unger for neurology journal

22. (b) (5)

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rmc

From: [Pink Sheet](#)
To: [Califf, Robert](#)
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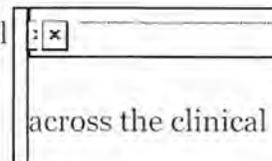
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Smith, Celeste

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From: [Evans, Dana](#)
To: [Califf, Robert](#)
Subject: FW: Pink Sheet | Highlights Of The Week
Date: Monday, October 24, 2016 11:28:56 AM

Dana Evans, M.P.A.

Program Support Specialist to the Commissioner
Office of the Commissioner Immediate Office
U.S. Food and Drug Administration
Phone: 301-796-2021
BB: 301-467-8987
Email: dana.evans@fda.hhs.gov

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To: Commissioner FDA
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EU/UK Drug Approval System

By Maureen Kenny

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By Joanne Eglovitch

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WEEKLY HIGHLIGHTS

Look below for key developments and intriguing perspectives from the past week to inform your strategic decision-making. And check out our new hot topic pages on the drug pricing debate and US elections.



THIS WEEK'S TOP STORIES

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'Standardized' Comment From Brexit Minister Raises Hopes For Parallel EU/UK Drug Approval System

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Investor compares the development construct to homeopathic medicine.

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Only 8% of original ANDAs submitted in the user fee program's third year were approved on the first cycle, compared...

NEWS

Japan Drug Cost Concerns Rise To The Top

Sharply rising medical spending in Japan, driven in part by expensive new drugs, is now attracting attention at the highest...



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10 Questions For Bayer's UK CEO On Market Access Reforms In England

Bayer AG's CEO for the UK and Ireland, Dr. Alexander Moscho, outlines his concerns about the reformed cancer drugs reimbursement...

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NIH Funding Component of 21st Century Cures May Get White House Boost

Vice President's Cancer Moonshot project could provide final thrust for '21st Century Cures' bill in the lame duck Congressional session...

ANALYSIS

FDA Continues To Speed PD-1/L1 Drugs To Market

The four-month review of Merck's Keytruda for first-line lung cancer is a reminder of how quickly the agency has acted...

NEWS

Merck's C. Diff Drug Zinplava Clears FDA With Heart Failure Warning

Following panel recommendation, label includes warning of use of bezlotoxumab in patients with history of congestive heart failure; postmarketing commitments...

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EMA Maps Global Drug Supply Chain Regulatory Gaps For ICMRA

Gaps and overlaps in global and regional efforts to protect pharmaceutical supplies from intrusion of fake drugs, manufacturing quality problems...

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FDA Enforcement And Compliance In Brief

FDA traces B. cepacia to PharmaTech, Nippon Workers blocked FDA investigator, Yangzhou Hengyuan used wrong API, FDA bans two Chinese...

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Subject: Readings
Date: Wednesday, October 26, 2016 8:14:58 AM
Attachments: [HHS Secretary's News Briefing for Wednesday October 26 2016.msg](#)
[The FDA News Summary for Wednesday October 26 2016.msg](#)
[Center for Tobacco Products News Briefing for Wednesday October 26 2016.msg](#)

Smith, Celeste

From: Bulletin Intelligence <HHS@BulletinIntelligence.com>
Sent: Wednesday, October 26, 2016 6:04 AM
To: HHS@BulletinIntelligence.com
Subject: HHS Secretary's News Briefing for Wednesday, October 26, 2016

HHS SECRETARY'S NEWS BRIEFING

WEDNESDAY, OCTOBER 26, 2016 6:00 AM EDT

Zika Virus News:

ZIKA VIRUS "NOT CONTROLLABLE": CDC DIRECTOR'S GRIM WARNING

USA Today (10/25, Alan Gomez)

USA Today reports that Centers for Disease Control and Prevention director Dr. Thomas Frieden "delivered a grim assessment Tuesday of the government's ability to contain Zika." According to Frieden, "Zika and other diseases spread by (the *Aedes aegypti* mosquito) are really not controllable with current technologies." He added, "We will see this become endemic in the hemisphere." Speaking at the CityLab 2016 conference, Frieden said the best case scenario for a Zika vaccine is "two to three years" away, and emphasized the importance of mosquito control, public health funding, and education.

More Coverage. [Scientists Are Bewildered By Zika's Path Across Latin America](#) (Washington Post, 10/25, Dom Phillips And Nick Miroff), [Zika Virus: "We Will See This Become Endemic" CDC Says](#) (Miami Herald, 10/25, Daniel Chang)

Flint Water News:

DEMS CHALLENGE STATE BAN ON CITY OF FLINT LAWSUITS

Detroit News (10/25)

The Detroit News reports five Democratic members of Michigan's congressional delegation have requested that the US Department of Justice review the decision of the Flint Receivership Transition Advisory Board to require that any "city-initiated litigation" be approved by the board. The five Representatives "argue the move was illegal and raises constitutional due process, equal protection and environmental justice issues." MLive (MI) reports the five Representatives made their request in a letter to Attorney General Loretta Lynch. The article points out that the decision by the state board prevents the city from filing a lawsuit against the state over the city's water crisis.

More Coverage. [Kildee, Congressional Dems Ask DOJ If Flint Can Sue State Over Water Crisis](#) (MLive (MI), 10/25), [State Legal Tab Tops \\$1M For Workers Not Charged In Flint Water Probe](#) (MLive (MI), 10/25), [Court Declines To Investigate Gov. Snyder's Use Of Public Money For Private Attorneys](#) (MLive (MI), 10/25), [No Grand Jury Probe Of Snyder's Attorney Fees](#) (Detroit News, 10/25), [Ingham Court Says No To Grand Jury On Snyder Legal Fees Over Flint](#) (Detroit Free Press, 10/25, Paul Egan)

Top National Stories:

DONALD TRUMP SAYS 'OBAMACARE IS JUST BLOWING UP,' CITING RATE INCREASES

New York Times (10/25, Patrick Healy and Abby Goodnough)

There is heavy print news media and television coverage this morning of Donald Trump's criticism of the Affordable Care Act on Tuesday after the Obama Administration said on Monday that premiums would increase by about 25 percent in 2017. News outlets highlighted the fact that during his remarks, Trump misspoke, suggesting that either he did not provide full healthcare coverage for his employees, or he did not understand how the ACA works. On its front page, the New York Times reports that on Tuesday, Donald Trump, who needs "a winning political issue in the final two weeks of the presidential race," attacked Hillary Clinton, linking her to the high premium increases for Affordable Care Act plans. He said the "election is going to be about Obamacare," adding that the ACA "is just blowing up." The article points out that on Monday, HHS announced that premiums for ACA plans would rise by an average of 25 percent next year. The piece also says ACA premium hikes pose a last-minute "test for both Mr. Trump and Mrs. Clinton in a campaign that, since starting in the spring of 2015, has not revolved around policy issues to any great extent."

More Coverage: TV. [Trump Misspoke During Criticism Of ACA's Double-Digit Premium Hikes \(CBS Evening News, 10/25\)](#), [Trump Misspoke During Criticism Of ACA's Double-Digit Premium Hikes \(NBC Nightly News, 10/25\)](#), [Trump Misspoke During Criticism Of ACA's Double-Digit Premium Hikes \(ABC World News Tonight, 10/25\)](#)

More Coverage: Print and Online. [Trump: 'My Employees Are Having A Tremendous Problem With Obamacare' \(CNN, 10/25, Jeremy Diamond, Julia Manchester and Ashley Killough\)](#), [Trump: 'My Employees Are Having A Tremendous Problem With Obamacare' \(Politico, 10/25, Louis Nelson\)](#), [Trump Cites Support Of His Golf Course Employees As He Attacks Obamacare \(Washington Post, 10/25, Sean Sullivan, Anne Gearan and Ed O'Keefe\)](#), [Donald Trump Serves Up Piping Hot Nonsense On Obamacare \(Huffington Post, 10/25, Jeffrey Young\)](#), [Health-Coverage Confusion As Trump Attacks 'Horrible' Obamacare \(Wall Street Journal, 10/25\)](#), [Donald Trump Had A Chance To Talk About Bad News For Obamacare. He Got Very Distracted \(Los Angeles Times, 10/25\)](#), [Trump Highlights His Employees' 'Tremendous' Struggles With Obamacare \(Washington Examiner, 10/25\)](#), [Trump Trips Up As He Trashes Obamacare \(CNBC, 10/25\)](#), [Trump: Obama Using 'phony Number' On Healthcare Increase \(New York Post, 10/25\)](#), [Parsing Donald Trump's Confused, Confusing Explanation Of Why He Doesn't 'use' Obamacare \(Washington Post, 10/25, Philip Bump\)](#), [Trump: Obamacare Is 'just Blowing Up,' 25 Percent Rate Hike A 'phony Number' \(Washington Times, 10/25, David Sherfinski\)](#), [Media Pounce On Trump's Obamacare Misstatement \(Washington Examiner, 10/25\)](#), [Trump Contradicts Himself On Obamacare Attack \(USA Today, 10/25, Eliza Collins\)](#), [Trump Calls ObamaCare Stats 'A Lie' \(The Hill, 10/25, Peter Sullivan\)](#), [Trump Blasts Obamacare At His Miami Golf Course But Misstates Employees' Coverage : NPR \(NPR, 10/25\)](#), [Trump Seizes On Obamacare Cost Increases To Try And Boost Campaign \(Bloomberg Politics, 10/26\)](#), [Trump Urges Big Turnout In Florida Early Voting, Rips Obamacare \(Newsday \(NY\) 10/25\)](#)

Health Insurance Marketplaces:

AETNA SAYS OBAMACARE PLANS 'AREN'T WORTH IT' TO HEALTHY PEOPLE

Bloomberg News (10/25, Zachary Tracer)

Bloomberg News reports that according to Aetna Inc. CEO Mark Bertolini, healthier Americans "will avoid buying Affordable Care Act health insurance plans as premiums climb, threatening the stability of the market." He said during a summit in New York, "As the rates rise, the healthier people pull out because the out-of-pocket costs aren't worth it."

DAYTON ASKS LEGISLATIVE LEADERS TO CRAFT FIX FOR RISING PREMIUMS IN INDIVIDUAL MARKET

Minneapolis Star Tribune (10/25)

The Minneapolis Star Tribune reports that on Monday, Minnesota Gov. Mark Dayton said "legislative leaders need to craft a plan by Nov. 1 or 'for a short while thereafter' if he is to convene legislators for an emergency legislative session." Dayton seeks "to provide relief to thousands of Minnesotans who face steep premium increases on plans purchased through the individual health insurance market."

Health Reform & Healthcare:

BURWELL TOUTS ACA GAINS, EXPANSION OF FEDERAL SUBSIDIES DURING INTERVIEW

CNN (10/25)

CNN interviewed HHS Secretary Sylvia Burwell about the Obama Administration's recent announcement regarding rising premiums for Affordable Care Act plans. Burwell explained that the premium hikes will not impact some 85 percent of Healthcare.gov users because they will receive Federal subsidies to offset the higher costs. She pointed out that even in Arizona, where premiums are expected to more than double in 2017, "75% of the folks actually have subsidies that will help them so that they're insulated from the changes. Additionally, the state of Arizona, because they did have lower rates to begin with, will see a large number of people who are eligible now for the subsidies." Burwell went on to tout ACA gains, such as the fact that some 20 million Americans have gained access to healthcare coverage thanks to the healthcare law. She also pointed out that the Administration continues to develop tools to improve the enrollment process.

More Coverage. [Burwell Does Damage Control On Obamacare Price Hikes \(Washington Examiner, 10/25\)](#), [Obama Admin Shamelessly Spins Premium Hikes \(Daily Caller, 10/25, Robert Donachie\)](#)

WHY HEALTH CARE PREMIUMS ARE RISING UNDER OBAMACARE

ABC News (10/25)

On its website, ABC News reports that on Monday, the Obama Administration said premiums for Affordable Care Act plans will increase by 25 percent in 2017. By comparison, premiums rose by just 7.5 percent in 2016. The article says HHS Secretary Sylvia Mathews Burwell warned that insurers "are 'continuing to adapt' to a market that looks very different than it did before Obamacare, one in which they are trying to compete for customers 'based on price and quality,' and not necessarily by 'finding the healthiest customers.'" She added that efforts to hinder the ACA are also contributing to rising premiums.

OBAMACARE PREMIUM HIKES COULD BE GOOD NEWS FOR REPUBLICANS. BUT JUST HOW GOOD?

Washington Post (10/25, Amber Phillips)

Amber Phillips writes in the Washington Post "The Fix" that congressional Republicans were ready on Monday when the Obama Administration announced premiums for Affordable Care Act plans would rise by an average of 25 percent. The piece says Sen. John McCain (R-AZ) "was first out of the gate because he likely knows some of the biggest hikes could come in his state as the number of participating health insurance plans in Arizona drops from 65 to four." Other GOP lawmakers are expected to follow suit. They are betting that "in the final few weeks of the campaign, Obamacare is going to become toxic," yet, that is not a certainty, because evidence suggests "no party is going to reap any significant Obamacare-related vote: The country is split along party lines on approval or disapproval of the law, and health-care costs don't seem to be topping voters' concerns right now."

More Coverage. [Obamacare Premiums Are Going Up 25 Percent. So What Happens Next?](#) (Politico, 10/25), [Republicans Go On Offense Over Obamacare](#) (CNN, 10/25, Stephen Collinson), [GOP Candidates Seize On Premium Increases In Affordable Care Act](#) (Wall Street Journal, 10/25, Louise Radnofsky and Reid J. Epstein), [Trump, GOP Rediscover Familiar Campaign Foe: Obamacare](#) (Politico, 10/25, By Paul Demko and Rachana Pradhan), [ObamaCare Hikes Create Opening For GOP](#) (The Hill, 10/25, Sarah Ferris), [Obamacare Rates Surge – The Morning Call](#) (Allentown (PA) Morning Call, 10/25), [Hillary Clinton Ignores Obamacare's Bad News, Says Repealing Law Would Be Counterproductive](#) (Washington Times, 10/25, Tom Howell Jr.), [#ObamacareInThreeWords Spikes Along With Premiums](#) (USA Today, 10/25, William Cummings), [Trump, GOP Look To 'Obamacare' Report As Comeback Lifeline](#) (Associated Press, 10/25, Steve Peoples and Jonathan Lemire)

REPUBLICANS POUNCE ON OBAMACARE AFTER WHITE HOUSE ANNOUNCEMENT

Fox News (10/25)

Fox News reports that on Monday, Republicans "blasted" the Obama Administration after it announced that premiums for Affordable Care Act plans would rise by 25 percent in 2017, and that many marketplaces would have just one option. For instance, Donald Trump declared that the ACA was "over." Meanwhile, House Speaker Paul Ryan (R-WI) "accused Democrats of only wanting to double-down on Obamacare instead of fix it and vowed that Republicans would 'replace it with real, patient-centered solutions that fit your needs and your budget.'"

More Coverage. [Premiums To Skyrocket For Some Obamacare Customers](#) (U.S. News & World Report, 10/25), [ObamaCare Fallout: As Premiums Rise, So Does Cost To Taxpayers](#) (Fox News, 10/25)

DEMS COME TO OBAMACARE'S DEFENSE AFTER PREMIUM HIKES

The Hill (10/25, Peter Sullivan)

The Hill reports that on Tuesday, Democrats defended the Affordable Care Act "amid Republican attacks over premium increases." White House Press Secretary Josh Earnest pointed out that most ACA "enrollees receive financial assistance to shield them from the effect of such increases, and he said about 7 in 10 people will still be able to find a plan for \$75 or less a month." Meanwhile, former President Bill Clinton acknowledged that the ACA can be improved in some ways, and mentioned "Hillary Clinton's proposals to add a public option to increase competition among insurers and to let people 55 and over buy into Medicare."

More Coverage. [Baldwin Says Obamacare Needs Some Fixes, But Not Repeal](#) (Associated Press, 10/25)

WHAT WILL THE OBAMACARE PREMIUM HIKE MEAN FOR YOU?

Christian Science Monitor (10/25)

The Christian Science Monitor reports that increases in premiums for Affordable Care Act plans will not impact all consumers, given that most Americans have employer-sponsored healthcare coverage. In addition, most Healthcare.gov users will be able to take advantage of Federal subsidies. HHS data show that among "the 11 million Americans who bought health plans on the federal exchanges through June of this year, 84 percent used federal subsidies to help defray the cost."

More Coverage: TV. [Consumers Uncertain How ACA Premium Hikes Will Impact Them](#) (NBC Nightly News, 10/25)

More Coverage: Print and Online. [Premium Rates Rise For New Jersey Residents](#) (Press of Atlantic City (NJ), 10/25), [Double-digit Premium Hikes Unlikely To Affect Most Obamacare Shoppers](#) (Modern Healthcare, 10/25), [Wisconsin Obamacare Rates To Increase By Average Of 16% In 2017; Deductibles Rising](#) (Milwaukee Business Journal, 10/25, Rich Kirchen), [Obamacare Premiums Set To Increase In N.D.](#) (Grand Forks (ND) Herald, 10/25), [Minn. Health Premiums In Individual Market Now Considered Above Average](#) (Minneapolis Star Tribune, 10/25), [New York To Be Spared Worst Of ObamaCare Premium Increases](#) (New York Post, 10/26), [Arizona Faces Steepest Obamacare Hike In U.S.; Subsidies Could Curb Pain](#) (Arizona Daily Sun, 10/26)

CLINTON: HEALTH CARE COSTS WOULD 'SKYROCKET' UNDER TRUMP

Politico (10/25, By Brent Griffiths)

Politico reports that on Tuesday, Hillary Clinton acknowledged that "many Americans are seeing their premiums go up under" the Affordable Care Act, yet she "cautioned against scrapping" the ACA, "and said health care costs would 'skyrocket' under a President Trump."

More Coverage. [Clinton Promises To 'Tackle' Rising ObamaCare Premiums](#) (The Hill, 10/25, Peter Sullivan), [Hillary Clinton's Poorly Worded Defense Of Obamacare](#) (Washington Examiner, 10/25)

WILL OBAMACARE RATE SPIKE CREATE SMALL BIZ JOB STARVATION?

Fox Business (10/25)

Fox Business reports that rising premiums for Affordable Care Act plans mean "business owners are being dealt a fresh blow." Commenting on the news that ACA premiums will increase by an average of 25 percent next year, Kevin Kuhlman, Director of Federal Public Policy at the National Federation of Independent Business, stated, "Our members are disappointed but aren't surprised to see health-insurance premiums increased significantly. ... The rising cost of health insurance has been the biggest problem confronting their businesses for decades, and the Affordable Care Act exacerbated the cost problem."

AMERICANS' SALARIES CAN'T KEEP UP WITH RISING MEDICAL COSTS

New York Post (10/26)

The New York Post reports a new study released by the Commonwealth Fund found that "Americans are spending more of their paychecks on health insurance because stagnant wages aren't keeping up with spiraling medical costs." Data show that "premiums and deductibles grabbed 6.5 percent of workers' paychecks in 2006, growing to 8.4 percent in 2010 and 10.1 percent in 2015." The article points out that those figures did not include co-pays for physician office visits and prescription drugs.

US FDA ADDS ABUSE WARNING TO PRESCRIPTION TESTOSTERONE

Reuters (10/25, Toni Clarke)

Reuters reports that the Food and Drug Administration has added a new warning to the labels of drugs used to treat low testosterone. According to the FDA, the new warning "will alert prescribers to the abuse potential of testosterone and the serious adverse outcomes, especially those related to heart and mental health." The move "is the latest in a series of actions the agency has taken to try to curb prescriptions of a product whose use has soared over the past decade, especially among middle-aged men."

More Coverage. [FDA Steps Up Warnings For Testosterone, Other Steroids](#) (NBC News, 10/25, Maggie Fox)

SHOULD THE FOOD INDUSTRY SNEAK VEGETABLES INTO FOOD?

New York Times (10/25, Bettina Elias Siegel)

The New York Times analyzes the idea of food companies "sneaking" healthy ingredients into food products with the aim of children eating healthier food and compares it to parents doing the same thing with their own children. The article points out several questions raised by such practices and also highlights companies that have sold such products, often marketed to parents concerned about their children's diets. The article points out that nine out of 10 American children do not eat enough vegetables and six out of ten do not eat enough fruit, according to the Centers for Disease Control and Prevention.

Blogs:

GOVERNMENT FILES BRIEF IN HOUSE V. BURWELL; ASPE LAYS OUT 2017 PLANS AND PREMIUMS

Health Affairs (10/25, Timothy S. Jost)

In a blog entry for Health Affairs, Timothy S. Jost, JD, a member of the Institute of Medicine, writes that on Oct. 24, HHS "Secretary Sylvia Burwell and Treasury Secretary Jacob Lew filed their initial brief in their appeal of House v. Burwell in the Court of Appeals of the District of Columbia Circuit." Also on Oct. 24, "Healthcare.gov also opened for consumers to window shop for 2017 plans," and "to accompany the opening of window shopping, the HHS Assistant Secretary for Planning and Evaluation [ASPE] released a report on Health Plan Choice and Premiums in the 2017 Health Insurance Marketplace."

OBAMACARE PREMIUMS TO INCREASE BY 25 PERCENT

Business Insider (10/25, Noah Friedman and Linette Lopez)

In a video blog entry for the Business Insider, Noah Friedman and Linette Lopez write, "President Obama is defending the upcoming 25% premium increase in health insurance plans under the Affordable Care Act," even as "Republicans such as presidential candidate Donald Trump say the double-digit increase is proof the system is not working."

JOE SCARBOROUGH: EVERYTHING CONSERVATIVES PREDICTED ABOUT OBAMACARE HAS COME TRUE

Mediaite (10/25, Alex Griswold)

In a blog entry for the Mediaite, Alex Griswold writes, "After the Barack Obama administration announced Monday that healthcare premiums were expected to rise by double-digit percentages, the panel of MSNBC's Morning Joe noted just how prescient Republican criticisms of the Affordable Care Act really were." Host Willie Geist said that Trump now has "an issue he can use if he's smart, which is this Obamacare story about premiums going up 25% in certain plans, 22% in other plans, and choice shrinking. All things predicted by conservatives many years ago," he added. Co-host Joe Scarborough agreed, saying, "Everything conservatives predicted coming true with Obamacare."

5 POINTS ON THE OBAMACARE PREMIUM SPIKES AND WHAT THEY MEAN

Talking Points Memo (10/25, Tierney Sneed)

In a blog entry for the Talking Points Memo, Tierney Sneed provides "five points that help better understand the political and policy dynamics at play" behind Monday's announcement that Affordable Care Act individual marketplace premiums "will go up by an average of more than 20 percent for the 2017 plan year." Sneed points out that those premiums were anticipated to jump, subsidies "will help cushion the blow," geography "plays a drastic role in the premium increases customers will see," premium spikes "reflect an under-pricing of plans by insurers in the ACA's initial years that they are now correcting for," and the problems, while "real," are indeed "fixable," through "more generous subsidies" and a "stronger individual mandate."

4 FACTS ABOUT OBAMACARE PREMIUMS YOU SHOULD KNOW BEFORE YOU START FREAKING OUT

Think Progress (10/25, Tara Culp-Ressler)

In a blog entry for Think Progress, Tara Culp-Ressler provides "a few key pieces of context that help put the news about Obamacare's price hikes into perspective," namely that while premiums are rising, so are subsidies; the government anticipated that ACA premiums would rise; most Americans do not get health insurance through ACA plans; and finally, opponents of the ACA "keep standing in the way" of improving the health reform law.

THE WHITE HOUSE SERVED DONALD TRUMP THE CASE AGAINST OBAMACARE ON A SILVER PLATTER – AND HE STILL BLEW IT.

New Republic (10/25, Nicole Narea)

In a blog entry for the New Republic, Nicole Narea writes, "The White House served Donald Trump the case against Obamacare on a silver platter – and he still blew it." On Oct. 24, "the White House released a report estimating that Affordable Care Act premiums will go up by an average of 25 percent next year." Trump, however, "instead of empathizing with those affected by the hikes and proposing a solution...hailed it as an I-told-you-so moment," and went on to hold a "press conference in which he claimed that all of his employees are having 'a tremendous problem with Obamacare,' which is blatantly false."

TRUMP SAYS 'ALL' HIS EMPLOYEES STRUGGLE WITH OBAMACARE, THEN DIALS IT BACK

Talking Points Memo (10/25, Allegra Kirkland)

In a blog entry for the Talking Points Memo, Allegra Kirkland writes that on Tuesday, "Donald Trump told reporters...that soaring Obamacare premiums were taking a toll on 'all' of his employees. Then, a few "minutes later, the GOP nominee said the vast majority of his staffers don't receive health care from the federal exchanges created by the President Barack Obama's signature law."

DONALD TRUMP HAS NO IDEA WHAT OBAMACARE DOES

Think Progress (10/25, Ian Milhiser)

In a blog entry for Think Progress, constitutional lawyer and justice editor Ian Milhiser writes, "Republican presidential candidate Donald Trump's employees are having a 'tremendous problem' with health plans they don't actually have." What's more, "Trump himself doesn't make much use of a health plan that he also doesn't have." According to Milhiser, "all of this is a 'disaster' for the American people."

SUPPORTING EFFECTIVE ACTION ON ALTERNATIVE PAYMENT MODELS

Health Affairs (10/25, Samuel Nussbaum, Mark D. Smith, and Dr. Mark McClellan)

In a blog entry for Health Affairs, Samuel Nussbaum, MD, who serves as Chair of the Health Care Payment Learning & Action Network's Alternative Payment Model Framework and Progress Tracking Work Group, Mark D. Smith, MD, MBA, who serves as Co-chair of the Health Care Payment Learning and Action Network's Guiding Committee, and Dr. Mark McClellan, a former administrator of the Centers for Medicare & Medicaid Services and former commissioner of the Food and Drug Administration write, "The Health Care Payment Learning & Action Network (LAN) has been working to support health care providers in achieving these goals by speeding adoption of effective alternative payment models." The Health Care Payment LAN and its "partners – HHS, states, private payers, providers, employers, consumer groups and others – believe that by better aligning health care payments with higher-value approaches to care, we can drive improvements

across the delivery system that translate to better patient outcomes."

Opinion:

THE A.C.A.'S PREMIUM INCREASES ARE A FIXABLE PROBLEM

New York Times (10/25)

The New York Times says in an editorial that the Affordable Care Act is "far from perfect," and offers several suggestions about how to boost enrollment. The Times explains that one way to achieve that goal "would be to increase the penalty." In addition, the law could be "further strengthen[ed]" by offering subsidies to middle-income families who currently receive little or no help." The Times also suggests that lawmakers "consider applying to the health care exchanges the kind of reinsurance program Congress has used to encourage insurers to participate in Medicare's Part D prescription drug benefit program."

TRUMP GAVE CLINTON A PASS ON THE DEATH-SPIRALING OBAMACARE

Washington Post (10/25, Jennifer Rubin)

Jennifer Rubin writes in the Washington Post "Right Turn" blog that the GOP nominated Donald Trump instead of "a policy-proficient, competent candidate who could have explained why Obamacare needs major renovation and spoken coherently about alternatives." As a result, Hillary Clinton "was allowed to skate by without answering hard questions about the long-term viability of Obamacare."

ON EARTH 2, THIS OBAMACARE NEWS IS ABSOLUTELY DEVASTATING FOR HILLARY CLINTON

Washington Post (10/25, Chris Cillizza)

Chris Cillizza writes in the Washington Post that the news about rising premiums for Affordable Care Act plans "is a gift of epic proportions" for Republicans, and it "should be a very bad development" for Hillary Clinton. But, Donald Trump "has spent the last few weeks dealing with allegations of sexual harassment from 11 women and a hot mic tape in which he made a series of lewd comments about women."

OBAMACARE IS NOT 'BLOWING UP.' BUT IT DOES NEED FIXING.

Washington Post (10/25)

The Washington Post argues in an editorial that while Donald Trump's claim that the ACA is "blowing up" is wrong, "that doesn't mean the rate-hike news is insignificant." The Post calls the magnitude of the rate increases "unsustainable" and says the law "is facing a big test." The law, the Post argues, is "a work in progress," and if officials "are interested in solutions rather than point-scoring, there are fixes they can consider."

ACCOUNTABILITY FOR OBAMACARE

Wall Street Journal (10/25)

A Wall Street Journal editorial takes a more pessimistic view of the ACA, casting it as a failure for which voters must hold Democrats accountable. A Republican Congress, the Journal argues, would be well-positioned to negotiate solutions in line with the House GOP's "Better Way" blueprint and begin repairing the individual market and foster more choice and competition.

OBAMACARE HAS SOME PROBLEMS. HERE'S HOW WE CAN FIX THEM.

Washington Post (10/25, Paul Waldman)

Paul Waldman writes in the Washington Post "Plum Line" blog that Donald Trump's comments about the Affordable Care Act on Tuesday suggest he lacks an understanding of the law, yet to be fair, "the Republican presidential nominee is not the only one laboring under misconceptions about what the ACA is, how it works, what its genuine problems are, and how they might be fixed." Indeed, "most people don't understand the law, and given how complicated the topic of health insurance and health policy is, you can't blame them."

OBAMACARE PREMIUMS ARE SPIKING 25% FOR NEXT YEAR. HOW BAD IS THAT?

Los Angeles Times (10/25, Michael Hiltzik)

Michael Hiltzik writes in his Los Angeles Times column that despite the significant increase in Affordable Care Act premiums for 2017, some 84 percent of enrollees will still be able to afford their plans thanks to Federal subsidies. Consumers can also switch to cheaper plans, but Hiltzik points out that this is "an element of Obamacare that has turned the yearly open-enrollment period an annual chore for many people."

OBAMACARE IS A POLICY TRIUMPH AND A POLITICAL FAILURE

Daily Intelligencer (NY) (10/25, Jonathan Chait)

Jonathan Chait writes in the Daily Intelligencer (NY) that despite all its issues, the Affordable Care Act "has made American health care both dramatically more affordable and humanitarian." He points out that some 20 million consumers have gained access to healthcare coverage because of the ACA, yet there is still strong opposition to the healthcare law.

OBAMACARE JUST MADE MY EYES WATER

Forbes (10/25, Simon Constable)

Contributor Simon Constable writes in a Forbes piece that his "eyes are still watering" over the news that premiums for Affordable Care Act plans will rise by an average of 25 percent in 2017. He adds that the problem is likely to worsen in 2018.

2017 RATE HIKES PROVE OBAMACARE IS ONE FAILURE AFTER ANOTHER

The Hill (10/25, Jillian Melchior)

Jillian Melchior, a senior fellow at the Independent Women's Forum, writes in The Hill "Contributors" blog that the Administration's announcement about rising premiums for Affordable Care Act plans highlights the healthcare law's issues. She adds that the ACA "has drastically failed to deliver on its promises of cost-effective insurance."

THE PREDICTABLE OBAMACARE HOUSE OF CARDS COLLAPSE

New York Daily News (10/25, S.E. Cupp)

S.E. Cupp writes in a New York Daily News op-ed that Republicans were right to criticize the Affordable Care Act for being unaffordable, because HHS recently announced that premiums for ACA plans would increase by 25 percent on average. In fact, rates in some states are expected to rise even more.

BIGGEST LOSERS FROM OBAMACARE'S PREMIUM HIKES

Washington Examiner (10/25, Hadley Heath Manning)

Contributor Hadley Heath Manning writes in the Washington Examiner that HHS announced premiums for Affordable Care Act plans will increase by 25 percent next year. He adds, "The biggest losers are Americans who must either buy Obamacare plans with no subsidy or pay a penalty."

MEET THE MAN WHOSE OBAMACARE HEALTH INSURANCE PREMIUM MORE THAN DOUBLED

Fox News (10/25, Todd Starnes)

Todd Starnes writes in a Fox News op-ed about Jay Wells, who has "become a national symbol for the complete and utter failure of President Obama's Affordable Care Act." Starnes adds that Wells "is facing a massive (and I do mean massive) increase in his monthly health insurance premiums, according to a letter he received from BlueCross BlueShield of Georgia."

IS AFFORDABLE HEALTHCARE AFFORDABLE? IS IT PROFITABLE?

The Hill (10/25, Dana Connolly)

Dana Connolly, PhD, a senior staff writer for Sovereign Health, writes in The Hill "Contributors" blog that the Affordable Care Act has succeeded in expanding healthcare coverage to more Americans, but it "is far from perfect." Connolly adds that ACA plans are unaffordable, and many insurers are unhappy because of significant losses.

WILL RISING INSURANCE PREMIUMS SINK OBAMACARE?

Boston Globe (10/25, Evan Horowitz)

Evan Horowitz writes in a Boston Globe op-ed that premiums for Affordable Care Act plans will increase by an average of 25 percent in 2017. He wonders if this spells the end for the ACA, or if it is simply "a one-time course correction, a blip that will barely register in people's budgets," and says that remains unclear at this time.

THE TRUTH ABOUT THOSE RISING HEALTH INSURANCE PREMIUMS

CNN (10/25, Timothy Jost)

Timothy Jost, JD, emeritus professor of law at Washington and Lee University, writes in a CNN piece that the media "and politicians will undoubtedly seize on" HHS' announcement about rising premiums "as further evidence that the Affordable Care Act is a failure," yet "a deeper dig reveals a different story." According to Jost, "while these increases are eye-catching, insurers generally underpriced their plans when the marketplaces opened in 2014, and the current increases simply bring the premiums up to the level predicted when Congress debated the Affordable Care Act in 2009."

TRUMP JUST MADE A BIG MESS OF HIS ATTACK ON OBAMACARE. BUT HE ALSO GOT ONE BIG THING RIGHT.

Washington Post (10/25, Greg Sargent)

Greg Sargent writes in the Washington Post "Plum Line" blog that Donald Trump "botched his attack" on the Affordable Care Act because of rising premiums, but "he reminded us that having health coverage means economic security – before reiterating that he would take it away from many millions of people."

NORTH CAROLINA'S CHANCE FOR A FRESH SENATE VOICE

New York Times (10/26)

A New York Times editorial offers its support for Deborah Ross, a Democrat seeking to unseat Sen. Richard Burr (R-NC),

who has been “caught up...in the controversy over the ‘bathroom bill’ championed by Gov. Pat McCrory,” and has been “in lock step with the Senate Republicans’ irresponsible refusal to grant a hearing to Merrick Garland, Mr. Obama’s nominee for the Supreme Court.” The Times says that Ms. Ross, who supports the Affordable Care Act, “has become pivotal in the Democrats’ hope to take control of the Senate from the Republicans led by Mitch McConnell, who has made it his mission to block President Obama’s initiatives.”

EDITORIAL: PRICE INCREASES COMING FOR OBAMACARE POLICIES. FIXES MUST FOLLOW.

St. Louis Post-Dispatch (10/25)

The St. Louis Post-Dispatch editorializes that the price hikes for insurance plans sold on ACA exchanges are “bad news,” but “private insurers underpriced their plans, and this is a course correction.” The law “need[s] some fixes” but polls show that “most Americans are happy with, or at least unaffected by” the ACA, and that the “loud opposition to it has been politically driven.”

THE WORST OF OBAMACARE IS YET TO COME

New York Post (10/25)

In an editorial, The New York Post writes that rising ACA premiums are “only the tip of the iceberg.” The law “is inflicting damage all across America’s health-care sector – with no end in sight,” just “as critics warned from the start.” The law has “fallen far short” of achieving “universal health insurance,” because the law “was never really written to work, but assembled from the wish-lists of various left-wing wonks and ideologues – hastily stitched together and passed before the voters could stop it.” Now the ACA “is collapsing, and presidential frontrunner Hillary Clinton vows to ‘fix’ it with new spending and even more Washington control of the market.”

RISING BILLS FOR HEALTH CARE LAW ARE NO REASON TO JUNK PLAN

San Francisco Chronicle (10/25)

The San Francisco Chronicle editorializes that the rising cost of healthcare insurance and insurers exiting the Affordable Care Act marketplace are not good reasons for “junking a system that has enrolled 11 million people who wouldn’t have medical coverage otherwise.” GOP legislators have yet to “put forward a replacement for covering the uninsured,” and instead of ending the law, “Washington should concentrate on fixing the Affordable Care Act.”

OBAMACARE IN THREE WORDS? IT’S VERY COMPLICATED

Oregonian (10/25)

In commentary for The Oregonian, Eder Campuzano writes on the #ObamacareInThreeWords hashtag on Twitter, in which people shared stories of the merits and shortcomings of the Affordable Care Act. Campuzano says “summing up the law’s universal effects in three words is extraordinarily difficult, if not impossible,” and though the hashtags are a “great rallying cry” they don’t do much to encourage discourse on the issue.

EDITORIAL: OBAMACARE CONTINUES TO CRUMBLE

Detroit News (10/25)

The Detroit News editorializes that the “Affordable Care Act hasn’t worked since it was implemented in 2013, and it’s becoming increasingly unaffordable.” The legislation “has failed to deliver the improved health care system” the President “promised” when he signed the law six years ago. The Detroit News argues that the ACA “needs a massive overhaul before more damage is done.”

DESPITE OBAMACARE WOES, CENTENE GROWS FROM MEDICAID EXPANSION

Forbes (10/25, Bruce Japsen)

Forbes contributor Bruce Japsen writes that Centene Corp. is “grabbing headlines” because its revenue continues to grow from the Affordable Care Act’s expansion of Medicaid and the company continues to offer health insurance plans on ACA exchanges in markets where other insurers have withdrawn. Japsen says Centene will benefit if more states expand Medicaid.

A SMALL VICTORY, BUT VIRGINIA’S ABORTION WARS RAGE ON

Washington Post (10/25)

In an editorial, the Washington Post asserts “it would be nice” if the decision by the Virginia Board of Health to exempt abortion clinics from a law that had “ultimately failed...to regulate state abortion clinics out of business” would “put paid to the abortion wars in the commonwealth.” However, the Post laments that despite the “small victory” in the state, the anti-abortion lobby and lawmakers “have little regard for court precedent and are sure to continue their attacks.” Although “the rule of law has prevailed and abortion services remain available in Virginia,” the Post concludes, “sadly, they...remain vulnerable.”

HIRSHBERG TO PODESTA: WE DON’T REALLY KNOW ANYTHING ABOUT GMOS

The Hill (10/25, Julie Kelly)

In an opinion piece for The Hill "Contributors" blog, Julie Kelly, a National Review Online contributor, writes that several emails between Gary Hirshberg, "a wealthy Democratic Party donor and chairman of the organic yogurt company Stonyfield Farm," and Clinton campaign chair John Podesta "released by WikiLeaks expose Hirshberg's duplicitous narratives" about GMO foods. According to Kelly, the emails show Hirshberg admits that GMO labels "are a marketing attack against major food companies." Kelly warns that anti-GMO activists "will continue to work behind the scenes in a Clinton Administration to get mandatory, on-package GMO labels."

National Front Page News:

HEADLINES FROM TODAY'S FRONT PAGES.

Wall Street Journal:

[Apple Pins Hopes On iPhone Revival](#)

[Florida Once Again A Focus In 2016 Campaign](#)

["There Are No More Panes Of Glass Left In Aleppo"](#)

[IPO Market Is Finally Looking Up Again](#)

New York Times:

[The Pentagon's "Terminator Conundrum": Robots That Could Kill On Their Own](#)

[Seizing On Rising Costs, Trump Says Health Law Is 'Over'](#)

[What Drives Donald Trump? Fear Of Losing Status, Tapes Show](#)

[AT&T Cheerleading Squad For Merger: Nearly 100 Lobbyists](#)

[Steven Banks Was Hired To Stem New York's Homelessness Crisis. It Didn't Happen.](#)

[As ID Laws Fall, Voters See New Barriers Rise](#)

Washington Post:

[Zika Leaves A Confusing Trail Across Americas](#)

[Leak Shows Turmoil On Clinton Team Over Emails](#)

[Trump's Big-Donor Events Ending](#)

[In Lawsuits, Race And Gender Can Diminish Awards](#)

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Smith, Celeste

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TO: THE COMMISSIONER AND SENIOR OFFICIALS

DATE: WEDNESDAY, OCTOBER 26, 2016 6:00 AM EDT

TODAY'S EDITION

FDA In The News

The Health Care Payment Learning And Action Network Supports Effective Action On APMs. 1

Medical Product Safety

FDA Warns On Decorative Contact Lenses. 1

FDA Issues Draft Guidance On Design Of Late-Stage Trials For Female Libido Drugs. 2

FDA Adds Warning Of Abuse Potential For Medications Treating Low Testosterone. 2

Efforts To Increase Hospital Sinks May Have Backfired By Contributing To Several Outbreaks. 2

Device To Heal Bone Fractures May Be Ineffective, Study Suggests. 2

PhRMA Asks Members For An Additional \$100 Million Annually To Prepare For Post-Election Battle On Drug Pricing. 2

Arformoterol May Be Safe In Combination With Tiotropium In COPD Treatment, Study Suggests. 2

HeartWare Recalls Some Of Its HVAD Ventricular Assist Device Pumps Due To Design Problem. 3

Researchers Hopeful Nanoparticle Ultraviolet Radiation Technology May Be Next Step In Killing Cancer Cells While Cutting Down On High-Energy Radiation Doses. 3

FDA Launches Whistleblower Website For Medical Device "Regulatory Misconduct." 3

FDA Approves sNDA To Update US Prescribing Information For Enzalutamide Capsules To Include New Clinical Data From TERRAIN Trial. 3

"External FDA Expert" Criticizes Agency's Approval Of Eteplirsen In JAMA. 3

FDA Issues Warning Letter To Alabama Drug Compounder. 3

Food Safety

Food Companies "Sneaking" Healthy Ingredients Into Food Products Raises Questions. 3

Opinion: WikiLeaks Emails Show GMO Labeling Advocates Advance Duplicitous Narratives. 4

USDA Investigation Of Raw Milk Farm Expands To Buying Clubs. 4

Wildly Unbalanced Consumption Of Omega-6 Vs Omega-3 Fatty Acids Contributing To Growing Rates Of Obesity, T2D, Researchers Contend. 4

FDA IN THE NEWS

The Health Care Payment Learning And Action Network Supports Effective Action On APMs.

In a blog entry for [Health Affairs](#) (10/25, 29K), Samuel Nussbaum, MD, who serves as Chair of the Health Care Payment Learning & Action Network's Alternative Payment Model Framework and Progress Tracking Work Group, Mark D. Smith, MD, MBA, who serves as Co-chair of the Health Care Payment Learning and Action Network's Guiding Committee, and Dr. Mark McClellan, a former administrator of the Centers for Medicare & Medicaid Services and former commissioner of the Food and Drug Administration write, "The Health Care Payment Learning & Action Network (LAN) has been working to support health care providers in achieving these goals by speeding adoption of effective

alternative payment models" (APMs). The Health Care Payment LAN and its "partners – HHS, states, private payers, providers, employers, consumer groups and others – believe that by better aligning health care payments with higher-value approaches to care, we can drive improvements across the delivery system that translate to better patient outcomes."

MEDICAL PRODUCT SAFETY

FDA Warns On Decorative Contact Lenses.

[ABC World News Tonight](#) (10/25, story 8, 0:20, Muir, 14.63M) reported that the Food and Drug Administration is "urging people not to wear nonprescription decorative contact lenses with their" Halloween "costumes, saying they may cause severe eye problems, even possible blindness." The contact lenses, which "are sold over the counter," may "be contaminated with bacteria or contain chemicals that could infect your eyes."

nebulized arformoterol tartrate (Brovana) with the commonly prescribed tiotropium (Spiriva)." The findings were presented at a poster discussion at CHEST 2016, the annual meeting of the American College of Chest Physicians. The study "was a requirement of the Food and Drug Administration as part of the approval process for arformoterol tartrate," researchers mentioned.

HeartWare Recalls Some Of Its HVAD Ventricular Assist Device Pumps Due To Design Problem. Cardiovascular Business (10/25, Casey) reports that "HeartWare recalled some of its HVAD ventricular assist device pumps due to a design problem that could cause serious adverse events, including death." According to Cardiovascular Business, "The FDA classified the action as a class I recall."

ACC.org (10/25, 10K) reports, "A design flaw in the driveline tube that connects the pump to the external controller and power source may result in fluid and other materials entering the pump." Fierce Biotech (10/25, 3K) provides additional coverage.

Researchers Hopeful Nanoparticle Ultraviolet Radiation Technology May Be Next Step In Killing Cancer Cells While Cutting Down On High-Energy Radiation Doses. DOT Med News (10/25, Dworetzky, 61K) reports that "researchers are hopeful that nanoparticle ultraviolet radiation technology may be the next step in killing cancer cells while cutting down on dangerous high-energy radiation doses." According to DOT Med News, "The nanoparticle is made of stable inorganic material that is housed in a capsule of nontoxic material already approved by the FDA." This "patented approach, called Radio Luminescence Therapy, is now being tested by Indiana-based Lodos Theranostics."

FDA Launches Whistleblower Website For Medical Device "Regulatory Misconduct." In continuing coverage, Mass Device (10/25, Perriello, 1K) reports that the Food and Drug Administration "launched a whistleblower website designed to let whistleblowers let the federal safety watchdog know about allegations of 'regulatory misconduct' on the part of medical device makers." According to a spokesperson, "The FDA encourages people submitting allegations to include supporting information and contact information in case additional information is needed for the FDA to understand the allegation and act on the report; however you can choose to submit a report anonymously."

FDA Approves sNDA To Update US Prescribing Information For Enzalutamide

Capsules To Include New Clinical Data From TERRAIN Trial. Cancer Therapy Advisor (10/25, Hoffman,) reports that the FDA "has approved a supplemental New Drug Application (sNDA) to update the US prescribing information for Xtandi (enzalutamide) capsules to include new clinical data from the TERRAIN trial...which compared enzalutamide with bicalutamide among patients with metastatic castration-resistant prostate cancer (CRPC)." The new "label now includes data that show enzalutamide reduces the risk of radiographic progression or death by 40% vs bicalutamide." Additionally, "median radiographic progression-free survival was 19.5 months with enzalutamide compared with 13.4 months with bicalutamide."

"External FDA Expert" Criticizes Agency's Approval Of Eteplirsen In JAMA. Fierce Biotech (10/25, Adams, 3K) reports that "external FDA expert" Aaron Kesselheim, who counseled the agency against approving Sarepta's Exondys 51 (eteplirsen) as a Duchenne muscular dystrophy treatment, "has used a JAMA article to hit out at the regulator's processes and the biotech that led to its green light last month." In his article, Kesselheim writes that many patient advocacy groups, such as those arguing for the approval of eteplirsen at an advisory hearing, "are financially supported by drug manufacturers to help advance their goals." Kesselheim notes that Center for Drug Evaluation and Research director Janet Woodcock "overruled" concerns about approving the drug, and the internal review staff at the FDA "took the unusual step of appealing to Commissioner Robert Califf, MD, who upheld Woodcock's decision." Kesselheim also argues that the drug's conditional approval is "problematic" because additional clinical data is not required for another five years and a placebo is not required.

FDA Issues Warning Letter To Alabama Drug Compounder. Fierce Pharma (10/25, Keenan, 3K) reports that Alabama drug compounder Eagle Pharmacy "was slapped with a warning letter by the FDA for unsanitary conditions and failing to register new compounds." In its letter, the FDA "noted in its warning that some of Eagle's responses to the inspection fell short of FDA regulations and without prompt action the company could face legal action, including seizure of the facility."

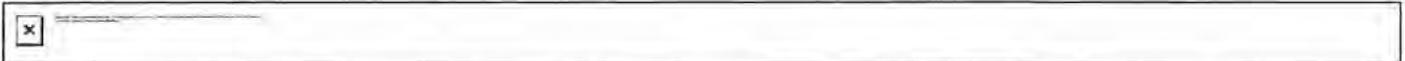
FOOD SAFETY

Food Companies "Sneaking" Healthy Ingredients Into Food Products Raises Questions. The New York Times (10/25, Siegel, Subscription Publication, 13.42M) analyzes the idea of food companies "sneaking" healthy ingredients into food products

Smith, Celeste

From: CTP-Editors-BulletinNews
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Subject: Center for Tobacco Products News Briefing for Wednesday, October 26, 2016

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DATE: WEDNESDAY, OCTOBER 26, 2016 6:00 AM EDT

TODAY'S EDITION

FDA NEWS

- Survey Analysis Shows 73 Percent Of Teens Believe E-Cigarettes Are Safer Than Cigarettes
- 69th Plaintiff Joins Federal Lawsuit Against Natural American Spirit For Marketing Violations

TOBACCO POLICY NEWS

- Missouri Constitutional Amendment To Raise Cigarette Taxes Favors Big Tobacco, Targets Those With Lower Income

TOBACCO INDUSTRY NEWS

- British American Acquisition Of Reynolds American Could Add To Big Tobacco's E-Cigarette Dominance
- JP Morgan Analyst Supports Shift From Cigarettes To Reduced-Risk Products

HEALTH NEWS

- Study Suggests E-Cigarettes Could Be Used To Help Combat Obesity In Smokers Trying To Quit

INTERNATIONAL NEWS

- Shengzhou, China City Officials Call Off Cigarette Butt Exchange Campaign Due To Too Much Interest

FDA NEWS

Survey Analysis Shows 73 Percent Of Teens Believe E-Cigarettes Are Safer Than Cigarettes.

HealthDay (10/25, Reinberg, 24K) reports in continuing coverage that an analysis published in the journal Pediatrics used data from the 2012 and 2014 National Youth Tobacco Survey to determine that "73 percent of teens believed e-cigarettes were less harmful than cigarettes," much greater than the 20 and 26 percent of teens who thought the same of smokeless tobacco and cigars, respectively. Lead researcher Dr. Stephen Amrock said, "E-cigarettes are now the most commonly used tobacco product among U.S. youth, and the increases in e-cigarettes' perceived safety mirrors rapid increases observed in their use. ... This is not a no-risk situation. The FDA has just recently begun to consider e-cigarettes as tobacco and regulate them accordingly. That is an important part of the process in getting these products out of the hands of children."

Reuters Health (10/25) adds that Amrock said, "U.S. youth may not be wrong that e-cigarettes are less harmful than cigarettes, but such a view captures only half the story." The 2014 data showed that "almost three quarters said e-cigarettes are less harmful than cigarettes"

and “almost half said e-cigarettes are less addictive than cigarettes.” Thomas J. Glynn, consulting professor at the Stanford Prevention Research Center in California, said youths should not use e-cigarettes even though they are at “the low end of a continuum of risk of tobacco products, below snus, cigarettes and cigars.”

69th Plaintiff Joins Federal Lawsuit Against Natural American Spirit For Marketing Violations.

The Winston-Salem (NC) Journal (10/25, Craver, 259K) reports the number of plaintiffs in the New Mexico federal court lawsuit against Santa Fe Natural Tobacco’s Natural American Spirit brand over its organic and additive-free marketing claims now sits at 69, “including at least one from North Carolina.” The lawsuits come after the FDA sent a warning letter to Santa Fe over its use of “additive-free” and “natural” in its advertisements, which itself came out a month after Santa Fe had launched a national advertising campaign for the brand. According to the Journal, “Santa Fe spokesman Seth Moskowitz has said the company has provided the FDA with a written explanation of its marketing strategy.”

TOBACCO POLICY NEWS

Missouri Constitutional Amendment To Raise Cigarette Taxes Favors Big Tobacco, Targets Those With Lower Income.

U.S. News & World Report (10/25, 759K) features commentary from American Enterprise Institute scholar Michael McShane in which he argues that, though Missouri’s constitutional amendment on the November ballot to institute a “60-cent tax per pack of cigarettes to create a fund for pre-K education” sounds like a good idea, it is actually designed to eliminate small tobacco’s companies’ edge in the marketplace over big tobacco companies. McShane also argues the tax is regressive due to the fact that people who smoke are more likely to be poor. McShane writes, “We have a cigarette tax campaign that is funded by big tobacco companies and opposed by the American Cancer Society. If I’m a skunk at the garden party, at least I’m in good company.”

TOBACCO INDUSTRY NEWS

British American Acquisition Of Reynolds American Could Add To Big Tobacco’s E-Cigarette Dominance.

In continuing coverage, Reuters (10/25, Mincer, Geller) reports Reynolds American’s possible acquisition by British American Tobacco for \$47 billion could be the latest sign that big tobacco companies are set to dominate the e-cigarette market going forward. Reuters reports that a successful takeover “would create a company with significant share of two of the biggest e-cigarette markets ... and pit it more directly against the efforts of rival Philip Morris International Inc, and U.S. partner Altria Group Inc, to devise a successful alternative to traditional cigarettes.” Further consolidation of the tobacco industry, combined with the FDA’s recently announced and costly deeming rule regulations, could lead to “a huge contraction of the vaping market with most of the market share going to the tobacco companies,” according to public health professor Dr. Michael Siegel.

Convenience Store News (10/25, 212K) reports on the findings of Wells Fargo Securities LLC’s latest Tobacco Talk survey, quoting Bonnie Herzog, managing director of tobacco, beverage and convenience store research, who said, “interest in heat-not-burn technologies and IQOS specifically has increased, laying the groundwork we think for an eventual industry pivot toward RRP’s as the next growth catalyst on the horizon.” She added, “we see this as strongly positive for

Altria given its alliance with PMI on iQOS since we continue to expect the commercialization of iQOS as early as late fiscal year 2017/early fiscal year 2018. More immediately, this bodes well for RAI as retailers are also optimistic about the new VUSE Vibe platform.”

JP Morgan Analyst Supports Shift From Cigarettes To Reduced-Risk Products.

In a one-minute segment on [BBC News \(UK\) Business Live](#)  (10/25), Nandini Ramakrishnan, an analyst from JP Morgan, responds to viewer comments on the idea that tobacco companies want consumers to switch to reduced-risk alternatives. One viewer suggested that if this is the case, the companies “should stop making cigarettes,” to which the presenter says “that would be a good idea.” Another viewer, however, said abandoning traditional cigarettes would be “business suicide.” Ramakrishnan is fairly supportive of the strategy, emphasizing that it is not corporate suicide as there is a replacement product that smokers are being encouraged to buy, and suggesting that in the public health context that it is a good idea to have customers switch from traditional to reduced risk products. BBC Business also tweeted on the subject of whether tobacco companies can “really kick the habit.”

HEALTH NEWS

Study Suggests E-Cigarettes Could Be Used To Help Combat Obesity In Smokers Trying To Quit.

[Reuters](#) (10/25) reports that in a review published in the journal *Nicotine & Tobacco Research*, researchers found that while the nicotine in cigarettes “makes smokers less likely to overeat,” e-cigarettes, “which contain nicotine but no tobacco, may help prevent them from eating too much when they quit.” The article notes that smoking tobacco “is known to suppress appetite and smokers often say they smoke to keep their body weight in check.” But for smokers trying to quit and prevent weight gain, the researchers said, e-cigarettes with food flavorings “may replicate some of the sensations of eating.” [The Guardian \(UK\)](#) (10/25, Davis, 4.42M) and the [Daily Caller](#) (10/25, Birr, 576K) also reports.

INTERNATIONAL NEWS

Shengzhou, China City Officials Call Off Cigarette Butt Exchange Campaign Due To Too Much Interest.

The [Wall Street Journal](#) (10/25, Chao, 6.37M) reports local government officials in Shengzhou, China have called off a program that sought to clean up the city’s many cigarette butts by offering a pack of tissues for every 50 cigarette butts exchanged after the program proved too popular, with people coming from outside of Shengzhou to take advantage of the program.

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From: [Loge, Peter](#)
To: [Califf, Robert](#)
Cc: [Goldie, Christina](#); [Cristinzio, Dayle](#); [Stuckey, Carla](#); [Roth, Deborah](#); [Tomasello, Jennifer](#); [Conover, Katie](#); [Auchincloss, Kalah](#); [Jones, Elizabeth](#)
Subject: AMC Tour update
Date: Thursday, October 27, 2016 5:42:41 PM
Attachments: [AMC travel fall 2016.doc](#)
[image001.png](#)

RMC AMC FDA USA 2017 Tour Update

Updated 10/27/16

Per this morning's email appropriately noting the schedule seems a bit daunting over the next three weeks, I have added more detail on the events below.

Let me know what you need for the upcoming events and we'll get it to you.

Sen. Warren Sen. Warren's state scheduler and I spoke this morning. The Senator is travelling next week so will not be able to meet. The scheduler and Chrisy have connected about RMC attending a roundtable event in Boston in December – apparently an annual roundtable with the FDA Commissioner is a tradition started by Sen. Kennedy, continued by Sen. Kerry, and now taken up by Sen. Warren. *They have landed on Monday December 12 as a tentative date.*

OL is letting the Massachusetts Senate and local US Rep offices he will be in the area next week, but we are otherwise not planning any Congressional outreach on this trip.

Johns Hopkins Oct 28

10:00am – 11:00am

Tour FastForward East

No remarks

11:15am – 11:45am

One-on-one with Dr. Paul Rothman

No remarks

12:00pm-12:45pm

Lunch with leadership from Johns Hopkins medical school and School of Public Health

No remarks, list of participants in RMC event binder

1:00pm – 2:00pm

Fireside chat

Guided questions on: Drug prices, clinical trials, LDTs, UDIs, regulatory science, future vision for the FDA, increased coordination between the FDA and AMCs. A full detailed list of potential questions is in the event binder.

Boston Nov 1 -2

November 1

8:00am - 9:30am

Brigham and Women's Leadership meeting including guests from Mass General, Broad, and industry

Small leadership meeting, "handful of senior hospital leaders." No agenda

9:30am - 10:30am

Fireside chat in Brigham and Women's amphitheater (seats about 175). Led by Dr. Betsy Nabel, president of Brigham and Women's hospital. 30 minute talk, 30 minute Q&A

"Successes and challenges in translational research and advancing new discoveries into patients, how academic medicine can better partner with the FDA, what's top-of-mind at the FDA, what's in store for the future" – 30 minutes, followed by 30 minutes Q&A

10:30am – 11:15am

Meet privately with Dr. Nabel

No remarks

12:30pm – 1:30pm

Dr. Jeffrey Drazen, Editor, New England Journal of Medicine informal conversation.

No remarks

2:00pm

MIT, Dr. Albright, tour facilities and meet with leaders

Small meeting, seeking "feedback on the research findings from the first 18 months of work focused on improving the broad system of Clinical Trials"

4:30pm – 5:30pm

Kennedy School talk; 30 minute talk, 30 minute guided Q&A

"Inform the Harvard community about the direction of health policy at FDA and to have a conversation about pressing health policy issues." 30 minute talk, 30 minute Q&A

Widely promoted to the Harvard community

NOTE: Possible Press – Peter will coordinate with OEA

6:00pm

Small dinner, Kennedy School

No remarks

November 2

7:00am – 8:00am

Breakfast with Dr. Elliot Antman, location TBD

No remarks

8:00am – 10:00am

Meeting with Dr. Barbara McNeil, interim Dean, Harvard Medical School and other HMS leadership.

No remarks

10:30am – Noon

Dr. Richard Platt, Harvard Medical School, Sentinel town hall/Q&A

Dr. Platt is open to our suggestions on questions

12:30pm – 2:00pm

Roundtable with Dr. Chris Newton-Cheh Mass General

Learning more – small discussion group, not a speech or prepared remarks

2:00pm – 3:00pm

Mass General tour the Translational Clinical Research Center

No remarks

3:00pm - 4:00pm

Meet with MGH leadership, including Dr. Harry Orf, Sr. VP Research, MGH; Mason Freeman, MD – Director, Translational Research Center, Professor of Medicine; Dr. David M. Nathan, MD, Director, Diabetes Center, Diabetes Research

No remarks

4:30pm – 7:00pm

Alexandria Summit fireside chat and reception

From a call with Alexandria Summit: Priorities that impact the Boston-area ecosystem, especially the Moonshot/OCE – is the OCE a model that the FDA may want to replicate for other topics? The relationship between the FDA, biotech, AMCs, health systems, and industry; improving the design and efficacy of clinical trials. There may also be questions about Sarepta and other potentially controversial topics

Houston Nov 4 -5

November 4

Possible dinner

November 5

8:00am – 8:20am

Keynote speech at the 4th international conference on Cancer and the Heart, MD Anderson

12:00pm – 2:30pm

Tour Texas Medical Center

Possible other meetings, including with Dr. Lynda Chin, associate vice chancellor for health transformation and chief innovation officer for health affairs.

Johns Hopkins Leadership Retreat, Middleburg VA Nov 11

11:00 a.m. – 12:00 p.m.

Embracing Biological Variation, on a panel with Scott Zeger, Ph.D., Sezin Palmer, Alan Coultri

TENTATIVE: Palo Alto and San Francisco Dec 6 – 8

Commissioner Califf reaching out colleagues. Chrisy is holding the dates until the trip is either confirmed or cancelled.

For Discussion

Mayo, University of Wisconsin, Penn, UAB, Kentucky

Waiting to hear back from Ole Miss about Spring 2017

Peter Loge

Senior Advisor

U.S. Food and Drug Administration
Tel: 301-796-9276 | Cell: 240-565-3128
Peter.Loge@fda.hhs.gov



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For Discussion

Mayo, University of Wisconsin, Penn, UAB, Kentucky

Waiting to hear back from Ole Miss about Spring 2017

From: [Sherman, Rachel](#)
To: [Califf, Robert](#)
Subject: McK patient engagement
Date: Friday, October 28, 2016 9:46:04 AM

Do you want to bring up the Sarepta issue next time you meet with them? If there something specific you'd like added or considered?

From: [McCall, Jonathan *](#)
To: [Califf, Robert](#)
Cc: [Palmer, Kelly](#); [Roth, Deborah](#)
Subject: Rob's Report edits for your review
Date: Friday, October 28, 2016 4:09:03 PM
Attachments: [20161027 RR evolving-mission JM-edits DR JM-CLEAN.doc](#)
[20161027 RR evolving-mission JM-edits DR JM-TRACKED.doc](#)

Here you go. Let me know if you need any further changes.

Thanks!

—
Jonathan

From: McCall, Jonathan *
Sent: Friday, October 28, 2016 4:03 PM
To: Roth, Deborah; Palmer, Kelly
Subject: RE: first draft

Here you go!

From: Roth, Deborah
Sent: Friday, October 28, 2016 3:49 PM
To: McCall, Jonathan *; Palmer, Kelly
Subject: RE: first draft

Let's go with the second one, but condense it a bit.

Jonathan - could you please take a shot at this?

From: Palmer, Kelly <Kelly.Palmer@fda.hhs.gov>
Date: October 28, 2016 at 3:36:34 PM EDT
To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>, Roth, Deborah <Deborah.Roth@fda.hhs.gov>
Subject: RE: first draft

The Office of Women's Health (OWH) sent me these two bullets...

- OWH resources were included in the FDA Health Literacy Month Social Media Toolkit (e.g. OWH's Pinterest post on '4 Ways to Prevent Medication Mistakes').
- During Health Literacy Month, the Office of Women's Health conducted outreach to promote our digital and print plain language resources on topics such as safe medication use, mammography, and clinical trials. Through our Pink Ribbon Sunday Program, OWH partnered with a national network of churches to educate women about mammography screening and the MQSA program. OWH also

conducted a Twitter Chat on October 27 with NICHD, CDC, text4baby, March of Dimes, and MotherToBaby (OTIS) to disseminate plain language messages on medication use during pregnancy.

From: Roth, Deborah
Sent: Friday, October 28, 2016 12:59 PM
To: McCall, Jonathan *; Palmer, Kelly
Subject: RE: first draft

Kelly – per Rob’s comment in the document – could you please call the Office of Women’s Health and get one bullet about something they’ve done related to health literacy month?

If they didn’t do anything related to health literacy month, we need to just pick something they’ve done that sounds like it is related to health literacy.

Thanks!

From: McCall, Jonathan *
Sent: Friday, October 28, 2016 11:21 AM
To: Roth, Deborah; Palmer, Kelly
Subject: RE: first draft

(b) (5)



Will be standing by if you need another pass.

Thanks!

—
J

From: Roth, Deborah
Sent: Friday, October 28, 2016 9:40 AM
To: McCall, Jonathan *; Palmer, Kelly
Subject: RE: first draft

Jonathan,

I think this looks great and if you can keep editing, that would be great. I really don’t have any edits other than the use of the word “we” without saying who “we” is.

(b) (5)



Ok?

Thanks!

From: McCall, Jonathan *
Sent: Thursday, October 27, 2016 4:55 PM
To: Roth, Deborah; Califf, Robert; Palmer, Kelly
Subject: RE: first draft

Here are some preliminary edits. There are still a few spots to be filled in, and I'd like to take another pass at it tomorrow AM.

Thanks!

—
J

From: Roth, Deborah
Sent: Thursday, October 27, 2016 3:11 PM
To: McCall, Jonathan *; Califf, Robert; Palmer, Kelly
Subject: RE: first draft

Perfect – thanks!!

From: McCall, Jonathan *
Sent: Thursday, October 27, 2016 3:04 PM
To: Roth, Deborah; Califf, Robert; Palmer, Kelly
Subject: RE: first draft

I can look at it momentarily. I'm not sure I'll finish, but I can send you what I've got at 5 or a little after, and pick up on Friday AM?

Thanks!

—
J

From: Roth, Deborah
Sent: Thursday, October 27, 2016 2:55 PM
To: Califf, Robert; Palmer, Kelly; McCall, Jonathan *
Subject: RE: first draft

This looks great!

Jonathan – are you available to do the first pass?

Thank you!

From: Califf, Robert
Sent: Thursday, October 27, 2016 2:48 PM
To: Palmer, Kelly; McCall, Jonathan *; Roth, Deborah

Subject: first draft

I had to defer on IT and cybersecurity till later. Next week will be about ethics, right?
rnc

Rob's Report: Engaging Directly with Patients and Consumers: An Evolving Mission

Saying that engaging directly with consumers and patients is a core part of FDA's mission and a key strategic goal for the Agency may be stating the obvious, but the "devil is in the details." With a purview that spans medical product development, tobacco control, nutrition, and food safety, the Agency must be able to communicate effectively and appropriately with broad and varied groups of constituents, including patients and the public.

As an academic clinical investigator, I spent considerable time on the concepts and organization of patient advocacy. However, my learning has expanded significantly since I arrived at the FDA. Hardly a day goes by without an interaction with patients and their advocates, or consideration of a policy issue that involves patients as advocates. And in just the few months since my July 15th Report, I have seen tremendous progress in our approaches to these interactions across the Agency.

The intertwined history of patient advocacy and the FDA is a long one, but there's no doubt that the HIV epidemic created major and lasting changes in both urgency and tactics. Many of our current leaders were working at the old FDA Parklawn Building when the ACT UP effort was at its peak. Since then, many of us at FDA have considered it critically important to engage directly with patient advocacy and public health groups. Given the breadth of our mission, it is unsurprising that almost every facet of FDA has developed its own approach in reaching out to constituents.

The recent Sarepta decision raised many questions about the nature of appropriate relationships between FDA reviewers and advocacy groups. Differences of opinion within the FDA highlight the need for continued learning, internal dialogue, and sharing of best practices. Another issue to watch closely in the coming year will be the wider uptake of approaches that use research on cognition to guide the creation of product labels that are understandable to consumers and patients. As simple as this sounds, it is fundamental to our mission to provide information in ways that enable everyone to use products wisely.

Speaking of communication: October is Health Literacy Month, which we kicked off with Twitter and Facebook messages (#HealthLiteracy) encouraging the public to read a refreshed Consumer Update on "Making Decisions for Your Health." Agency staff are also publicizing our many initiatives to make cutting-edge scientific information accessible to broader audiences through social media and external newsletters. In addition:

- The Risk Communications Staff (RCS) offers a volunteer message testing service for pre-testing FDA communications to help ensure that messaging is clear and audience-appropriate.

- The Office of Women’s Health (OWH) contributed resources to the FDA Health Literacy Month Social Media Toolkit; promoted digital and print plain-language resources on topics such as safe medication use, mammography, and clinical trials; helped educate women about mammography screening through the Pink Ribbon Sunday program; and conducted a Twitter Chat in conjunction with other organizations to disseminate plain-language messages on medication use during pregnancy.
- Staff from CDER’s Professional Affairs and Stakeholder Engagement group and a panel from our Office of Minority Health, Office of External Affairs, and RCS attended the 2016 Health Literacy Research Conference to discuss what the FDA is doing to support health literacy.
- RCS Director Jodi Duckhorn recently returned from China, where she’d been invited by the Chinese government to share how we use risk communication best practices.

Clearer communication is key to advancing FDA’s public health goals. I encourage you to attend the presentation of the draft Strategic Plan for Risk Communication and Health Literacy at the November 7 meeting of the Risk Communication Advisory Committee. In the coming months, we will be performing an internal study of approaches to interactions with patients and their advocates, focusing on advancing internal knowledge and creating an ecosystem in which patients and consumers are most likely to benefit from the products we regulate.

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From: [Califf, Robert](#)
To: [Zimmer, Natale](#); [Sharp, Jeremy](#)
Cc: [Auchincloss, Kalah](#); [Kux, Leslie](#); [Maloney, Lesley](#)
Subject: RE: Emailing: FDA Owners Manual - Transition 2016 10272016.docx
Date: Friday, October 28, 2016 8:08:00 AM
Attachments: [FDA Owners Manual - Transition 2016 10272016.docx](#)

Natale and team,

Here are some edits to the first part. I think the meat of it is fine (although I obviously haven't read the whole thing), but I was struck by 3 things in the intro:

(b) (5)



RMC

-----Original Message-----

From: Zimmer, Natale
Sent: Thursday, October 27, 2016 5:17 PM
To: Sharp, Jeremy; Califf, Robert
Cc: Auchincloss, Kalah; Kux, Leslie; Maloney, Lesley; Zimmer, Natale
Subject: Emailing: FDA Owners Manual - Transition 2016 10272016.docx

Some minor things to clean up tomorrow, but here is the owner's manual for your review, should you choose to have a look.

I'll get the rest cleaned up and out to HHS by the end of the day tomorrow.

Thanks,
Natale



2016 HHS Presidential Transition Team

OWNER'S MANUAL

January 2017

2016 Presidential Transition Owner's Manual

U.S. Food and Drug Administration (FDA)

(b) (5)



From: [Pink Sheet](#)
To: [Califf, Robert](#)
Subject: Pink Sheet | Highlights Of The Week
Date: Monday, October 31, 2016 11:21:34 AM

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31 Oct 2016

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Pink



WEEKLY HIGHLIGHTS

Look below for key developments and intriguing perspectives from the past week to inform your strategic decision-making. And check out our new hot topic pages on the drug pricing debate and US elections.



THIS WEEK'S TOP STORIES

26 Oct 2016 | **ANALYSIS**

How To Save A Drug: Iressa's Return Relied On Consistency Across Totality Of Evidence

By **Bridget Silverman**

Drug Review Profile of the second life of AstraZeneca's Iressa shows how FDA adapts to imperfect but improving information without putting undue burden on sponsors – and how the agency recently applied a similar iterative approach to another EGFR inhibitor, Astellas and Genentech's Tarceva.

27 Oct 2016 | **ANALYSIS**

Brazil: The Next Hot Spot For Biosimilar Substitution?

By **Michael Cipriano**

Biosimilars manufacturers could reach a wider patient population in Brazil if they can demonstrate interchangeably, as they do not face the potential barrier of discretion from states.

24 Oct 2016 | **ANALYSIS**

Biosimilar Prescribing Decisions May Depend Upon Disease State

By Sue Sutter

Express Scripts' Eichholz says clinicians may be less inclined to use a biosimilar in 'life or death' oncology indications compared to inflammatory diseases.



25 Oct 2016 | **NEWS**

UK Industry Urges Quick Adoption Of Accelerated Access Proposals As Brexit Clouds Gather

By Ian Schofield

UK review proposes key changes to the way that new medicines and medical technologies are identified, developed and adopted for use in the National Health Service, including an Accelerated Access Partnership of stakeholders that will manage the accelerated pathway to patients, a new government unit to discuss commercial arrangements, and a "transformative designation" to flag up products of greatest interest.



24 Oct 2016 | **NEWS**

Korea Plans Breakthrough System To Encourage Innovation

By Jung Won Shin

Following up on its May announcement of a conditional approval scheme to shorten R&D and approval periods, and aiming to ensure the prompt and stable supply of life-saving drugs, South Korea is planning a new law on breakthrough therapies and for drugs for public health crises.

26 Oct 2016 | **NEWS**

FDA's Teva Warning Letter Sets Agenda For Investigating, Remediating Sterility Failures

By Bowman Cox

FDA has published a warning letter that not only provides detailed guidance for Teva's ongoing remediation of sterility assurance failures at a plant in Godollo, Hungary, but also suggests a game plan for any manufacturer of sterile drug products that's seeing signs of issues with aseptic operations.

25 Oct 2016 | **ANALYSIS**

FDA Continues To Speed PD-1/L1 Drugs To Market

By Mary Jo Laffler & Bridget Silverman

The four-month review of Merck's Keytruda for first-line lung cancer is a reminder of how quickly the agency has acted on the immune checkpoint inhibitors.



23 Oct 2016 | **ANALYSIS**

Will Alkermes Data Package Support ALKS 5461 Approval?

By Mandy Jackson

Alkermes revealed successful completion of its third Phase III trial for the depression drug ALKS 5461 as well as a risky plan to seek FDA approval based on two negative and one positive late-stage study.

24 Oct 2016 | **NEWS**

Pharma Firm ISO OTC Switch Partner; NDA Experience, Resources Needed

By Eileen Francis

Success in OTC switches can hinge on finding the right partner, say switch consultants during a CHPA webinar. Due diligence in negotiations can help determine if a potential partner is the right fit for the time- and labor-intensive processes.

25 Oct 2016 | **ANALYSIS**

FDA's Fears Realized: Sponsors Pitching Investors 'Sarepta Model'

By Derrick Gingery

Investor compares the development construct to homeopathic medicine.



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From: [Mason W. Freeman](#)
To: [Califf, Robert](#)
Subject: Re: next week
Date: Sunday, October 30, 2016 7:34:30 PM

Ok, I will send it along to the MGH participants.

See you later this week.

Mason

On Oct 30, 2016, at 4:27 PM, Califf, Robert <RMC1@fda.hhs.gov> wrote:

Mason,

This looks good. As for the issues we're seeing at FDA, its no surprise:

1. Protocols that are not rigorous
2. No statistical plan
3. Inadequate validation of biomarkers
4. Not using randomization or blinding when they would help greatly
5. Inadequate documentation of procedures to give confidence that results recording and reporting were not biased

We don't have to stick exactly to the time frame. The FDA team is basically me and Peter, so I'm there to toss out some issues and learn about how you think about them.

rmc

rmc

From: Mason W. Freeman [<mailto:freeman@molbio.mgh.harvard.edu>]
Sent: Sunday, October 30, 2016 11:48 AM
To: Califf, Robert
Cc: Loge, Peter
Subject: Re: next week

Rob,

It sounds like our time will fly by and we won't get to it all. I have consolidated the proposed agenda below and you can tell me if you think we have any prayer of getting through it. You can re-prioritize it if you think some areas are more likely to be productive than others.

- 2:00-2:20 Tour of MGH TCRC (Kathy Hall, nurse director of unit will discuss unit operations while giving the tour)
- 2:20-2:30 Lessons learned from Duke Translational Medicine Center in operating a facility that is designed to support industry studies (Rob Califf and MGH TCRC team discussion)
- 2:30-3:00 Policies to improve NIH funded "academic trial" performance in

studies of potential relevance to product development (FDA team will identify major issues it is seeing in trials and discussion of how to address those will ensue)

3:00-3:25 FDA-academic regulatory science/training opportunities and value of more tripartite interactions (academia/industry/govt) (Open discussion of opportunities for collaborative interactions)

3:25-3:35 Posting of trial activities on clintrials.gov (Harry Orf, Director of Research to lead discussion of challenges academic centers facing in this arena)

3:35-4:00 Capturing academic human phenotyping capabilities with respect to drug, device, and behavioral interventions in early phase trials (Open discussion of issues that would have to be addressed to make this happen)

If you want to re-configure this, please do. Once finalized, we can circulate to participants. With the agenda determined, I might also invite one or two other individuals from the MGH community that I think could contribute to the discussion (particularly the topics you listed) if their schedules permit this last minute request. I am sure they would be thrilled to meet you.

Mason

On Oct 30, 2016, at 9:34 AM, Califf, Robert <RMC1@fda.hhs.gov> wrote:

Mason,

This is a great list. I've copied Peter who is working on logistics. We are definitely seeing that as time from NIH grant to startup to first clinical trial shortens, "academic" trials are coming under regulatory scrutiny, and it ain't pretty.

So, my 2 top issues in your space are:

1. What policies could clean up the large number of poorly done inadequately sized trials without clean protocols and good stats funded by NIH that end up being critical in translation to real products?
2. How do we capture the amazing capability for human phenotyping in AMC's, particularly what is revealed by perturbations caused by drugs, devices and behavioral interventions in early phase trials?

But with 90 mins we could cover your other great topics. Perhaps we can iterate on a list.

rmc

From: Mason W. Freeman [<mailto:freeman@molbio.mgh.harvard.edu>]

Sent: Sunday, October 30, 2016 8:35 AM

To: Califf, Robert

Subject: Re: next week

Hi Rob

I got back late last night from London after going to a Gates Foundation Grand Challenge meeting, so sorry for the delay in replying.

Absolutely delighted that you are coming by to meet with us this week.

We finally opened our new clinical research facility, two weeks ago, which we will show you on your visit. Its creation owes a lot to you and the Duke Translational facility, so thanks for all that past help. One of the things I would like to discuss has less to do with your current position than your former one and that is how do you think we can make this kind of academic trial facility successful at serving its intended partners. I know your team found it hard to get industry business in the early days and I was hoping to hear a little about your experiences at Duke and any advice you could give us.

On other fronts, some things we could potentially discuss are :

1) Do academic centers have a role to play in helping the FDA improve regulatory science ? So, for example, at the Gates meeting, Don Ingber, a biomedical engineer who runs the Wyss Institute at Harvard, presented a series of “organ-on-a chip” devices which represent mini-organs constituted from human cells. He has some pretty cool examples of tissue mimics his group has created (e.g., lung cells and matrix that appear to respire and that create an alveolar-vascular connection-he has a tool for making them smoke and creating inflammatory injury via this toxin). Could these kinds of systems be expanded and give better toxicology insights into human organ responses than our typical rodent models now do. It still won't give you whole organism biology but it might do a better job on organ-specific issues. He also has a intestinal chip, so maybe one could validate them for bioavailability parameters compared to actual data from human study subjects. How does the FDA view that technology and its utility for future drug development.

2) Does the FDA see any need to create new interchanges with the biotech and pharma community about guidances its is developing or just how it is seeing drug development evolve in the coming decade (e.g, how you are thinking about rare disease development post the Sarepta experience). I am wondering if an academic center like the MGH (and others in our community) could host forums where the FDA could present what it is doing and perhaps hear some feedback from the biotech industry on those decisions all done at an independent academic site. Since we now have about 500 biotechs within one or two subway stops from our door, it could be a really efficient way for the FDA to interact with a community that is

working on everything from CRISPR technology to complex drug-device combos.

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4) Maybe there are projects the FDA is currently supporting, like the diabetes/CV issue we discussed by e-mail a couple months back, that we at the MGH should know about but probably don't. Any update you could provide on that would be great.

5) Finally, I know that Harry Orf, our head of research, wanted to have a brief discussion with you about clinical trial reporting on clintrials.gov by academic investigators. He said it wouldn't take long but wanted to get your input.

There are probably many other things we could discuss, but let me know if any of these are things you feel would be worth your time and we can put the agenda together for the meeting. Obviously, any thing specific you think worth discussing, we would be glad to do. I think the tour of our facility and some explanation of how it will work in conjunction with our CTSA funded (at least for now) CRC by our head nurse, Kathy Hall, should take only 30 mins or so, so that leaves up to 90 mins for the other items.

Thanks again for coming by to meet with us. Look forward to seeing you.

Best,

Mason

On Oct 29, 2016, at 6:28 PM, Califf, Robert
<RMC1@fda.hhs.gov> wrote:

Mason,

I look forward to seeing you next week. What would be your idea of a good agenda?

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: [Pink Sheet](#)
To: [Califf, Robert](#)
Subject: Pink Sheet | Today's News & Analysis
Date: Friday, November 04, 2016 6:18:48 AM

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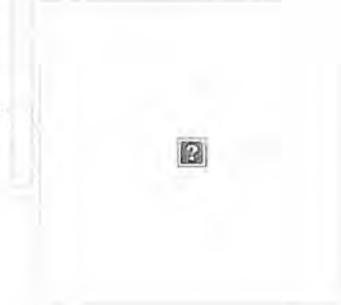
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From: [Young, Jason](#)
To: [Califf, Robert](#); [Woodcock, Janet](#)
Cc: [Shreeve, Chris](#); [Quinn, Kathleen](#); [Conover, Katie](#)
Subject: HEADS UP: before your public appearances today
Date: Friday, November 04, 2016 6:38:03 AM

Good morning Commissioner and Dr. Woodcock-

Before your public appearances today, I wanted you to be aware of Politico's most recent reporting on DMD. There are more than a dozen reporters at today's BioPharma/Friends of Cancer Research event. Fortunately we've already addressed this matter publicly and have been very transparent. See below for the news item.

Thanks,
Jason

EYE ON FDA

Newly released documents reveal internal frustration with Califf over Sarepta. Top drug reviewers challenged Commissioner Robert Califf's decision to side with drug center director Janet Woodcock, who overruled her staff and approved Sarepta's Duchenne muscular dystrophy treatment in September.

That's according to a 300-page trove of FDA documents made public on Thursday night, with questions still simmering about the [controversial decision](#) and critics pointing to the lack of evidence that the drug was effective.

... In one memo to Califf, division director Ellis Unger challenges Woodcock's scientific judgement and warns that Califf and Woodcock's decision could set a new precedent for the accelerated approval of rare disease medicines.

Unger also disputes Califf's conclusion that Woodcock followed proper procedures, arguing instead "there was no scientific basis underlying the conclusion ... this was simply a judgement call by Dr. Woodcock."

See the documents: [More](#).

From: [Evans, Dana](#)
To: [Califf, Robert](#)
Subject: Rose & Pink
Date: Friday, November 04, 2016 7:31:24 AM
Attachments: [Rose Sheet Today's News Analysis.msg](#)
[Pink Sheet Today's News Analysis.msg](#)

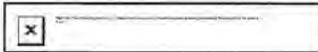
Smith, Celeste

From: Rose Sheet <info@pharmamedtechbi.net>
Sent: Friday, November 04, 2016 7:06 AM
To: Commissioner FDA
Subject: Rose Sheet | Today's News & Analysis

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From: [Woodcock, Janet](#)
To: [Califf, Robert](#)
Subject: RE: HEADS UP: before your public appearances today
Date: Friday, November 04, 2016 8:45:24 AM

The media love that. Look at the election. jw

From: Califf, Robert
Sent: Friday, November 04, 2016 8:28 AM
To: Young, Jason; Woodcock, Janet
Cc: Shreeve, Chris; Quinn, Kathleen; Conover, Katie
Subject: RE: HEADS UP: before your public appearances today

Funny how they get so excited about personality stuff

rmc

From: Young, Jason
Sent: Friday, November 04, 2016 6:38 AM
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See the documents: [More](#).

From: [Mason Freeman](#)
To: [Califf, Robert](#)
Subject: Re: next week
Date: Saturday, November 05, 2016 5:44:51 PM

Rob

Very much appreciate your dropping in to visit with us. Have been thinking about several of your comments as we now turn from getting the facility built to making something useful of it. I will be watching what happens in DC after Jan 20th, but hope to find more ways to interact, regardless of your position in the coming years.

Best

Mason

Sent from my iPhone

On Nov 5, 2016, at 2:14 PM, Califf, Robert <RMC1@fda.hhs.gov> wrote:

Mason,

Thanks again for your hospitality. The visit was very helpful. Stay in touch.

rmc

From: Mason W. Freeman [<mailto:freeman@molbio.mgh.harvard.edu>]
Sent: Sunday, October 30, 2016 8:35 AM
To: Califf, Robert
Subject: Re: next week

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Mason,

I look forward to seeing you next week. What would be your idea of a good agenda?

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: [Dickey, Jennifer S.](#)
To: [Califf, Robert](#)
Cc: [El Mubarak, Haja Sittana](#); [Donaldson, Eric](#); [Zinn, Rebekah *](#); [Solomon, Shari](#)
Subject: 2nd Annual GGT Symposium slides and thank you
Date: Monday, November 07, 2016 8:34:36 AM
Attachments: [image001.png](#)
[1-Welcome and Opening Remarks_Haja_slides.pptx](#)
[2-Dickey GGT_Slides.EFD.v2.pptx](#)
[3-Slides-Rao FDA GGS 2017reviewed.pptx](#)
[4-Slides-Doug.Jeffery.FINAL.pptx](#)
[5- Slides-Dorff - Precision Medicine in Protein-Based Therapeutic Development.pptx](#)
[6-Slides-Anna-Gene Editing GGT 2016_final.ppt](#)
[7-Slides-Tyson Genomics Seminar.pptx](#)
[8-Slides-WenmingGGS_2016_Updated.ppt](#)
[9-Slides-cfDNA EGFR PMAs updated.pptx](#)
[10-Slides-Hobart-Oligonucleotides-Updated.pptx](#)
[11-Slides-CART_KLWSchultz_v4_Updated.pptx](#)

Dear Dr. Califf,

As you requested, please find attached the slides that were presented at the 2nd Annual Genetics and Genomics Team Symposium last Friday (November 4th). On behalf of the organizing committee, thank you for taking the time to come by and speak with us. It was a wonderful day filled with exciting information on the initiatives around the Agency centered on the tools and technologies that enable precision medicine. More information on our program (including the recordings from our lecture series) can be found at the SharePoint link below.

<http://sharepoint.fda.gov/orgs/OC-OCS/ORSI/GGT/GGTSymposium/SitePages/Home.aspx>

Thanks again for your participation and support for our program!

Best regards,
Jennifer

Jennifer S. Dickey, Ph.D., RAC
Senior Scientific Reviewer
Center for Devices and Radiological Health
Office of In Vitro Diagnostics and Radiological Health
U.S. Food and Drug Administration
Tel: 301-796-5028
jennifer.dickey@fda.hhs.gov

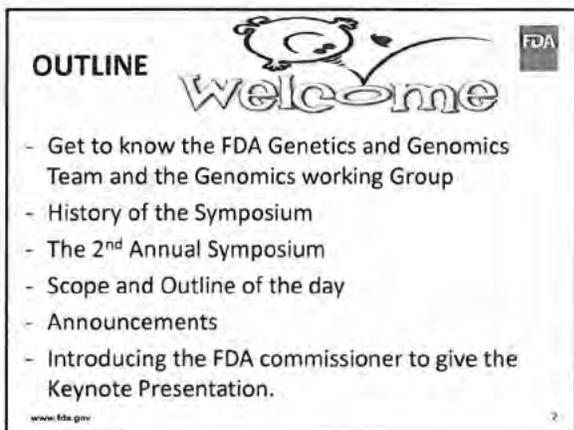


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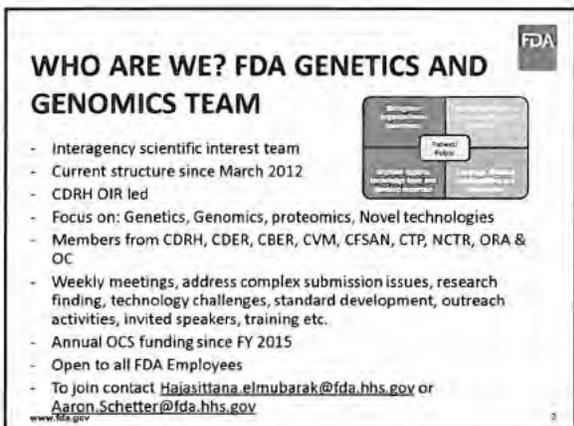
2nd FDA Genetics and Genomics Symposium
 The Tools and Technologies that Enable Precision Medicine
 November 4, 2016
 9:00 am – 4:30 pm
 W031 (1503A) The Great Room
 Poster Session and Contest
 Hosted by
 FDA Genetics & Genomics Team and Genomics Working Group
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WELCOME AND OPENING REMARKS
 Haja Sittana El Mubarak



OUTLINE

Welcome

- Get to know the FDA Genetics and Genomics Team and the Genomics working Group
- History of the Symposium
- The 2nd Annual Symposium
- Scope and Outline of the day
- Announcements
- Introducing the FDA commissioner to give the Keynote Presentation.



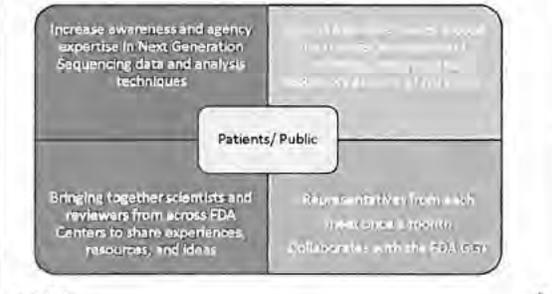
WHO ARE WE? FDA GENETICS AND GENOMICS TEAM

- Interagency scientific interest team
- Current structure since March 2012
- CDRH OIR led
- Focus on: Genetics, Genomics, proteomics, Novel technologies
- Members from CDRH, CDER, CBER, CVM, CFSAN, CTP, NCTR, ORA & OC
- Weekly meetings, address complex submission issues, research finding, technology challenges, standard development, outreach activities, invited speakers, training etc.
- Annual OCS funding since FY 2015
- Open to all FDA Employees
- To join contact Hajasittana.elmubarak@fda.hhs.gov or Aaron.Schetter@fda.hhs.gov

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HISTORY: THE 1ST ANNUAL FDA GENETICS AND GENOMICS SYMPOSIUM 

1. Focus: Next Generation sequencing Applications in Oncology and Microbiology
2. Theme: Invited External speakers, followed by FDA presentations and panel discussion
3. Main Goals: Improve; knowledge base, internal communication & organizational awareness. Develop recommendations for research and training needs for the Genetics and Genomics team for 2016.
4. Outcomes and Resources:
http://sharepoint.fda.gov/orgs/OC-OC/ORSI/GGT/GG_Symposium/SitePages/Home.aspx

www.fda.gov/OC/ORSI/GGT/GG_Symposium/SitePages/Home.aspx 8

THE 2ND ANNUAL FDA GENETICS AND GENOMICS SYMPOSIUM



1. Focus: The Tools and Technologies that Enable Precision Medicine
2. Organized by: The FDA GGT and the GWG
3. Theme: Invited External speakers lecture series, followed by one day FDA Symposium, oral presentations, poster presentations and panel discussion
4. Main Goals:
 - Get to know each other, the research resources, tools, our application challenges and areas of overlap.
 - Identify potential collaboration opportunities, research needs, training needs and policy needs
 - Have fun!!!
5. Sharepoint site: <http://sharepoint.fda.gov/orgs/DC-OCS/ORS/OGGT/GGT/Symposium/SitePages/Home.aspx>



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OUTLINE OF THE DAY



- Keynote address from our Commissioner Dr. Califf.
- Overview of the invited speaker sessions by Drs. Eric Donaldson and Jennifer Dickey
- Symposium divided into 2 tracks & 3 main focus areas categories (biomarkers, assays, therapeutic approaches).
 - Protein based tools (Morning)
 - nucleic acid based tools (afternoon)
- 2015- Poster Award Winner Invited Session
- Poster Session and Awards
- Networking and more Networking!!



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- Mute phones
- Poster setup in break
- discussion at the end of each session
- poster award winner announced after panel discussion
- Questions or concerns see Rebekah Zinn and Shari Solomon



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**KEYNOTE PRESENTATION:
FDA'S ROLE IN PRECISION MEDICINE**

Dr. Robert Califf, FDA Commissioner

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Jennifer Dickey and Eric Donaldson

INTRODUCTION TO THE SCIENTIFIC TRACKS

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1st FDA Genetics and Genomics Symposium

- Focused on Next-Generation Sequencing
- Breakthrough technology
- New clearances
- http://sharepoint.fda.gov/orgs/OC-OCS/ORSI/GGT/GG_Symposium/SitePages/Home.aspx
- 2nd Symposium – “The Tools and Technologies that Enable Precision Medicine”

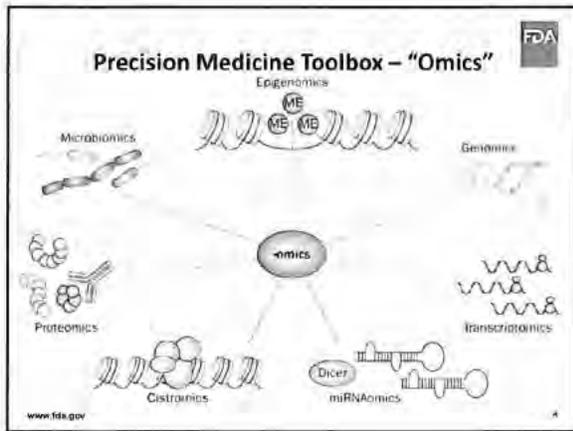


Precision Medicine Initiative

“Building on President Obama’s announcement in his State of the Union Address, today the Administration is unveiling details about the Precision Medicine Initiative, a bold new research effort to revolutionize how we improve health and treat disease. Launched with a \$215 million investment in the President’s 2016 Budget, the Precision Medicine Initiative will pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients.”




<http://www.fda.gov/oc/precisionmedicine/2016/08/08/160808-precisionmedicine>



-
- Symposium Goals**
1. Bring top minds in precision medicine to discuss opportunities and challenges in the lecture series
 2. Have an internal FDA symposium to discuss our own opportunities and challenges
 3. Think about ways to best prepare for the accelerating pace of technology
- The FDA logo is in the top right corner, and the website 'www.fda.gov' is in the bottom left corner.

-
- Symposium Activities**
- Lecture Series (6 lectures across precision medicine topics)
 - Internal FDA symposium to discuss advancements, challenges, and opportunities across the Agency
 - Poster Session/Networking to make connections across the Agency
 - SharePoint Site collection of resources
- The FDA logo is in the top right corner, and the website 'www.fda.gov' is in the bottom left corner.

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"Central Dogma" Axis

The diagram illustrates the flow of genetic information. On the left, a circular inset shows several chromosomes. An arrow points to a central DNA double helix. Another arrow points from the DNA to a 3D model of a protein structure on the right.

Chromosomes are single pieces of DNA that contain many genes.

DNA is a molecule that carries genetic information. Genes contain instructions for how to make proteins.

Proteins act alone or in groups to perform many functions.

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The Tools and Technologies that Enable Precision Medicine

<p>Protein-based Tools</p> <ul style="list-style-type: none"> • External Speakers <ul style="list-style-type: none"> - Dan Luo, Cornell - Greg Tsongalis, Dartmouth - Feng Zhang, Broad • Internal Speakers <ul style="list-style-type: none"> - Ashutosh Rao, CDER - Doug Jeffrey, CDRH - Sarah Dorff, CDER - Anna Kwilas, CBER 	<p>Nucleotide Based Tools</p> <ul style="list-style-type: none"> • External Speakers <ul style="list-style-type: none"> - Curtis Harris, NCI - Deanna Church, Personalis - Eliezer Van Allen, Dana Farber • Internal Speakers <ul style="list-style-type: none"> - Wenming Xiao, NCTR - Karen Bijwaard, CDRH - Bart Rogers, CDER - Kimberly Schultz, CBER
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Protein-based Tools and Technologies that Enable Precision Medicine

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Unique Challenges of Proteomics

- **One gene can encode more than one protein** (even up to 1,000). The human genome contains about 21,000 protein-encoding genes, but the total number of proteins in human cells is estimated to be between 250,000 to one million.
- **Proteins are dynamic.** Proteins are continually undergoing changes, e.g., binding to the cell membrane, partnering with other proteins to form complexes, or undergoing synthesis and degradation. The genome, on the other hand, is relatively static.
- **Proteins are co- and post-translationally modified.** As a result, the types of proteins measured can vary considerably from one person to another under different environmental conditions, or even within the same person at different ages or states of health. Additionally, certain modifications can regulate the dynamics of proteins.
- **Proteins exist in a wide range of concentrations in the body.** For example, the concentration of the protein albumin in blood is more than a billion times greater than that of interleukin-6, making it extremely difficult to detect the low abundance proteins in a complex biological matrix such as blood. Scientists believe that the most important proteins for cancer may be those found in the lowest concentrations.





DNA-based Materials



Dan Luo, PhD
Professor
Department of Biological and Environmental Engineering
Cornell University

- Engineering DNA as both genetic (bio-) materials and generic (nano-) materials.
- DNA as polymers in order to develop bulk-scale, DNA-based biomaterials for real-world applications.
- Branched DNA and DNA-based hydrogels and will demonstrate a number of real-world applications from diagnostics to pharmaceuticals.
- Nanoscale barcodes for the detection of pathogens.
- DNA hydrogel efficiently expresses proteins in a cell-free manner.
- A bird-nest like DNA microsphere was created to condense and carry millions of dosages of the CpG motif for immune-stimulation.

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Making Sense of the Chaotic World Of Precision Medicine



Gregory J. Tsongalis, PhD, HCLO, CC
Director, Laboratory for Clinical Genomics and Advanced Technology (CGAT)
Professor of Pathology
Department of Pathology
Audrey and Theodor Geisel School of Medicine at Dartmouth
Dartmouth Hitchcock Medical Center
Norris Cotton Cancer Center

- "Our ability to generate enormous amounts of data in an attempt to profile human cancers is significantly limited by assay validation, quality control and interpretation."
- What keeps him up at night
 - Rapid Pace of Field
 - Defining Clinically Actionable/Relevant
 - Commercialization and Claims

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Genome Editing: Prospects and Challenges 



Feng Zhang, PhD
Core Member, Broad Institute of MIT and Harvard
Investigator, McGovern Institute for Brain Research at MIT
Associate Professor, Department of Brain and Cognitive Sciences at MIT

- CRISPR-CAS as a genome editing toolbox
- CRISPR screens to discover unknown gene function (CHD8 role in autism)
- Engineering Cas9 for better specificity
- Cpf1 – a new genome editing enzyme

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Focus Questions 

- Understand the continuum of moving protein-based biomarkers through research and into assay development.
- Clarify the challenges and opportunities for regulating this rapidly evolving field and how to prepare reviewers.
- Define some lessons learned from which others across the FDA could benefit.
- Clarify the role that regulatory science/FDA research can play in preparing for precision medicine.
- Discuss how the rapid evolution of new tools in precision medicine from research to the clinic has impacted review practices and labeling discussions.

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Nucleotide-based Tools and Technologies that Enable Precision Medicine

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The Promise of Genomic Medicine Is Just Beginning

[f](#) [t](#) [p](#) [e](#) [s](#)

GENOMIC

A Decade Later, Genetic Map Yields Few New Cures, said a New York Times feature in June 2010. It declared the failure of the \$3 billion Human Genome Project and claimed that medicine had seen none of the benefits that Bill Clinton had promised in announcing the first draft of the human genome sequence in 2000. According to the article, geneticists were "almost back to square one in knowing where to look for the roots of common disease."

The New York Times judged the project too soon.

<http://www.fda.gov/oc/2016/08/2016-08-10-genomic-medicine-04066404.html>

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A Few Major Breakthroughs in Genomics

- Analyzing fetal DNA in a pregnant woman's blood was a more accurate and less intrusive way of screening for Down syndrome and other chromosomal disorders than methods such as ultrasound imaging
- Genomic strategies, driven by the plummeting cost of genome sequencing, have led to the identification of the genomic defects for more than 5,000 of the inherited diseases caused by mutations in a protein-encoding gene
- "Instead of classifying cancers by the tissue where they are first detected — colon, breast or brain, doctors are beginning to categorize cancer by its genomic characteristics and select treatments based on the signature of different mutations." -Eric Green
- In a report dated September 23, 2016, a clinical trial for types of advanced cancer showed that patients with advanced cancer who underwent gene mapping to inform tailored treatment, resulted in a 30X reduction in tumor growth compared to other therapies*
- Out of 1110 patients, the 199 who underwent genetic mapping had a variety of types of cancer, including lung, breast, head and stomach, among others. Their cancers were delayed in returning by as much as 32 months, according to the researchers*

* <https://www.sciencedaily.com/releases/2016/09/16/20160916091647.htm>

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Genetic testing fumbles, revealing 'dark side' of precision medicine



STAT | Report (July 2016) the limitations of health and medicine

<http://www.statnews.com/2016/07/03/16genetic-testing-precision-medicine/>

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QW

Misdiagnoses: A hidden risk of genetic testing

By Stephanie Lippman, MD



GOOD MEDICINE OR TM?
Panel 12: DNA Sequencing, Genetic Testing, and the Law

http://www.fda.gov/oc/2016/10/03/12-panel-genetic-testing-misdiagnoses-res/index.html

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Risks of Genetic Testing

- A 13-year-old boy died in his sleep of apparent heart failure
- The brother's EKG showed that he had an inherited heart condition known as long QT syndrome
- Genetic testing in the brother identified a mutation linked to long QT syndrome, confirming the EKG result. A heart defibrillator was surgically implanted in the brother's heart
- Dozens of relatives underwent genetic testing and nearly two dozen were found to have the long QT mutation
- Neither the parents nor distant relatives had any symptoms of long QT syndrome, including on EKGs; the brother's anomalous EKG event never recurred
- Mayo Clinic researchers conducted a molecular autopsy, in which DNA was isolated and sequenced from the boy who died, and he did not have a mutation for long QT syndrome

Journal Mayo Clinic Proceedings

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Challenges of Genetic Testing

- DNA sequencing has improved exponentially in recent years, but to interpret a genomic sequence requires a "reference human genome" and public or proprietary databases to see if mutations are related to disease
- Unfortunately, databases often disagree and some mutations once thought to be dangerous are still listed that way in databases
- When inaccurate databases are used to interpret genetic profiles this can lead to inappropriate treatment with devastating consequences
- "We must become wiser users of genetic testing and even wiser interpreters of the genetic test results so that we can make wise conclusions."

Precision Medicine Challenges

- The great promise of precision medicine has to be tempered with robust science and proven tools and technologies
- As tools and technologies emerge and advancements are made, new issues will arise that will require careful preparation and planning
- Standardization of data collection, management and regulation of databases, and storage of Big Data will be key issues to be addressed
- FDA is continuing to address many of the issues surrounding Precision Medicine with new draft guidances for Next Generation Sequencing assay development, the Biomarker Qualification program, precisionFDA, etc. (just to name a few)
- The purpose of the lecture series and the symposium was to keep this conversation going and to increase our awareness and understanding of the important issues surrounding the tools and technologies that enable precision medicine

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Integration of Multiple “Omics” Biomarkers: A Precision Medicine Strategy for Lung Cancer



Curtis Harris, MD
Chief, Laboratory of Human Carcinogenesis
National Cancer Institute

Discussed biomarkers associated with lung cancer, one of the most common forms of cancer

- **The goal:** Identify non-invasive lung cancer biomarkers that could be detected in the blood or urine
- **Lung cancer risk screening biomarkers** to expand identification of at-risk patients for early diagnosis. Low-Dose Computed Tomography has a 96.4% false-positive rate. Serum IL-8 and high C-reactive protein are biomarkers of lung cancer risk.
- **Early diagnostic biomarkers** that can aid in early diagnosis. Serum IL-8, IL-6 and CRP are robust biomarkers of lung cancer diagnosis.
- **Prognostic biomarkers** to identify 25% of Stage I lung cancer patients whose cancer will recur. Discussed several biomarkers: MIR-21, XPO1, BRCA1, HIF1a, DLC1, HOXA9, p53, etc. Combined scores likely to be better.

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Improving Individual Genome Analysis



Deanna M. Church, PhD
Senior Director of Applications
10x Genomics

- **NGS diagnostic yields** remain around 25-50%, which may be caused by missing large scale rearrangements
- **Extracting information on large-scale events**, including copy number variants (CNVs) and complex structural variants (SVs), is challenging using only short read data and is typically excluded from clinical analyses of exome sequences
- **New “linked reads” technology** allows one to obtain long range information while retaining the power, accuracy, and scalability of short read sequencing technologies
- **Haplotype-level dilution** of long input molecules into over 1 million barcoded partitions allows for high-resolution reference-based analysis
- **Coupling Linked-Reads** with novel algorithms that take advantage of these linkages allows for improved performance in regions of the genome that are typically inaccessible due to the presence of paralogous sequence
- **Validation of these variant calls** has been challenging as they typically fall outside the Genome in a Bottle (GIAB) high confidence regions

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Tools and Technologies to Enable Precision Cancer Medicine



Eliezer Van Allen, MD
Asst. Prof. of Medicine,
Harvard Medical School
Associate Member,
Broad Institute

- **Clinical computational oncology** to build and apply the engine to clinically interpret a patient's cancer genome; to discover response and resistance mechanisms to cancer therapies through patient-centered 'omic profiling; and exploring the inherited and environmental impact on the (cancer) genome
- **Paradigm shift in precision cancer medicine** where targeted therapies (Vemurafenib for *BRAF^{V600E}*) are much more effective
- **Modeling clinical response** with the goal of identifying genomic resistance and characterizing resistance heterogeneity and identification of synergistic activity between targeted agents to inform clinical trial design
- **Establishing surrogate biomarkers** – requires being built into trial design, should include integrative analysis with existing markers, and integration with clinical data are critical.

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Nucleotide-based Focus Questions



What are the challenges associated with making NCTR research available to reviewers? What are the tools/resources that NCTR is developing to help FDA review?

What were some of the regulatory challenges in evaluating cell-free DNA based precision assays? How has Center-to-Center communication evolved to account for precision assay inclusion in drug labels?

What are some of the data infrastructure challenges around precision medicine and big data? How has the rapid continuum of moving biomarkers from investigations to clinical practice impacted your review practices?

What role did regulatory science/FDA research play in preparing for this new technology? How has the rapid evolution of new tools in precision medicine from research to the clinic impacted review practices?

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FDA Speakers for Nucleotide Track



1. **Biomarker discovery and characterization:** Wenming Xiao, NCTR, *Genetics and Genomics of Cancer Biomarkers Leading to Precision Medicine*
2. **Precision assays:** Karen Bijwaard, CDRH, *First cfDNA CDx Tests for EGFR Positive NSCLC Patient Treatment Selection*
3. **Therapeutic considerations;** Hobart Rogers, CDER, *Synthetic Oligonucleotides and Precision Medicine: Guiding the Way Forward*
4. **Gene editing:** Kimberly Schultz, CBER, *CAR T-cells: Steering the Immune Response to Target Disease*

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HajaSittana.ElMubarak@fda.hhs.gov, Eric.Donaldson@fda.hhs.gov,
Jennifer.Dickey@fda.hhs.gov

SUGGESTIONS/RECOMMENDATIONS

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Thank You!!!

<http://sharepoint.fda.gov/orgs/OC-OCS/ORSI/GGT/GGTSymposium/SitePages/Home.aspx>

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ADMINISTRATION

Protein Carbonylation as a Biomarker of Drug Quality, Safety and Efficacy

Ashutosh Rao, Ph.D.
Chief, Laboratory of Applied Biochemistry
Division of Biotechnology Review and Research III
Office of Biotechnology Products
Office of Pharmaceutical Quality
FDA/CDER

2nd FDA Genetics and Genomics Symposium
November 4, 2016

Outline of presentation

- The biomarker
 - Protein oxidative carbonylation
- Proof-of-principle clinical context
 - Cardiac damage from oncology agents
- The preclinical model
 - Tumor-bearing spontaneously hypertensive rat
- Challenges and other clinically-relevant opportunities
 - Human breast cancer and adjacent healthy tissue
 - Metabolic disorder Barth syndrome and mitochondrial proteins

2

Background

- Several clinical safety and product quality concerns arise from excessive oxidative stress, either *in vivo* or *in vitro*.
- Excessive oxidative stress has the potential to impact safety and efficacy of small molecule and biologic drugs.
- The same analytical tools are used for investigating protein oxidation *in vivo* or *in vitro*.
- **This presentation will focus on *in vivo* protein oxidation as a potential biomarker for the safety of oncology agents and the efficacy of cardioprotective agents.**

3

Regulatory issues being addressed



- Oncology agents with dose-limiting cardiotoxicity include CDER-regulated small molecules (e.g. anthracyclines, tyrosine kinase inhibitors) and biotechnology-derived drugs (e.g. mAbs, toxins, some cytokines).
- Several FDA advisory committee meetings related to these adverse events have occurred. Meta analysis by NIH indicates 24% of all cancer patients experience some form of a cardiac adverse event (Swain, 2003; Schimmel, 2004).
- Excessive oxidative stress is, at least partly, responsible for the adverse events.
- Dexrazoxane, an approved iron chelating 'anti-oxidant', provides cardioprotection but not completely or against agents that do not target iron.
- Cardioprotective strategies with general antioxidants and biologic hematopoietic factors have not successfully translated, even though animal models showed cardioprotection.

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Scientific gaps being addressed



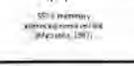
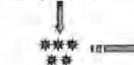
- Traditionally, two separate animal models are used to examine cardiotoxicity (e.g. spontaneously hypertensive rats without a tumor) and tumor reduction (e.g. immune-deficient mice xenografted with a tumor).
- A gap exists in the animal models being used for screening cardioprotective and chemotherapeutic agents because current models do not test both end points in a reliable single model with a functional immune system.
- There is a need for understanding the structure-function relationship between protein oxidation and selective cardiac toxicity, and how cellular resistance mechanisms influence the outcome.

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Establishing a preclinical model



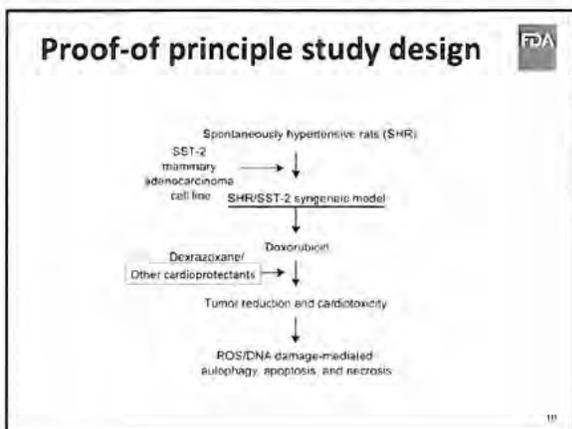
Spontaneously hypertensive rats (SHR)

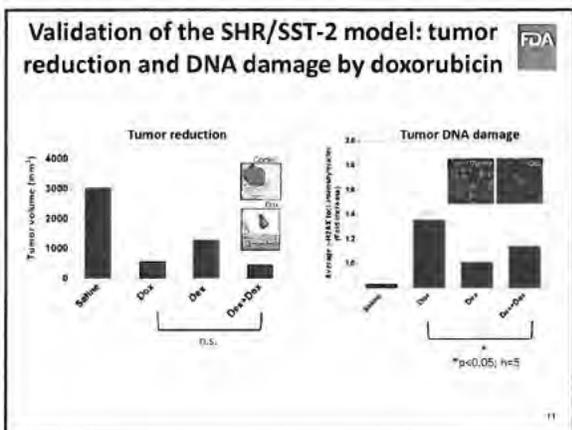


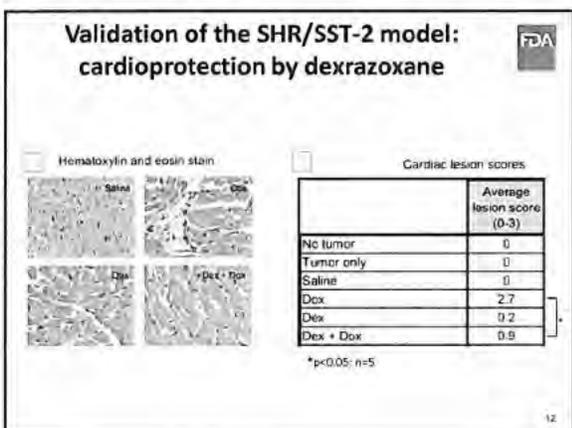
- A tumor-bearing spontaneously hypertensive rat (SHR) model leverages the previously used SHR (cardiac safety) and xenografted nude rodent (efficacy) models into a single immune-competent preclinical model for breast cancer drug discovery.
- Technology transferred to industry through CDER/OTS.

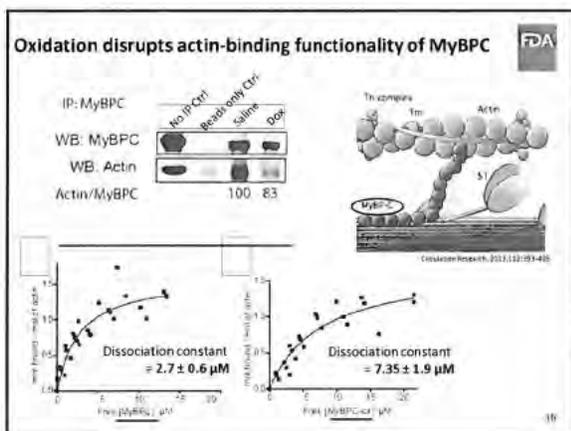
Syngeneic transplant of SST-2 cells into naïve SHRs

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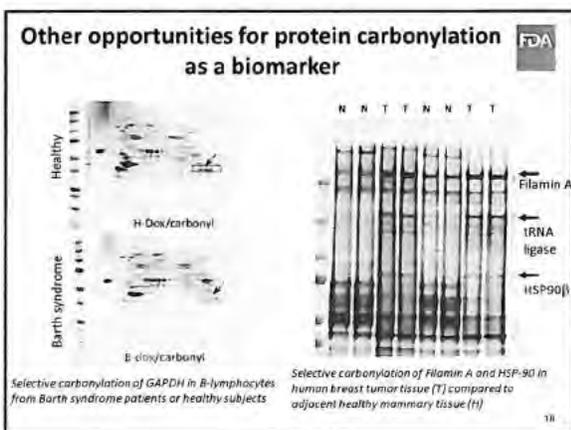












Take home messages

- Protein oxidation is a mechanistically-relevant post-translational modification that can serve as an indicator of drug safety, efficacy, and quality.
- Current analytical methods allow fairly robust and quantitative measurement of protein oxidation.
- Oxidative carbonylation of specific proteins may represent a clinically-relevant biomarker because it is irreversible and relatively selective under certain conditions.

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Abstract

Disassembly-induced carbonylation and degradation of antibody-antigen binding protein C promote autoimmunity

David J. ...

Department of ...

Supporting Information ...

Research Article ...

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Acknowledgements

- FDA/CDER Critical Path Initiative
- FDA Office of Women's Health
- NCI-FDA IOTF Program
- University of Wisconsin-Madison
- NCI/Experimental Therapeutics Branch
- NIH/NHLBI
- OBP, OPQ and OND colleagues












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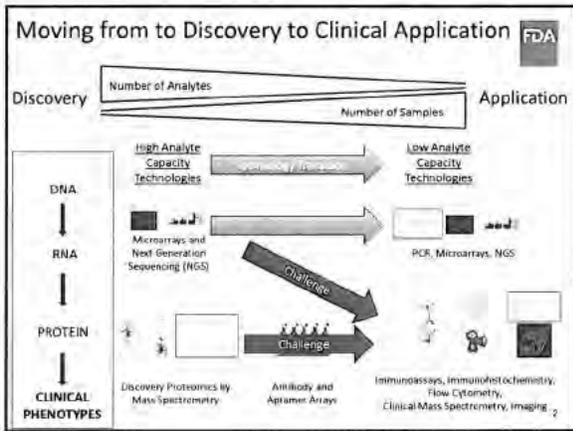
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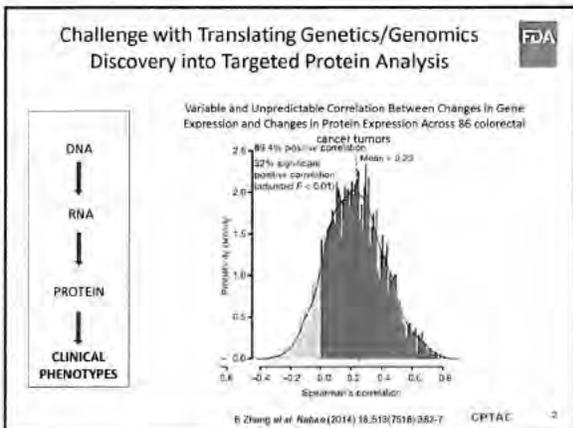
2nd Genetics and Genomics Symposium: The Tools and Technologies that Enable Precision Medicine

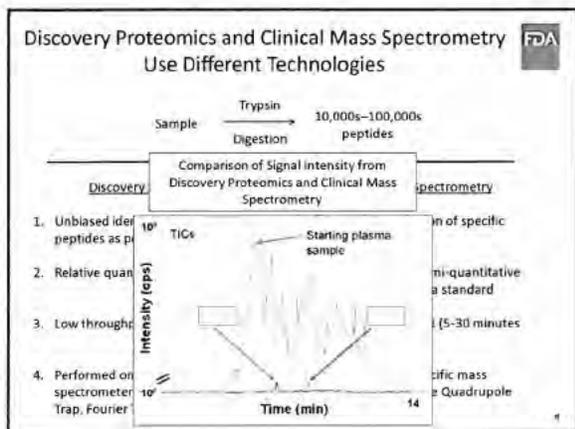
Challenges and Opportunities in Moving from Discovery to Regulation of Protein Assay Technologies

November 4, 2016

Doug Jeffery
CDRH/DIR/DIHD
Building 66, Room 5614
240-402-6648
doug.jeffery@fda.hhs.gov

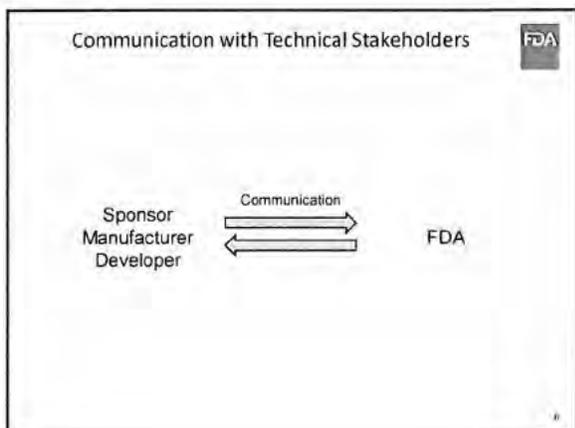






Technical, Clinical, and Regulatory Challenges for IVDs

	Immunofluorescence	IHC	Flow Cytometry	Protein Mass Spectrometry
Reagent/Assay Development	++	+	++	+
Assay Execution/Throughput	+++/High	+/Low	+/Moderate	+/Moderate
Types of Samples	All fluids (blood, urine, CSF, etc.)	Tissue and Cells	Cells (whole blood, bone marrow, lymph node)	All (blood, urine, CSF, tissue, cells)
Sample procurement	+++	+/-	+/-	+++/-
Sample proximity to Disease	+++/-	+++	+++	+++/-
Result Interpretation	+++	+/-	+/-	-
Regulatory Maturity	+++	++	+	+/-
IVD Examples	Mira	P1500L, P1500T, P150A27, P1600L, P1500F	Immunotherapy [B and NK Cells]	Metabolic drug analysis and microbiology, on Legend protein IVD



History of FDA Outreach with the Clinical LC-MS Community

The collage includes several items:

- Workshops:** "Recent Food Veterinary Analytical Developments for the LC-MS Analyst" and "Analysis of Antibiotic Residues in Food of Veterinary Origin - A Workshop Report by the FDA Emerging Markets LC-MS in Veterinary Research".
- Attendance and Presentations:** "Attendance and Presentations of LC-MS Conferences: AACL, AACC/MSSS, METAC, NUSP, AASB".
- Special Reports:** "US Food and Drug Administration Perspectives on Clinical Mass Spectrometry".
- Meetings:** "FDA/CDER Mass Spectrometry Interest Group Scientific Interest Series" and "Meetings in 2015/2016 from Academia and Industry talking about clinical applications of LC-MS: Brian Booth from CDER".
- Other:** "Expertise Learning Program (ELP) visits to Waters Corporation and ThermoFisher" and "Special Public Awareness: Proteomics in the Clinic".

Conclusions

- Translation of discovery results to clinical application for proteins is difficult:
 - Technologies are different in discovery and clinical applications
 - Current technologies still require extensive outlay of resources (time, reagents, sample procurement)
- Outreach to stakeholders requires sustained effort and helps to:
 - Educate reviewers about the state of the field
 - Educate stakeholders on FDA review processes and requirements
 - Establish direct relationships that can make problem-solving easier

Acknowledgements

OIR Mass Spectrometry Interest Group

- Julie Lathrop
- Yvonne Shea
- Matt Humbard
- Ricky Song
- Jinong Li

Kelly Oliner

Mandy Paulovich (Fred Hutchinson Cancer Center)

PD-L1 IHC Companion Diagnostics

Submission	Analyte	Reviewer	Branch, Division Management
P150013	PD-L1	Shyam Kalavar	Eunice Lee, Reena Philip
P150025	PD-L1	Shyam Kalavar	Eunice Lee, Reena Philip
P150027	PD-L1	Janaki Veeraraghavan	Donna Roscoe, Reena Philip
P160002	PD-L1	Aaron Schetter	Donna Roscoe, Reena Philip
P160006	PD-L1	Shyam Kalavar	Eunice Lee, Reena Philip

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Precision Medicine in Protein-Based Therapeutic Development

Sarah Dorff, Ph.D.
Genomics and Targeted Therapy Group
CDER/OTS/OCP



Outline

- Role of biomarkers in the development of precision medicines
- Highlight a few recent approvals of precision biologics (or those with the potential for precision)
- Discuss lessons learned from these approvals and opportunities for precision in protein therapeutics

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Precision Medicines

- Drug or biologic intended for use with a genomic, proteomic, or other specific biomarker that identifies patients for treatment or monitors response to treatment
- Reasonable expectation that the pharmacology of the therapeutic depends on the biomarker
- Targeted strategy may stem from mechanistic relationship to well-understood biomarker, or evidence for differential effects in experimental studies or clinical trials

PMID: 2554972 unofficial definition 3

Biomarkers FDA

- A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions
- Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers
- A biomarker is not an assessment of how a patient feels, functions, or survives
- Categories: diagnostic, monitoring, pharmacodynamic/ response, predictive, prognostic, safety, susceptibility/risk



Site: <http://www.ncbi.nlm.nih.gov/books/NBK326791/>
 Feedback: biomarkers@hcbi.nlm.nih.gov

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Pathways to Integrate Biomarkers in Drug Development FDA

Objective: Use the biomarker in a single drug development program

Biomarkers in Drug Development

Acceptance through IND, IDE and BLA submissions (drug approval process)

- **Responsible Parties:** One sponsor contacts the review division
- **Process:** Discuss, provide rationale and data to the review division
- **Risk and Resource:** Burden on one sponsor
- **Biomarker Information:** Embedded in drug labels

Objective: Establish the biomarker for use in multiple development programs

Biomarker Qualification

- **Responsible Parties:** Generally, consortia contact the BQ Program
- **Process:** Submit letter of intent, follow the BQ process
- **Risk and Resource:** Shared among consortia members
- **Biomarker Information:** Qualified biomarkers announced as draft guidance

www.fda.gov
 Slide Courtesy: Shashi Amur Amur et al. Clin. Pharm Ther. 96(5):54-60, 2015 5

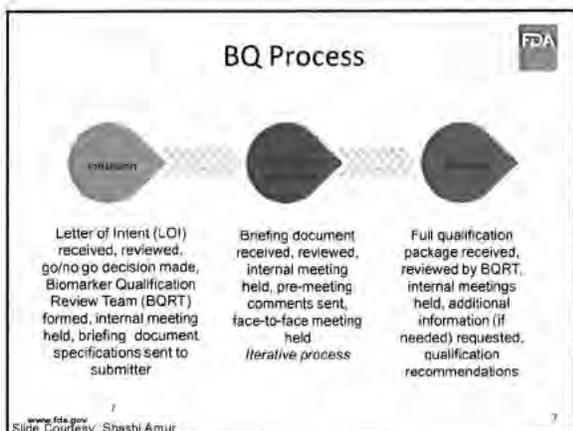
Biomarker Qualification (BQ) FDA

Definition: A conclusion that, within a carefully and specifically stated "context of use," the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development

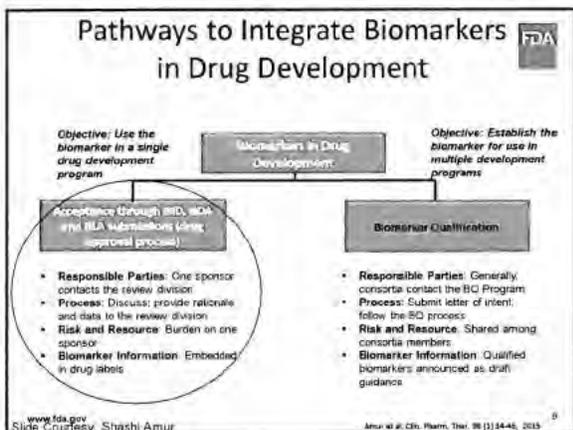
Context of Use (COU): A comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development

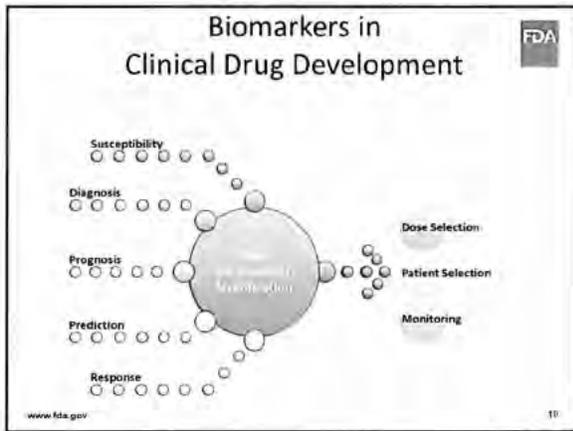


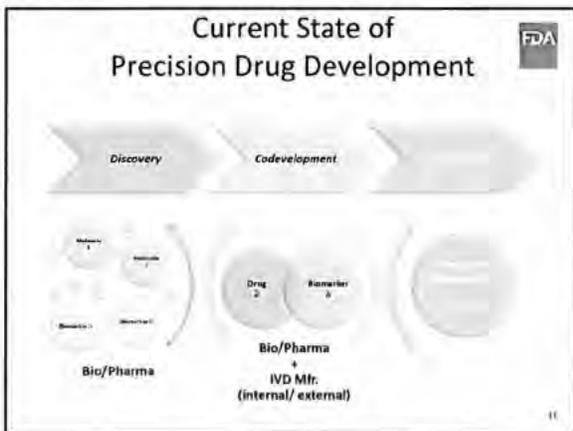
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 Slide Courtesy: Shashi Amur 6











- ### Setting the Stage for Targeted Drug Development
- Transition points
 - Ideally, codevelopment planned from outset
 - Typically, established at EOP2 or post-marketing
 - Exceptionally, discovered in late-phases, post-approval
 - Evidence base
 - Strong hypothesis (e.g., experimental evidence) or well-understood biomarker
 - Harm or lack of activity from early clinical studies in patients without the biomarker
 - Modest benefit in an unselected population, but significant toxicity
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FDA Regulated Biological Products

CDER

- Monoclonal antibodies
 - *Necitumumab*
- Cytokines
- Growth factors
- Enzymes
 - *Idursulfase*
- Immunomodulators

Protein Therapeutic Examples

CBER

- Allergenic extracts
- Blood and blood components
- Gene therapy products
- Devices and test kits
- Human tissue and cellular products used in transplantation
- Vaccines

www.fda.gov
<http://www.fda.gov/CDER/Products/Concepts/Update/ucp00644.htm>

Necitumumab

- A recombinant human monoclonal antibody against EGFR
 - Expression and activation of EGFR has been correlated with malignant progression, induction of angiogenesis, and inhibition of apoptosis
- Indicated, in combination with gemcitabine and cisplatin, for the first-line treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)
- Biomarker: EGFR, expressed at the protein level in ~86% of squamous NSCLC [PMID: 19046792]
 - EGFR protein expression (IHC) was assessed in archived tumor tissue as a potential predictor of response to necitumumab
 - EGFR membrane staining recorded via H-score (calculated based on the percentage and intensity of cell staining, with a possible continuous range of H-scores from 0 to 300)
- SQUIRE was the pivotal Phase 3 study, with a primary endpoint of overall survival (OS)

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EGFR H-Score in SQUIRE

- Pre-specified H-score cutoff of 200 (≥ 200 vs. < 200)
 - Chosen based on results from the FLEX trial in NSCLC with cetuximab added to vinorelbine/cisplatin [PMID: 22056021]
 - No association was found
- Exploratory analysis of H-score > 0 vs. $= 0$
 - Subpopulation ($= 0$) with a worse estimate of OS when necitumumab was added to gemcitabine/cisplatin



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Lessons and Opportunities from Necitumumab FDA

- Importance of mechanistic understanding of the therapeutic and target
 - Although exploratory and of limited sample size (n=47), patients lacking target (EGFR H-score = 0) may have a potential for risk without benefit after receiving necitumumab
- Importance of cutoff selected
 - Pre-specified EGFR H-score cutoff of 200 failed to identify a subset of patients more likely to derive benefit from necitumumab
 - Findings from EGFR H-score cutoff of 0 was considered to be exploratory and hypothesis generating
- Importance of validation of the assay around multiple cut-points

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Idursulfase FDA

- Enzyme replacement therapy for patients with Hunter syndrome (Mucopolysaccharidosis Type II, MPS II)
- Hunter Syndrome is a rare, X-linked lysosomal storage disorder caused mutation in the *IDS* gene leading to deficiency of iduronate-2-sulfatase
- Supplemental BLA submitted to expand indication to children <5 years of age
- Biomarker: *IDS* mutation, genotyping was performed and patients were separated into 3 groups

IDS Mutation	n
Complete Deletion/Large Rearrangement	8
Frameshift/Splice site	5
Missense	13

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Impact of *IDS* Mutations on Idursulfase FDA

- Retrospective analyses looked at the impact of *IDS* mutation groups on PK, PD, immunogenicity, and safety
- Patients with more severe mutations had:
 - Reduced idursulfase exposure
 - Blunted decrease in urinary GAGs and rebound in liver and spleen volumes
 - Development of antibodies against idursulfase
 - Higher frequency of infusion-related and serious AEs

Figure 4. PK, PD, and Immunogenicity Parameters by IDS Mutation Group. The graph plots PK (AUC, C_{max}), PD (urinary GAGs, liver/spleen volumes), and immunogenicity (antibody levels) against time for three mutation groups: Complete Deletion/Large Rearrangement, Frameshift/Splice site, and Missense. Severe mutations show lower PK exposure and higher immunogenicity.

Figure 4. PK, PD, and Immunogenicity Parameters by IDS Mutation Group. The graph plots PK (AUC, C_{max}), PD (urinary GAGs, liver/spleen volumes), and immunogenicity (antibody levels) against time for three mutation groups: Complete Deletion/Large Rearrangement, Frameshift/Splice site, and Missense. Severe mutations show lower PK exposure and higher immunogenicity.

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Lessons and Opportunities from Idursulfase

- Importance of mechanistic understanding of the therapeutic and target
 - Lack of endogenous iduronate-2-sulfatase (complete deletion/large rearrangement group) results in differential response and safety profiles
- Grouping patients based on similar functional effect of a mutation, as opposed to specific mutation, may allow for identification of relevant subgroups
 - Incidences of IDS mutation groups differed between young children and older patients, with the complete deletion/large rearrangement genotype found exclusively in the younger age group
- Possibility of mitigating subgroup-specific effects
 - PMR to develop a validated cross-reactive immunologic material (CRIM) assay, potential for immune tolerance induction regimens for some patients

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Considerations for Successful Precision Protein Therapeutic Development

- Does the patient express the target?
 - Protein-based therapeutics are highly specific for the target
 - Opportunity to replace missing enzyme in patients with deficient activity
- Are there patient factors and/or therapeutic aspects that predispose to immunogenicity and SAEs?
- Engage in early discussions of prospective/retrospective approaches
- Prepare for contemporaneous approval of Co-Dx

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Questions?

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ADMINISTRATION

Gene Editing Technology: Enabling a New Generation of Precision Gene Therapies

Anna Kwilas, Ph.D.
CMC Reviewer, Gene Therapy Branch
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
Food and Drug Administration

2nd Annual FDA Genetics and Genomics Symposium
November 4, 2016

Gene Therapy

- Gene therapy products mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host genetic sequences.
- Common gene therapy products:
 - Plasmids
 - Viral vectors
 - Bacterial vectors
 - *Ex vivo* genetically modified cells
 - **Gene editing products**



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Gene Editing Technology

- Process by which DNA is inserted, deleted, or replaced in the genome of an organism using engineered site-specific nucleases
- Nucleases create site-specific double strand breaks (DSBs) at desired locations in the genome
- Induced DSBs are repaired through non-homologous end-joining (NHEJ) or homology directed repair (HDR)

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Examples of Therapeutic Genome Modification

a Gene disruption: silences a pathogenic gene. Pathogenic protein. Truncated nonfunctional protein. mRNAs. Nontranscribed DNA.

b NHEJ gene correction: deletion of a pathogenic insertion. Nonfunctional protein. Functional protein.

Source: Han & Zhang, Nat Rev Genet 2012

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Examples of Therapeutic Genome Modification

c HDR gene correction: correct a deleterious mutation. Mutant protein. Corrected HDR template. Corrected protein.

d HDR gene addition: introduce a therapeutic gene. Site of function (RFP) protein. Corrective HDR template. Functional protein.

Source: Han & Zhang, Nat Rev Genet 2012

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Potential Therapeutic Applications of Gene Editing Technologies

- Hematologic disorders
 - SCID, SCD, hemophilia, β -thalassemia
- Neuromuscular disorders
 - Muscular dystrophy, SMA, ALS, Huntington's
- Ocular disease
 - Leber Congenital Amaurosis type 2, retinitis pigmentosa
- Skin disease
 - Dystrophic epidermolysis bullosa
- Lysosomal storage disorders
 - Fabry, Pompe, MPS
- Viral infections
 - HIV, HBV, HPV
- Cancer

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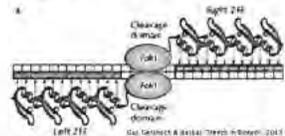
Current Gene Editing Technologies

- Four families of engineered site specific nucleases:
 - Zinc Finger Nucleases (ZFNs)
 - Transcription Activator-Like Effector Nucleases (TALENs)
 - Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas systems)
 - Engineered Meganucleases

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7

Zinc Finger Nucleases (ZFNs)

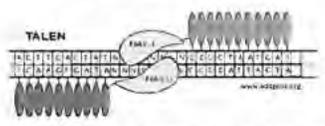


- Fusion of the non-specific DNA cleavage domain from the FokI restriction endonuclease with linked zinc-finger proteins
 - Zinc fingers are among the most common DNA-binding motifs
 - Each zinc finger recognizes 3-4 bp
 - FokI functions as a dimer
 - Only a small number of positional mismatches will be tolerated
 - Difficult to target non-G-rich sequences
 - May require substantial protein engineering to design

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8

Transcription Activator-Like Effector Nucleases (TALENs)

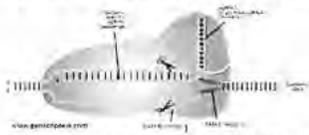


- Fusion of the FokI DNA cleavage domain with DNA-binding domains derived from TALE proteins
 - TALE proteins were identified in plant pathogenic bacteria
 - Each TALE recognizes a single base pair
 - Only a small number of positional mismatches are tolerated
 - Each TALEN requires a 5' T residue
 - Easier to design because of the more straightforward code but may require complex molecular cloning methods

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Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas9) 



- Ribonucleoprotein complex composed of Cas9 protein and a guide RNA (gRNA)
 - gRNA is composed of homologous CRISPR RNA (crRNA) anchored into the Cas9 protein by the trans-activating crRNA (tracrRNA)
 - Cas9 contains 2 DNA cleavage domains
 - Identified as a bacterial defense mechanism against invading viruses
 - Protospacer-adjacent motif (PAM) required downstream (3') of target site
 - Efficient and easily designed using oligo synthesis and standard cloning procedures
 - Can exhibit a high rate of off-target cleavage due to tolerance of 1-5 mismatches

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Considerations for Developing Therapies using Gene Editing Technologies 

- Nuclease design
- Optimization of targeting elements
- Type & degree of modification needed
- Delivery method
 - Viral vectors, plasmid DNA, mRNA, protein (RNP)
 - Direct administration
 - Modification of cells ex vivo

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Considerations for Developing Therapies using Gene Editing Technologies 

- Safety and efficacy
 - Target validation studies
 - Mono-allelic vs. bi-allelic
 - Preclinical studies
 - What models are available/appropriate?
 - What will you monitor – sequence, expression, function?
 - Clinical trial design, patient monitoring, long-term follow-up

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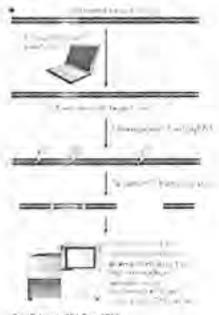
Gene Editing Safety Concerns FDA

- **Specificity**
 - Minimizing off-target editing events
 - Sensitivity of off-target screening methods
- **Additional adverse effects due to genomic DNA cleavage at on- and off-target sites**
 - Translocations
 - General genomic instability
 - Possible enhanced cell aging
- **Immunogenicity**
- **Adverse impact of the delivery system**

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Methods of Analyzing Off-target Editing FDA

- ***In silico* methods**
 - BowTie2, BFAST, COSMID, Cas-Off-Finder
 - Computational methods identifying areas of homology to targeting sequence
 - Confirmed by PCR amplification
 - Platforms are based on different algorithms and often give different results

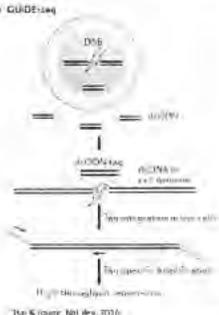


The K Joung, Nat Rev, 2016. 14

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Methods of Analyzing Off-target Editing FDA

- **Unbiased whole genome methods**
 - GuideSeq, BLESS, IDLV Capture, high-throughput genome-wide translocation sequencing
 - DSBs are tagged
 - PCR amplification of tagged sequences allows identification of edited regions
 - Off-target editing events may be cell type specific



The K Joung, Nat Rev, 2016. 15

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**Minimizing Off-target Effects
CRISPR/Cas9** 

- Optimizing Cas9 expression
 - Transient/inducible – dose titration
 - Orthologs with longer/less rigorous PAM requirements, alternate cleavage activity
 - Rationally engineered variants
- Optimizing gRNAs/donor sequences
 - Avoid complete matches in the seed region (10-12 bases closest to the 3' end)
 - Use shorter gRNAs – off-target strand separation becomes weaker
 - Destruction of the PAM site – eliminates re-editing

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**Assessing the Safety of Gene Therapies
using Gene Editing Technology** 

- How are nucleases and donor sequences produced?
- What are the kinetics of nuclease cleavage and persistence of cleavage activity?
- What is the percentage of cleavage at the on-versus off-target sites?
- Has there been thorough evaluation of potential off-target sites?
 - What types of off-target editing events are occurring?
 - What is the impact of off-target editing events?

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**Assessing the Safety of Gene Therapies
using Gene Editing Technology** 

- What models have been used to display safety and efficacy?
 - Are they appropriate/informative for both on- and off-target editing?
 - What data been generated to inform long term follow-up of potential patients?
- In the case of direct administration, has there been identification and characterization of off-target cells/tissues?

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Regulation of Gene Editing Technologies 

- CBER has been regulating gene therapy products since 1989 and gene edited products since 2008
- Science-based approach
- Risk-benefit analyses
 - Potential to correct or remove defective genes
 - Risk of off-target genome modification
 - Unknown long term effects of on- or off-target genome editing

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Conclusions 

- Gene editing technology has enabled a new class of gene therapies
- There is still significant need for fundamental and translational work in order to minimize potential risks and realize the full promise of these technologies for widely treating human disease
- The rapid progress in the field is likely to continue to lead to new technologies to evaluate and expand the scope of therapeutic genome editing
- The enormous excitement surrounding genome editing needs to be coupled with strategic planning and rigorous but enabling regulatory processes to ensure the successful development of this class of potentially life-changing medicines

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Acknowledgements 

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 - Gene Therapy Branch Chief
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Contact Information



Anna Kwilas, Ph.D.

Product CMC Reviewer, Gene Therapy Branch

OTAT/CBER/FDA

10903 New Hampshire Avenue

Building 71, Room 5209B

Silver Spring, MD 20993

Anna.Kwilas@fda.hhs.gov



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22



Using Genomics to Measure Antimicrobial Resistance in *Salmonella*

Gregory Tyson, Ph.D.
Microbiologist
Center for Veterinary Medicine
Office of Research

Disclaimer
This communication is consistent with 21 CFR 30.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.



Outline

- Antimicrobial resistance background
- Previous resistance/genomics work
- Methods
- Results
- Conclusions/precision medicine implications




- Interagency program operating since 1996
- Monitors antimicrobial resistance of foodborne pathogens in animals, retail meats, humans
 - FDA measures resistance in *Campylobacter*, *Salmonella*, *E. coli*, and *Enterococcus*
- Data used to understand trends in resistance, transmission of foodborne pathogens, risk assessment for antibiotic approval, etc.

Salmonella and antimicrobial resistance



- One million *Salmonella* infections/yr in United States
- Most infections self-resolve
 - Serious infections require treatment
- Antimicrobial resistance critical health threat of global importance
- Over 23,000 deaths/yr in United States from resistant pathogens




Antibiotics: what do they do?



- Antibiotics target conserved bacterial structures or pathways to kill bacteria or inhibit their growth
 - Also called antibacterials
- Type of antimicrobial
 - Can include antifungals, antivirals, antiparasitics...
- Used primarily for treatment of bacterial disease
 - Some prevention, other uses as well



(Huguenin: Nature Microbiology, 2016)
© (Chen and Fung)

★ Antibiotic



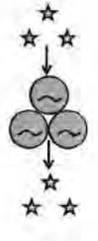
Salmonella (wildtype)



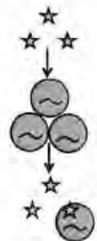
Salmonella (mutated)



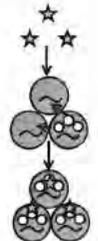
Salmonella (gene acquired)



Bacteria killed



Bacteria with mutation survive



Bacteria with gene survive

Susceptibility Testing FDA

- Antimicrobial susceptibility testing by broth microdilution to 13 antimicrobials
 - Uses standard methods of the Clinical and Laboratory Standards Institute (CLSI)
- Susceptibility testing involves detecting minimum inhibitory concentrations (MIC)
 - High numbers indicate resistance ($\mu\text{g/L}$)

Growth No growth

Concentration ($\mu\text{g/ml}$) 2 4 8 16 32

MIC

Resistance cutoffs FDA

- Clinical breakpoints are based on the likelihood of treatment success, with resistant (R), susceptible (S), and intermediate (I) categories
- Epidemiological cutoff values (ECVs) are used to differentiate wild-type from non-wild-type isolates based on MIC distributions
- ECVs are useful tools to report resistance for surveillance
 - EUCAST bases them on phenotypically detectable resistance mechanisms
- Now have enough genotypic data to do something different

Gentamicin

Sequencing and resistance gene ID FDA

- Whole-genome sequencing performed on MiSeq platform
 - Assembly by CLC Genomics Workbench
 - Resistance genes identified by in-house scripts, with 85% identity cutoff to genes in ResFinder database
- Presence of resistance determinants correlated to previously determined MICs

FDA

Previous work

- Previously were able to correlate presence of resistance genes/resistance-associated mutations with clinical resistance
 - For *Salmonella*, *E. coli*, *Campylobacter*
 - Correlations agreed approximately 99% of the time
- For some drugs, correlations much lower

Whole Genome Sequencing for Detecting Antimicrobial Resistance in Non-typhoidal Salmonella

Journal of Antimicrobial Chemotherapy

Whole Genome Sequencing Analysis Accurately Predicts Antimicrobial Resistance Phenotypes in *Campylobacter* spp.

WGS accurately predicts antimicrobial resistance in *Escherichia coli*

FDA

Genotypic cutoff value (GCV)

- Term coined to denote: the highest MIC of the population of bacteria lacking resistance determinants to a given drug. A majority of isolates above this MIC should possess resistance mechanisms
- Previously used this technique (but didn't call it GCV) to change NARMS cutoffs for streptomycin

Number of isolates

Streptomycin MIC (µg/mL)

Number of isolates

Streptomycin MIC (µg/mL)

Legend: * No genes, ** No resistance

Tyran ON, U.L. Aprio S, McDermott W, Zhao F. *PLoS One* 2016; 11(2): e0153114.

FDA

Isolates in study

- 1,738 *Salmonella* isolates
 - 1,297 retail meat (chicken, pork chops, ground turkey, ground beef)
 - 337 food-producing animals (young chicken, young turkey, beef cattle, dairy cattle, swine)
 - 104 human isolates
- All isolates sequenced, subject to susceptibility testing to 13 antimicrobials

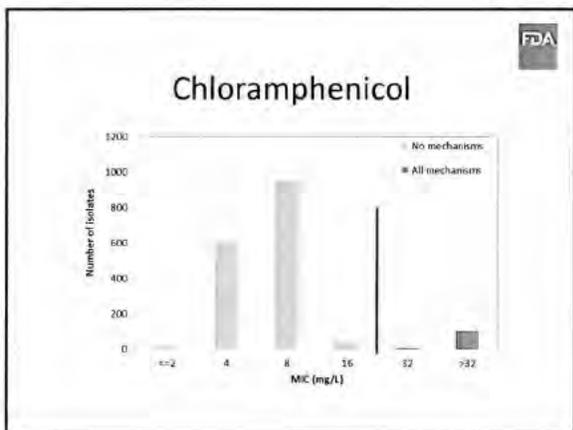


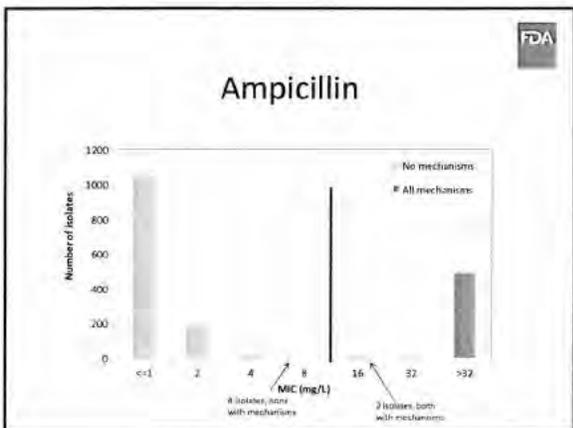
Example results

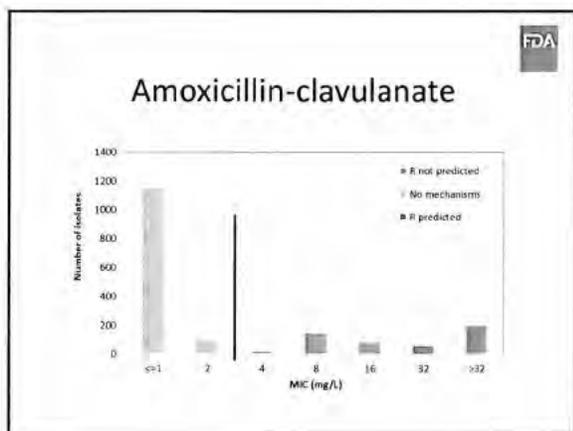
Isolate ID	YEAR	SOURCE	SEROTYPE
07345	2012	Ground Turkey	<i>Syphimurum</i>

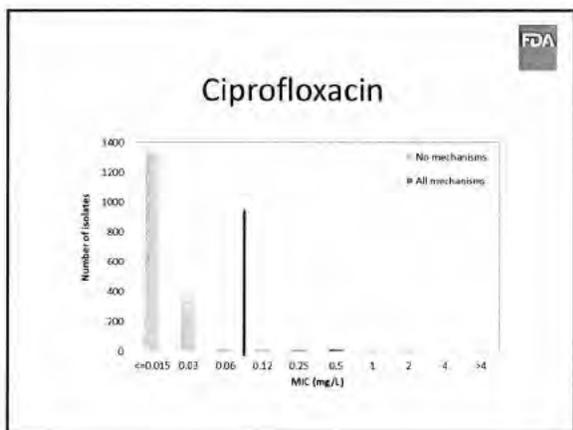
Drug	MIC	Mechanism
Chl	> 4	None

CHL MIC	No mechanisms	All mechanisms	floR	catA1	catA2	cmA1	catA1 floR	cmA1 floR
≤2	16							
4	61							
8	95							
16	38	2	1			1		
32	7	7				7		
> 32			107	92	4	1	3	1









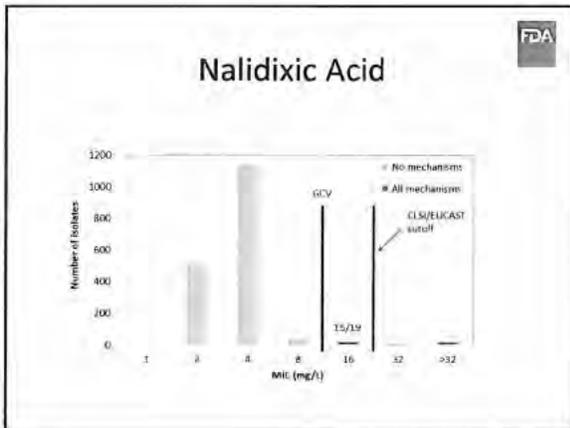
Ciprofloxacin MICs by mechanism

MIC (mg/L)	No mechanisms	qnr genes	One gyrA mutation	Two gyrA mutations
≤ 0.015	1333			
0.03	344			
0.06	17			
0.12		1	7	
0.25	1	4	5	
0.5		17	1	
1		4		
2		1		
4				
>4				3

FDA

Summary of GCVs

Drug	CLSI susceptible (S): treatment success likely	EUCAST GCV: wild-type (WT)	GCV: no resistance mechanism (NRM)
Ampicillin	≤ 8	≤ 4	≤ 8
Amoxicillin-clavulanate	≤ 8	None	≤ 2
Cefepime	≤ 8	≤ 8	≤ 8
Ceftazidime	≤ 1	None	≤ 1
Ceftiofur	≤ 2	≤ 2	≤ 2
Gentamicin	≤ 4	≤ 1	≤ 2
Tetracycline	≤ 4	≤ 4	≤ 4
Chloramphenicol	≤ 8	≤ 16	≤ 16
Oprofloxacin	≤ 0.06	≤ 0.06	≤ 0.06
Nalidixic acid	≤ 16	≤ 16	≤ 8
Azithromycin	None	None	≤ 16
Sulfisoxazole	≤ 256	None	≤ 256
Trimethoprim-sulfamethoxazole	≤ 1	≤ 1	≤ 0.05



FDA

Summary of results

- 81 total MICs do not fit GCV definitions, many due to overlap of population with and without acquired resistance mechanisms
 - Out of 22,486 total MICs
 - 99.6% total correlation
- Can provide more accurate measure for resistance reporting
- Demonstrates ability to predict MIC based on genotypic information alone
 - Some resistance mechanisms differ markedly by level of resistance conferred



Opportunities for precision medicine

- Human genomics has opportunity for personalized treatments
- Same is true for bacterial infections
 - Genomics can reveal resistance mechanisms and likely treatment failures
 - Can eliminate ambiguities such as 'intermediate' interpretations
- Genomics already used to inform HIV, tuberculosis treatment
- Genomics provides vast amounts of useful information from one technique
 - Can also infer serotype, virulence factors, help with traceback of pathogens to their source
 - Precision medicine potential based on resistance alleles, not phenotypic resistance or MICs



Acknowledgements

- | | |
|---------------------------|---|
| Office of Research | Office of New Animal Drug Evaluation |
| • Patrick McDermott | • Ron Miller |
| • Shaohua Zhao | |
| • Cong Li | |
| • Sherry Ayers | |
| • Jonathan Sabo | |
| • Claudia Lam | |



**Genetics and Genomics of Cancer Biomarkers
Leading to Precision Medicine**

Wenming Xiao

Division of Biinformatics and Biostatistics
National Center for Toxicological Research
Food and Drug Administration

Precision Medicine and Pharmacogenomics

• Response rate ↑
• Adverse event ↓


Predictive!
 $Y = f(X)$


Rx

MDx - Omics info. (X)
 GWA, NGS

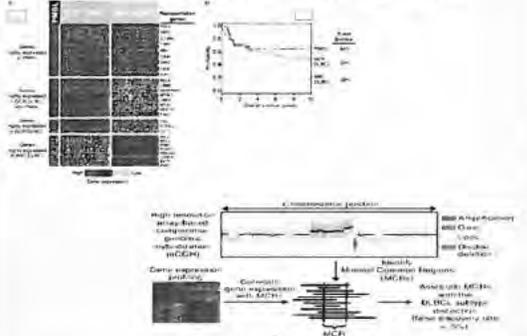

Y


 Optimal
response

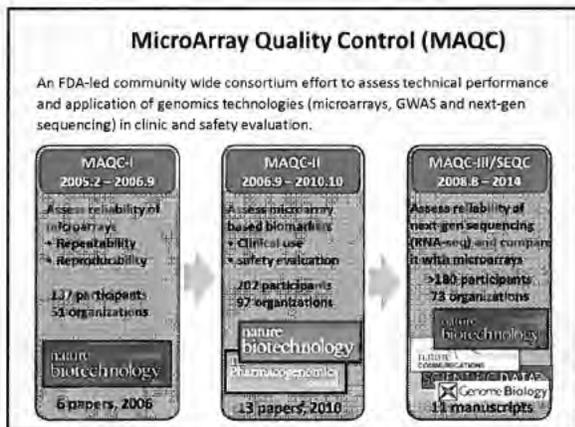

 Adverse
Event

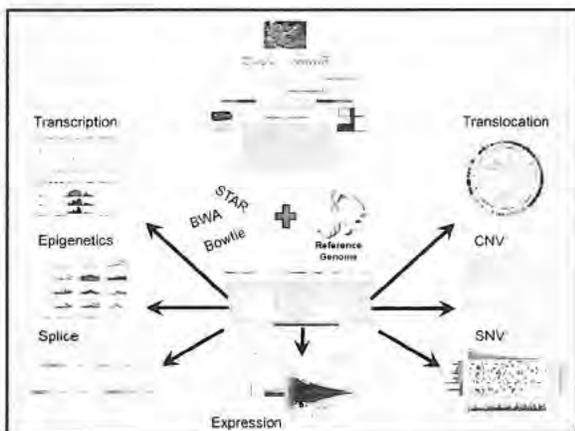
How to match right patients with right drugs?

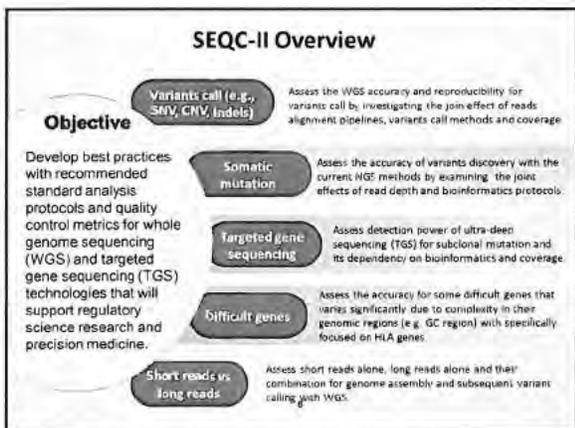
Microarray for genomics biomarkers

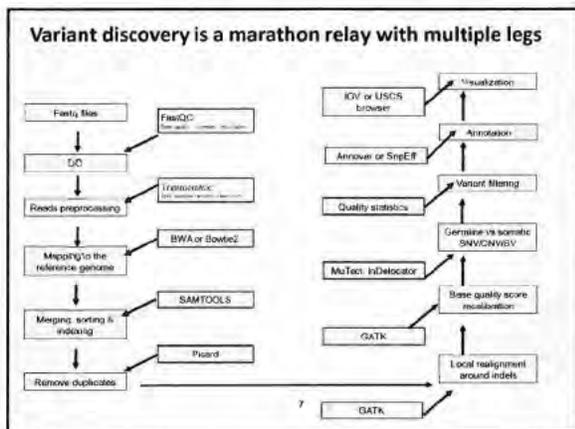


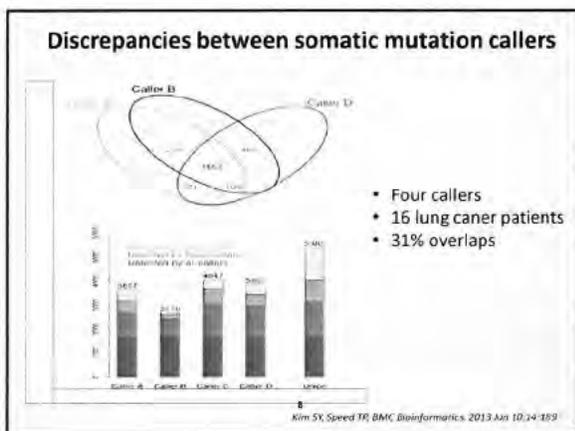
The diagram illustrates the workflow for microarray-based genomics biomarkers. It starts with a microarray chip showing gene expression profiles. This data is processed to identify differentially expressed genes (DEGs). A schematic shows a gene being transcribed into mRNA, which is then reverse-transcribed into cDNA and hybridized to a microarray. The resulting fluorescence intensity is measured and analyzed to identify biomarkers. The process involves high-throughput gene expression analysis, identification of differentially expressed genes (DEGs), and subsequent analysis using methods like MCF (Microarray Classification Function) to identify biomarkers. The final step involves validation of these biomarkers using techniques like qPCR and Western blotting.

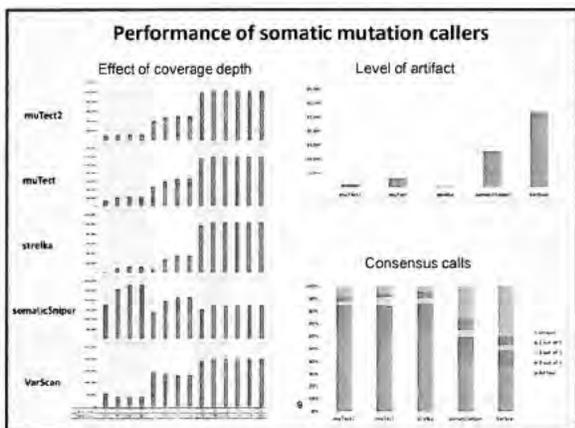


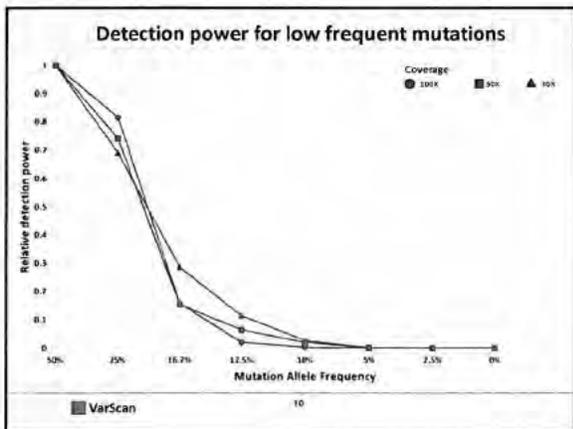


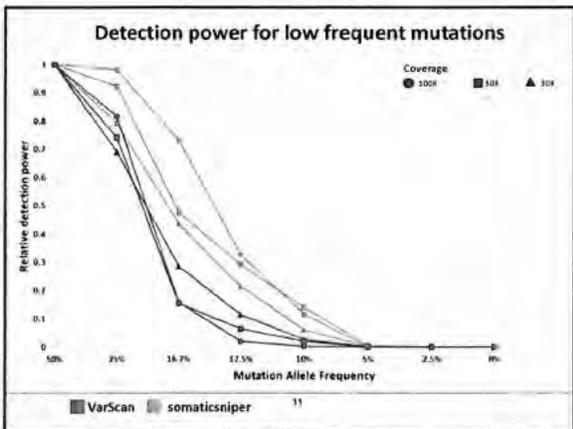


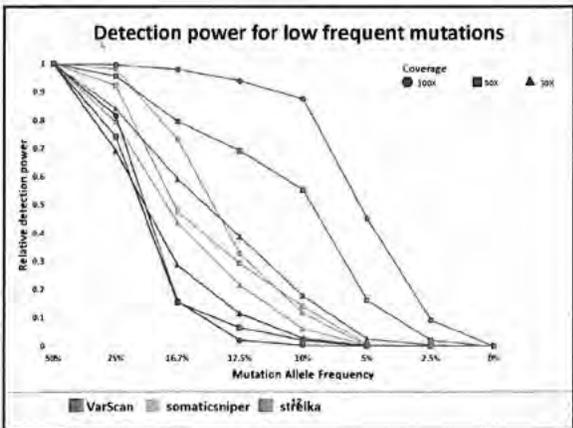


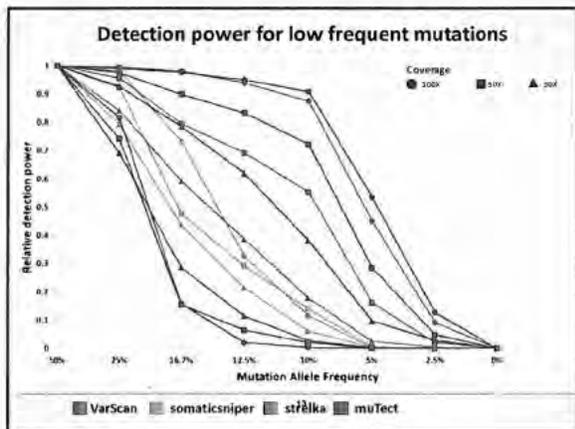


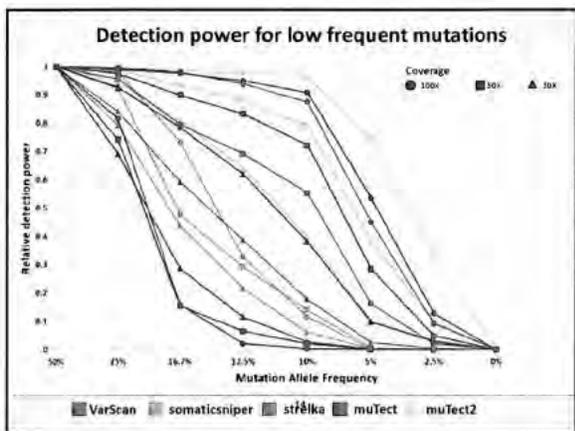












Objectives for SEQC-II

Determine factors that affect the accuracy of somatic mutation calling

- * Sample sources (FF vs. FFPE)
- * Amount of DNA
- ** NGS platform (WGS vs. WES)
- *** Bioinformatics (aligner)
- * Library Prep. (PCR vs PCR free)
- ** NGS platform (short vs. long)
- *** Bioinformatics (preprocessing)
- *** Bioinformatics (mutation caller)

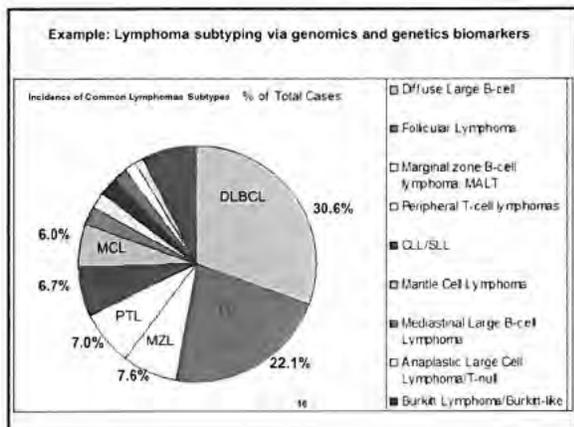
Understand the reproducibility of somatic mutation calling

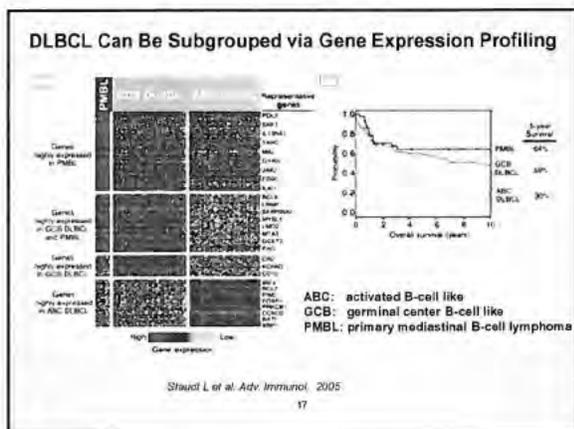
- ** Sequencing sites
- *** Bioinformatics pipelines

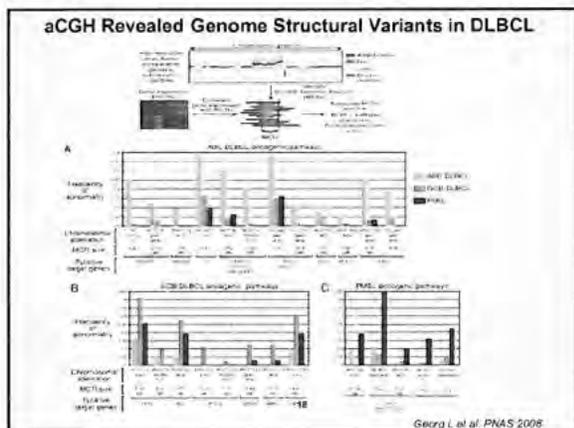
Establish reference data sets and samples

- ** Series of data sets for public
- ** Reference tumor samples
- ** Reference spike-ins
- ** Confident mutation calls

15







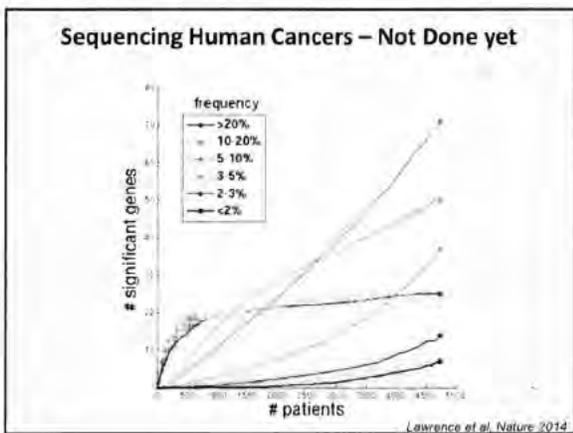
Genes with Somatic Mutation in Lymphoma Subgroup

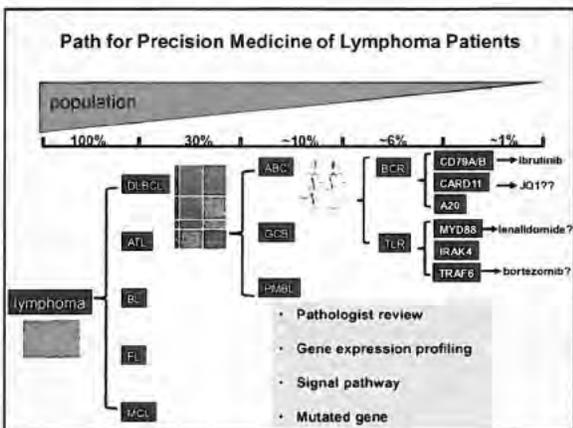
ABC DLBCL (n=155): • CD79A/B(23%) • CARD11 (8%) • A20 (23%) • MYD88 (29%)	GCB DLBCL (n=99): • TP53 (17%) • BCL-2 (30%) • EZH2 (26%) • CREBBP (10%)	Burkitt Lymphoma (n=41): • MYC(70%) • ID3 (53%) • TP53(34%) • TCF3 (29%)
--	---	---

Ngo V et al. Nature. 2011 *Schmitt R et al. Nature. 2012*

Adult T-cell Lymphoma (n=53): • CCR4(26%)	NK/T-cell Lymphoma (n=51): • STAT3 (6%) • STAT5B (6%)
---	--

Naragawa M et al. J Exp Med. 2014 *Kiuchi C et al. Nat Commun. 2015*





Take home messages

- **Genomics biomarkers**
 - Chromosome structure changes
 - mRNA profiling
 - microRNA profiling
 - DNA methylation
 - Larger patient group
 - Less effective/precise
- **Genetics biomarkers**
 - Driver somatic mutations (mechanistic biomarkers)
 - Mostly leads to targeted therapeutics
 - Companion diagnostic biomarkers
 - Very small populations
 - Highly precise
- **Genetics and genomics biomarkers for precision medicine**
 - Genomics biomarkers: patient group stratification
 - Genetics biomarkers: targeted therapeutics

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 Chunlin Xiao
 Joaquim Dopazo
 Pasmie Buchel
 Andreas Scherer
 Cesare Furlanello
 Matthias Fischer
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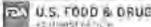
Louis M. Staudt
 Thomas Waldmann

City of Hope Medical Center

John Chan
 Can Kucuk

University of Nebraska Medical Center

Javeed Iqbal
 Yeiwei Xiang



First cfDNA CDx Tests for EGFR Positive NSCLC Patient Treatment Selection

PMA Approvals
6/1/2016 and 9/28/2016



Companion Diagnostics

- An *in vitro* device or imaging tool which provides information that is essential for the safe and effective use of a corresponding drug or biological product
- Oncology Drugs – standard specimen type for solid tumors is formalin-fixed, paraffin-embedded tissue (FFPET)
 - Biomarker (EGFR, KRAS, BRAF, PD-L1, etc.) established for specific therapeutic/biological product in specific tumor tissue

Current list of Cleared/Approved CDx Devices
<http://www.fda.gov/companiondiagnostics>



cobas® EGFR Mutation Test Regulatory History

- May 14, 2013 – 1st approval for Tarceva® (erlotinib) using FFPE
- Nov. 13, 2015 – 2nd approval for Tagrisso™ (osimertinib) using FFPE
- May 2014 – RMS contacted FDA regarding plasma testing
- Nov. 23, 2015 & Dec. 9, 2015 – PMAs filed
- June 1, 2016 – 1st approval for Tarceva® (erlotinib) using plasma
- Sept. 28, 2016 – 2nd approval for Tagrisso™ (osimertinib) using plasma

Known Discordances Between Tissue & Plasma

- Tumor heterogeneity
 - Different mutations identified in different clonal populations within tumor biopsy or between metastases
- Analytical Sensitivity
 - Limit of Detection
- Circulating tumor/cell-free DNA pre-analytical factors
 - Stability
 - Time to processing
- Affect on Intended Use/Indications for Use

Intended Use/Indications for Use

The cobas® EGFR Mutation Test v2 is a real-time PCR test for the qualitative detection of defined mutations of the epidermal growth factor receptor (EGFR) gene in non-small cell lung cancer (NSCLC) patients. Defined EGFR mutations are detected using DNA isolated from formalin-fixed paraffin-embedded tumor tissue (FFPET) or circulating free tumor DNA (cfDNA) from plasma derived from EDTA anti-coagulated peripheral whole blood.

The test is indicated as a companion diagnostic to aid in selecting NSCLC patients for treatment with the targeted therapies listed in Table 1 below in accordance with the approved therapeutic product labeling:

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	Exon 19 deletions and L858R	Exon 19 deletions and L858R
TAGRISSO™ (osimertinib)	T790M	T790M*

Patients with positive cobas® EGFR Mutation Test v2 test results using plasma specimens for the presence of the EGFR mutations listed above are eligible for treatment with the corresponding drug as indicated in Table 1 (see Note* for T790M). Patients who are negative for these mutations by this test should be referred to routine biopsy and testing for EGFR mutations with the FFPET sample type.

*The efficacy of TAGRISSO™ (osimertinib) has not been established in the EGFR T790M plasma positive, EGFR negative or unknown population and clinical data for T790M plasma-positive patients are limited; therefore, testing using plasma specimens is most appropriate for consideration in patients from whom a tumor biopsy cannot be obtained.

Drug safety and efficacy have not been established for the EGFR mutations listed in Table 2 below that are also detected by the cobas® EGFR Mutation Test v2:

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	G719X, exon 20 insertions: T790M, S768 and L859R	G719X, exon 20 insertions: T790M, S768 and L859R
TAGRISSO™ (osimertinib)	G719X, exon 19 deletions, L858R, exon 20 insertions: S768 and L859R	G719X, exon 19 deletions, L858R, exon 20 insertions: S768 and L859R

For manual sample preparation, FFPET specimens are processed using the cobas® DNA Sample Preparation Kit and plasma specimens are processed using the cobas® cfDNA Sample Preparation Kit. The cobas 2480 analyzer is used for automated amplification and detection.

Differences between tests – tissue vs. plasma FDA

Component	Tissue	Plasma	Differences?
cobas® EGFR Mutation Test v2 kit	✓	✓	None
cobas® Sample Preparation Kit	cobas® DNA Sample Preparation Kit	cobas® cfDNA Sample Preparation Kit	Identical except cfDNA kit includes a High Pure Extender Assembly filter housing – sample volume
Analysis Software	EGFR Tissue P1 AP v1.0.0.1560	EGFR Plasma P2 AP v1.0.1.1567	Cut-offs and algorithm

Performance Studies FDA

Analytical Performance Studies	
Limit of Detection (LoD): Predominant Mutations	Commutability/Contrived Sample Comparison Study
LoD Verification of Rare Mutations	Clinical Specimen Confirmation of LoD
Reproducibility (with EGFR WT NSCLC plasma)	Precision (Repeatability)
Robustness	Reference Method Validation
Analytical Accuracy	Reagent Lot Interchangeability
Potentially Interfering Substances ¹	
Sample Preparation Kit Reagent Stability ¹	Prepared Specimen Stability ¹
cobas EGFR Mutation Test v2 Reagent Stability ¹	Activated MMx Stability ¹
cfDNA KR Open Container Stability ¹	Prepared Specimen/Activated MMx Stability ¹
cobas EGFR Mutation Test v2 Kit Open Container Stability ¹	Plasma Specimen Handling Stability ^{1,2}
Clinical Performance Studies	
Clinical Bridging Study - Efficacy	Correlation between Plasma and FFPE

¹preliminary data provide; ²post-market commitment.

- ### Plasma Specimens
- Unable to obtain sufficient clinical specimens to perform analytical studies
 - RMS proposed intact cell line DNA diluted in healthy donor plasma
 - Compared:
 - Intact cell line DNA diluted in healthy donor plasma
 - Sheared cell line DNA diluted in healthy donor plasma
 - Intact cell line DNA diluted in EGFR wt NSCLC plasma
 - Sheared cell line DNA diluted in EGFR wt NSCLC plasma
 - Dilutions from estimated 10x LoD to 0.03x LoD
 - In this instance DNA diluted in healthy donor plasma seemed to fail earlier than NSCLC plasma

Limit of Detection FDA

- 11 member panel
 - Serial dilutions of sheared DNA in healthy donor plasma
- Tested pooled clinical specimens to confirm
 - "Mini-repro study" – 3 sites x 2 lots/site x 2 operators x 2 days

Panel Member	Mutations in Panel	Target Concentration (copies/mL)	Est. LoD by contrived specimens
1	0	WT	N/A
2 - 3	Ex 19del (2235_2249DEL15)	75 / 150	75
4 - 5	Ex 19del (2236_2250DEL15)	75 / 150	N/A
6 - 7	Ex 19del (2240_2257DEL18)	75 / 150	N/A
8 - 9	T790M	100 / 200	100
10 - 11	L858R	100 / 200	100

- Results
 - Contrived panel
 - All but one level for all samples tested showed 100% agreement
 - 23/24 T790M at 1x LoD = 95.8% (78.9, 99.9)
 - All clinical samples confirmed LoD

Analytical Performance FDA

- LoD by Mutation:
 - All but one level for all samples tested showed 100% agreement
 - 23/24 T790M at 1x LoD = 95.8% (78.9, 99.9)

Repro FDA

WT panel member 100% (72/72)	S768I 100% (72/72) – 100 copies/mL 100% (71/71) – 300 copies/mL
Ex. 19del 100% (72/72) – 100 copies/mL 100% (72/72) – 300 copies/mL	L861Q 100% (72/72) – 100 copies/mL 100% (72/72) – 300 copies/mL
L858R 98.6% (70/71) – 100 copies/mL 98.6% (71/72) – 300 copies/mL	Ex 20ins 100% (72/72) – 100 copies/mL 100% (72/72) – 300 copies/mL
T790M 97.2% (139/143) – 100 copies/mL 98.6% (142/144) – 300 copies/mL	G719X 90.3% (65/72) – 100 copies/mL 98.6% (70/71) – 300 copies/mL

- G719X most problematic
 - Majority of failures at 1 site with both operators

Clinical Studies



- Tarceva® (erlotinib)
 - Bridging (Clinical) Study:
 - ENSURE Study
 - Multicenter Phase III, randomized, open-label study [erlotinib vs. cisplatin in combination with gemcitabine (chemotherapy)]
 - Conducted in Asia, Malaysia, and the Philippines
 - Similar design to original EURTAC
 - Insufficient sample volume to test by NGS (Accuracy) – used samples for different study
 - Performed using specimens from 3 different studies in stage IIIb/IV NSCLC patients to compare plasma vs. tissue (ASPIRATION Cohort)
- TAGRISSO™ (osimertinib)
 - Accuracy & Bridging (Clinical) Study:
 - AURA2
 - Study used to approve tissue indication

Tarceva® (erlotinib) Indication



Accuracy Study



- Validated NGS method used
 - Tarceva: Used specimens from 3 different studies in studies in stage IIIb/IV NSCLC patients to compare plasma vs. tissue
 - All plasma specimens tested regardless of volume
 - ASPIRATION Cohort
 - ASPIRATION Study (n = 231)
 - MetMab (n = 110; WT specimens only)
 - MetLung (n = 70)
 - Only 340/411 w/ plasma specimens
 - 128/340 with valid tissue results (using v1 test) and 2.0 mL plasma

ENSURE

Valid cobas® EGFR Tissue Test v1 Result	Total (N=517)	Plasma Volume		
		2.0 mL (n=441)	1.5 - 1.9 mL (n=44)	< 1.5 mL (n=32)
Mutation Detected	251 (48.5%)	212 (48.1%)	22 (50.0%)	17 (53.1%)
No Mutation Detected	266 (51.5%)	229 (51.9%)	22* (50.0%)	15 (46.9%)

180/212 patients w/ valid tissue result and 2.0 mL plasma

Subjects enrolled in clinical study

Plasma Volume	Treatment Arm	cobas® EGFR Plasma Test v2 Result (no. of patients)		
		MD	NMD	Invalid
2.0 mL (N = 180)	Erlotinib	68	22	1
	Chemotherapy	69	20	0

Accuracy

- Used validated NGS method to establish analytical accuracy

cobas® EGFR Plasma Test v2	NGS (Plasma)									
	Ex. 19del					L858R				
	MD	NMD	Invalid	Not Tested	Total	MD	NMD	Invalid	Not Tested	Total
MD	17	2	0	0	19	11	1	0	0	12
NMD	2	106	1	0	109	2	113	1	0	116
Invalid	0	0	0	0	0	0	0	0	0	0
Total	19	108	1	0	128	13	114	1	0	128

With only Valid Result

PPA (95% CI)	89.5% (68.6%, 97.1%)	84.6% (57.8%, 95.7%)
NPA (95% CI)	98.1% (93.5%, 99.5%)	99.1% (95.2%, 99.8%)
PPV (95% CI)	89.5% (68.6%, 97.1%)	91.7% (64.6%, 98.5%)
NPV (95% CI)	98.1% (93.5%, 99.5%)	98.3% (93.9%, 99.5%)

Agreement of cobas® EGFR Tissue Test v1 and cobas® EGFR Plasma Test v2

cobas® EGFR Plasma Test v2		cobas® EGFR Tissue Test v1		Total
		MD	NMD	
	MD	161	4	165
	NMD	49	217	266
	Invalid Test Result	2	8	10
	Invalid - Plasma Volume <2mL	39	37	76
	No Plasma Sample	9	75	84
	Total	260	341	601

With only Valid Result

PPA (95% CI)	76.7% (70.5%, 81.9%)
NPA (95% CI)	98.2% (95.4%, 99.3%)
PPV (95% CI)	97.6% (93.9%, 99.1%)
NPV (95% CI)	81.6% (76.5%, 85.8%)

Assumed EGFR Prevalence Based on Tissue Samples	PPV	NPV
10%	82.8% (71.3%, 93.7%)	97.4% (96.2%, 98.7%)
15%	88.6% (75.7%, 96.9%)	96.0% (94.3%, 97.6%)
20%	91.6% (85.0%, 97.8%)	94.4% (92.3%, 96.3%)
30%	94.8% (90.0%, 98.6%)	90.9% (88.4%, 93.4%)
40%	96.8% (93.0%, 99.4%)	86.4% (83.3%, 89.4%)
50%	97.8% (95.0%, 100.0%)	80.8% (77.4%, 84.8%)

Agreement between cobas EGFR Plasma Test v2 and the NGS for Detection of Ex 19del and L858R Mutations in Aggregate Based on Different Tissue Mutation Prevalence (2 mL plasma)

Tissue Mutation Prevalence	Agreement between cobas EGFR Plasma Test v2 and NGS			
	PPA (95% CI)	NPA (95% CI)	PPV (95% CI)	NPV (95% CI)
10%	76.6% (65.2, 89.2)	98.2% (97.1, 99.3)	78.3% (67.9, 90.8)	98.0% (96.9, 99.1)
20%	83.7% (76.1, 91.6)	97.9% (96.5, 99.0)	86.7% (79.2, 93.8)	97.3% (96.0, 98.6)
30%	86.3% (79.8, 92.4)	97.3% (95.7, 98.7)	89.2% (83.2, 94.4)	96.5% (94.7, 98.1)
40%	87.7% (82.6, 92.7)	96.6% (94.8, 98.2)	90.5% (85.7, 95.0)	95.5% (93.7, 97.3)
50%	88.6% (84.5, 92.8)	95.8% (93.9, 97.7)	91.3% (87.4, 95.3)	94.3% (92.2, 96.5)

Efficacy Results Comparison (cobas® Plasma Test v2 MD Population vs. ENSURE FAS)

Parameter	cobas® Plasma Test v2 MD Population (N = 137)		ENSURE FAS (Tissue) (N = 217)	
	Chemotherapy N = 69	Erlotinib N = 68	Chemotherapy N = 107	Erlotinib N = 110
PFS (Investigator)				
Patients with event	60 (87.0%)	41 (60.3%)	87 (81.3%)	61 (55.5%)
Patients without event	9 (13.0%)	27 (39.7%)	20 (18.7%)	49 (44.5%)
Median (months)	4.6	8.3	5.5	11.0
Hazard ratio	0.29		0.33 ¹	
Hazard ratio 95% CI	[0.19; 0.45]		[0.23; 0.47]	
P-value (log-rank test)	<0.0001		<0.0001	
PFS (IRC)				
Patients with event	41 (59.4%)	53 (48.5%)	55 (51.4%)	51 (46.4%)
Patients without event	28 (40.6%)	35 (51.5%)	52 (48.6%)	59 (53.6%)
Median (months)	5.6	11.0	5.7	11.1
Hazard ratio	0.32		0.45	
Hazard ratio 95% CI	[0.19; 0.33]		[0.29; 0.64]	
P-value (log-rank test)	<0.0001		<0.0001	
Overall Survival				
Patients with event	45 (65.2%)	36 (52.9%)	57 (53.3%)	58 (52.7%)
Patients without event	24 (34.8%)	32 (47.1%)	50 (46.7%)	52 (47.3%)
Median (months)	21.9	23.7	25.5	26.3
Hazard ratio	0.78		0.91	
Hazard ratio 95% CI	[0.50; 1.20]		[0.63; 1.31]	
P-value (log-rank test)	0.2560		0.6073	

TAGRISSO™ (osimertinib) Indication

ORR Rate by Plasma Result Status among Enrolled Patients with Confirmed Responses

Analysis Population	Plasma Test Result	Enrolled N	# of Patients with ORR	ORR (95% CI)
tFAS	T790M+	117	72	61.5% (55.2%, 73.7%)
	T790M(-)	89	53	59.6% (51.3%, 73.0%)
	Overall	210	128	61.0% (57.0%, 70.8%)
tERAS	T790M+	111	72	64.9% (52.1%, 70.4%)
	T790M(-)	83	52	62.7% (48.6%, 69.8%)
	Overall	198	127	64.1% (54.0%, 67.6%)

cobas® EGFR Tissue Test v2 T790M+		Enrolled N	# of Patients with ORR	ORR (95% CI)
FAS	BICR	204	127	62.3% (55.2%, 68.9%)
	Investigator		133	65.2% (58.2%, 71.1%)

Clinical Study Conclusions

- Based on agreements observed between tissue vs. plasma
 - Reflex approach was most appropriate
 - Poorer agreements noted for T790M
 - Efficacy of TAGRISSO™ hasn't been established in the EGFR T790M plasma-positive, tissue-negative or unknown population
 - Clinical data for T790M plasma-positive patients are limited
 - Therefore - most appropriate for consideration in patients from whom a tumor biopsy cannot be obtained.
 - Post-market commitment developed w/ CDER/OHOP/DDP2 requesting real-world efficacy data from AstraZeneca & Roche Molecular from clinical studies enrolling patients based on plasma result.

Key Issues Faced with Submissions

- Clinical Studies – enrollment based on tissue
 - Poor agreement observed with T790M
- Preanalytic sample handling
- Use of Contrive Samples:
 - Volume plasma needed for analytical performance problematic
 - Performance of contrived specimens
 - Commutability study

Key Issues con't 

- Appropriate commutability study design is unclear
 - Different sponsors proposing different sample types (e.g., cell line DNA, plasmids, oligos spiked into healthy plasma, cfDNA from cell line conditioned media, etc.)
- Project with OSEL - look at preanalytical factors and commutability study designs (Critical Path)

Thank you.

Karen Bijwaard, MS, RAC
FDA/CDRH/OIR/DMGP/MPCB
karen.bijwaard@fda.hhs.gov

 **U.S. FOOD & DRUG**
ADMINISTRATION

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Synthetic Oligonucleotides and Precision Medicine: Guiding the Way Forward

Hobart L. Rogers Pharm.D., Ph.D.
Reviewer, Genomics and Targeted Therapy Group,
Office of Clinical Pharmacology

Objectives

- Overview of the different types/targets of oligonucleotides
- Explain the regulatory history of oligonucleotide drug development
- Provide high-level overview of current status of synthetic oligonucleotide drug development
- Explain the current challenges in oligonucleotide drug development

What are Synthetic Oligonucleotides?

2' MOE 2' Deoxy
(Supports Ribase H Activity) 2' MOE

G C C T C | A G T C T G C T T C | G C A C C

Phosphorothioate Backbone



- Modified nucleic acids typically designed to bond to complimentary DNA/RNA sequence and sometimes a protein (aptamers)
- Effects typically mediated by Watson-Crick base-pairing
- Modified to increase specificity and slow degradation
- Various means of backbone modification (phosphorothioate, 2'-Fluoro, morpholino)

Types/Targets of Oligonucleotide Therapeutics

DNA ← Gene Editing: CRISPR, Editas, Sangamo

RNA ← Translation: Antisense: e.g. Ionis (mipomersen), Wave Therapeutics; Splice-altering: Sarepta (eteplirsen), Ionis (nusinersen); siRNA: Alnylam (patisiran), Dicerna; microRNA: Regulus, Mirna, Miragen; mRNA replacement: Moderna, Curevac, Ethris

← Transcription

PROTEIN ← Aptamers: Noxon (pegatinib); CpG/TLR: Dynavax, Idera

FDA approved drugs in RED

A New Therapeutic Target

- Small molecule/protein based therapeutics – turn on/off light switches to modulate an effect
- Oligonucleotides – modulate the number of switches available
- CRISPR – install different types of switches

Oligonucleotide Mechanisms

1. CpG Immunostimulatory
2. siRNA RNA silencing
3. miRNA mimic
4. Antagomir steric block
5. RNase H mediated degradation
6. Aptamer as a small molecule
7. Antisense

Figure from Lundin et al. PMID: 27040602

Mechanism of Action

Rizzo et al. PMID: 23027901

History of FDA Approved Oligonucleotide Products

- 1998 Fomiversen – antisense; treatment of CMV retinitis withdrawn from market for lack of demand
- 2004 Pegaptanib – aptamer; treatment of wet age-related macular degeneration
- 2012 Mipomersen – antisense; treatment of homozygous familial hypercholesterolemia
- 2016 Eteplirsen – splice-altering; treatment of DMD in individuals amenable to exon 51 skipping

FDA-Industry Interactions

FDA Meetings/Year

Year	FDA Meetings/Year
2010 (August)	10
2011	25
2012	25
2013	28
2014	45
2015	60
2016 (August)	20

www.fda.gov

Eteplirsen FDA

- Accelerated approval for treatment of DMD mutations amenable to exon-51 skipping
- Targeted to exon-51 of the pre-mRNA for dystrophin
- 30-mer phosphorodiamidate morpholino backbone
- MOA is to induce skipping of exon-51 to re-establish the reading frame to produce a truncated dystrophin protein
- Produce truncated dystrophin similar to what is found in Becker's Muscular Dystrophy

www.fda.gov 10

Oligonucleotide mediated exon-skipping FDA

17

Eteplirsen FDA

- Accelerated approval based on an increase in dystrophin expression
- Dosed as 30 mg/kg once weekly IV infusion
- Safety concerns minimal
- Increased dystrophin at higher doses?

Study	Population	MOA	Primary Endpoint
Phase 1	Healthy Volunteers	Exon skipping	Safety, tolerability, PK
Phase 2	DMD patients	Exon skipping	Dystrophin expression, safety
Phase 3	DMD patients	Exon skipping	Dystrophin expression, safety, efficacy

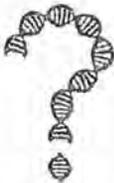
Source: FDA product labeling 18

Conclusions

- Increase in oligonucleotide drug based drug-development over the last decade
- Significant challenges remain, primarily centered around drug delivery and safety
- Backbone chemistry and dose of key importance
- Lag from discovery to clinical approval exists, but beginning to see some breakthroughs

www.fda.gov 19

Questions





 U.S. FOOD & DRUG
ADMINISTRATION

CAR T-cells: Steering the Immune Response to Target Disease

Kim Schultz, PhD
CBER/OTAT
Division of Cell and Gene Therapy



Gene Therapy Products

"mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host genetic sequences"

- Variety of diseases
 - Cancer
 - Genetic diseases
 - Infectious disease
- Variety of products
 - Viral vectors
 - Bacterial vectors
 - Plasmid DNA
 - Gene editing
 - Ex vivo genetically modified cells
- Variety of delivery mechanisms
 - Cleared or investigational



Product Type	Percentage
Retro	21%
Plasmid	21%
Adeno	18%
Lentiv	8%
Pox	9%
AAV	5%
HSV	2%
Bacteria/Yeast	4%
Other	4%

www.fda.gov

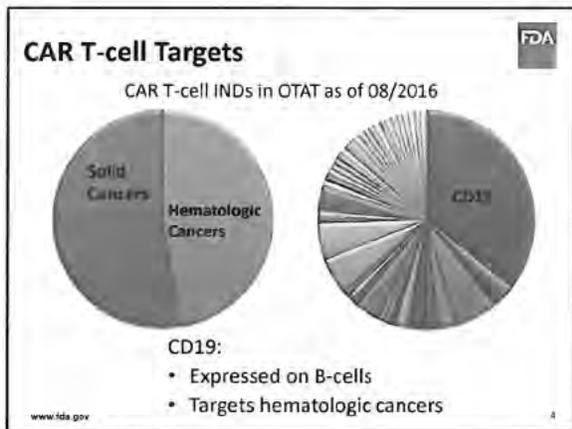


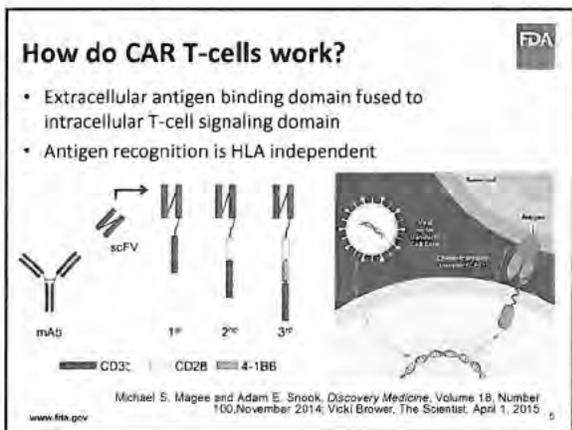
CAR T-cells: Chimeric Antigen Receptor T-cells

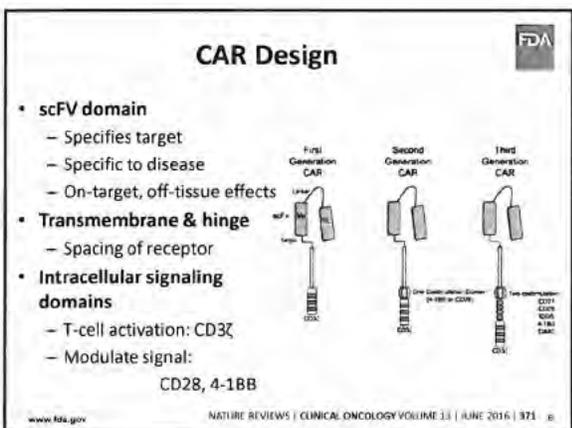
- **Impressive clinical outcomes for CD19 CAR T-cell therapy in the literature:**
 - Complete response rates of 70–90% consistently observed
- A single treatment can potentially be "curative"



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CAR Delivery Vectors FDA

- Delivery vectors are not reagents
- Must be manufactured under cGMP
- Need in-process and lot release testing of the viral vectors
 - Potency
 - Identity
 - Safety
 - Purity
- Testing and characterization
 - Cell banks
 - Viral Banks

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Regulatory Considerations for Integrating Viral Vectors FDA

- Design safety into the vector
 - Replication incompetent
 - Low chance of generating replication competent virus with split plasmid design
 - Minimize overlapping regions
 - Self-inactivating to minimize insertional mutagenesis
- CAR T-cell testing
 - Average integrations per cell
 - Replication competent virus
 - Long-term follow up

TWV: <http://www.twv.us/reverse-transcription/> 8

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How are CAR T-cells made? FDA

Review the CMC information for both the vector and the CAR T-cells

1. CAR vector

2. CAR T-cells

www.fda.gov Cancer Gene Therapy (2015) 22, 79-84 6

Challenges in Product Development 

- Controlling a complicated manufacturing process for a consistent product
 - Reagents, process, testing
- Developing meaningful biological potency assays
- Setting lot release specifications
 - Lack of reference standard materials
 - Limited material for testing
- Demonstrating product comparability due to wide process variability

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Control of Starting Materials & Critical Reagents 

- Cells from patient apheresis
 - Autologous leukapheresis collection
 - Heterogeneous starting material
 - Select or not to select?
- Cytokines, antibodies, and beads
 - T-cell stimulation & selection
 - Affect final composition of T-cells
 - Positive/Negative selection of intended target cells
 - Monitor T-cell populations by flow cytometry

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Manufacturing Process Control 

Goal: minimize variations to consistently produce a safe, pure, and potent product

- Build in quality and safety
- Defining processes and procedures
- Identify Critical Process Parameters (CPPs)
- Process qualification and formal process validation
- Control of critical quality attributes (CQA)
 - Testing intermediates, drug substances, drug products
 - Analytical assay qualification and validation

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Develop Meaningful Biological Potency Assays FDA

- Quantitative and demonstrates biological activity
- Measures multiple product CQAs
 - Transduction efficiency (e.g. %CAR+)
 - Level of CAR expression (e.g. CAR MFI)
 - Cytokine production upon stimulation (e.g. IFN-γ)
 - Biological functions based on MOA (e.g. target cell killing)
 - Potential to persist after infusion (e.g. cell phenotyping)
- Progressive implementation of potency assays
- Guidance for industry — Potency Tests for Cellular and Gene Therapy Products”

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Difficult to Set Lot Release Specifications FDA

- Reference standards are not yet developed
 - In-house standards should be developed
 - Retain samples of each lot
- “Living Drug” that expands in vivo
 - Dose according to transduced cell
 - Recommend that Sponsors evaluate cell subtypes in the final product
 - Potential to persist/engraft post infusion
 - CMC CD19 CART-cell database to identify CPPs & CQAs

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Expectations for product development FDA

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Difficulty Validating Process Changes with Comparability Studies



- Manufacturing transitioning from academic to commercial settings
- Labor intensive to semi-automated process
- Comparability is based on analysis of CQA data
- Ability for production "scale-out"



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10

The Future of CARs



- Off the shelf product
 - Gene editing
- ON/OFF or suicide switches
 - Membrane-permeable small molecules
- CAR cytokine production
 - Encoded by CAR
 - Modulate tumor microenvironment
- Combination therapy
 - Block T-cell exhaustion
 - Target multiple pathways



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11

OTAT Contact Information



- Kimberly Schultz: Kimberly.Schultz@fda.hhs.gov
- **Regulatory Questions:**
Contact the Regulatory Management Staff in OTAT at CBEROCTGTRMS@fda.hhs.gov or Lori.Tull@fda.hhs.gov
- **References for the regulatory process for OTAT**
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm>
- **OTAT Learn Webinar Series:**
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>

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12



From: [Evans, Dana](#)
To: [Califf, Robert](#)
Subject: FW: Pink Sheet | Highlights Of The Week
Date: Monday, November 07, 2016 10:35:13 AM

Dana Evans, M.P.H.

Program Support Specialist to the Commissioner
Office of the Commissioner Immediate Office
U.S. Food and Drug Administration
Phone: 301-796-2021
BB: 301-467-8987
Email: dana.evans@fda.hhs.gov

From: Pink Sheet [<mailto:info@pharmamedtechbi.net>]
Sent: Monday, November 07, 2016 10:34 AM
To: Commissioner FDA
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Look below for key developments and intriguing perspectives from the past week to inform your strategic decision-making. And in the week ahead, look for our coverage of how the US election outcomes affect biopharma (remember, we have a hot topic page on the US elections).



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Biosimilars: Sandoz Pegfilgrastim Review, Amgen Adalimumab Launch Extended To 2018

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Parliament may get to vote on the terms of the UK's departure from the EU if an important legal decision handed down today is upheld. Industry has its-eye on ongoing talks with the government.



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From: [Peter Pitts](#)
To: [Califf, Robert](#); [Woodcock, Janet](#)
Subject: Sarepta Op-Ed
Date: Thursday, November 10, 2016 8:40:31 AM

FYI:

<https://morningconsult.com/opinions/sarepta-regulation-hope/>

Hope I've hit the right note.

Peter

From: [Peter Pitts](#)
To: [Califf, Robert](#); [Woodcock, Janet](#)
Subject: Sarepta
Date: Thursday, November 10, 2016 8:41:19 AM

FYI:

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From: [Pink Sheet](#)
To: [Califf, Robert](#)
Subject: Pink Sheet | Today's News & Analysis
Date: Wednesday, November 16, 2016 6:14:30 AM

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Sarepta says US FDA said no, but agency repeatedly urged the company to pursue the approach.

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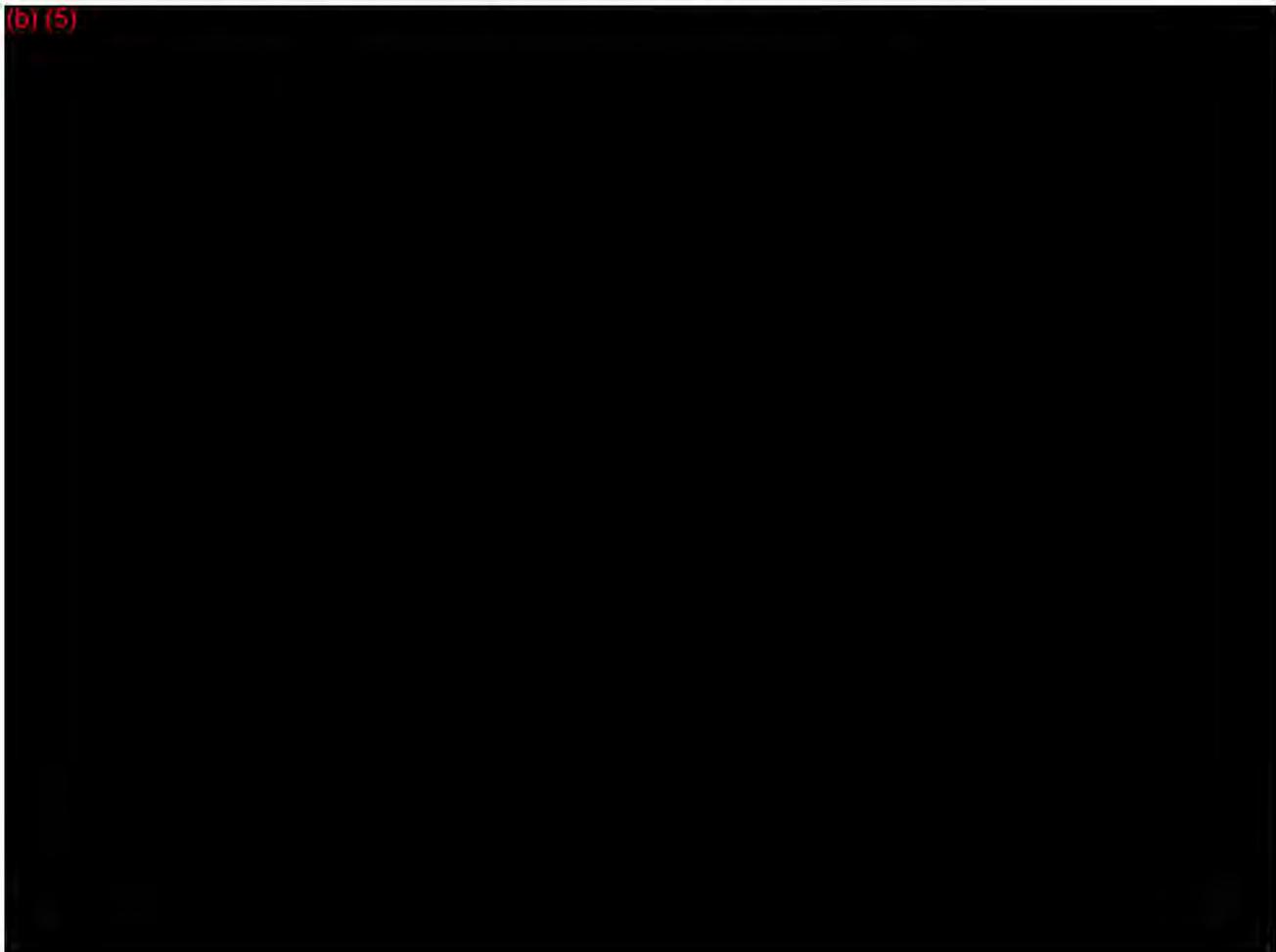
From: [Marchand, Heidi](#)
To: [Califf, Robert](#); [Fiuzat, Mona](#); [Conover, Katie](#); [Shuren, Jeff](#); [Maisel, William](#); [Cooper, Jeffrey \(CDRH\)](#); [Andrews, Sharon M](#); [Bell, Glenn](#); [Gutierrez, Alberto](#); [Schwartz, Suzanne](#); [O'Callaghan, Kathryn](#); [Tenenbaum, Cara](#); [Maloney, Diane](#); [Buch, Barbara D](#); [Pretti, Jeffery](#); [Jarow, Jonathan](#); [Beitz, Julie G](#); [Griebel, Donna](#); [Joffe, Hylton](#); [Yao, Lynne P](#); [Whyte, John](#); [Klafehn, Cristina](#); [Gebbia, Emily](#)
Cc: [Evans, Dana](#); [Fiuzat, Mona](#); [Kozlowski, Steven](#); [Kuntze, Patricia M](#)
Subject: RE: Stakeholder Listening Session with the FDA Commissioner on Genitourinary, Gastrointestinal, & Gynecology/Reproductive Health
Date: Wednesday, November 16, 2016 12:38:13 PM
Attachments: [Final Briefing Document for 11.18.16 Stakeholder Listening Session.doc](#)

Dear All,

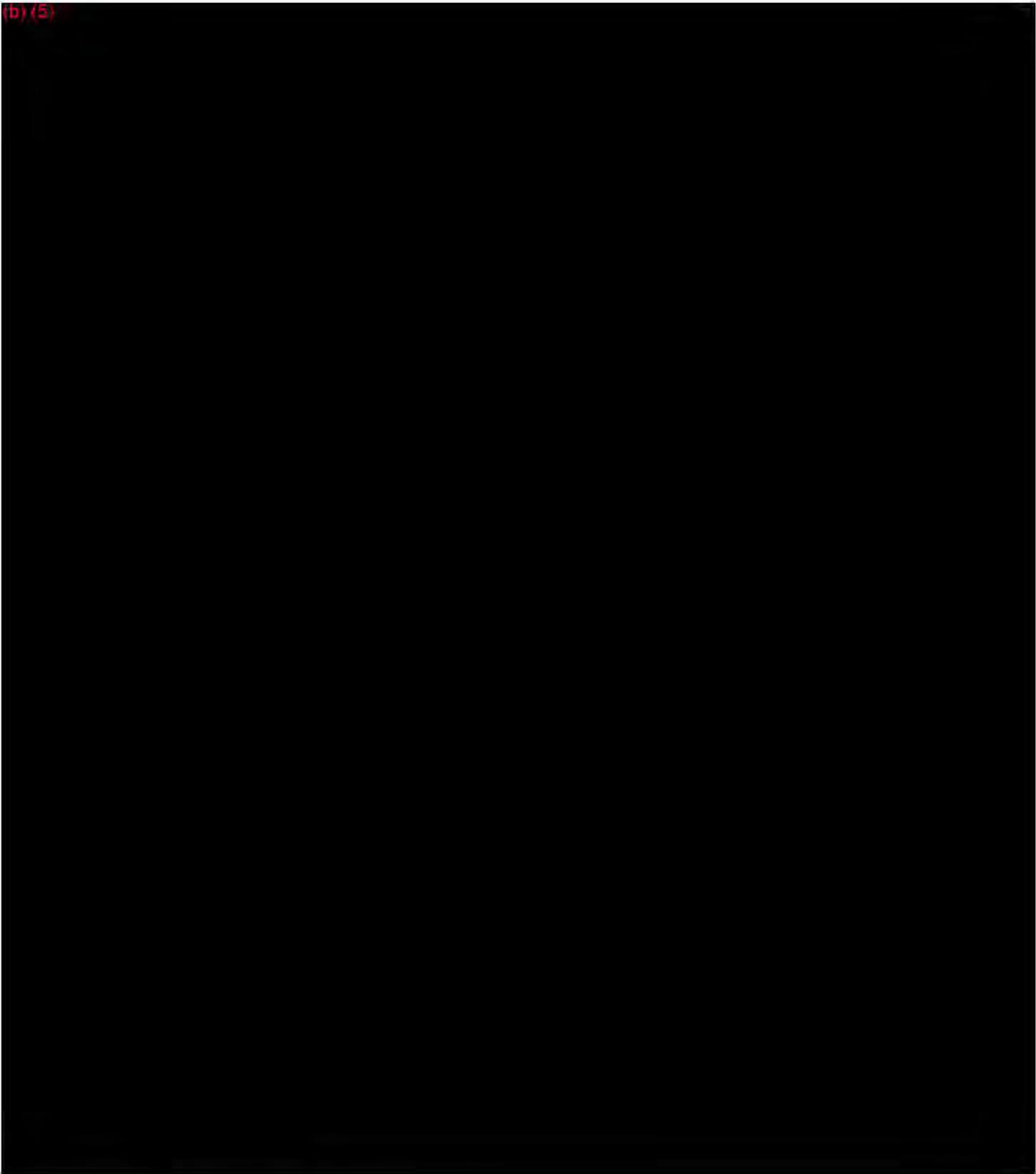
Please find an updated briefing document for the Friday, November 18 Listening Session from 9AM-12:30PM for our stakeholder engagement with organizations representing GU, GI, GYN organizations. In addition to the briefing materials several other topics of interest that may be raised are provided from recent stakeholder monitoring. Regards, Heidi

Due to the recent presidential elections, there may be additional issues raised that are not included in the briefing document but, which we want you to be aware.

(b) (5)



(b) (5)



-----Original Appointment-----

From: Califf, Robert

Sent: Tuesday, November 15, 2016 10:40 AM

FDAOC0002956

To: Califf, Robert; Fiuzat, Mona; Conover, Katie; Marchand, Heidi; Shuren, Jeff; Maisel, William; Cooper, Jeffrey (CDRH); Andrews, Sharon M; Bell, Glenn; Gutierrez, Alberto; Schwartz, Suzanne; O'Callaghan, Kathryn; Tenenbaum, Cara; Maloney, Diane; Buch, Barbara D; Pretti, Jeffery; Jarow, Jonathan; Beitz, Julie G; Griebel, Donna; Joffe, Hylton; Yao, Lynne P; Christl, Leah A; Whyte, John; Klafehn, Cristina; Gebbia, Emily

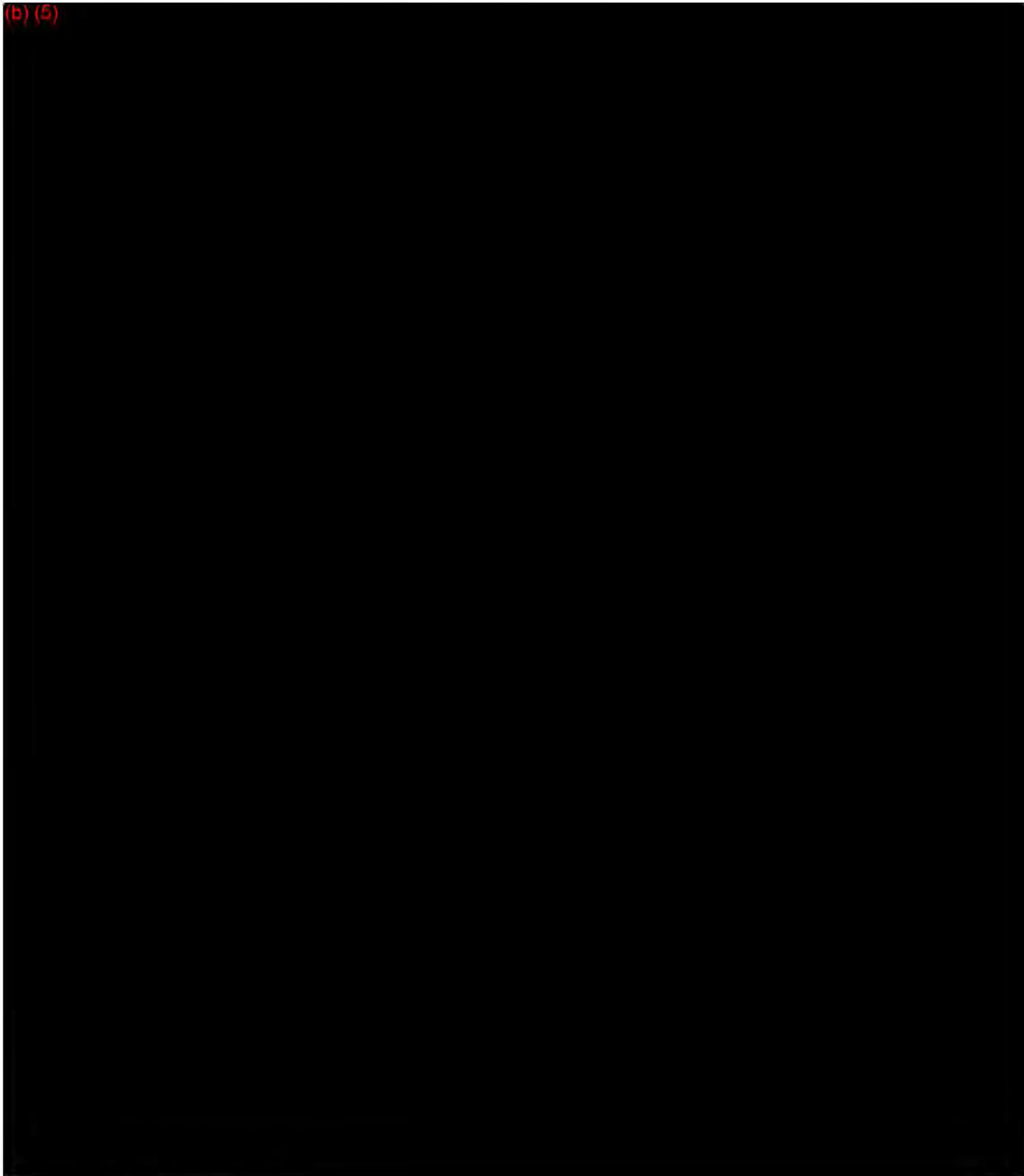
Subject: Stakeholder Listening Session with the FDA Commissioner on Genitourinary, Gastrointestinal, & Gynecology/Reproductive Health

When: Friday, November 18, 2016 9:00 AM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).

Where: Building 32, Room 1243

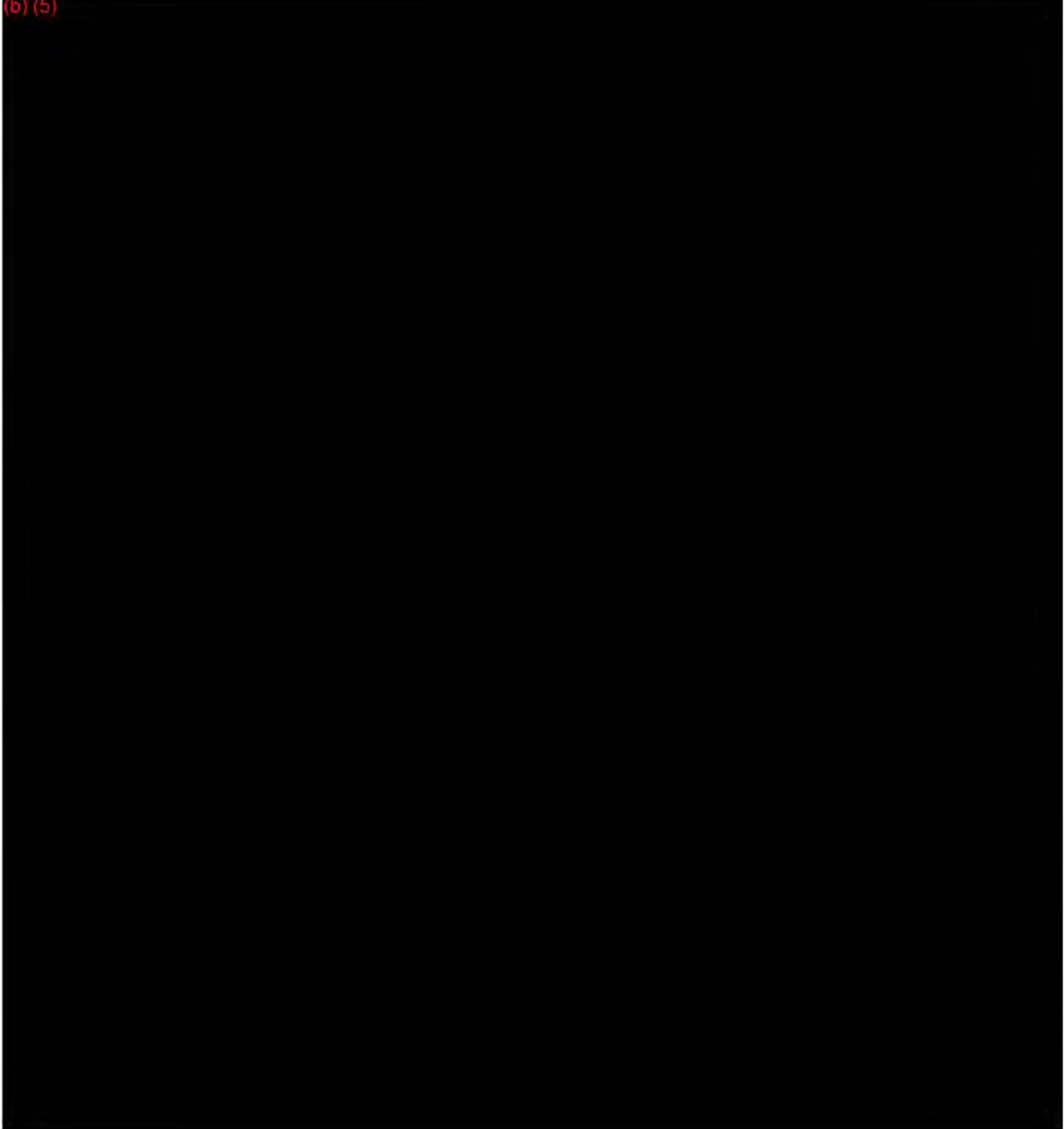
**Stakeholder Listening Session with the FDA Commissioner:
Genitourinary, Gastrointestinal, & Gynecology/Reproductive Health
BACKGROUND SUMMARY DOCUMENT**

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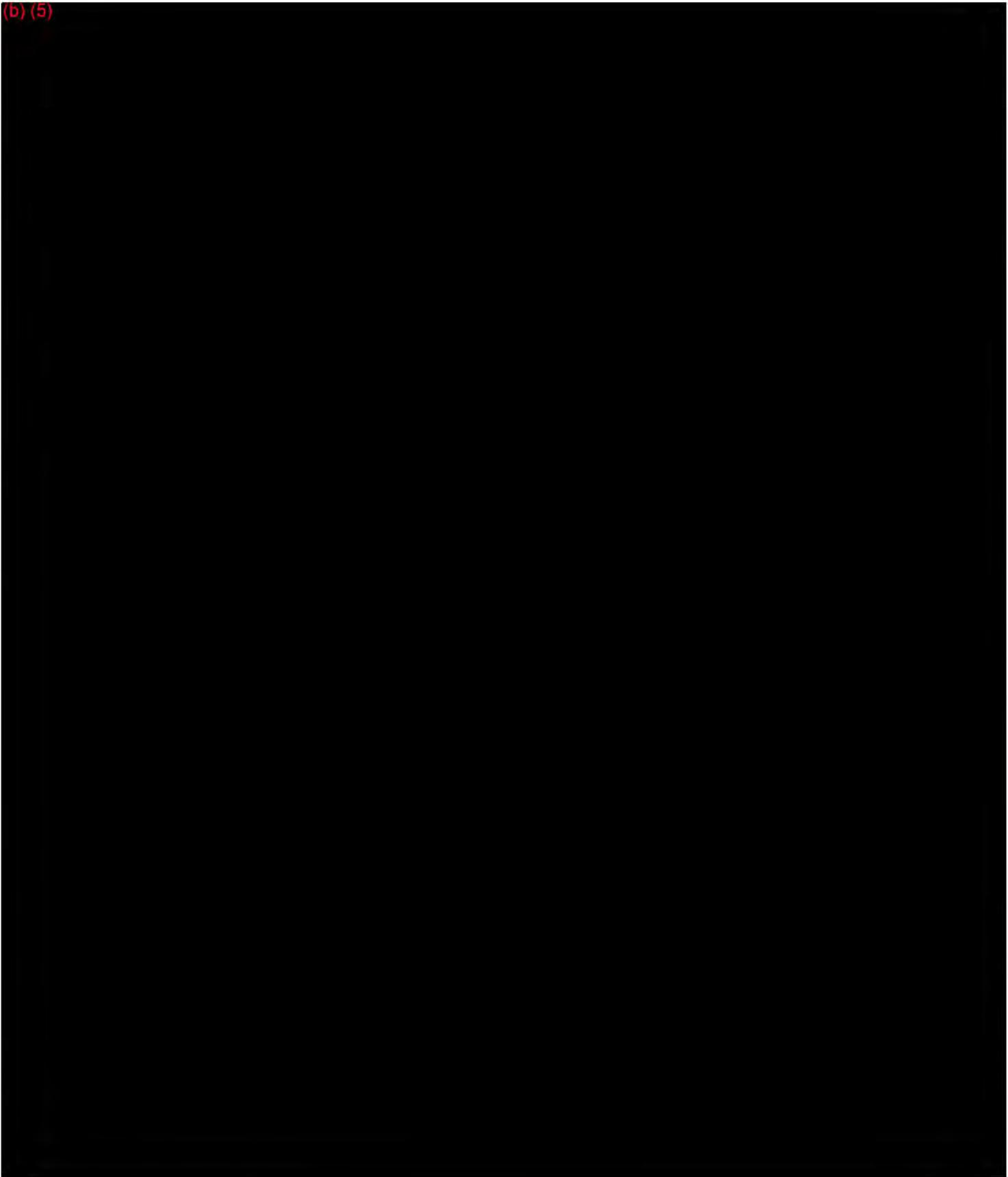


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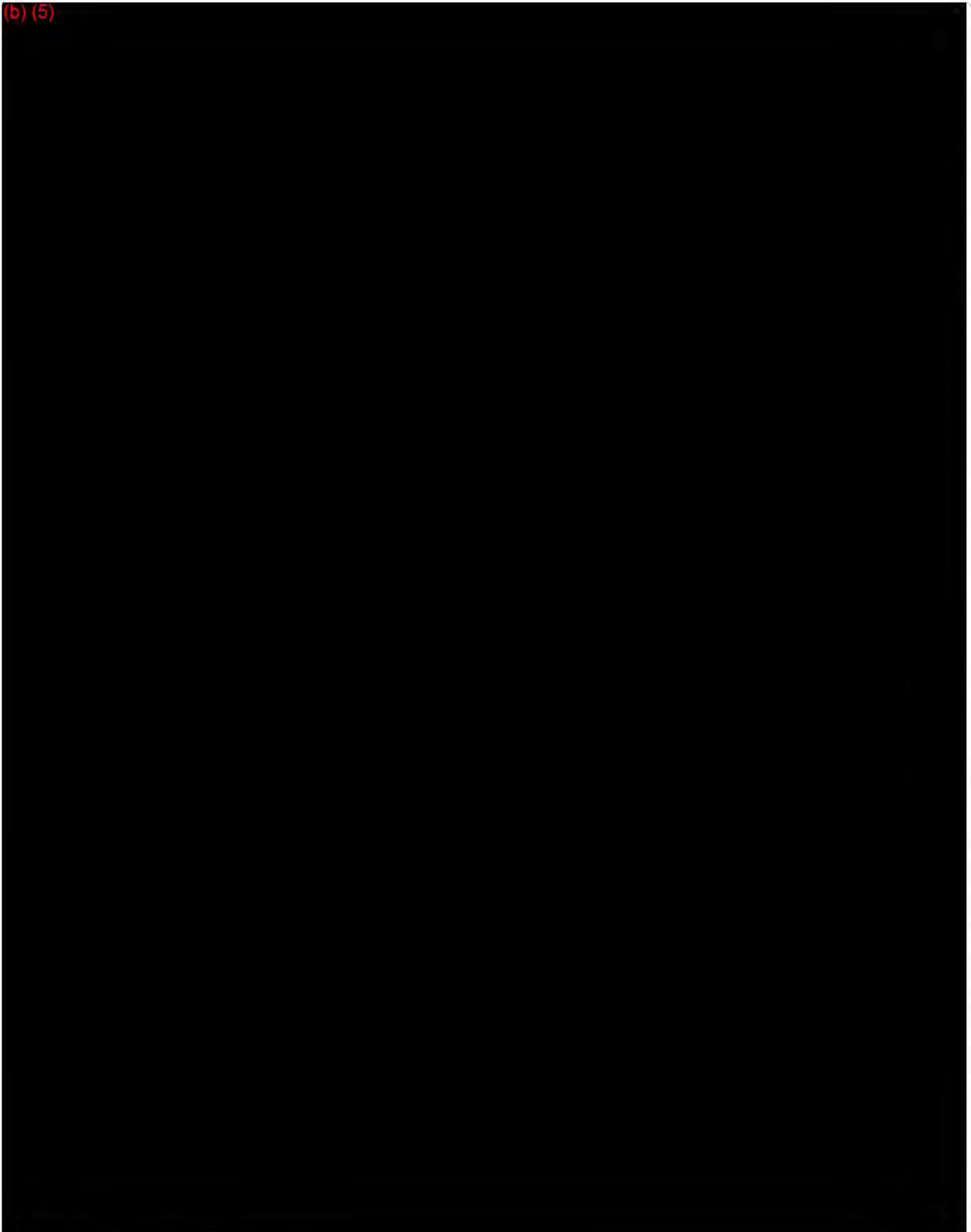
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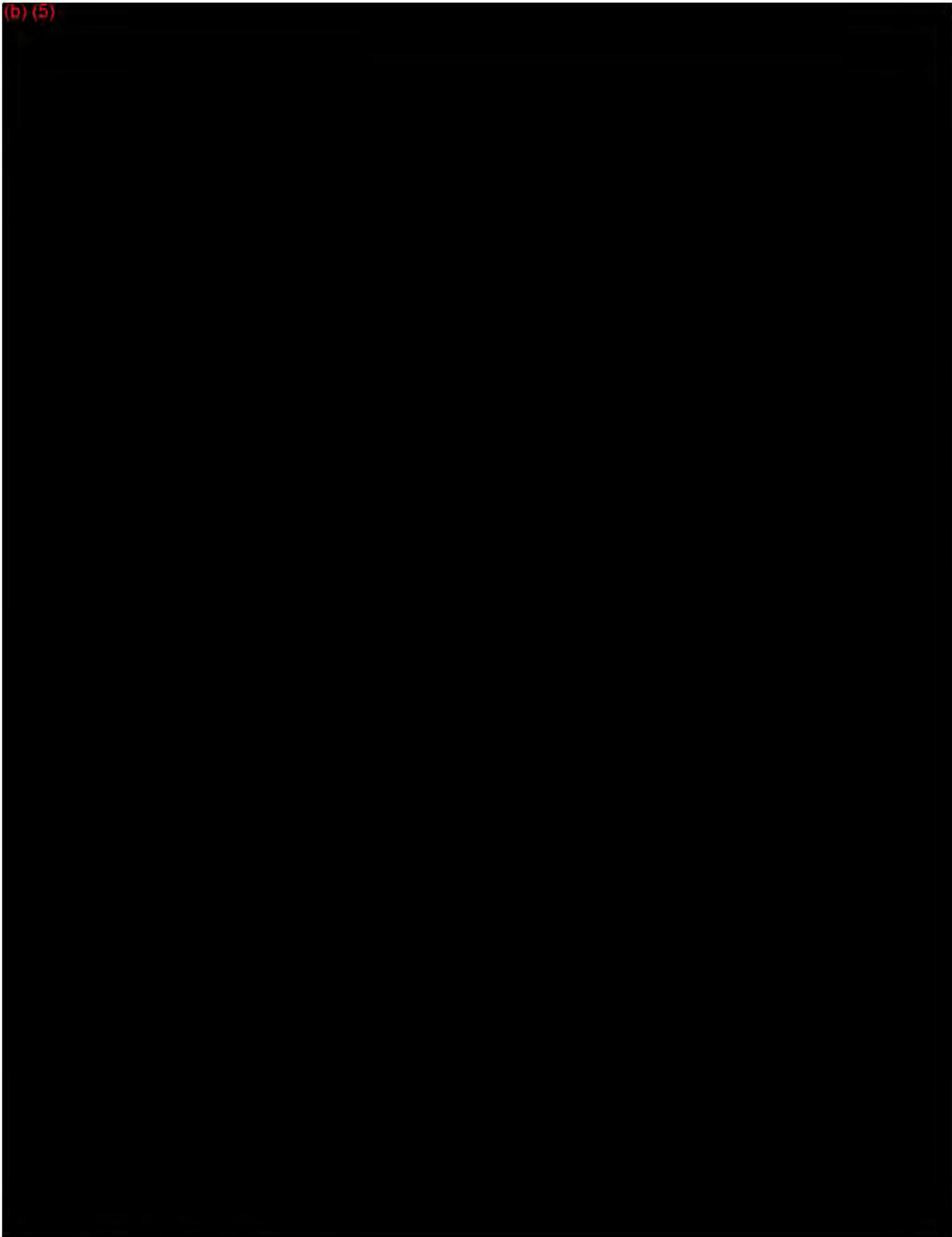


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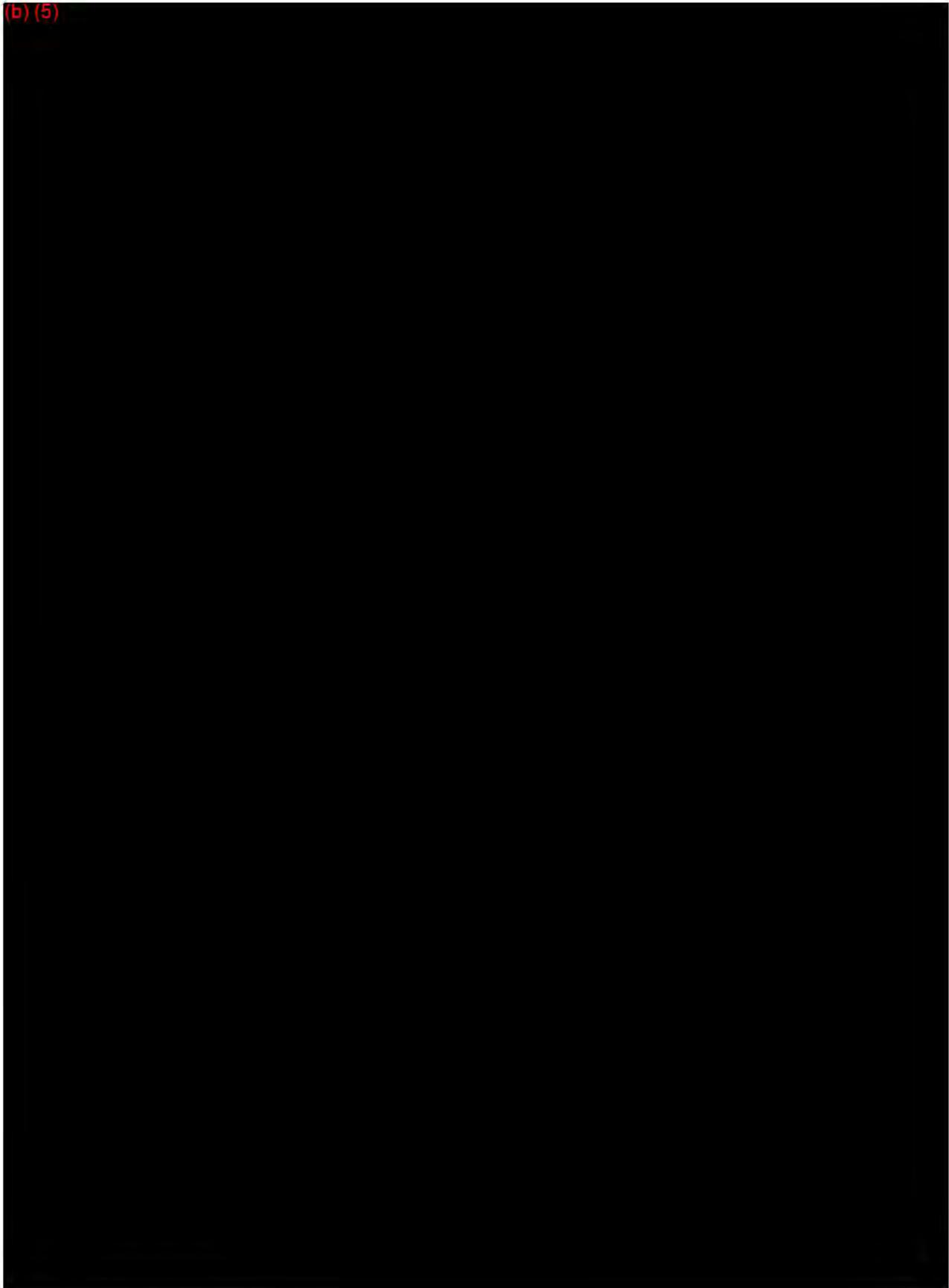
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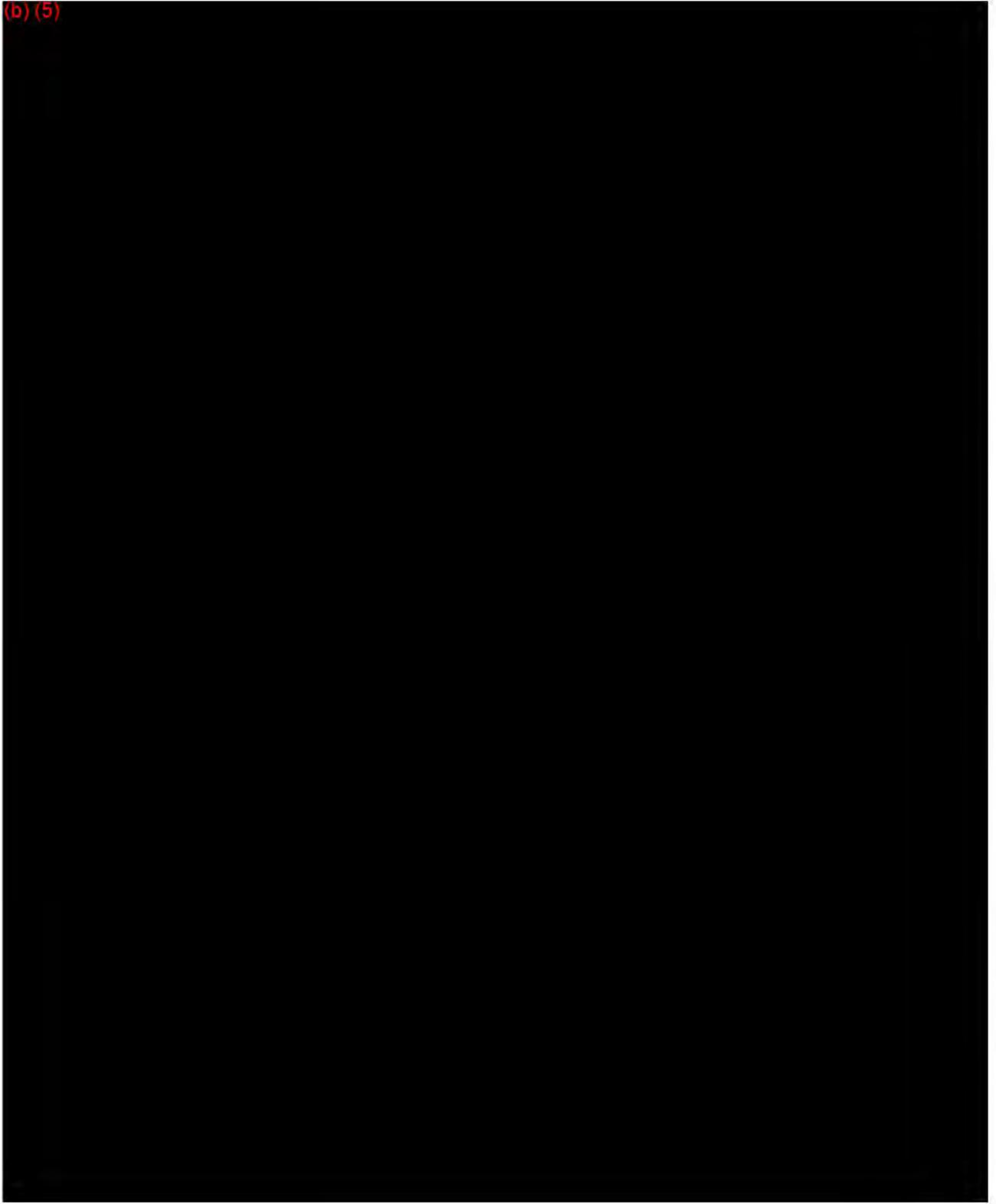
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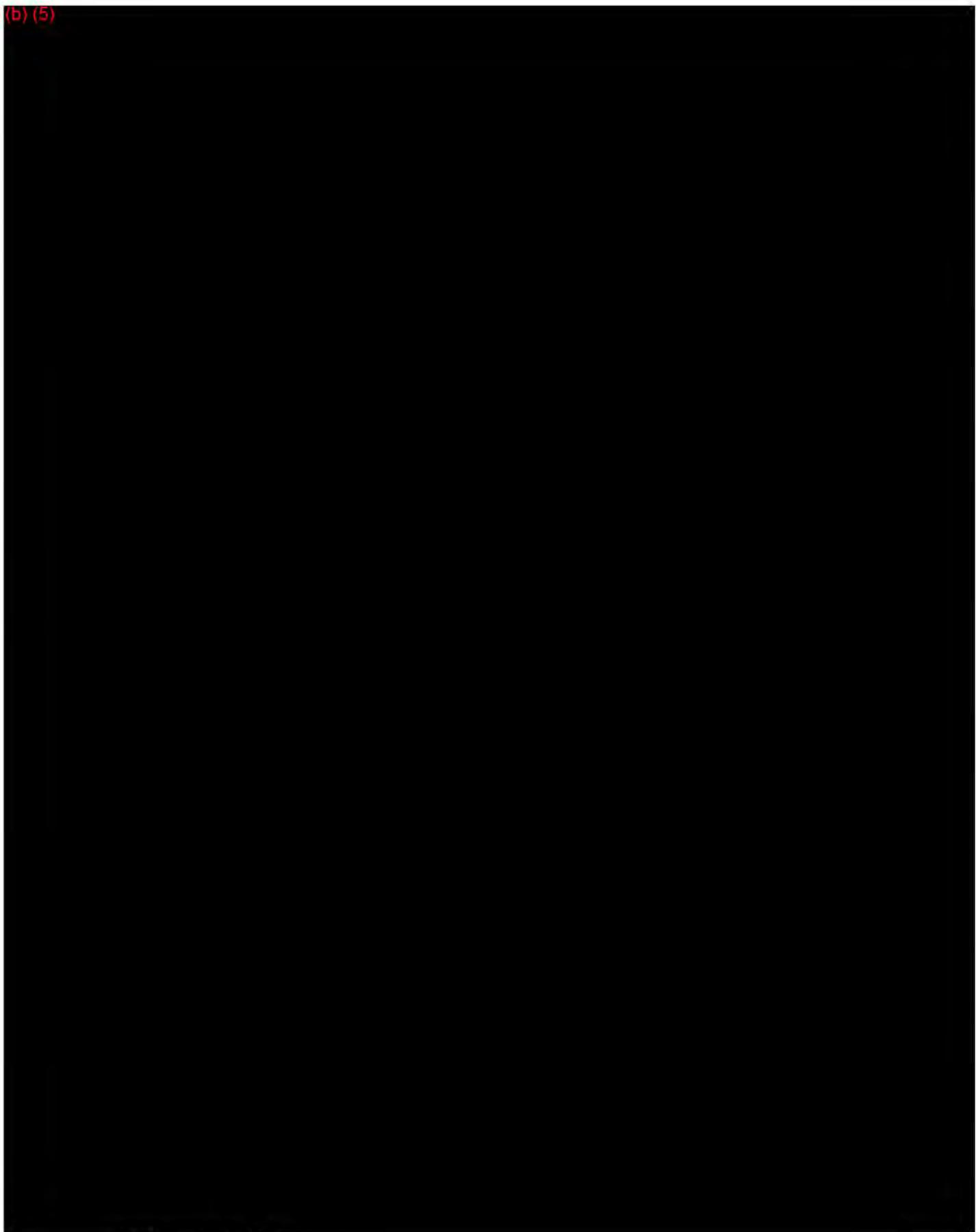
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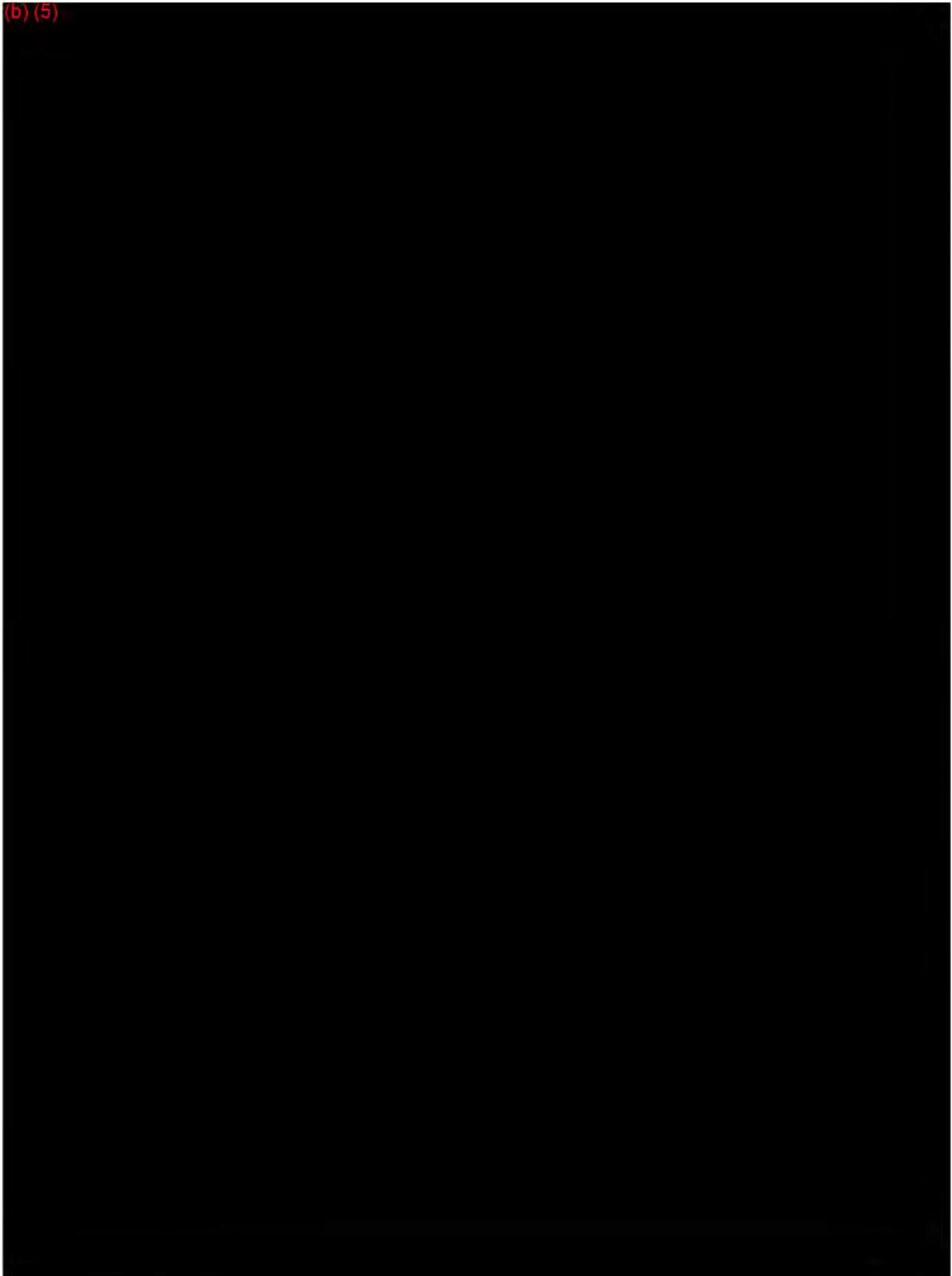
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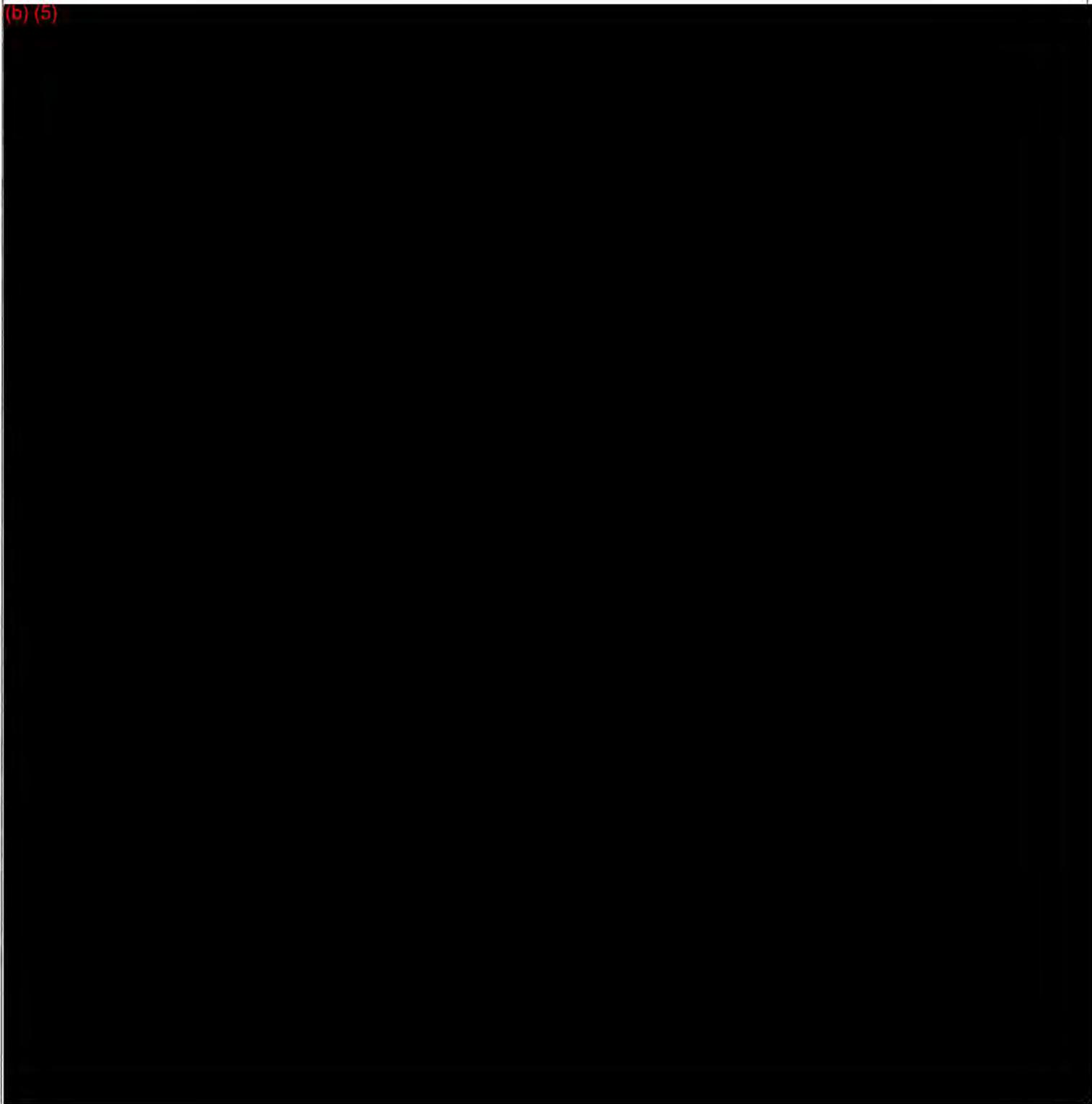


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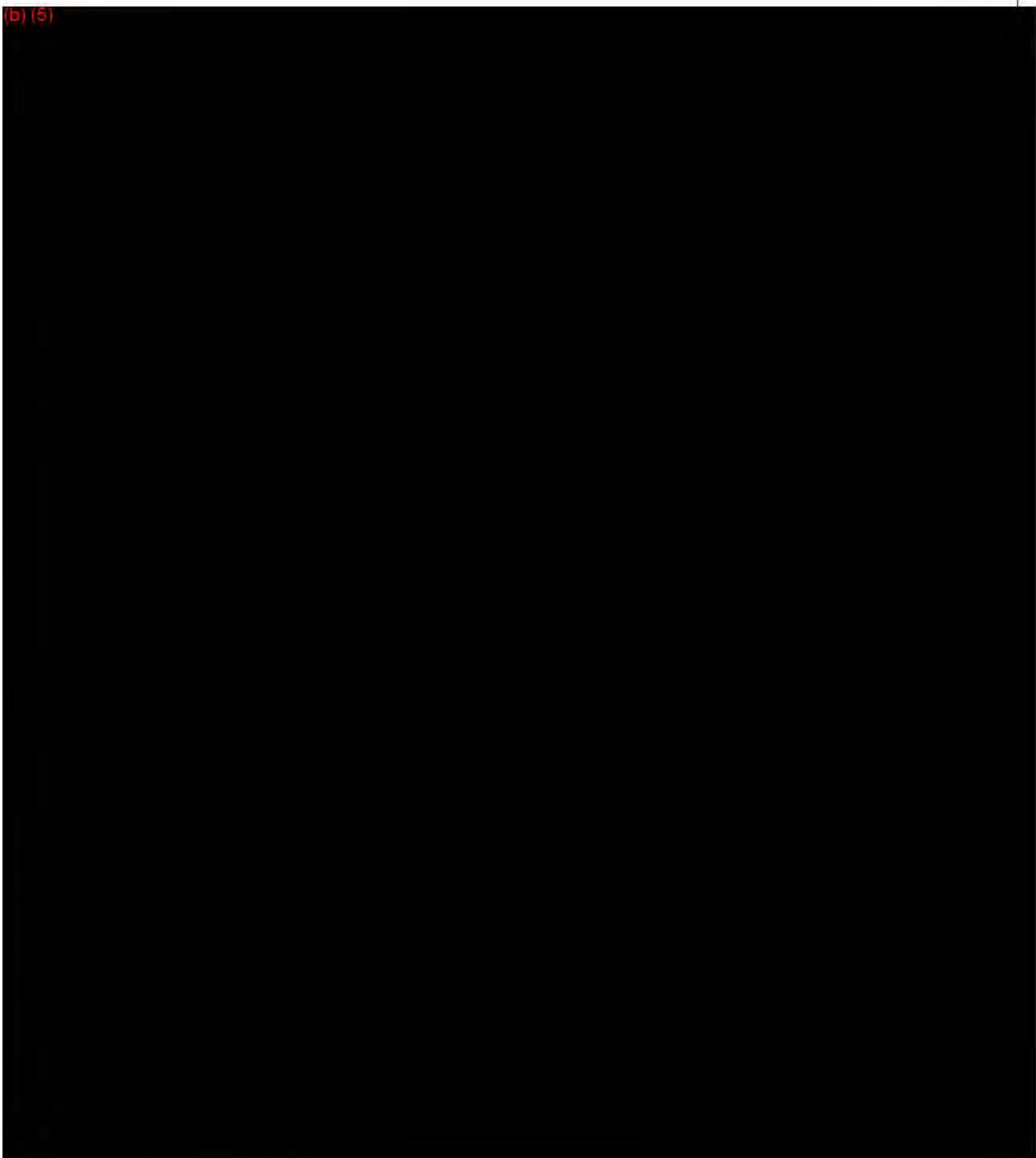


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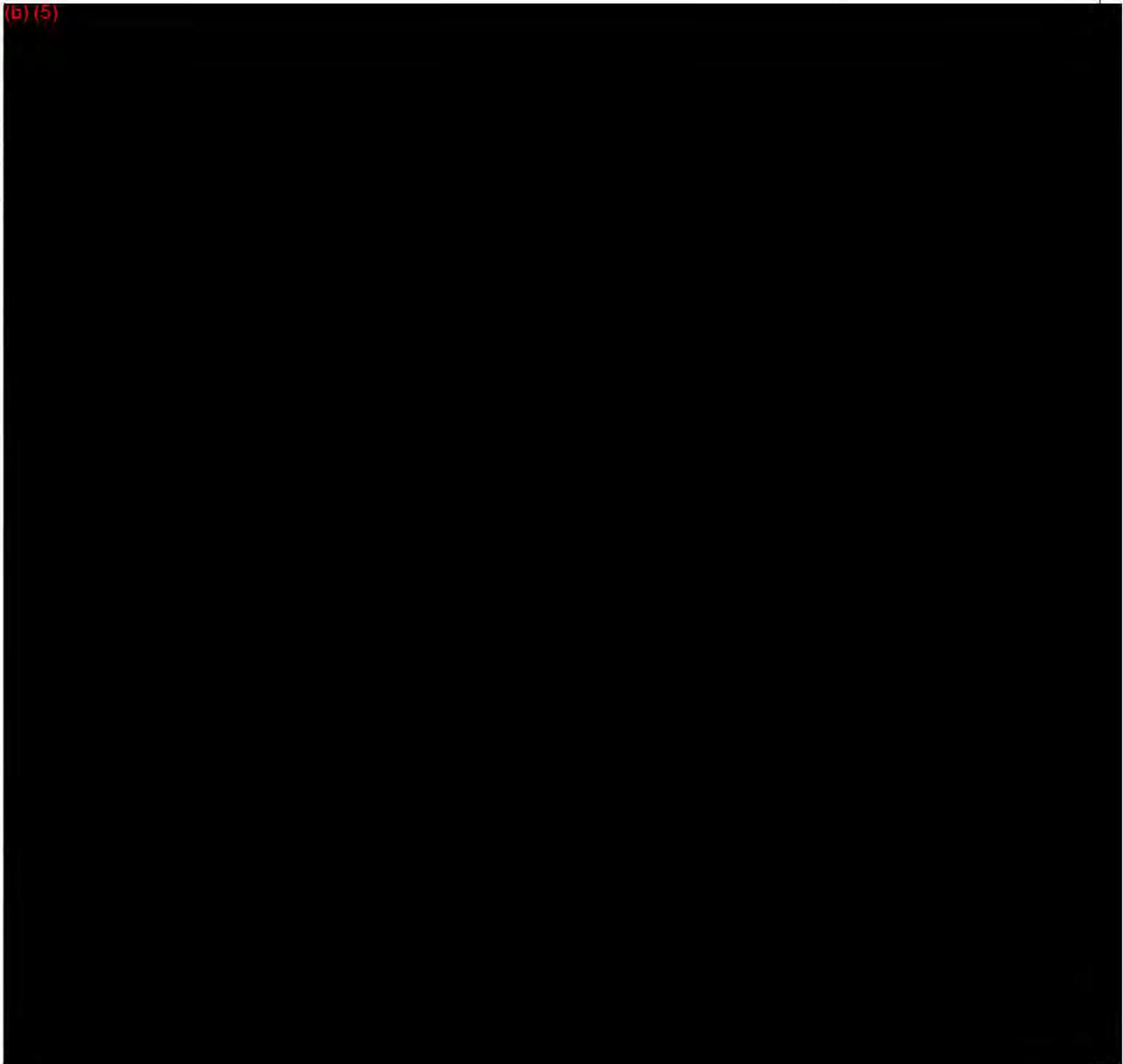


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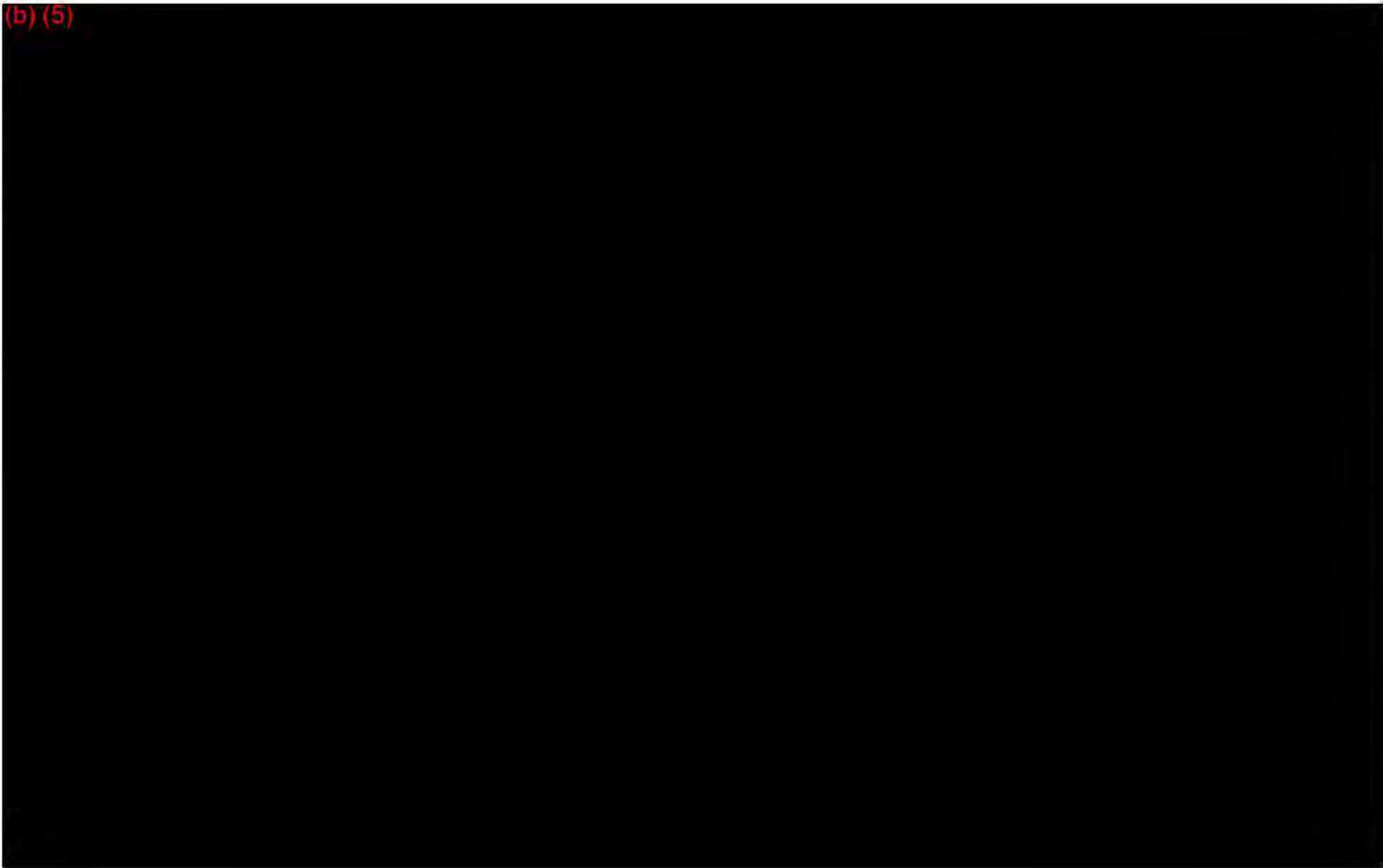
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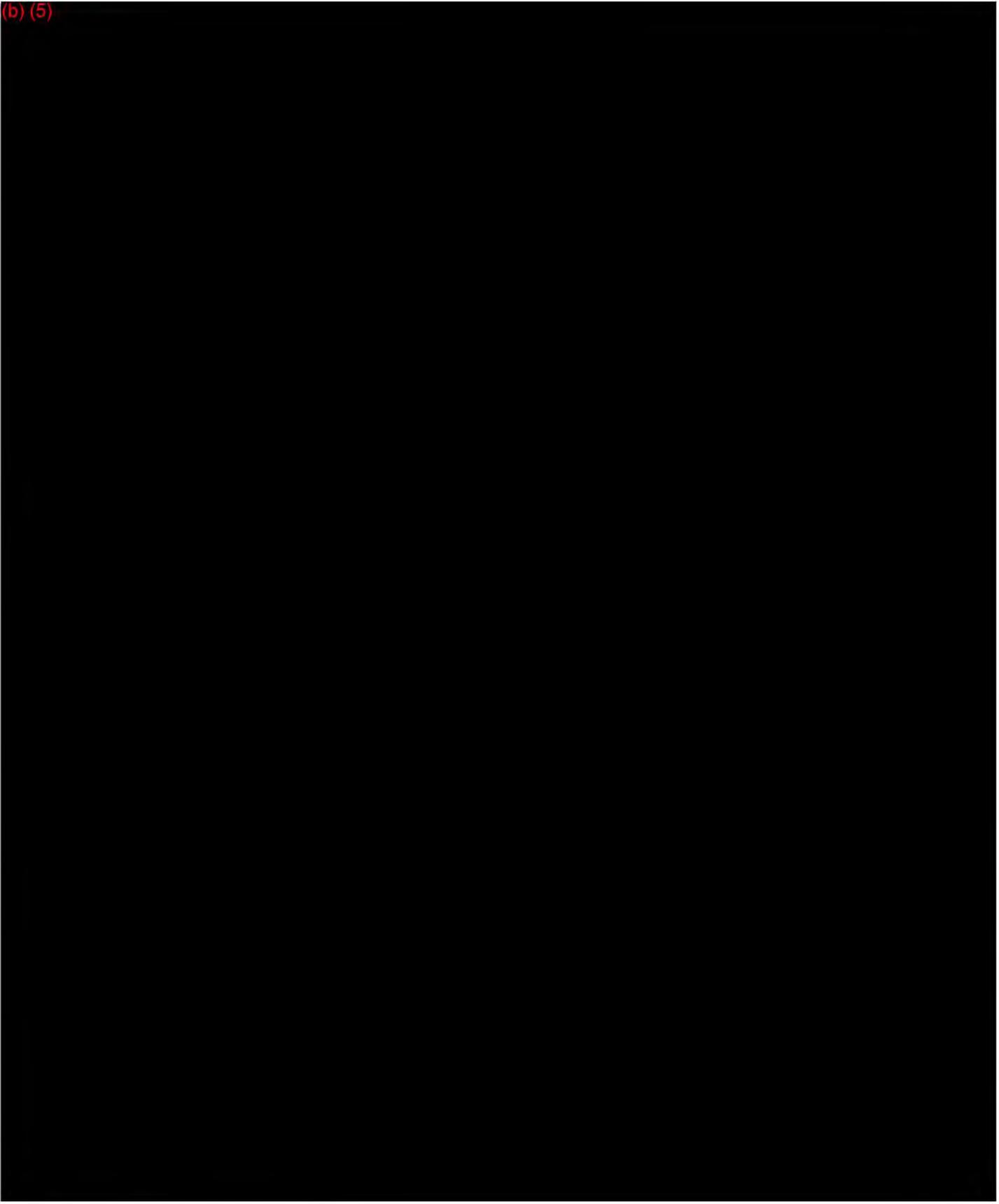


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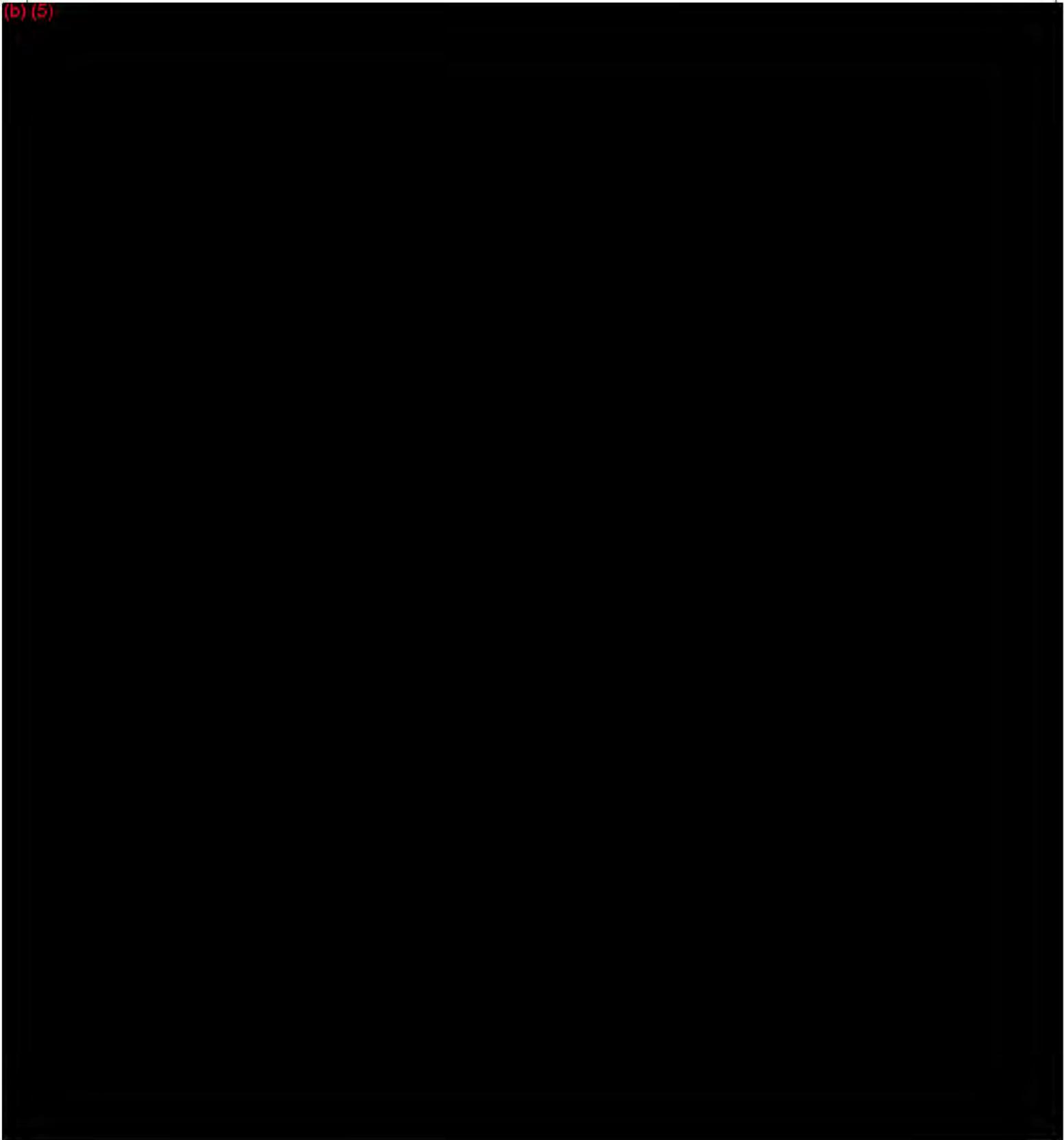


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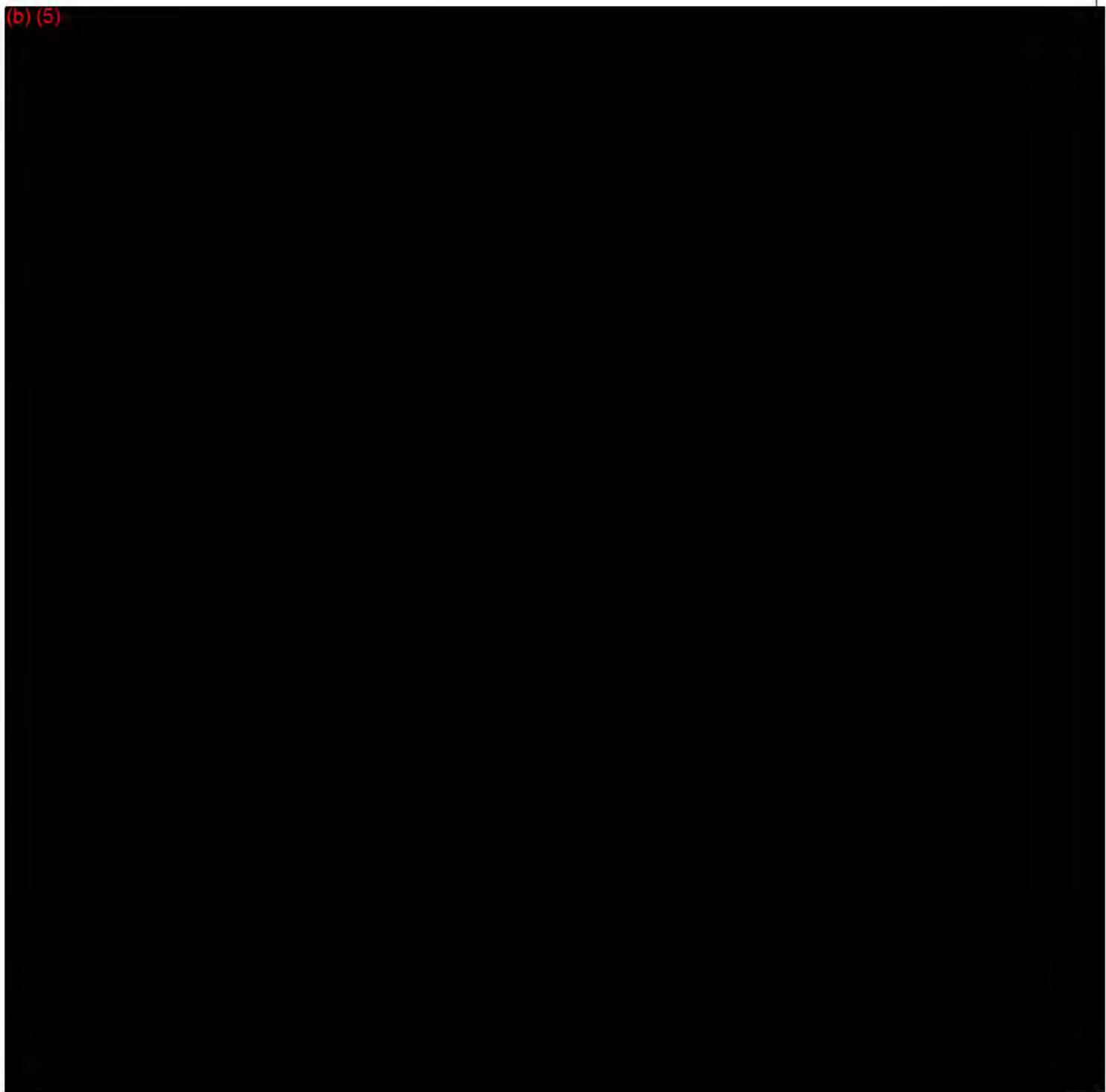


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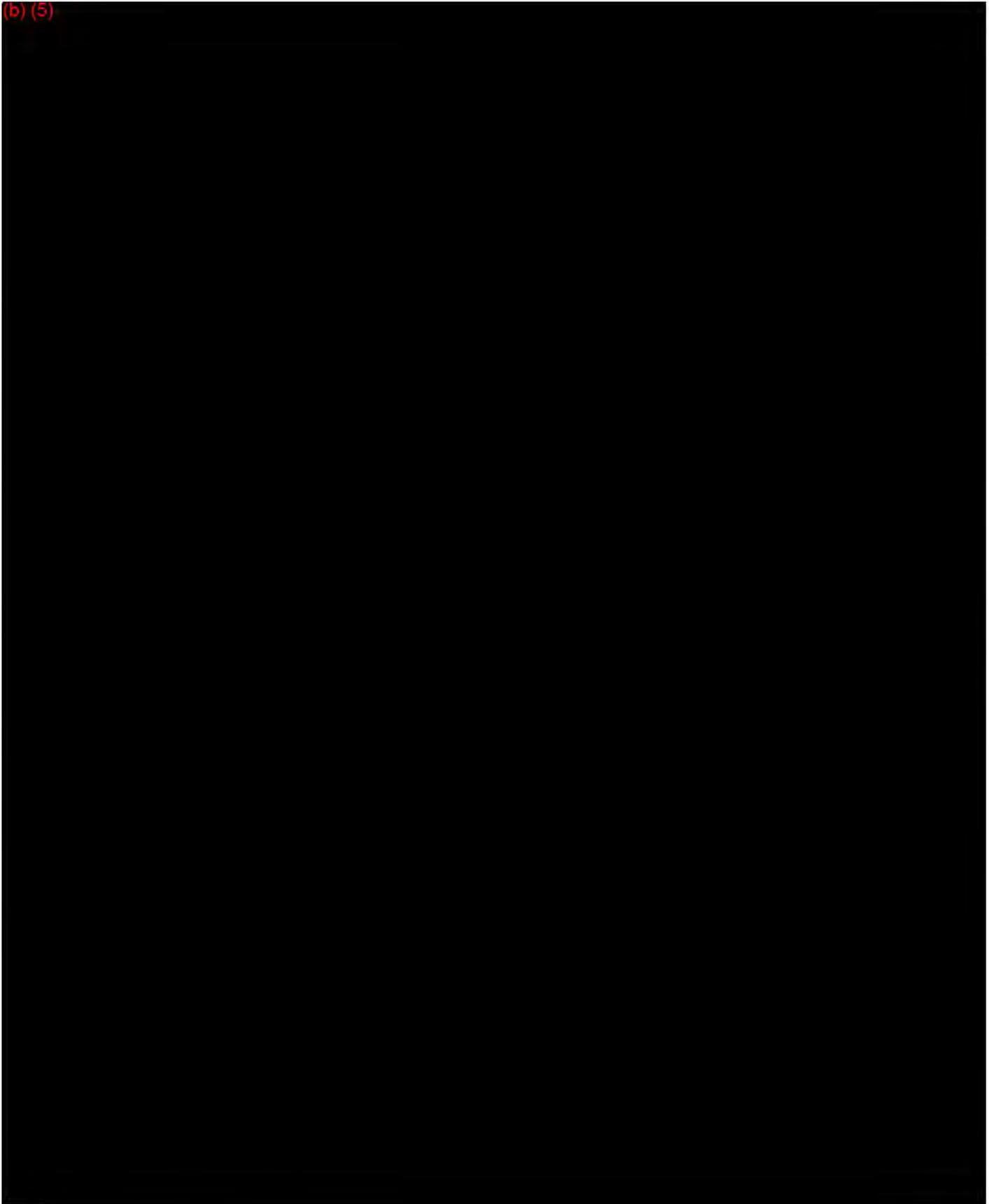
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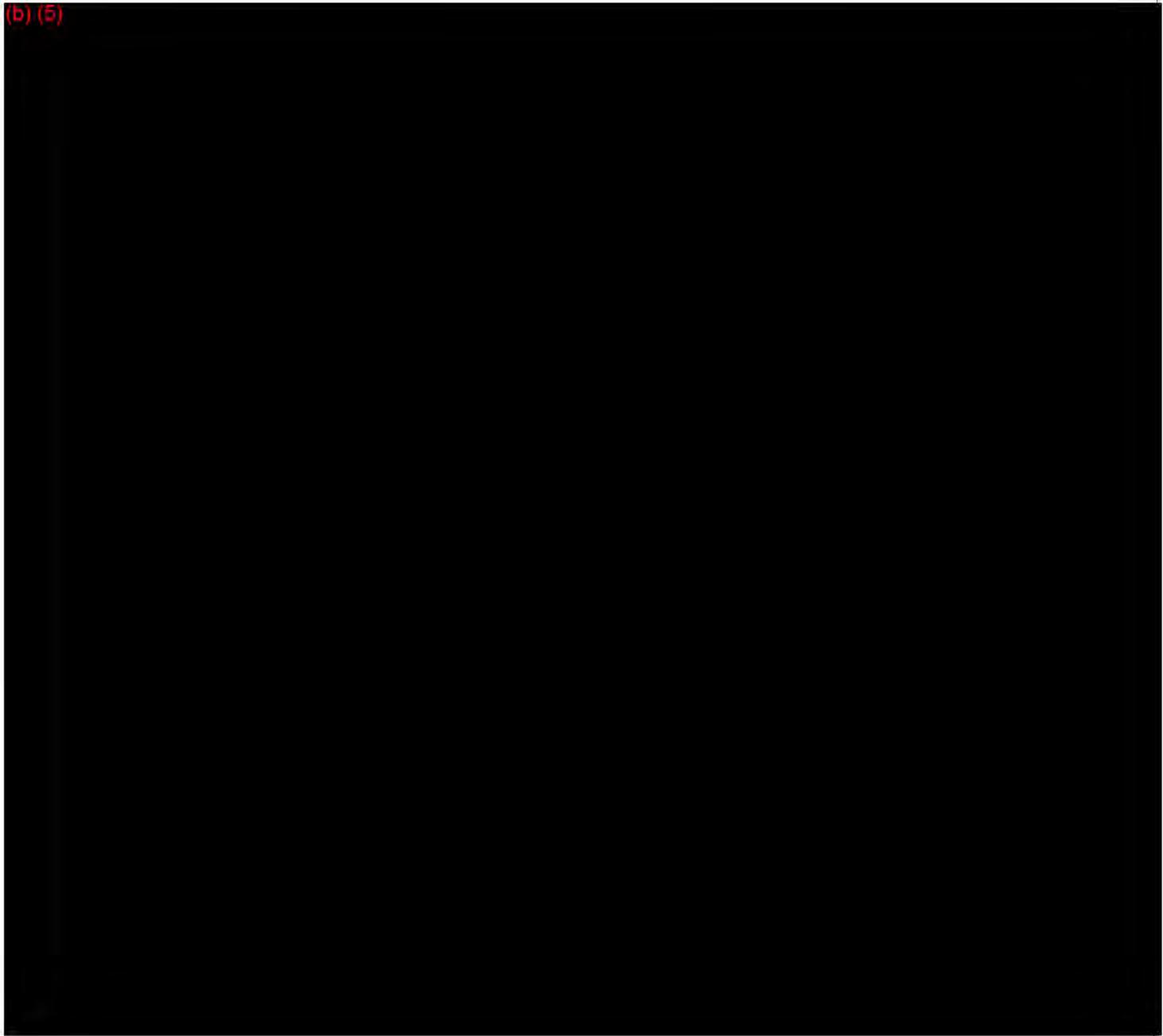
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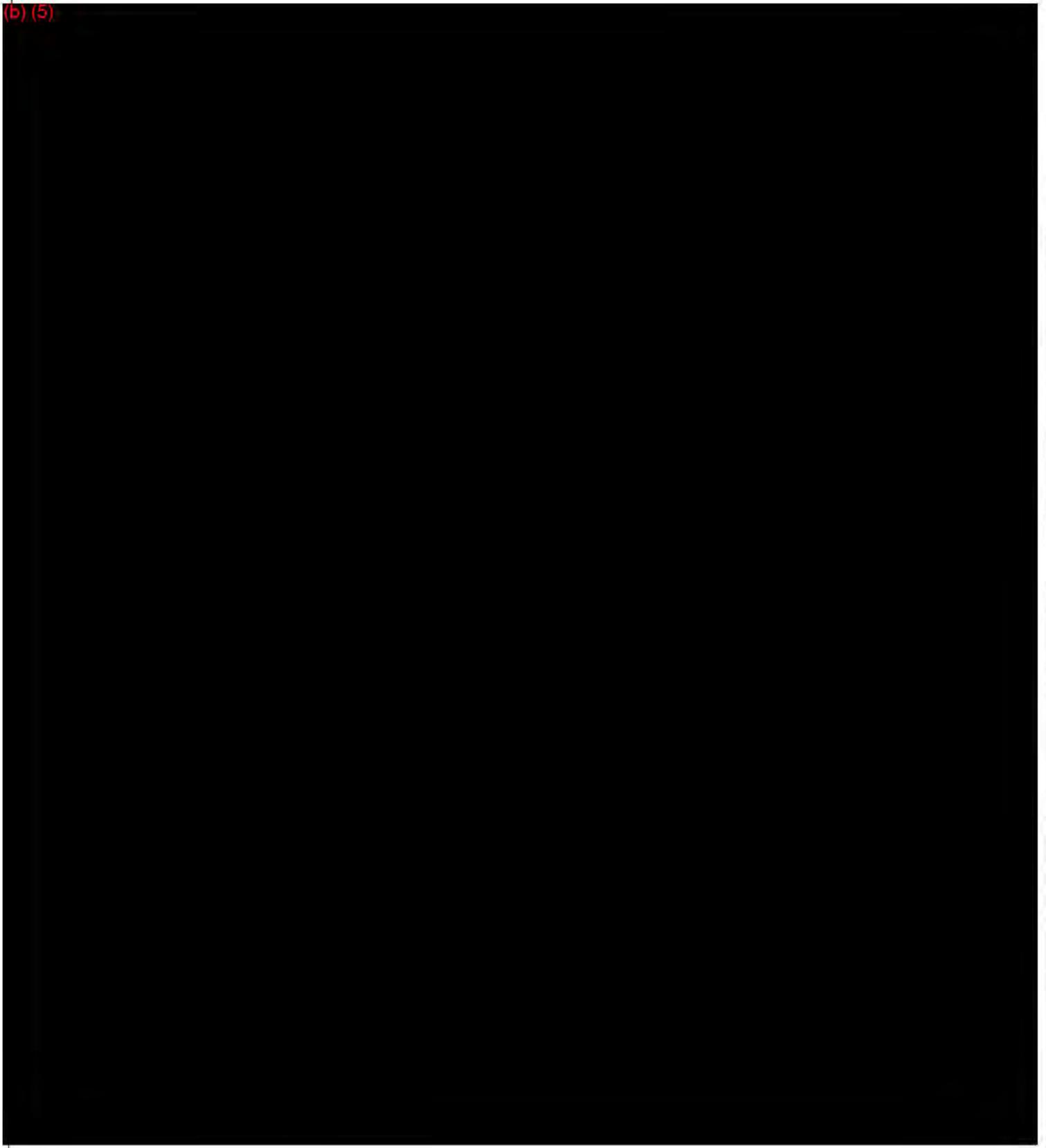


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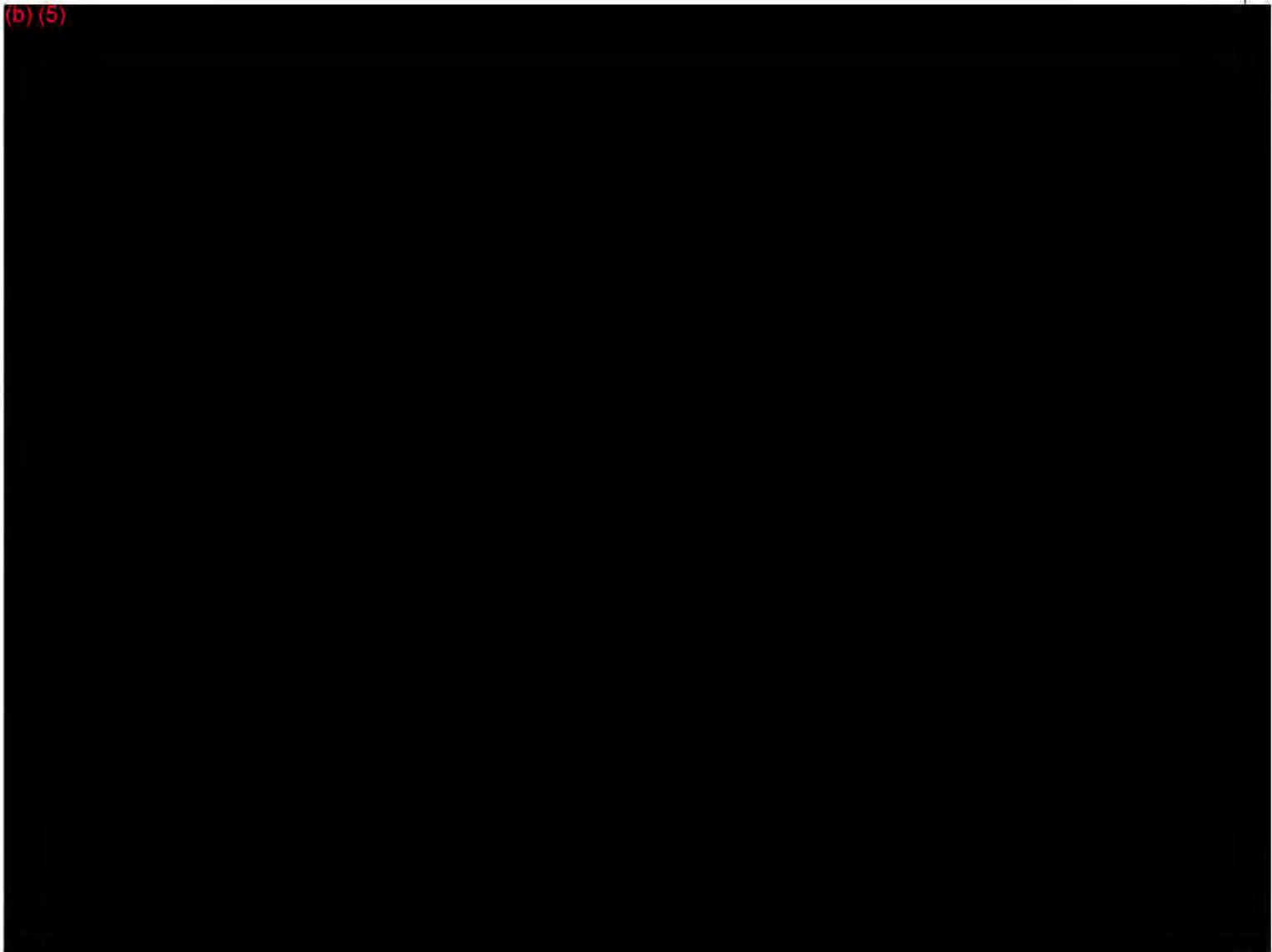


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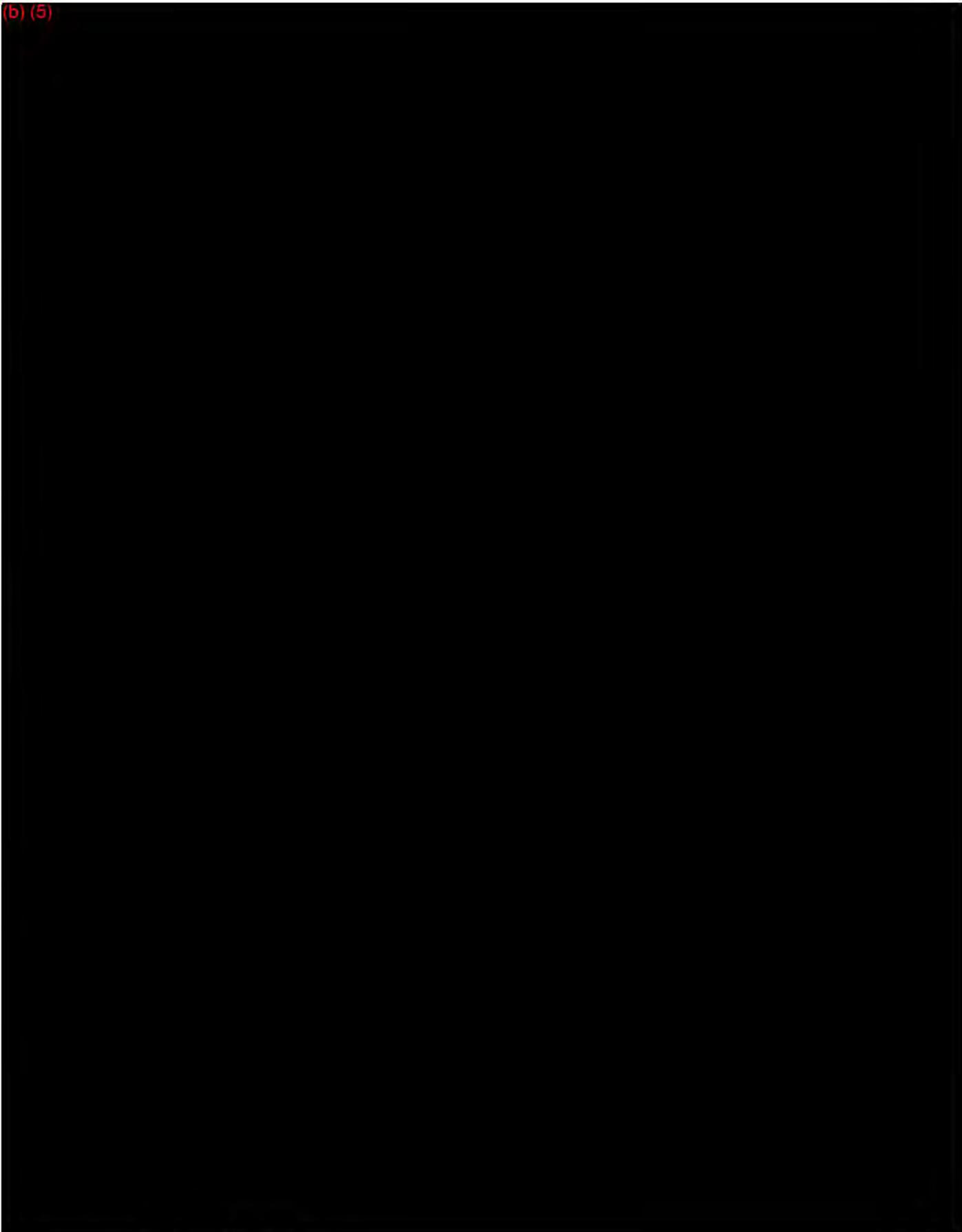
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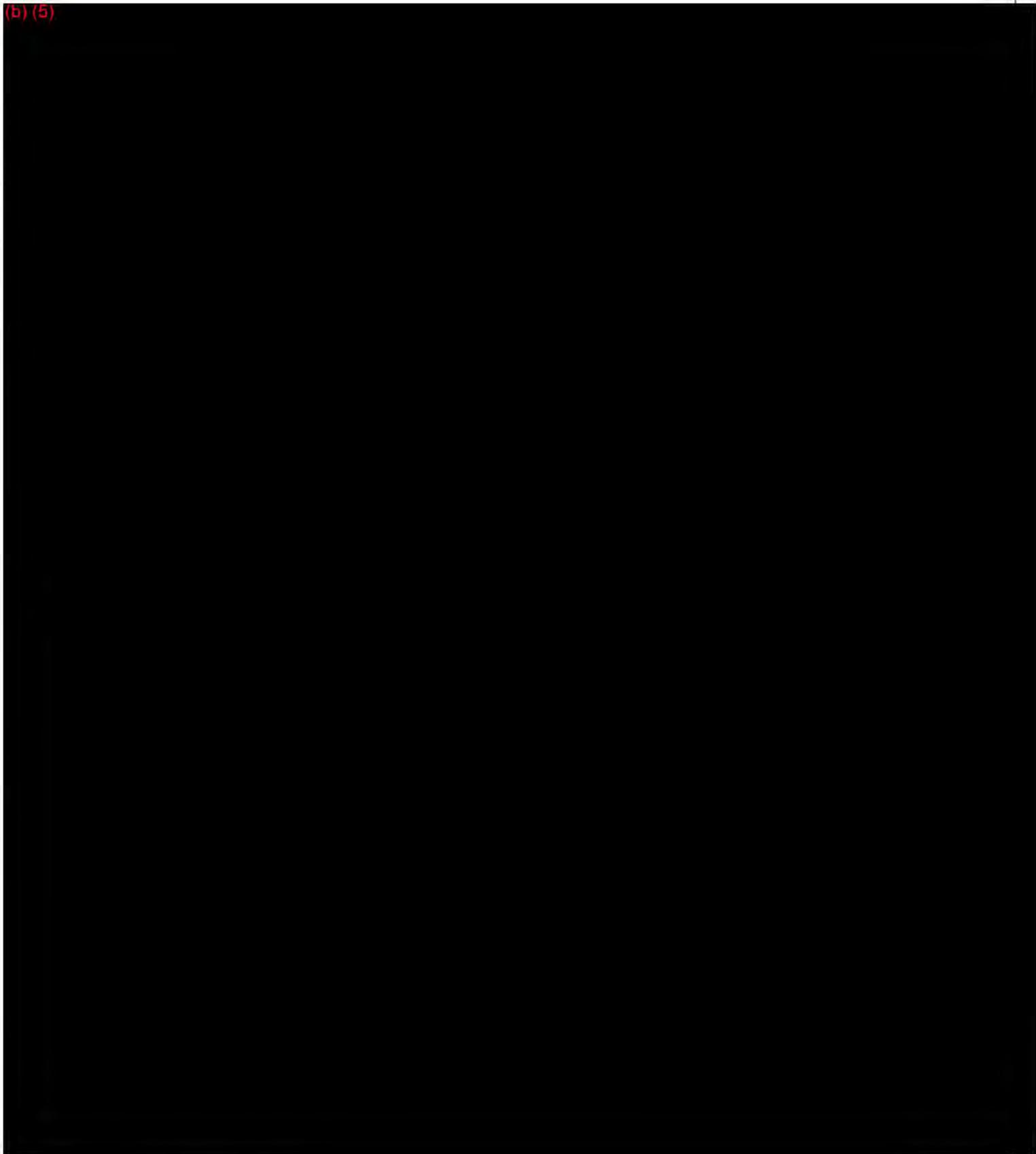
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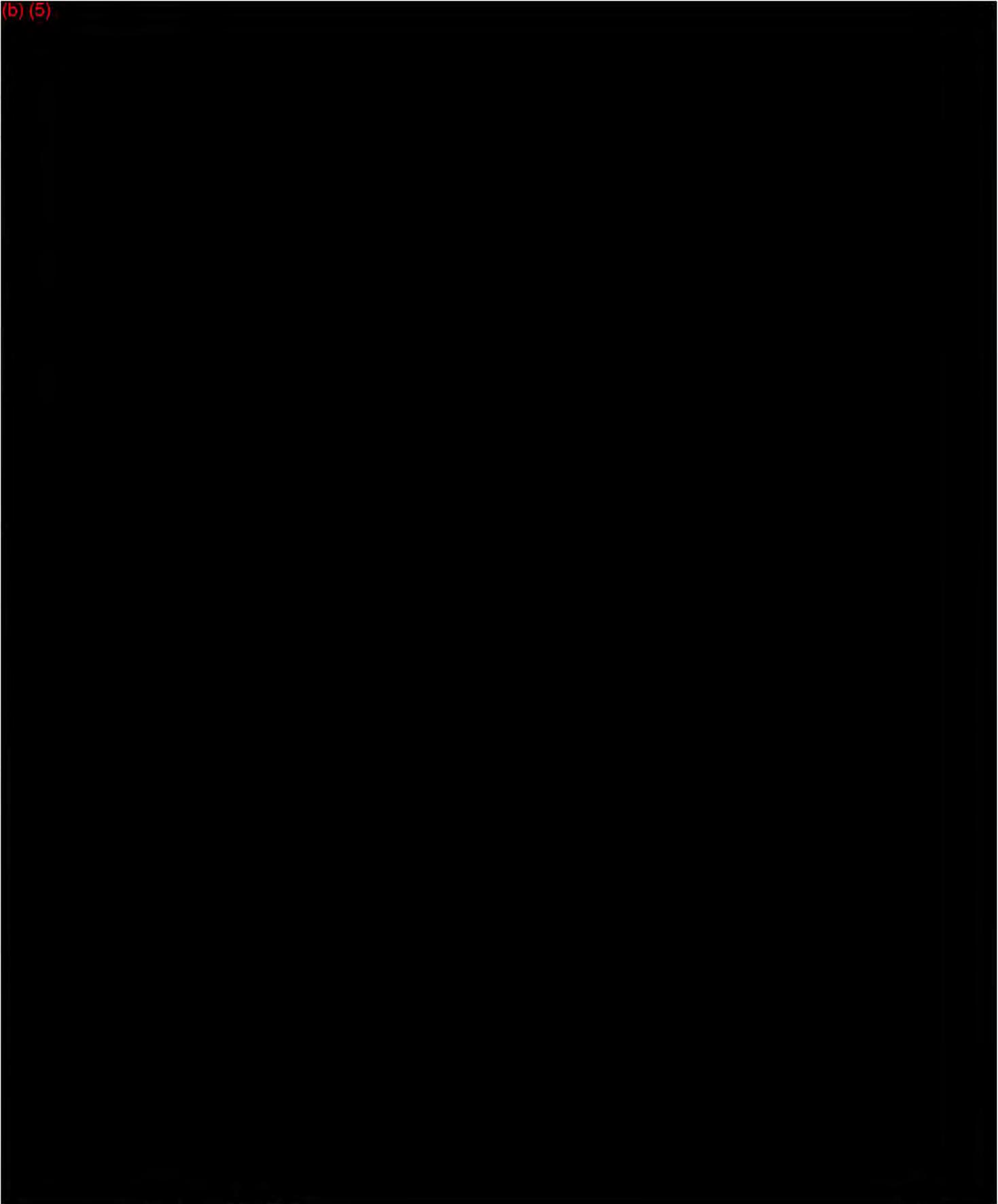
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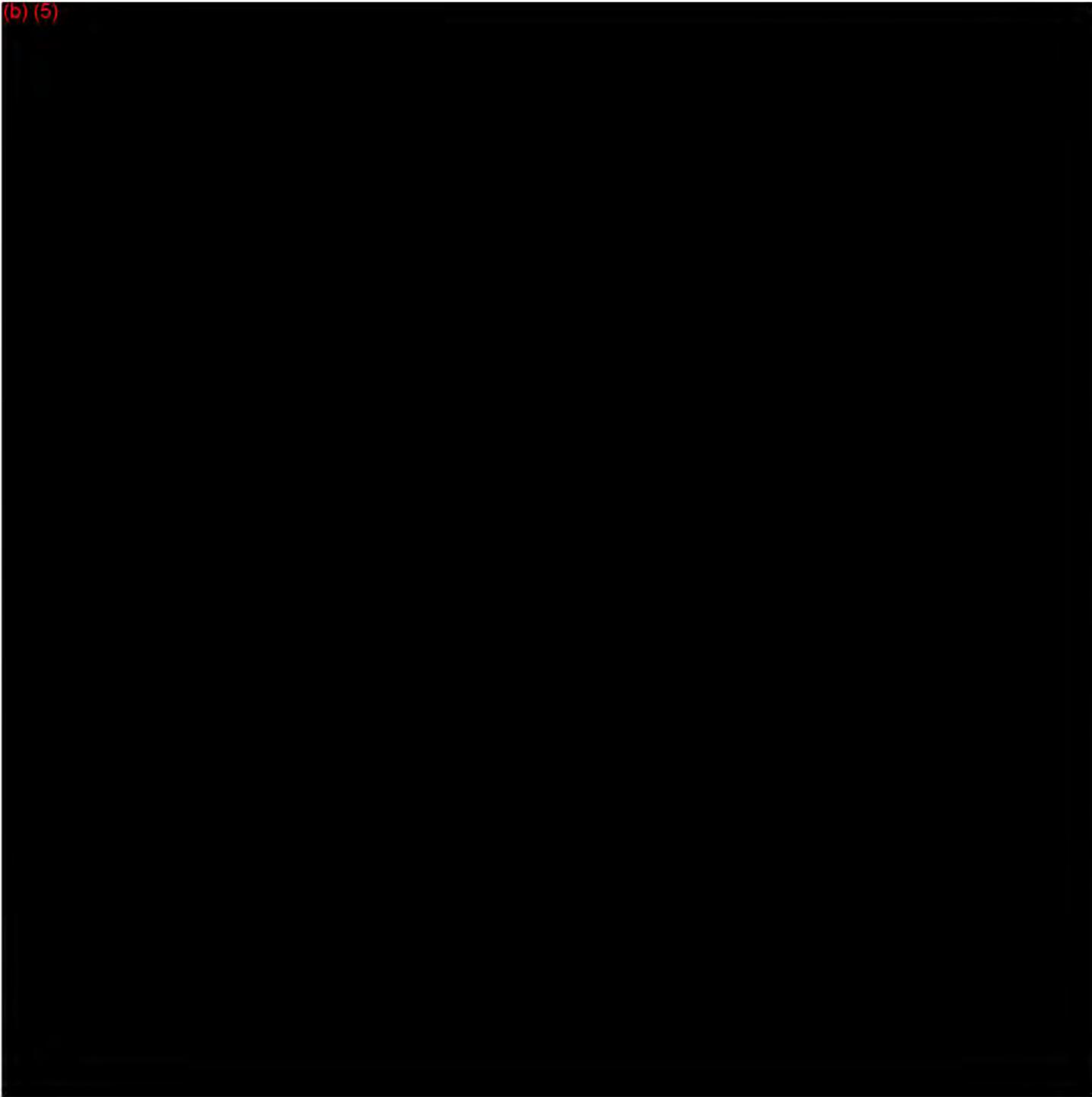


(b) (5)

(b) (5)



(b) (5)



Smith, Celeste

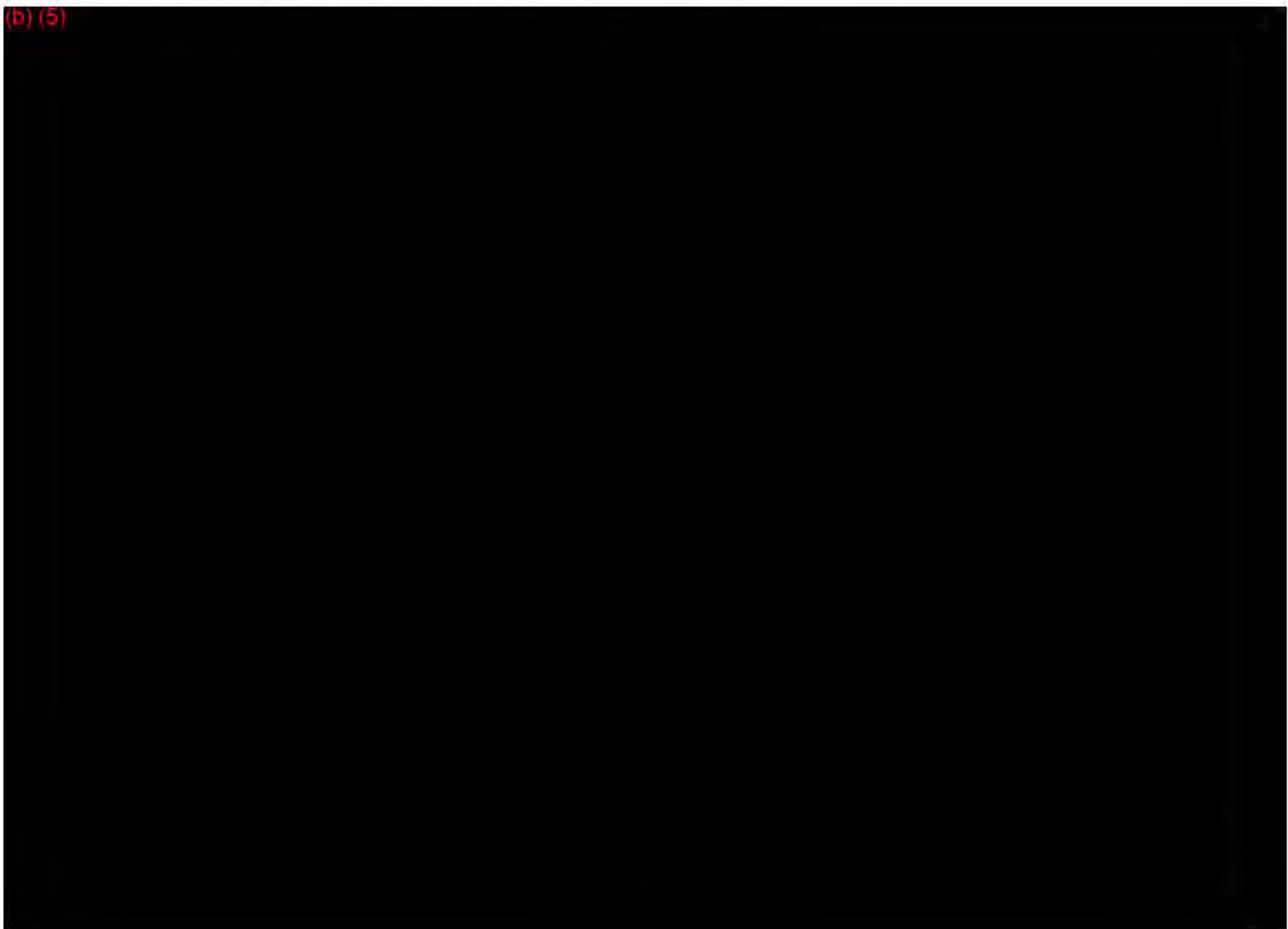
From: Sherman, Rachel
Sent: Sunday, November 20, 2016 10:55 AM
To: Califf, Robert; McCall, Jonathan *
Cc: Hunter, Nina L; Robb, Melissa; Davies, Kathleen
Subject: RE: Reg Action/SE combined draft - latest version

Hi,

Please see below.

From: Califf, Robert
Sent: Sunday, November 20, 2016 8:22 AM
To: McCall, Jonathan *
Cc: Sherman, Rachel; Hunter, Nina L; Robb, Melissa; Davies, Kathleen
Subject: RE: Reg Action/SE combined draft - latest version

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(b) (5)

rnc

From: McCall, Jonathan *
Sent: Friday, November 18, 2016 5:31 PM
To: Califf, Robert
Cc: Sherman, Rachel; Hunter, Nina L; Robb, Melissa; Davies, Kathleen
Subject: Reg Action/SE combined draft - latest version

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Look forward to everyone's thoughts.

Thanks!

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J

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Cc: Hunter, Nina L; Robb, Melissa; Davies, Kathleen
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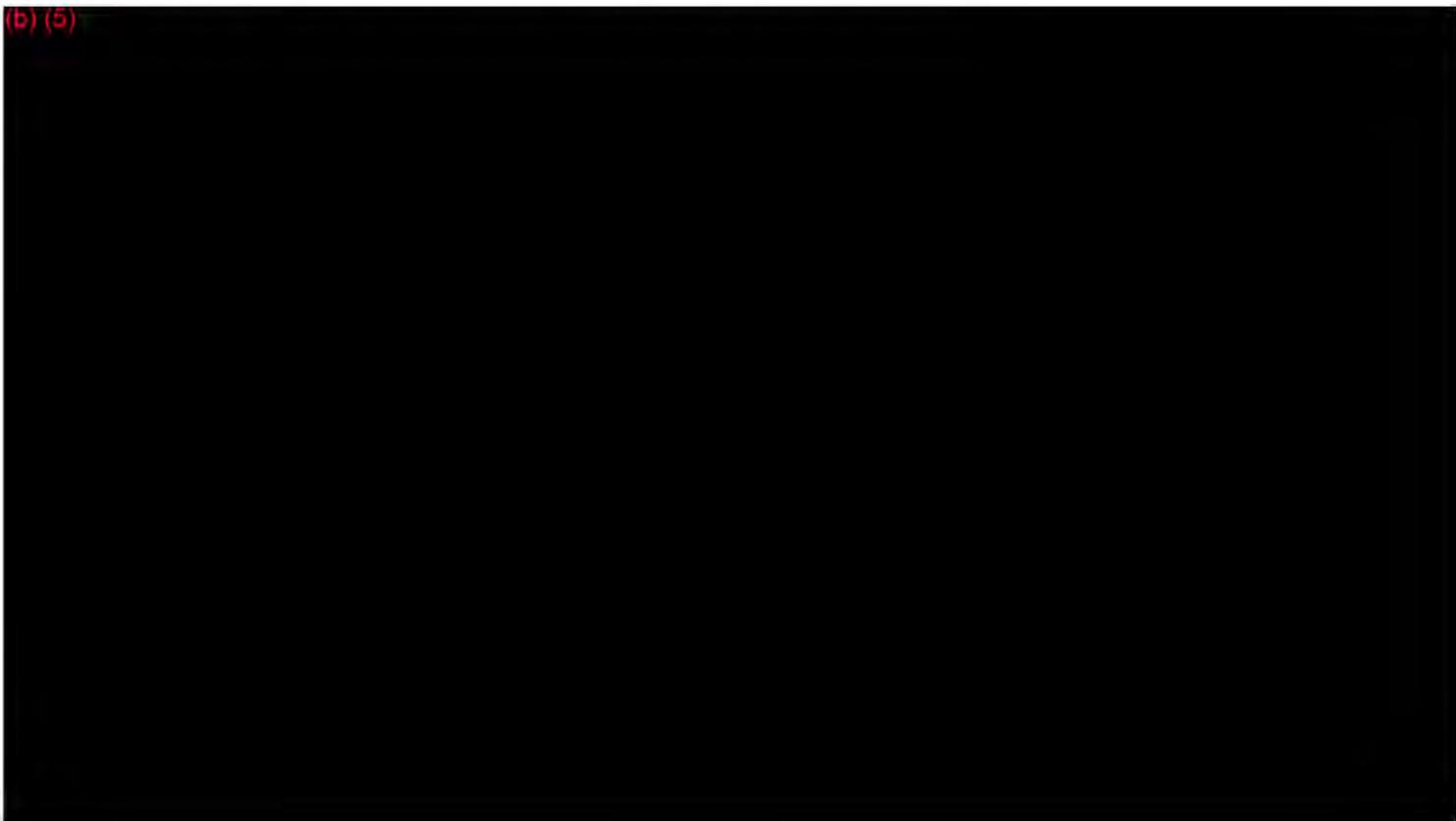
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J

Smith, Celeste

From: Sherman, Rachel
Sent: Sunday, November 20, 2016 4:44 PM
To: McCall, Jonathan *; Califf, Robert
Cc: Davies, Kathleen; Robb, Melissa; Hunter, Nina L
Subject: RE: Reg Action/SE combined draft - latest version

OK

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: November 20, 2016 at 12:46:52 PM EST
To: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>, Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Cc: Hunter, Nina L <Nina.Hunter@fda.hhs.gov>, Robb, Melissa <Melissa.Robb@fda.hhs.gov>, Davies, Kathleen <Kathleen.Davies@fda.hhs.gov>
Subject: RE: Reg Action/SE combined draft - latest version

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Sent: Sunday, November 20, 2016 10:55 AM
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Cc: Hunter, Nina L; Robb, Melissa; Davies, Kathleen
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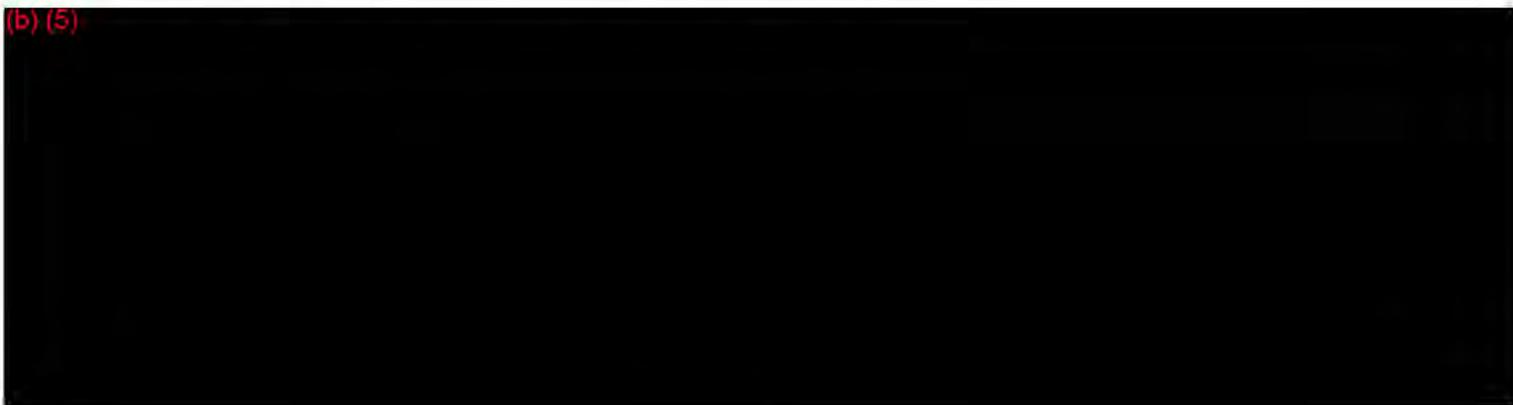
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Please see below.

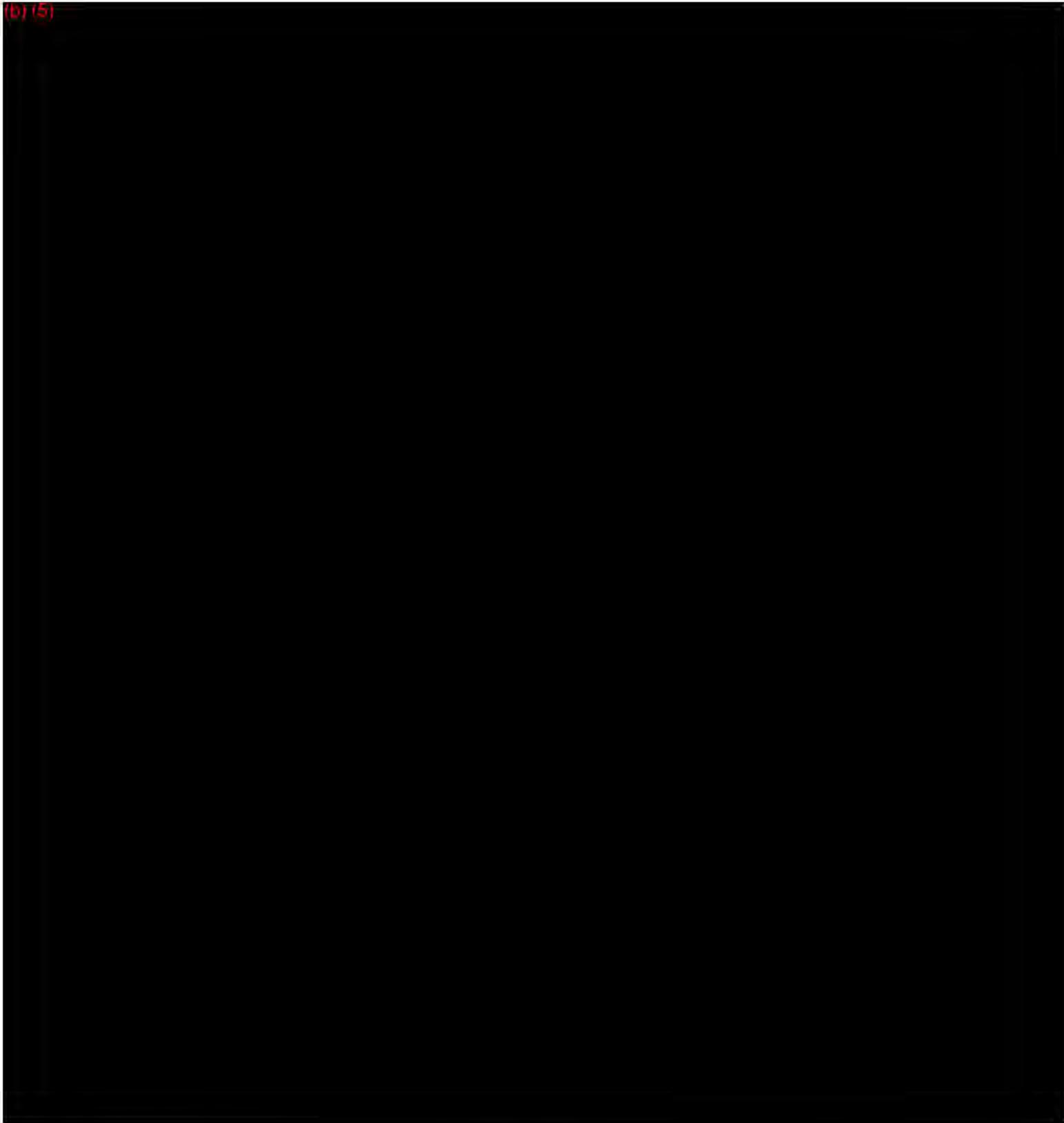
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(b) (5)



rmc

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To: Califf, Robert

Cc: Sherman, Rachel; Hunter, Nina L; Robb, Melissa; Davies, Kathleen

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--
J

From: [Sherman, Rachel](#)
To: [Califf, Robert](#); [McCall, Jonathan *](#)
Cc: [Hunter, Nina L](#); [Robb, Melissa](#); [Davies, Kathleen](#)
Subject: RE: Reg Action/SE combined draft - latest version
Date: Sunday, November 20, 2016 4:54:49 PM

I think we have a plan to get this back to you for Thanksgiving reading.

From: Califf, Robert
Sent: Sunday, November 20, 2016 12:47 PM
To: Sherman, Rachel; McCall, Jonathan *
Cc: Hunter, Nina L; Robb, Melissa; Davies, Kathleen
Subject: RE: Reg Action/SE combined draft - latest version

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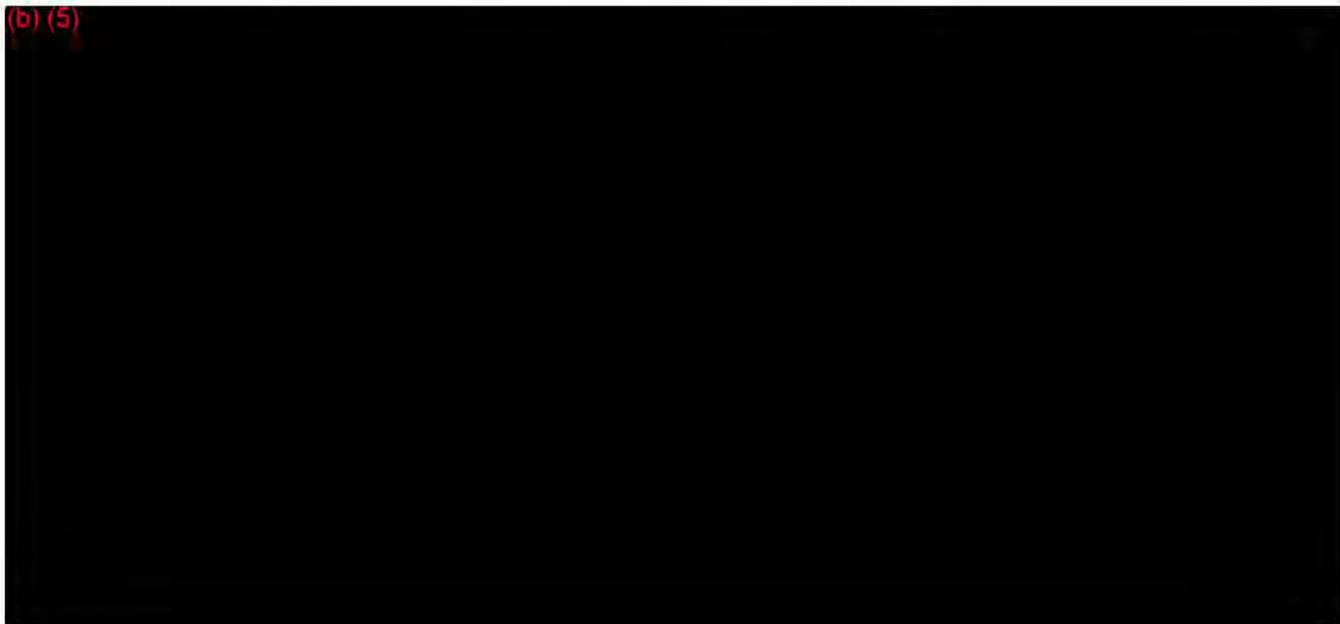
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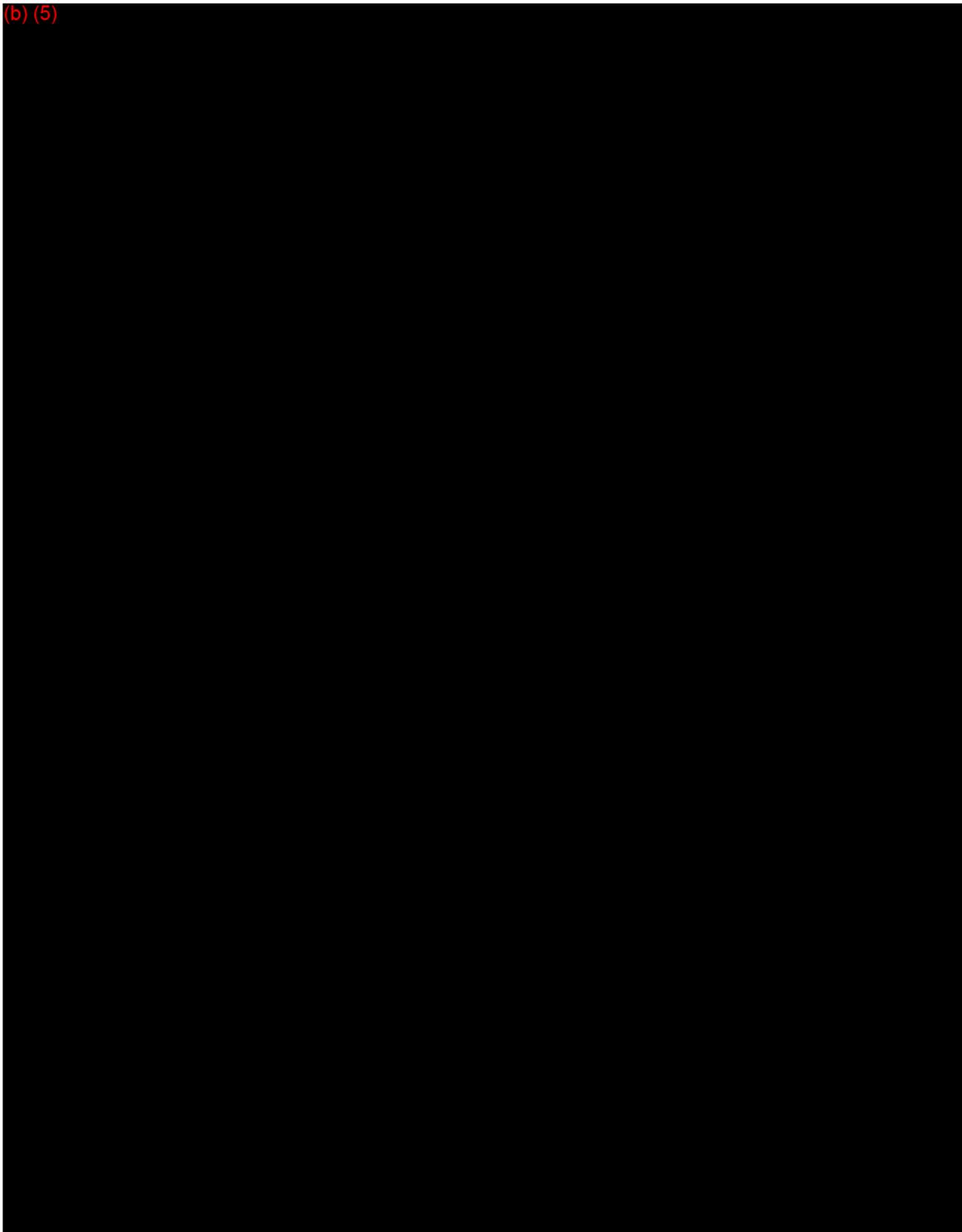
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(b) (5)



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Cc: Sherman, Rachel; Hunter, Nina L; Robb, Melissa; Davies, Kathleen

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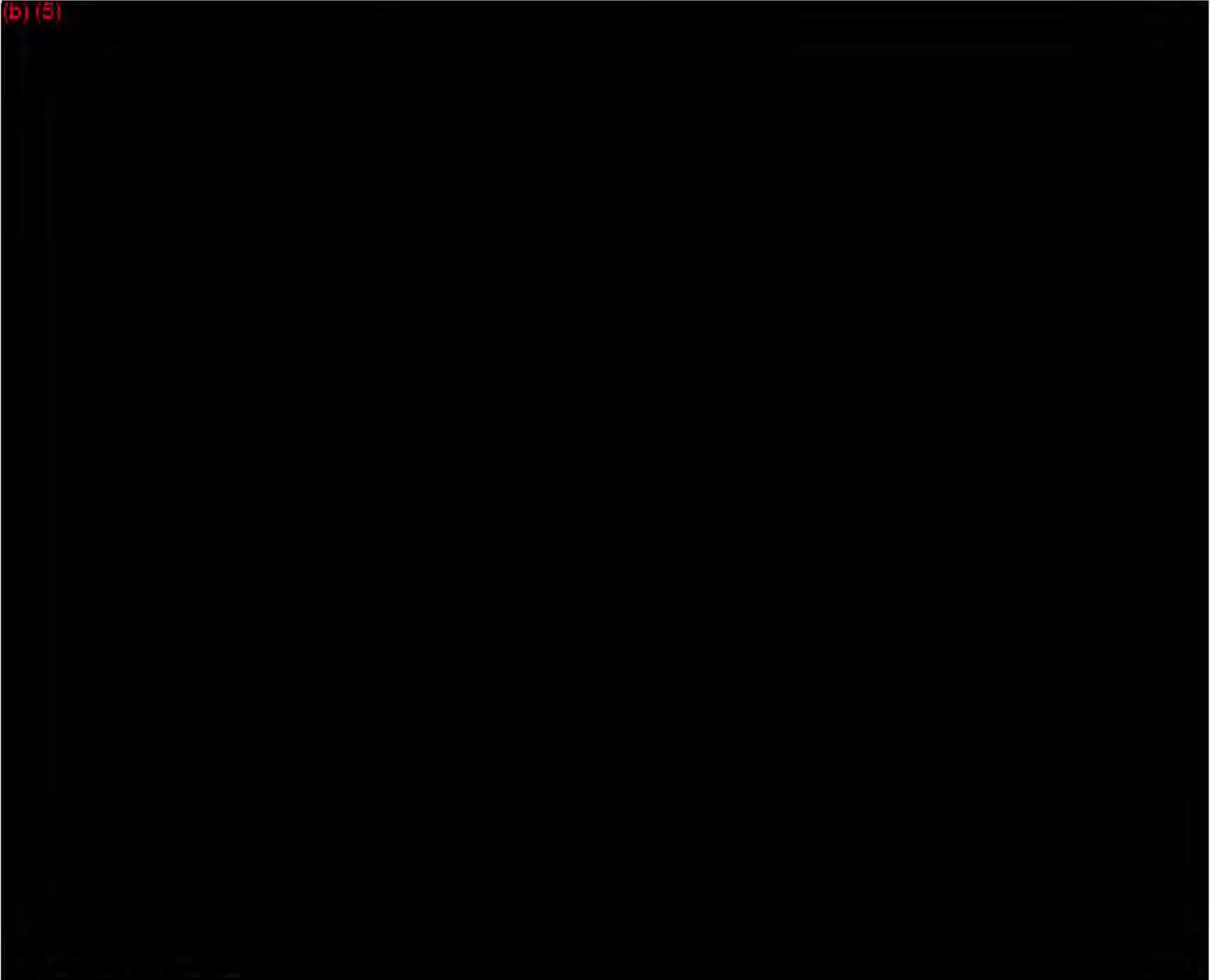
--

J

Smith, Celeste

To: McCall, Jonathan *
Cc: Sherman, Rachel; Hunter, Nina L; Robb, Melissa; Evans, Dana; Davies, Kathleen
Subject: RE: New Draft - use this one Jonathan - Reg_Action_R3_Draft_11-18-2016__CLEAN_rmc_nlh_mr.docx

(b) (5)



Robert M Califf MD
Commissioner of Food and Drugs

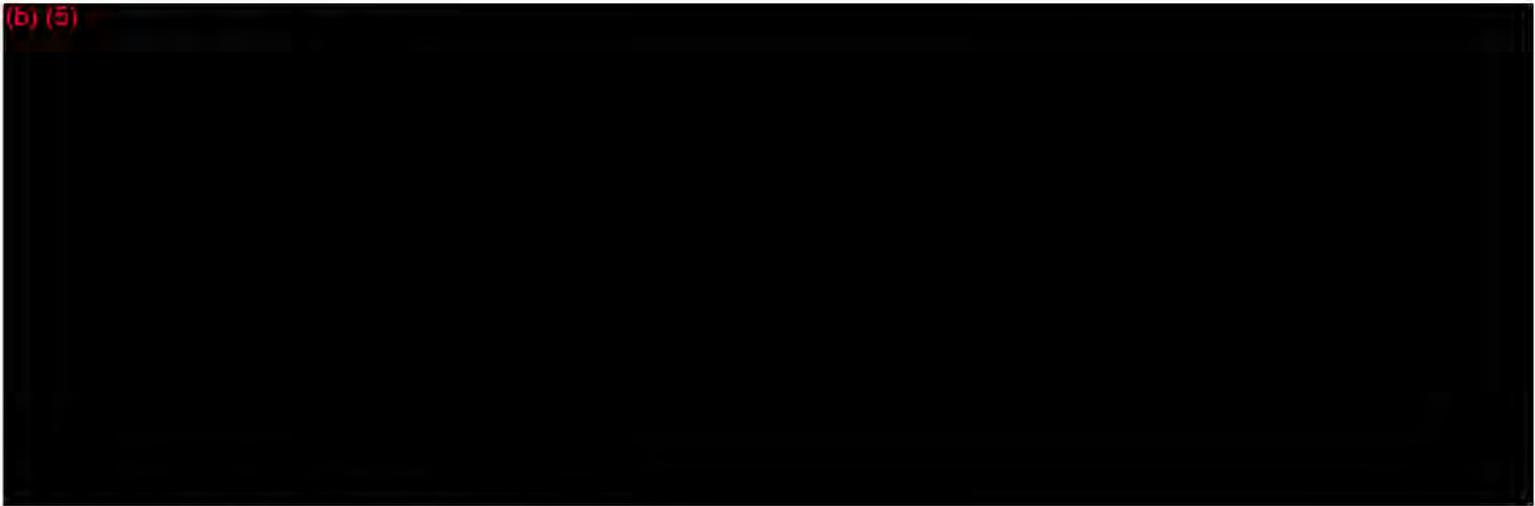
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Sent: Wednesday, November 23, 2016 5:47 PM
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Cc: Sherman, Rachel; Hunter, Nina L; Robb, Melissa; Evans, Dana; Davies, Kathleen
Subject: RE: New Draft - use this one Jonathan - Reg_Action_R3_Draft_11-18-2016__CLEAN_rmc_nlh_mr.docx

Hello all –

Here's the latest version. Thanks to all for your additional edits, input, and comments. The "clean" version may be a little easier for the initial read-through; I've also decluttered the comments where possible.

A few remaining thoughts:

(b) (5)



Hope this helps. Happy Thanksgiving to everyone!

Best,

--
J

From: Davies, Kathleen
Sent: Tuesday, November 22, 2016 4:01 PM
To: McCall, Jonathan *
Cc: Sherman, Rachel; Hunter, Nina L; Robb, Melissa
Subject: New Draft - use this one Jonathan - Reg_Action_R3_Draft_11-18-2016__CLEAN_rmc_nlh_mr.docx

Hi Jonathan,

New draft with edits per my discussion with Rachel.

When we send this, we also want to note (b) (5)




Thanks so much! Let me know how else I can help.

From: [Pink Sheet](#)
To: [Califf, Robert](#)
Subject: Pink Sheet | Highlights Of The Week
Date: Monday, November 21, 2016 11:20:04 AM

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21 Nov 2016

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Pink



WEEKLY HIGHLIGHTS

Find many more articles assessing the US elections' implications for biopharma at our hot topic page.



THIS WEEK'S TOP STORIES



11 Nov 2016 | **ANALYSIS**

Trump, Congress And The Future Of Value-Based Drug Contracting

By Cathy Kelly

CMS-driven experiments in value-based purchasing may slow in the new US administration, but commercial pressures to price drugs according to their value will not.

11 Nov 2016 | **ANALYSIS**

OTC Drug Industry Could Stand To Gain With 'Pragmatist' In White House



With the Trump administration ahead, CHPA's highest regulatory priorities include eliminating a requirement from the Obama era that consumers get a prescription in order to pay for OTC drugs with pre-tax savings accounts and improving the Nixon-era monograph program.



16 Nov 2016 | **NEWS**

Japan Slashes Opdivo Price 50% After Prescriptions Surge

By Ian Haydock

Merck's Keytruda could see its launch price set lower too after Opdivo's rapidly rising use in lung cancer triggers maximum statutory price cut.

17 Nov 2016 | **ANALYSIS**

Enforcement Of Second Medical Use Patents: Landmark Case Sets The Scene For Future Battles

Mike Snodin discusses the UK Court of Appeal's recent decision on second medical use patents and "skinny label" generic products that, whilst containing encouraging signs for the innovative pharmaceutical industry, leaves open key questions that can only be answered in further disputes.



17 Nov 2016 | **ANALYSIS**

'Wildcard' Patents: Why A REVAMP-ed Proposal Might Work In 2017

By Michael McCaughan & Laura Helbling

Before election day, the idea of a new transferrable exclusivity incentive seemed like an extreme long shot for enactment. But now advocates think it has a real chance – and a strategy to redraft the idea to answer Democratic critics and avoid a high CBO score.



15 Nov 2016 | **NEWS**

Brexit Minister Says 'No' To UK Staying In EU Drug Regulatory Framework

By Ian Schofield

Liam Fox, one of the ministers in charge of leading the UK out of the EU, does not want the country to stay within the wider European drug regulatory system, even though many in the life science sector see this as vital if regulatory divergence and drug marketing delays are to be avoided.



14 Nov 2016 | **ANALYSIS**

Payers Want Access To US FDA's Pre-Submission Meetings

By Derrick Gingery

As sponsors push for more access to physicians, payers hope to be able to gather more pre-approval information about drugs – like they now can with devices – for budgeting and patient access.



16 Nov 2016 | **ANALYSIS**

Amgen Exec Backs WHO's 'Biological Qualifier', Says First Ones Could Be Issued By End Of 2017

By Ian Schofield

An Amgen executive says that the WHO should press ahead with its “biological qualifier” proposal, and suggests that the first BQs could be issued towards the end of 2017.



16 Nov 2016 | **ANALYSIS**

Sarepta's Aftermath: FDA Staff Still Working Together, Califf Says

By Derrick Gingery

US FDA commissioner and others say they have put disagreements from controversial decision to approve Sarepta's Duchenne muscular dystrophy drug behind them.

15 Nov 2016 | **NEWS**

OTC Homeopathic Labels Must Include Scientific Disclaimers – FTC

By Malcolm Spicer

US trade regulator will require an "inherent contradiction" for homeopathic OTC labels: disclaimers to FDA-compliant label indications indicating a lack of scientific evidence that the product works.

17 Nov 2016 | **ANALYSIS**

Focus On Equipment And Software For Validating Continuous Manufacturing Processes – FDA

By Joanne Eglovitch

US FDA officials outline the agency's expectations for validating processes for drugs manufactured on a continuous line and see growing interest among manufacturers in developing continuous manufacturing systems.



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<https://pink.pharmamedtechbi.com/pdf-library> to access the latest issue and browse previous issues.

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clientservices@pharmamedtechbi.com



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From: [Evans, Dana](#)
To: [Califf, Robert](#)
Subject: Pink & Rose
Date: Monday, November 21, 2016 12:02:18 PM
Attachments: [Pink Sheet Highlights Of The Week.msg](#)
[Rose Sheet Weekly Roundup Cosmetics.msg](#)

From: Rose Sheet <info@pharmamedtechbi.net>
Sent: Monday, November 21, 2016 11:14 AM
To: Commissioner FDA
Subject: Rose Sheet | Weekly Roundup: Cosmetics

[View our online version](#)

21 Nov 2016

[Subscribe](#) | [Contact Us](#)



WEEKLY HIGHLIGHTS

Cosmetics news, analysis and features from the past week. Stay tuned for more coverage of regulatory, legal and marketplace developments in the cosmetics sector.



15 Nov 2016 | **NEWS**

Consumers, Health Practitioners Heeded FDA's Call For WEN-Related AEs

By Lauren Nardella

FDA's safety alert in July, asking WEN users and their doctors to share information regarding hair loss-related adverse events, yielded approximately 1,000 reports in just over two months, contributing to a massive increase in cosmetic AE reports for FY 2016.

18 Nov 2016 | **NEWS**

WEN Consumers To Begin Filing Claims Under Approved Class Settlement

By Lauren Nardella

A class action settlement preliminarily approved in California's Central District will establish a \$26.25m fund for compensating WEN hair-care consumers for purchases and alleged injuries, but the fairness of payments to up to 6 million class members may have to be

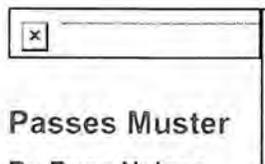
revisited if more claims are filed than expected. Notices to class members will issue by year-end, and their claims must be submitted by late April 2017.

15 Nov 2016 | **NEWS**

Oral Care, Topical Product 'Natural' Claims Paint Bullseye For Class Action

By Malcolm Spicer

Class action complaints alleging misleading "natural" claims for food products have been stayed pending completion of FDA's look at whether it should formally define the term for use in food, but there is no parallel FDA consideration of how the term is used for oral care products and topicals.



16 Nov 2016 | **NEWS**

P&G's Oral B 100% Stain Removal Claim With ASA

Passes Muster

By Ryan Nelson

Following a Colgate challenge, the ASA examines a P&G clinical study submitted in support of its claim that Oral B 3D White Luxe Perfection toothpaste "removes up to 100% of surface stains in 3 days."

14 Nov 2016 | **ANALYSIS**

Lauder Innovation Shift: Deemphasize Blockbusters, Let Winners Evolve

By Ryan Nelson

"The future of our innovation is changing," according to leadership at Lauder, which is reducing innovation risk by cutting back on blockbuster launch investments. It's a sensible strategic move at a time when consumers are avid about experimenting with and owning a rich variety of products, the firm suggests.



16 Nov 2016 | **NEWS**

Lauder's Too Faced Acquisition Grows Firm's Specialty-Multi Presence

By Ryan Nelson

The \$1.45bn acquisition follows Lauder's purchase of BECCA Cosmetics, both of which are expected to strengthen the company's

position in specialty-multi channels and score Millennial business. The firm's expanding distribution is helping to offset sluggishness in US mid-tier department stores and tourist traffic, which has weighed particularly heavily on MAC Cosmetics.

17 Nov 2016 | **NEWS**

L'Oreal 'Surfing' Makeup Wave To Projected Strong Finish For FY 2016

Acquired brands NYX and Urban Decay are leading growth in L'Oreal's makeup business, up 15% for the year to date. Strong demand for color cosmetics in the mass and luxury channels drove the firm's Q3 sales, surpassing analyst expectations, if not L'Oreal's.

17 Nov 2016 | **NEWS**

Weekly Trademark Review Nov 8, 2016

Personal-care and cosmetic product trademark filings compiled from Official Gazette of the U.S. Patent and Trademark Office, Class 3 – Cosmetics and Cleaning Preps.



Sent to robert.califf@fda.hhs.gov. You are receiving this email as a Rose Sheet subscriber. If you are not a subscriber or do not have your password, call US Support at + 1 617 374 22 42 / UK support at + 44 (0) 20 7017 4161 or email clientservices@pharmamedtechbi.com

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Smith, Celeste

From: Sherman, Rachel
Sent: Thursday, November 24, 2016 11:24 AM
To: Califf, Robert; McCall, Jonathan *
Cc: Hunter, Nina L; Robb, Melissa; Evans, Dana; Davies, Kathleen
Subject: RE: New Draft - use this one Jonathan - Reg_Action_R3_Draft_11-18-2016__CLEAN_rmc_nlh_mr.docx

My suggested order:

Rachel
Nina/Melissa
Kathleen/Jonathan

Everyone is off the hook until they hear from me and that won't be until next week.

Rob

From: Califf, Robert
Sent: Thursday, November 24, 2016 10:34 AM
To: McCall, Jonathan *
Cc: Sherman, Rachel; Hunter, Nina L; Robb, Melissa; Evans, Dana; Davies, Kathleen
Subject: RE: New Draft - use this one Jonathan - Reg_Action_R3_Draft_11-18-2016__CLEAN_rmc_nlh_mr.docx

(b) (5)



(b) (5)

Happy thanksgiving.

rmc
Robert M Califf MD
Commissioner of Food and Drugs

From: McCall, Jonathan *
Sent: Wednesday, November 23, 2016 5:47 PM
To: Califf, Robert
Cc: Sherman, Rachel; Hunter, Nina L; Robb, Melissa; Evans, Dana; Davies, Kathleen
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A few remaining thoughts:

(b) (5)

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Best,

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From: Davies, Kathleen
Sent: Tuesday, November 22, 2016 4:01 PM

To: McCall, Jonathan *

Cc: Sherman, Rachel; Hunter, Nina L; Robb, Melissa

Subject: New Draft - use this one Jonathan - Reg_Action_R3_Draft_11-18-2016__CLEAN_rmc_nlh_mr.docx

Hi Jonathan,

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When we send this, we also want to note (b) (5)

A large black rectangular redaction box covers the majority of the text in this paragraph, starting from the end of the word 'note' and extending across the width of the page.

Thanks so much! Let me know how else I can help.

From: [Nelson, Robert "Skip"](#)
To: [Soreth, Janice M](#)
Cc: [Jenkins, John K](#); [Califf, Robert](#)
Subject: Presentation to the Muscular Dystrophy Coordinating Committee on Tuesday November 29
Date: Friday, November 25, 2016 2:21:00 PM
Attachments: [Nelson - MDCC 11-29-16.pptx](#)
[MDCC Nov 2016 agenda DRAFT 11-1.docx](#)

Dear Janice,

Attached please find my slides for a 20 minute presentation on Tuesday morning on the ethics of pediatric clinical trials at the Muscular Dystrophy Coordinating Committee Meeting on November 29, 2016. I also have attached the draft agenda. I apologize for not getting these to you earlier, and hope you can look at the slides on Monday and provide comment and clearance. As I quote Rob Califf's Sept. 16 letter on the eteplirsen approval (my slide 15) and borrow ideas from John Jenkin's presentation to NORD on October 18 (my slide 19), I am also copying Rob and John to see if they have any comments. I do not plan to give an opinion on the eteplirsen approval. My main message is the moral responsibility we have to get it right when conducting a clinical trial that involves considerable burden on the enrolled children. The meeting is public and webcast. Let me know if you have any questions. Thanks.

Skip

Robert "Skip" Nelson, M.D., Ph.D.

Acting Director and Senior Pediatric Ethicist

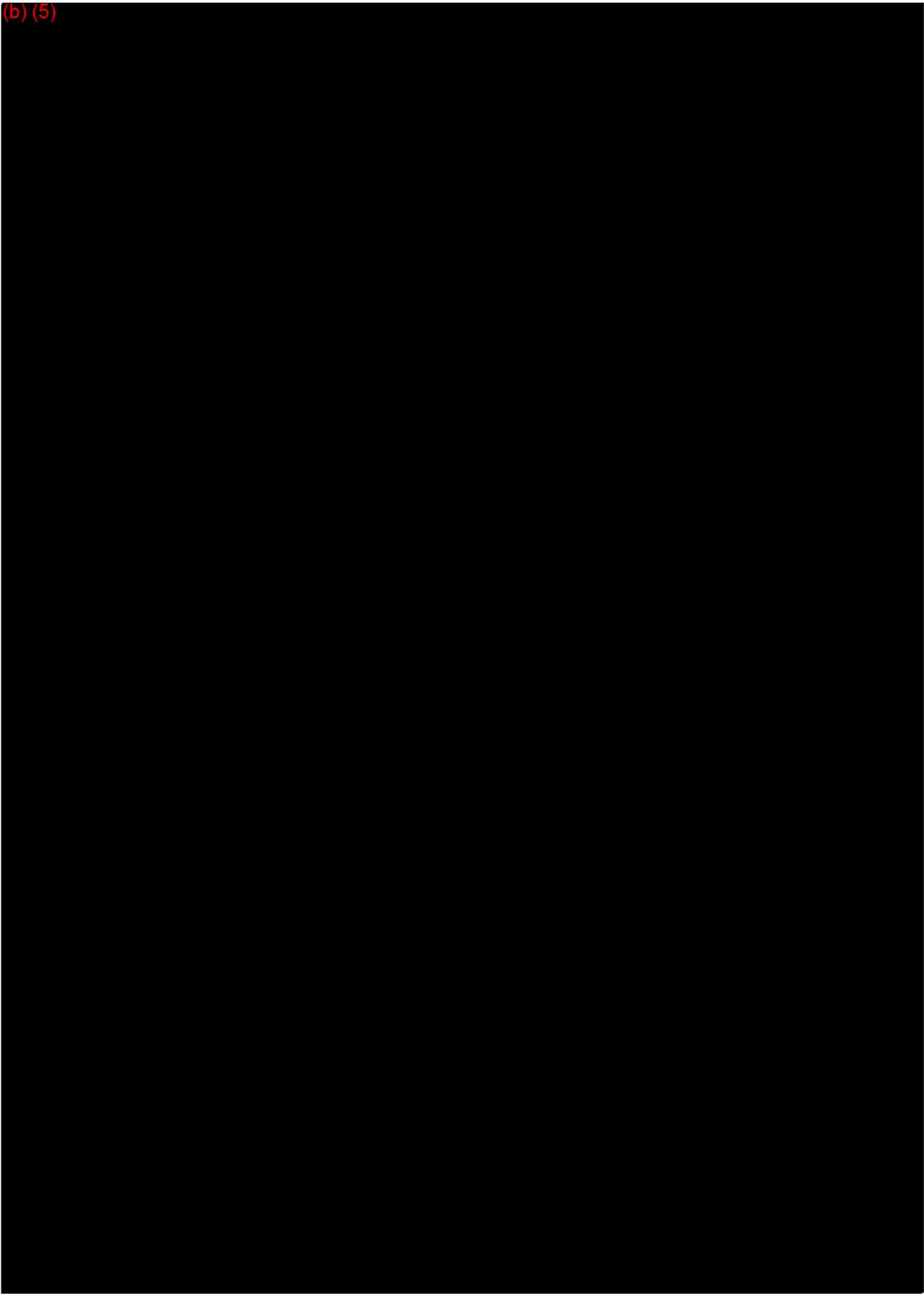
Office of Pediatric Therapeutics (OPT)

Office of the Commissioner (OC)

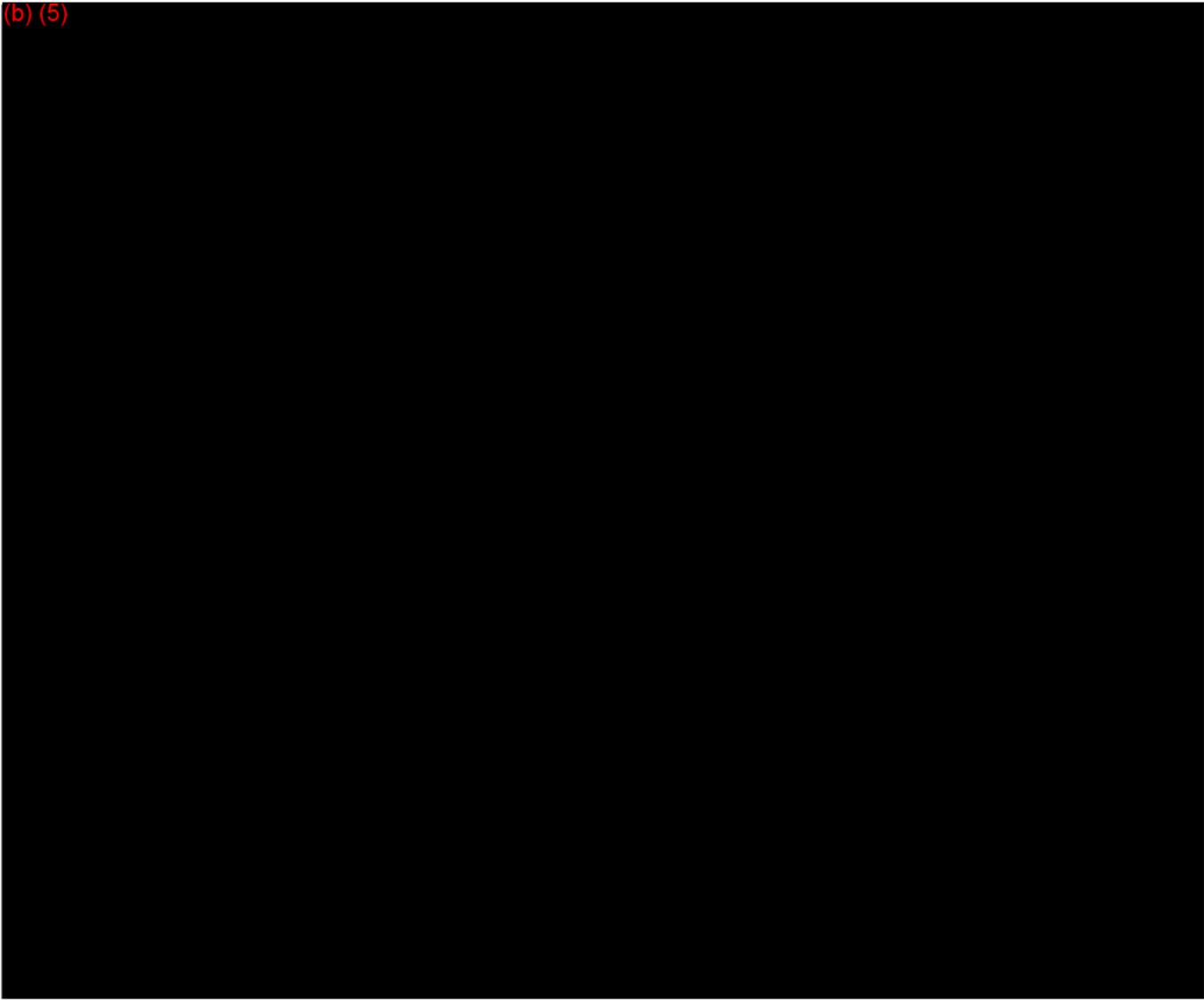
Tel: 301-796-8665

robert.nelson@fda.hhs.gov

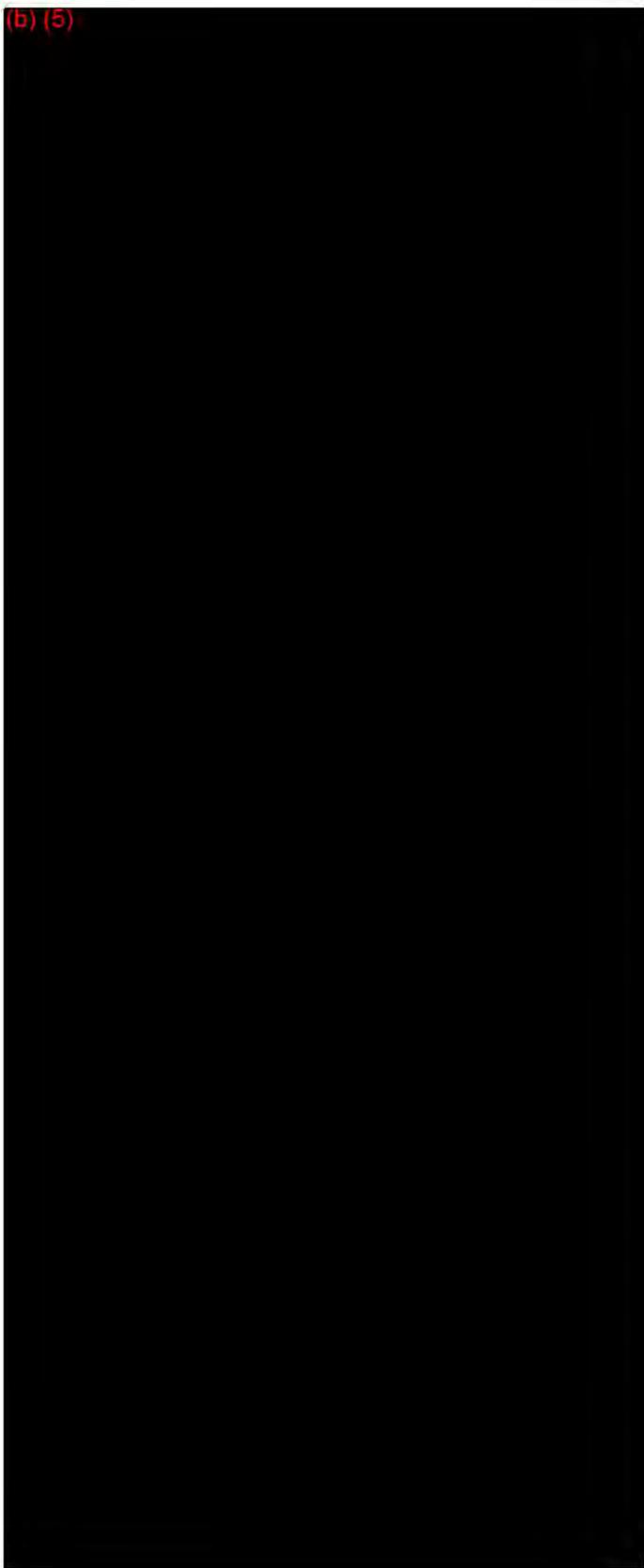
(b) (5)



(b) (5)

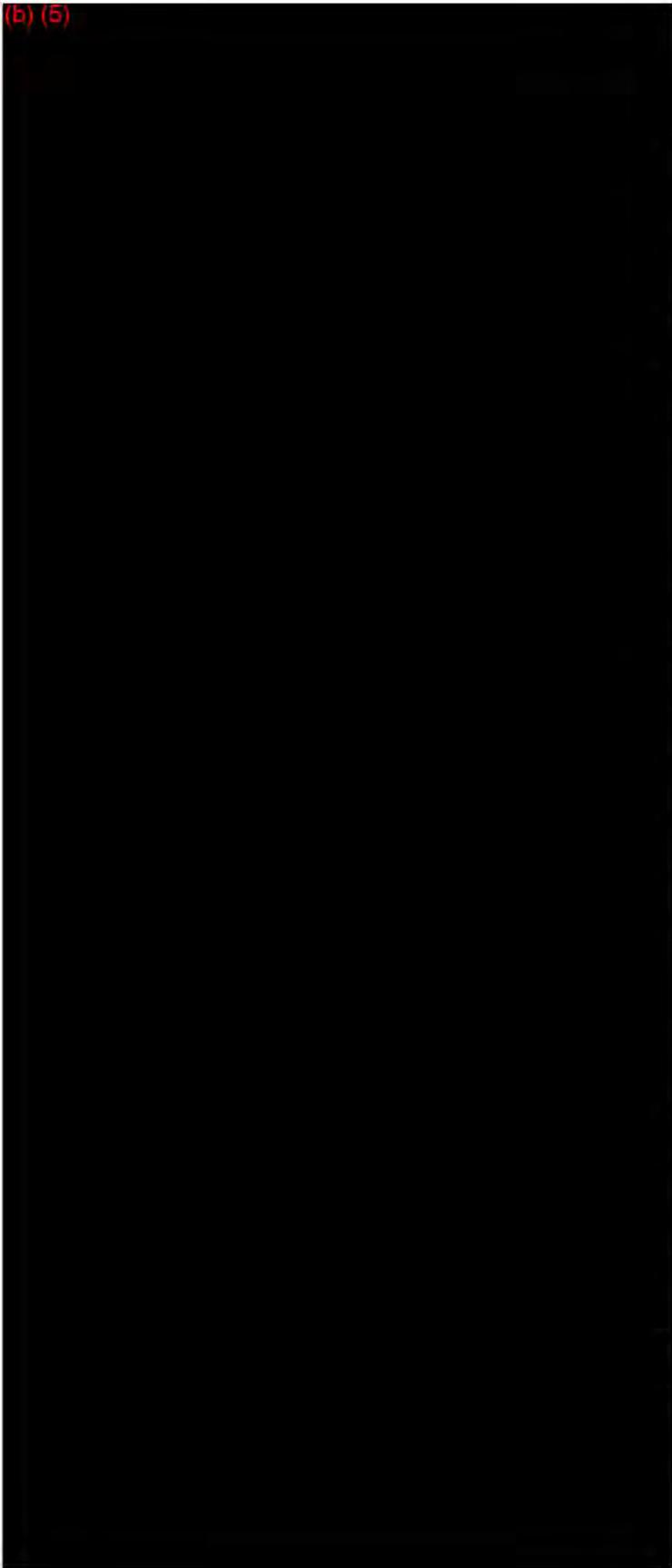


(b) (5)



Multiple sets of horizontal lines, likely representing redacted text or a form structure, are visible on the right side of the page. There are three distinct groups of lines, each consisting of approximately seven horizontal lines.

(b) (5)



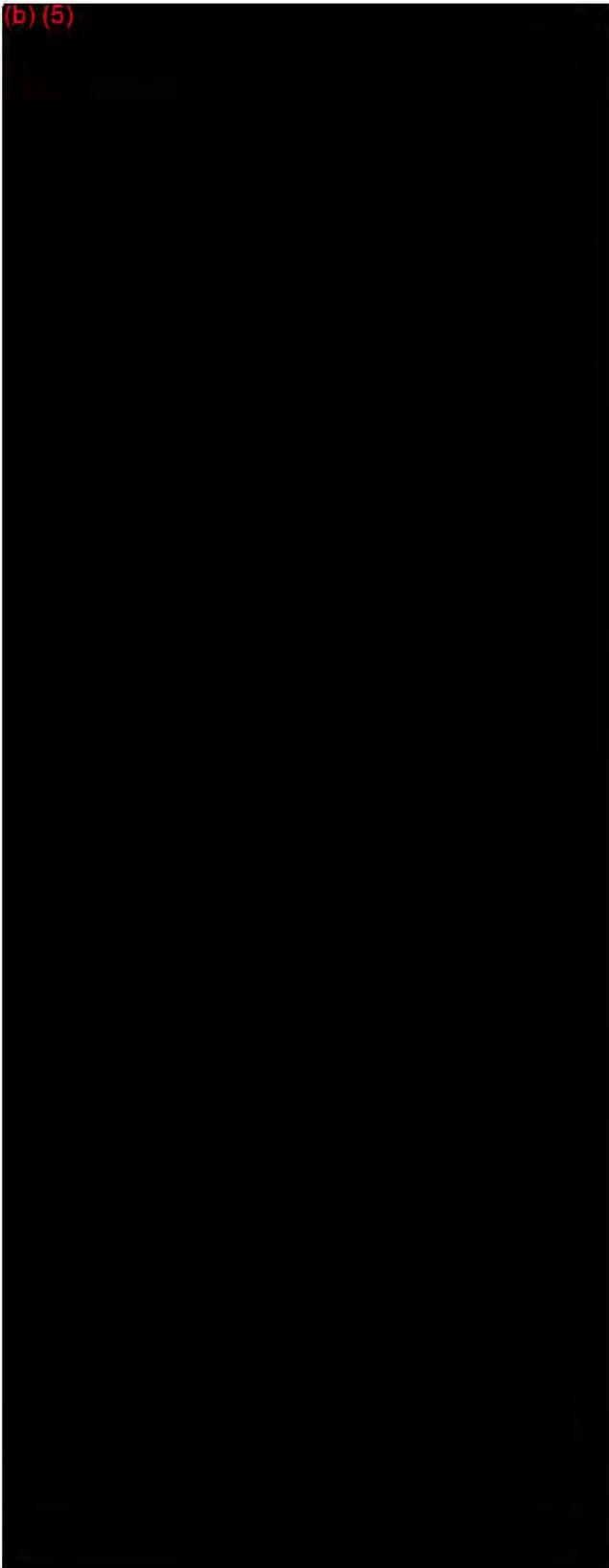
A series of horizontal lines, likely representing a table or a list, are visible on the right side of the page. The lines are evenly spaced and extend across the width of the page, but they are mostly empty, suggesting that the content has been redacted or is otherwise obscured.

(b) (5)



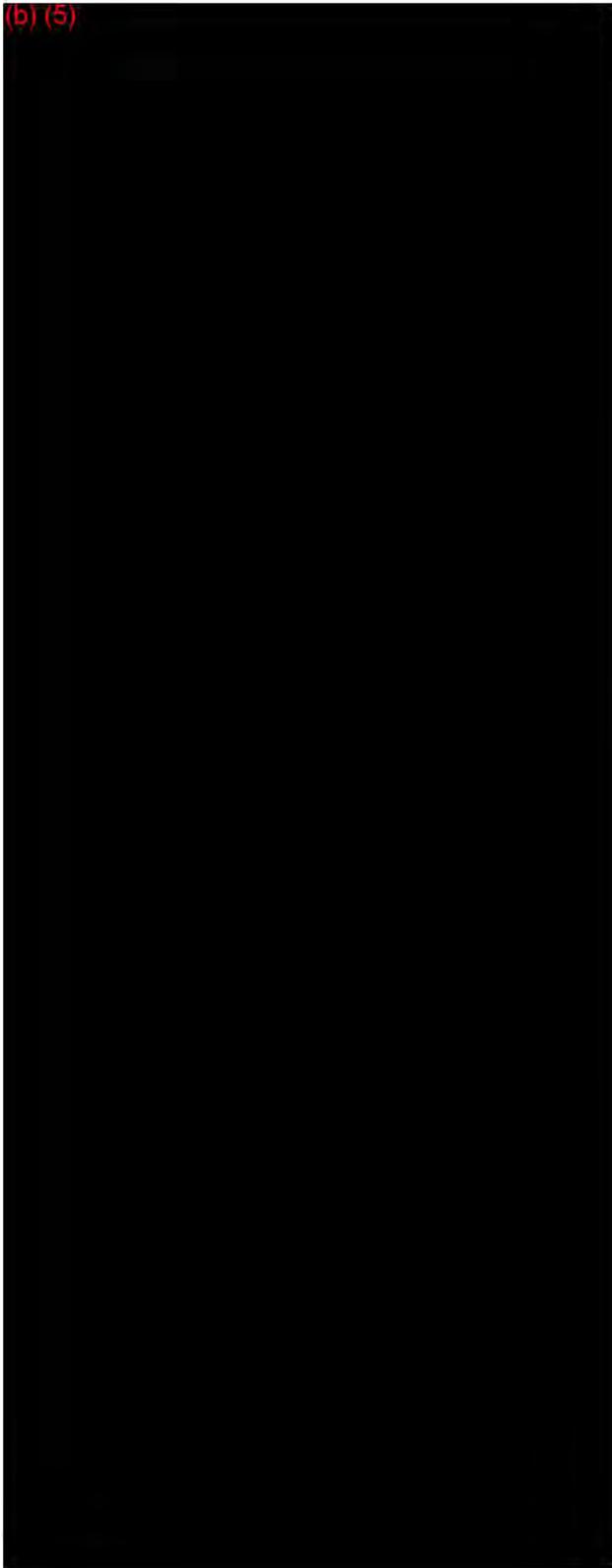
Multiple horizontal lines for text entry, organized into three distinct groups of five lines each, separated by larger vertical gaps.

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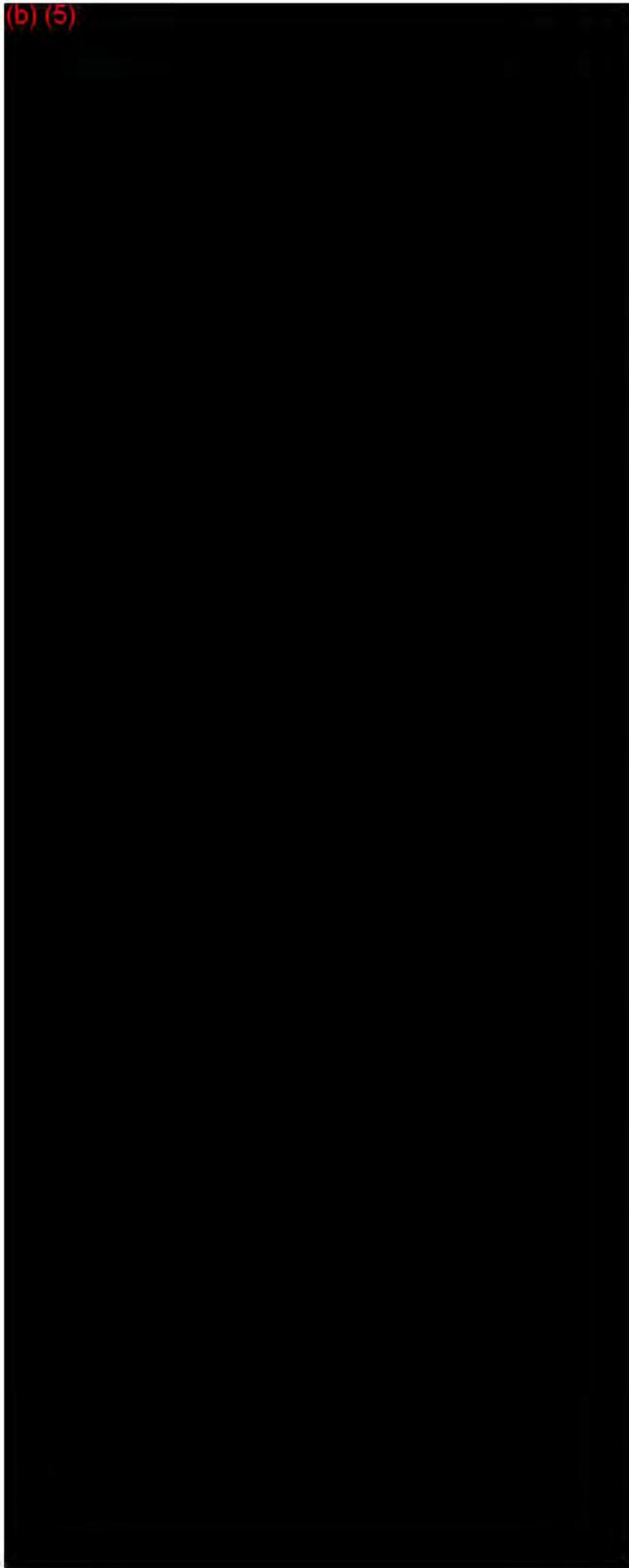
Horizontal lines for text entry, organized into three groups of five lines each, separated by larger gaps.

(b) (5)



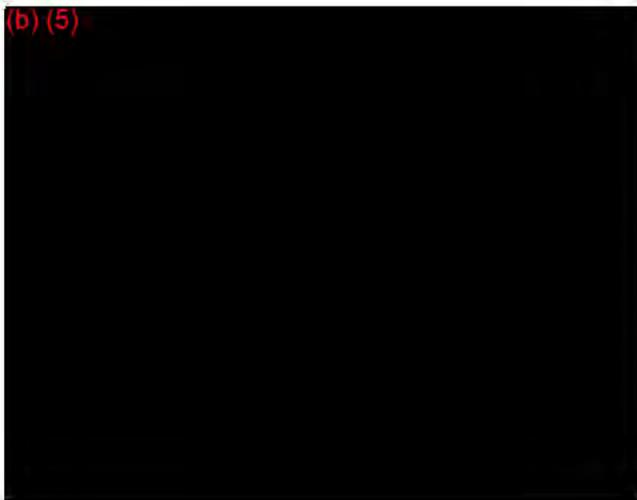
Multiple horizontal lines for text entry, organized into three distinct sections. The first section contains 7 lines, the second section contains 7 lines, and the third section contains 7 lines.

(b) (5)



Multiple horizontal lines for text entry, organized into three distinct sections. The first section contains 7 lines, the second section contains 7 lines, and the third section contains 7 lines.

(b) (5)



From: Quinn, Kathleen
To: Califf, Robert
Cc: Conover, Katie; Kraus, Tom; Pennington, Caitlin
Subject: FW: STAT - Two more cancer patients just died in a clinical trial. Should the FDA be blamed?
Date: Friday, November 25, 2016 3:38:38 PM

Commissioner-

You may already be aware of this issue from the program level, but because of the holiday and the fact that clips weren't circulated, we didn't want it to fall through the cracks. Juno's study of CAR-T immunotherapy, in which it appears five patients have now died, is generating some media interest and is raising questions about FDA's practices, including when and how we institute and lift clinical holds. Here is one of the recent articles that details the concerns. We've had inquiries from Reuters, Bloomberg, MIT Technology Review and other trades.

Our response has been along our standard lines of not confirming/denying/not being able to discuss. We will continue to monitor and clips will be back on track for Monday.

KKQ

From STAT :

<https://www.statnews.com/2016/11/23/cancer-patients-fda-juno/>

Two more cancer patients just died in a clinical trial. Should the FDA be blamed?

By REBECCA ROBBINS

NOVEMBER 23, 2016



When three cancer patients died earlier this year while on an experimental therapy, the Food and Drug Administration promptly halted the clinical trial. A few days later, the hold was lifted — a turnaround so fast that it stunned the world of drug development.

On Wednesday, the company behind the trial said two more patients were dead.

“In light of what happened, I think the FDA really dropped the ball,” said Maxim Jacobs, a health care analyst at Edison Investment Research who researches oncology drugs.

“What did the FDA review during that period from when the hold was announced to when it was lifted? What exactly was the decision-making process? What was the logic behind going so quickly towards lifting the hold?” Jacobs asked.

The FDA declined to comment Wednesday on its decision. But the debate over whether the agency moved too quickly underlines a central tension over its role in both fostering medical innovation and protecting patient safety. It also raises questions over whether the agency is forthcoming enough about how it makes its decisions.

Jacobs and other experts emphasized that there’s no way to know where the FDA might have misstepped in the case of this therapy, developed by Juno Therapeutics. That’s because the curtain is drawn on how the FDA decides whether to halt and restart a trial, giving the public no way to know whether the decisions were made wisely based on the information available.

It’s possible that the FDA has a systematized process to review clinical holds, but it’s impossible to tell because companies consider that information to be trade secrets, said Dr. Aaron Kesselheim, who studies the intersection of law, regulation, and drug development at Brigham and Women’s Hospital.

Other than disclosures for panel hearings that are sometimes held to debate the risks and benefits of a drug up for approval, any glimpse into the FDA’s deliberations before approval is funneled through companies, who can be “overzealous” in withholding some of the information, Kesselheim said.

Juno has been testing a promising but still unproven treatment called U-AR-1 immunotherapy, one of the many varied approaches to harnessing the immune system to fight cancer.

In July, the company announced that the FDA had placed its study on clinical hold, prohibiting the enrollment of new patients, after three patients died after excess fluids flooded their brains.

But Juno insisted that the problem was not with the genetically engineered blood cells known as CAR-Ts infused into patients’ bodies, but rather with how the CAR-Ts reacted with a chemotherapy drug used to prepare patients for treatment. The

company proposed the simple fix of removing that chemotherapy drug — and apparently that explanation for the deaths quickly persuaded the FDA.

The company announced that the FDA had lifted the hold just five days after announcing the halt.

By comparison, a 2015 analysis that looked at 29 instances in which the FDA halted a drug study between 2008 and 2014 found that these holds were in place for a median of eight months. Another company's drug trial for hepatitis C, halted by the FDA during the summer at about the same time it halted Juno's study, still appears to be paused nearly five months later.

Juno said Wednesday that it had voluntarily halted the clinical trial after two more patients died from the same problem and informed the FDA. The agency declined to comment on whether it will impose a hold of its own on Juno's trial, though an FDA hold typically follows such a move as a matter of procedure.

In a written statement from agency spokeswoman Andrea Fischer, the FDA said that because of the "great promise" of CAR-T and other cellular therapies, the agency does "everything possible to assist sponsors in advancing clinical development programs in an effort to bring promising therapies to patients." The statement also said that the agency "constantly looks at the risk-benefit profile of experimental therapies and when we have concerns about the risks, we may place the clinical trials on hold."

Experts said they understood the FDA's impulse to move quickly on a trial for cancer patients running out of time. "I think the key here is just how sick these patients are and what few options they have," said Ramsey Baghdadi, cofounder of Washington analysis firm Prevision Policy, who added that he thought the agency had acted appropriately on the case.

Still, the FDA's ability to appropriately weigh risks and benefits is contingent on the information it has to work with, said Brad Loncar, founder of a cancer immunotherapy fund.

"The onus is on Juno to take to the FDA a well-thought-out, credible hypothesis of why these problems are happening," Loncar said. "And in this case, especially with the benefit of hindsight, it's clear they didn't do that."

Experts said it would be premature to call for the FDA to immediately shut down Juno's other trials or other companies' CAR-T trials. But Jacobs said given these

alarming safety problems, the FDA should make sure that companies are collecting a lot of data before they move on to later-stage trials or seek approval.

“We’ve really been rushing into things with these CAR-Ts,” Jacobs said, “and we don’t really have any long-term data with any of these guys.”

In March, the FDA proposed creating new databases that would allow it to monitor the safety of experimental CAR-T treatments across different trials. At the time, the agency said it planned to collect data, store it in a database, and analyze it across the different studies.

But such plans could be stalled as the agency braces for upheaval in the aftermath of the election. Legislation that could reduce requirements for clinical trials may finally make it across the finish line in the next session, and the Trump administration is expected to call for further deregulation.

Rolling back the FDA’s standards would speed the path of new medicines to market, but it could also expose patients to added risks. Pending legislation would allow for FDA approval based on Phase 1 data. Juno’s therapy had already progressed to Phase 2.

“This is a good reminder of why we have a relatively strong FDA, why we have a premarket approval system, and why we want there to be data that can demonstrate that drugs are safe and effective before they’re opened up to wide populations,” said Patricia Zettler, a professor at Georgia State University’s College of Law who specializes in FDA regulations.

Damian Garde and Meghana Keshavan contributed reporting.

From: [Pink Sheet](#)
To: [Califf, Robert](#)
Subject: Pink Sheet | Highlights Of The Week
Date: Monday, December 12, 2016 11:16:00 AM

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Jenkins' Retirement From US FDA Was Several Years In The Making

By Derrick Gingery

Outgoing Office of New Drugs director dismisses speculation that his decision to leave the agency was related to events surrounding Sarepta's controversial Exondys 51 approval.

04 Dec 2016 | **ANALYSIS**

Will US FDA Wind Up With More Political Positions Under Trump?

By Derrick Gingery

The European Medicines Agency says it has been disappointing to see previously rejected applications for its PRIME scheme sent back to the agency with no additional data. On the other hand, the scheme, which is designed to get drugs for unmet medical needs to patients faster, is going from strength to strength. Kick-off meetings are identifying issues that sometime surprise companies but can be dealt with early on, well before a product is filed for authorization.

06 Dec 2016 | **ANALYSIS**

Waiting For The Perfect Case: Why EMA Has Yet To Hold A Public Drug Safety Hearing

By Maureen Kenny

The European Medicines Agency has yet to use the power it has to hold public hearings on marketed medicines that raise safety concerns. It says it will do so only when the time is right.

07 Dec 2016 | **NEWS**

Global Pharma Guidance Tracker – November 2016

By Vibha Sharma

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New Japan Price Cut Push Has Industry Worried

By Ian Haydock

Industry groups in Japan have reacted swiftly and strongly to planned government discussions on changes to drug pricing policies, warning that the adoption of annual price cuts would "undo all the policy achievements" of the past few years.

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Consumer Industry Roundup: Catalent Acquires Accucaps; CHPA Adds Lobbyist; Zeasorb Recall

Mylan's Schloss joins CHPA government affairs; Catalent expands softgel capabilities with Accucaps acquisition; GSKs recalls a half million bottles of mislabeled Zeasorb; and more news in brief.



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From: [Evans, Dana](#)
To: [Califf, Robert](#)
Subject: FW: Pink Sheet | Highlights Of The Week
Date: Monday, December 12, 2016 3:48:34 PM

Dana Evans, M.P.H.

Program Support Specialist to the Commissioner
Office of the Commissioner Immediate Office
U.S. Food and Drug Administration
Phone: 301-796-2021
BB: 301-467-8987
Email: dana.evans@fda.hhs.gov

From: Pink Sheet [<mailto:info@pharmamedtechbi.net>]
Sent: Monday, December 12, 2016 11:11 AM
To: Commissioner FDA
Subject: Pink Sheet | Highlights Of The Week

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Will US FDA Wind Up With More Political Positions Under Trump?

By Derrick Gingery

Incoming administration could appoint key legal and policy positions to shape agenda's agenda.

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Jardiance's Cardiovascular Benefit Claim Bodes Well For Other Products Too

By Sue Sutter

US labeling for Boehringer/Lilly's SGLT-2 inhibitor empagliflozin includes results from MACE primary endpoint and its individual components in the EMPA-REG trial, but indication statement is limited to CV risk reduction benefit.

07 Dec 2016 | **ANALYSIS**

Trump's Drug Pricing Remarks: A Gambit For Industry Self-Restraint?

By Cathy Kelly

Comments during recent interview shows president-elect continues to view drug pricing as populist issue, revives speculation he may take action to control prices.

02 Dec 2016 | **ANALYSIS**

Price Increases Accounted For Over Half Of Drug Spending Growth In 2015

By Cathy Kelly

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05 Dec 2016 | **NEWS**

EMA PRIME Rejects Told: 'Add Something New' If You Resubmit

By Neena Brizmohun

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From: [Marchand, Heidi](#)
To: [Califf, Robert](#); [Fiuzat, Mona](#); [Conover, Katie](#); [Shuren, Jeff](#); [Maisel, William](#); [Sheets, John](#); [Kiang, Tina](#); [Purohit-Sheth, Tejashri](#); [Gutierrez, Alberto](#); [Bahadori, Lila](#); [O'Callaghan, Kathryn](#); [Schwartz, Suzanne](#); [Tenenbaum, Cara](#); [Marks, Peter](#); [Witten, Celia \(CBER\)](#); [Maloney, Diane](#); [Woodcock, Janet](#); [Goldsmith, Jonathan](#); [Whyte, John](#); [Pretti, Jeffery](#); [Rao, Gayatri](#); [Cox, Edward M](#); [Chowdhury, Badrul A](#); [Unger, Ellis](#); [Bastings, Eric](#); [Roman, Dragos](#); [Soreth, Janice M](#); [Borio, Luciana](#)
Cc: [Runner, Susan](#); [Rare Disease Program Meetings](#); [Cuff, Althea](#); [Chavez, Javier](#)
Subject: RE: Stakeholders Listening Session with the FDA Commissioner & Rare Dx., Rheumatology and Infx. Dx. Organizations
Date: Monday, December 12, 2016 7:27:10 PM
Attachments: [Seating Chart for Rheumo & Rare Disease Listening Session as of Dec 12.pptx](#)
[Timeline for Speakers.pub](#)
[DRAFT Backgrounder for Dec 13th Stakeholder Listening Session as of Decdoc](#)

Hi All,

Materials for tomorrow's listening session. Please note that this is our largest group and we have also developed a more detailed time schedule to assure that we hear from all.

Appreciate it to holding comments from FDA until the designated times for clarification. I'll plan to announce at the beginning of the meeting and throughout the 3.5 hour timeframe.

Thanks so much,

Heidi

-----Original Appointment-----

From: Califf, Robert

Sent: Friday, November 18, 2016 3:57 PM

To: Califf, Robert; Fiuzat, Mona; Conover, Katie; Marchand, Heidi; Shuren, Jeff; Maisel, William; Sheets, John; Kiang, Tina; Purohit-Sheth, Tejashri; Gutierrez, Alberto; Bahadori, Lila; O'Callaghan, Kathryn; Schwartz, Suzanne; Tenenbaum, Cara; Marks, Peter; Witten, Celia (CBER); Maloney, Diane; Woodcock, Janet; Goldsmith, Jonathan; Whyte, John; Pretti, Jeffery; Rao, Gayatri; Cox, Edward M; Chowdhury, Badrul A; Unger, Ellis; Bastings, Eric; Roman, Dragos; Soreth, Janice M; Borio, Luciana

Cc: Runner, Susan; Rare Disease Program Meetings; Cuff, Althea

Subject: Stakeholders Listening Session with the FDA Commissioner & Rare Dx., Rheumatology and Infx. Dx. Organizations

When: Tuesday, December 13, 2016 9:00 AM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).

Where: Building 32, Room 1243

FDA Commissioner Listening
Session on Rare Diseases,
Rheumatology, Infectious Disease
and Cystic Fibrosis

December 13, 2016

Mona Fiuzat, PharmD,
Senior Scientific
Advisor to the
Commissioner, OC

Peter Marks,
MD, Director,
CBER

Jeffrey Shuren,
MD, JD,
Director,
CDRH

Robert Califf, MD,
Commissioner of
Food and Drugs

Heidi Marchand,
PharmD, Assistant
Commissioner,
OHCA

Janet Woodcock,
MD, Director, CDER

John Sheets, MD,
Director, CDRH

Tina Kiang, PhD, Acting
Director, Div of
Anesthesiology, CDRH

Foundation for Prader-
Willi Research

Theresa Strong, Director
of Research Programs,
Foundation for Prader-
Willi Research

William Maisel, MD,
Deputy Director for
Science and Chief
Scientist, CDRH

Tejashri Purohit-Sheth,
MD, Clinical Deputy
Director CDRH

Rosángel Cruz,
Associate Research
Director of Clinical
Affairs, Cure SMA

Kenneth Hobby,
President, Cure SMA

Alberto Gutierrez, PhD,
Director, In Vitro
Diagnostics and
Radiological Health,
CDRH

Harry Gewanter, MD,
American College of
Rheumatology,
RheumPAC Chair

Molly White, Chief
Executive Officer,
Myotonic Dystrophy
Foundation

Guy Eakin, Vice
President, Scientific
Strategy, Arthritis
Foundation

Morie Gertz, MD, Chair
of Internal Medicine,
Mayo Clinic,
Amyloidosis
Foundation

Isabelle Lousada,
President & CEO,
Amyloidosis Foundation

David Borenstein, MD,
American College of
Rheumatology, Past-
President

Lila Bahadori, MD,
Medical Officer, CDRH

Celia Witten, MD, PhD,
Deputy Director, CBER

Ann M. Palmer,
President & CEO,
Arthritis Foundation

Suzanne Schwartz, M.D.,
MBA, Associate
Director for Science and
Strategic Partnerships,
CDRH

Annie Kennedy, Sr
Vice-President,
Legislation & Policy,
Parent Project Muscular
Dystrophy

Pat Furlong, Founding
President & CEO, Parent
Project Muscular
Dystrophy

Christopher Busky,
CEO, Infectious Disease
Society of America

Billy Dunn, MD,
Director, Division of
Neurology Products,
CDER

Mary Dwight, Senior
Vice-President for Policy
and Patient Programs,
Cystic Fibrosis
Foundation

Kathryn O'Callaghan,
Assistant Director for
Strategic Programs,
CDRH

Janet Shoemaker,
Director Public Affairs,
American Society for
Microbiology

Michael P. Boyle, MD,
Sr VP of Therapeutics
Development, Cystic
Fibrosis Foundation

Preston W. Campbell III,
MD, President & CEO,
Cystic Fibrosis
Foundation

Kimberly E. Walker,
PhD, Manager of Public
Affairs, American
Society for Microbiology

Melanie Swick,
Advocacy Assistant,
NORD

Katie Conover, Acting
Associate
Commissioner, Office
of External Affairs

Gaytri Rao, MD,
JD, Orphan
Products

Nicole Boice,
Founder and CEO,
Global Genes

Emil D. Kakkis,
MD, PhD, President
& Founder, Everylife
Foundation

Edward Cox, MD,
Office of
Antimicrobial
Products

Jonathan
Goldsmith, MD,
Director, Rare
Disease

Paul Melmeyer,
Associate Director
of Public Policy,
NORD

Javier Chavez
OHCA

Diane Maloney, JD,
Associate Director for
Policy, CBER

Jeffery Pretti, PhD,
Advisor to the Center
Director, CDER

Cara Tenenbaum, JD,
MBA, Senior Policy
Advisor, CDRH

Max Bronstein, Director
of Advocacy & Science
Policy, Everylife
Foundation

Badrul Chowdhury,
Director, Div of
Pulmonary, Allergy
and Rheumatology
Products

Lori Haughey,
PASE, CDER

Pat Kuntze,
OHCA

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December 13, 2016

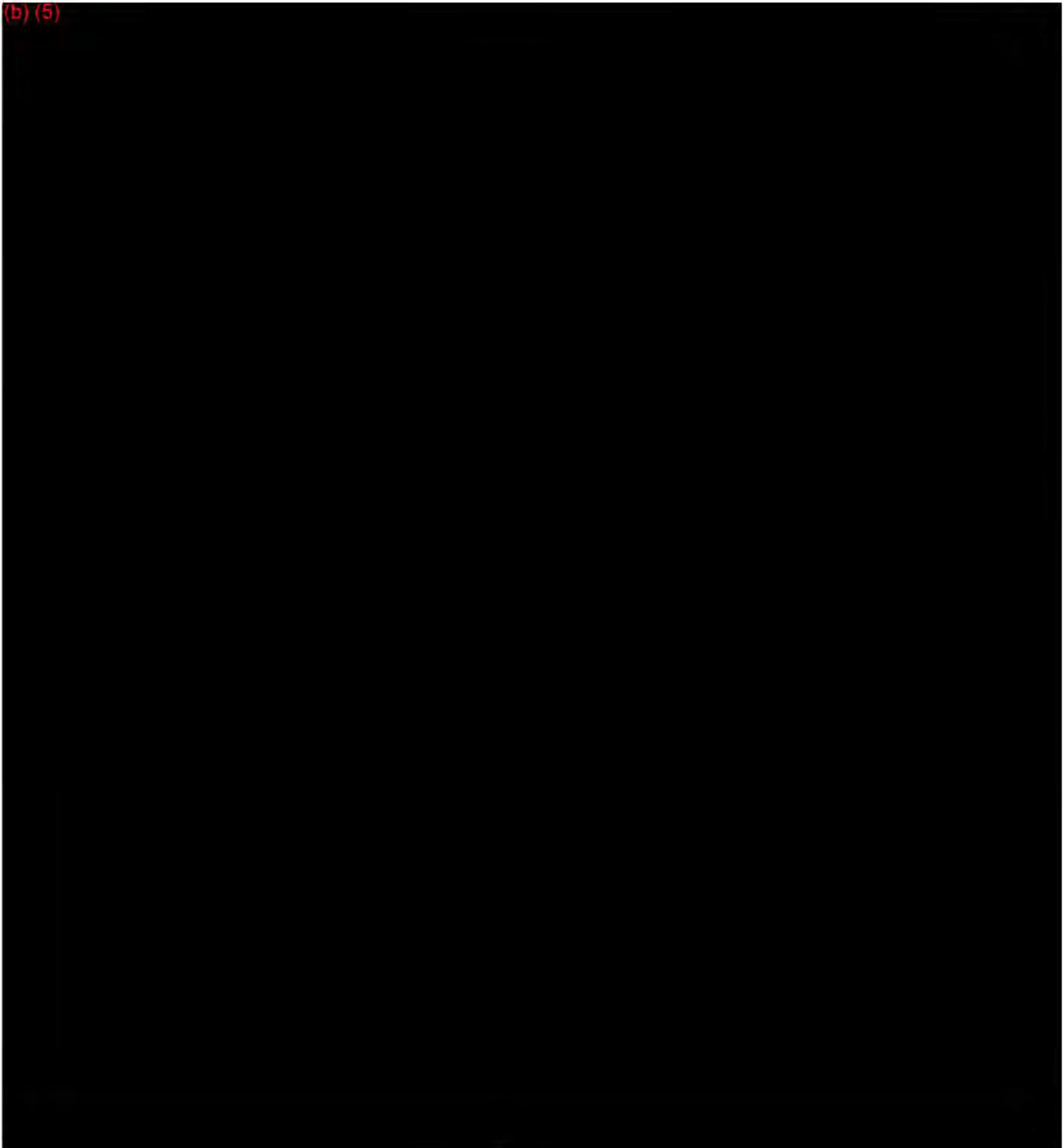
**FDA Commissioner Listening Session on Rare Diseases, Rheumatology,
Infectious Disease and Cystic Fibrosis**

Stakeholder Timeline of presentation:

- | | | |
|---------------------|--------------------------|--|
| 10:05 to 10:10 a.m. | <input type="checkbox"/> | American College of Rheumatology
David Borenstein, M.D., Past President |
| 10:10 to 10:15 a.m. | <input type="checkbox"/> | Arthritis Foundation
Ann M. Palmer, B.S., President and CEO |
| 10:15 to 10:20 a.m. | <input type="checkbox"/> | <u>FDA Clarification</u> |
| 10:20 to 10:25 a.m. | <input type="checkbox"/> | Infectious Disease Society of America
Christopher D. Busky, CAE, CEO |
| 10:25 to 10:30 a.m. | <input type="checkbox"/> | American Society for Microbiology
Janet Shoemaker, Director, Office of Public Affairs |
| 10:30 to 10:35 a.m. | <input type="checkbox"/> | <u>FDA Clarification</u> |
| 10:35 to 10:40 a.m. | <input type="checkbox"/> | National Organization for Rare Disorders (NORD)
Paul Melmeyer, Associate Director of Public Policy |
| 10:40 to 10:45 a.m. | <input type="checkbox"/> | Everylife Foundation
Emil D. Kakkis, M.D., Ph.D., President and Founder |
| 10:45 to 10:50 a.m. | <input type="checkbox"/> | Global Genes
Nicole Boice, Founder and CEO |
| 10:50 to 10:55 a.m. | <input type="checkbox"/> | <u>FDA Clarification</u> |
| 10:55 to 11:00 a.m. | <input type="checkbox"/> | Cystic Fibrosis Foundation
Preston W. Campbell, III, M.D., President and Chief Executive Officer |
| 11:00 to 11:05 a.m. | <input type="checkbox"/> | Parent Project Muscular Dystrophy
Pat Furlong, Founding President & CEO |
| 11:05 to 11:10 a.m. | <input type="checkbox"/> | Amyloidosis Foundation
Isabelle Lousada, President and CEO |
| 11:10 to 11:15 a.m. | <input type="checkbox"/> | Myotonic Dystrophy Foundation
Molly White, Chief Executive Officer |
| 11:15 to 11:20 a.m. | <input type="checkbox"/> | Cure SMA (Spinal Muscular Atrophy)
Kenneth Hobby, President |
| 11:20 to 11:25 a.m. | <input type="checkbox"/> | ALS Association
Patrick Wildman, Senior Vice President, Public Policy |
| 11:25 to 11:30 a.m. | <input type="checkbox"/> | Foundation for Prader-Willi Research
Theresa Strong, Director of Research Programs |
| 11:30 to 11:35 a.m. | <input type="checkbox"/> | <u>FDA Clarification</u> |
| 11:35 to 12:15 p.m. | <input type="checkbox"/> | Open Discussion |

**Stakeholder Listening Session with the FDA Commissioner:
Rare Diseases, Rheumatology, Infectious Disease and Cystic Fibrosis
BACKGROUND SUMMARY DOCUMENT**

(b) (5)



58 pages have been withheld in full as b(5) immediately following this page

From: [Evans, Dana](#)
To: [Califf, Robert](#)
Subject: Readings
Date: Thursday, December 15, 2016 7:57:34 AM
Attachments: [HHS Secretary's News Briefing for Thursday December 15 2016.msg](#)
[The FDA News Summary for Thursday December 15 2016.msg](#)
[Center for Tobacco Products News Briefing for Thursday December 15 2016.msg](#)

Smith, Celeste

From: Bulletin Intelligence <HHS@BulletinIntelligence.com>
Sent: Thursday, December 15, 2016 6:09 AM
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Subject: HHS Secretary's News Briefing for Thursday, December 15, 2016

HHS SECRETARY'S NEWS BRIEFING

THURSDAY, DECEMBER 15, 2016 6:00 AM EST

Zika Virus News:

BIRTH DEFECTS ARE COMMON FOR ZIKA-INFECTED PREGNANT WOMEN IN THE U.S.

Washington Post (12/14, Lena H. Sun)

The Washington Post reports new research published in the Journal of the American Medical Association reveals "about 6 percent of Zika-infected pregnant women in the United States had a baby or fetus with at least one birth defect related to the viral infection." Investigators analyzed data from 442 Zika-infected women "who completed their pregnancies between Jan. 15 and Sept. 22." Women who were infected with the virus during the first trimester had an 11 percent chance of delivering a child with birth defects, "underscoring earlier research that Zika poses the greatest risk early in pregnancy." The Post adds, "CDC officials said the findings show that the rate of microcephaly and other fetal abnormalities related to Zika is similar among these babies born in the United States – whose mothers were infected during travel – to the estimated rate in Brazil, the epicenter of the Zika outbreak." CDC Director Dr. Tom Frieden said in an interview Wednesday that the findings "basically puts to rest speculation that Brazil was different in some way."

More Coverage. [Birth Defects Seen In 6 Percent Of US Pregnancies With Zika \(Associated Press, 12/14, Mike Stobbe\)](#), [Babies Exposed To Zika Virus In First Trimester More Likely To Have Birth Defects, Study Says \(ABC News, 12/14\)](#), [Birth Defects Seen In 6 Percent Of Zika Pregnancies: U.S. Study \(Reuters, 12/14, Julie Steenhuisen\)](#), [Zika Virus Damages 6 Percent Of Fetuses In U.S. Study \(NBC News, 12/14, Maggie Fox\)](#), [Negative Effects Of Zika During Pregnancy More Common Than Realized \(Forbes, 12/14\)](#), [CDC Says 6 Percent Of Pregnant Women Infected With Zika Had Babies With Birth Defects \(McClatchy, 12/14, Tony Pugh\)](#), [Federal Government Awards \\$40 Million To Combat Zika In U.S. Territories \(NBC News, 12/14\)](#), [Women Giving Birth In The U.S. Vulnerable To Zika Effects : Shots \(NPR, 12/14\)](#), [New Zika Findings Reveal How Virus Does Its Damage, And Two Weapons That Might Help Fight It \(Los Angeles Times, 12/14, Melissa Healy\)](#), [Zika Virus: Six Percent Chance Of Birth Defects When Moms Infected During Pregnancy, CDC Says \(Miami Herald, 12/14\)](#), [CDC Issues Zika Travel Guidance For Texas Border City \(Washington Post, 12/14, Lena H. Sun\)](#), [CDC Issues Travel Advisory For Brownsville, Texas, Over Zika \(Reuters, 12/14, Julie Steenhuisen\)](#), [In Light Of Zika Findings, Stepped-Up Monitoring Of Children's Symptoms Urged \(Kaiser Health News, 12/14, Shefali Luthra\)](#), [CDC Issues Texas City Warning For Pregnant Women After Zika \(Associated Press, 12/14\)](#), [CDC Cautions Pregnant Women About Zika In Brownsville, Texas \(Wall Street Journal, 12/14, Melanie Evans\)](#), [CDC Declares Texas Town A 'Yellow' Zika Virus Zone \(NBC News, 12/15\)](#), [Zika Cases In Texas Prompt Warning \(Washington Examiner, 12/15\)](#), [Federal Health Officials Issue Zika Warning For Brownsville \(Texas Tribune, 12/14\)](#), [Pregnant Women Warned To Avoid Brownsville, Tex., Because Of Zika \(New York Times, 12/14, Donald G. McNeil Jr.\)](#), [The Zika Disaster Will Test The GOP's Capacity To Manage Serious Healthcare Emergencies \(Los Angeles Times, 12/14, Michael Hiltzik\)](#), [CDC Urges Pregnant Women To Postpone Travels To Brownsville \(San Antonio Express-News, 12/14\)](#), [Zika Concerns Prompt Warning For Pregnant Women Living In, Traveling To Brownsville \(Dallas Morning News, 12/14\)](#)

Flint Water News:

FLINT'S STATE OF EMERGENCY – ONE YEAR LATER

WUOM-FM Ann Arbor (MI) (12/14)

On its website, Michigan Radio reports one year has passed since the mayor of Flint declared a state of emergency because the city's water was contaminated with lead. The article points out that the Flint water crisis "attracted national outrage and sympathy, as well as millions of gallons of donated water" a year ago, but now "donations have slowed to a trickle and unfiltered water is still unsafe to drink."

More Coverage. [Lawmakers OK Quicker Notification Of Water Problems \(Detroit Free Press, 12/14\)](#), [Judge: There Was No Authority For Secretive Flint Order Jennifer Chambers \(Detroit News, 12/14, Jennifer Chambers\)](#)

Top National Stories:

SIGN-UPS FOR 2017 AFFORDABLE CARE ACT HEALTH PLANS RUN SLIGHTLY AHEAD OF LAST YEAR

Washington Post (12/14, Amy Goldstein)

The Washington Post reports that according to HHS, the number of consumers enrolling in Affordable Care Act plans through HealthCare.gov "is running slightly ahead of a year ago, even as President-elect Donald Trump and a Republican Congress prepare to dismantle the law that provides the coverage." Yet, new customers are accounting for only about 25 percent of total sign-ups so far, "compared with almost 40 percent at about the same time last year." On Wednesday afternoon, HHS Secretary Sylvia Burwell praised the enrollment figures, saying in a tweet, "Momentum building...Americans want coverage."

More Coverage. [More Than 4 Million Sign Up For Obamacare](#) (Washington Examiner, 12/14), [As Obamacare Deadline Nears, More Than 92,000 In WPB Market Sign Up](#) (Palm Beach (FL) Post, 12/14), [Obamacare Sign-Ups Top 4 Million As First Deadline Approaches](#) (Bloomberg News, 12/14, Zachary Tracer), [Obamacare Enrollment Deadline Looms Amid Questions About Replacement](#) (USA Today, 12/14, Jayne O'Donnell), [First Obamacare Deadline Looms With N.J. Signups On The Rise](#) (Press of Atlantic City (NJ), 12/14), [Snapshot Shows 1.1 Million New Obamacare Enrollees](#) (Congressional Quarterly, 12/14), [4 Million People Sign Up For Obamacare As Deadline Nears](#) (CNN Money, 12/14), [Obamacare Sees Strong Enrollment Despite Price Hikes, Repeal Threats](#) (U.S. News & World Report, 12/14, Kimberly Leonard), [Obamacare Sign-Ups Close To Last Year](#) (Morning Consult, 12/14), [Obamacare Signups Soaring As Deadline Nears](#) (North Jersey (NJ) Media Group, 12/14), [As Obamacare Deadline Looms, Illinois Sign-ups On Rise Despite Uncertainty](#) (Chicago Tribune, 12/14)

Health Reform & Healthcare:

BURWELL URGES CONSUMERS TO ENROLL IN ACA PLANS DURING INTERVIEW

MSNBC's Morning Joe (12/14)

MSNBC's Morning Joe interviewed HHS Secretary Sylvia Burwell about whether consumers should be enrolling in Affordable Care Act plans, given that Republicans have vowed to repeal the healthcare law in January. Burwell explained that the current ACA open enrollment period is ongoing, but people must sign up by December 15 for coverage which begins on January 1. Asked what will happen to ACA plans in 2017, Burwell said coverage for next year should not be disrupted by any changes. In the long run, however, "repeal would mean important things for the 20 million who have become insured, or for any American who has a pre-existing condition and gets insurance through their job, or if your child is on a policy up to 26, or if you use any of those preventive services without co-pays." Burwell also urged Americans to contact their Republican lawmakers, and tell them why it is crucial to preserve as much of the ACA as possible.

HEALTH CHIEF: GOP PLAN IS REALLY 'REPEAL AND COLLAPSE'

The Hill (12/14, Sarah Ferris)

The Hill reports that during an interview with PBS Newshour this week, Burwell gave "her starkest post-election outlook yet about the fate of ObamaCare, warning that the GOP's plan will immediately unravel the insurance marketplace." She said, "The idea of 'repeal and replace' is really, 'repeal and collapse.'" The article says Burwell "is now emerging as a vocal critic of the GOP's push to sign a repeal bill within Donald Trump's first 100 days as president." She warned that repealing the ACA will push insurers to raise prices, or to decide not to enter certain markets due to uncertainty.

BOOKER GEARING UP FOR OBAMACARE FIGHT

Politico (12/14)

Politico reports that on Wednesday, Sen. Cory Booker (D-NJ) joined HHS Secretary Sylvia Burwell in a last-ditch effort "to encourage people to sign up for Obamacare plans before the Dec. 15 deadline for coverage starting Jan. 1." According to Booker, "Republicans are caught in a bind when it comes to repealing President Obama's signature health care law." He added, "Republican[s] and Democrats around this country do not want to go back to a time where children were being kicked off their parents' health insurance, where people were being denied health insurance because of pre-existing conditions, where people were being denied health insurance...for trivial manners and giving health insurance companies that kind of power."

More Coverage: TV. [Sen. Booker Joins Burwell In Encouraging Consumers To Sign Up For ACA Coverage](#) (News 12-TV New Jersey, 12/14)

More Coverage: Print and Online. [At N.J. Diner, Cory Booker Vows To Fight Obamacare Repeal Effort](#) (New Jersey Local News, 12/14), [Booker Says He Is Ready To Fight For Obamacare](#) (New York Observer, 12/14), [Booker Comes To Diner To Tout Health Insurance, Vow Fight](#) (Washington Times, 12/14), [Political Leaders Urge NJ Residents To Sign Up For ACA](#) (NJTV Trenton (NJ), 12/14), [Sen. Cory Booker, Health Secretary Sylvia Burwell Tout Affordable Care Act](#) (News

GOP COALESCING AROUND TAX CUTS, GUTTING OBAMACARE FOR AGENDA

Politico (12/14, Burgess Everett)

Politico reports Donald Trump's transition team and congressional Republicans "are coalescing around an agenda focused on slashing taxes and repealing Obamacare early next year, a blueprint that could potentially avoid an intraparty clash over infrastructure investment early in Trump's presidency." Incoming White House Chief of Staff Reince Priebus said on Wednesday that "the GOP will concentrate on budgetary issues and health care reform in the first nine months of the year," a strategy which "largely overlaps with House Speaker Paul Ryan and Senate Majority Leader Mitch McConnell's focus on tax reform and Obamacare repeal, and suggests the party will spend much of its energy and momentum on those two issues." Priebus is quoted as saying, "We're probably going to lead with Obamacare repeal and replace."

More Coverage. [Priebus Tells Hugh Hewitt Trump's First Move In Office, And It's Bad News For You Obamacare Fans \[VIDEO\]](#) (Daily Caller, 12/14, Christian Datoc)

TRUMP'S PICKS FOR AGRICULTURE, HOUSING COULD AFFECT AMERICANS' HEALTH

Fortune (12/14)

Fortune reports that President-elect Donald Trump "and the incoming GOP Congress could change the face of American health care in significant ways." Given Trump's strong opposition to the Affordable Care Act, as well as House Speaker Paul Ryan's (R-WI) and HHS nominee Tom Price's (R-GA) "support for both repealing the law and scaling back social safety net programs like Medicare and Medicaid, several of the nation's largest entitlements may see major transformations." Yet, Trump's nominees for other cabinet posts such as the Department of Agriculture and HUD "may also harbor consequences for Americans' wellness." The article explains that is "because access to basic social needs like heating, electricity, food, and medicine can play a significant role in health outcomes, according to a new study published in the journal JAMA Internal Medicine."

More Coverage. [Donald Trump's Impact On American Health Goes Well Beyond Obamacare](#) (Fortune, 12/14)

TRUMP TO MEET WITH OBAMACARE ARCHITECT

The Hill (12/14, Lisa Hagen)

The Hill reports President-elect Donald Trump is scheduled to meet with Zeke Emanuel, one of the architects of the Affordable Care Act, on Wednesday. The two will meet at Trump Tower in Manhattan. The article says that although Trump has vowed to repeal the ACA, "since the election, he has expressed a willingness to keep some parts of the law intact."

More Coverage. [Trump To Meet Wednesday With Obamacare Architect](#) (Washington Examiner, 12/14), [Trump To Meet With Chief Architect Of Obamacare](#) (Daily Caller, 12/14, Robert Donachie), [Trump Meets With Obamacare Architect, Rahm Brother, Zeke Emanuel](#) (Chicago Sun-Times, 12/14), [Donald Trump Meeting With ObamaCare Architect](#) (New York Post, 12/14)

KEVIN BRADY CALLS LAWMAKERS BACK TO WASHINGTON TO PLAN OBAMACARE REPEAL

Houston Chronicle (12/14, Kevin Diaz)

The Houston Chronicle reports Rep. Kevin Brady (R-TX), "who has emerged as the point man on House GOP efforts to undo Obamacare, called in all the Republican members of his tax-writing panel Wednesday for a rare, recess conference." The article says Brady, who is chairman of the Ways and Means Committee, brought his colleagues back to DC to prepare "a GOP plan on taxes and health care in advance of the new administration of President-elect Donald Trump."

More Coverage. [GOP Huddles On Obamacare Replacement](#) (Washington Examiner, 12/14)

THESE ARE THE HEALTHIEST AND UNHEALTHIEST STATES IN THE COUNTRY

USA Today (12/15, Mary Bowerman)

USA Today says that according to a survey sponsored by United Health Foundation, Hawaii is the healthiest state in the US for the fifth straight year. Data show that although "smoking among U.S. adults decreased by 41% since the start of the report in 1990, and the percentage of the population that is uninsured decreased by 35% in the past five years, for the first time in the report's history, cardiovascular deaths increased over the past year." In addition, during the last "two years, the rate of premature death has also increased." The survey revealed that "Hawaii ranked first in overall health, with a low percentage of uninsured people, low rates of obesity and a low prevalence of obesity," while Mississippi dropped from 49th to 50th this year. The article points out that the survey is based on data from the CDC, the American Medical Association, the Census Bureau, and the FBI.

HARRY REID ON THE GOP: 'THEY DON'T HAVE ENOUGH NERVE TO REPEAL OBAMACARE'

Huffington Post (12/14)

The Huffington Post reports outgoing Senate Minority Leader Harry Reid (D-NV) said in an interview that Republicans "don't have the nerve to repeal Obamacare. And if they do, they are just a lot more visionless than I can imagine." He adds that the GOP will "rue the day" if they repeal the law. Reid also said Republicans "might not mind – and might even welcome – such deterioration in the hopes that it would pressure Democrats to negotiate a new health care regime."

OBAMA ADMINISTRATION BLOCKS STATES FROM CUTTING OFF GRANTS TO PLANNED PARENTHOOD

Washington Post (12/14, Sandhya Somashekhar)

The Washington Post reports the Obama Administration issued a rule that would restrict states' ability to block organizations from receiving Title X funding. The rule is "designed" to prevent states from blocking Title X funding for Planned Parenthood and other organizations on the grounds that they provide abortions.

More Coverage. [Obama Administration Bars States From Withholding Federal Money From Planned Parenthood](#) (New York Times, 12/14, Jackie Calmes), [Obama Blocks States From Defunding Planned Parenthood](#) (Huffington Post, 12/14, Laura Bassett), [New Rule Protects Planned Parenthood Funding At State Level](#) (The Hill, 12/14, Sarah Ferris), [Obama Bans States From Defunding Clinics That Offer Abortion](#) (New York Magazine, 12/14), [Obama Administration Blocks States From Defunding Planned Parenthood](#) (U.S. News & World Report, 12/14, Kimberly Leonard), [Feds Bar States From 'Defunding' Planned Parenthood](#) (Associated Press, 12/14), [Obama Moves To Protect Planned Parenthood Funding : Shots](#) (NPR, 12/14), [Obama Administration Shores Up Protections For Planned Parenthood](#) (Reuters, 12/14, Julie Steenhuysen)

TRUMP DOESN'T JUST THREATEN BARACK OBAMA'S LEGACY. HE COULD RUIN MICHELLE'S, TOO.

Washington Post (12/14, Caitlin Dewey)

The Washington Post "Wonkblog" reports President-elect Donald Trump could "roll back" some of the public health and nutrition initiatives that were fostered by First Lady Michelle Obama. Some supporters of Michelle Obama's work to reduce childhood obesity and improve nutrition are concerned that Trump "will uproot the healthy food movement Obama has championed."

U.S. HOUSE MEMBERS WANT AUDIT OF FEDERAL DOG EXPERIMENTS

McClatchy (12/14, Rob Hotakainen)

McClatchy reports US Rep. Mike Simpson (R-ID) and other members of the House wrote a letter to the Government Accountability Office are calling for a federal audit of experiments conducted by federal agencies that involved dogs. The White Coat Waste Project, "a group that wants to stop the animal testing and force the agencies to disclose more information on exactly what they've been doing," says that five federal agencies, including the CDC, FDA, and NIH, used 294 dogs in experiments last year.

ANESTHESIA MAY HARM THE BRAINS OF CHILDREN UNDER 3, FDA WARNS

Washington Post (12/14, Laurie McGinley)

In "To Your Health," the Washington Post reports the Food and Drug Administration "warned Wednesday that repeated or lengthy use of general anesthesia or sedation drugs for children younger than 3 or pregnant women in their third trimester may affect youngsters' developing brains."

More Coverage. [FDA Warns That Repeated Anesthesia Exposure Could Hurt Young Brains](#) (STAT, 12/14), [Surgery On Babies Risks Brain Damage](#) (HCP Live, 12/14), [Anesthesia May Harm Brains Of Kids Under 3, FDA Warns](#) (New York Magazine, 12/14)

Blogs:

SELLING ACROSS STATE LINES GOP OBAMACARE REPLACEMENT TRIED AND FAILED

Business Insider (12/14, Bob Bryan)

In a blog entry for the Business Insider, Bob Bryan writes that the Republican idea of selling health insurance across state lines has "been tried, and it hasn't worked." What's more, "the National Association of Insurance Commissioners has come out against the idea of allowing plans across state lines," fearing that "if insurers begin to abuse rules, it would be difficult for state-level regulators to assist patients across the country."

WHA!? GOP NOW CLAIMS OBAMACARE DOESN'T REALLY AFFECT THAT MANY PEOPLE

Talking Points Memo (12/14, Lauren Fox and Tierney Sneed)

In a blog entry for the Talking Points Memo, Lauren Fox and Tierney Sneed write now that Republicans are "on the verge of upending Obamacare, they are claiming that its reach is not so big after all." All of a sudden, the problems involving the

Affordable Care Act – “and the number of people that repealing it will affect – are ‘relatively small.’” Fox and Sneed characterize “this reduction in rhetorical scope” as “striking, given the language Republicans used to denounce the” ACA since 2010.

A RETURN TO THE ‘OLD NORMAL?’

Health Affairs (12/14, Yevgeniy Feyman)

In a blog entry for Health Affairs, Yevgeniy Feyman, a senior research assistant in the department of Health Policy and Management at the Harvard T.H. Chan School of Public Health, writes, “It’s becoming ever more clear that the unexpected and remarkably consistent slowdown in health care spending that began in the early 2000s is” finished. Now, “according to updated data from the economists and statisticians at the Centers for Medicare and Medicaid Services, 2015’s health spending hit \$3.2 trillion, growing at 5.8 percent from” the previous year. That puts “us ever closer to the growth rate just before the Great Recession, when health spending grew around 6.5 percent.”

US INPATIENT EMERGENCY DEPARTMENT CASES MAY LEAD TO SURPRISE MEDICAL BILLS

Health Affairs (12/14)

In a blog entry, Health Affairs writes, “A new study, released by Health Affairs as a Web First,” examines “surprise medical bills – an unexpected bill from an out-of-network provider or a bill from an out-of-network provider not chosen by a patient.” The study revealed that “in 2014, 20 percent of US hospital inpatient admissions originating in the emergency department (ED), 14 percent of outpatient visits to the ED, and 9 percent of elective inpatient admissions likely led to a surprise medical bills.” The study also concluded that “the rate of surprise medical bills may be even higher for patients with Marketplace plans, since many of these plans have narrow hospital and physician networks, something Marketplace customers are likely not to realize.”

Opinion:

CALL PAUL RYAN’S BLUFF ON OBAMACARE

Washington Post (12/14, Jennifer Rubin)

Jennifer Rubin writes in the Washington Post “Right Turn” blog that one does not have to believe the Affordable Care Act “is perfect or even the best health-care system we can devise to think its repeal would be problematic, to say the least.” She argues that House Speaker Paul Ryan (R-WI) wants to repeal the ACA immediately, yet “by cutting revenue to support the exchange subsidies, Republicans risk eliminating coverage for tens of millions.” Meanwhile, Ryan has not convinced “all Republicans that it is politically smart to yank the plug on Obamacare with no alternative ready to go.”

REAL PEOPLE RELY ON OBAMACARE: COLUMN

USA Today (12/15, Topher Spiro)

Topher Spiro, vice president for health policy at the progressive think tank Center for American Progress, writes in a USA Today column that as congressional Republicans prepare to repeal the Affordable Care Act, “we at the Center for American Progress (CAP) are collecting stories from people who would be affected,” and in certain instances, whose “very lives are at stake.” Spiro recounts the stories of several Democratic voters who say the ACA literally saved their lives, and adds that “more than 20 million Americans of all political persuasions have insurance under the law, and many are terrified that they will lose a great source of peace of mind and financial security.”

NEW LAW EASES SMALL BUSINESS HEALTH CARE BURDEN (BUT MAY MAKE REPEALING OBAMACARE HARDER)

Forbes (12/14, Robb Mandelbaum)

Robb Mandelbaum writes in a Forbes piece that President Obama signed the 21st Century Cures Act into law on Tuesday, and points out that the law includes a provision which may encourage small businesses to stop offering group plans, and instead reimburse employees for individual coverage. According to Mandelbaum, this could help ACA advocates who want to prevent the healthcare law from being repealed.

LESSONS FROM CALIFORNIA’S SUCCESSFUL IMPLEMENTATION OF OBAMACARE

Sacramento (CA) Bee (12/14, Micah Weinberg)

Micah Weinberg writes in a Sacramento (CA) Bee op-ed that before moving forward with plans to repeal the Affordable Care Act, congressional Republicans “should look to California’s success in implementing the law.” He argues that it is crucial that “some of these lessons of this success” not “be misinterpreted or ignored.”

MAINTAIN AND IMPROVE MEDICARE INNOVATION

The Hill (12/14, Mary Grealy and Ted Okun)

Mary Grealy, President of the Healthcare Leadership Council, and Ted Okun, Executive Director of the Community Oncology Alliance, write in The Hill “Congress Blog” that as congressional Republicans and the Trump Administration “prepare to embark on significant changes to federal healthcare policy, we should not lose sight of an important goal:

making Medicare and Medicaid, which serve the health needs of tens of millions of Americans, more value-driven by enhancing patient quality and controlling costs." They argue that lawmakers should maintain the Center for Medicare and Medicaid Innovation, which is an "agency charged with testing new healthcare delivery and payment innovations, while instituting improvements that ensure beneficiary safety."

21ST CENTURY CURES ACT AND REVITALIZING THE BIOPHARMA INDUSTRY

The Hill (12/14, Jonathan C. Javitt)

Jonathan C. Javitt, the founder and CEO of NeuroRx Inc., writes in The Hill "Pundits Blog" that the 21st Century Cures Act "potentially heralds a new era of" healthcare leadership by the US through reforming the FDA approval process, which will help pharmaceutical and biotech companies bring new products to market. Javitt argues that the pharmaceutical and biotech industries have been stagnant under the Obama Administration, but the partnership between the FDA and the NIH will be the "economic engine" that improves the industries.

CURES ACT: HEALTHCARE INNOVATION, GRAB BAG GIVEAWAY, OR BOTH?

The Hill (12/14, Harry Nelson)

Harry Nelson, the founding and managing partner of Nelson Hardiman LLP, writes in an opinion piece in The Hill "Pundits Blog" that the 21st Century Cures Act "could have a more immediate impact" than the "the impending repeal of the Affordable Care Act." Nelson argues that the new law "will translate to significant immediate funding for medical research, investment and treatment for people suffering from mental health illness and addiction," unlike the repeal of the Affordable Care Act, which could be delayed and "ultimately take years to unwind."

A FREE-MARKET APPROACH TO HEALTH CARE

Washington Times (12/14, Andy Lazris)

Andy Lazris, a physician, writes in the Washington Times that a free-market medical system "would not use financial incentives but rather health-outcome incentives to help patients negotiate the health care morass." A conservative approach to healthcare reform, Lazris says, is a free-market system that should "allows patients to be treated at home if that is what they prefer; that pays doctors more to think and discuss, and less to perform tests and procedures; that assures patients can access accurate information before being forced to make profound medical decisions; and that eliminates protocol-based treatment." To get such a system implemented, both Democrats and Republicans "must confront powerful special interests who are now calling the shots and who would be financial losers from genuine changes."

SUNSET OBAMACARE

Washington Times (12/14, Matt Mackowiak)

Matt Mackowiak, president of Potomac Strategy Group, writes in an op-ed for the Washington Times that "Obamacare is objectively failing," pointing out that "several states only have one exchange" and health insurance companies are exiting, "with all eyes on what the individual Blue Cross state plans do in the next 60 days." Mackowiak supports repealing the ACA but questions what its replacement will be. He also says, "There will need to be a consensus around one proposal, between the Trump administration, Capitol Hill Republicans, and whichever Democrats can join the coalition." Another question is, "what do you do about those who are covered by the guaranteed issue...or by staying on their parents until age 26?" By establishing a date by which to sunset the ACA, it could give the healthcare industry enough time to "prepare for the transition and the markets can calmly receive the news."

HOW TO SAVE HEALTHCARE FROM THE OBAMA LEGACY

The Hill (12/14, Jared Whitley)

Contributor Jared Whitley writes in The Hill's "Pundits" blog that modern healthcare "doesn't follow standard consumer trends," but applying "market principles to help cut through the maze is difficult but rewarding and – ultimately – necessary for saving money and lives in the long run." Whitley says price controls "force people to wait for what they need" and calls for the dismantling of the IPAB and CMMI provisions of the Affordable Care Act, "while Medicare Part D must be protected." According to Whitley, HHS nominee Rep. Tom Price (R-GA) is "the best person to lead us through this maze."

National Front Page News:

HEADLINES FROM TODAY'S FRONT PAGES.

Wall Street Journal:

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[Yellen And Trump On The Same Page, For Now](#)

[Trump Tells Tech Chiefs He Will Foster Innovation](#)

[Yahoo Discloses New Breach Of 1 Billion User Accounts](#)

[In Syria, Russia Acts As US Pulls Back](#)

New York Times:

Yahoo Says 1 Billion User Accounts Were Hacked

Multimedia Feature: How The World Closed Its Eyes To Syria's Horror

A Man Is Shot In The Back, And Only The Police Are Kept In The Dark

To Combat Trump, Democrats Ready A GOP Tactic: Lawsuits

Fed Raises Key Interest Rate, Citing Strengthening Economy

Washington Post:

Trump Adviser Shared Secrets "Inappropriately"

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Oil, Gas Allies Amass Power

As More Players Take "The Leap," The NFL May Ban It

"Chaos" Theory Is Working For Putin

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Smith, Celeste

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TO: THE COMMISSIONER AND SENIOR OFFICIALS

DATE: THURSDAY, DECEMBER 15, 2016 6:00 AM EST

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FDA IN THE NEWS

FDA Commissioner Says Agency Is Ready To Take Advantage Of Opportunities Created By 21st Century Cures Act. [Health IT Analytics](#) (12/14, Bresnick) reports FDA Commissioner Dr. Robert M. Califf said the agency is ready to take advantage of the opportunities created by the 21st Century Cures Act. Califf said in a blog post that the law will help the FDA advance treatments by removing some requirements for new therapies to come to market. The article extensively quotes Califf's blog post explaining how the law will help the FDA. The article mentions that the law will provide additional funding to the National Institutes of Health.

States Competing For Grants To Fight Opioid Addiction Under 21st Century Cures Act. The [Connecticut Mirror](#) (12/14, Radelat) reports states are now competing for the \$1 billion in grants to fight opioid addiction authorized by the 21st Century Cures Act. Sen. Richard Blumenthal (D-CT) wrote a letter to HHS Secretary Sylvia Burwell and Attorney General Loretta Lynch that said, "As the opioid epidemic continues to spread, I urge the federal agencies tasked with distributing these funds to ensure that Connecticut receives a fair and ample allocation." Blumenthal cited statistics about drug overdoses in the state, but the article points out that "Connecticut is not among the top states as far as overdose-related deaths," according to the Centers for Disease Control and Prevention.

The [Connecticut Post](#) (12/14, Ryser, 268K) reports Blumenthal and Sen. Chris Murphy (D-CT) are both advocating for Connecticut to receive its "full share of funding to combat the opioid epidemic" from the 21st Century Cures Act. Blumenthal and Murphy have both contacted HHS Secretary Sylvia Burwell and others to advocate for Connecticut.

Opinion: 21st Century Cures Act Could Restore US As Global Healthcare Leader. Jonathan C. Javitt, the founder and CEO of NeuroRx Inc., writes in [The Hill](#) (12/14, Javitt, Contributor, 1.25M) "Pundits Blog" that the 21st Century Cures Act "potentially heralds a new era of" healthcare leadership by the US through reforming the FDA approval process, which will help pharmaceutical and biotech companies bring new products to market. Javitt argues that the pharmaceutical and biotech industries have been stagnant under the Obama Administration, but the partnership between the FDA and the NIH will be the "economic engine" that improves the industries.

Opinion: 21st Century Cures Act Could Have More Immediate Impact Than Potential Repeal Of Affordable Care Act. Harry Nelson, the founding and managing partner of Nelson Hardiman LLP, writes in an opinion piece in [The Hill](#) (12/14, Nelson, Contributor, 1.25M) "Pundits Blog" that the 21st Century Cures Act "could have a more immediate impact" than the "the impending repeal of the Affordable Care Act." Nelson argues that the new law "will translate to significant immediate funding for medical research, investment and treatment for people suffering from mental health illness and addiction," unlike the repeal of the Affordable Care Act, which could be delayed and "ultimately take years to unwind."

FDA Approves Treatment For Mild To Moderate Atopic Dermatitis. [Reuters](#) (12/14, Berkrot) reports the Food and Drug Administration approved Eucrisa [crisaborole] for the treatment of mild to moderate atopic dermatitis, or eczema. In clinical trials, many patients who received crisaborole "experienced clear or almost clear skin after 28 days of treatment." The FDA said the drug's most common side effect is "application site pain, including burning or stinging."

[Medscape](#) (12/14, Brown, 339K) reports Amy Egan, the deputy director of the FDA's Office of Drug Evaluation III, said in a news release, "Today's approval provides another treatment option for patients dealing with mild to moderate atopic dermatitis."

Drugmakers Push Lucrative, But Unproven Abuse-Deterrent Opioids. A joint investigation by the [AP](#) (12/15) and the Center for Public Integrity reports that drugmakers are pushing "harder-to-manipulate" opioids

known as abuse-deterrent formulations (ADFs) "that have racked up billions in sales, even though there's little proof they reduce rates of overdoses or deaths." While making painkillers more difficult to abuse "is a common-sense step," it is also a "multibillion-dollar sales opportunity, allowing drugmakers to corner the market with their newly patented, higher-priced versions." According to the article, the FDA is walking a "careful line on the new drugs," simultaneously "promoting them as a promising approach to discouraging abuse" while acknowledging that the agency has not concluded ADFs have a "real-world impact" on measures like overdose deaths, said Dr. Douglas Throckmorton, an FDA deputy inspector. CDC Director Tom Frieden said, "Abuse-deterrent' sounds to people sometimes like 'Oh, maybe it's not addictive.' But it's no less addictive." Nevertheless, Throckmorton said in a recent statement that the agency by projections "that the reformulations will eventually translate into public health results."

FDA Warns On 11 Anesthetics That May Harm Developing Brains In Fetuses And Very Young Children. In "To Your Health," the [Washington Post](#) (12/14, McGinley, 11.43M) reports the Food and Drug Administration "warned Wednesday that repeated or lengthy use of general anesthesia or sedation drugs for children younger than 3 or pregnant women in their third trimester may affect youngsters' developing brains."

[STAT](#) (12/14, Joseph) reports the agency announced Wednesday that it will begin to require new warnings on certain anesthetic and sedation drugs. STAT says, "The warnings will...pertain to procedures that last longer than three hours or to repeated exposure to the drugs." Eleven drugs "will be required to add the warnings to their labels." In light of the new warning, FDA's Center for Drug Evaluation and Research Director Dr. Janet Woodcock said, "We recognize that in many cases these exposures may be medically necessary and these new data regarding the potential harms must be carefully weighed against the risk of not performing a specific medical procedure." Also covering the story are [HealthDay](#) (12/14, Preidt, 21K), [Medscape](#) (12/14, Brooks, 339K), [New York Magazine](#) (12/14, 6.86M) and [HCP Live](#) (12/14, Scott, 2K).

Opinion: Incoming FDA Commissioner Needs To Inspire Staff, Be Fearless In Executing Agency's Mission To Promote Health. In an opinion piece for [The Hill](#) (12/14, 1.25M) "Contributors" blog, Joseph Gulfo, executive director of the Rothman Institute of Innovation and Entrepreneurship at Fairleigh Dickinson University, writes that President-elect Donald Trump needs to appoint a Food and Drug Administration commissioner that "can inspire its staff," a person who is "fearless in executing

the agency's congressionally mandated mission to promote health." The incoming FDA commissioner "needs to project pride in FDA decisions and engender confidence in the American people that the FDA is more interested in the well-being of patients than its own image." The agency also "needs to get back to its lawful mission, which is to promote health," as well as return to using "safety and effectiveness as the sole basis of approval."

Trump's FDA Candidates Support Faster Drug Approvals. The Washington Examiner (12/15, King, 400K) reports that one of President-elect Donald Trump's candidates to lead the FDA, Jim O'Neill, managing director at the investment firm Mithril Capital, has previously called on the agency to "approve drugs based solely on safety and not on effectiveness, a radical departure from the current approach." Another candidate, "agency veteran and physician" Scott Gottlieb, has advocated a "different regulatory approach at the agency, but hasn't gone to the same extremes as O'Neill." He supports the 21st Century Cures Act because it would "enable the agency to approve drugs using a different clinical endpoint called a surrogate measure."

Trump's Nominees For USDA, HUD Could Also Impact Health. Fortune (12/14, Mukherjee, 7.12M) reports that President-elect Donald Trump "and the incoming GOP Congress could change the face of American health care in significant ways." Given Trump's strong opposition to the Affordable Care Act, as well as House Speaker Paul Ryan's (R-WI) and HHS nominee Tom Price's (R-GA) "support for both repealing the law and scaling back social safety net programs like Medicare and Medicaid, several of the nation's largest entitlements may see major transformations." Yet, Trump's nominees for other cabinet posts such as the Department of Agriculture and HUD "may also harbor consequences for Americans' wellness." The article explains that is "because access to basic social needs like heating, electricity, food, and medicine can play a significant role in health outcomes, according to a new study published in the journal JAMA Internal Medicine."

Meanwhile, Clifton Leaf writes in a Fortune (12/14, 7.12M) piece that according to Mukherjee's post, President-elect Donald Trump's nominees "for various cabinet posts – apart from his selection of Rep. Tom Price to head the Department of Health and Human Services – could well have a significant effect on Americans' health and well-being over the next several years." Clifton mentions Thomas McKeown's "controversial" 1976 treatise which maintained that "it wasn't medical interventions that were most responsible for the decline in mortality (and subsequent flourishing of the population) in" England and Wales, but rather "better sanitation, nutrition, and other 'external influences.'"

Potential FDA Chief May implement Progressive Approval For Drugs. Forbes (12/14, 15.17M) carries a

piece by contributor Patrick Cox who writes President-elect Donald Trump's "potential FDA chief...is Jim O'Neill," who has publicly supported proposals to do away with the FDA's requirement for phase 2 and 3 trials." Instead, O'Neill favors "progressive approval" of drugs and other medical technologies." If he is approved "he could implement progressive approval for drugs. But he would face fierce opposition from those who profit from the current system." Potential FDA Chief May implement Progressive Approval For Drugs. Forbes contributor Patrick Cox writes President-elect Donald Trump's "potential FDA chief...is Jim O'Neill," who has publicly supported proposals to do away with the FDA's requirement for phase 2 and 3 trials." Instead, O'Neill favors "progressive approval" of drugs and other medical technologies." If he is approved "he could implement progressive approval for drugs. But he would face fierce opposition from those who profit from the current system."

FDA's Woodcock Discusses DMD Drug Approval, Effect Of Cures Act On FDA. CNBC (12/14, Tirrell, 2.17M) features an interview with the Food and Drug Administration's Center for Drug Evaluation and Research Director Dr. Janet Woodcock, in which she touches on the agency's approval process of Sarepta Therapeutics' experimental drug for Duchenne muscular dystrophy and discusses the effect of the 21st Century Cures Act on the FDA. Woodcock also opines on the influence that the new president may have on drug regulation.

MEDICAL PRODUCT SAFETY

Group Of House Members Calls For Federal Audit Of Federal Agencies Using Dogs In Experiments. McClatchy (12/14, Hotakainen, 74K) reports US Rep. Mike Simpson (R-ID) and other members of the House wrote a letter to the Government Accountability Office are calling for a federal audit of experiments conducted by federal agencies that involved dogs. The White Coat Waste Project, "a group that wants to stop the animal testing and force the agencies to disclose more information on exactly what they've been doing," says that five federal agencies, including the CDC, FDA, and NIH, used 294 dogs in experiments last year.

Noninvasive Cancer Treatment Device Could Be Safe And Effective Alongside Paclitaxel For Patients With Recurrent Ovarian Cancer, Phase 2 Study Suggests. Fierce Biotech (12/14, Al Idrus, 2K) reports Novocure's Optune device, a noninvasive cancer treatment, "is safe and effective when delivered alongside paclitaxel to patients with recurrent ovarian cancer,"

according to data from a phase 2 study. Optune was originally approved by the FDA in 2011 to treat patients with recurrent glioblastoma, and later gained an expanded indication "as a first-line therapy for the brain cancer."

FDA Issues Warning Letter To Pocono Coated Products For Poor Product Testing.

Fierce Pharma (12/14, Palmer, 3K) reports the Food and Drug Administration issued a warning letter to Pocono Coated Products, which manufactures transdermal patches and other products, because of poor product testing. In the warning letter, the FDA said, "test results demonstrating that your product was subpotent indicate that your un-validated manufacturing process is not capable of consistently delivering products that meet their specifications." The article mentions that some of the company's patches were recently recalled by one of its customers.

FDA Criticizes Sanofi, Celgene For TV Ads That Obscure Risk Information.

Fierce Pharma (12/14, Bulik, 3K) reports the FDA's Office of Prescription Drug Promotion sent untitled letters to Sanofi and Celgene for television ads promoting Toujeo (insulin glargine) and Otezla (apremilast), respectively. The letters claimed the ads made "false or misleading representations about the risks associated with" the featured drug, a violation of the Food, Drug and Cosmetics Act. The letters said the casual usage of images and music that accompany the individual ads' disclosures are distracting and make it difficult for the consumer to process the drugs' side effects. STAT (12/14, Silverman) also reports on this story.

Georgia Pharmacists Can Now Dispense Naloxone.

The AP (12/14) reports Georgia Gov. Nathan Deal asked the state Department of Public Health to allow pharmacists to dispense the anti-opioid overdose drug naloxone. The Georgia Board of Pharmacy "also has removed the drug from its dangerous drug list."

Group Files Suit Against FDA Over Formaldehyde Use In Hair-Straightening Products.

CNN (12/14, Scutti, 29.79M) reports the Environmental Working Group filed a lawsuit Wednesday charging the Food and Drug Administration "with failure to respond to the danger posed by hair-straightening treatments that contain formaldehyde, a known carcinogen." Scott Faber, the group's senior vice president of government affairs, "said the group is ultimately asking the FDA to examine whether a warning is required" on the hair products and "also wants the FDA to examine whether methylene glycol (a form of formaldehyde) should be used at all in these products and, if so, what amount is permissible."

Long-Term Regular Use Of NSAIDs May Be Linked To Higher Risk Of Hearing Loss In Women.

The New York Times (12/14, Bakalar, Subscription Publication, 13.9M) "Well" blog reports that research published in the American Journal of Epidemiology suggests "long-term use of pain relievers may increase the risk for hearing loss."

TIME (12/14, Park, 6.98M) reports that investigators "found that people who reported using an NSAID like ibuprofen or acetaminophen for more than six years showed 9% to 10% higher risk of having hearing loss more than a decade later." Meanwhile, "those who used aspirin did not show similar problems with hearing."

FDA Approves Crisaborole As A Treatment For Atopic Dermatitis In Patients Ages Two Years And Older.

MedPage Today (12/14, Gever, 97K) reports that the FDA has "approved crisaborole (Eucrisa) as a treatment for eczema – known technically as atopic dermatitis – in patients ages 2 years and older." The medication's "approval was based on two phase III trials, reported earlier this year at the American Academy of Dermatology annual meeting."

App-Based Ultrasound Scanners Receive 510(k) Clearance From FDA.

Aunt Minnie (12/14, 1K) reports, "Ultrasound technology start-up Clarius Mobile Health has received 510(k) clearance from the" FDA "for its Clarius C3 and Clarius L7 app-based ultrasound scanners."

FOOD SAFETY

FDA Approves Genetically Engineered Pink Pineapple.

NBC News (12/15, Fox, 2.67M) reports the FDA said on Wednesday that a pineapple genetically engineered to be pink is safe to sell. The FDA said the pink pineapple "simply has some genes toned down to keep the flesh of the fruit pinker and sweeter," according to NBC. The fruit, grown by Del Monte Fresh Produce in Costa Rica, will be labeled "extra sweet pink flesh pineapple." Packer (12/14, 39K) also covers the approval.

US Concerned About Antibiotic-Tainted Seafood Imported From China.

In an over 3,500 word article, Bloomberg News (12/15, 2.41M) reports there is growing concern about the US importing seafood from China that is tainted with antibiotics, which could foster the spread of antibiotic-resistant bacteria. The article reports that the "Food and Drug Administration intensified its monitoring" of seafood imported from China in 2006 and found many samples "contained residues of unapproved drugs and unsafe food

additives." There is now growing pressure on the FDA to take action against possibly tainted food imports from China.

Pinnacle Recalls Duncan Hines Cake Mix Over Possible Salmonella Contamination. Food Safety News (12/15, 8K) reports Pinnacle Foods Canada Corp. said it was recalling Duncan Hines Apple Caramel flavor cake mix from Canadian retailers due to "possible Salmonella contamination." The article says the reasons for the voluntary recall were not provided in any further detail, adding that no illnesses associated with the product have been reported.

H-E-B Issues Recall Of Pistachios Linked To Salmonella. The Houston Chronicle (12/14, Lewis, 1.91M) reports H-E-B issued a recall Wednesday on bulk and packaged raw shelled pistachios because they may be contaminated with salmonella. The possible contamination was discovered "after a routine sampling of the product by the Food and Drug Administration, but there have been no reports of illness to date."

Food Safety News (12/15, 8K) reports that "Texas locations of two of the retailer's grocery banners – H-E-B and Central Market – received the recalled shelled pistachios."

Harvard Study Examines Long-term Health Impacts Of Soda Taxes. The Christian Science Monitor (12/14, Sparling, 387K) reports a new Harvard study suggests soda taxes not only reduce consumption of sugary beverages, but "can improve the health and economic wellbeing of communities." The Childhood Obesity Intervention Cost-Effectiveness Study at Harvard's school of public health examined "the long-term cost-effectiveness of soda taxes" and concluded the "these policy measures could reduce rates of obesity and prevent diabetes, leading to a long-term reduction in healthcare costs nationwide." Business Insider (12/14, Taylor, 3.42M) reports the study examined what "would happen if the 15 largest US cities with the ability to pass a 1-cent-per-ounce tax on sugary drinks did so" and found that the tax would "raise almost \$1 billion in revenue every year." Jim Krieger of Healthy Food America, the food policy nonprofit that funded the Harvard study, said "cities have a golden opportunity to help their people avoid premature death and illness and cut health costs while raising revenue to make residents' lives better in other ways."

The Daily Meal (12/13, 240K) and Food Tank (12/13) also provided coverage of this report.

Impacts Of Soda Tax In Baltimore Examined In Harvard Study. The Baltimore Sun (12/13, McDaniels, 714K) reports a tax on soda in Baltimore "could bring in \$25.6 million to go toward health programs and help reduce rates of diabetes and obesity," according to the new Harvard study. As one of the cities examined in the study, the research

suggests Baltimore could see "a 6 percent decline in the rates of diabetes, 4,950 fewer cases of obesity, and \$31.6 million in health care costs savings over a decade." Executive Vice President Ellen Valentino of the Maryland-Delaware-DC Beverage Association said, "such a tax in places such as Mexico, Arkansas and West Virginia had little impact on health outcomes" and rank among the highest areas of obesity.

TOBACCO

FDA Denies Swedish Tobacco's Request For Two Snus Label Changes, Keeps Other Two Requests On The Table. The AP (12/14, Perrone) reports the FDA is denying the request by Swedish Match to remove warnings related to gum disease and tooth loss from its snus chewable tobacco products. While the agency denied its requests to make those two labeling changes, it also asked for more information regarding the company's request to remove the warning concerning mouth cancer, as well as their request to include a statement on packaging claiming their products are less risky than cigarettes.

Convenience Store News (12/14, 212K) reports Mitch Zeller, director of the FDA's Center for Tobacco Products, said, "The lessons learned through these first applications provide key insights moving forward. For example, companies should carefully consider how they plan to present and substantiate a modified risk claim. ... While the FDA is not authorizing modified risk orders for these products at this time, our guidance to the company will enable it to amend its applications if it chooses."

Additional coverage is provided by: Reuters (12/14, Clarke), MedPage Today (12/14, Boyles, 97K), the Richmond (VA) Times-Dispatch (12/14, Blackwell, 324K), The Hill (12/14, Wheeler, 1.25M), the Wall Street Journal (12/14, Maloney, Subscription Publication, 6.37M), and Medscape (12/14, Ault, 339K).

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TODAY'S EDITION

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INTERNATIONAL NEWS

- Volunteers In China Publicly Criticizing, Educating Smokers

FDA NEWS

FDA Denies Two Snus Label Changes, Defers Two Others.

The [AP](#) (12/14, Perrone) reports the U.S. Food and Drug Administration (FDA) is denying requests by Swedish Match to remove warnings related to gum disease and tooth loss from its snus chewable tobacco products. At the same time, the agency asked for more information regarding the company's requests to remove the warning concerning mouth cancer and to include a statement claiming the products are less risky than cigarettes. Mitch Zeller, director of the FDA Center for Tobacco Products, said in an interview, "The door is absolutely open and we've tried to show the steps they would need to take to come back to us." Swedish Match said the guidance was "encouraging."

The [Wall Street Journal](#) (12/14, Maloney, Subscription Publication, 6.37M) reports the FDA instructed Swedish Match to be more precise in its health claims, stating, for example, that the product reduces specific toxic exposures or less likely to cause certain diseases. Jim Solyst, vice president for federal regulatory affairs at Swedish Match, also expressed optimism regarding the

process. PMI's application is also noted.

Reuters (12/14) reports Dr. Lars-Erik Rutqvist, senior vice president of scientific affairs at Swedish Match, said, "There doesn't seem to be a disagreement between the company and the FDA as to whether snus is a modified risk product. The disagreement seems to be the way to communicate this to the general public." Matthew Myers, president of the Campaign for Tobacco-Free Kids, a public health group, claimed "the FDA had no choice but to reject the company's application since it asked for the removal of statutory warning labels." He said, "A properly prepared application could well have received a different result." Reuters notes PMI's modified risk application this month. The Hill (12/14, Wheeler, 1.25M) reports Swedish Match Vice President of Regulatory Affairs Fredrik Peyron said, "Our goal has been to work to communicate truthfully to consumers about our snus products and that snus is a less harmful alternative to cigarette smoking. We took a major step towards our vision 'a world without cigarettes' by having the first MRTTP (Modified Risk Tobacco Product) application ever accepted by FDA in history, and we believe it's a sign that we're moving in the right direction."

The Winston-Salem (NC) Journal (12/14, 204K) reports Swedish Match's "application has been watched closely by both the public health community and tobacco companies." Gregory Conley, president of the American Vaping Association, said the FDA decision on General Snus is "a transparent giveaway" to Zeller's former employer, Nicorette maker GlaxoSmithKline, and shows it is "openly hostile to tobacco harm reduction." Scott Ballin, past chairman of the Coalition on Smoking or Health, said the decision "is instructive for any company wishing to file a modified risk tobacco product application." He lamented, "It has long been accepted that snus is more than 90 percent less harmful than the deadly cigarette, and yet the Tobacco Control Act makes it virtually impossible for truthful information to be provided by the public." He said Zeller has "not followed through" in introducing tobacco regulations that reflect a "continuum of risk" as promised.

The Richmond (VA) Times-Dispatch (12/14, Blackwell, 324K) recalls that Swedish Match wanted the warnings on snus to read: "No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes." PMI's application is also noted.

Convenience Store News (12/14, 212K) reports Zeller said, "The lessons learned through these first applications provide key insights moving forward. For example, companies should carefully consider how they plan to present and substantiate a modified risk claim. ... While the FDA is not authorizing modified risk orders for these products at this time, our guidance to the company will enable it to amend its applications if it chooses."

MedPage Today (12/14, Boyles, 97K) and Medscape (12/14, Ault, 339K) also provide coverage.

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Trump's FDA Candidates Support Faster Drug Approvals. The Washington Examiner

(12/15, King, 400K) reports that one of President-elect Donald Trump's candidates to lead the FDA, Jim O'Neill, managing director at the investment firm Mithril Capital, has previously called on the agency to "approve drugs based solely on safety and not on effectiveness, a radical departure from the current approach." Another candidate, "agency veteran and physician" Scott Gottlieb, has advocated a "different regulatory approach at the agency, but hasn't gone to the same extremes as O'Neill." He supports the 21st Century Cures Act because it would "enable the agency to approve drugs using a different clinical endpoint called a surrogate measure."

FDA Data Suggests E-Cigarette Battery-Related Injuries On The Rise.

The AP (12/14, Eltman) reports instances of e-cigarettes exploding in users' pockets have increased over the past year, with the FDA identifying "about 66 explosions in 2015 and early 2016, after recording 92 explosions from 2009 to September 2015." Some attorneys and medical professionals suggest those figures may be an undercount of the real number of burn instances connected to e-cigarettes, with attorney Gregory Bentley saying, "The problem is defectively manufactured batteries. ... Consumers need to know it's next to impossible to sue a Chinese company. If people want to seek compensation they have to target distributors, wholesalers and retailers."

Commentary Criticizes FDA E-Cigarette Regulations' Potential Effect On Public Health, Vaping Industry.

The Cleveland Plain Dealer (12/14, 976K) features commentary from Ohio vape shop owner James Jarvis in which he expresses concern that the FDA's "prohibitively expensive" e-cigarette regulations will threaten not just his business but also the health of Ohioans trying to quit smoking. Jarvis is attempting to reach out to US Rep. Marcia Fudge (D-OH) to request she support the vape regulation-changing Cole-Bishop amendment, stating, "By doing this, she will be defending small businesses, like Vapor Station, that have a large economic impact in her district; moreover, she is supporting thousands of thriving businesses nationwide. If it's not passed into law, the amendment will disappear along with the vapor industry."

US, UK Public Health Officials Take Opposing Stances On E-Cigarettes.

The Dallas Morning News (12/14, Yasmin, 1.12M) features an analysis of the opposing positions taken by UK and US health officials on the issue of regulating e-cigarettes as a public health risk or supporting them as a smoking cessation tool. Amid conflicting evidence concerning e-cigarettes healthfulness and their potential as smoking cessation aids, "Public health experts continue to disagree about the safety of e-cigarettes, leaving the more than 9 million Americans who use them in the middle of a heated debate." "In fact, the Food and Drug Administration has not licensed e-cigarettes as a tool for smoking cessation," but instead "offers a warning about the risks posed by e-cigarettes."

TOBACCO POLICY NEWS

East Lansing, Michigan City Council Approves Outdoor Smoking Ban.

The Lansing (MI) State Journal (12/14, LeBlanc, 183K) reports the city council of East Lansing, Michigan unanimously approved a smoking ban in its parks, plazas, and recreational facilities. However, the ordinance does not apply to e-cigarettes, and "does not ban smoking on sidewalks, unless the smoker is within 50 feet of the entrance to a building owned by" the city.

California Assemblyman Introduces Bill To Ban Smoking, Vaping In Public Housing.

The Los Angeles Times (12/14, McGreevy, 4.52M) reports a bill has been introduced in the California legislature to ban public housing residents from smoking or using e-cigarettes in or near their buildings. Bill sponsor Assemblyman Jim Wood said, "This is a great step forward in protecting families by significantly reducing exposure to second-hand smoke and this bill codifies federal regulations. ... In AB 62, we are taking it a step further by including the use of e-cigarettes to be consistent with California's definition of tobacco products which includes e-cigarettes and other vaping products."

Michigan Anti-Smoking Group Pushing Legal Tobacco Purchasing Age Increase In Muskegon County.

MLive (MI) (12/14, Gaertner, 878K) reports Muskegon County, Michigan's anti-smoking group Knowsmoke Coalition is trying to get the legal purchasing age for tobacco products raised to 21 in the county. According to MLive, "The group's plan is to present the signatures and give a presentation" about the proposal to the "Muskegon County Board of Commissioners during its Dec. 20 board meeting."

Campaign For Tobacco-Free Kids Ranks New Jersey, Connecticut Last For Efforts To Prevent Youth Smoking.

The Newark (NJ) Star-Ledger (12/14, Livio, 438K) reports the Campaign for Tobacco-Free Kids ranked New Jersey last in the nation for the fifth straight year in terms of efforts to prevent youth from smoking, in light of the fact that the state continues to put no public money towards efforts to deter kids from smoking. Gov. Chris Christie (R) vetoed legislation earlier this year to raise the legal smoking age in the state to 21, leading the group's president, Matthew Myers, to say, "New Jersey is putting children's health at risk and costing taxpayers money by refusing to fund tobacco prevention programs that save lives and health care dollars."

The Hartford (CT) Business Journal (12/14, Stearns, 23K) reports Connecticut tied New Jersey for last in the Campaign for Tobacco-Free Kids' rankings, for largely the same reason: no state money was spent "this year for tobacco prevention and cessation programs."

Chicago Alderman Approve Plan To Roll Back Flavored Tobacco Product Regulation.

The Chicago Tribune (12/14, Byrne, 2.54M) reports Chicago Aldermen approved a plan to allow menthol cigarettes, candy flavored cigars, and other tobacco products to once again be sold within 500 feet of grade schools. One of the aldermen who voted against the measure, Raymond Lopez, said, "This ordinance, while I appreciate the collaboration, I think that our goal should be to keep cigarettes as far away from children as possible. ... Because even going into a store and seeing them, seeing other people buying them, will get their interest piqued. And that is the last thing we need to do now to grade schoolers who are already under intense pressure from neighborhood life, gang life, and now there will be easy access to these kinds of cigarettes, which they don't need."

INTERNATIONAL NEWS

Volunteers In China Publicly Criticizing, Educating Smokers.

The AP (12/14, Merchant) reports a group of volunteers in China are publicly chastising smokers for smoking in public and for discarding their cigarette butts in the open. The volunteers "must pledge never to have smoked before," and anyone in the cohort "caught smoking is expelled from

the group.” The AP explains that smoking is embedded in modern Chinese culture, as “national leaders dating back to Mao Zedong were well-known smokers.” Wu Yiqun, vice director of the ThinkTank Research Center for Health Development, said that as the country works to reduce smoking, “Top officials must take the lead. ... How could smoking be allowed in the offices of the top officials?”

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From: Sherman, Rachel
To: Califf, Robert
Subject: RE: wsj article
Date: Friday, December 23, 2016 10:05:53 AM

This is worth a conversation. Perhaps I do not understand your point but I am relatively sure you do not understand mine.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: December 23, 2016 at 9:55:02 AM EST
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: RE: wsj article

We disagree

Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Friday, December 23, 2016 9:54 AM
To: Califf, Robert
Subject: RE: wsj article

The one has absolutely nothing to do with the other.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: December 23, 2016 at 9:50:52 AM EST
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: RE: wsj article

The worst thing for patients is to give them false hope

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Friday, December 23, 2016 9:47 AM
To: Califf, Robert
Subject: RE: wsj article

They are right about us not undercutting our decision. Not fair to the patients.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: December 23, 2016 at 9:16:07 AM EST
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: RE: wsj article

Does WSJ own stock in the company or something?

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Sherman, Rachel
Sent: Friday, December 23, 2016 9:13 AM
To: Califf, Robert
Subject: Fwd: wsj article

From: Davies, Kathleen <Kathleen.Davies@fda.hhs.gov>
Date: December 23, 2016 at 9:00:17 AM EST
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>
Subject: wsj article

The FDA Empire Strikes Back

The bureaucracy is talking down a drug the agency approved.

The cost of the drug is high: Price is based on weight and can run \$300,000 a year. Yet fewer than 2,000 patients in the U.S. are amenable, which means insurers won't have an influx of beneficiaries. Care for Duchenne patients in their late teens or early 20s is already expensive, from hospitalizations to cardiac medication, so insurers will pay in any event.

Insurers are usually hypersensitive to avoid public shaming campaigns, but here they don't seem too concerned. That's probably because the reporters who cover FDA have taken the side of the reviewers and insurers. Thus one of the grim ironies of this story: The men who in the 1980s beat down the doors at FDA to demand approval for AIDS treatments are rightly regarded as heroes, yet these boys and their families have been treated as desperate losers.

Still, the genesis of these mixed messages is FDA, which should stop undercutting a drug the agency has approved. But that will require changing the bureaucracy's toxic culture of political control and contempt for private innovation, and Donald Trump's FDA commissioner should make that his first priority.

Kathleen Davies
Senior Project Coordinator
Office of Medical Products and Tobacco
U.S. Food and Drug Administration
Tel: 301-796-2205
kathleen.davies@fda.hhs.gov

2

From: [Evans, Dana](#)
To: [Califf, Robert](#)
Date: Thursday, December 29, 2016 8:30:48 AM
Attachments: [Rose Sheet Today's News Analysis.msg](#)
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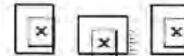
Smith, Celeste

From: Rose Sheet <info@pharmamedtechbi.net>
Sent: Thursday, December 29, 2016 7:05 AM
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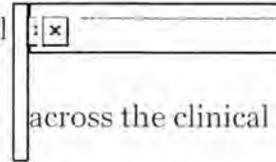
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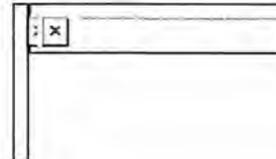
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From: [Young, Jason](#)
To: [Califf, Robert](#)
Cc: [Kraus, Tom](#); [Sharp, Jeremy](#); [Conover, Katie](#)
Subject: Washington Post article from Laurie McGinley
Date: Thursday, December 29, 2016 3:23:34 PM

Commissioner- The Post piece just posted a few hours ago. The headline and intro are a little tough, because they don't get at the heart of the points you made in your sit-down with Laurie. Otherwise, she ran your comments practically verbatim – as a Q&A – but notably she skipped over the questions related to whether you'd choose to stay on if asked. Hope you're enjoying the holiday break. Best, Jason

https://www.washingtonpost.com/news/to-your-health/wp/2016/12/29/the-head-of-the-fda-defends-the-importance-of-drug-effectiveness/?utm_term=.ed9c945edf87

The head of the FDA defends the importance of drug effectiveness

By [Laurie McGinley](#) December 29 at 11:22 AM

Food and Drug Commissioner Robert Califf (Win McNamee/Getty Images)

First things first: Food and Drug Commissioner Robert Califf says that he has not had any contact with the Trump transition team. That's the latest sign that the cardiologist, confirmed as FDA chief less than a year ago, will be heading back to Durham, N.C., where he's on leave from Duke University. Still, he has no regrets: "Everyone who knows me knows I have just had fun every day on the job," he said in an interview.

Some days were presumably more fun than others. Take the controversy surrounding a drug for Duchenne muscular dystrophy.

Studies did not show a clear benefit to the drug and an FDA advisory committee voted against approving it, but patient advocacy groups pushed for the drug. After much infighting, the drug was granted accelerated approval this fall by the agency's top drug-review official, and Califf allowed the decision to stand.

Meanwhile, Califf strongly defended the FDA's requirement that a drug must be shown to be effective for approval. Jim O'Neill, an associate of PayPal co-founder Peter Thiel who has been mentioned as a possible successor to Califf in the Trump administration, has suggested that the agency require only safety testing for approval.

Califf also talked about his mother, who has multiple myeloma.

(This interview has been edited for brevity and clarity.)

What do you think are the biggest challenges facing the agency?

We're seeing increasingly complex information, so we need really good people to deal with it, and there were limitations in terms of hiring and information technology and infrastructure that are really critical to a science-based public health agency with a regulatory mandate. So that's something I have really focused on, and it's going to be an ongoing challenge because the world is moving faster, not slower.

The second big need is . . . evidence generation. I started off as a doc, running intensive-care units. You make decisions about individual people, multiple decisions a day, your decisions have consequences. It's exciting. There's a lot at stake. The middle part of my career has been as a researcher and research administrator where at the end of every article you say, "More research is needed." And that's

wonderful, too, because the goal is open exploration.

But then at the FDA, you have a lot of the same science issues but you have to make decisions. And it's very noticeable when we make decisions with good evidence. It's still emotionally charged because we regulate such a large part of the economy, and there are winners and losers. But when we have good evidence, it's easy to defend the decisions and the arguments are typically good arguments to have about how you interpret good evidence.

But we are often in situations where we have to make decisions because there are time limits and we don't have the kind of evidence we really need to make a good decision, and then things are not so pretty. Here we are in a time when everything is digitized, we have scads of information, but as a society we haven't been so good at turning that information into knowledge, particularly in the medical arena.

When you look back at the controversy over the Duchenne muscular dystrophy drug, do you have any second thoughts about the way that turned out?

One great thing about having been an intensive care doctor, I don't lose sleep over second thoughts because you should learn from your experience and try to do things better the next time, so my thoughts were really reflected in what I wrote [which was to defer to the FDA's top drug-review official].

We didn't have the evidence we really wanted and a decision had to be made. But the steps that should be taken in the future to reduce the number of times we get into this situation, I think I clearly laid out. By law, the FDA is given a lot of discretion in cases of serious and life-threatening diseases with no available treatment. We are

instructed by law to consider all sources of evidence beyond the traditional and to use unvalidated biomarkers [such as molecules that may be affected by a drug and measured] if we think that it's reasonably likely they will predict a clinical benefit. So as I pointed out in the document, the definition of "reasonably likely" is not defined and "all sources of evidence" includes a lot of possible things.

We have been working closely with NIH because with 5,000 rare genetic diseases and this being such an exciting time of not just quantifying the genome, which Francis Collins started, but now understanding the functional aspects, we are going to have cures for a lot of rare genetic diseases.

I hope people will look at the Sarepta case [Serapta Therapeutics produces the Duchenne muscular dystrophy drug], and say there are some things that regardless of whether we think FDA made the right decision, let's look at what needs to be done for the next 4,999 rare genetic diseases because patients and their families have reason to want things to get done.

What's your reaction to the argument that drugs should not have to be proven effective before getting approved by the FDA?

There's a history to proving effectiveness of drugs that goes back to pre-1962, that I think many people are aware of, and the requirements are written into law. I think what many people lose sight of is that what's been called a standard is actually quite flexible. As an intensive-care-unit doc, and now I'm of the age where I'm a patient, too (I'm on drugs for lipids and hypertension), I think people will want to take drugs that have a benefit because all drugs have a risk. I don't know of any that are completely free of risk.

Almost 90 percent of drugs that get into Phase One [the earliest stage of clinical trials] don't make it to market because of toxicity or they actually don't work or they can't be manufactured on a scale that's needed to be safely produced and distributed in a global market. And so that means if you are not demonstrating that a drug has a benefit, most of what they take won't work.

And I think we have pretty clear evidence from the public that they would like to have a system that's giving them some assurance that the treatments they are given work.

But again, to get back to the flexible standard, that means in the case of rare genetic disease with no available treatment, "working" means changing a biomarker, it doesn't mean improving a clinical outcome, and then the proof of that is developed post-market.

How do you think the 21st Century Cures law will affect the agency?

I think 21st Century Cures worked out quite well for us. The personnel issues are clear and we are very happy with what Congress agreed to do there. [The bill allows FDA to give pay raises to scientists and other expert staff.] And the sections on real-world evidence and modernizing clinical trials are all quite consistent with the direction we hoped we would be going in and I think will be helpful.

In the debate over high drug prices, the FDA sometimes gets criticized for not approving generic drugs quickly enough. Some in Congress want to set a 150-day deadline for some generic-drug approvals. What's your reaction?

We need to approve generics as quickly as we can, keeping in mind that the laws for generics are pretty simple in terms of what a company needs to do for a generic drug. But a company also needs to be able to manufacture the drug and show that it's high quality throughout the supply chain. In some of the dialogue about this, people may have lost sight of the fact that if you look at the backlog in generics it's almost all compounds that have had multiple applications because there were deficiencies that needed to be corrected. I don't know that 150 days is necessarily the right number. But there's no objection at FDA to going as fast as we can as long as we keep a quality standard.

What else is on your mind?

My mom has multiple myeloma. If you were a cancer patient, you would want the industry to do well, but you want there to be a rational approach that optimizes getting the right treatments out there at the right time. She's a beneficiary of accelerated approval of a drug for multiple myeloma. Just recently, I got a call saying it's time for hospice for your mom. She has had 89 good years. I'm saying all this with her agreement and permission.

I called [FDA oncology chief Richard] Pazdur and said, What's new? And he said, We have a few things that look good and they are tolerated well and even for someone age 89 might work. And it's worked in her. And I'm insistent that we need to then bring in the evidence after accelerated approval. For this particular drug, I won't go into the specifics of the drug, but I was pleased a couple weeks ago to see they did randomized trials in follow-up and they were positive and got additional indications.

From: [Pink Sheet](#)
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Program Support Specialist to the Commissioner
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U.S. Food and Drug Administration
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BB: 301-467-8987
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By Ian Haydock

With the Trans-Pacific Against the protests of the innovative pharma industry, Japan is pushing ahead with an overhaul of its drug reimbursement pricing system that will include a shift to annual price revisions.

22 Dec 2016 | **ANALYSIS**

Is ICER Too NICE? A Comparison Of Drug Assessments Programs

By Cathy Kelly

Drug companies are accusing the US Institute for Clinical and Economic Review of approaching cost effectiveness assessments in the same way as the UK National Health Service gatekeeper, the National Institute for Health and Care Excellence.

19 Dec 2016 | **ANALYSIS**

PDUFA VI: Industry Ready For 'Hard Sell' To Keep Agreement Intact

By Sue Sutter

Biopharma industry is preparing for the unwelcome possibility that the new Congress and Trump Administration will seek to revisit provisions in the negotiated agreement for the US FDA user fee program's reauthorization.

22 Dec 2016 | **NEWS**

Dermalex Eczema 'Breakthrough' Claim Breaks Down In UK Review

By Malcolm Spicer

Omega Pharma argues its product provides eczema treatment with multiple benefits commonly available only by using separate products – emollients to protect skin from moisture loss and reducing dryness and topical corticosteroids to reduce inflammation and redness.

28 Dec 2016 | **ANALYSIS**

Exondys Approval: Measured Efficacy Outcomes Vs. Patient 'Anecdotes'

By Sue Sutter

Pink Sheet's Drug Review Profile looks at US FDA clinical memos opposing approval of Sarepta's Duchenne muscular dystrophy drug eteplirsen, revealing challenges patient advocates and agency face in transforming patient experiences into hard data that can be used for approvals.

28 Dec 2016 | **NEWS**

Biosimilars Get Bespoke Service: EMA To Pilot Tailored Scientific Advice

By Vibha Sharma

Quality data will be focus of 'extra advice' offered by European Medicines Agency's pilot, which will suggest directions for sponsors' next steps but stop short of formal data evaluation.



VIEW FROM *IN VIVO*'S ARCHIVE

Please enjoy this **complimentary** article from our sister publication *In Vivo*.

Drug Approval Rates Grow With Deal Up-Fronts

There's a correlation between up-front payments and actual drug approval rates. First in a series of follow-ups to *In Vivo*'s 2014 study comparing/contrasting likelihood of approval and up-front payments on alliances, and the outcomes of relevant deals.

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Approval of Biogen/Ionis' Spinraza gives the drug development community a successful, collaborative model for a rapid pathway to full approval...

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“Thousands and thousands of people” will be using the EU clinical trials portal and database after it goes live late...



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US agency's decision not to hold a February advisory committee review of tardive dyskinesia treatment viewed positively by Neurocrine, which...

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With data integrity problems on the rise, pharmaceutical manufacturers must ensure in auditing their contract manufacturing partners that they have...

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Top 16 From '16: Pink Sheet's Most Popular Stories

Big developments, key biopharma trends, and other topics that most intrigued and impacted our readers in 2016.

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OTC industry trade groups will more aggressively push for an education program to encourage proper disposal of Rx and OTC...

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FDA's ANDA Approvals

US Generic drug approvals and tentative approvals for late December and early January.

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Recent And Upcoming FDA Advisory Committees

Recent and upcoming US FDA advisory committee meetings and a summary of topics covered.

NEWS

FDA's NDA And BLA Approvals: Caspofungin

Original new drugs and biologics recently approved by US FDA.

VIEW FROM *IN VIVO*'S ARCHIVE

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Mining the Microbiome: Are Gut Microbes The Next Big Source Of Drugs?

There is growing interest in the gut microbiome as a source of new therapies across a wide range of diseases. Although it is still an emerging field, pharmaceutical firms and other investors are engaging, with more expected to follow.

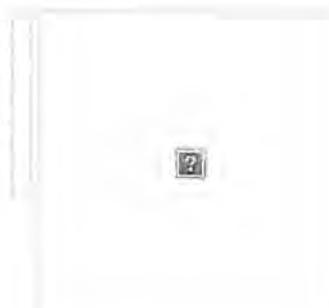
Drug Approval Rates Grow With Deal Up-Fronts

There's a correlation between up-front payments and actual drug approval rates. First in a series of follow-ups to In Vivo's 2014 study comparing/contrasting likelihood of approval and up-front payments on alliances, and the outcomes of relevant deals.

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Don't let your drug discovery program stop after late lead optimization. Here are the options for your program and how you can continue to achieve success. Click here to find out how.



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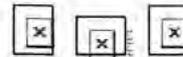
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Subject: Center for Tobacco Products News Briefing for Monday, January 9, 2017

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TODAY'S EDITION

FDA NEWS

- Trump's Choice For FDA Could Have Significant Impact On A Variety Of Issues
- CTP To Gather Information On E-Cigarette Battery Issues

TOBACCO POLICY NEWS

- Attorneys Seek Fees In Arkansas Cigarette Litigation
- Indiana Lawmakers To Consider Bill Relaxing Regulations On E-Cigarette Industry

TOBACCO INDUSTRY NEWS

- Value Of "Heat Not Burn" Technology Stalling Deal Between BAT, Reynolds

INTERNATIONAL NEWS

- Northern Ireland Regulators Considering Banning Smoking In Cars With Children

FDA NEWS

Trump's Choice For FDA Could Have Significant Impact On A Variety Of Issues.

Nature (1/6, Heidi, 153K) reported that although President-elect Donald Trump has not yet made a selection for Food and Drug Administration Commissioner, "if Trump's choices for other posts are any guide, he will look for an FDA commissioner to shake up the status quo." According to Nature, "the next FDA chief could shift the agency's stance on everything from medical testing to clinics that claim to provide stem-cell therapies." The article considers the issues facing the next FDA commissioner and how a Trump Administration might approach them.

CTP To Gather Information On E-Cigarette Battery Issues.

Convenience Store News (1/6, 212K) reported that the Center for Tobacco Products "will host a science-based workshop to gather information and stimulate discussion on batteries used in electronic nicotine delivery systems (ENDS), including electronic cigarettes" on April 19-20. According to the article, CTP "seeks to gather information about battery safety concerns — for example, overheating, fire, explosion, other modes of failure, risk mitigation, and design parameters related to ENDS."

Convenience Store Decisions (1/6, 129K) reported that the workshop "is open to scientific and medical experts; ENDS manufacturers, importers, distributors, wholesalers and retailers; manufacturers of batteries for ENDS and other consumer products; federal, state, and local

government agencies; and other interested stakeholders, such as academic researchers and public health organizations.”

TOBACCO POLICY NEWS

Attorneys Seek Fees In Arkansas Cigarette Litigation.

The Arkansas Democrat Gazette (1/6, Lynch, 278K) reported the attorneys for Arkansas Marlboro Lights smokers are asking the judge “to decide how much they should be paid for their efforts, money that would come out of the settlement fund.” According to the attorneys, they “worked more than 15,000 hours — time they valued at \$10.2 million — and spent \$2.2 million of their own money to pursue the litigation over 13 years.” While they don’t request a specific amount, “they state that there is court precedent in Arkansas that would allow [the judge] to award them anywhere from the \$12.4 million they say they’ve invested in pursuing the litigation to as much as \$30 million, which would be based on the value the judge places on their representation.”

Indiana Lawmakers To Consider Bill Relaxing Regulations On E-Cigarette Industry.

The Indianapolis Business Journal (1/7, Colombo, 77K) reported that Indiana lawmakers are considering changes to the state’s e-cigarettes law that “has been roundly criticized as unfair and even corrupt.” State Sen. Randy Head (R) will introduce a bill to end the “monopoly” created by the law and lessen restrictions on the industry.

TOBACCO INDUSTRY NEWS

Value Of “Heat Not Burn” Technology Stalling Deal Between BAT, Reynolds.

The Telegraph (UK) (1/7, Williams, 1.04M) reported that talks between British American Tobacco and Reynolds on a merger “are stuck” on the value of “heat not burn” technology. The companies “have been attempting to thrash out a deal... amid volatility in the value of consumer staples and against the backdrop of the election of Donald Trump.”

INTERNATIONAL NEWS

Northern Ireland Regulators Considering Banning Smoking In Cars With Children.

BBC News (UK) (1/6, 2.39M) reported that Northern Ireland’s Health Minister Michelle O’Neil announced that regulators banning smoking in vehicles with children are being discussed. The consultation on the rules “will run from 6 January 2017 to 3 March 2017.”

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TODAY'S EDITION

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FDA Highlights Cybersecurity Risks For Medical Devices.

Dominic Tyer writes in PMLIVE's (1/9) "Digital Intelligence" blog that the FDA stressed the importance of cybersecurity for medical device manufacturers. FDA's associate director for science and strategic partnerships at the Center for Devices and Radiological Health Suzanne Schwartz said, "In today's world of medical devices that are connected to a hospital's network or even a patient's own internet service at home, we see significant technological advances in patient care and, at the

same time, an increase in the risk of cybersecurity breaches that could affect a device's performance and functionality." Schwartz added, "With this guidance, we now have an outline of steps the FDA recommends manufacturers take to remain vigilant and continually address the cybersecurity risks of marketed medical devices."

MEDICAL PRODUCT SAFETY

FDA Agrees To Priority Review For Bladder Cancer Drug's Additional Treatments.

Reuters (1/9, Miller) reports in brief that the Food and Drug Administration agreed to priority review of Roche's "Tecentriq immunotherapy for an additional type of bladder cancer." The FDA "will make a decision within six months on Roche's application for Tecentriq's use in patients with metastatic urothelial carcinoma who are ineligible for cisplatin chemotherapy and who are either previously untreated or have disease progression at least 12 months after receiving chemotherapy."

Opioid Overdose Deaths Continue To Climb, Federal Data Indicate.

The Wall Street Journal (1/6, Kamp, Subscription Publication, 6.37M) reported that new Federal data indicate opioid overdose fatalities rose 16 percent in 2015 from the previous year, totaling 33,091. Many

local jurisdictions are still compiling data from last year, but many expect there was another increase in 2016.

The New York Times (1/6, Subscription Publication, 13.9M) reported that opioid overdose deaths "were nearly equal to the number of deaths from car crashes" in 2015, while "for the first time, deaths from heroin alone surpassed gun homicides."

Maryland Has Highest Rate Of Hospitalization For Opioid Use In US, Data Indicate. The Baltimore Sun (1/6, Cohn, 714K) reported that Maryland "has the nation's highest rate of hospitalizations for opioid use, according to newly released federal data." According to the US Agency for Healthcare Research and Quality, the "rate of hospital admissions in Maryland was 362 for every 100,000 residents in 2014."

Opinion: Suggestions For Congress To Improve Healthcare Right Now.

In an op-ed in the National Review (1/9, Miller, 696K), Henry Miller, the Robert Wesson Fellow in Scientific Philosophy and Public Policy at Stanford University's Hoover Institution, discusses ways that the government can deal with data from the National Center for Health Statistics showing the "US death rate has increased for the first time in a decade." Miller suggests that Congress should "enact smart, evidence-based policies, invest in private-public partnerships that enhance innovation, and eliminate roadblocks to America's innovators" to combat the problem. He explains that the Trump administration will dictate policy by appointing a new FDA head, and notes current FDA commissioner Dr. Robert Calif "has not really had time to make his mark" since he took up the post in February 2016.

Newly-Approved Nusinersen Giving Hope To Patients With SMA.

The AP (1/8, Miller) reported that Spinraza (nusinersen), a drug recently approved by the Food and Drug Administration to treat spinal muscular atrophy, is giving hope to patients who have lacked a treatment option until now. According to experts, "having a treatment option can also be a catalyst for adding SMA to the newborn screening panel." Since the drug was well-tolerated in "the young and fragile population," it also may "have implications beyond SMA" and become a treatment for other disorders.

Black Americans Underrepresented In Diabetes Drug Safety Trials, Research Suggests.

Reuters (1/6, Rapaport) reported that a study published in The Lancet Diabetes and Endocrinology suggested that black patients "may be far less likely to be included in drug safety trials," despite the fact that diabetes is almost twice as prevalent in black Americans as in white Americans. Researchers pointed out that black people

constituted less than five percent of participants in seven diabetes drug safety trials. According to Reuters, "about 13 percent of black people in the U.S. have diabetes, compared with 7.6 percent of white Americans."

Genetic Test To Determine Whether A Patient Will Effectively Respond To Clopidogrel Not The Standard Of Care For All Stent Patients.

The Baltimore Sun (1/6, McDaniels, 714K) reported that a "genetic test to determine" whether a patient will effectively respond to clopidogrel "is now part of the University of Maryland's routine care for stent patients, but it still is not the standard of care for all stent patients." The Sun pointed out that in 2010, the FDA began requiring "a black-box warning...on clopidogrel's packaging to make people aware of the genetic effect."

FDA Approves Injection Drug For Treatment Of mCNV.

Medscape (1/6, Brooks, 339K) reported the Food and Drug Administration approved Genentech's ranibizumab injection [Lucentis] for the treatment of myopic choroidal neovascularization (mCNV). The drug is "the first FDA-approved anti-vascular endothelial growth factor therapy for mCNV."

Dynavax Lays Off 38% Of Employees, Halts Manufacturing Of Experimental HBV Vaccine.

Fierce Biotech (1/6, Taylor, 2K) reported that Dynavax "has laid off 38% of its workforce and halted manufacturing of its experimental hepatitis B vaccine," Heplisav-B, after the Food and Drug Administration declined to approve it for a second time. Dynavax had "hoped to land a partner that would commit the time and money needed to get Heplisav-B ready for a third run at FDA" but was unable to, so it has reorganized to focus on immuno-oncology.

GAO: FDA's White Oak Campus "Not Up To Standard."

Federal News Radio (DC) (1/6, Somers, 16K) reported that a report by the Government Accountability Office suggests that the Food and Drug Administration's headquarters at the White Oak, Maryland campus "is not up to standard for its high-risk status, and the agency's plans to address cramped offices and parking spaces need more detail before they're put into action." The GAO report "recommended three actions for FDA to take: implement vehicle access control measures to meet high-risk facility standards, explain more clearly the connection between FDA's strategic and facilities plans, and collect and document more information about the daily operations of the campus." According to Department of Health and Human Services Assistant Secretary for Legislation Jim Esquea, HHS agrees

with the GAO's recommendations and is in the process of putting them into effect.

FDA's Final Guidance For Medical Device Accessories Allows "Greater Flexibility" For Classification.

Med Device Online (1/6, Hodsden) reported the FDA "issued a finalized guidance outlining the agency's approach to classifying and regulating medical device accessories." The FDA defined a medical accessory as designed to "support, supplement, and/or augment the performance of one or more parent devices." The FDA's finalized guidance says "devices will no longer automatically fall into the same classifications as parent devices, and describes a shift in policy that will allow manufacturers greater flexibility when seeking reclassification for accessory types currently on the market."

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WEEKLY HIGHLIGHTS

Look below for key developments and intriguing perspectives from the past week to inform your strategic decision-making. And check out our daily reporter notebooks from last Monday, Tuesday and Wednesday at the J.P. Morgan health care conference.



THIS WEEK'S TOP STORIES

11 Jan 2017 | **ANALYSIS**

Trump Makes A Nasty News Day For Pharma – But What Will It Really Mean?

By Cathy Kelly



President-elect threatens a government bidding process to control drug pricing in his first post-election press conference.

11 Jan 2017 | **ANALYSIS**

The Trump Administration: Seven More Things To



Watch Out For

By Emily Hayes

Beyond pricing, industry experts weigh in on how the next administration has shifted expectations across a range of areas – including tax reform, FDA standards and the Cancer Moonshot Initiative.

06 Jan 2017 | **OPINION**

Biogen Spinraza Approval: The Perfect Antidote To Sarepta Headlines?



By Cole Werble

Approval of Biogen/Ionis' Spinraza gives the drug development community a successful, collaborative model for a rapid pathway to full approval for a rare disease therapy; it also provides a timely, compelling rebuttal to claims that US FDA's drug review operations are in dire need of reform.

06 Jan 2017 | **ANALYSIS**

How To Audit Contract Manufacturers For Data Integrity Breaches

By Joanne Eglovitch

With data integrity problems on the rise, pharmaceutical manufacturers must ensure in auditing their contract manufacturing partners that they have the robust electronic controls needed to survive an FDA inspection. The analytical lab is a good place to start when doing audits because it's where a majority of problems are found by FDA investigators.



06 Jan 2017 | **NEWS**

Training For 'Huge' EU Clinical Trials Portal And Database On Track For 2017

By Neena Brizmohun

"Thousands and thousands of people" will be using the EU clinical trials portal and

database after it goes live late next year and the European Medicines Agency plans to "invest a lot" this year in teaching trial sponsors and EU member state authorities how to use the new system. The EMA is also still working on ironing out the tricky areas of user management and how to transition legacy trials.

12 Jan 2017 | **ANALYSIS**

Global Pharma Guidance Tracker – December 2016

By **Vibha Sharma**

Stay up to date on regulatory guidelines from around the world, with the Pink Sheet's Guidance Tracker.

12 Jan 2017 | **ANALYSIS**

Biologic Product Naming: US FDA Sticks With Suffixes 'Devoid Of Meaning'

By **Sue Sutter**

Final guidance adds new factors for biosimilar and innovative sponsors to consider in developing distinguishable suffixes for nonproprietary names but FDA is unswayed by calls for meaningful suffixes derived from license holder's name; timing of retrospective application to previously approved products remains in question.

12 Jan 2017 | **NEWS**

Aspirin Wearing Hearts On Packages Needs CV Statement, Too – CDER

By **Malcolm Spicer**

In a draft US guidance, CDER encourages firms marketing OTC aspirin products with "cardiovascular-related imagery" on packaging to add a statement reminding consumers to talk to their health care providers before using aspirin for secondary prevention of CV events.



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The End Of Drug Innovation In Diabetes?

Lacking revolutionary new treatment mechanisms in type 2 diabetes, pharma is relying on combinations, convenience, and beyond-the-pill services. As prices are squeezed, the winners will be those who can deliver the best-value outcomes, not necessarily those with

a best-in-class drug.

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To: [Califf, Robert](#)
Cc: [Conover, Katie](#); [Rodriguez, Jennifer](#); [Evans, Dana](#); [Pennington, Caitlin](#)
Subject: RE: Interview Memo in prep for Matt Herper/Forbes interview
Date: Wednesday, January 18, 2017 8:10:16 AM

Thanks, Commissioner. We requested this time with Matt, so you should feel free to go beyond these questions here and give him the bigger picture. Hope it will be a fun conversation in that way. See you this afternoon.

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: January 18, 2017 at 8:04:33 AM EST
To: Young, Jason <Jason.Young@fda.hhs.gov>
Cc: Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>, Evans, Dana <Dana.Evans@fda.hhs.gov>, Pennington, Caitlin <Caitlin.Pennington@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>
Subject: RE: Interview Memo in prep for Matt Herper/Forbes interview

See below

From: Young, Jason
Sent: Tuesday, January 17, 2017 11:22 PM
To: Califf, Robert
Cc: Rodriguez, Jennifer; Conover, Katie; Evans, Dana; Pennington, Caitlin
Subject: RE: Interview Memo in prep for Matt Herper/Forbes interview

Here is what he just shared, and I have bracketed a few notes:

(1) What is the accomplishment you're proudest of from your tenure as FDA commissioner?

(b) (5)

A large black rectangular redaction box covers the response to question (1). The text "(b) (5)" is written in red at the top left corner of the redaction.

(2) What is it that you regret, or that you haven't been able to get done?

(b) (5)

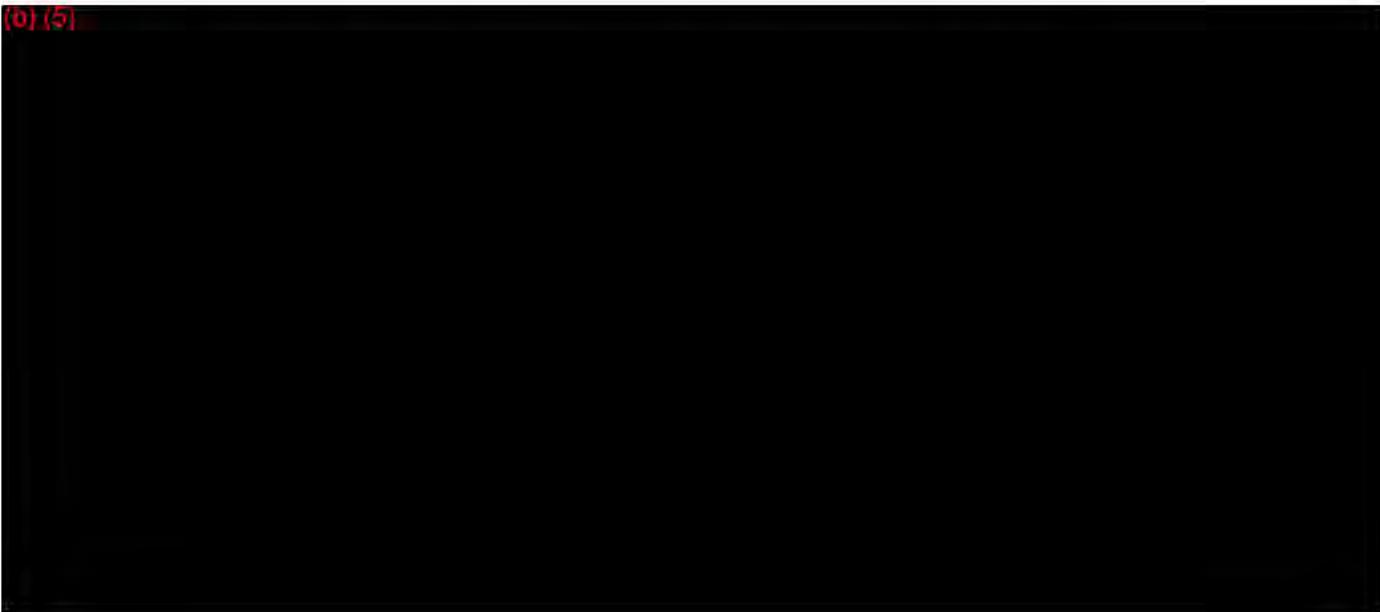
A large black rectangular redaction box covers the response to question (2). The text "(b) (5)" is written in red at the top left corner of the redaction.

(b) (5)



(3) How difficult is it for a commissioner to set goals for the agency? How much of the job is, essentially, responsive? How much of it involved tasks you did not imagine doing previously?

(b) (5)



(4) The Sarepta decision was one of the most dramatic you had to make -- a rare case where a drug approval went up to the commissioner. Would you talk about why you decided not to overrule Janet Woodcock's decision?

{you already answer this perfectly}

Got this one

(5) There's been a lot of discussion lately about whether it would be possible to replace clinical trials as a tool for drug approval. Do you think that's possible?

(b) (5)



(6) What would be your advice to the next commissioner?

(b) (5)

(7) What's next?

(b) (5)

From: Califf, Robert <RMC1@fda.hhs.gov>
Date: January 17, 2017 at 10:08:25 PM EST
To: Young, Jason <Jason.Young@fda.hhs.gov>
Cc: Pennington, Caitlin <Caitlin.Pennington@fda.hhs.gov>, Conover, Katie <Priscilla.Conover@fda.hhs.gov>, Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>, Evans, Dana <Dana.Evans@fda.hhs.gov>
Subject: RE: Interview Memo in prep for Matt Herper/Forbes interview

No word from Herper on questions?

rnc

Robert M Califf MD
Commissioner of Food and Drugs

From: Young, Jason
Sent: Tuesday, January 17, 2017 2:31 PM
To: Califf, Robert
Cc: Conover, Katie; Rodriguez, Jennifer; Evans, Dana; Pennington, Caitlin
Subject: Interview Memo in prep for Matt Herper/Forbes interview

Commissioner-

We have prepared a quick memo – primarily to share with you some of Matt Herper's recent

FDAOC0003167

reporting in Forbes – in advance of our prep today and your interview with him tomorrow.
Looking forward to talking with you at 4p today.

Best,

Jason

Jason Young

*Acting Assistant Commissioner for Media Affairs
and Senior Advisor to the Commissioner*

Office of Media Affairs

Office of External Affairs

U.S. Food and Drug Administration

Tel: 301-796-9187 / Cell: 301-512-8662

Jason.Young@fda.hhs.gov



From: Young, Jason
To: Califf, Robert
Cc: Conover, Katie; Rodriguez, Jennifer
Subject: RE: Matt Herper/Forbes: "What Trump's Libertarian Pals Don't Understand About The FDA -- Or Reality"
Date: Thursday, January 19, 2017 11:43:59 AM

Matt said he's been delayed since he had a (b) (6) to take care of all last night. He expects to get his piece up sometime in the next few days, he said. Thanks, Jason

From: Young, Jason
Sent: Wednesday, January 18, 2017 5:21 PM
To: Califf, Robert
Cc: Conover, Katie; Rodriguez, Jennifer
Subject: RE: Matt Herper/Forbes: "What Trump's Libertarian Pals Don't Understand About The FDA -- Or Reality"

Matt says his piece will post tomorrow morning. I'll monitor and distribute once it's up. Thanks!

From: Califf, Robert
Sent: Wednesday, January 18, 2017 3:08 PM
To: Young, Jason
Cc: Conover, Katie; Rodriguez, Jennifer
Subject: RE: Matt Herper/Forbes: "What Trump's Libertarian Pals Don't Understand About The FDA -- Or Reality"

Smart guy

From: Young, Jason
Sent: Wednesday, January 18, 2017 1:03 PM
To: Califf, Robert
Cc: Conover, Katie; Rodriguez, Jennifer
Subject: Matt Herper/Forbes: "What Trump's Libertarian Pals Don't Understand About The FDA -- Or Reality"

Commissioner-

Matt just published this piece – well worth a quick read, in advance of your 3:30p conversation with him. He doesn't address devices, but that would be a strong point too.

Best,
Jas

<http://www.forbes.com/sites/matthewherper/2017/01/18/what-trumps-libertarian-pals-dont-understand-about-the-fda-or-reality/#3f4122854004>

Jan 18, 2017 @ 12:25 PM 252 views

What Trump's Libertarian Pals Don't

Understand About The FDA -- Or Reality

Matthew Herper, Forbes Staff

I cover science and medicine, and believe this is biology's century.

Days before Donald Trump's inauguration as President of the United States, there's already a reality-TV-sized dose of drama. For a case in point, zoom past the pyrotechnics around Trump's cabinet nominees, currently being grilled in Congress, to the machinations around who will be named commissioner of the Food and Drug Administration.

Trump is unlikely to name an FDA commish until the conclusion of the nomination process for Senator Tom Price, his pick to run the Department of Health and Human Services, because the FDA chief reports to HHS. But the inside track appears to go to Scott Gottlieb, an oncologist, cancer survivor, and former FDA deputy commissioner who has been pushing the FDA to approve drugs faster and cut bureaucratic red tape for years. (Disclosure: Gottlieb is a Forbes contributor.)

But there has been a battle inside the Trump transition team because Gottlieb – who has written Wall Street Journal op-eds accusing the FDA of breaking the law by not approving drugs and causing generic drug shortages through over-regulation – is not libertarian enough. Someone, probably Paypal billionaire Peter Thiel, is pushing for even more radical libertarians from Silicon Valley.

Last week, Trump met with two erstwhile FDA commissioners: Jim O'Neill, a venture capitalist who works closely with Theil, and Balaji Srinivasan, who is a co-founder of genetics testing firm Counsyl, a venture capitalist at Andreessen Horowitz, and chief executive of a firm related to Bitcoin. O'Neill had given talks saying that FDA, counter to federal law, FDA should approve drugs only based on safety, not efficacy. Srinivasan, in a Twitter conversation with me, argued that the system was better in the 1920s when insulin was developed in only a few years.

Neither man is a doctor, traditionally a requirement for heading the FDA. StatNews is reporting that Srinivasan, who deleted all his tweets after they resulted in a negative press, is not in the running anymore. But the idea that the FDA is preventing a flood of new drugs from hitting the market has become a bit of conservative doctrine. Last year, Senator Ted Cruz introduced a bill arguing that the FDA should automatically approve medicines that are approved elsewhere, a plan that would lead drug companies to go jurisdiction-shopping to avoid regulation. It's an argument Gottlieb used to repeat ad nauseum, too, though not in recent years. All this is stunning because it addresses a problem that either doesn't exist or is getting better very quickly.

When it comes to new medicines, the idea that the FDA is holding up innovation just isn't so. Margaret Anderson, the executive director of the Milken Institute's FasterCures initiative, systematically interviewed pharma execs about what was holding up innovation. "Not one person said the FDA is the root of all evil," she says. Instead, Anderson says, executives were worried about getting medicines paid for by insurers.

The FDA usually approves cancer drugs before Europe does, according to a 2011 study. The median time regulators spent reviewing these medicines was just six months. Yale researchers found the FDA is at least a month faster than Europe or Canada when reviewing any type of drug.

Since 2008, the total time between when a drug is patented, shortly after its invention, and when the FDA approves it has dropped 31% to 145 months, a savings of five-and-a-half years, according to the QuintilesIMS Institute, a unit of clinical research outsourcing firm Quintiles. In recent years, the controversies about FDA have not been that it rejects too many drugs, but that it let's iffy ones, like Addyi, for female libido, through despite little evidence about safety and efficacy.

This rapid pace has been hard won. Talk of speeding up drug approvals for serious diseases first gained traction in the early 2000s, when George W. Bush nominated Mark McClellan to head the FDA. But it was derailed by a series of controversies involving drugs with serious side effects, including, most famously, the Merck pain pill Vioxx, which was withdrawn because it caused heart attacks. Between 2004 and 2008, the FDA three times refused to approve a drug that was then approved elsewhere to the world only to be removed from the market due to a deadly side effect: Exanta, an AstraZeneca blood thinner, caused liver failure; so did Prexige, a Novartis pain pill. Acomplia, which Sanofi had pitched as a pill to treat both obesity and addiction, raised the risk of psychiatric problems and suicidal thoughts.

It wasn't just that drug companies we're trying to push risky drugs to large numbers of patients, though they were. The FDA also made a handy political target for Democrats in Congress. FDA policy is often shaped as much by the fear of being called onto the carpet by Congress as by the President's direction. Presidents, after all, have a lot to do, and often can't spend much political capital defending the FDA.

The biggest strides toward fast drug approvals were made under Obama, when a Republican Congress was combined with an FDA chief, Margaret Hamburg, who was not a scientist with dramatic views on what the agency should do but instead a skilled manager. The big lesson for Silicon Valley types: the FDA is like a computer, with 17,000 employees serving as processors and thickets of regulations and rules as lines of code. You don't change anything with big proclamations. You create change by making small edits in those lines of code.

An FDA commissioner almost never makes decisions on individual drugs. That's happened only twice in recent memory. Hamburg said the Plan B morning after contraceptive should be sold over the counter, and was overruled by the Obama Administration. And Robert Califf, the outgoing commissioner, decided not to overrule the decision of another FDA official to approve a controversial muscular dystrophy drug from Sarepta Therapeutics.

That's not to say that the Silicon Valley types don't have an honest gripe. The areas they are watching most closely are those where innovation may well be getting slowed down. But their solutions are the result of myopia. For instance, many in the world of genetics bristle at FDA requirements. This is exactly the field that Srinivasan, the candidate who deleted his tweets, worked in with his startup, Counsyl. No wonder he got radicalized Peers in genetics praise him. "Balaji is one of the smartest guys I've met, and I know the tweets being quoted don't capture the nuance of his

position on the FDA," says Daniel MacArthur, the co-director of medical and population genetics at the Broad Institute of Harvard and MIT. He's known Srinivasan for 10 years, and owns some shares in Counsyl.

But Srinivasan's qualifications sound like a fit for the role of deputy commissioner, not the top job. This is the role Gottlieb had a decade ago, when, by the way a former editor of the New England Journal of Medicine said he had "an orientation which belies the goal of the FDA." The actual commissioner will spend his time on other things, like outbreaks of foodborne disease and the safety of the blood supply.

A commissioner is far more likely to achieve his goals if he can take what works in the agency and spread it. If you want faster drug approvals across the board, there would be no better way to make it happen than to have Richard Pazdur, who is in charge of oncology drugs, run the FDA's Office of New Drugs. Richard Klausner, a member of the board of directors of anti-cancer firm Juno Therapeutics, told me recently that he thinks one concern for companies like Juno, which are developing cancer-killing cells, is that they will be reviewed not by Pazdur's division, but by more conservative reviewers in a different FDA division.

This is the kind of management that someone like Gottlieb, who has already spent years in and around the FDA, might be able to pull off that a radical from the left coast wouldn't. It's likely that a Gottlieb FDA would loosen restrictions on genetic tests, and on other controversial products like e-cigarettes, while also guarding its flank against drug safety advocates on the left. Here's the reality of government: it's fine to want to drain the swamp, as Trump likes to say. But to do it you're going to first have to find allies who can live there.

From: [Mason W. Freeman](#)
To: [Califf, Robert](#)
Subject: Re: next week
Date: Thursday, January 19, 2017 1:48:11 PM

Hi Rob

Saw the news item that you would be stepping down tomorrow as FDA commissioner. Too bad for the country but hope you enjoyed your time in the job.

After you have transitioned back to Duke, let me know if your old e-mail still works or if you have a new one. We should continue the conversation we started in November about how we might work together more in the Translational sphere.

Thanks for serving at the FDA, it is an incredibly important role and we were lucky to have you there.

Best wishes,

Mason

On Nov 5, 2016, at 5:14 PM, Califf, Robert <RMCI@fda.hhs.gov> wrote:

Mason,

Thanks again for your hospitality. The visit was very helpful. Stay in touch.

rmc

From: Mason W. Freeman [<mailto:freeman@molbio.mgh.harvard.edu>]
Sent: Sunday, October 30, 2016 8:35 AM
To: Califf, Robert
Subject: Re: next week

Hi Rob

I got back late last night from London after going to a Gates Foundation Grand Challenge meeting, so sorry for the delay in replying.

Absolutely delighted that you are coming by to meet with us this week.

We finally opened our new clinical research facility, two weeks ago, which we will show you on your visit. Its creation owes a lot to you and the Duke Translational facility, so thanks for all that past help. One of the things I would like to discuss has less to do with your current position than your former one and that is how do you think we can make this kind of academic trial facility successful at serving its intended partners. I know your team found it hard to get industry business in the early days and I was hoping to hear a little about your experiences at Duke and any advice you could give us.

On other fronts, some things we could potentially discuss are :

1) Do academic centers have a role to play in helping the FDA improve regulatory science? So, for example, at the Gates meeting, Don Ingber, a biomedical engineer who runs the Wyss Institute at Harvard, presented a series of "organ-on-a-chip" devices which represent mini-organs constituted from human cells. He has some pretty cool examples of tissue mimics his group has created (e.g., lung cells and matrix that appear to respire and that create an alveolar-vascular connection-he has a tool for making them smoke and creating inflammatory injury via this toxin). Could these kinds of systems be expanded and give better toxicology insights into human organ responses than our typical rodent models now do. It still won't give you whole organism biology but it might do a better job on organ-specific issues. He also has an intestinal chip, so maybe one could validate them for bioavailability parameters compared to actual data from human study subjects. How does the FDA view that technology and its utility for future drug development.

2) Does the FDA see any need to create new interchanges with the biotech and pharma community about guidances it is developing or just how it is seeing drug development evolve in the coming decade (e.g, how you are thinking about rare disease development post the Sarepta experience). I am wondering if an academic center like the MGH (and others in our community) could host forums where the FDA could present what it is doing and perhaps hear some feedback from the biotech industry on those decisions all done at an independent academic site. Since we now have about 500 biotechs within one or two subway stops from our door, it could be a really efficient way for the FDA to interact with a community that is working on everything from CRISPR technology to complex drug-device combos.

3) Is there any interest in creating a training program between the FDA and academic medical centers with translational research activities. MGH is now partnered with Northeastern Univ here in Boston on creating a MS program in project management in life sciences. I wonder if there might be a program in regulatory science where fellows could spend several months in a rotation at the FDA learning how it works and perhaps bringing some new energy to the agency. Might be a pipeline for hiring young workers for the agency as well as filling biotech and industry roles.

4) Maybe there are projects the FDA is currently supporting, like the diabetes/CV issue we discussed by e-mail a couple months back, that we at the MGH should know about but probably don't. Any update you could provide on that would be great.

5) Finally, I know that Harry Orf, our head of research, wanted to have a brief discussion with you about clinical trial reporting on clintrials.gov by academic investigators. He said it wouldn't take long but wanted to get your input.

There are probably many other things we could discuss, but let me know if any of these are things you feel would be worth your time and we can put the agenda together for the meeting. Obviously, any thing specific you think worth discussing, we would be glad to do. I think the tour of our facility and some

explanation of how it will work in conjunction with our CTSA funded (at least for now) CRC by our head nurse, Kathy Hall, should take only 30 mins or so, so that leaves up to 90 mins for the other items.

Thanks again for coming by to meet with us. Look forward to seeing you.

Best,

Mason

On Oct 29, 2016, at 6:28 PM, Califf, Robert <RMC1@fda.hhs.gov> wrote:

Mason,

I look forward to seeing you next week. What would be your idea of a good agenda?

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: cs-author@wiley.com
To: [Califf, Robert](#)
Subject: IMPORTANT: Your article accepted in Annals of Neurology
Date: Wednesday, January 25, 2017 3:23:51 AM

Dear ,

Article ID: ANA24842

Article DOI: 10.1002/ana.24842

Internal Article ID: 13746326

Article: Regarding eteplirsen for the treatment of Duchenne muscular dystrophy

Journal: Annals of Neurology

Congratulations on the acceptance of your article for publication in Annals of Neurology.

Your article has been received by production. You may wish to access Wiley Author Services to view your article record. Please click [here](#) or paste this link into your browser to register for Wiley Author Services.

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From: [Pink Sheet](#)
To: [Califf, Robert](#)
Subject: Pink Sheet | Today's News & Analysis
Date: Monday, January 30, 2017 6:17:59 AM

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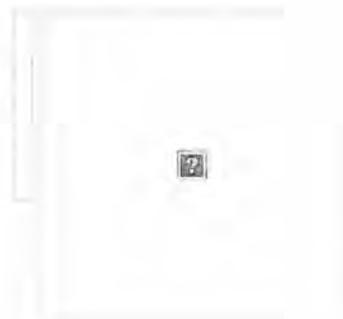
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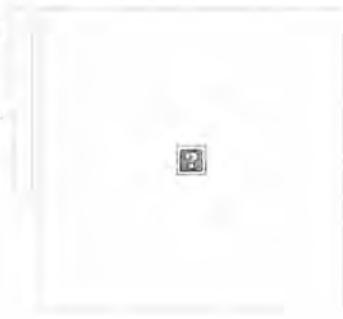
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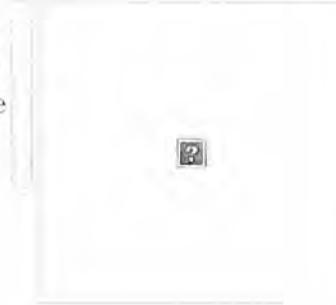
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To: [Califf, Robert](#)
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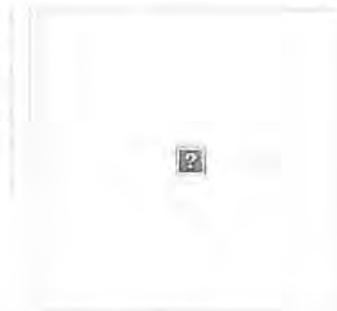
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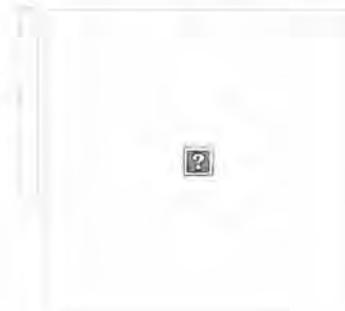
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From: [The Pink Sheet](#)
To: [Califf, Robert](#)
Subject: "The Pink Sheet" | This Week's Issue
Date: Monday, December 21, 2015 2:02:34 AM

i



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i



Pipeline Update

No One-Trick Pony: Alexion's Evolution Into A Multi-Asset Drug Company Alexion has been recognized mainly as the marketer of Soliris since 2007, but in just eight weeks the rare disease specialist added two new drugs to its commercial portfolio. Management also laid out an impressive early- to mid-stage pipeline during its first-ever investor day, suggesting the company is well positioned for long-term growth.

FDA Performance Tracker

Keeping Track: Submissions Complete For Breakthrough Therapies From Portola And Catalyst; FDA Finally Approves Bridion, Basaglar The latest drug development news and highlights from our FDA Performance Tracker.

FDA's ANDA Approvals Generic drug approvals in early and mid-December.

FDA's NDA And BLA Approvals Original new drugs and biologics recently approved by FDA.

Recent And Upcoming FDA Advisory Committee Meetings Recent and upcoming FDA advisory committee meetings and a summary of topics covered.

Advisory Committees

Drisapersen Advisory Committee Is Rough Welcome To FDA For Patient Groups Advocates counter FDA's problems with Duchenne muscular dystrophy treatment's trial data using real-life experience.

The Califf Factor: Commissioner Nominee's Role In IMPROVE-IT Gets Notice TIMI Study Group's Eugene Braunwald says Robert Califf, his co-chair on the IMPROVE-IT steering committee, 'worked very hard for nine-and-a-half years' on trial before leaving Duke to join FDA.

Business & Finance

Deal Watch: Sanofi, Boehringer Swap Side Businesses Busy week for AstraZeneca sees buyout of Acerta and acquisition of remaining Daliresp/Daxas worldwide rights from Takeda. Amgen and GSK undo their cancer drug alliances from 2009 and 2010, with all rights reverting to the big biotech.

Drug Review Profile

Praluent Vs. Repatha: Interactive Timeline Of Regulatory Milestones Many key milestones in PCSK9 inhibitors' development happened within months or weeks of each other; as products reached FDA and edged toward approval, that separation narrowed to days and even hours.

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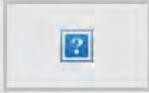
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FDA Can't Find Efficacy For BioMarin's Drisapersen On verge of advisory committee meeting, FDA says development program was exemplary, but is disappointed data are inconclusive.

HHS Drug Forum: CMS' Slavitt Highlights Price Transparency As One Key To Affordability In the HHS-sponsored "listen and learn" forum about pharmaceutical innovation, access and affordability, CMS chief Slavitt outlined three "domains" that he wants to address: value and value-based payments; pricing information transparency and availability; and government incentives and hurdles.

Flu Vaccines: Egg-Based Manufacturing Questioned At Hill Hearing Rep. DeGette criticizes 'market forces' that are delaying move to cell-based and recombinant technology in sharp questioning of FDA's Karen Midthun; HHS considering delay in finalizing vaccine composition.

Video: Interview With ADC Therapeutics' Richard Onyett Immunotherapy tie-ups will be key for the future of the ADC space, Onyett says on the sidelines of BIO-Europe 2015.



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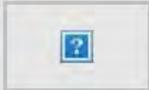
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BioMarin May Have To Find Subgroups For Drisapersen Efficacy FDA advisory committee has concerns about efficacy, says more work needed to identify responders.

Takeda Prices Oral Multiple Myeloma Follow-On Ninlaro On Par With Velcade FDA approval of the next-generation proteasome inhibitor ixazomib will pave the way for an all-oral combination with Revlimid and dexamethasone and give Takeda an opportunity to extend its oncology franchise beyond Velcade, which could see generic competition in late 2017.

ICER's Drug Review Agenda Includes Lung Cancer, MS, Psoriasis Products

Technology assessments planned for 2016 focus on drugs expected to be approved in the next six months.

Video: Sean Marett On BioNTech's Immunotherapy Alliance With Sanofi Company COO Marett reviews BioNTech's RNA technology and the potential for immunotherapy combination studies, on the sidelines of BIO-Europe 2015.



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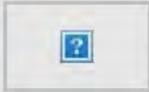
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Top Stories

J.P. Morgan Notebook, Jan. 14: Kite, Cellectis And Mannkind Round-up of news and notes from the last presentations at the 2016 J.P. Morgan Healthcare Conference in San Francisco.

Medicare's Proliferating Drug Databases The Sunshine Act required Medicare to list all payments to physicians by drug companies. Now that the database is established, how long before it is linked to other CMS sites - such as drug utilization and provider quality databases?

BioMarin's Drisapersen 'Compete Response' Shows FDA Flexibility Still Limited FDA wants another clinical trial for Duchenne muscular dystrophy treatment; focus moves to Sarepta's candidate, which gets committee review next week.

Patient Engagement Helps Nexavar Secure Scottish Reimbursement For Liver Cancer Scottish HTA approves product following a patient committee meeting, in contrast to NICE's stance.



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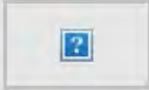
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Eyeing The Ear: Start-up Decibel Intends To Tackle Inner-Ear Indications With a better understanding of how to deliver and optimize therapeutics to the inner ear, the Third Rock-backed start-up intends to become the standard bearer for hearing loss therapeutics.

Duchenne Muscular Dystrophy Approval Race: BioMarin Pulls Back Into Lead FDA advisory committee reviews for BioMarin's drisapersen and Sarepta's eteplirsen, once eyed as back-to-back meetings, are now set months apart. Draft guidance may help firms overcome previous findings of inadequate data.

Part D In 2016: Higher Premiums, Deductibles And Cost-Sharing For Drugs On average, beneficiaries will pay 13% more in Medicare drug benefit monthly premiums than in 2015, the largest increase since 2009, Kaiser Family Foundation report finds. Plus, more plans are relying on deductibles and charging coinsurance for both preferred and non-preferred brand drugs.

EMA Pilot For Early Advice On Pediatric Research Finally Gets Going EMA has gotten applications from sponsors for early advice on developing medicines for pediatric indications, under one-year pilot project.



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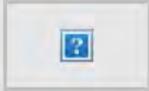
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Attached is the 90-Day Advisory Committee Meeting report for November of 2015 through January of 2016. There are a number of high-visibility meetings in the report. On November 13th there is a CBER meeting on maternal immunization to protect the infant and on November 24th there is a meeting on Duchenne muscular dystrophy. There are five more high-visibility meetings between December 1st and December 15th.

Have a good weekend,

...Michael

Michael Ortwerth, Ph.D.
Director, Advisory Committee Oversight and Management Staff
Office of Special Medical Programs
Office of the Commissioner
Direct: 301-796-8222
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FDA Advisory Committee 90-Day Report for April 2014 - June 2014

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			November 2 - November 6		
CDER	Joint Meeting of the Antimicrobial Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee	11/5/2015	The committees will discuss the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease, and uncomplicated urinary tract infections in the context of available safety information and the treatment effect of antibacterial drugs in these clinical conditions	10/1/2015 - C	N
NCTR	Science Advisory Board	11/5/2015	The NCTR Director will welcome the participants and provide a Center-wide update on scientific initiatives and accomplishments during the past year. The SAB will be presented with an overview of the Division of Biochemistry Subcommittee and the Subcommittee Site Visit Report. Following the public session, the SAB will hear an update from each of NCTR's research Division's, followed by a update on NCTR's Global Interactions	8/14/2015 - C	N
CDER	Anesthetic and Analgesic Drug Products Advisory Committee	11/6/2015	The committee will discuss new drug application (NDA) 022225, sugammadex sodium injection, submitted by Organon USA Inc, a subsidiary of Merck & Co, Inc, for the proposed indication of reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium	9/14/2015 - C	N
			November 9 - November 13		
CBER	Vaccines and Related Biological Products Advisory Committee	11/13/2015	The committee will meet in open session to discuss considerations for evaluation of the safety and effectiveness of vaccines administered to pregnant women to protect the infant	9/21/2015 - C	Y
			November 16 - November 20		
CBER	Joint Meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee	11/18/2015	The committees will discuss the safety and efficacy of Biologics License Application (BLA) 125593, Mycobacterium phlei Cell Wall- DNA Complex (MCNA), submitted by Telesta Therapeutics Inc. The proposed indication (use) for this product is treatment of non-muscle invasive bladder cancer (NMIBC) at high risk of recurrence or progression in adult patients who failed prior Bacillus Calmette-Guerin (BCG) immunotherapy	9/28/2015 - C	N
CDRH	Gastroenterology and Urology Devices Panel	11/18-19/2015	(b) (4)	10/07/2015 - C	N

FDA Advisory Committee 90-Day Report for April 2014 - June 2014

OC	Science Board to the FDA	11/18/2015	On November 18, 2015 the committee will hear updates from the CERSI Evaluation Subcommittee and the ORA Food Emergency Response Network Evaluation Subcommittee. The Board will hear about the scope of FDA's involvement in precision medicine, as well as an overview of specific health informatics initiatives including precisionFDA, Open FDA, and Chillax. The Board will also hear about FDA's laboratory safety initiative. A recipient of one of the FY2014 Scientific Achievement Awards (selected by the Board) will provide an overview of the activities for which the award was given.	11/3/2015 - C	N
CDER	Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee	11/19/2015	Information will be presented to gauge investigator interest in exploring potential pediatric development plans for two products in various stages of development for adult cancer indications. The subcommittee will consider and discuss issues concerning diseases to be studied, patient populations to be included, and possible study designs in the development of these products for pediatric use. The discussion will also provide information to the Agency pertinent to the formulation of written requests for pediatric studies, if appropriate. The products under consideration are: (1) ABT-414, application submitted by AbbVie, Inc., and (2) Lenvatinib, application submitted by Eisai, Inc.	9/17/2015 - C	N
November 23 - November 27					
CDER	Peripheral and Central Nervous System Drugs Advisory Committee	11/24/2015	The committee will discuss new drug application 206031, drisapersen solution for injection, sponsored by BioMarin Pharmaceutical Inc., for the treatment of patients with Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing.	10/15/2015 - C	Y
November 30 - December 4					
CDER	Psychopharmacologic Drugs Advisory Committee	12/1/2015	The committee will discuss the efficacy and safety data for new drug application (NDA) 21164, gepirone hydrochloride extended-release tablets, submitted by Fabre-Kramer Pharmaceuticals, Inc., for the proposed indication of major depressive disorder.	9/9/2015 - C	Y
December 7 - December 11					
CFSAN	Food Advisory Committee	12/7-8/2015	The committee will discuss FDA's policies regarding the contamination of foods with the pathogen <i>Listeria monocytogenes</i> (<i>L. monocytogenes</i>).	11/9/2015 - C	Y
CDER	Pulmonary/Allergy Drugs Advisory Committee	12/9/2015	The committee will discuss the biologics licensing application (BLA) 761033 for reslizumab injection solution, submitted by Teva Pharmaceuticals for the proposed indication to reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents 12 years of age and above with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.	9/21/2015 - C	Y
CDER	Joint Meeting of the Pulmonary/Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee	12/10/2015	The committees will discuss the safety of codeine in children 18 years of age and younger. Codeine (most often in combination with acetaminophen) is used for the treatment of pain in children; however, it is contraindicated for the management of pain after tonsillectomy and/or adenoidectomy. Codeine (in combination with other medicines) is used for the relief of cough associated with upper respiratory allergies or the common cold in children. Codeine is available by prescription and also through the over-the-counter (OTC) Drug Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (21 CFR 341.14, 21 CFR 341.74, and 21 CFR 341.90). The focus of the meeting will be the risk of serious adverse events, such as respiratory depression and death, including reports in children who are CYP2D6 ultra-rapid metabolizers. The committees will discuss whether the use of codeine in children should be restricted further beyond the current contraindication described previously and whether codeine should be available through the OTC Drug Monograph.	10/27/2015 - C	Y
December 14 - December 18					

FDA Advisory Committee 90-Day Report for April 2014 - June 2014

CDER	Endocrinologic and Metabolic Drugs Advisory Committee	12/14/2015	The committee will discuss, in general, a supplemental new drug application for ezetimibe/simvastatin (Vytorin) by Merck for the reduction of major cardiovascular events The results of the IMPROVE-IT (IMProved Reduction of Outcomes: VYTORIN Efficacy International Trial) study, which compared VYTORIN (ezetimibe/simvastatin) to simvastatin monotherapy will be discussed	10/5/2015 - 10/26/2015 - E	Y
OC	Risk Communication Advisory Committee	12/14-15/2015	The Committee will discuss recent developments in risk communications and related sciences, and possible approaches and applications in the context of FDA communications	10/5/2015 - 10/26/2015 - E	N
CDER	Blood Products Advisory Committee	12/15/2015	(b) (4)	10/5/2015 - 10/26/2015 - E	Y
			December 1 - December 25		
			No Meetings Currently Scheduled		
			December 28 - January 1		
			No Meetings Currently Scheduled		
			January 4 - January 8		
			No Meetings Currently Scheduled		
			January 11 - January 15		
CDER	Psychopharmacologic Drugs Advisory Committee	1/12/2016	The committee will discuss new drug application (NDA) 204442, PROBUPHINE (buprenorphine hydrochloride and ethylene vinyl acetate) subdermal implant, submitted by Braeburn Pharmaceuticals, Inc. for the proposed indication of maintenance treatment of opioid dependence	11/3/2015 - 11/24/2015 - E	Y
CDER	Gastrointestinal Drugs Advisory Committee	1/13/2016	(b) (4)	11/3/2015 - 11/24/2015 - E	N
			January 18 - January 22		
CDER	Peripheral and Central Nervous System Drugs Advisory Committee	1/22/2016	The committee will discuss NDA 206488, eteplirsen for injection, submitted by Sarepta, Therapeutics, for the treatment of Duchenne muscular dystrophy	11/12/2015 - 12/3/2015 - E	Y
			January 25 - January 29		
			No Meetings Currently Scheduled		
			February 1 - February 5		
CDER	Psychopharmacologic Drugs Advisory Committee	2/3/2016	The committee will discuss NDA 204447/sNDA 006, the effectiveness of vortioxetine for the treatment of cognitive dysfunction in major depressive disorder (MDD) submitted by Takeda Development Center Americas, Inc	12/23/2015 - 1/13/2016 - E	Y
			February 8 - February 12		
CDER	Arthritis Advisory Committee	2/9/2016	The committee will discuss Celtrion's infliximab biosimilar product	12/28/2015 - 1/18/2016 - E	Y
CDER	Arthritis Advisory Committee	2/10/2016	(b) (4)	12/28/2015 - 1/18/2016 - E	Y

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Director, Advisory Committee Oversight and Management Staff
Office of Special Medical Programs
Office of the Commissioner
Direct: 301-796-8222
Main Line: 301-796-8220

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			August 3 - August 7		
			No Meetings Currently Scheduled		
			August 10 - August 14		
			No Meetings Currently Scheduled		
			August 17 - August 21		
			No Meetings Currently Scheduled		
			August 24 - August 28		
			No Meetings Currently Scheduled		
			August 31 - September 4		
			No Meetings Currently Scheduled		
			September 7 - September 11		
CDER	Anesthetic and Analgesic Drug Products Advisory Committee	9/10/2015	The committees will discuss new drug application (NDA) 206830, oxycodone immediate-release tablets, submitted by Purdue Pharma, with the proposed indication of the management of moderate to severe pain where the use of an opioid analgesic is appropriate	7/17/2015 - 8/7/2015 - E	Y
CDER	Anesthetic and Analgesic Drug Products Advisory Committee	9/11/2015	The committees will discuss NDA 208090, Oxycodone Deterx, a new extended release oxycodone product with abuse-deterrent properties	7/17/2015 - 8/7/2015 - E	Y
			September 14 - September 18		
CBER	Vaccines and Related Biological Products Advisory Committee	9/15/2015	The Committee will meet to discuss and make recommendations on the safety and immunogenicity of seasonal trivalent Influenza Vaccine, Surface Antigen, Inactivated, Adjuvated with MF59 (Fluad) manufactured by Novartis	7/17/2015 - C	Y
OC	Pediatric Advisory Committee	9/16/2015	Pediatric Advisory Committee (PAC) will meet to discuss pediatric-focused safety reviews, as mandated by the Best Pharmaceuticals for Children Act (Public Law 107-109) and the Pediatric Research Equity Act (Public Law 108-155) The PAC will meet to discuss the following products: DUREZOL (difluprednate ophthalmic emulsion) 0.05%, Phenylephrine Hydrochloride Ophthalmic Solution, ZYLET (loteprednol etabonate and tobramycin ophthalmic suspension), BETHKIS (tobramycin Inhalation Solution), INTELENCE (etravirine), PREZISTA (darunavir), VIRAMUNE XR (nevirapine), EPIDUO (adapalene and benzoyl peroxide), EXJADE (deferasirox), DOTAREM (gadoterate meglumine), FYCOMPA (perampanel), RECOTHROM (thrombin, topical [recombinant]), PREVNAR 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]), PLEXIMMUNE, ELANA SURGICAL KIT (HUD), Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD), ENTERRA™ Therapy System, and CONTEGRA Pulmonary Valved Conduit	8/10/2015 - 8/20/2015 - E	Y
CDRH	Obstetrics and Gynecology Devices	9/24/2015	The committee will discuss current knowledge about the safety and effectiveness of the Essure System (Bayer HealthCare Pharmaceuticals Inc) intended for permanent birth control FDA is convening this committee to seek expert scientific and clinical opinion on the risks and benefits of this device when used for permanent birth control, based on available scientific data The committee will make recommendations regarding the appropriate use, labeling, and other potential risk mitigations for this device	7/22/2015 - C	Y
			September 28 - October 2		

FDA Advisory Committee 90-Day Report for April 2014 - June 2014

			No Meetings Currently Scheduled		
			October 5 - October 9		
			No Meetings Currently Scheduled		
			October 12 - October 16		
			No Meetings Currently Scheduled		
			October 19 - October 23		
			No Meetings Currently Scheduled		
			October 26 - October 30		
CDER	Pharmacy Compounding Advisory Committee	10/27-28/2015	TBD	9/3/2015 - 9/24/2015 - E	Y
			November 2 - November 6		
CDER	Bone, Reproductive, and Urologic Drugs Advisory Committee	11/3/2015	(b) (4)	9/16/2015 - 10/7/2015 - E	N
CDER	Bone, Reproductive, and Urologic Drugs Advisory Committee	11/4/2015	The committee will discuss a guidance document for osteoporosis	9/16/2015 - 10/7/2015 - E	N
CDER	Joint Meeting of the Antimicrobial Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee	11/5/2015	The committees will discuss the balance of risk and benefit for certain "milder" infectious diseases such as uncomplicated urinary tract infection, acute sinusitis, acute exacerbation of chronic bronchitis and the serious adverse reactions caused by the fluorquinolone class of drugs	9/16/2015 - 10/7/2015 - E	N
CDER	Anesthetic and Analgesic Drug Products Advisory Committee	11/6/2015	The committee will discuss NDA 022225, Sugammadex sodium injection, submitted by Organon USA Inc for the proposed indication of reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium	9/16/2015 - 10/7/2015 - E	N
NCTR	Science Advisory Board	11/5/2015	The NCTR Director will welcome the participants and provide a Center-wide update on scientific initiatives and accomplishments during the past year. The SAB will be presented with an overview of the Division of Biochemistry Subcommittee and the Subcommittee Site Visit Report. Following the public session, the SAB will hear an update from each of NCTR's research Division's, followed by a update on NCTR's Global Interactions	9/28/2015 - 10/9/2015 - E	N
			November 9 - November 13		
			No Meetings Currently Scheduled		
			November 16 - November 20		
CBER	Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee	11/18/2015	The committees will discuss the safety and efficacy of Biologics License Application (BLA) 125593, Mycobacterium phlei Cell Wall- DNA Complex (MCNA), submitted by Telesta Therapeutics Inc. The proposed indication (use) for this product is treatment of non-muscle invasive bladder cancer (NMIBC) at high risk of recurrence or progression in adult patients who failed prior Bacillus Calmette-Guerin (BCG) immunotherapy	9/4/2015 - 10/19/2015 - E	N
CDER	Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee	11/19-20/2015	The committee will discuss up to 6 products for potential pediatric development	10/1/2015 - 10/22/2015 - E	N

FDA Advisory Committee 90-Day Report for April 2014 - June 2014

November 23 - November 27					
CDER	Peripheral and Central Nervous System Drugs Advisory Committee	11/23/2015	The committee will discuss NDA 206031, drisapersen solution, sponsored by BioMarin Pharmaceutical, Inc , for the treatment of Duchenne muscular dystrophy	10/5/2015 - 10/26/2015 - E	Y
CDER	Peripheral and Central Nervous System Drugs Advisory Committee	11/24/2016	The committee will discuss eteplirsen, sponsored by Sarepta Therapeutics, Inc , for the treatment of Duchenne muscular dystrophy	10/5/2015 - 10/26/2015 - E	Y

From: [Ortwerth, Michael](#)
To: [Bull, Jonca](#); [Califf, Robert](#); [Dawson, Rhonda](#); [Esposito, Denise](#); [Franklin, Joseph](#); [Hamilton, Kimberly](#); [Hays, Teresa](#); [Helmanis, Lisa M](#); [Howard, Sally](#); [Johnican, Tonya](#); [Lurie, Peter](#); [Maloney, Lesley](#); [Morris, Larry](#); [Quinn, Kathleen](#); [Roth, Deborah](#); [Soreth, Janice M](#); [Spell LeSane, Dornette D](#); [Varnado, Martina](#); [Warner, Jill](#)
Subject: 90-Day Advisory Committee Meeting Report: September - November, 2015
Date: Tuesday, September 08, 2015 4:21:30 PM
Attachments: [90DayMeetingList_Sept2015ThroughNov2015_FINAL.xls](#)

Hello,

Attached is the 90-Day Advisory Committee Meeting report for September through November of 2015. There are a number of high-visibility meetings in the report. This Thursday and Friday CDER will be holding two meetings to address oxycodone products with abuse-deterrent properties.

Have a good evening,

...Michael

Michael Ortwerth, Ph.D.
Director, Advisory Committee Oversight and Management Staff
Office of Special Medical Programs
Office of the Commissioner
Direct: 301-796-8222
Main Line: 301-796-8220

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FDA Advisory Committee 90-Day Report for April 2014 - June 2014

NOT FOR PUBLIC DISCLOSURE

CENTER / OFFICE	COMMITTEE	MEETING DATE	TOPIC/AGENDA	Estimated Date Range (E) or Confirmed (C) Date of FR Notice Publication (e.g., enter "10/1 - 31/2012 - E" or "5/27/2012 - C")	Hi Visibility Y/N
			August 31 - September 4		
			No Meetings Currently Scheduled		
			September 7 - September 11		
CDER	Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee	9/10/2015	The committees will be asked to discuss new drug application (NDA) 206830, oxycodone immediate-release tablets, submitted by Purdue Pharma, with the proposed indication of the management of moderate to severe pain where the use of an opioid analgesic is appropriate. It has been formulated with the intent to provide abuse-deterrent properties. The pharmacokinetic data demonstrate that there is a significant food effect resulting in a significant delay in absorption and peak plasma concentration of oxycodone when taken with food. The applicant proposes to address this finding by labeling the product to be taken on an empty stomach, but patients may have difficulty complying with these instructions as the product is dosed every 4 to 6 hours as needed. The committees will be asked to discuss the potential safety risks and the potential effects on efficacy associated with the delayed peak concentration when taken with food, and the feasibility of labeling to be taken on an empty stomach as a means to mitigate the potential risks. The committees will also be asked to consider whether the potential public health benefit of the product's abuse deterrent properties are sufficient to outweigh the risk to patients who are prescribed the product for the management of pain.	8/10/2015 - C	Y
CDER	Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee	9/11/2015	The committees will discuss new drug application (NDA) 208090, oxycodone extended-release capsules for oral use, submitted by Collegium Pharmaceuticals, proposed for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate. This product has been formulated with the intent to provide abuse-deterrent properties. Pharmacokinetic data demonstrate that, in order to deliver the intended amount of oxycodone, the drug product must be taken with food. The committees will be asked to discuss the potential safety risks and the potential effects on efficacy associated with the extent of the food effect, and potential fluctuations in oxycodone levels that may occur if the product is not taken consistently with the same amount of food. In addition, the committees will be asked to review and discuss whether the data characterizing the abuse-deterrent properties support the likelihood that this drug product will have a meaningful effect on abuse and whether potential benefits to the public from abuse-deterrent properties outweigh potential risks to patients from the effect of food. The committees will be asked to vote on whether this product should be approved for marketing in the United States.	8/10/2015 - C	Y
			September 14 - September 18		
CBER	Vaccines and Related Biological Products Advisory Committee	9/15/2015	The Committee will meet to discuss and make recommendations on the safety and immunogenicity of seasonal trivalent Influenza Vaccine, Surface Antigen, Inactivated, Adjuvated with MF59 (Fluad) manufactured by Novartis.	7/17/2015 - C	Y

FDA Advisory Committee 90-Day Report for April 2014 - June 2014

OC	Pediatric Advisory Committee	9/16/2015	Pediatric Advisory Committee (PAC) will meet to discuss pediatric-focused safety reviews, as mandated by the Best Pharmaceuticals for Children Act (Public Law 107-109) and the Pediatric Research Equity Act (Public Law 108-155) The PAC will meet to discuss the following products: DUREZOL (difluprednate ophthalmic emulsion) 0.05%, Phenylephrine Hydrochloride Ophthalmic Solution, ZYLET (loteprednol etabonate and tobramycin ophthalmic suspension), BETHKIS (tobramycin Inhalation Solution), INTELENCE (etravirine), PREZISTA (darunavir), VIRAMUNE XR (nevirapine), EPIDUO (adapalene and benzoyl peroxide), EXJADE (deferasirox), DOTAREM (gadoterate meglumine), FYCOMPA (perampanel), RECOTHROM (thrombin, topical [recombinant]), PREVNAR 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]), PLEXIMMUNE, ELANA SURGICAL KIT (HUD), Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD), ENTERRA™ Therapy System, and CONTEGRA Pulmonary Valved Conduit	8/12/2015 - C	Y
			September 21 - September 25		
CDRH	Obstetrics and Gynecology Devices	9/24/2015	The committee will discuss current knowledge about the safety and effectiveness of the Essure System (Bayer HealthCare Pharmaceuticals Inc) intended for permanent birth control FDA is convening this committee to seek expert scientific and clinical opinion on the risks and benefits of this device when used for permanent birth control, based on available scientific data The committee will make recommendations regarding the appropriate use, labeling, and other potential risk mitigations for this device	7/22/2015 - C	Y
			September 28 - October 2		
			No Meetings Currently Scheduled		
			October 5 - October 9		
			No Meetings Currently Scheduled		
			October 12 - October 16		
			No Meetings Currently Scheduled		
			October 19 - October 23		
CDER	Arthritis Advisory Committee	10/23/2015	The committee will discuss new drug application (NDA) 207988, lesinurad oral tablets, submitted by Ardea Biosciences, Inc, for the treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor	8/19/2015 - C	N
			October 26 - October 30		
CDER	Pharmacy Compounding Advisory Committee	10/27-28/2015	The committee will discuss revisions FDA is considering to the list of drug products that may not be compounded under the exemptions provided by the FD&C Act because the drug products have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective The list of those drug products is currently codified at 21 CFR 216.24 FDA now is considering whether to add one more drug to the list: quinacrine Additionally, the committee will discuss 13 bulk drug substances nominated for inclusion on the section 503A bulk drug substances list FDA intends to discuss the following nominated bulk drug substances: quinacrine, methylsulfonylmethane, boswellia, d-ribose, curcumin, germanium sesquioxide, rubidium chloride, deoxy d-glucose, alanyl-l-glutamine, glutaraldehyde, glycyrrhizin, ubiquinol 30% powder, and domperidone The nominators of these substances will be invited to make a short presentation supporting the nomination Other nominated substances will be discussed at future committee meetings	9/14/2015 - 9/25/2015 - E	Y
			November 2 - November 6		

FDA Advisory Committee 90-Day Report for April 2014 - June 2014

CDER	Bone, Reproductive, and Urologic Drugs Advisory Committee	11/3/2015	(b) (4)	8/20/2015 - C	N
CDER	Bone, Reproductive, and Urologic Drugs Advisory Committee	11/4/2015	The committee will discuss a guidance document for osteoporosis	9/16/2015 - 10/7/2015 - E	N
CDER	Joint Meeting of the Antimicrobial Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee	11/5/2015	The committees will discuss the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease, and uncomplicated urinary tract infections in the context of available safety information and the treatment effect of antibacterial drugs in these clinical conditions	9/16/2015 - 10/7/2015 - E	N
NCTR	Science Advisory Board	11/5/2015	The NCTR Director will welcome the participants and provide a Center-wide update on scientific initiatives and accomplishments during the past year The SAB will be presented with an overview of the Division of Biochemistry Subcommittee and the Subcommittee Site Visit Report Following the public session, the SAB will hear an update from each of NCTR's research Division's, followed by a update on NCTR's Global Interactions	9/28/2015 - 10/9/2015 - E	N
CDER	Anesthetic and Analgesic Drug Products Advisory Committee	11/6/2015	The committee will discuss new drug application (NDA) 022225, sugammadex sodium injection, submitted by Organon USA Inc , a subsidiary of Merck & Co , Inc , for the proposed indication of reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium	9/16/2015 - 10/7/2015 - E	N
November 9 - November 13					
CBER	Vaccines and Related Biological Products Advisory Committee	11/13/2015	The committee will meet in open session to discuss considerations for evaluation of the safety and effectiveness of vaccines administered to pregnant women to protect the infant	8/30/15 - 10/14/2015 - E	Y
November 16 - November 20					
CBER	Joint Meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee	11/18/2015	The committees will discuss the safety and efficacy of Biologics License Application (BLA) 125593, Mycobacterium phlei Cell Wall- DNA Complex (MCNA), submitted by Telesta Therapeutics Inc The proposed indication (use) for this product is treatment of non-muscle invasive bladder cancer (NMIBC) at high risk of recurrence or progression in adult patients who failed prior Bacillus Calmette-Guerin (BCG) immunotherapy	9/4/2015 - 10/19/2015 - E	N
CDRH	Gastroenterology and Urology Devices Panel	11/18-19/2015	(b) (4)	10/1/2015 - 10/22/2015 - E	N

FDA Advisory Committee 90-Day Report for April 2014 - June 2014

CDER	Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee	11/19/2015	(b) (4)	10/1/2015 - 10/22/2015 - E	N
November 23 - November 27					
CDER	Peripheral and Central Nervous System Drugs Advisory Committee	11/23/2015	The committee will discuss new drug application 206031, drisapersen solution for injection, sponsored by BioMarin Pharmaceutical Inc , for the treatment of patients with Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing	10/5/2015 - 10/26/2015 - E	Y
November 30 - December 4					
CDER	Psychopharmacologic Drugs Advisory Committee	12/1/2015	The committee will discuss the efficacy and safety data for new drug application (NDA) 21164, gepirone hydrochloride extended-release tablets, submitted by Fabre-Kramer Pharmaceuticals, Inc , for the proposed indication of major depressive disorder	9/9/2015 - C	Y
December 7 - December 11					
CDER	Pulmonary/Allergy Drugs Advisory Committee	12/9/2015	The committee will discuss the biologics licensing application (BLA) 761033 for reslizumab injection solution, submitted by Teva Pharmaceuticals for the proposed indication to reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents 12 years of age and above with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids	10/5/2015 - 10/26/2015 - E	Y
CDER	Joint Meeting of the Pulmonary/Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee	12/10/2015	The committees will discuss codeine combination products for cough/cold indications and the risk in pediatric patients	10/5/2015 - 10/26/2015 - E	Y
December 14 - December 18					
CDER	Endocrinologic and Metabolic Drugs Advisory Committee	12/14/2015	The committee will discuss, in general, a supplemental new drug application for ezetimibe/simvastatin (Vytorin) by Merck for the reduction of major cardiovascular events The results of the IMPROVE-IT (IMProved Reduction of Outcomes: VYTORIN Efficacy International Trial) study, which compared VYTORIN (ezetimibe/simvastatin) to simvastatin monotherapy will be discussed	10/5/2015 - 10/26/2015 - E	Y

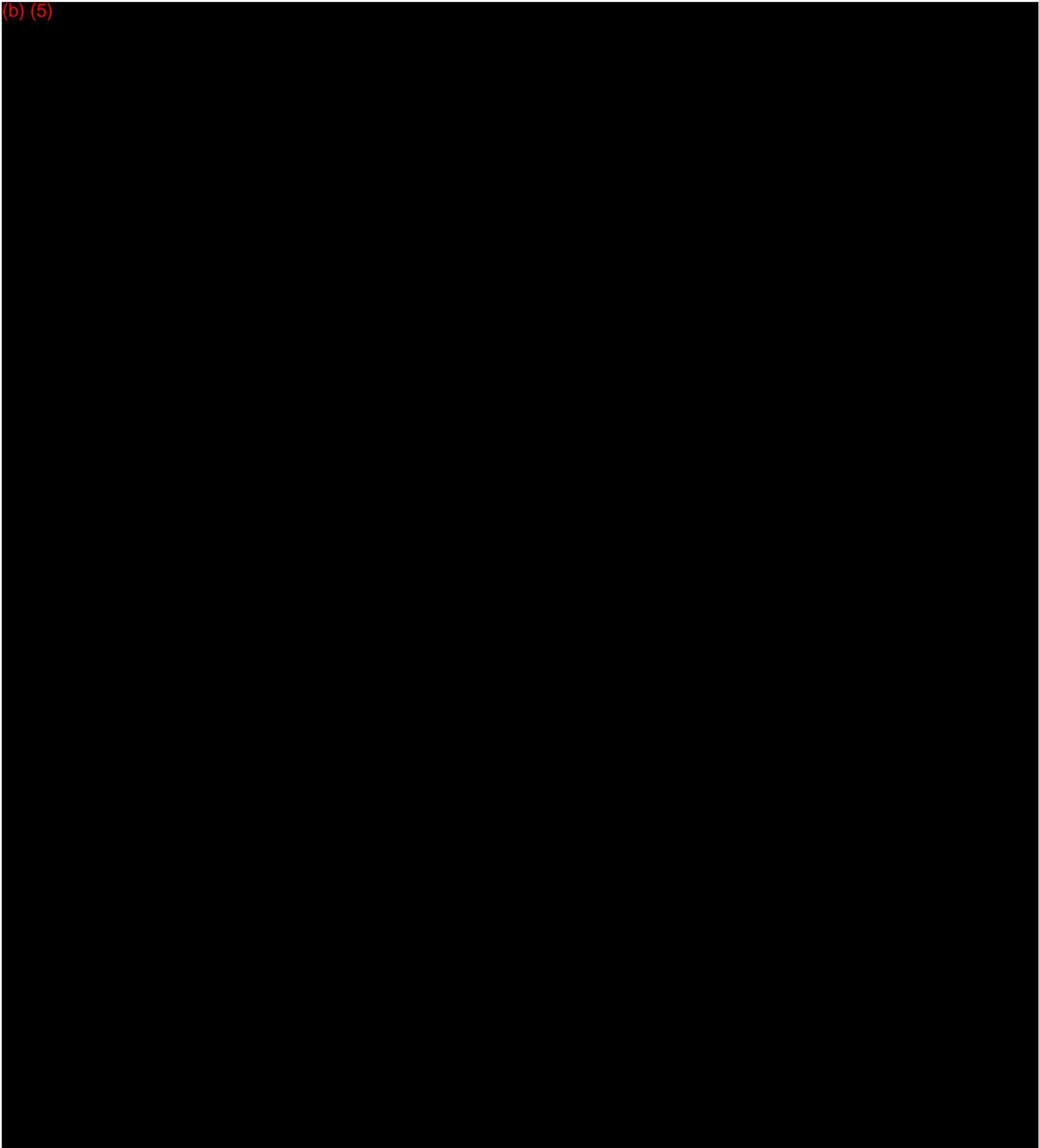
From: [Sherman, Rachel](#)
To: [Evans, Dana](#)
Cc: [Califf, Robert](#); [Dickinson, Elizabeth \(FDA\)](#)
Subject: Clean copy of the appeal memo
Date: Tuesday, September 13, 2016 1:36:16 PM
Attachments: [2016 Sept 012 R2 Eteplirsen CLEAN.doc](#)

Dana – would you be able to combine both files (this one and the one Liz just sent) into one email so that Rob has them together?

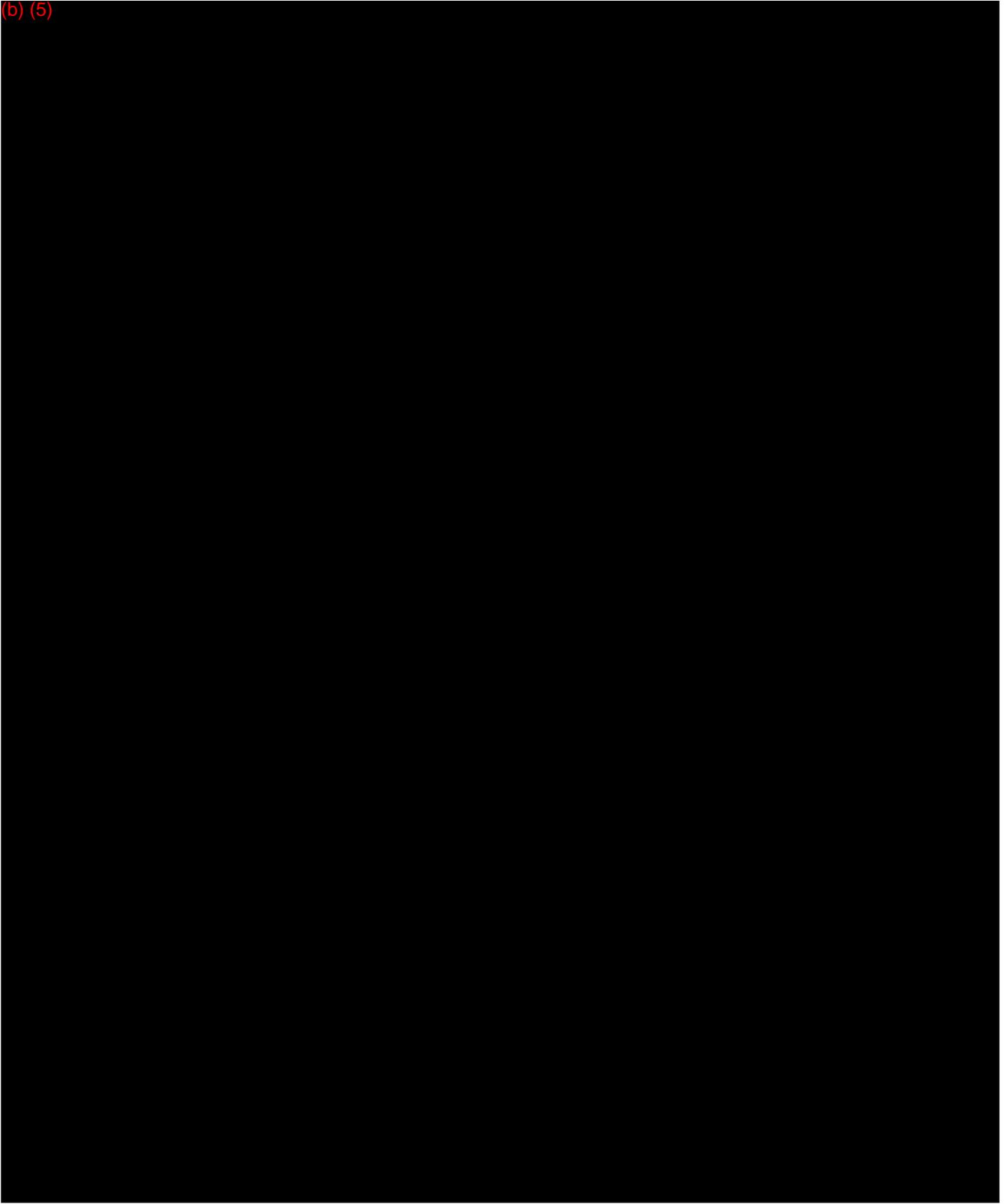
Thanks much!

Rachel

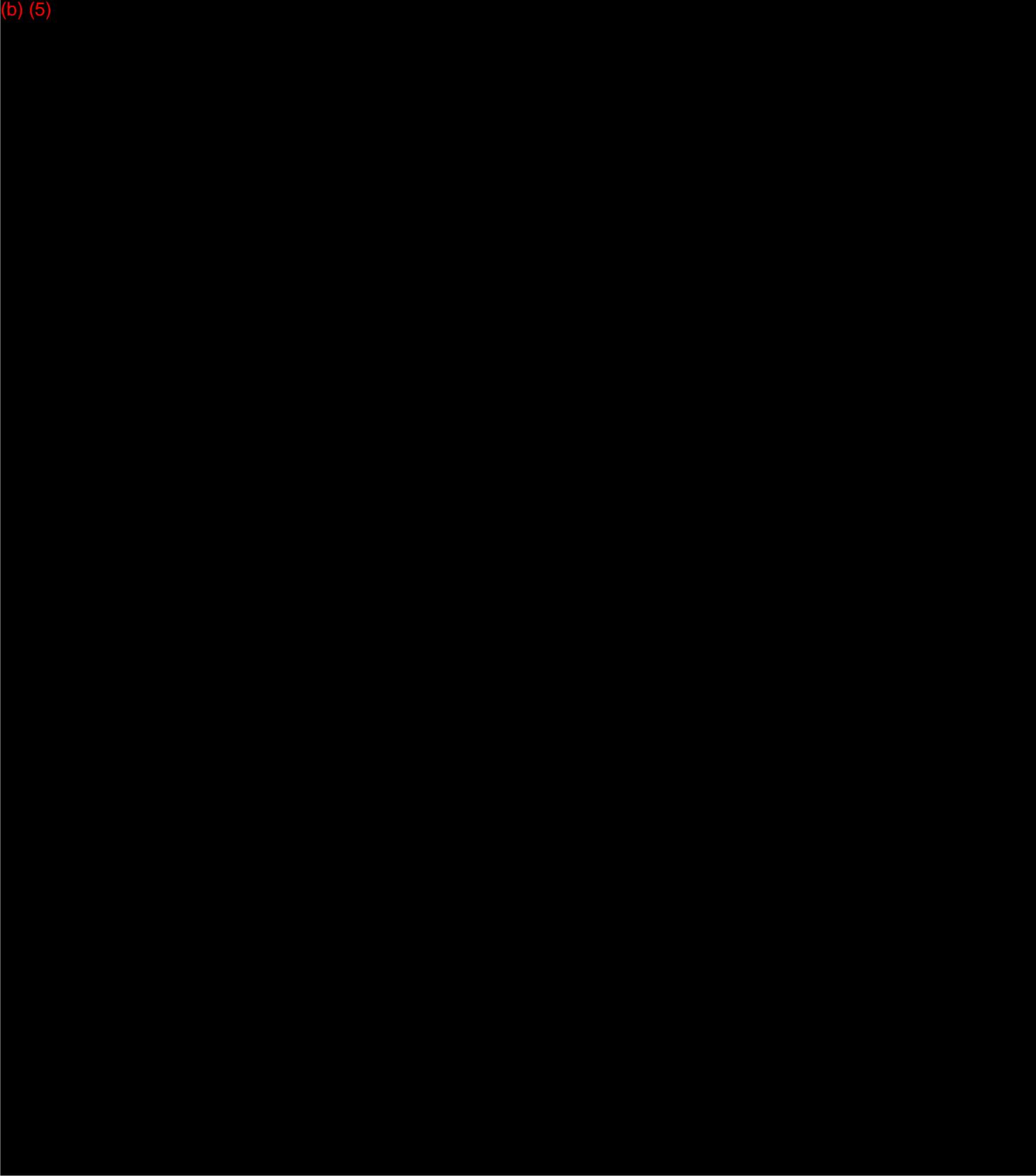
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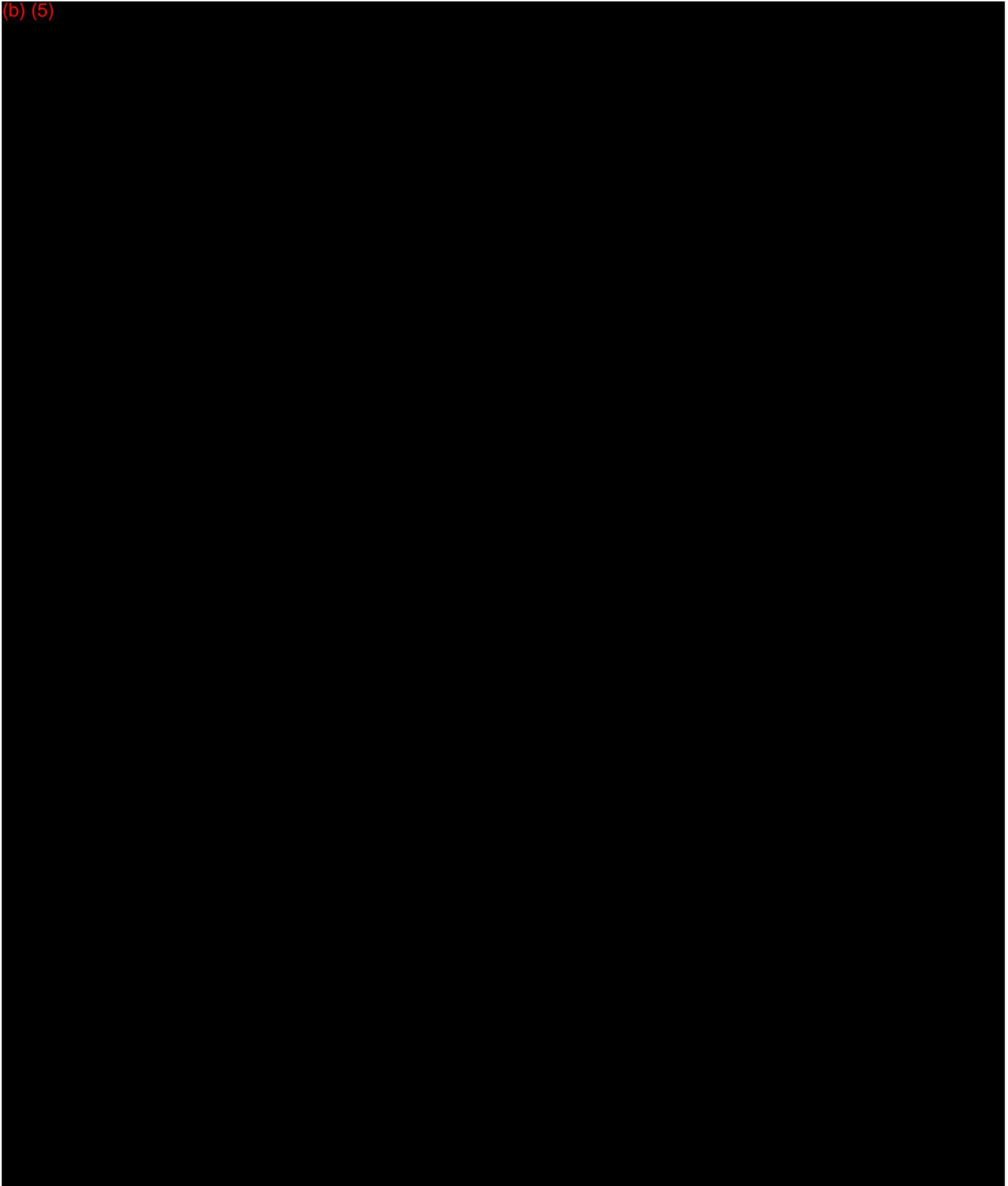
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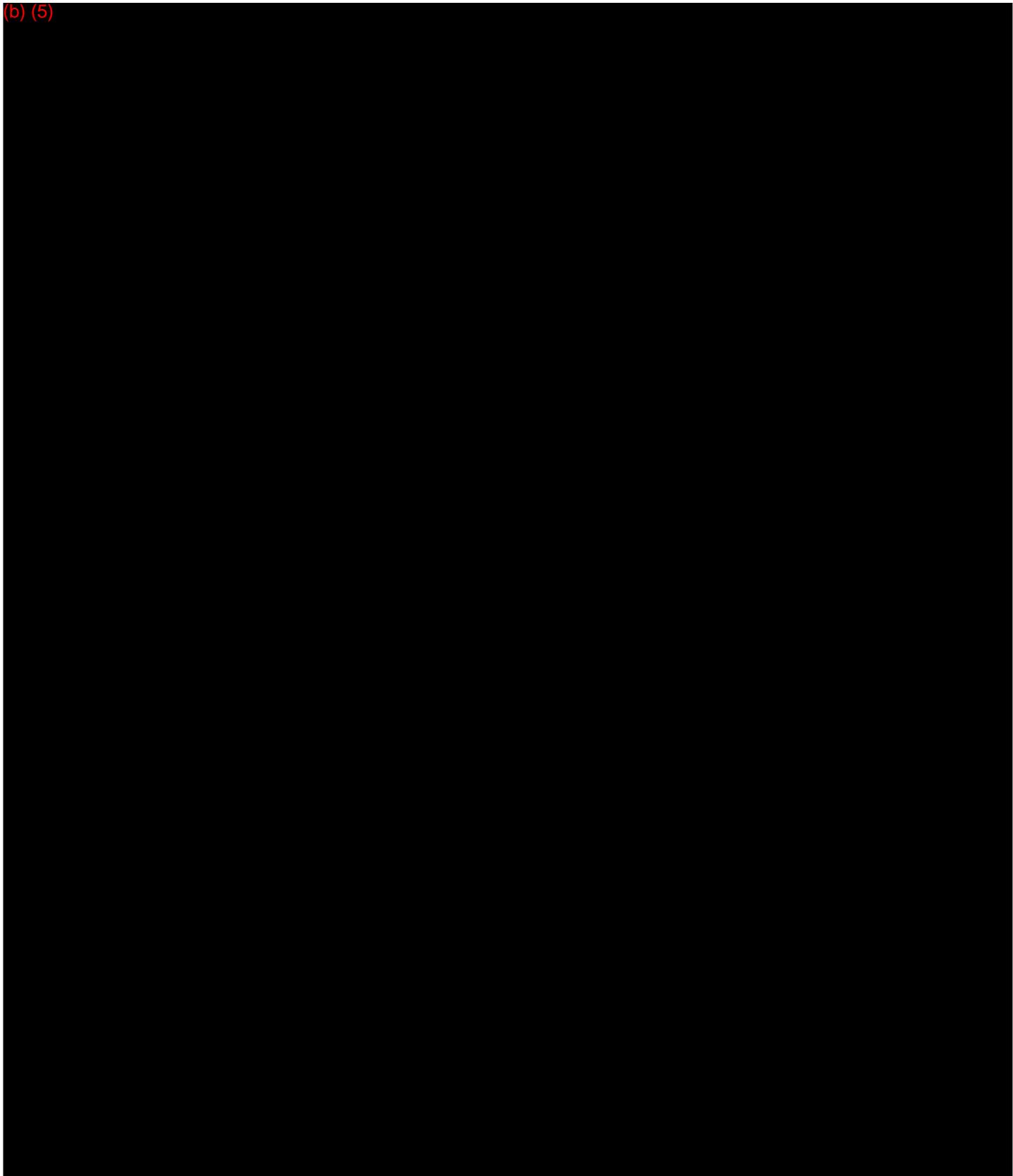
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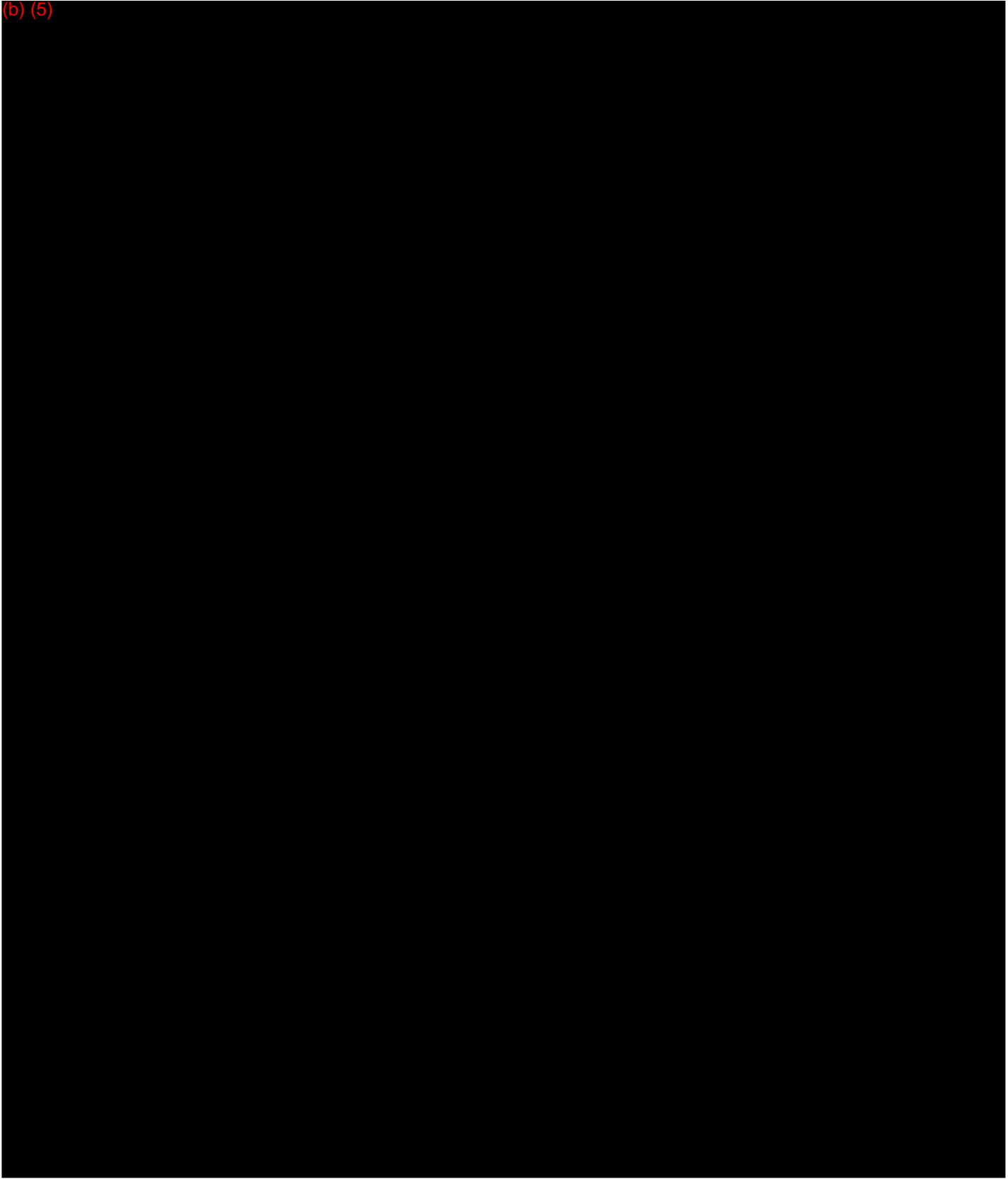
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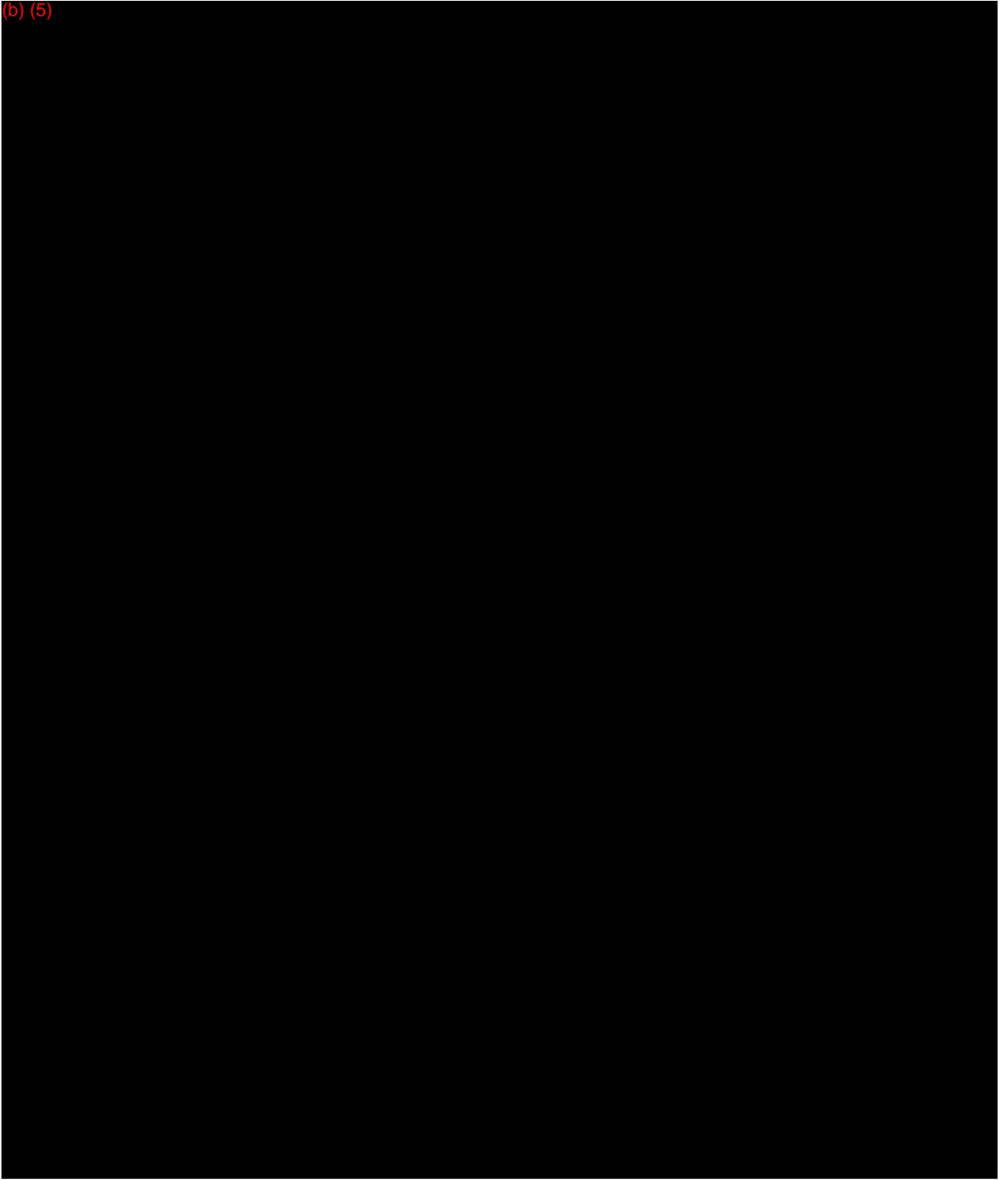
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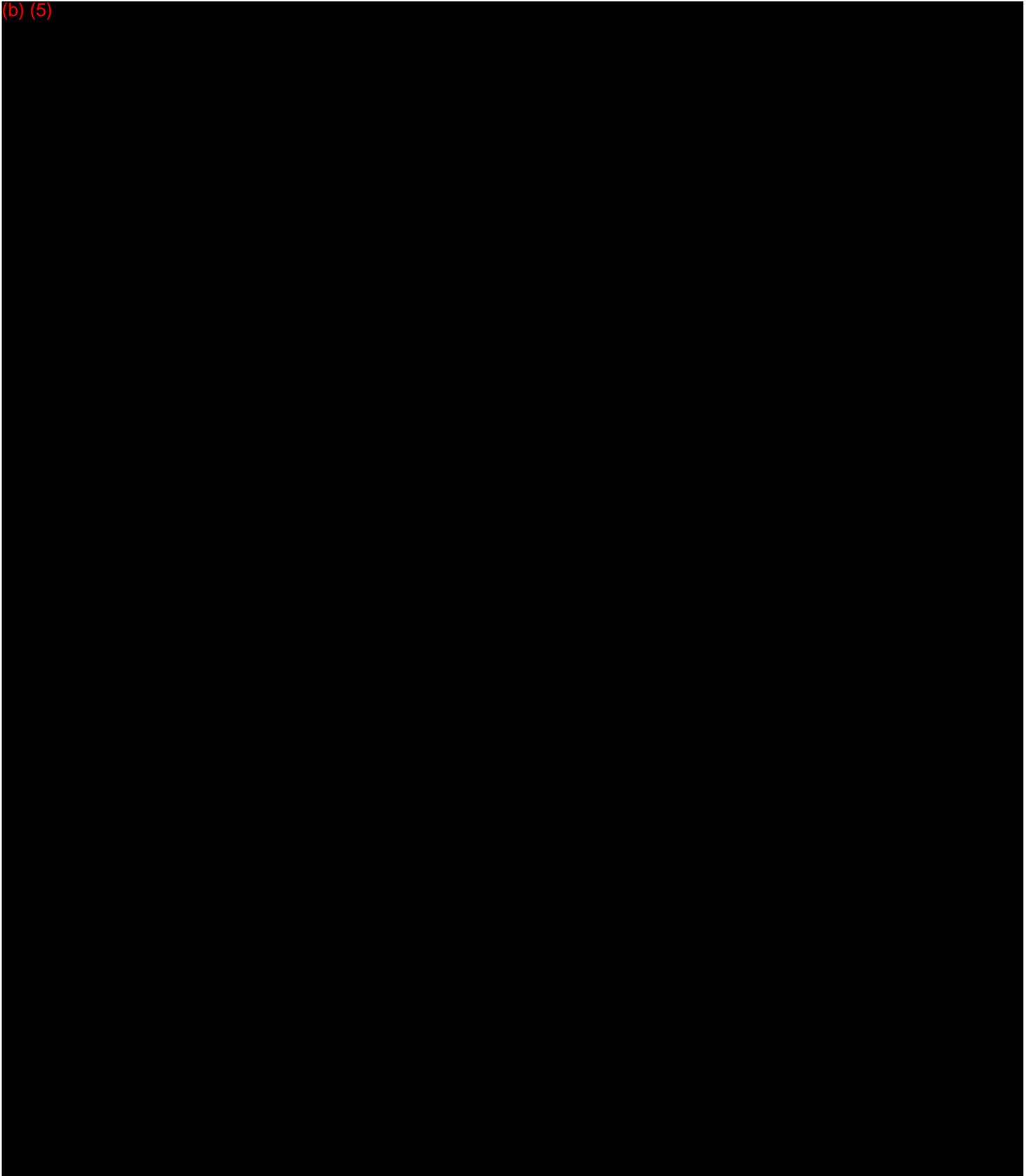
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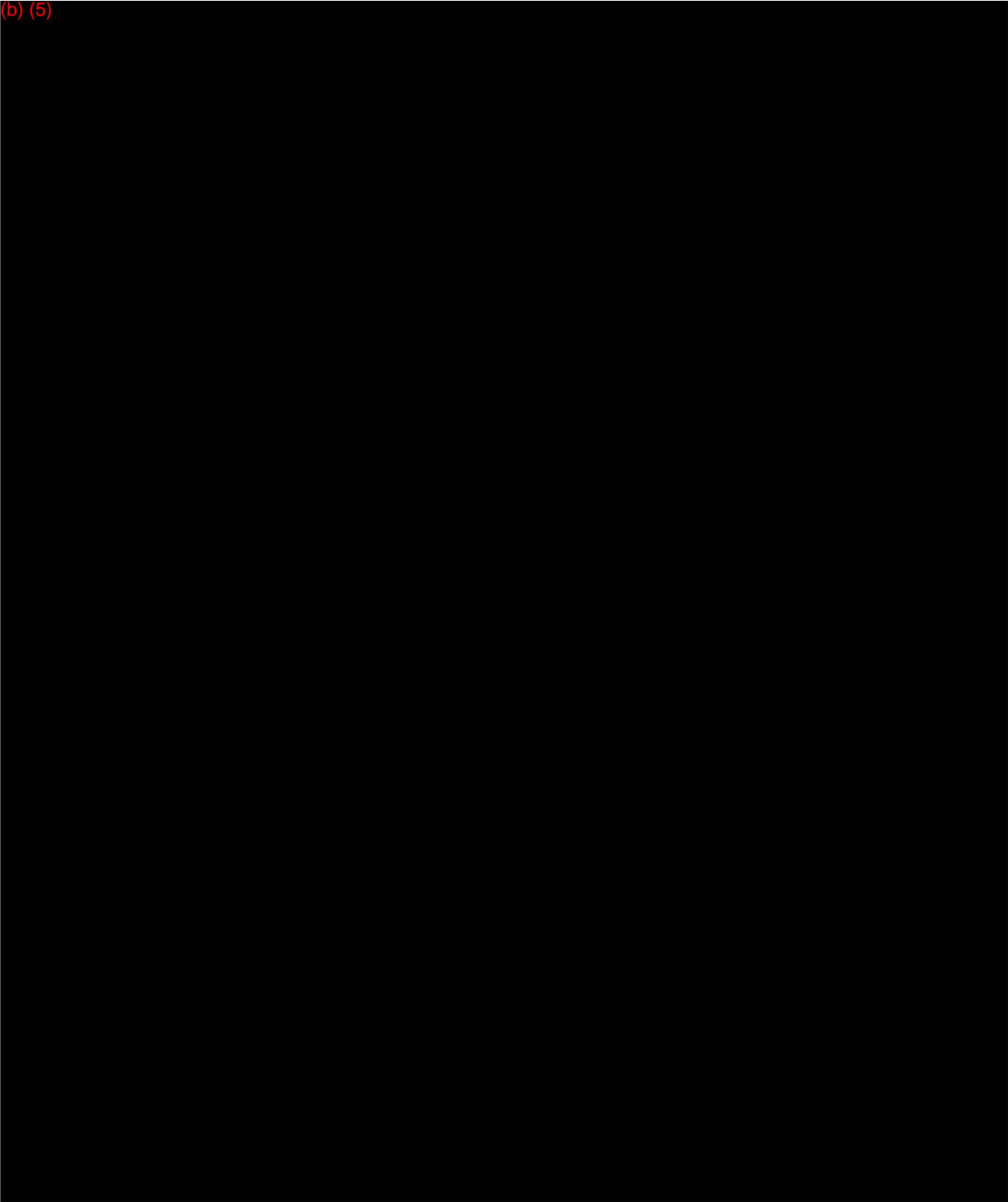
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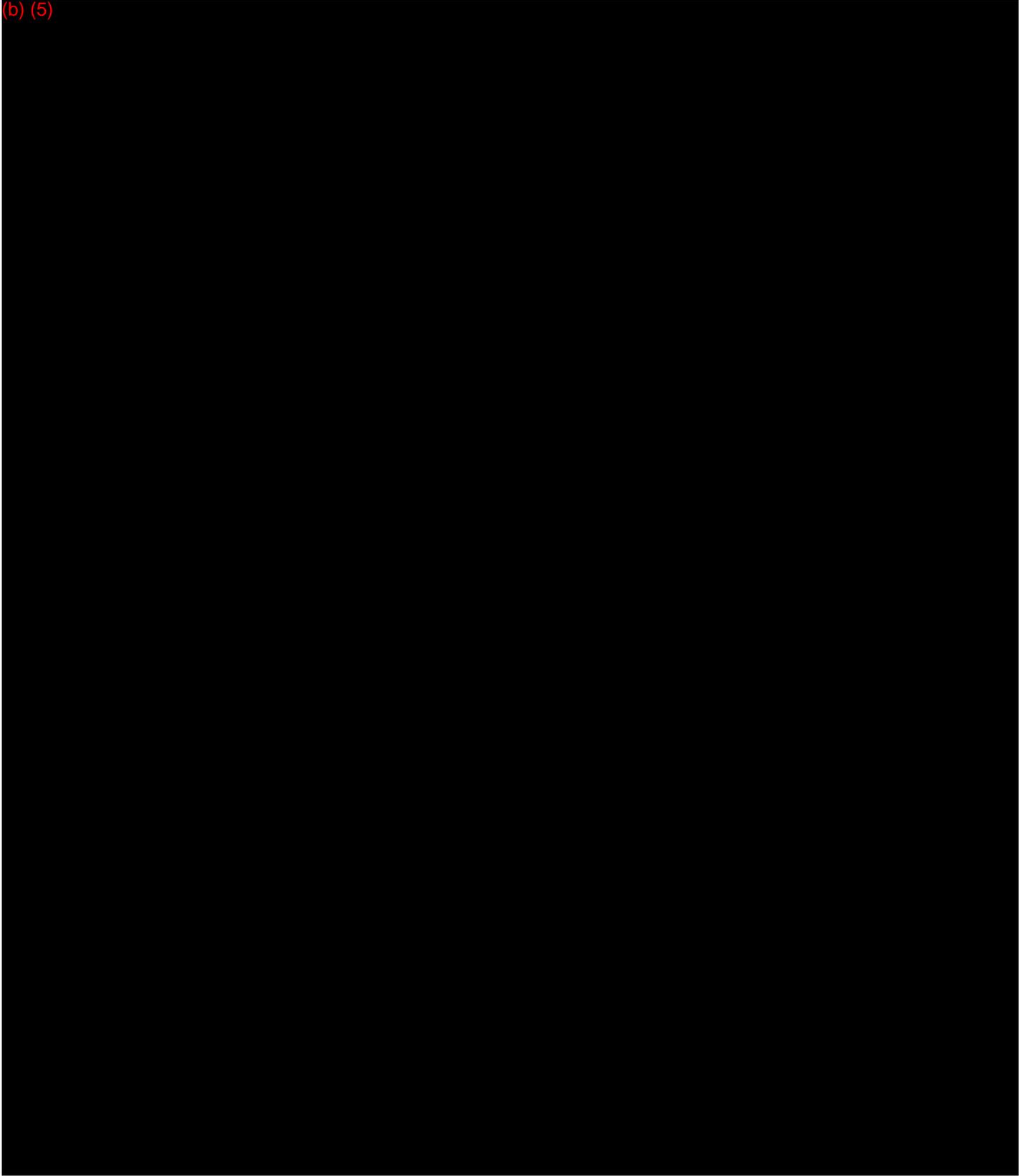
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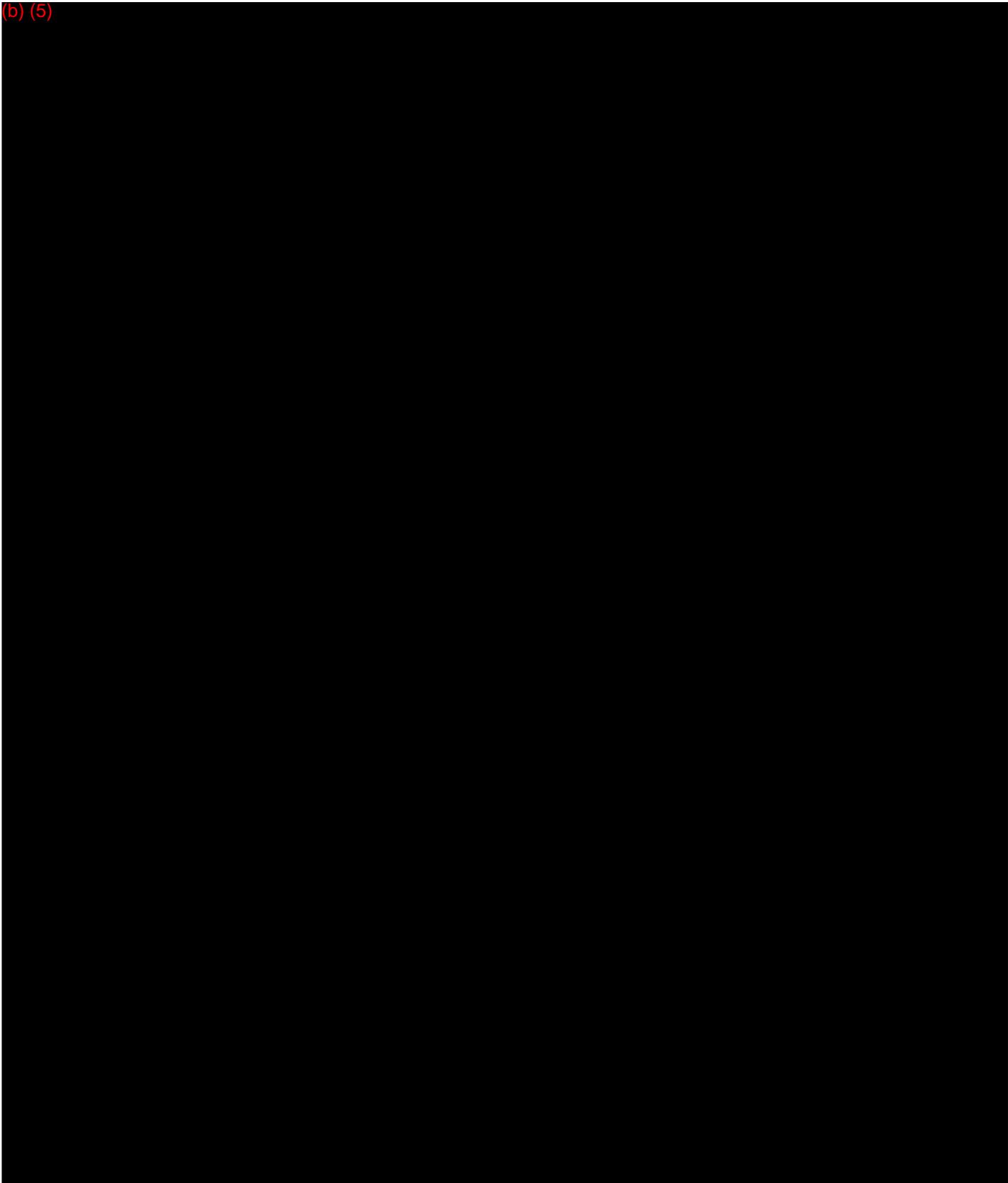
(b) (5)



(b) (5)



(b) (5)



From: [O'Neill, Jeff](#)
To: [FDA Senior Staff](#)
Cc: [Perloni, Andrei](#); [Harper, Kristina](#); [Henderson, Marsha B](#); [Kempic, Annamarie](#); [Kerry, Audrey](#); [Kux, Leslie](#); [Less, Joanne](#); [Ligon, Sharnell \(CDER\)](#); [Lyons, Matthew](#); [Maloney, Diane](#); [Maloney, Lesley](#); [Marchand, Heidi](#); [McChesney, Daniel G](#); [Meister, Karen G](#); [Murphy, Dianne - OC](#); [Nardinelli, Clark](#); [Nguyen, Thinh \(FDA/OC\)](#); [Norcio, Catherine T.](#); [Ortwerth, Michael](#); [Rao, Gayatri](#); [Ray, Seth](#); [Raza, Mark](#); [Rebello, Heidi](#); [Rovin, Lisa](#); [Sheehy, Janice](#); [Solomon, Steven M](#); [Throckmorton, Douglas C](#); [Toigo, Theresa A](#); [Valdez, Mary Lou](#); [Vaughn, Steven D](#); [Wion, Ann](#); [Yeboah, Michelle](#); [OC-Executive Secretariat-Policy Analysts](#); [Bull, Jonca](#); [Plaisier, Melinda K](#); [Dupont, Jarilyn](#); [Palmer, Kelly](#); [Clapp, Nicole](#); [Folden, Amy R](#); [Russo, Mark](#); [Schweitzer, Roxanne K](#); [Soreth, Janice M](#); [Smith, Crystal](#); [Saben, Alyson L](#); [Wiley, Elizabeth](#); [Lewis, Crystal](#); [Hileman, Christine](#); [Zawisza, Julie](#)
Subject: December 14 Senior Staff Meeting
Date: Thursday, December 17, 2015 3:19:20 PM
Attachments: [Chapter 2.pdf](#)

All,

Please see below the highlights from Monday's Senior Staff meeting.

Tom Kraus chaired the Senior Staff meeting on Monday, December 14. Dr. Ostroff is on leave this week. Tom discussed the new Senior Staff meeting schedule and focus of discussion on major issues or projects that the Office/Center will be working on in the coming month that are important for the Commissioner or other attendees to know about. Tom mentioned that Senator Barbara Mikulski is visiting the White Oak Campus in early January and will deliver a speech.

OMPT – Califf, Rob – Rob discussed ongoing activities for a learning health network focusing on the advancement of cancer research/therapies that is being championed by Vice President Biden. Related activities have included high level meetings and collaborations with NIH. Rob is working with Janet Woodcock, Peter Marks, and Rick Pazdur. Rob thanked everyone who worked so hard to provide him with preparation briefings for his confirmation hearing and expressed his wish that the public could fully understand the breadth of work done by the Agency. Rob also mentioned Karen's retirement and noted all the great work she has done for the Agency. Opioids and the high price of drugs will be big issues for the coming year.

OCS – Borio, Lu – Lu announced that Matt Warren will be joining OCS as the new Director of the Office of Scientific Integrity; FDA will participate in ASPR-led pandemic influenza strategy meeting; there is a need to refine agency's position on priority review vouchers and proposed expansions to the program that is apparently being supported by external stakeholders.

GO – Sklamberg, Howard – The Trans-Pacific Partnership (TPP) might not get a vote until after the 2016 elections and FDA may be called to testify on why TPP is not problematic; Brazil/ANVISA is visiting this week and is meeting with Rob Califf, Mitch Zeller, Howard Sklamberg, ORA imports, and others; GO is working with CDER and OFVM on the data integrity issues we are seeing in drugs and food and will intensify this work in the new year.

CBER – Midthun, Karen – Next week is the rollout of FDA's final guidance on reducing the risk of human immunodeficiency virus transmission by blood and blood products; Karen expressed her gratitude for all whose work led to the Agency's lifting of a consent decree with the Red Cross.

ORA – Plaisier, Mel – Gary Coody is retiring on January 9; rounds of field visits begin in January.

CVM – Dunham, Bernadette – Last week, FDA approved a biologic license application for Kanuma (sebelipase alfa), manufactured by Alexion Pharmaceuticals, as the first treatment for patients with a rare disease known as lysosomal acid lipase (LAL) deficiency; and 2) a new animal drug application approval related to the line of genetically engineered (GE) chickens that produces the human therapeutic biologic in its egg whites; CVM has a call with EMEA this week.

CTP – Zeller, Mitch – Regarding Deeming, CTP is working on OMB pass back and there is discussion on the Hill of riders related to waiving premarket review of products currently on the market; however, if no riders, hope to see passing of Deeming in January.

OMH – Bull, Jonca – The December 2 FDA and JHU CERSI co-sponsored conference “Clinical Trials: Assessing Safety and Efficacy for a Diverse Population” was successful. The minority report was submitted.

CDER – Moscicki, Richard – Richard discussed several FDA actions including: On December 14, the Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT); meeting this week to discuss BSUFA reauthorization; several approvals expected and CDER is on track to exceed last year; meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to discuss drisapersen to treat Duchene muscular dystrophy; fluoroquinolone labeling changes; and request for extension of gestational age for Mifeprex.

OCET – Maher, Carmen - Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Stakeholder's Workshop; National Science Advisory Board for Biosafety and Biosecurity (NSABB) full board meeting that will discuss the Gain of Function (GOF) Studies risk assessment reports.

OWH – Holloman, Marsha – Marsha reported that Senator Mikulski was happy to see that the Women’s Health Research Roadmap had posted; OWH and the NIH Office of Research on Women’s Health are collaborating on an initiative to raise awareness of the importance of participation of diverse women in clinical trials and to share best practices about clinical research design, recruitment, and subpopulation analyses. The Diverse Women in Clinical Trials Initiative will target priority groups including: national disease groups and affinity groups; principal investigators/ health professionals; and women of diverse ages, races, and ethnic backgrounds who have chronic health conditions. OWH and NIH’s ORWH will join forces to: conduct educational outreach in select disease or therapeutic areas; convene scientific dialogues; and develop training resources for investigators and health professionals. The awareness campaign will launch in January 2016. Marsha also mentioned the findings of “Effects of Sex Differences in the Pharmacokinetics of Drugs and Their Impact on the Safety of Medicines in Women” authored by OWH’s Emmanuel Fadiran and CDER/OCP/OTS’s Lei Zhang (article attached).

CDRH – Silvis, Lauren – This week, CDRH plans to issue a draft guidance entitled “Public Notification of Emerging Postmarket Medical Device Signals”; up classification of vaginal mesh expected December 30; public action on Essure; CDRH is responding to HHS and OGC comments on the LDT guidance.

OPPLA – Rovin, Lisa – Reagan-Udall continues search for a new Chairman and Executive

Director.

OPPLA – Sharp, Jeremy – Jeremy updated the group on 21st Cure activities advising that work on the legislation has stalled – possible backup plans being explored.

OF – Mettler, Erik

OCC – Dickinson, Liz – Liz provided an update on two recent court cases involving Pacira and Amarin.

OES – O’Neill, Jeff – Expecting many reports to Congress this month, most due in January.

OEA – Turner/Lisa/Conover, Katie – Katie mentioned media plans for metal-on-metal and messaging on drug pricing and opioids in the new year. Lisa reported that we are on track for a record number of visits to our web site, with over 50 million visits. We are working on some modernization for the web site (minimizing pages, organizing information in chapters). Possible OEA Leadership Council discussion.

CFSAN – Mayne, Susan – On December 7 - 8, The Food advisory Committee met to discuss FDA’s policies related to the presence of *Listeria monocytogenes* in foods; On November 30, briefed HHS on the Nutrition Facts Label/Added Sugars; Mike is visiting the Vermont Agency of Agriculture Food & Markets to discuss the FDA Food Safety Modernization Act final rules on preventive controls for human and animal food and on produce safety; Douglas Valentine has been hired as a new office Director of Nutrition, Labeling, and Dietary Supplements; GMA rollout on their smart label.

COO – Harris, Walter – Status of CR; 4 hours leave granted for Christmas Eve.

IOC – Blass, Bronwen – Bronwen announced that she is starting a new position in CDER’s ORP, Kalah Auchincloss has joined IOC as a Deputy Chief of Staff.

OSMP – Warner, Jill - FDA and the Office for Human Research Protections have issued joint draft guidance entitled, “Minutes of Institutional Review Board (IRB) Meetings: Guidance for Institutions and IRBs”. This draft guidance was prepared jointly by FDA and OHRP and is intended for institutions and IRBs responsible for oversight of human subject research under FDA and HHS regulations; HHS extended the comment period on the Common Rule NPRM for 30 days. The new date is January 6, 2016. As of December 2, HHS has received about 330 comments (50 were extension requests). Most of the comments so far are from individuals – researchers and patients. There is quite a bit of concern over the biospecimen proposal (to require consent for almost all secondary research); launch of FDA/NIH Rare Disease Device Needs Assessment: in response to IOM and other recommendations, FDA in collaboration with NIH, launched the Rare Disease Device Needs Assessment to document critical diagnostic and therapeutic device needs for the rare disease population. A comprehensive web-based survey was developed and disseminated to over 800 clinicians participating in CDRH’s advisory committees. OOPD plans to further survey clinicians participating in FDA’s Pediatric Device Consortia Grant Program and the Pediatric Advisory Committee, as well as clinicians in NIH’s Rare Disease Clinical Research Network in early 2016. This initiative is led by OOPD and Office of Rare Diseases Research in NCATS/NIH, with collaboration from FDA’s CDRH and OPPLA, and in coordination with the National Organization for Rare Disorders (NORD), Advamed, AAP, and AMA. GAO is wrapping up

its report on the Rare Pediatric Disease Priority Review Voucher Program as required by FDASIA. It is anticipated that the report will be issued in March 2016 per the statutory requirement.

NCTR – Slikker, Bill – The Chief Scientist has regular meetings with NIEHS officials from the National Toxicology Program to evaluate chemicals/drugs that may require more safety information to protect the American public from their use or exposure. Attention being given to stem cell research (NCTR is working with other FDA Centers to propose the evaluation of stem cells as experimental toxicological models, as well as examining the safety of stem cells as therapeutic agents. NCTR wishes to work with the other Centers to propose stem cells as a FY18 Initiative for possible funding from Congress); meeting with NIH regarding dietary supplements (NCTR and NIH in the past and currently have discussed the safety of dietary supplements and that the regulation of these supplements by FDA depends on a better understanding on how the American public uses these compounds as therapeutic agents).

OPPLA – Lurie, Peter – OPPLA has prepared a report on products that looked promising at the end of Phase II, but turned out to have safety and/or efficacy problems in Phase III. They are hoping to put the report into clearance early in the new year.

OP – Kux, Leslie – The Office of Policy is working with staff to develop the 2015 priority regulations and guidances document and assessment of workload needs.

Most senior leaders gave a brief overview of activities in their areas for the week. For further detail on general related issues or approvals, please review the FDA Weekly or the center/office website and reports.

*Thank you,
Office of the Executive Secretariat*

Chapter 2

Effects of Sex Differences in the Pharmacokinetics of Drugs and Their Impact on the Safety of Medicines in Women

Emmanuel O. Fadiran and Lei Zhang

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E.O. Fadiran (✉)

Office of Women's Health, Office of the Commissioner, Food and Drug Administration,
Building 32, Room 2312 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA
e mail: Emmanuel.Fadiran@fda.hhs.gov

L. Zhang

Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation
and Research, Food and Drug Administration, Silver Spring, MD 20993, USA
e mail: LeiK.Zhang@fda.hhs.gov

From: [Conover, Katie](#)
To: [Califf, Robert](#); [Sharp, Jeremy](#); [Kraus, Tom](#); [Kuhlik, Bruce](#)
Cc: [Rodriguez, Jennifer](#); [Walsh, Sandy](#); [Kotz, Deborah](#)
Subject: DMD Media Coverage Report
Date: Tuesday, April 26, 2016 5:09:06 PM
Attachments: [2016 MCR-Eteplirsen Updated Report 4.26.16.doc](#)
[image002.png](#)

Hello all,

As promised, attached is short snapshot of media coverage from yesterday's DMD AdComm.

The attached document provides a sampling of the media coverage from the April 25 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee on new drug application for Serepta's eteplirsen. If approved, the drug would be the first for Duchenne Muscular Dystrophy, a disease that affects about 3,500 boys and men in the U.S.

Media coverage on April 25 included more than 20 stories in national print and TV, local print and TV, Hill-focused and trade media; and included coverage from morning "curtain raisers" to coverage of the meeting vote. The morning's "curtain rising" media stories focused on the uncertainty of the outcome of eteplirsen. Nearly all the stories detail a patient anecdote and the FDA's skepticism over the results of this trial (which included only 12 patients and did not contain a traditional placebo control).

Reporters covered several different angles, including the impact on Serepta's stock and whether FDA has gone too far in terms of its "patient preference" initiative, potentially trying to please patients who are desperate for a treatment against the lack of science to demonstrative effectiveness for this drug. Public health advocates weighed in with some in favor of approval, but many taking a firm position against. Overall the morning's stories were balanced, accurate, and declined to predict the outcome of today's vote.

A second wave of coverage followed the committee's vote, and some of the top-tier and Hill media included the New York Times, Associated Press, Wall Street Journal, Washington Post, Reuters, and Politico. Major TV news networks including Fox News, NBC, and CNBC, also attended the meeting and provided live coverage and stand-up interviews with Sarepta's CEO Ed Kaye after the vote; who said it was ultimately the FDA, and not the committee, that would decide the drug's fate. However, reporters took different tacks when it came to couching how the FDA interacts with its advisory committee; some noting the FDA usually follows the committee's advice, while others said the FDA is not required to follow the vote. Several media outlets quoted 15-year-old Duchenne patient Billy Ellsworth who said at the open public hearing, "FDA, please don't let me die early." Coverage also quoted FDA officials Janet Woodcock and Billy Nunn who repeatedly emphasized the importance of the patient testimonials during the open public hearing. Overall, the publications portrayed the FDA as sympathetic to the patients' plight and hindered by the lack of a significant efficacy in the study that contrasted sharply with patient and parental testimony at the meeting. Coverage was generally balanced and accurate.

Let us know if you have questions.

Best,

Katie, Jen, Sandy and Debbie

Katie Conover

Acting Associate Commissioner

Assistant Commissioner, Office of Media Affairs

Office of External Affairs

U.S. Food and Drug Administration

Tel: 240-402-2402 / Cell: 301-512-9120

priscilla.conover@fda.hhs.gov



Media Coverage Report:

Eteplirsen for Duchenne Muscular Dystrophy

Advisory Committee Meeting April 25, 2016

This document provides a sampling of the media coverage from the April 25 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee on new drug application for Serepta's eteplirsen. If approved, the drug would be the first for Duchenne Muscular Dystrophy, a disease that affects about 3,500 boys and men in the U.S.

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Following is a snapshot of the meeting media coverage from April 25-26:

1. **The Washington Post**, *“To sway drug approval, patient advocates turn up the heat on the FDA”* [View Online](#) [See Full Text](#)
2. **Forbes**, *“Could Desperate Parents’ Pleas Sway The FDA To Approve A Drug Even If Evidence It Works Is Lacking?”* [View Online](#) [See Full Text](#)
3. **Santa Fe New Mexican**, *“Families lean on FDA to back experimental drugs”* [View Online](#) [See Full Text](#)
4. **Boston Globe**, *“FDA panel now weighing Sarepta’s experimental drug”* [View Online](#) [See Full Text](#)
5. **The Street**, *“Sarepta Therapeutics FDA Panel Live Blog”* [View Online](#) [See Full Text](#)
6. **Fierce Biotech**, *“Sarepta soars as FDA questions revive advocates’ hope for Duchenne drug”* [View Online](#) [See Full Text](#)
7. **Fierce Biotech**, *“With Sarepta’s fate uncertain, BioMarin CEO Bienaimé weighs the future of Duchenne drug”* [View Online](#) [See Full Text](#)
8. **Reuters**, *“FDA panel meets to discuss Sarepta muscular dystrophy drug”* [View Online](#) [See Full Text](#)
9. **The Wall Street Journal**, *“The FDA vs. Austin Leclaire”* [View Online](#) [See Full Text](#)
10. **Bio world**, *“FDA briefing docs suggest nearly foregone conclusion in eteplirsen review”* [View Online](#) [See Full Text](#)
11. **Syracuse**, *“CNY mom, sons to testify before FDA panel for approval of experimental drug”* [View Online](#) [See Full Text](#)
12. **Barron’s**, *“Sarepta Slammed by FDA, Stock Is Now Intriguing”* [View Online](#) [See Full Text](#)
13. **Boston Business Journal**, *“FDA chief lays out rationale for Duchenne drug to be granted temporary approval”* [View Online](#) [See Full Text](#)
14. **NBC**, *“Does muscular dystrophy drug work? Advocates pack FDA meeting”* [View Online](#) [See Full Text](#)
15. **Fierce Biotech**, *“In setback, a majority of FDA experts reject Sarepta’s emotional campaign to gain Duchenne drug OK”* [View Online](#) [See Full Text](#)

16. **Washington Post**, “*FDA committee votes against approval of controversial muscular dystrophy drug*” [View Online](#) [See Full Text](#)
 17. **STAT**, “*FDA panel votes against Sarepta’s drug for Duchenne muscular dystrophy*” [View Online](#) [See Full Text](#)
 18. **Wall Street Journal**, “*FDA Panel Votes Not to Recommend Approval for Muscular Dystrophy Drug*” [View Online](#) [See Full Text](#)
 19. **Forbes**, “*Lip Service To Patients And Caregivers, Or Respect? The Significance Of An FDA Panel's Review*” [View Online](#) [See Full Text](#)
 20. **Bloomberg**, “*Families Plead for FDA Advisers to Recommend Sarepta Muscle Drug*” [View Online](#) [See Full Text](#)
 21. **Politico**, “*AN FDA PANEL TODAY WILL DECIDE THE FUTURE OF SAREPTA*” [View Online](#) [See Full Text](#)
 22. **Boston Globe**, “*FDA panel rejects Sarepta drug to treat Duchenne muscular dystrophy*” [View Online](#) [See Full Text](#)
-

To sway drug approval, patient advocates turn up the heat on the FDA [TOP](#)

Carolyn Y. Johnson, The Washington Post

Billy Ellsworth, a teenager with an inexorable and devastating degenerative muscle disease, will bring a football with him to a Maryland hotel conference center on Monday. For months, he has been brainstorming a way to prove to a panel of scientists and physicians that the experimental drug he has been taking for more than four years has kept him strong and well — and he’d like to punctuate his brief testimony in the clearest possible way: by throwing them the ball.

When he was 4¼, Billy was diagnosed with Duchenne muscular dystrophy, a rare and lethal disease that typically forces boys to use wheelchairs by their teens and kills them in their 20s or 30s. His mother, Terri, has always measured her son’s life in fractions; Billy is 15¼ now, and the reason he isn’t in a wheelchair yet, they believe, is the experimental drug eteplirsen.

On Monday, the panel of scientists and physicians who catch Billy’s pass — if he’s allowed to throw it — will vote on whether the drug is effective. It is more than just a major make-it-or-break-it milestone for the Massachusetts drug company Sarepta Therapeutics and the families who support approval. The meeting also provides a window into the growing sophistication of grass-roots patient groups, whose well-organized lobbying efforts are exerting intense pressure on the drug-approval process. The Duchenne parent groups are orchestrating webinars on how to participate in the meeting, providing travel grants to help families attend, gathering their own data on the risks families are willing to accept and lobbying Congress.

The disease affects 1 in 3,500 boys, and it works only on a gene mutation carried by 13 percent of boys with Duchenne. A dozen boys were included in the key trial under scrutiny at the FDA meeting. But close to 900 community members are expected to attend, revealing the tensions that arise when patients adamantly believe that a drug works but the evidence is far less clear.

“It can, I think, at times border on patients putting a lot of pressure on the agency that’s inappropriate — to make decisions that aren’t based on science,” said Sarah Sorscher, of the consumer watchdog Public Citizen. “Really, I’ve never seen a drug that was even considered for approval with this poor quality of data. . . . If the drug is really a miracle, why don’t they have the data?”

The FDA has been working to incorporate the patient perspective into the drug-approval process, especially over the past five years, under growing pressure from advocacy groups and Congress. The Duchenne parent groups have been especially active on this front, running studies of the benefits and risks patients and caregivers are willing to accept — to try to “quantify the tears” for regulators as Pat Furlong, president of the Parent Project Muscular Dystrophy, says.

The parent group led a coalition that drafted a paper to help guide companies on best practices for successfully creating drugs for the disease that the [FDA credited and drew from](#) when it published its own guidance last summer — a first that other disease groups are working to follow. This month, they have worked to get two dozen senators to [sign a letter](#) reminding the FDA to prioritize the patient perspective when considering drugs for diseases with no treatments.

The Duchenne parent groups “have been an active leader. They have a strategy they call ‘aggressive engagement’: We’re going to the FDA on this, and we’re not going to stop,” said John F.P. Bridges, a researcher at the Johns Hopkins Bloomberg School of Public Health who works with advocacy groups and pharmaceutical companies to quantify and rigorously measure patient preference.

The meeting may reveal the limitations of the patient perspective for regulators. In the run-up to it, the FDA released documents that are critical of the way Sarepta’s small trial of just a dozen boys has been designed, saying “there are significant concerns regarding the ability to draw valid conclusions.” The FDA’s documents show that although the agency views the drug as safe, there is clear skepticism that it works: They say the ability of boys on the drug to walk declines over time, consistent with natural disease progression. And a crucial protein called dystrophin missing in people with Duchenne was present at less than 1 percent of normal levels after patients took the drug for three and a half years.

A group of 36 experts — some of whom with ties to the company — sent a letter in February rebutting FDA critiques of the evidence, stating that they have observed 5,000 patients over 15 years and that the boys on the drug are “clearly performing better than our collective clinical experience and the published literature would predict.”

The patient view can be extremely valuable: Patients know better than anyone what a meaningful benefit would be or what risks they would accept. But the patient’s view on whether the drug works may be influenced by hope.

“I think a lot of it is the desire — that people really want the drug to work, because there is nothing else,” said Richard Klein, director of the FDA’s patient liaison program, who said he was not speaking about any particular drug. “The downside is that people don’t understand the scientific rigors of what needs to be done, and they want the drug to be approved on extremely small bits of data.”

Contrast that with a parent’s experience:

“We’re not asking for something that’s not worthy or didn’t prove itself; we’re asking for flexibility for a rare disease,” Terri Ellsworth said. “My son gets himself to bed, gets himself out of bed every morning, dresses himself . . . eats breakfast and carries his dishes to the sink. Most boys are losing upper-body strength at [Billy’s] age. Here’s my son, and we don’t even own a wheelchair.”

Parents like Ellsworth say that since the FDA agrees that there are no known risks to eteplirsen and the disease is fatal, parents should be able to decide whether to give the drug, even if the benefit is unclear to regulators. The outcome for their sons, otherwise, is tragic and unavoidable.

Thomas Rando, a neurologist at Stanford University School of Medicine, said in an email that it’s hard to fault the FDA for being critical — and yet, it’s also hard to fault parents for pushing for approval of a drug that appears safe even if it has only subtle benefits in a clinical trial.

“Essentially, the question is should the FDA lower the bar for devastating disease, which is not a scientific question, it’s a policy question — an ethical question, too,” Rando said.

The agency’s attempt to consider the patient’s point of view was jump-started by HIV and AIDS activists in the late 1980s. But the effort to incorporate the patient viewpoint has been accelerated by recent law. Since 2013, the FDA has held “patient-focused drug development” meetings that are listening sessions for the agency to hear from patients suffering from various diseases. In 2015, the agency approved an obesity device called the Maestro Rechargeable System — something Bridges, the Johns Hopkins researcher, said was a watershed.

In that case, the device fell short of its endpoint: that people with the device would lose at least 10 percent more weight than a comparison group. But the agency, in its approval, cited a survey of patient preferences that showed patients would accept risk for the degree of benefit the device was expected to provide.

More recently, Diana Zuckerman, president of the National Center for Health Research, pointed to last year’s controversial drug approval of a female libido drug, flibanserin, as a milestone that might have emboldened Sarepta.

“In that case, a campaign by patients persuaded an FDA Advisory Committee and the FDA to approve a drug they knew had little benefit and substantial risk,” Zuckerman wrote. “Sarepta probably assumed a campaign by desperate parents would be even more persuasive.”

Could Ron Cohen, chairman of the Biotechnology Innovation Organization, a trade group for biotech drug companies, said that listening to patients is essential for companies and for regulators.

But he also noted that clinical trials remain critically important — something he learned personally years ago, when his company, Acorda Therapeutics, tested a therapy for spinal-cord injury. During a trial in which patients and medical practitioners were blind to who was getting the drug and who was getting the placebo, there were four excited calls from nurses, saying they thought the drug was working: Partially paralyzed patients were moving their legs.

“We were high-fiving back at the office and the lab — we were so thrilled,” Cohen said.

But the company then found that half of the patients that had seen marked improvements were on a placebo. “You’d never think someone with a spinal-cord injury would spontaneously move their leg when they haven’t moved it in years,” Cohen said. “And yet there it was.”

###

Desperate Parents' Pleas Sway The FDA To Approve A Drug Even If Evidence It Works Is Lacking? [TOP](#)

Rita Rubin, Forbes

You don’t usually hear people compare Food and Drug Administration advisory committee meetings to a world-class sporting event, but this is how Brian Denger described the [one set for Monday](#):

“For the Duchenne community, this is going to be more like the Super Bowl,” Denger, a supermarket manager from Biddeford, Maine, told me.

The “Duchenne community” refers to people touched by Duchenne muscular dystrophy, or DMD, the most common and most severe form of muscular dystrophy. Denger is a member because he is the father of two sons with DMD.

Worldwide, about 1 in 3,500 boys—DMD almost exclusively affects boys—inheriting the genetic disease, which is passed on the “X” chromosome from mothers to sons. Affected boys begin to exhibit symptoms of muscle weakness between the ages of 3 and 5. By 12, most can no longer walk. Eventually, the disease weakens their heart and the muscles involved in breathing, and they die, typically before their 30th birthday.

No approved drug can slow the course of any type of muscular dystrophy, let alone reverse or cure it, which is why hundreds of members of the Duchenne community—parents, patients, doctors, scientists and other advocates—are expected Monday to pack the [Chesapeake Ballroom](#) at the College Park Marriott Hotel and Conference Center in the [Washington](#), D.C., suburb of Hyattsville, Md., a few miles from the FDA’s sprawling Silver Spring campus.

Their mission: to convince members of the FDA's [Peripheral and Central Nervous System Drugs Advisory Committee](#) that they should recommend approval of Sarepta Therapeutics' New Drug Application, or NDA, for eteplirsen. The agency usually follows its advisory committee recommendations but is not bound by them.

Can the DMD community, which argues that "[eteplirsen keeps more boys on their feet](#)," trump FDA scientists' unfavorable assessment of the drug? Should it? While the FDA doesn't consider cost when deciding whether to approve a new drug, the thought that what is bound to be an extremely expensive treatment (Vertex has priced Kalydeco, which treats people with certain mutations in the cystic fibrosis gene, at [more than \\$300,000 a year](#)) might be only minimally effective, if that, is sobering.

"Although FDA is prepared to be flexible with respect to a devastating illness with no treatment options, flexibility does not mean approving drugs for which substantial evidence of effectiveness has not been established," concluded a [briefing document](#) posted Thursday by the FDA. Still, the FDA reviewers noted, "it is important to recognize that no final conclusions have been reached on the approvability of this application."

Pat Furlong, founding president and CEO of [Parent Project Muscular Dystrophy](#), an advocacy group based in Hackensack, N.J., says she's optimistic. "I do think that hearing the patients' stories, hearing the patients' experience with this compound...will be persuasive," Furlong, whose two sons died of DMD, told me. "I think the FDA learns a great deal from listening to patients."

Few so-called disease communities are as well-organized and as well-connected as Furlong's. "Take a Stand. Fill a Seat. Raise Your Voice," urges [MakeDuchenneHistory.com](#). "We represent friends, families, and patients affected by Duchenne Muscular Dystrophy who want to see safe, effective treatments approved by the FDA."

They have friends in high places:

- In a [letter](#) dated April 15, a bipartisan group of 24 senators urged Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, to use the agency's "broad regulatory flexibility...to help advance new DMD therapies."
- Rick Santorum, former U.S. Senator and former Republican presidential candidate, [tweeted](#) Saturday that he plans to attend the advisory committee meeting. Santorum's own daughter was born with a genetic disorder called [Trisomy 18](#).
- Sen. Marco Rubio, R-Fla., another former Republican presidential candidate, [tweeted](#) earlier this month that he "met with DMD advocates to chat about how FDA can accelerate approval of innovative therapies."

Scores of DMD advocates, including Denger, are scheduled to address the advisory panel at a public hearing after lunch. Demand was so great that the FDA added a half-hour to the hearing's originally scheduled two hours (already about twice as long as a typical FDA public hearing) and held a lottery to pick the people who'd get the coveted three-minute slots to speak. To squeeze in

as many speakers as possible, some advocates who won a slot will split their time with others who didn't.

According to Sarepta, based in Cambridge, Mass., eteplirsen increases levels of a protein called dystrophin. DMD is associated with errors in the gene that codes for dystrophin, one of a group of proteins that strengthen and protect muscle fibers. People with DMD typically don't produce any functional dystrophin.

Eteplirsen is designed to treat boys with the most common type of mutation in the dystrophin gene, who make up about 13% of all DMD patients, according to Sarepta. Annie Kennedy, senior vice president of legislation and public policy for Parent Project Muscular Dystrophy, estimates that about 2,300 U.S. boys with DMD have the type of mutation amenable to treatment with eteplirsen.

Using an approach similar to eteplirsen, Sarepta's [website](#) says, the company has also begun early human testing of drugs for the second and third most common types of DMD mutation. Sarepta says it is in the discovery or pre-human testing phase of potential treatments for DMD caused by seven other types of mutations in the dystrophin gene.

"I think what the community understands (is) even if your child is not amenable to this drug, the ramifications for the entire community are huge," said Will Nolan, senior vice president of administration and communications for Parent Project Muscular Dystrophy.

The advisory committee meeting was originally scheduled for Friday, Jan. 22, but the FDA [postponed](#) it at the last minute because of "[Snowzilla](#)," a major winter storm forecast for that weekend in the Washington area. The delay presented advocates and Sarepta with an unusual opportunity—a long lead time to prepare responses to the FDA scientists' evaluation.

"FDA should be influenced little, if at all, by patient wishes but a lot by the risks of the disease—and it is," Henry Greely, director of Stanford Law School's [Center for Law and the Biosciences](#), told me. For example, he said, "pancreatic cancer drugs can be much less safe and effective than acne medication."

"I'm sure FDA is taking the fact that DMD is untreatable and awful into account," Greely said. "But it still *must*, by law, and *should* (emphasis Greely's), by ethics and policy, approve only drugs that are proven sufficiently safe and effective."

Clearly, the FDA has set a higher bar than the advocates., but if any disease community is going to be able to sway the advisory committee and the FDA, it might well be the DMD community.

"In an effort to influence the direction of DMD research, Parent Project Muscular Dystrophy...recently initiated and drafted guidance for the pharmaceutical industry," Dr. Yoram Unguru, a Johns Hopkins bioethicist and pediatric hematologist/oncologist, noted in an [article](#) published in 2015.

The DMD guidance was the first FDA guidance drafted by a disease community “and speaks to the degree of influence the DMD advocacy community carries,” Unguru wrote. Significantly, he wrote, the very first section of the guidance “discusses families’ willingness to accept undetermined and more risky interventions because of the progressive and unpredictable nature of DMD.”

Still, FDA regulations governing drug approvals “are there for a very good reason,” Unguru, who sees patients at the Children’s Hospital at Sinai in Baltimore, told me. “We need to make sure that patients...and their parents are not given false hope. We all have hope, and hope is good, and hope is important.” But if it’s misguided hope, hope based on a false promise, “we’re getting into a difficult situation.”

Agency staff who reviewed Sarepta’s NDA found that scientific evidence of eteplirsen’s safety and effectiveness is lacking.

The single randomized, double-blind, placebo-controlled study in the NDA was conducted with only 12 boys for 24 weeks at a single medical center, the FDA reviewers have noted in briefing documents for the advisory committee. In this type of study, considered the gold standard for evaluating new treatments, the equivalent of a coin toss determines which participants will receive the experimental therapy and which will get a placebo. “Double blind” means that neither the research subjects nor the researchers learn who got which treatment until the treatment period ends.

At the end of 24 weeks, the boys who had been getting eteplirsen couldn’t walk farther in six minutes—a standard test—than the boys who’d been getting the placebo, according to the FDA reviewers. At that point, the four boys who’d been receiving the placebo were switched over to eteplirsen, and all 12 boys in the study have continued to receive weekly infusions of the drug.

The FDA reviewers said they might have accepted levels of dystrophin in patients’ muscles as evidence that the drug was working, but biopsies after 3 1/2 years of treatment found that the boys’ levels were still far below those generally seen in a milder form of muscular dystrophy. On top of that, the FDA scientists said, there was no apparent correlation between how far the treated boys could walk in six minutes and the dystrophin levels in their muscles.

Dr. Michael Carome, a kidney specialist who directs the [Public Citizen Health Research Group](#), a consumer watchdog organization in Washington, D.C., is blunt about what the FDA should do.

“Based upon the evidence presented and reviewed by the FDA and described in the briefing packet, the drug should not be approved,” Carome, who previously worked for the [Office for Human Research Protections](#) in the Department of Health and Human Services, told me. “These clinical trials were too small, and the evidence from those trials does not show that the drug provides any meaningful clinical benefit.

“It would be a mistake for the FDA to approve this,” he continued. “It would be giving in to political pressure and essentially eviscerating their standard for approval. What these patients need is a drug that works... To put out a drug that’s not effective isn’t helping anyone.”

But the FDA scientists have it wrong, according to a [lengthy letter](#) sent Feb. 24 to Dr. Billy Dunn, director of the division of neurology products at the FDA. M. Carrie Miceli and Dr. Stanley Nelson, co-directors of the Center for Duchenne Muscular Dystrophy at UCLA, wrote the letter, which was also signed by 34 other U.S. and Australian basic scientists and physicians with expertise in the disease.

“It is remarkable that a viable treatment option may soon be available to add to our clinical approach to this devastating disease,” they wrote.

One thing they did not mention in the letter is that [they are married to each other and have a 15-year-old son named Dylan Miceli-Nelson who has Duchenne](#), although he is not a candidate for eteplirsen. The 8th-grader is a “sit-down comedian” whose [YouTube video](#) has garnered more than 330,000 views.

I talked recently with Miceli and Nelson, who told me they have no ties to Sarepta, financial or otherwise.

“People advocate for their patients, without a doubt,” Miceli said. “But I think the data have really gotten sufficiently robust, even though it is only a small number of boys.”

The boys who’ve been on eteplirsen for nearly five years are more likely to still be walking than other boys with DMD who are the same age but have not been treated with the drug, Nelson said. “Our perspective as scientists in this area is we don’t need to come up with complete cures to make a meaningful impact.”

Brian Denger says this family portrait, shot in January 2013, was the last to include son Matthew (front right),. Denger’s wife, Alice, stands behind son Patrick.

As Pauline McCormack, a senior research associate at Newcastle University’s Policy, Ethics and Life Sciences Research Center in England told me, “something that might seem insignificant in another disease, such as retaining movement in a few muscles, can be more meaningful in Duchenne.” McCormack added, “I think the patient voice is vital and has a role alongside clinical expertise and the scientific evidence.”

Brian Denger would agree. His older son, Matthew, died in February 2013, six weeks shy of his 21st birthday. He was halfway through his second year of college. “He actually went to school the morning of his death,” his father said.

Denger’s younger son, Patrick, 21, is in his third year of college, majoring in psychology. Even without any treatment, Patrick’s DMD hasn’t progressed as rapidly as his brother’s did, their father said. Matthew stopped walking at age 8, Patrick not until age 13.

Patrick barely missed qualifying for an eteplirsen trial in Boston in which older patients who can no longer walk are receiving the drug, Denger said.

Although Patrick can still drive a specially equipped car, he can't touch his face with his hands, which made him ineligible for the eteplirsen study in older patients, his father said. "We were both very disappointed."

They've settled for what they view as the next best thing: a trial of drisapersen, a different drug with a similar mechanism of action as eteplirsen. Every Tuesday for the past 15 weeks (except one, when winter weather in Maine grounded them), Denger and his son have caught a 5:30 a.m. flight to Baltimore, where Patrick receives an infusion of drisapersen at the [Kennedy Krieger Institute](#). They then take Amtrak to Washington and get on the Metro to Reagan National Airport for a direct flight home.

Patrick received his first infusion of drisapersen right around the same time the FDA [notified](#) BioMarin, based in San Rafael, Calif., that its NDA for the drug was not approvable in its current form.

Denger considers himself to be a practical man, one not susceptible to false hopes. "We realize that this is the first generation for both of these drugs," he said of himself and Patrick. "We also realize that neither one of these drugs represents a cure."

###

Families lean on FDA to back experimental drugs [TOP](#)

Santa Fe New Mexican

Billy Ellsworth, a teenager with an inexorable and devastating degenerative muscle disease, will bring a football with him to a Maryland hotel conference center on Monday. For months, he has been brainstorming a way to prove to a panel of scientists and physicians that the experimental drug he has been taking for more than four years has kept him strong and well — and he'd like to punctuate his brief testimony in the clearest possible way: by throwing them the ball.

When he was 4, Billy was diagnosed with Duchenne muscular dystrophy, a rare and lethal disease that typically forces boys to use wheelchairs by their teens and kills them in their 20s or 30s. Billy is 15 now, and the reason he isn't in a wheelchair yet, they believe, is the experimental drug eteplirsen.

On Monday, the panel of scientists and physicians who catch Billy's pass — if he's allowed to throw it — will vote whether the drug is effective. It is more than just a major make-it-or-break-it milestone for the Massachusetts drug company Sarepta Therapeutics and the families who support approval.

The meeting also provides a window into the growing sophistication of grass-roots patient groups, whose well-organized lobbying efforts are exerting intense pressure on the drug-approval process. The Duchenne parent groups are orchestrating webinars on how to participate in the meeting, providing travel grants to help families attend, gathering their own data on the risks families are willing to accept and lobbying Congress.

The disease affects one in every 3,500 boys, and it works only on a gene mutation carried by 13 percent of boys with Duchenne. A dozen boys were included in the key trial under scrutiny at the FDA meeting. But close to 900 community members are expected to attend, revealing the tensions that arise when patients adamantly believe that a drug works but the evidence is far less clear.

“It can, I think, at times border on patients putting a lot of pressure on the agency that’s inappropriate — to make decisions that aren’t based on science,” said Sarah Sorscher, of the consumer watchdog Public Citizen. “Really, I’ve never seen a drug that was even considered for approval with this poor quality of data. ... If the drug is really a miracle, why don’t they have the data?”

The FDA has been working to incorporate the patient perspective into the drug-approval process, especially over the past five years, under growing pressure from advocacy groups and Congress. The Duchenne parent groups have been especially active on this front, running studies of the benefits and risks patients and caregivers are willing to accept — to try to “quantify the tears” for regulators as Pat Furlong, president of the Parent Project Muscular Dystrophy, says.

The parent group led a coalition that drafted a paper to help guide companies on best practices for successfully creating drugs for the disease that the FDA credited and drew from when it published its own guidance last summer — a first that other disease groups are working to follow. This month, they have worked to get two dozen senators to sign a letter reminding the FDA to prioritize the patient perspective when considering drugs for diseases with no treatments.

The Duchenne parent groups “have been an active leader. They have a strategy they call ‘aggressive engagement’: We’re going to the FDA on this, and we’re not going to stop,” said John F.P. Bridges, a researcher at the Johns Hopkins Bloomberg School of Public Health who works with advocacy groups and pharmaceutical companies to quantify and rigorously measure patient preference.

The meeting may reveal the limitations of the patient perspective for regulators. In the run-up to it, the FDA released documents that are critical of the way Sarepta’s small trial of just a dozen boys has been designed, saying “there are significant concerns regarding the ability to draw valid conclusions.”

The FDA’s documents show that although the agency views the drug as safe, there is clear skepticism that it works: They say the ability of boys on the drug to walk declines over time, consistent with natural disease progression. And a crucial protein called dystrophin missing in people with Duchenne was present at less than 1 percent of normal levels after patients took the drug for three and a half years.

A group of 36 experts — some of whom with ties to the company — sent a letter in February rebutting FDA critiques of the evidence, stating that they have observed 5,000 patients over 15 years and that the boys on the drug are “clearly performing better than our collective clinical experience and the published literature would predict.”

The patient view can be extremely valuable: Patients know better than anyone what a meaningful benefit would be or what risks they would accept. But the patient’s view on whether the drug works may be influenced by hope.

“I think a lot of it is the desire — that people really want the drug to work, because there is nothing else,” said Richard Klein, director of the FDA’s patient liaison program, who said he was not speaking about any particular drug. “The downside is that people don’t understand the scientific rigors of what needs to be done, and they want the drug to be approved on extremely small bits of data.”

Thomas Rando, a neurologist at Stanford University School of Medicine, said in an email that it’s hard to fault the FDA for being critical — and yet, it’s also hard to fault parents for pushing for approval of a drug that appears safe even if it has only subtle benefits in a clinical trial.

“Essentially, the question is should the FDA lower the bar for devastating disease, which is not a scientific question, it’s a policy question — an ethical question, too,” Rando said.

The agency’s attempt to consider the patient’s point of view was jump-started by HIV and AIDS activists in the late 1980s. But the effort to incorporate the patient viewpoint has been accelerated by recent law. Since 2013, the FDA has held “patient-focused drug development” meetings that are listening sessions for the agency to hear from patients suffering from various diseases. In 2015, the agency approved an obesity device called the Maestro Rechargeable System — something Bridges, the Johns Hopkins researcher, said was a watershed.

In that case, the device fell short of its endpoint: that people with the device would lose at least 10 percent more weight than a comparison group. But the agency, in its approval, cited a survey of patient preferences that showed patients would accept risk for the degree of benefit the device was expected to provide.

More recently, Diana Zuckerman, president of the National Center for Health Research, pointed to last year’s controversial drug approval of a female libido drug, flibanserin, as a milestone that might have emboldened Sarepta.

“In that case, a campaign by patients persuaded an FDA Advisory Committee and the FDA to approve a drug they knew had little benefit and substantial risk,” Zuckerman wrote. “Sarepta probably assumed a campaign by desperate parents would be even more persuasive.”

###

FDA panel now weighing Sarepta’s experimental drug [TOP](#)

Robert Weisman, The Boston Globe

One of the most closely watched hearings on a proposed drug in years has convened Monday morning in Hyattsville, Md., where a panel of medical experts will consider an application by Cambridge’s Sarepta Therapeutics Inc. for approval of a Duchenne muscular dystrophy treatment.

Scientists from Sarepta and the Food and Drug Administration will discuss their conflicting interpretations of clinical trial data for the experimental drug -- called eteplirsen -- while boys with muscular dystrophy and their family members are prepared to testify about their experience with the drug and the need for new therapies to treat the muscle-wasting disease.

The influential panel, called the Peripheral and Central Nervous System Advisory Committee, is expected to make a recommendation to the FDA early Monday evening on the drug's safety and effectiveness. While the committee's recommendation is non-binding, the FDA usually follows the lead of its outside experts. It is scheduled to rule on Sarepta's application next month.

Sarepta's shares swung wildly last week. They plunged when the FDA's staff released a briefing document Thursday that was critical of Sarepta's clinical trial design, but bounced back Friday when the FDA posted a list of questions for the advisory panel that raised investors' hopes that the panel could favor approval of the drug candidate.

More than 800 patient advocates have registered to appear at Monday's hearing, making it among the best attended FDA advisory committee meetings in history.

###

Sarepta Therapeutics FDA Panel Live Blog [TOP](#)

Adam Feuerstein, The Street

The live blog above is tracking all the action at a U.S. Food and Drug Administration advisory committee meeting, convened to review eteplirsen, Sarepta's experimental drug for the treatment of Duchenne muscular dystrophy.

TheStreet Senior Columnist Adam Feuerstein is providing live coverage and analysis of the Sarepta FDA advisory panel as it happens near Washington, D.C.

At the end of Monday's meeting, a panel of 13 independent experts will vote on a series of questions which will provide recommendation to the FDA on whether or not eteplirsen should be approved, or not.

Sarepta shares are halted for trading while the advisory panel is in session. The stock last traded Friday at \$14.95.

###

Sarepta soars as FDA questions revive advocates' hope for Duchenne drug [TOP](#)

John Carroll, Fierce Biotech

Friday afternoon, Sarepta's (\$SRPT) path to a formal marketing decision from the FDA on its Duchenne muscular dystrophy drug eteplirsen took yet another bizarre twist.

The FDA posted a set of discussion points and questions for Monday's advisory panel review of the drug. It was immediately apparent to a varied group of analysts that the language reflected the agency's harsh view of the sparse and questionable data used to ask for an accelerated approval based on the results of a trial that enrolled only 12 boys.

Question: "Has the Applicant provided substantial evidence from adequate and well controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit?"

Based on the FDA's stubborn opinion issued in two analyses, the agency would never call Sarepta's study "adequate and well controlled." And it clearly discounted any evidence of dystrophin production.

But asking the panel any question opens the possibility that the intense public pressure being applied on the FDA by patient advocates and *The Washington Post* editorial page could influence the outside experts to vote for an early OK. And the biotech's shares--battered yesterday by an internal FDA review that adopted a clearly negative tone--soared more than 40%.

"We view the fact that panel members will have to vote on Monday as an incremental positive for SRPT," wrote RBC's insightful Simos Simeonidis, "simply because of the understandable pressure committee members will be under, in the presence of the DMD community and families." After all, if the FDA had intended a negative outlook Monday, why would they put the advisers on the spot?

But that didn't prevent analysts from taking a skeptical view of Sarepta's chances.

"Despite that view, when we read through the actual questions and the language of the accompanying discussion (see below), we see a document with the exact same tone and tenor as the January and April briefing documents," Simeonidis observed. "The questions and the discussion ask the panelists to focus on the trial conduct, the evidence for dystrophin and clinical efficacy. And we expect the answer to all of these to be No."

"Prepare for a wild ride," noted Baird's Brian Skorney. "After years of ambiguity surrounding this review, we head into Monday expecting nothing more than to be surprised."

After the roller coaster ride that has taken investors and biotech observers through plenty of dramatic plot twists in recent years-- including high-level exits, disputes over dealings with the FDA and more--Sarepta can still surprise when it's least expected.

###

With Sarepta's fate uncertain, BioMarin CEO Bienaimé weighs the future of Duchenne drug [TOP](#)

John Carroll, Fierce Biotech

Come Monday, Sarepta (\$SRPT) will get a very clear idea of the odds it faces on finally achieving its years-long quest to gain an FDA approval of its Duchenne muscular dystrophy drug eteplirsen. And you can expect that BioMarin CEO Jean-Jacques Bienaimé will be paying close attention to all of the opinions voiced by the FDA's outside experts on DMD as the agency panel meets to discuss the drug's fate.

Back in early January, Bienaimé was disappointed by the FDA's decision to reject its rival drug, drisapersen, with regulators left unimpressed by the efficacy data that was submitted for an approval. In an interview with me Wednesday afternoon, the CEO made it clear that the company (\$BMRN) may face some tough choices on their drug, which cost \$680 million in cash. And if the cards don't start turning in its favor, time may be running out on at least one of the three drugs that's been making an uphill run at a fast marketing OK.

"The European decision is the next step," says Bienaimé. If they can keep drisapersen on track at the EMA, an opinion should arrive in two or three months. "If they reject it," he noted, "we have to decide if we continue it."

Given the fact that the company is probably looking at mounting a late-stage study to get the drug back up in front of the U.S. regulators--though they're still waiting on a final debrief with the FDA following the January rejection--BioMarin can decide if it should devote the resources necessary for that or move on to the early-stage programs the company has in place for DMD.

It's not simply a question of resources, he adds, but the "practicality" of doing another study under the circumstances.

Bienaimé was in Manhattan on Wednesday to give analysts an update on the company's pipeline, including some encouraging extended data on its mid-stage drug vosorotide for dwarfism (achondroplasia), now moving to Phase III, as well as a promising early-stage gene therapy for hemophilia A (BMN 270). In his perspective, the company has a set of late-stage drugs--including the rare disease drug pegvaliase and a therapy for a form of Batten disease--and a sizable pipeline overall that will command a significant amount of R&D resources.

If the regulatory hurdles at the agencies on both sides of the Atlantic are too steep on DMD, the company will have plenty of other work on its plate.

A rejection in Europe is by no means a sure thing just because the FDA rejected the drug. PTC Therapeutics (\$PTCT) won a conditional OK in Europe two years ago for its DMD drug, even though it had failed a mid-stage study and was on its way to failing a late-stage trial. Those back-to-back failures prompted the FDA to refuse to even file the biotech's application for review, satisfied that investigators never provided a convincing case on efficacy. But just days ago the U.K.'s drug watchdog NICE reversed itself and recommended the PTC drug, though European regulators say that they will revisit their decision at some point.

And so it goes. The FDA also provided a harsh review for eteplirsen a few months ago, though analysts are waiting now to see whether new documents out tomorrow could change in light of

additional data. In the meantime, patients are rallying in the hundreds to mount a show of support in the looming panel review.

But Bienaimé says he doubts that kind of lobbying campaign will make much difference.

“I don’t think they’ll be swayed by that,” he noted with a shake of his head. “The FDA wants to see data.”

#

FDA panel meets to discuss Sarepta muscular dystrophy drug [TOP](#)

Toni Clarke, Reuters

Hundreds of patients and advocates packed a hotel ballroom in Hyattsville, Maryland on Monday to try to persuade advisors to the U.S. Food and Drug Administration to support approval of an experimental drug to treat Duchenne muscular dystrophy.

In briefing documents last week the FDA reiterated a negative earlier assessment of the drug, made by Sarepta Therapeutics Inc. It questioned the validity of the clinical trials and said it was unable to draw reliable conclusions about the drug's efficacy

Dr. Billy Dunn, director of the FDA's Division of Neurology Products, opened the proceedings on Monday by emphasizing that the FDA has not yet made its decision as to whether to approve the drug, eteplirsen. He also addressed patients, assuring them that their voices have been heard.

"It is not the volume of the message but the content," he said. "We listened, and we listened closely."

He also laid out the FDA's responsibility under the law to ensure the drugs it approves are effective. And he urged the panel to make its decision based on science in what could be an emotional meeting.

"Anecdote and emotion do not change the data," he said.

Duchenne's is a rare and devastating genetic disorder characterized by progressive muscular weakness and degeneration. It is caused by a lack of dystrophin, a protein needed to keep muscles healthy and primarily affects young men.

The disease typically emerges in childhood, causing weakness in the arms and legs and eventually the lungs and heart. Patients typically lose the ability to walk during adolescence and frequently die in their 20s or 30s, according to the National Institutes of Health.

Sarepta's senior vice president of regulatory affairs, Shamim Ruff, acknowledged that the company had not produced a "traditional" data set since the company did not conduct a randomized, controlled clinical trial, the gold standard.

Instead it measured the progress of patients in the trial against how patients with the disease progress historically. But Ruff said the benefit of the drug as measured by the production of dystrophin, and clinical benefit as measured by a six-minute walk test, was strong enough to warrant accelerated approval for the drug.

The panel will vote at the end of the day on a number of questions, including whether results of the study provide substantial evidence that eteplirsen is effective.

#

The FDA vs. Austin Leclaire [TOP](#)

The Wall Street Journal

No government agency controls the fate of more people than the Food and Drug Administration, which has the power to deny children a treatment that could help them walk. The FDA is reviewing an experimental drug for muscular dystrophy, and the outcome could determine the quality of life for thousands—and whether companies continue to invest in curing rare diseases.

On Monday an FDA advisory committee will consider eteplirsen, a drug by Boston-based Sarepta designed to treat a strain of Duchenne muscular dystrophy, which is a genetic disorder that weakens every muscle in the body. The condition usually affects boys, who by age 12 or so can no longer walk, and over time damages the heart and lungs. The fatality rate is 100%, and most do not live past 25.

Eteplirsen essentially pumps out the protein missing in patients with Duchenne, known as dystrophin, by skipping over faulty genetic code. Sarepta's clinical trial started in 2011 and treated boys about 9-years-old whose abilities seemed to be deteriorating rapidly. After four years of treatment, 10 out of 12 children can still walk. In a comparable group of 11 boys who weren't treated, only one could still walk. No side effects or safety concerns were reported.

One beneficiary is Max Leclaire, who is now 14. His mother, Jenn McNary, became one of the earliest advocates for the drug after noticing her son's marked improvement. She had another reason: Her son Austin is also affected by Duchenne but wasn't eligible for the trial, as he already had lost the ability to walk. So for years Austin was denied the care that helped his brother continue to play sports and dress himself.

Ms. McNary and Christine McSherry, who also has a son with Duchenne, have organized some 900 people to show up at Monday's committee meeting, which forced the FDA to book a bigger venue. Among those offering public comment will be Austin, who began an eteplirsen trial about 18 months ago. He will tell the committee of his brother's persistence and his own—and of friends who have lost dexterity and have no options without FDA action.

Sarepta has gone back and forth with the FDA since 2013, and this is somehow considered the *expedited* track: A 2012 law allows the agency flexibility to accelerate approval in first-in-class drugs for lethal diseases, though the FDA seems to be flouting the spirit of this directive. The agency planned to assemble an advisory committee—which offers recommendations that the

FDA typically follows—in January. But the meeting was postponed due to a blizzard in Washington, one that apparently snowed in the FDA for four months.

In January the agency issued a harsh report about eteplirsen, haggling over minutiae on the trial's design and findings, and here's why: The FDA is religious in trusting only large trials in which half of participants receive a placebo treatment. Yet such trials would prove near impossible since Duchenne patients are so rare.

And more important, unethical: What parent would sign up a child for years of weekly muscle injections and high-risk biopsies if the cocktail might be saline? FDA acknowledges these concerns and admitted in a Thursday report that the agency previously told Sarepta it would consider the type of study the company performed—only to change its mind. At the FDA, process trumps patients.

More than 35 physicians and leading experts, who have seen some 5,000 Duchenne patients and hail from the likes of UCLA and Harvard, offered their opinion in a February letter to the FDA, not that the agency asked. The doctors say the FDA's work includes "scientifically questionable comparisons" and even errors.

The boys are "clearly performing better than our collective clinical experience and the published literature would predict," and the data show "substantial evidence of efficacy," wrote the doctors. Accelerated approval and continuing further trials as the 2012 law prescribes, they concluded, "is the most ethical choice."

Adding more weight to the decision is that eteplirsen can only treat a certain mutation of Duchenne, and a no from the FDA would scuttle iterations in the drug-development pipeline that might help more patients. Biotech companies working on treatments for other rare conditions are also watching. If a drug with no safety risks, a four-year record of effectiveness, and a strong legal and ethical basis can't win approval, what can?

Sarepta, with 200-odd employees, may not have the resources for several more rounds with an agency that seems to enjoy issuing ominous reports and watching the company's stock crater; Sarepta tanked 44% on Thursday when the FDA issued another unfavorable briefing ahead of Monday's meeting. The stock fell more than 50% when the January report emerged. The result of this political control is fewer companies taking the risks that result in cures.

The FDA will review the advisory committee's recommendations and is scheduled to issue a decision by May 26. Allow us to underscore the urgency: The continued use of limbs—raising your hand to scratch an itch—is a miracle for boys facing a slow path to death. The FDA owes children with Duchenne access to every treatment human ingenuity can design.

###

FDA briefing docs suggest nearly foregone conclusion in eteplirsen review [TOP](#)
Marie Powers, Bio World

Shares of Sarepta Therapeutics Inc. (NASDAQ:SRPT) plunged 44 percent in heavy trading Thursday after the FDA posted revised briefing documents for Monday's re-scheduled meeting of the Peripheral and Central Nervous System Drugs (PCNS) Advisory Committee (adcom) to discuss the new drug application (NDA) for its Duchenne muscular dystrophy (DMD) candidate, eteplirsen.

Shares closed at \$11.02 for a loss of \$8.69 on volume of 22.7 million shares – about 10 times the stock's three-month moving average.

The review, originally scheduled for Jan. 22, was postponed after a winter storm closed government offices in Washington on that day. But the three-month delay, which also reset the PDUFA date for eteplirsen from Feb. 26 to May 26, didn't do Sarepta any favors. If anything, FDA reviewers seemed to take an even more skeptical view of the eteplirsen dataset, posing no voting questions for the PCNS members and citing, as a final discussion point, the possible design of any future efficacy and safety studies.

The tone of the briefing docs and the roster of panelists – which includes nine voting members with expertise in neurology but only two specializing in movement disorders or DMD – along with the surprise appearance of Janet Woodcock, director of the Center for Drug Evaluation and Research, as an FDA panelist, seemed to broadcast the agency's intentions.

Perhaps sensing the die was cast, Debra Miller, founder and CEO of the nonprofit CureDuchenne, issued a statement that sounded like a thinly veiled criticism of the adcom agenda. She cited the organization's disappointment at the FDA's initial review of eteplirsen, maintaining that Sarepta attempted during the three-month delay to address the FDA's preliminary questions and to strengthen its case by providing supporting materials and broadening its dataset.

"Any drug that uses a new technology, like eteplirsen's exon-skipping method, is bound to face scrutiny," Miller noted. "But a pioneering approach is needed to address a disease as complex as Duchenne."

CureDuchenne provided early funding for the development of eteplirsen, designed to treat DMD patients who have a mutation of the dystrophin gene amenable to exon 51 skipping, which accounts for about 13 percent of boys with the condition.

"While we understand the FDA needs to make sure drugs are safe and effective, we also know the consequence of inaction for those with Duchenne," added Miller, who said she plans to speak in support of the drug during the adcom's public hearing, expanded to more than two hours. "We are hopeful for accelerated approval."

Much of the criticism about the openly negative briefing documents focused on Sarepta's bid for accelerated approval, but the underlying questions surrounding eteplirsen are hardly new.

In April 2012, Sarepta (then AVI Biopharma Inc.) reported in top-line findings that eteplirsen hit its primary endpoint in a phase IIb trial by showing a statistically significant increase in

dystrophin after 24 weeks. However, investors panned the stock over the lack of clinical outcome improvement and analysts were cautious about the company's intention to meet with the FDA to discuss a pivotal trial based on findings in 12 patients – four of them on placebo before being moved to treatment groups studying the drug's effect at 30 mg/kg dose and 50 mg/kg dose. (See *BioWorld Today*, April 3, 2012.)

But in July of that year, Sarepta reported that eteplirsen, administered once weekly at 50 mg/kg over 36 weeks, resulted in a 69.4 meter benefit on the primary clinical outcome, the six-minute walk test (6MWT), compared to placebo for 24 weeks followed by 12 weeks of eteplirsen in an open-label extension. That finding represented a turnaround for the candidate, and the company's shares more than doubled as Sarepta made known its plans to meet with the FDA to discuss the design of a pivotal study and to seek accelerated approval. (See *BioWorld Today*, July 25, 2012.)

The eteplirsen findings were essentially repeated in October, based on another 12 weeks of data in the open-label extension study. But in 2013, Sarepta disclosed that the FDA wanted more data on the acceptability of dystrophin – a protein that plays a key structural role in muscle fiber function – as a surrogate endpoint to predict clinical benefit before ruling on an NDA filing based on accelerated approval. Two additional meetings between the company and the FDA in 2013 failed to sway the agency's opinion, especially after a phase III miss by competing DMD candidate drisapersen, then in development by Prosensa Holding NV, of Leiden, the Netherlands.

In 2014, Sarepta said the FDA had changed its view on eteplirsen, signaling in a letter that the NDA "should be fileable" with existing data. But the guidance came with caveats. The FDA also cited "significant concerns regarding [its] ability to draw valid conclusions" from the 6MWT data and remained "skeptical about the persuasiveness of the (dystrophin) data" as a biomarker of efficacy. Sarepta maintained, however, that four meetings with the agency had resulted not only in a more favorable regard for the existing dataset but also in clear guidance on an open-label, historically controlled confirmatory study of the compound. (See *BioWorld Today*, April 22, 2014.)

That outlook was all but rescinded later in the year when Sarepta reported 144-week phase IIb results from the extension study showing a decline in walking ability – albeit at a rate slower than would be expected compared to historical controls, and with stable respiratory muscle function. More deliberation by the FDA forced Sarepta to delay the rolling submission of its NDA filing until May of last year. (See *BioWorld Today*, May 21, 2015.)

'WE SEE LIMITED UPSIDE FROM HERE'

Although the FDA accepted the filing, prospects for eteplirsen's approval took a considerable blow, along with the rest of the space, during the PCNS adcom for drisapersen (Kyndrisa), which had subsequently been acquired by Biomarin Pharmaceutical Inc. That panel's voting questions focused on the strength of clinical trials rather than potential approval. Despite gripping testimony from patients and family members, the session seemed to raise more questions than answers, especially about the use of dystrophin as a biomarker. Thus, it came as little surprise to the DMD community when the FDA issued a complete response letter (CRL) on the drisapersen NDA. (See *BioWorld Today*, Nov. 25, 2015, and Jan. 15, 2016.)

The original briefing docs for eteplirsen, issued in January, were equally negative, with FDA staff voicing "considerable doubt" regarding the degree to which the drug improved dystrophin production in DMD patients and questioning whether improvements seen in the small trials could be reliably attributed to the drug. (See *BioWorld Today*, Jan. 19, 2016.)

FDA reviewers found no significant safety signals for eteplirsen in studies of the drug but took issue with trial design, efficacy, dystrophin measurement methods and statistical analysis approaches.

The revised documents revisited those issues by criticizing the size and design of Sarepta's phase II trial, raising concerns that the purported 6MWT benefit over natural history comparisons could be skewed by the post-hoc analysis and systematically discrediting Sarepta's method of quantifying dystrophin expression.

As if to prepare for the public blowback, the agency stated, "Although FDA is prepared to be flexible with respect to a devastating illness with no treatment options, we cannot approve drugs for which substantial evidence of effectiveness has not been established."

Analysts circled around the briefing docs like a Greek chorus. In a hot comment, Piper Jaffray analyst Edward Tenthoff wrote that, "with or without outside pressure, FDA looks set to reject eteplirsen."

He suggested the FDA used the briefing docs to gain the upper hand in what has become an emotional battle involving an impassioned DMD constituency, writing that "FDA devoted considerable time to undermining Sarepta's clinical and scientific arguments."

Tenthoff pointed out that, after the initial docs were released, Sarepta highlighted what it called "key inaccuracies" in the agency's analysis that, when remedied, would yield a more favorable outlook for the drug. "FDA rejected these inaccuracies on a point by point basis, he said, "including the contentious issue of where the idea for an external control came from, pointing out, that if Sarepta had merely acquiesced to the agency's desire for a robustly controlled trial, this would not be an issue at all."

Jefferies Group analyst Gena Wang also predicted low probability of approval, noting that the revised briefing doc re-stated the original conclusions.

"The FDA appears to follow the same principle for BMRN's drisapersen (complete response letter) and PTCT's ataluren (refuse to file letter) and focuses on fundamental data to make the approval decision," Wang wrote in a flash note. "While we thought ambulation at the 4th year could be the strongest argument for SRPT, the FDA expressed its 'concerns about the reliability, completeness and comparability of the clinical data for eteplirsen-treated patients and external controls.'"

Moreover, "the FDA scrutinized the weak biomarker and maintained its view that 'considerable doubt remains about how much, or perhaps even whether, dystrophin levels were increased by eteplirsen,'" she wrote, adding, "We see limited upside from here."

Leerink Partners LLC analyst Joseph Schwartz pointed to the appearance of Woodcock on the adcom as reflective of "the high degree of scrutiny on this panel" and suggested the FDA was armed for a confrontation.

"Having had multiple months to review this additional submission, the FDA has become even more critical by identifying many potential confounding factors," Schwartz wrote, "including two matched historical control patients that were reported to have lost ambulation but also had 10 [meter] walk test values reported as well as a secondary analysis showing that when 6MWT scores are plotted based on [patient] age (rather than years of treatment) that there is substantial overlap between eteplirsen-treated patients and the control group."

With an agenda exceeding 10 hours, "the FDA plans to be exhaustive in this meeting," he concluded.

In his note, RBC Capital Markets analyst Simos Simeonidis opined that FDA reviewers were "doubling down on the negative view of the data," predicting a CRL as the most likely outcome following the panel.

Oppenheimer & Co. analyst Christopher Marai was a rare holdout, citing FDA satisfaction with the eteplirsen safety dataset and natural history control group as a potential upside and contending that broad FDA involvement, including Woodcock's participation, represented a "clear advantage" for eteplirsen compared to previous DMD applicants.

Amid a general sense of fatalism, two questions seemed to swirl around social media discussions of the adcom. Was the FDA's decision to accept the eteplirsen NDA rather than sending the company back to the starting blocks a missed opportunity for the agency, the company or both? And if the FDA openly stacks the deck against a sponsor in the run-up to an advisory committee meeting, does the ensuing discussion offer an opportunity to gather meaningful information or simply serve as a charade that wastes participant time and taxpayer dollars? Neither is likely to be addressed Monday in Hyattsville, Md.

###

CNY mom, sons to testify before FDA panel for approval of experimental drug [TOP](#)

Elizabeth Doran, Syracuse

Manlius mom Alison Dwyer Willis and her twin sons are scheduled to testify this afternoon before a federal advisory panel to urge approval of an experimental drug to treat Duchenne muscular dystrophy.

[Jack and Nolan Willis](#), 14, who are freshmen at Fayetteville-Manlius High School, have Duchenne muscular dystrophy, a genetic disorder where the muscles progressively degenerate and weaken. Most people with the disease die by age 30.

"We are making a plea for approval of the drug," said Alison Willis.

The boys have been part of a clinical trial for the past four years with the experimental drug eteplirsen, manufactured by [Sarepta Therapeutics Inc.](#) Sarepta is seeking accelerated approval for eteplirsen, which is designed to treat the disease. Currently, there are no Food and Drug Administration-approved treatments for the disease.

The drug has kept the boys' muscles stronger for longer, and helped stabilize their heart and respiratory function, Alison Willis said. "At their age, they would have seen much more marked deterioration without this drug," she said.

Duchenne muscular dystrophy is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. Symptoms appear in early childhood, usually between ages 3 and 5. The disease primarily affects boys.

The Willises are among hundreds of "patient advocates" attending the hearing, and have been selected along with others to testify at the Peripheral and Central Nervous System Drugs Advisory Committee meeting Monday at the Marriott in Hyattsville, MD. Each group is given three minutes to speak, Alison Willis said.

The public portion of the hearing starts at 2 p.m., although the hearing lasts all day.

[Jack and Nolan Willis](#) are among a dozen males with Duchenne muscular dystrophy who are part of the clinical trial, and Alison Willis said she believes 10 of those in the drug trial will be at the hearing.

Alison Willis said some critics have pointed to the fact that both of her sons stopped walking in 2012, while on the experimental drug. The critics say that's proof the drug doesn't work, she said.

But Alison Willis and others argue that losing the ability to walk is part of the disease. Even though the boys both use wheelchairs now, the drug has helped prevent their muscles from deteriorating more, and given them near-normal heart and respiratory functions, she said.

The Willis family wants to see others with the disease get the chance to use this drug, which will only happen if it gets approved by the FDA, Alison Willis said.

Jack Willis said he's ready for his testimony, and not afraid to speak in front of such a large group. "I'm not nervous," he said. "They're just people."

The panel's first hearing was postponed after a snowstorm in January, and many families have been waiting for this opportunity to advocate for the drug, Alison Willis said.

"This drug could save a whole population of children with DMD," she said. "And it's imperative that my boys stay on this drug or they will deteriorate. We don't want this drug to go away."

The panel is expected to make a recommendation by May 26 after taking in account FDA reviews, the company's data and public comments.

###

Sarepta Slammed by FDA, Stock Is Now Intriguing [TOP](#)

Andrew Bary, Barron's

Sarepta Therapeutics' [shares are down sharply](#) this morning, falling \$8, or 40%, to \$11.71, following the release this morning of a harsh assessment by the Food and Drug Administration of the company's novel treatment for Duchenne muscular dystrophy.

The FDA briefing document was prepared by the agency's neurology division ahead of an advisory committee hearing planned for Monday. The meeting, in Hyattsville, Md., just outside Washington D.C., could draw more than 1,000 people, including a huge contingent of Sarepta (ticker: [SRPT](#)) supporters from the DMD community.

It is unclear if the advisory committee will be asked to offer an opinion on whether the drug should be approved. In any event, the FDA is due to render a decision on whether to grant accelerated approval for the Sarepta drug, eteplirsen, by May 26. The new briefing document was compiled after a snowstorm in January resulted in the cancellation of a planned advisory committee hearing and also followed new clinical and other data provided by Sarepta.

Sarepta shares look inexpensive now, with the company's market value totaling \$600 million. But the odds of accelerated approval, which had been rising in recent weeks, have fallen sharply with the new briefing document, which is as negative and perhaps more so than the original one in January. The stock had doubled off its January low of \$10, hitting a recent high of \$22, after a group of 36 doctors involved in treating boys with DMD expressed strong support for eteplirsen approval. There also is widespread patient and political support for the drug.

[Barron's has been upbeat on Sarepta](#) and the prospects for eteplirsen in a series of stories in recent years, including a story that ran in last week's issue. There is huge revenue potential for a DMD drug. Eteplirsen, which treats a genetic mutation in about 13% of DMD cases, could have \$600 million of U.S. annual revenue potential and a family of DMD drugs could ultimately generate \$3 billion of annual sales.

The FDA countered nearly every argument that Sarepta has made for approval, including data on the production of dystrophin, the muscle protein missing in boys with DMD, and walking data from a small Phase 2 clinical trial involving 12 boys. The briefing document summary concluded that "Although FDA is prepared to be flexible with respect to a devastating disease with no treatment options, flexibility does not mean approving drugs for which substantial evidence of effectiveness has not been established." The FDA neurology division clearly is skeptical of eteplirsen's efficacy.

DMD is a fatal muscle-wasting disease affecting boys that puts them in wheelchairs by their early teens and usually leads to death by age 20 to 30. Eteplirsen is designed to stimulate the production in muscle cells of the protein dystrophin, which is critical to muscle health. Sarepta offered quantitative evidence that the drug produced dystrophin and that 12 boys in a clinical trial fared better on a 6-minute walking test than an untreated group of boys who were evaluated in a separate study in Europe.

Leerink analysts wrote this morning in a client note that the briefing document “remains largely negative citing concerns with trial design, efficacy, dystrophin measurement methods, laboratory measurements and statistical analysis.” They are cautious on the stock.

The FDA attacked the dystrophin data, noting that after 3.5 years, the boys in the Sarepta study showed just 0.9% of the normal level of the protein based on muscle biopsy data, and that it probably would take a greater amount of dystrophin for clinical effectiveness.

One of Sarepta’s strongest arguments has been that 10 of the 12 boys in its study were walking after four years, compared with just one of 11 in the European study. The FDA wrote that on closer analysis, two of the boys in the European study “who were reported to have lost ambulation” actually could walk at least 10 meters. This makes the Sarepta comparison less compelling.

Like in the original briefing document, the FDA raised the issue of “whether there is convincing evidence that the clinical course of the 12 patients” in the Sarepta study “differs appreciably from the expected natural history of DMD.”

The [FDA advisory committee hearing](#) Monday promises to be a dramatic event and probably the most widely attended hearing ever. Sarepta and the FDA will present their cases to the committee, and a block of two-and-a-half hours is set aside for public comment. Many patients and family members of boys with DMD are expected to speak passionately in favor of the drug, arguing that the drug is slowing the progression of the disease and clearly showing a clinical benefit.

The FDA is under enormous patient and political pressure to approve the drug. Reflecting this, a senior FDA official, Janet Woodcock, the head the agency’s Center for Drug Evaluation and Research, will testify at the committee hearing.

If eteplirsen doesn’t get accelerated approval in May, it will dim but not kill the drug’s chances for approval. Sarepta now is conducting a confirmatory Phase 3 trial, and some results are expected next year or in 2018. If those results are positive, Sarepta could approach the FDA again and seek approval. Accelerated approval is granted in cases of a high unmet medical need and can be based on more limited clinical trials than are normally required for drug approval.

The long Sarepta saga continues and the prospects for eteplirsen approval clearly are diminished. At the current price, investors are putting low odds on approval. What’s the downside? If approval is denied in May, the stock could fall into the high single digits. If eteplirsen accelerated approval is granted, however, the stock could trade at \$60. The risk/reward is looking better now, but there is a lot of risk with Sarepta because it has no approved drug now and largely has staked its commercial future on eteplirsen and a group of similar drugs to treat DMD.

###

FDA chief lays out rationale for Duchenne drug to be granted temporary approval [TOP](#)
Don Seiffert, Boston Business Journal

Janet Woodcock, the Food and Drug Administration’s director of drug evaluation, told panelists reviewing a potential drug for Duchenne muscular dystrophy this morning that there is a clear danger to patients in not approving a drug that works.

In comments before the advisory committee to review a drug developed by Cambridge-based [Sarepta Therapeutics](#) (Nasdaq: SRPT), Woodcock's comments will be seen as largely supportive of accelerated approval of the drug. She seemed to outline a rationale under which the drug could be given accelerated approval, despite much speculation on Wall Street to the contrary in the past three months. She told the panel and the audience of hundreds who packed into the room that just as there is a danger in approving a drug that does not work, "Often there is never consideration of another error — that of not approving a drug that works," she said.

Woodcock said there is "an inherent presumption" in the idea of accelerated approval of a drug that "more uncertainty is going to be tolerated, at least at the beginning."

She said her comments were meant to be a "framework" for the panel to consider the information that is being presented today by the company, by world-renowned experts in Duchenne muscular dystrophy, by patient advocates, and by the FDA scientists. She allowed that "it's possible to reach different conclusions about these comparisons" to patients who have been treated with the drug to what is known about patients who have not, seemingly allowing for the wide gap in interpretations of the data between Sarepta and the FDA.

She said "there is agreement that the drug does achieve primary pharmacodynamic effect," which is increasing a protein needed for muscle production known as dystrophin. The amount that it increased that protein was not as much as hoped, at least in the small study, but she acknowledged that there is evidence that even a small amount may help patients.

Woodcock's comments came at the end of a two-hour presentation by the company and top scientists that was mostly supportive of approval of the drug, but before the FDA's comments that are expected to be highly critical of it. While they do not ensure the panel will approve the drug — or that she will approve the drug regardless of the vote — her comments were perceived by many observers on Twitter as more positive toward the company than expected.

Earlier comments by the FDA's director of the Division of Neurology Products, [William Dunn](#) (a subordinate of Woodcock's) seemed to emphasize the need for "substantial" data needed for even accelerated approval. He said accelerated approval can't make up for bad or inconclusive data (the agency's main argument so far has been Sarepta's data is inconclusive), and even hinted that the company may have "misled" the agency into allowing a submission for approval of the drug.

In the end, it is Woodcock who will make the final approval decision on the drug, meaning that while she was speaking to the 10-member panel that will make the recommendation as to whether eteplirsen ought to be approved, she doesn't necessarily have to abide by that recommendation.

Patient testimony is expected to take up most of the afternoon, to be followed by the panel votes on seven key questions.

###

Does muscular dystrophy drug work? Advocates pack FDA meeting [TOP](#)

Maggie Fox, NBC

The video is distressing even though it's taken from too far away to see clearly — a boy trying to take a few steps and collapsing in a pile in the shiny hospital corridor.

"His quads just give out, giving him no time or warning to break his fall," says Christine McSherry, mother of a muscular dystrophy patient and one of the many advocates speaking out at a Food and Drug Administration hearing about an experimental new drug for muscular dystrophy, a genetic condition that cripples boys.

Patients, activists and advocates gave McSherry a standing ovation after her presentation at what, a few years ago, would have been a dry and quiet Food & Drug Administration hearing. Patients, advocates and others lined up outside the hearing at a hotel just outside Washington, D.C., hoping to grab an empty seat, craned to hear.

This hearing is just the latest to show the effects of the FDA's efforts to give patients a bigger voice in the drug approval process. This time, that patient voice has the help of several high-octane public relations firms and is encouraged by the success of a big PR effort to back the [controversial approval of Addyi](#), a female libido drug OK'd amid considerable media coverage last August.

FDA officials are worried about a repeat of accusations that they were pressured by the coverage.

This time, they say they'll listen to the patients, while not being unduly swayed by the emotional appeals of the parents, patients and advocates.

"It is not the volume of the message, but the content. We listen and listen closely," Dr. Billy Dunn, director of the FDA division of neurology products, said in opening the hearing.

The FDA is considering a drug aimed at just 13 percent of muscular dystrophy patients. It's a highly tailored therapy that uses a completely new approach to treating the condition.

Muscular dystrophy is a catchall term for a group of genetic diseases that gradually disable kids. Most patients are boys. Some die young as the muscles that control breathing break down, while others may live long lives with only moderate disability. There's no cure for any form and not even a real treatment, although steroids can help.

The drug in question is called eteplirsen. It's aimed at a mutation seen in a subset of children with Duchenne muscular dystrophy, a degenerative disease that causes muscles to break down because cells produce faulty versions of a protein called dystrophin.

Eteplirsen, made by a small company called Sarepta Therapeutics, uses an approach called RNA antisense to cause the body to "skip over" the mutation that causes the disease, as cells "read" the DNA to do their daily work.

The hope is that skipping over the mistake would help cells start making normal dystrophin again. But it's not clear it actually does that.

Sarepta's chief medical officer Dr. Edward Kaye says the company has shown this. "These data clearly indicate that eteplirsen is working as intended," Kaye told the packed-out hearing.

Dr. Jerry Mendell, who helped run the clinical trials of the drug at Nationwide Children's Hospital in Columbus, Ohio, says he's seen no evidence the drug has any side-effects and showed images of a 15-year-old boy he treated who walked in a marathon. "Usually boys this age with Duchenne muscular dystrophy don't walk," Mendell said.

"I can't see any grounds for withholding this drug for Duchenne muscular dystrophy boys."

But FDA officials say the evidence the company has presented is not clear at all. They're not sure that the 12 boys tested are producing dystrophin. They are also not fully convinced by videos that show the boys walking.

The boys were not treated in what's called a randomized trial — there were not untreated boys with similar backgrounds used to compare what happens when some get the drug and some do not. So the agency and its expert advisers have to just look at what happened before and after treatment, a notoriously unreliable way to assess how or whether a drug is actually working.

"The FDA is certainly keen on looking at the data in different ways," Dr. Ronald Farkas, who's helping lead the FDA team evaluating the drug, told the hearing.

Farkas, clearly aware that he was speaking to a hostile crowd, said repeatedly the FDA was not trying to keep a good drug off the market.

"I think that you haven't heard the whole story. But I really want to reassure everybody that I will remain open to what I hear from the community," he added. "I have made no final decision."

Farkas he said he and other experts cannot tell whether the boys tested were being helped by the drug. Different patients are affected differently by muscular dystrophy, he said.

Dr. Janet Woodcock, a senior FDA official, noted that the FDA does worry about approving a drug that doesn't work.

"There often is little consideration of another error — which is failing to approve a drug that actually works," she added. "But most of this consequence is borne by patients who have little say."

Advocates note there is nothing at all for muscular dystrophy patients.

"We fully understand that eteplirsen is not a cure and that it only slows progression of disease," said McSherry, whose Jett Foundation is named for her 20-year-old son who has muscular dystrophy.

"The collective evidence suggests to us that eteplirsen is having a real and concrete effect on disease."

And McSherry noted the extreme need. "Jett took his last step when he was 13," she said. Not only do patients then have to use wheelchairs, but this can over time affect their spines and their ability to breathe.

###

In setback, a majority of FDA experts reject Sarepta's emotional campaign to gain Duchenne drug OK [TOP](#)

John Carrol, Fierce Biotech

Sarepta lost a major battle in its years-long quest to gain an accelerated approval for its Duchenne muscular dystrophy drug eteplirsen.

An FDA panel of outside experts voted 7 to 6 that Sarepta did not provide substantial evidence from "adequate and well controlled" studies that the drug produced dystrophin at a level that was reasonably likely to produce a clinical benefit. Seven of the agency advisers also voted that there could not be an objective, valid comparison that was free of bias between patients receiving eteplirsen and a historical control group that was used to demonstrate efficacy.

Then there was the full approval question. Do the clinical results of the single study provide "substantial evidence" of eteplirsen's efficacy?

Again, 7 panel members voted no, with three voting yes and three abstaining.

On Wednesday morning, Sarepta's shares plunged 45% in premarket trading, continuing the roller coaster ride that some investors have been on for some time now. RBC's Simos Simeonidis, who was skeptical going into the vote, expects that it will be much easier now for the FDA to issue a formal rejection of marketing approval.

Joseph Schwartz at Leerink noted that it was the panel members with the greatest expertise in the field who lined up against the drug. "Ultimately, some ~900 pt. advocate attendees were once again left frustrated and upset at the rigidity of the FDA panelists precipitating in a heated outcry against Dr. Chiadi U. Onyike," he noted, "who recommended that the community support a placebo controlled trial going forward."

Sarepta stumbled on crucial questions regarding the drug's ability to safely tap the brakes on DMD, which the advisory committee considered after FDA insiders and Sarepta supporters outlined starkly different views of eteplirsen and the data used to support an accelerated approval.

The vote came after a grueling 11-hour session during which a large crowd of patients and drug advocates lent a loud and emotional voice demanding that the agency go ahead with an accelerated approval for marketing the drug in the U.S.

From the start, Sarepta balanced its position on the data with an emotional, sometimes tearful, call for a positive response to their drug.

"I can't see any grounds for denying this drug for DMD boys," said Jerry Mendell, the principal investigator in the key study under review, whipping up cheers from the largely pro-eteplirsen crowd.

In an extremely unusual twist for an FDA panel review, Sarepta execs quickly handed the podium over to Duchenne drug activist Christine McSherry, who presented video clips of some of the boys recruited for the study. Those testimonials might be viewed as entirely anecdotal by experts, but they've proved powerfully persuasive for the advocacy community, especially the parents who have to watch helplessly while their sons are slowly crippled and then killed by DMD.

Her testimony and videos were greeted by whoops and cheers, something else you don't hear much of during FDA panel reviews.

After a cautionary remark from the FDA's Janet Woodcock, who encouraged the committee to weigh a need to avoid erroneously endorsing drugs that might not be effective while remaining sensitive to the need of OKing a drug that might work, the hearing offered two radically different conclusions on one drug.

Agency insiders repeated a harsh assessment of Sarepta's data, insisting that the company repeatedly ignored its advice on the right way to run a study on this drug. A late revision failed to provide convincing data that the drug did what it was designed to do: significantly increase dystrophin, the lack of which clearly triggers the fatal disease.

Repeatedly, the regulators highlighted the suspect results cited by Sarepta in its pursuit of an approval. In particular, the agency officials noted a questionable use of an inappropriate historical control group, even though there were stark differences between the data gathered from patients in earlier studies and the data on patients in their own, limited clinical study.

There are "reasons to be concerned this was not an appropriate control to pick," noted the FDA's Ronald Farkas, highlighting how investigators improperly compared dystrophin levels in different types of muscles.

In addition, the regulators noted that the company has repeatedly spotlighted major efficacy results that were never borne out by credible data. And they added that the biotech ignored repeated instances when the agency underscored the need for larger, decisive trials that could provide solid evidence of success or failure.

Added up, the regulators' remarks created enough doubt to sway the vote against eteplirsen.

Dozens of parents and Duchenne kids, though, weren't buying it. They insisted that the drug was working and offered this vulnerable group of dying kids their only chance of extended survival, their only chance of more hugs, more love and more hope for the future.

The FDA's skepticism, for patients and their families, represents a simple denial of the obvious. And the patients' hope, for the FDA, represents a simple human devotion to wishful thinking in the face of a nightmare.

The final decision on eteplirsen's immediate fate now passes to the FDA. Sarepta, meanwhile, is pursuing a pivotal study that won't read out until 2019.

The last few months have proven to be excruciating for patients and families, who currently have nothing to turn to to slow or stop a disease that first cripples and then kills boys. BioMarin tried and failed with drisapersen, with an FDA rejection landing in January. PTC Therapeutics never made it through the door with their therapy, as regulators refused to even file an application they found too weak to warrant careful consideration. And now, barring a last-minute surprise, it looks like Sarepta's eteplirsen faces the same fate.

###

FDA committee votes against approval of controversial muscular dystrophy drug [TOP](#)
Carolyn Johnson, WashPo

In a split vote on Monday, a Food and Drug Administration advisory committee effectively recommended against approval of an experimental drug for the rare and lethal disease Duchenne muscular dystrophy, ending a day of emotional testimony that [tested the power of patient advocacy against scientific data](#).

The closely watched meeting stretched for nearly 12 hours, as young patients and caregivers gave impassioned and occasionally tearful accounts of how the drug eteplirsen had curbed progression of the degenerative muscle disease.

"FDA, please don't let me die early," said 15-year-old Billy Ellsworth, who is in the drug trial considered by the committee.

But the results of that trial were questionable. The committee voted 7 to 3 that there was not substantial evidence the drug is effective, with three committee members abstaining. The vote was closer on whether eteplirsen increased production of a critical missing protein enough to be likely to provide benefit -- the committee voted 7 to 6 that it did not.

The committee's votes are not binding, but the FDA usually follows the recommendations of its advisers. The decision imperils the possibility that the drug made by the Massachusetts company Sarepta Therapeutics will be approved.

It also leaves in frustrated limbo hundreds of supporters and patient advocates, who had put intense pressure on the agency to approve the drug. Some parents yelled angrily after the

committee's final vote, and throughout the day, there were murmurs of disagreement and cynical laughter when the FDA presented its view of the data.

Duchenne muscular dystrophy is a rare degenerative muscle disease that affects between 9,000 and 12,000 boys in the United States. Boys with the disease typically rely on a wheelchair by their teens and die in their 20s or 30s. Eteplirsen would be the first drug marketed for the disease and is aimed at a fraction of those affected – just 13 percent who carry a particular mutation.

On display Monday was an agency striving to show compassion for the experiences and passion of patients but also considering data from the company's drug trial that agency officials said do not adequately support their testimonials.

In a confident opening presentation, the company and specialists working as consultants presented data showing that the drug had an effect on the disease, leading to an average gain in the distance boys could walk over 6 minutes of 162 meters – or nearly two football fields, as Sarepta interim chief executive Edward Kaye said.

“I can’t see any grounds for withholding this drug” for boys with Duchenne, said Jerry Mendell, the director of the Center for Gene Therapy at Nationwide Children’s Hospital in Columbus, Ohio and the principal investigator of the key trial being considered by the panel, who showed a video of Ellsworth walking the last mile of the Pittsburgh marathon and even breaking into a jog.

The tiny 12-person study that the company presented to support its case for clinical effectiveness was unpersuasive to many on the panel, but several committee members noted that the patients and parents spoke about compelling benefits-- such as the ability for boys to open a bag of chips, feed themselves or maintain upper body strength and questioned why those weren't rigorously measured in the study.

Panel members said they found the testimony from patients mattered, and made a difference.

"I've been extraordinarily influenced and impressed by the people who spoke about this drug earlier and their observations," said Mark Green, a professor of neurology, at the Icahn School of Medicine at Mount Sinai, and a member of the committee.

In a sign of the importance of the hearing, Janet Woodcock, director of the Center for Drug Evaluation and Research at the FDA, spoke at the meeting and attended the entire day. In her opening remarks, Woodcock noted that one much-discussed risk of error in drug approval was the worry of letting an unsafe drug through the process. A little-considered error, she added, was the harm that could be done by failing to approve a drug that does work.

“In devastating disease, the consequences of this mistake can be extreme, but most of these consequences are borne by patients,” Woodcock said.

###

FDA panel votes against Sarepta’s drug for Duchenne muscular dystrophy [TOP](#)

Ed Silverman, STAT

A federal advisory panel voted Monday that a drug from Sarepta Therapeutics was not effective for treating Duchenne muscular dystrophy, a rare and fatal muscle-wasting disease. About 13,000 children, mostly boys, are afflicted.

The vote came after a daylong session punctuated by emotional pleas from dozens of parents and their children, some of whom appeared in wheelchairs, to describe how the Sarepta drug, called eteplirsen, made a substantial difference in clinical trials. Their testimony was balanced by presentations from US Food and Drug Administration staff who [took a dim view](#) of the Sarepta trial data.

The panel vote, however, is not the last word. The agency must now determine by May 26 whether to follow the recommendation.

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One FDA official appeared to leave the door open as the meeting concluded. “I assure you, we listened very carefully and will take the information we heard here today under serious consideration,” Dr. Billy Dunn, who heads the FDA division of neurology products, told the crowd.

Beyond this one medicine, the meeting was something of a caucus on regulatory policy.

The fate of the Sarepta drug has been closely watched as a litmus test for an intensifying struggle between the FDA and patient groups that want the agency to take a more expansive view toward approving medicines for unmet medical needs. In this instance, patient advocates hope the FDA will use the accelerated approval process to endorse eteplirsen. This approach relies on a substitute outcome in a clinical trial to suggest a drug may have, but not does not guarantee, a benefit.

Acknowledging the climate, Janet Woodcock, who heads the agency division that approves drugs, attempted to appease the large crowd of DMD parents and their supporters.

“It’s possible to reach different conclusions based on the data presented today,” she said during brief remarks shortly after the meeting began. “Failing to approve a drug that actually works in devastating diseases — these consequences are extreme.”

In recent months, the FDA had [rejected](#) two other drugs for DMD. And during the run-up to Monday’s meeting, FDA staffers released lengthy documentation that took a dim view of the Sarepta drug.

The possibility that DMD parents faced a “three strikes” scenario lent an unprecedented sense of urgency to the proceedings.

The session, in fact, was easily one of the most politically charged FDA advisory panel meetings held for a new drug approval.

The first public speaker underscored the tension. Representative Mike Fitzpatrick, a Republican from Pennsylvania, noted that more than 100 lawmakers had signed a letter that urged the agency to endorse the Sarepta treatment. All but one of the 52 slotted public commentators spoke in favor of approval.

Among them was one boy with DMD, Billy Ellsworth, who appeared with his mother and testified before the crowd. “I’m going to beat this bloody disease but I need your help,” he told the panel, prompting cheers and applause from the overflow audience. “FDA, please don’t let me die early.”

Much of the day, however, focused on the technical aspects of whether the clinical trials that tested eteplirsen demonstrate whether the drug is actually beneficial.

At issue was whether eteplirsen can sufficiently produce higher levels of a protein called dystrophin. Without this protein, muscle fibers degenerate and voluntary movement becomes impossible. The FDA staff had raised doubts about the veracity of a small, 12-patient clinical trial that Sarepta relied on to make its case, as well as the viability of six-minute walking tests that trial participants underwent.

The agency usually views small trials with skepticism. And during the meeting, FDA officials reiterated such concerns.

One FDA official, Dr. Eric Bastings, told the panel that there was “no apparent correlation between muscle levels of the protein dystrophin and a change” in the boys’ performance in a walk test.

The panel took a mixed view. In a 7-to-6 vote, they decided the drug failed to demonstrate that it produced enough dystrophin to yield a clinical benefit. This is the basis for using the accelerated approval process.

Seven panelists also voted the drug was not effective in treating DMD. Three voted the drug was effective, while three others abstained. “The data wasn’t there to approve on basis of one poorly controlled trial,” Dr. Caleb Alexander, a physician-scientist at the Johns Hopkins Bloomberg School of Public Health and the panel chair, said in summarizing the vote.

Nonetheless, the FDA is under pressure to demonstrate flexibility in listening to patients as part of the drug review process — a mandate that was written into a 2012 law.

One Wall Street analyst believes no one should be surprised if the FDA does approve the drug.

“Everyone was visibly moved by the audience and their testimony, and that is not going to go unnoticed,” said Steven Brozak, who runs WBB Securities and tracks biotech stocks. “It’s not

just political pressure. It's advocacy pressure of the sort that I've not seen since the days of HIV and AIDS. And that can make the difference here."

The only outright opposition to approval came from Laura Gottschalk, a senior fellow at the National Center for Health Research, a nonprofit think tank. "Unfortunately, the data do not meet a scientific standard of evidence of effectiveness," she told the panel. "These boys and their families deserve better."

###

FDA Panel Votes Not to Recommend Approval for Muscular Dystrophy Drug [TOP](#)

Thomas Burton, WSJ

An advisory panel to the Food and Drug Administration voted not to recommend approval of a drug for the crippling disease called Duchenne muscular dystrophy.

The advisory committee voted 7-3, with three abstentions, on the central question of whether evidence of effectiveness for the drug eteplirsen from [Sarepta Therapeutics Inc.](#) had been proven by a single, small study of just 12 patients.

"I felt this wasn't a well-controlled study," said panel chairman G. Caleb Alexander, an associate epidemiology professor at the Johns Hopkins School of Public Health. The panel members who abstained said they were undecided because they were moved by public testimony from parents who believed their children had been helped by the drug.

The decision followed decidedly negative comments from FDA reviewers who concluded that the study [fell far short of producing enough evidence](#).

"Although FDA is prepared to be flexible with respect to a devastating illness with no treatment options," FDA reviewers said in a report to the panel, "flexibility does not mean approving drugs for which substantial evidence of effectiveness has not been established."

The federal agency isn't required to follow the advice of its advisory panels, but generally does so. In November, the same panel concluded that [clinical data were lacking on another muscular dystrophy drug](#), from BioMarin Pharmaceutical Inc.

"While we're disappointed in the vote by the panel, we will address the information raised today with FDA as it completes its review of our comprehensive" new drug application, said Edward Kaye, Sarepta's chief medical officer and interim chief executive.

The FDA's hearing and decision highlighted the tension between the agency's requirement that a drug be proven to work and the need to find anything that might help the people with a lethal disease that has no cure.

As was the case with HIV drugs decades ago, patients and their families often are willing to take big risks and are pressing the FDA to approve a drug regardless of seemingly thin evidence of effectiveness.

The parents appearing before the panel Monday said they believed their children have benefited from the drug and that studies simply haven't proven it.

"Eteplirsen is giving my son a fighting chance," said Beth Perez of Yorktown, Va., who testified with her 12-year-old son, Caden. "He would not be ambulatory without this drug." Comments from parents and patients were frequently punctuated by applause at the FDA advisory meeting. The meeting ended with angry shouts from some audience members about the outcome.

Sarepta didn't immediately comment on the vote.

Duchenne muscular dystrophy is a disorder occurring in male children—about 1 in 3,500 boys. It is often fatal by the time the boy reaches his 20s or early 30s. It is typically first noticeable in children from 3 to 5 with advancing muscle weakness. Children with the disease often start to lose their ability to walk in their teens. They then can lose respiratory function and begin to have severe cardiac problems.

The genetic disease is caused by absence of a protein called dystrophin, which leads to degeneration of muscle fibers. Patients fall frequently. This is followed by loss of muscle and muscle function. Often, such children become wheelchair-bound by age 10 to 14.

There aren't any FDA-approved treatments for the disease. Such patients often get steroids to help with symptoms. But these create risks of infection, diabetes, obesity and other conditions.

Sarepta [has been unusually combative with the FDA](#), releasing a statement earlier this year decrying "key inaccuracies" in the agency's findings.

The agency focused on a small Sarepta study of 12 patients that was called Study 201/202. Such tiny studies are often viewed with considerable skepticism by the FDA. The agency's reviewers concluded that, for various reasons of clinical-study design, the trial "did not provide interpretable evidence of benefit." However, FDA senior officials expressed caution on this point at the end of the meeting.

Dr. Janet Woodcock, who heads the FDA's drug center, said the agency now has "flexibility and that's where we should take the views of the community into account."

In the Sarepta research, two patients were unable to walk soon after the study began. Sarepta then compared six patients on different doses of its drug, to four patients getting a placebo. The agency wasn't convinced by the findings, which primarily dealt with the children's ability to walk.

At the hearing, one FDA official, Dr. Eric Bastings, said there is “no apparent correlation between muscle levels of the protein dystrophin and a change” in the boys’ performance in a walk test.

In fact, the FDA reviewers said in the report to the panel, the agency had “strongly encouraged” Sarepta to “conduct an adequately powered, randomized, placebo-controlled trial(s) to assess the clinical effect” of its drug. Among other things, FDA doctors found they were skeptical that the Sarepta studies truly showed an improvement in the amount of dystrophin found in muscle fibers.

The FDA also noted that for much of the study, the research was “open-label,” meaning that doctors knew who got the drug. Thus, the FDA doctors found, the children’s performance on a walk test “could be influenced by expectation bias, motivation and coaching.”

###

Lip Service To Patients And Caregivers, Or Respect? The Significance Of An FDA Panel's Review [TOP](#)

Elaine Schattner, Forbes

Today an [FDA advisory panel](#) held a meeting to review information about a drug that might help kids with a rare and disabling, fatal condition called Duchenne [muscular dystrophy](#) (DMD). I have no particular interest in biotech investing or the company, Sarepta Therapeutics, which has developed the experimental medication, eteplirsen, which might be approved.

The [live-blog](#), tweets and [commentary](#) surrounding the patients and their parents, company spokespeople, FDA data reviewers, physicians and other experts at the scene, in a hotel ballroom in Hyattsville, Maryland, are noteworthy. They’re significant first, for patients with DMD who might gain access to this drug, or not. According to [the NIH](#), which cites the CDC, this condition affects one in every 3,500 to 6000 male children born each year in the United States.

Today’s hearing is not just about whether the FDA should approve a medication for boys with Duchenne muscular dystrophy and certain genetic mutations, which is nicely [summarized here](#). It’s about how and why the agency might approve – or deny – almost any targeted drug in the future. The panel’s review highlights the issue of data, and what constitutes sufficient clinical evidence of a drug’s value.

If [patient-reported outcomes](#) matter equally as doctor-reported outcomes, those patients’ impressions should count as data, as evidence in a trial, as reasons to recommend a drug. At center, today, were reports by affected patients and caregivers that the drug is helping a few to keep walking, or otherwise moving. They and their doctors say the medication is slowing their neurologic decline, compared to what they’d expected, based on historical observations of the condition.

It's easy to write that physicians [need listen more to patients](#), and believe them, if they're hurting, or whatever it is that limits an individual's well-being, or (as in DMD) causes paralysis and early death. But when it comes to drug approval and interpreting clinical information, it seems, some people turn or stay hard and cry about the e-word ([emotion](#)), as if mothers telling an FDA panel about what's happening to their kids is the opposite of science.

The fact is, it's hard to know if a drug will help an individual, but to try it.

Here, there's no pretense of a big clinical trial to guide the FDA's decision, on eteplirsen. The limited Duchenne data are difficult to interpret, an agency official, [Janet Woodcock](#), observed. Two of the three outcomes measured are biochemical markers, surrogates for possible clinical improvement, which in itself has been hard to compare between a small group of patients with DMD and historical controls.

Evidently the company and the FDA agree that the drug has been well-tolerated, so safety is not what's at issue, today. If approved, as with other drugs, thorough post-marketing safety monitoring will be crucial.

###

Families Plead for FDA Advisers to Recommend Sarepta Muscle Drug [TOP](#)

Anna Edney, Bloomberg

Families of patients with a deadly muscle-wasting disease pleaded with government advisers to back Sarepta Therapeutics Inc.'s experimental treatment, setting up a showdown between patient advocates and U.S. regulators who have questioned the drug's effectiveness.

Parents and advocates of patients with [Duchenne muscular dystrophy](#) are trying Monday to sway the panel to recommend Sarepta's eteplirsen to be the first treatment ever to gain Food and Drug Administration approval for the progressive disorder that mainly afflicts young boys. Hopes for a therapy have fallen as two other drugs developed by biotech companies have failed to get government clearance.

Sarepta's key trial didn't include a group receiving a placebo, normally the gold standard for clinical testing, and instead compared the 12 patients getting the drug with data from external patient registries. The company has sparred with FDA over whether the trial was properly designed to show the drug's effectiveness.

"Know that if these results were from a well designed and interpretable trial, there likely wouldn't be much to talk about," said Billy Dunn, director of the division of neurology products in the FDA's Center for Drug Evaluation and Research in opening remarks to the committee, as a crowd of several hundred looked on. "We come to you with sincere concerns."

Drugs Rejected

Sarepta's shares have been on a roller coaster as some data released last year appeared to support the drug, while competitors' entries foundered. After reaching \$39.12 in late December, the shares have fallen 62 percent to \$14.95 as of Friday's close in New York. The company said last month that it was cutting about 17 percent of its workforce. The shares were halted during the panel's meeting.

The advisory panel meeting has been delayed since January, when the FDA postponed it because of an approaching [snowstorm](#). Parents and patients who had traveled to the event were forced to turn around.

Patients' hopes suffered another blow in January when the FDA rejected BioMarin Pharmaceutical Inc.'s experimental drug. The agency refused in February to review PTC Therapeutics Inc.'s application for its drug after the company failed to show that patients getting the drug did better than those on placebo.

Dunn reminded the Sarepta panel to focus on the four years of studies provided by the company.

"Emotions will run high," he said in the meeting at the College Park Marriott Hotel and Conference Center in Hyattsville, Maryland. "People are invested."

Public Support

Christine McSherry, executive director of the [Jett Foundation](#), showed video of boys in Sarepta's trial talking about vast improvements the drug made in their lives. Some boys in the patient advocacy organization's video said they were no longer spontaneously falling and were able to get around school without the help of a wheelchair. The room burst into cheers and applause after the presentation.

Representative Mike Fitzpatrick, a Pennsylvania Republican, spoke first among 52 scheduled members of the public, most of whom will likely address the panel in support of eteplirsen. Fitzpatrick urged approval on behalf of a 15-year-old in his district named Jake whose disease has progressed "year after year" without an effective treatment for the disease.

Dystrophin Data

Among the issues the panel will consider is the drug's impact on levels of dystrophin, a muscle protein that's missing in boys with the disease. FDA staff in a report that data suggesting that the drug raises levels of dystrophin were "unreliable."

When FDA was first in discussions with Sarepta "it was our understanding that dramatic increases in dystrophin were being observed," Dunn said.

Patients' average dystrophin levels on the drug rose from 0 to 0.9 percent of normal levels, an increase that was "very disappointing," said Eric Bastings, deputy director of the division of neurology products in FDA's Center for Drug Evaluation and Research. Bastings said while he

was understanding of patients' desire to see the drug approved, his job is to present an accurate scientific review.

"I do understand your situation," he said. "You have a devastating disease and there is great hope that this experimental treatment will change your disease."

A 17-year-old boy named Austin who, along with his brother Max, has been taking eteplirsen in Sarepta's trials took issue with Bastings's characterization of the results.

"I can only guess that you don't know anything about Duchenne," he said. "Making 0.9 percent is amazing. It lets me feed myself. It keeps Max walking. It gives us a chance."

###

AN FDA PANEL TODAY WILL DECIDE THE FUTURE OF SAREPTA [TOP](#)

Dan Diamond, Politico

AN FDA PANEL TODAY WILL DECIDE THE FUTURE OF SAREPTA — An independent panel of experts will vote on whether the company's new muscular-dystrophy drug should be approved. The recommendations aren't binding — but the FDA normally goes along with its advisory panel's guidance.

Many patients with Duchenne muscular dystrophy and their families have pinned their hopes on the drug, eteplirsen, and it's seen as a make-or-break moment for Sarepta, too. However, FDA staff reviewers blasted data on the drug's effectiveness last week.

— **What's Duchenne muscular dystrophy?** The rare muscle-wasting condition affects about 20,000 boys in the United States every year, and it's devastating; most patients afflicted with it need a wheelchair by age 12 and die by their mid-30s.

— **How patients are trying to sway regulators.** Writing at Wonkblog, Carolyn Johnson examines how the fight over Sarepta is being shaped by grass-roots lobbying from families. <http://wapo.st/1SE6GPd>

— **Watch the webcast.** It's scheduled to run from 8 a.m. to 6:30 p.m., with the panel expected to begin hearing grueling testimony from patients and families around 2:30 p.m. and begin voting on a series of questions around 4:30 p.m. Live stream here: <http://bit.ly/1VwTjnA>

###

FDA panel rejects Sarepta drug to treat Duchenne muscular dystrophy [TOP](#)

Robert Weisman, Boston Globe

An influential advisory committee narrowly declined to recommend US sale of an experimental treatment for Duchenne muscular dystrophy Monday, disappointing hundreds of patient advocates who argued for approval of the medicine.

The panel of medical experts concluded in a 7-6 vote that a clinical study by Cambridge biotech Sarepta Therapeutics Inc. failed to meet the Food and Drug Administration's standard for accelerated approval. In a separate 7-3 vote, with three members abstaining, the committee determined that Sarepta's clinical trial was poorly designed and didn't prove the drug candidate was effective in treating the fatal muscle-wasting disease.

Coming at the end of a 12-hour meeting marked by emotionally-charged testimony from boys with Duchenne and family members, the nonbinding votes leave the fate of Sarepta's drug, called Eteplirsen, in the hands of the FDA. The agency, which is set to rule on the drug application by May 26, historically has relied heavily on its advisory committees for guidance.

Summing up a widely held view on the panel, committee member Aaron S. Kesselheim, associate professor at Harvard Medical School in Boston, said "the studies provided by [Sarepta] were not adequate and well controlled." But he acknowledged that it remains an "open question" whether Eteplirsen produces a clinical benefit to patients who take it.

Jenn McNary spoke with Austin Leclaire, who suffers from Duchenne muscular dystrophy, during the FDA advisory committee hearings on Monday.

Parents of boys with Duchenne were sobbing after the meeting, but some said they refused to abandon hope for the drug's approval.

"It's not over," said Debra Miller, founder of the advocacy group CureDuchenne. "It wasn't just the panel that heard the patient testimony. The FDA heard it, too, and their mandate is to listen to the patient perspective."

A number of boys who took the drug in Sarepta's study testified at an overflowing hearing Monday that it was effective in slowing progression of the disease. They called on the advisory panel, meeting in Hyattsville, Md., to recommend it be allowed on the US market.

"It lets me feed myself," said 17-year-old Austin Leclaire of Pembroke, one of dozens of Duchenne patients, family members, and doctors from around the country who spoke in favor of approval. "It keeps my brother] Max walking. It gives us a chance. . . . It's time to listen to the real experts. So to make that easier, we brought them here today. Please use them."

"The worst thing you can do is deny access to a drug and then find out that it works after we've lost a generation of boys," said Miller, whose 19-year-old son Hawken is a student at the University of Southern California.

Earlier in the day, scientists from Sarepta clashed with FDA regulators over their conflicting interpretations of findings from Sarepta's clinical trial — with FDA staffers questioning whether there was clear evidence that the company's drug was slowing progression of the disease and contending they had warned Sarepta the design of its trial was flawed.

While applauding the packed audience for being "passionate and invested," William Dunn, director of the division of neurology products at the FDA's Center for Drug Evaluation and

Research, said the agency has a responsibility to approve drugs based on scientific proof of their safety and effectiveness. “Anecdote and emotions don’t change the data,” he said.

Monday’s meeting was the most closely watched FDA hearing in years on a proposed therapy, with advocates arguing failure to approve the drug could not only worsen life for Duchenne patients but also discourage biotechs from developing drugs to treat other rare diseases.

“There is a very human cost to making a determination that a drug doesn’t work when it really does,” said patient advocate Christine McSherry, whose 20-year-old son Jett suffers from Duchenne. She said boys who took part in the trial experienced fewer spontaneous falls — a common symptom of the disease — and less fatigue than others.

Jenn McNary kissed Austin LeClaire after he spoke during hearings over conflicting interpretations of findings from Sarepta’s clinical trial of its Duchenne muscular dystrophy drug.

The drug produces a protein known as dystrophin that is missing in boys with Duchenne. It would be the first medicine to treat the genetic cause of the disease rather than just symptoms. The disease strikes one in 3,500 boys, who typically lose the ability to walk by age 12 and don’t live past age 25. Sarepta’s drug would treat about 13 percent of those boys who have a specific gene mutation.

But the FDA scientists questioned whether Sarepta’s small clinical study, which enrolled only 12 patients, adequately demonstrated an increase in dystrophin.

They also criticized the company for relying on historical “control data,” comparing the progress of boys in their study to those of a similar age who had the disease in the past, rather than giving some boys in the study a placebo. Sarepta maintained there weren’t enough patients qualifying for the study to conduct a so-called placebo-controlled study where patients wouldn’t know if they were given the drug or not.

FDA officials “consistently and strongly encouraged” a placebo-controlled trial and “expressed strong doubts regarding the interpretability of comparison” to historic data, FDA clinical team leader Ronald Farkas told the advisory committee.

Sarepta chief executive Edward Kaye said the study showed Eteplirsen was effective with little safety risks to the boys taking it.

“The data clearly demonstrate that Eteplirsen is working as intended. . . .” Kaye said. “The observed increase in dystrophin results in a clinically meaningful benefit.”

Trading in Sarepta shares was halted by the Nasdaq stock exchange Monday while the advisory committee considered the company’s drug candidate.

Underscoring the high stakes of the meeting, Janet Woodcock, the FDA’s director of drug evaluation, attended in person. Without taking a position on the Sarepta data, she noted that the company’s experimental drug was granted an accelerated approval process for unmet medical

need treatments in which “more uncertainty is going to be tolerated” than in conventional drug approvals.

From: [Rodriguez, Jennifer](#)
To: [Califf, Robert](#); [Kraus, Tom](#); [Sharp, Jeremy](#); [Kuhlik, Bruce](#)
Cc: [Conover, Katie](#)
Subject: Eteplirsen AC Updated Media Report
Date: Monday, April 25, 2016 5:01:04 PM
Attachments: [2016 MCR-Eteplirsen Updated Report 4.25.16.doc](#)

Hi All,

Attached please find an updated media report. There were four additional media stories from trade and business publications since the morning coverage report. Much of the coverage was the same, but one publication, the Boston Business Journal, covered remarks made by Janet Woodcock at the meeting that were perceived to be largely supportive of accelerated approval of eteplirsen.

The meeting is running behind and will likely continue into the evening. We plan to continue to monitor coverage, anticipating additional stories following the vote, and will send an updated media recap tomorrow.

Best,
Jen

From: Rodriguez, Jennifer
Sent: Monday, April 25, 2016 1:11 PM
To: Califf, Robert; Kraus, Tom; Sharp, Jeremy; Kuhlik, Bruce
Cc: Conover, Katie
Subject: Eteplirsen AC Mid-Day Media Report

Hi All,

Attached please find a mid-day media report out of today's DMD advisory committee meeting. Initial coverage has primarily included national media, with some local print and trade. The morning's "curtain rising" media stories have focused on the uncertainty of the outcome of Eteplirsen. Nearly all the stories detail a patient anecdote and include public health advocate comments (both in favor and against approval). Overall the stories have been balanced, accurate, and have declined to predict the outcome of today's vote. See attached for additional details and stories.

We plan to send an updated media report later today. In the meantime, please let us know if you have any questions.

Best,
Jen

Media Coverage Report:

Eteplirsen

April 25, 2016

Initial coverage has primarily included national media, with some local print and trade. The morning's "curtain rising" media stories have focused on the uncertainty of the outcome of eteplirsen. Nearly all the stories detail a patient anecdote, Billy Ellsworth or other teenage boys who have used this drug in clinical trials in an effort to retain their mobility with Duchenne Muscular Dystrophy. They also discuss the FDA's skepticism over the results of this trial, which is small (only 12 patients) and did not contain a traditional placebo control. Reporters have questioned whether FDA has gone too far in terms of its "patient preference" initiative, potentially trying to please patients who are desperate for a treatment against the lack of science to demonstrative effectiveness for this drug. The Washington Post compared it to flibanserin, while others focused on the business angle speculating on the financial future of Sarepta and the ups and downs of its stock price over the past few days. The Boston Business Journal covered remarks made by Janet Woodcock at the meeting that were perceived to be largely supportive of accelerated approval of eteplirsen. Public health advocates weighed in with some in favor of approval, but many taking a firm position against. Overall the stories have been balanced, accurate, and have declined to predict the outcome of today's vote.

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1. **The Washington Post, "To sway drug approval, patient advocates turn up the heat on the FDA" [View Online](#) [See Full Text](#)**
 2. **Forbes, "Could Desperate Parents' Pleas Sway The FDA To Approve A Drug Even If Evidence It Works Is Lacking?" [View Online](#) [See Full Text](#)**
 3. **Santa Fe New Mexican, "Families lean on FDA to back experimental drugs" [View Online](#) [See Full Text](#)**
 4. **Boston Globe, "FDA panel now weighing Sarepta's experimental drug" [View Online](#) [See Full Text](#)**

5. **The Street**, “*Sarepta Therapeutics FDA Panel Live Blog*” [View Online](#) [See Full Text](#)
 6. **Fierce Biotech**, “*Sarepta soars as FDA questions revive advocates’ hope for Duchenne drug*” [View Online](#) [See Full Text](#)
 7. **Fierce Biotech**, “*With Sarepta’s fate uncertain, BioMarin CEO Bienaimé weighs the future of Duchenne drug*” [View Online](#) [See Full Text](#)
 8. **Reuters**, “*FDA panel meets to discuss Sarepta muscular dystrophy drug*” [View Online](#) [See Full Text](#)
 9. **The Wall Street Journal**, “*The FDA vs. Austin Leclair*” [View Online](#) [See Full Text](#)
 10. **Bio world**, “*FDA briefing docs suggest nearly foregone conclusion in eteplirsen review*” [View Online](#) [See Full Text](#)
 11. **Syracuse**, “*CNY mom, sons to testify before FDA panel for approval of experimental drug*” [View Online](#) [See Full Text](#)
 12. **Barron’s**, “*Sarepta Slammed by FDA, Stock Is Now Intriguing*” [View Online](#) [See Full Text](#)
 13. **Boston Business Journal**, “*FDA chief lays out rationale for Duchenne drug to be granted temporary approval*” [View Online](#) [See Full Text](#)
 14. **NBC**, “*Does muscular dystrophy drug work? Advocates pack FDA meeting*” [View Online](#) [See Full Text](#)
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To sway drug approval, patient advocates turn up the heat on the FDA [TOP](#)

Carolyn Y. Johnson, The Washington Post

Billy Ellsworth, a teenager with an inexorable and devastating degenerative muscle disease, will bring a football with him to a Maryland hotel conference center on Monday. For months, he has been brainstorming a way to prove to a panel of scientists and physicians that the experimental drug he has been taking for more than four years has kept him strong and well — and he’d like to punctuate his brief testimony in the clearest possible way: by throwing them the ball.

When he was 4¼, Billy was diagnosed with Duchenne muscular dystrophy, a rare and lethal disease that typically forces boys to use wheelchairs by their teens and kills them in their 20s or 30s. His mother, Terri, has always measured her son’s life in fractions; Billy is 15¼ now, and the reason he isn’t in a wheelchair yet, they believe, is the experimental drug eteplirsen.

On Monday, the panel of scientists and physicians who catch Billy's pass — if he's allowed to throw it — will vote on whether the drug is effective. It is more than just a major make-it-or-break-it milestone for the Massachusetts drug company Sarepta Therapeutics and the families who support approval. The meeting also provides a window into the growing sophistication of grass-roots patient groups, whose well-organized lobbying efforts are exerting intense pressure on the drug-approval process. The Duchenne parent groups are orchestrating webinars on how to participate in the meeting, providing travel grants to help families attend, gathering their own data on the risks families are willing to accept and lobbying Congress.

The disease affects 1 in 3,500 boys, and it works only on a gene mutation carried by 13 percent of boys with Duchenne. A dozen boys were included in the key trial under scrutiny at the FDA meeting. But close to 900 community members are expected to attend, revealing the tensions that arise when patients adamantly believe that a drug works but the evidence is far less clear.

“It can, I think, at times border on patients putting a lot of pressure on the agency that's inappropriate — to make decisions that aren't based on science,” said Sarah Sorscher, of the consumer watchdog Public Citizen. “Really, I've never seen a drug that was even considered for approval with this poor quality of data. . . . If the drug is really a miracle, why don't they have the data?”

The FDA has been working to incorporate the patient perspective into the drug-approval process, especially over the past five years, under growing pressure from advocacy groups and Congress. The Duchenne parent groups have been especially active on this front, running studies of the benefits and risks patients and caregivers are willing to accept — to try to “quantify the tears” for regulators as Pat Furlong, president of the Parent Project Muscular Dystrophy, says.

The parent group led a coalition that drafted a paper to help guide companies on best practices for successfully creating drugs for the disease that the [FDA credited and drew from](#) when it published its own guidance last summer — a first that other disease groups are working to follow. This month, they have worked to get two dozen senators to [sign a letter](#) reminding the FDA to prioritize the patient perspective when considering drugs for diseases with no treatments.

The Duchenne parent groups “have been an active leader. They have a strategy they call ‘aggressive engagement’: We're going to the FDA on this, and we're not going to stop,” said John F.P. Bridges, a researcher at the Johns Hopkins Bloomberg School of Public Health who works with advocacy groups and pharmaceutical companies to quantify and rigorously measure patient preference.

The meeting may reveal the limitations of the patient perspective for regulators. In the run-up to it, the FDA released documents that are critical of the way Sarepta's small trial of just a dozen boys has been designed, saying “there are significant concerns regarding the ability to draw valid conclusions.” The FDA's documents show that although the agency views the drug as safe, there is clear skepticism that it works: They say the ability of boys on the drug to walk declines over time, consistent with natural disease progression. And a crucial protein called dystrophin missing in people with Duchenne was present at less than 1 percent of normal levels after patients took the drug for three and a half years.

A group of 36 experts — some of whom with ties to the company — sent a letter in February rebutting FDA critiques of the evidence, stating that they have observed 5,000 patients over 15 years and that the boys on the drug are “clearly performing better than our collective clinical experience and the published literature would predict.”

The patient view can be extremely valuable: Patients know better than anyone what a meaningful benefit would be or what risks they would accept. But the patient’s view on whether the drug works may be influenced by hope.

“I think a lot of it is the desire — that people really want the drug to work, because there is nothing else,” said Richard Klein, director of the FDA’s patient liaison program, who said he was not speaking about any particular drug. “The downside is that people don’t understand the scientific rigors of what needs to be done, and they want the drug to be approved on extremely small bits of data.”

Contrast that with a parent’s experience:

“We’re not asking for something that’s not worthy or didn’t prove itself; we’re asking for flexibility for a rare disease,” Terri Ellsworth said. “My son gets himself to bed, gets himself out of bed every morning, dresses himself . . . eats breakfast and carries his dishes to the sink. Most boys are losing upper-body strength at [Billy’s] age. Here’s my son, and we don’t even own a wheelchair.”

Parents like Ellsworth say that since the FDA agrees that there are no known risks to eteplirsen and the disease is fatal, parents should be able to decide whether to give the drug, even if the benefit is unclear to regulators. The outcome for their sons, otherwise, is tragic and unavoidable.

Thomas Rando, a neurologist at Stanford University School of Medicine, said in an email that it’s hard to fault the FDA for being critical — and yet, it’s also hard to fault parents for pushing for approval of a drug that appears safe even if it has only subtle benefits in a clinical trial.

“Essentially, the question is should the FDA lower the bar for devastating disease, which is not a scientific question, it’s a policy question — an ethical question, too,” Rando said.

The agency’s attempt to consider the patient’s point of view was jump-started by HIV and AIDS activists in the late 1980s. But the effort to incorporate the patient viewpoint has been accelerated by recent law. Since 2013, the FDA has held “patient-focused drug development” meetings that are listening sessions for the agency to hear from patients suffering from various diseases. In 2015, the agency approved an obesity device called the Maestro Rechargeable System — something Bridges, the Johns Hopkins researcher, said was a watershed.

In that case, the device fell short of its endpoint: that people with the device would lose at least 10 percent more weight than a comparison group. But the agency, in its approval, cited a survey of patient preferences that showed patients would accept risk for the degree of benefit the device was expected to provide.

More recently, Diana Zuckerman, president of the National Center for Health Research, pointed to last year's controversial drug approval of a female libido drug, flibanserin, as a milestone that might have emboldened Sarepta.

“In that case, a campaign by patients persuaded an FDA Advisory Committee and the FDA to approve a drug they knew had little benefit and substantial risk,” Zuckerman wrote. “Sarepta probably assumed a campaign by desperate parents would be even more persuasive.”

Could Ron Cohen, chairman of the Biotechnology Innovation Organization, a trade group for biotech drug companies, said that listening to patients is essential for companies and for regulators.

But he also noted that clinical trials remain critically important — something he learned personally years ago, when his company, Acorda Therapeutics, tested a therapy for spinal-cord injury. During a trial in which patients and medical practitioners were blind to who was getting the drug and who was getting the placebo, there were four excited calls from nurses, saying they thought the drug was working: Partially paralyzed patients were moving their legs.

“We were high-fiving back at the office and the lab — we were so thrilled,” Cohen said.

But the company then found that half of the patients that had seen marked improvements were on a placebo. “You’d never think someone with a spinal-cord injury would spontaneously move their leg when they haven’t moved it in years,” Cohen said. “And yet there it was.”

###

Desperate Parents' Pleas Sway The FDA To Approve A Drug Even If Evidence It Works Is Lacking? [TOP](#)

Rita Rubin, Forbes

You don't usually hear people compare Food and Drug Administration advisory committee meetings to a world-class sporting event, but this is how Brian Denger described the [one set for Monday](#):

“For the Duchenne community, this is going to be more like the Super Bowl,” Denger, a supermarket manager from Biddeford, Maine, told me.

The “Duchenne community” refers to people touched by Duchenne muscular dystrophy, or DMD, the most common and most severe form of muscular dystrophy. Denger is a member because he is the father of two sons with DMD.

Worldwide, about 1 in 3,500 boys—DMD almost exclusively affects boys—inheriting the genetic disease, which is passed on the “X” chromosome from mothers to sons. Affected boys begin to exhibit symptoms of muscle weakness between the ages of 3 and 5. By 12, most can no longer walk. Eventually, the disease weakens their heart and the muscles involved in breathing, and they die, typically before their 30th birthday.

No approved drug can slow the course of any type of muscular dystrophy, let alone reverse or cure it, which is why hundreds of members of the Duchenne community—parents, patients, doctors, scientists and other advocates—are expected Monday to pack the [Chesapeake Ballroom](#) at the College Park Marriott Hotel and Conference Center in the [Washington](#), D.C., suburb of Hyattsville, Md., a few miles from the FDA’s sprawling Silver Spring campus.

Their mission: to convince members of the FDA’s [Peripheral and Central Nervous System Drugs Advisory Committee](#) that they should recommend approval of Sarepta Therapeutics’ New Drug Application, or NDA, for eteplirsen. The agency usually follows its advisory committee recommendations but is not bound by them.

Can the DMD community, which argues that “[eteplirsen keeps more boys on their feet](#),” trump FDA scientists’ unfavorable assessment of the drug? Should it? While the FDA doesn’t consider cost when deciding whether to approve a new drug, the thought that what is bound to be an extremely expensive treatment (Vertex has priced Kalydeco, which treats people with certain mutations in the cystic fibrosis gene, at [more than \\$300,000 a year](#)) might be only minimally effective, if that, is sobering.

“Although FDA is prepared to be flexible with respect to a devastating illness with no treatment options, flexibility does not mean approving drugs for which substantial evidence of effectiveness has not been established,” concluded a [briefing document](#) posted Thursday by the FDA. Still, the FDA reviewers noted, “it is important to recognize that no final conclusions have been reached on the approvability of this application.”

Pat Furlong, founding president and CEO of [Parent Project Muscular Dystrophy](#), an advocacy group based in Hackensack, N.J., says she’s optimistic. “I do think that hearing the patients’ stories, hearing the patients’ experience with this compound...will be persuasive,” Furlong, whose two sons died of DMD, told me. “I think the FDA learns a great deal from listening to patients.”

Few so-called disease communities are as well-organized and as well-connected as Furlong’s. “Take a Stand. Fill a Seat. Raise Your Voice,” urges [MakeDuchenneHistory.com](#). “We represent friends, families, and patients affected by Duchenne Muscular Dystrophy who want to see safe, effective treatments approved by the FDA.”

They have friends in high places:

- In a [letter](#) dated April 15, a bipartisan group of 24 senators urged Dr. Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research, to use the agency’s “broad regulatory flexibility...to help advance new DMD therapies.”
- Rick Santorum, former U.S. Senator and former Republican presidential candidate, [tweeted](#) Saturday that he plans to attend the advisory committee meeting. Santorum’s own daughter was born with a genetic disorder called [Trisomy 18](#).
- Sen. Marco Rubio, R-Fla., another former Republican presidential candidate, [tweeted](#) earlier this month that he “met with DMD advocates to chat about how FDA can accelerate approval of innovative therapies.”

Scores of DMD advocates, including Denger, are scheduled to address the advisory panel at a public hearing after lunch. Demand was so great that the FDA added a half-hour to the hearing's originally scheduled two hours (already about twice as long as a typical FDA public hearing) and held a lottery to pick the people who'd get the coveted three-minute slots to speak. To squeeze in as many speakers as possible, some advocates who won a slot will split their time with others who didn't.

According to Sarepta, based in Cambridge, Mass., eteplirsen increases levels of a protein called dystrophin. DMD is associated with errors in the gene that codes for dystrophin, one of a group of proteins that strengthen and protect muscle fibers. People with DMD typically don't produce any functional dystrophin.

Eteplirsen is designed to treat boys with the most common type of mutation in the dystrophin gene, who make up about 13% of all DMD patients, according to Sarepta. Annie Kennedy, senior vice president of legislation and public policy for Parent Project Muscular Dystrophy, estimates that about 2,300 U.S. boys with DMD have the type of mutation amenable to treatment with eteplirsen.

Using an approach similar to eteplirsen, Sarepta's [website](#) says, the company has also begun early human testing of drugs for the second and third most common types of DMD mutation. Sarepta says it is in the discovery or pre-human testing phase of potential treatments for DMD caused by seven other types of mutations in the dystrophin gene.

"I think what the community understands (is) even if your child is not amenable to this drug, the ramifications for the entire community are huge," said Will Nolan, senior vice president of administration and communications for Parent Project Muscular Dystrophy.

The advisory committee meeting was originally scheduled for Friday, Jan. 22, but the FDA [postponed](#) it at the last minute because of "[Snowzilla](#)," a major winter storm forecast for that weekend in the Washington area. The delay presented advocates and Sarepta with an unusual opportunity—a long lead time to prepare responses to the FDA scientists' evaluation.

"FDA should be influenced little, if at all, by patient wishes but a lot by the risks of the disease—and it is," Henry Greely, director of Stanford Law School's [Center for Law and the Biosciences](#), told me. For example, he said, "pancreatic cancer drugs can be much less safe and effective than acne medication."

"I'm sure FDA is taking the fact that DMD is untreatable and awful into account," Greely said. "But it still *must*, by law, and *should* (emphasis Greely's), by ethics and policy, approve only drugs that are proven sufficiently safe and effective."

Clearly, the FDA has set a higher bar than the advocates., but if any disease community is going to be able to sway the advisory committee and the FDA, it might well be the DMD community.

"In an effort to influence the direction of DMD research, Parent Project Muscular Dystrophy...recently initiated and drafted guidance for the pharmaceutical industry," Dr. Yoram

Unguru, a Johns Hopkins bioethicist and pediatric hematologist/oncologist, noted in an [article](#) published in 2015.

The DMD guidance was the first FDA guidance drafted by a disease community “and speaks to the degree of influence the DMD advocacy community carries,” Unguru wrote. Significantly, he wrote, the very first section of the guidance “discusses families’ willingness to accept undetermined and more risky interventions because of the progressive and unpredictable nature of DMD.”

Still, FDA regulations governing drug approvals “are there for a very good reason,” Unguru, who sees patients at the Children’s Hospital at Sinai in Baltimore, told me. “We need to make sure that patients...and their parents are not given false hope. We all have hope, and hope is good, and hope is important.” But if it’s misguided hope, hope based on a false promise, “we’re getting into a difficult situation.”

Agency staff who reviewed Sarepta’s NDA found that scientific evidence of eteplirsen’s safety and effectiveness is lacking.

The single randomized, double-blind, placebo-controlled study in the NDA was conducted with only 12 boys for 24 weeks at a single medical center, the FDA reviewers have noted in briefing documents for the advisory committee. In this type of study, considered the gold standard for evaluating new treatments, the equivalent of a coin toss determines which participants will receive the experimental therapy and which will get a placebo. “Double blind” means that neither the research subjects nor the researchers learn who got which treatment until the treatment period ends.

At the end of 24 weeks, the boys who had been getting eteplirsen couldn’t walk farther in six minutes—a standard test—than the boys who’d been getting the placebo, according to the FDA reviewers. At that point, the four boys who’d been receiving the placebo were switched over to eteplirsen, and all 12 boys in the study have continued to receive weekly infusions of the drug.

The FDA reviewers said they might have accepted levels of dystrophin in patients’ muscles as evidence that the drug was working, but biopsies after 3 1/2 years of treatment found that the boys’ levels were still far below those generally seen in a milder form of muscular dystrophy. On top of that, the FDA scientists said, there was no apparent correlation between how far the treated boys could walk in six minutes and the dystrophin levels in their muscles.

Dr. Michael Carome, a kidney specialist who directs the [Public Citizen Health Research Group](#), a consumer watchdog organization in Washington, D.C., is blunt about what the FDA should do.

“Based upon the evidence presented and reviewed by the FDA and described in the briefing packet, the drug should not be approved,” Carome, who previously worked for the [Office for Human Research Protections](#) in the Department of Health and Human Services, told me. “These clinical trials were too small, and the evidence from those trials does not show that the drug provides any meaningful clinical benefit.”

“It would be a mistake for the FDA to approve this,” he continued. “It would be giving in to political pressure and essentially eviscerating their standard for approval. What these patients need is a drug that works... To put out a drug that’s not effective isn’t helping anyone.”

But the FDA scientists have it wrong, according to a [lengthy letter](#) sent Feb. 24 to Dr. Billy Dunn, director of the division of neurology products at the FDA. M. Carrie Miceli and Dr. Stanley Nelson, co-directors of the Center for Duchenne Muscular Dystrophy at UCLA, wrote the letter, which was also signed by 34 other U.S. and Australian basic scientists and physicians with expertise in the disease.

“It is remarkable that a viable treatment option may soon be available to add to our clinical approach to this devastating disease,” they wrote.

One thing they did not mention in the letter is that [they are married to each other and have a 15-year-old son named Dylan Miceli-Nelson who has Duchenne](#), although he is not a candidate for eteplirsen. The 8th-grader is a “sit-down comedian” whose [YouTube video](#) has garnered more than 330,000 views.

I talked recently with Miceli and Nelson, who told me they have no ties to Sarepta, financial or otherwise.

“People advocate for their patients, without a doubt,” Miceli said. “But I think the data have really gotten sufficiently robust, even though it is only a small number of boys.”

The boys who’ve been on eteplirsen for nearly five years are more likely to still be walking than other boys with DMD who are the same age but have not been treated with the drug, Nelson said. “Our perspective as scientists in this area is we don’t need to come up with complete cures to make a meaningful impact.”

Brian Denger says this family portrait, shot in January 2013, was the last to include son Matthew (front right),. Denger’s wife, Alice, stands behind son Patrick.

As Pauline McCormack, a senior research associate at Newcastle University’s Policy, Ethics and Life Sciences Research Center in England told me, “something that might seem insignificant in another disease, such as retaining movement in a few muscles, can be more meaningful in Duchenne.” McCormack added, “I think the patient voice is vital and has a role alongside clinical expertise and the scientific evidence.”

Brian Denger would agree. His older son, Matthew, died in February 2013, six weeks shy of his 21st birthday. He was halfway through his second year of college. “He actually went to school the morning of his death,” his father said.

Denger’s younger son, Patrick, 21, is in his third year of college, majoring in psychology. Even without any treatment, Patrick’s DMD hasn’t progressed as rapidly as his brother’s did, their father said. Matthew stopped walking at age 8, Patrick not until age 13.

Patrick barely missed qualifying for an eteplirsen trial in Boston in which older patients who can no longer walk are receiving the drug, Denger said.

Although Patrick can still drive a specially equipped car, he can't touch his face with his hands, which made him ineligible for the eteplirsen study in older patients, his father said. "We were both very disappointed."

They've settled for what they view as the next best thing: a trial of drisapersen, a different drug with a similar mechanism of action as eteplirsen. Every Tuesday for the past 15 weeks (except one, when winter weather in Maine grounded them), Denger and his son have caught a 5:30 a.m. flight to Baltimore, where Patrick receives an infusion of drisapersen at the [Kennedy Krieger Institute](#). They then take Amtrak to Washington and get on the Metro to Reagan National Airport for a direct flight home.

Patrick received his first infusion of drisapersen right around the same time the FDA [notified](#) BioMarin, based in San Rafael, Calif., that its NDA for the drug was not approvable in its current form.

Denger considers himself to be a practical man, one not susceptible to false hopes. "We realize that this is the first generation for both of these drugs," he said of himself and Patrick. "We also realize that neither one of these drugs represents a cure."

###

Families lean on FDA to back experimental drugs [TOP](#)

Santa Fe New Mexican

Billy Ellsworth, a teenager with an inexorable and devastating degenerative muscle disease, will bring a football with him to a Maryland hotel conference center on Monday. For months, he has been brainstorming a way to prove to a panel of scientists and physicians that the experimental drug he has been taking for more than four years has kept him strong and well — and he'd like to punctuate his brief testimony in the clearest possible way: by throwing them the ball.

When he was 4, Billy was diagnosed with Duchenne muscular dystrophy, a rare and lethal disease that typically forces boys to use wheelchairs by their teens and kills them in their 20s or 30s. Billy is 15 now, and the reason he isn't in a wheelchair yet, they believe, is the experimental drug eteplirsen.

On Monday, the panel of scientists and physicians who catch Billy's pass — if he's allowed to throw it — will vote whether the drug is effective. It is more than just a major make-it-or-break-it milestone for the Massachusetts drug company Sarepta Therapeutics and the families who support approval.

The meeting also provides a window into the growing sophistication of grass-roots patient groups, whose well-organized lobbying efforts are exerting intense pressure on the drug-approval process. The Duchenne parent groups are orchestrating webinars on how to participate in the

meeting, providing travel grants to help families attend, gathering their own data on the risks families are willing to accept and lobbying Congress.

The disease affects one in every 3,500 boys, and it works only on a gene mutation carried by 13 percent of boys with Duchenne. A dozen boys were included in the key trial under scrutiny at the FDA meeting. But close to 900 community members are expected to attend, revealing the tensions that arise when patients adamantly believe that a drug works but the evidence is far less clear.

“It can, I think, at times border on patients putting a lot of pressure on the agency that’s inappropriate — to make decisions that aren’t based on science,” said Sarah Sorscher, of the consumer watchdog Public Citizen. “Really, I’ve never seen a drug that was even considered for approval with this poor quality of data. ... If the drug is really a miracle, why don’t they have the data?”

The FDA has been working to incorporate the patient perspective into the drug-approval process, especially over the past five years, under growing pressure from advocacy groups and Congress. The Duchenne parent groups have been especially active on this front, running studies of the benefits and risks patients and caregivers are willing to accept — to try to “quantify the tears” for regulators as Pat Furlong, president of the Parent Project Muscular Dystrophy, says.

The parent group led a coalition that drafted a paper to help guide companies on best practices for successfully creating drugs for the disease that the FDA credited and drew from when it published its own guidance last summer — a first that other disease groups are working to follow. This month, they have worked to get two dozen senators to sign a letter reminding the FDA to prioritize the patient perspective when considering drugs for diseases with no treatments.

The Duchenne parent groups “have been an active leader. They have a strategy they call ‘aggressive engagement’: We’re going to the FDA on this, and we’re not going to stop,” said John F.P. Bridges, a researcher at the Johns Hopkins Bloomberg School of Public Health who works with advocacy groups and pharmaceutical companies to quantify and rigorously measure patient preference.

The meeting may reveal the limitations of the patient perspective for regulators. In the run-up to it, the FDA released documents that are critical of the way Sarepta’s small trial of just a dozen boys has been designed, saying “there are significant concerns regarding the ability to draw valid conclusions.”

The FDA’s documents show that although the agency views the drug as safe, there is clear skepticism that it works: They say the ability of boys on the drug to walk declines over time, consistent with natural disease progression. And a crucial protein called dystrophin missing in people with Duchenne was present at less than 1 percent of normal levels after patients took the drug for three and a half years.

A group of 36 experts — some of whom with ties to the company — sent a letter in February rebutting FDA critiques of the evidence, stating that they have observed 5,000 patients over 15

years and that the boys on the drug are “clearly performing better than our collective clinical experience and the published literature would predict.”

The patient view can be extremely valuable: Patients know better than anyone what a meaningful benefit would be or what risks they would accept. But the patient’s view on whether the drug works may be influenced by hope.

“I think a lot of it is the desire — that people really want the drug to work, because there is nothing else,” said Richard Klein, director of the FDA’s patient liaison program, who said he was not speaking about any particular drug. “The downside is that people don’t understand the scientific rigors of what needs to be done, and they want the drug to be approved on extremely small bits of data.”

Thomas Rando, a neurologist at Stanford University School of Medicine, said in an email that it’s hard to fault the FDA for being critical — and yet, it’s also hard to fault parents for pushing for approval of a drug that appears safe even if it has only subtle benefits in a clinical trial.

“Essentially, the question is should the FDA lower the bar for devastating disease, which is not a scientific question, it’s a policy question — an ethical question, too,” Rando said.

The agency’s attempt to consider the patient’s point of view was jump-started by HIV and AIDS activists in the late 1980s. But the effort to incorporate the patient viewpoint has been accelerated by recent law. Since 2013, the FDA has held “patient-focused drug development” meetings that are listening sessions for the agency to hear from patients suffering from various diseases. In 2015, the agency approved an obesity device called the Maestro Rechargeable System — something Bridges, the Johns Hopkins researcher, said was a watershed.

In that case, the device fell short of its endpoint: that people with the device would lose at least 10 percent more weight than a comparison group. But the agency, in its approval, cited a survey of patient preferences that showed patients would accept risk for the degree of benefit the device was expected to provide.

More recently, Diana Zuckerman, president of the National Center for Health Research, pointed to last year’s controversial drug approval of a female libido drug, flibanserin, as a milestone that might have emboldened Sarepta.

“In that case, a campaign by patients persuaded an FDA Advisory Committee and the FDA to approve a drug they knew had little benefit and substantial risk,” Zuckerman wrote. “Sarepta probably assumed a campaign by desperate parents would be even more persuasive.”

###

FDA panel now weighing Sarepta’s experimental drug [TOP](#)

Robert Weisman, The Boston Globe

One of the most closely watched hearings on a proposed drug in years has convened Monday morning in Hyattsville, Md., where a panel of medical experts will consider an application by Cambridge's Sarepta Therapeutics Inc. for approval of a Duchenne muscular dystrophy treatment.

Scientists from Sarepta and the Food and Drug Administration will discuss their conflicting interpretations of clinical trial data for the experimental drug -- called eteplirsen -- while boys with muscular dystrophy and their family members are prepared to testify about their experience with the drug and the need for new therapies to treat the muscle-wasting disease.

The influential panel, called the Peripheral and Central Nervous System Advisory Committee, is expected to make a recommendation to the FDA early Monday evening on the drug's safety and effectiveness. While the committee's recommendation is non-binding, the FDA usually follows the lead of its outside experts. It is scheduled to rule on Sarepta's application next month.

Sarepta's shares swung wildly last week. They plunged when the FDA's staff released a briefing document Thursday that was critical of Sarepta's clinical trial design, but bounced back Friday when the FDA posted a list of questions for the advisory panel that raised investors' hopes that the panel could favor approval of the drug candidate.

More than 800 patient advocates have registered to appear at Monday's hearing, making it among the best attended FDA advisory committee meetings in history.

###

Sarepta Therapeutics FDA Panel Live Blog [TOP](#)

Adam Feuerstein, The Street

The live blog above is tracking all the action at a U.S. Food and Drug Administration advisory committee meeting, convened to review eteplirsen, Sarepta's experimental drug for the treatment of Duchenne muscular dystrophy.

TheStreet Senior Columnist Adam Feuerstein is providing live coverage and analysis of the Sarepta FDA advisory panel as it happens near Washington, D.C.

At the end of Monday's meeting, a panel of 13 independent experts will vote on a series of questions which will provide recommendation to the FDA on whether or not eteplirsen should be approved, or not.

Sarepta shares are halted for trading while the advisory panel is in session. The stock last traded Friday at \$14.95.

###

Sarepta soars as FDA questions revive advocates' hope for Duchenne drug [TOP](#)

John Carroll, Fierce Biotech

Friday afternoon, Sarepta's (\$SRPT) path to a formal marketing decision from the FDA on its Duchenne muscular dystrophy drug eteplirsen took yet another bizarre twist.

The FDA posted a set of discussion points and questions for Monday's advisory panel review of the drug. It was immediately apparent to a varied group of analysts that the language reflected the agency's harsh view of the sparse and questionable data used to ask for an accelerated approval based on the results of a trial that enrolled only 12 boys.

Question: "Has the Applicant provided substantial evidence from adequate and well controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit?"

Based on the FDA's stubborn opinion issued in two analyses, the agency would never call Sarepta's study "adequate and well controlled." And it clearly discounted any evidence of dystrophin production.

But asking the panel any question opens the possibility that the intense public pressure being applied on the FDA by patient advocates and *The Washington Post* editorial page could influence the outside experts to vote for an early OK. And the biotech's shares--battered yesterday by an internal FDA review that adopted a clearly negative tone--soared more than 40%.

"We view the fact that panel members will have to vote on Monday as an incremental positive for SRPT," wrote RBC's insightful Simos Simeonidis, "simply because of the understandable pressure committee members will be under, in the presence of the DMD community and families." After all, if the FDA had intended a negative outlook Monday, why would they put the advisers on the spot?

But that didn't prevent analysts from taking a skeptical view of Sarepta's chances.

"Despite that view, when we read through the actual questions and the language of the accompanying discussion (see below), we see a document with the exact same tone and tenor as the January and April briefing documents," Simeonidis observed. "The questions and the discussion ask the panelists to focus on the trial conduct, the evidence for dystrophin and clinical efficacy. And we expect the answer to all of these to be No."

"Prepare for a wild ride," noted Baird's Brian Skorney. "After years of ambiguity surrounding this review, we head into Monday expecting nothing more than to be surprised."

After the roller coaster ride that has taken investors and biotech observers through plenty of dramatic plot twists in recent years-- including high-level exits, disputes over dealings with the FDA and more--Sarepta can still surprise when it's least expected.

###

With Sarepta's fate uncertain, BioMarin CEO Bienaimé weighs the future of Duchenne drug [TOP](#)

John Carroll, Fierce Biotech

Come Monday, Sarepta (\$SRPT) will get a very clear idea of the odds it faces on finally achieving its years-long quest to gain an FDA approval of its Duchenne muscular dystrophy drug eteplirsen. And you can expect that BioMarin CEO Jean-Jacques Bienaimé will be paying close attention to all of the opinions voiced by the FDA's outside experts on DMD as the agency panel meets to discuss the drug's fate.

Back in early January, Bienaimé was disappointed by the FDA's decision to reject its rival drug, drisapersen, with regulators left unimpressed by the efficacy data that was submitted for an approval. In an interview with me Wednesday afternoon, the CEO made it clear that the company (\$BMRN) may face some tough choices on their drug, which cost \$680 million in cash. And if the cards don't start turning in its favor, time may be running out on at least one of the three drugs that's been making an uphill run at a fast marketing OK.

"The European decision is the next step," says Bienaimé. If they can keep drisapersen on track at the EMA, an opinion should arrive in two or three months. "If they reject it," he noted, "we have to decide if we continue it."

Given the fact that the company is probably looking at mounting a late-stage study to get the drug back up in front of the U.S. regulators--though they're still waiting on a final debrief with the FDA following the January rejection--BioMarin can decide if it should devote the resources necessary for that or move on to the early-stage programs the company has in place for DMD.

It's not simply a question of resources, he adds, but the "practicality" of doing another study under the circumstances.

Bienaimé was in Manhattan on Wednesday to give analysts an update on the company's pipeline, including some encouraging extended data on its mid-stage drug vosorotide for dwarfism (achondroplasia), now moving to Phase III, as well as a promising early-stage gene therapy for hemophilia A (BMN 270). In his perspective, the company has a set of late-stage drugs--including the rare disease drug pegvaliase and a therapy for a form of Batten disease--and a sizable pipeline overall that will command a significant amount of R&D resources.

If the regulatory hurdles at the agencies on both sides of the Atlantic are too steep on DMD, the company will have plenty of other work on its plate.

A rejection in Europe is by no means a sure thing just because the FDA rejected the drug. PTC Therapeutics (\$PTCT) won a conditional OK in Europe two years ago for its DMD drug, even though it had failed a mid-stage study and was on its way to failing a late-stage trial. Those back-to-back failures prompted the FDA to refuse to even file the biotech's application for review, satisfied that investigators never provided a convincing case on efficacy. But just days ago the U.K.'s drug watchdog NICE reversed itself and recommended the PTC drug, though European regulators say that they will revisit their decision at some point.

And so it goes. The FDA also provided a harsh review for eteplirsen a few months ago, though analysts are waiting now to see whether new documents out tomorrow could change in light of additional data. In the meantime, patients are rallying in the hundreds to mount a show of support in the looming panel review.

But Bienaimé says he doubts that kind of lobbying campaign will make much difference.

“I don’t think they’ll be swayed by that,” he noted with a shake of his head. “The FDA wants to see data.”

#

FDA panel meets to discuss Sarepta muscular dystrophy drug [TOP](#)

Toni Clarke, Reuters

Hundreds of patients and advocates packed a hotel ballroom in Hyattsville, Maryland on Monday to try to persuade advisors to the U.S. Food and Drug Administration to support approval of an experimental drug to treat Duchenne muscular dystrophy.

In briefing documents last week the FDA reiterated a negative earlier assessment of the drug, made by Sarepta Therapeutics Inc. It questioned the validity of the clinical trials and said it was unable to draw reliable conclusions about the drug's efficacy

Dr. Billy Dunn, director of the FDA's Division of Neurology Products, opened the proceedings on Monday by emphasizing that the FDA has not yet made its decision as to whether to approve the drug, eteplirsen. He also addressed patients, assuring them that their voices have been heard.

"It is not the volume of the message but the content," he said. "We listened, and we listened closely."

He also laid out the FDA's responsibility under the law to ensure the drugs it approves are effective. And he urged the panel to make its decision based on science in what could be an emotional meeting.

"Anecdote and emotion do not change the data," he said.

Duchenne's is a rare and devastating genetic disorder characterized by progressive muscular weakness and degeneration. It is caused by a lack of dystrophin, a protein needed to keep muscles healthy and primarily affects young men.

The disease typically emerges in childhood, causing weakness in the arms and legs and eventually the lungs and heart. Patients typically lose the ability to walk during adolescence and frequently die in their 20s or 30s, according to the National Institutes of Health.

Sarepta's senior vice president of regulatory affairs, Shamim Ruff, acknowledged that the company had not produced a "traditional" data set since the company did not conduct a randomized, controlled clinical trial, the gold standard.

Instead it measured the progress of patients in the trial against how patients with the disease progress historically. But Ruff said the benefit of the drug as measured by the production of dystrophin, and clinical benefit as measured by a six-minute walk test, was strong enough to warrant accelerated approval for the drug.

The panel will vote at the end of the day on a number of questions, including whether results of the study provide substantial evidence that eteplirsen is effective.

#

The FDA vs. Austin LeClaire [TOP](#)

The Wall Street Journal

No government agency controls the fate of more people than the Food and Drug Administration, which has the power to deny children a treatment that could help them walk. The FDA is reviewing an experimental drug for muscular dystrophy, and the outcome could determine the quality of life for thousands—and whether companies continue to invest in curing rare diseases.

On Monday an FDA advisory committee will consider eteplirsen, a drug by Boston-based Sarepta designed to treat a strain of Duchenne muscular dystrophy, which is a genetic disorder that weakens every muscle in the body. The condition usually affects boys, who by age 12 or so can no longer walk, and over time damages the heart and lungs. The fatality rate is 100%, and most do not live past 25.

Eteplirsen essentially pumps out the protein missing in patients with Duchenne, known as dystrophin, by skipping over faulty genetic code. Sarepta's clinical trial started in 2011 and treated boys about 9-years-old whose abilities seemed to be deteriorating rapidly. After four years of treatment, 10 out of 12 children can still walk. In a comparable group of 11 boys who weren't treated, only one could still walk. No side effects or safety concerns were reported.

One beneficiary is Max LeClaire, who is now 14. His mother, Jenn McNary, became one of the earliest advocates for the drug after noticing her son's marked improvement. She had another reason: Her son Austin is also affected by Duchenne but wasn't eligible for the trial, as he already had lost the ability to walk. So for years Austin was denied the care that helped his brother continue to play sports and dress himself.

Ms. McNary and Christine McSherry, who also has a son with Duchenne, have organized some 900 people to show up at Monday's committee meeting, which forced the FDA to book a bigger venue. Among those offering public comment will be Austin, who began an eteplirsen trial about 18 months ago. He will tell the committee of his brother's persistence and his own—and of friends who have lost dexterity and have no options without FDA action.

Sarepta has gone back and forth with the FDA since 2013, and this is somehow considered the *expedited* track: A 2012 law allows the agency flexibility to accelerate approval in first-in-class drugs for lethal diseases, though the FDA seems to be flouting the spirit of this directive. The agency planned to assemble an advisory committee—which offers recommendations that the FDA typically follows—in January. But the meeting was postponed due to a blizzard in Washington, one that apparently snowed in the FDA for four months.

In January the agency issued a harsh report about eteplirsen, haggling over minutiae on the trial’s design and findings, and here’s why: The FDA is religious in trusting only large trials in which half of participants receive a placebo treatment. Yet such trials would prove near impossible since Duchenne patients are so rare.

And more important, unethical: What parent would sign up a child for years of weekly muscle injections and high-risk biopsies if the cocktail might be saline? FDA acknowledges these concerns and admitted in a Thursday report that the agency previously told Sarepta it would consider the type of study the company performed—only to change its mind. At the FDA, process trumps patients.

More than 35 physicians and leading experts, who have seen some 5,000 Duchenne patients and hail from the likes of UCLA and Harvard, offered their opinion in a February letter to the FDA, not that the agency asked. The doctors say the FDA’s work includes “scientifically questionable comparisons” and even errors.

The boys are “clearly performing better than our collective clinical experience and the published literature would predict,” and the data show “substantial evidence of efficacy,” wrote the doctors. Accelerated approval and continuing further trials as the 2012 law prescribes, they concluded, “is the most ethical choice.”

Adding more weight to the decision is that eteplirsen can only treat a certain mutation of Duchenne, and a no from the FDA would scuttle iterations in the drug-development pipeline that might help more patients. Biotech companies working on treatments for other rare conditions are also watching. If a drug with no safety risks, a four-year record of effectiveness, and a strong legal and ethical basis can’t win approval, what can?

Sarepta, with 200-odd employees, may not have the resources for several more rounds with an agency that seems to enjoy issuing ominous reports and watching the company’s stock crater; Sarepta tanked 44% on Thursday when the FDA issued another unfavorable briefing ahead of Monday’s meeting. The stock fell more than 50% when the January report emerged. The result of this political control is fewer companies taking the risks that result in cures.

The FDA will review the advisory committee’s recommendations and is scheduled to issue a decision by May 26. Allow us to underscore the urgency: The continued use of limbs—raising your hand to scratch an itch—is a miracle for boys facing a slow path to death. The FDA owes children with Duchenne access to every treatment human ingenuity can design.

###

FDA briefing docs suggest nearly foregone conclusion in eteplirsen review [TOP](#)

Marie Powers, Bio World

Shares of Sarepta Therapeutics Inc. (NASDAQ:SRPT) plunged 44 percent in heavy trading Thursday after the FDA posted revised briefing documents for Monday's re-scheduled meeting of the Peripheral and Central Nervous System Drugs (PCNS) Advisory Committee (adcom) to discuss the new drug application (NDA) for its Duchenne muscular dystrophy (DMD) candidate, eteplirsen.

Shares closed at \$11.02 for a loss of \$8.69 on volume of 22.7 million shares – about 10 times the stock's three-month moving average.

The review, originally scheduled for Jan. 22, was postponed after a winter storm closed government offices in Washington on that day. But the three-month delay, which also reset the PDUFA date for eteplirsen from Feb. 26 to May 26, didn't do Sarepta any favors. If anything, FDA reviewers seemed to take an even more skeptical view of the eteplirsen dataset, posing no voting questions for the PCNS members and citing, as a final discussion point, the possible design of any future efficacy and safety studies.

The tone of the briefing docs and the roster of panelists – which includes nine voting members with expertise in neurology but only two specializing in movement disorders or DMD – along with the surprise appearance of Janet Woodcock, director of the Center for Drug Evaluation and Research, as an FDA panelist, seemed to broadcast the agency's intentions.

Perhaps sensing the die was cast, Debra Miller, founder and CEO of the nonprofit CureDuchenne, issued a statement that sounded like a thinly veiled criticism of the adcom agenda. She cited the organization's disappointment at the FDA's initial review of eteplirsen, maintaining that Sarepta attempted during the three-month delay to address the FDA's preliminary questions and to strengthen its case by providing supporting materials and broadening its dataset.

"Any drug that uses a new technology, like eteplirsen's exon-skipping method, is bound to face scrutiny," Miller noted. "But a pioneering approach is needed to address a disease as complex as Duchenne."

CureDuchenne provided early funding for the development of eteplirsen, designed to treat DMD patients who have a mutation of the dystrophin gene amenable to exon 51 skipping, which accounts for about 13 percent of boys with the condition.

"While we understand the FDA needs to make sure drugs are safe and effective, we also know the consequence of inaction for those with Duchenne," added Miller, who said she plans to speak in support of the drug during the adcom's public hearing, expanded to more than two hours. "We are hopeful for accelerated approval."

Much of the criticism about the openly negative briefing documents focused on Sarepta's bid for accelerated approval, but the underlying questions surrounding eteplirsen are hardly new.

In April 2012, Sarepta (then AVI Biopharma Inc.) reported in top-line findings that eteplirsen hit its primary endpoint in a phase IIb trial by showing a statistically significant increase in dystrophin after 24 weeks. However, investors panned the stock over the lack of clinical outcome improvement and analysts were cautious about the company's intention to meet with the FDA to discuss a pivotal trial based on findings in 12 patients – four of them on placebo before being moved to treatment groups studying the drug's effect at 30 mg/kg dose and 50 mg/kg dose. (See *BioWorld Today*, April 3, 2012.)

But in July of that year, Sarepta reported that eteplirsen, administered once weekly at 50 mg/kg over 36 weeks, resulted in a 69.4 meter benefit on the primary clinical outcome, the six-minute walk test (6MWT), compared to placebo for 24 weeks followed by 12 weeks of eteplirsen in an open-label extension. That finding represented a turnaround for the candidate, and the company's shares more than doubled as Sarepta made known its plans to meet with the FDA to discuss the design of a pivotal study and to seek accelerated approval. (See *BioWorld Today*, July 25, 2012.)

The eteplirsen findings were essentially repeated in October, based on another 12 weeks of data in the open-label extension study. But in 2013, Sarepta disclosed that the FDA wanted more data on the acceptability of dystrophin – a protein that plays a key structural role in muscle fiber function – as a surrogate endpoint to predict clinical benefit before ruling on an NDA filing based on accelerated approval. Two additional meetings between the company and the FDA in 2013 failed to sway the agency's opinion, especially after a phase III miss by competing DMD candidate drisapersen, then in development by Prosensa Holding NV, of Leiden, the Netherlands.

In 2014, Sarepta said the FDA had changed its view on eteplirsen, signaling in a letter that the NDA "should be fileable" with existing data. But the guidance came with caveats. The FDA also cited "significant concerns regarding [its] ability to draw valid conclusions" from the 6MWT data and remained "skeptical about the persuasiveness of the (dystrophin) data" as a biomarker of efficacy. Sarepta maintained, however, that four meetings with the agency had resulted not only in a more favorable regard for the existing dataset but also in clear guidance on an open-label, historically controlled confirmatory study of the compound. (See *BioWorld Today*, April 22, 2014.)

That outlook was all but rescinded later in the year when Sarepta reported 144-week phase IIb results from the extension study showing a decline in walking ability – albeit at a rate slower than would be expected compared to historical controls, and with stable respiratory muscle function. More deliberation by the FDA forced Sarepta to delay the rolling submission of its NDA filing until May of last year. (See *BioWorld Today*, May 21, 2015.)

'WE SEE LIMITED UPSIDE FROM HERE'

Although the FDA accepted the filing, prospects for eteplirsen's approval took a considerable blow, along with the rest of the space, during the PCNS adcom for drisapersen (Kyndrisa), which had subsequently been acquired by Biomarin Pharmaceutical Inc. That panel's voting questions focused on the strength of clinical trials rather than potential approval. Despite gripping testimony from patients and family members, the session seemed to raise more questions than answers, especially about the use of dystrophin as a biomarker. Thus, it came as little surprise to

the DMD community when the FDA issued a complete response letter (CRL) on the drisapersen NDA. (See *BioWorld Today*, Nov. 25, 2015, and Jan. 15, 2016.)

The original briefing docs for eteplirsen, issued in January, were equally negative, with FDA staff voicing "considerable doubt" regarding the degree to which the drug improved dystrophin production in DMD patients and questioning whether improvements seen in the small trials could be reliably attributed to the drug. (See *BioWorld Today*, Jan. 19, 2016.)

FDA reviewers found no significant safety signals for eteplirsen in studies of the drug but took issue with trial design, efficacy, dystrophin measurement methods and statistical analysis approaches.

The revised documents revisited those issues by criticizing the size and design of Sarepta's phase II trial, raising concerns that the purported 6MWT benefit over natural history comparisons could be skewed by the post-hoc analysis and systematically discrediting Sarepta's method of quantifying dystrophin expression.

As if to prepare for the public blowback, the agency stated, "Although FDA is prepared to be flexible with respect to a devastating illness with no treatment options, we cannot approve drugs for which substantial evidence of effectiveness has not been established."

Analysts circled around the briefing docs like a Greek chorus. In a hot comment, Piper Jaffray analyst Edward Tenthoff wrote that, "with or without outside pressure, FDA looks set to reject eteplirsen."

He suggested the FDA used the briefing docs to gain the upper hand in what has become an emotional battle involving an impassioned DMD constituency, writing that "FDA devoted considerable time to undermining Sarepta's clinical and scientific arguments."

Tenthoff pointed out that, after the initial docs were released, Sarepta highlighted what it called "key inaccuracies" in the agency's analysis that, when remedied, would yield a more favorable outlook for the drug. "FDA rejected these inaccuracies on a point by point basis, he said, "including the contentious issue of where the idea for an external control came from, pointing out, that if Sarepta had merely acquiesced to the agency's desire for a robustly controlled trial, this would not be an issue at all."

Jefferies Group analyst Gena Wang also predicted low probability of approval, noting that the revised briefing doc re-stated the original conclusions.

"The FDA appears to follow the same principle for BMRN's drisapersen (complete response letter) and PTCT's ataluren (refuse to file letter) and focuses on fundamental data to make the approval decision," Wang wrote in a flash note. "While we thought ambulation at the 4th year could be the strongest argument for SRPT, the FDA expressed its 'concerns about the reliability, completeness and comparability of the clinical data for eteplirsen-treated patients and external controls.'"

Moreover, "the FDA scrutinized the weak biomarker and maintained its view that 'considerable doubt remains about how much, or perhaps even whether, dystrophin levels were increased by eteplirsen,'" she wrote, adding, "We see limited upside from here."

Leerink Partners LLC analyst Joseph Schwartz pointed to the appearance of Woodcock on the adcom as reflective of "the high degree of scrutiny on this panel" and suggested the FDA was armed for a confrontation.

"Having had multiple months to review this additional submission, the FDA has become even more critical by identifying many potential confounding factors," Schwartz wrote, "including two matched historical control patients that were reported to have lost ambulation but also had 10 [meter] walk test values reported as well as a secondary analysis showing that when 6MWT scores are plotted based on [patient] age (rather than years of treatment) that there is substantial overlap between eteplirsen-treated patients and the control group."

With an agenda exceeding 10 hours, "the FDA plans to be exhaustive in this meeting," he concluded.

In his note, RBC Capital Markets analyst Simos Simeonidis opined that FDA reviewers were "doubling down on the negative view of the data," predicting a CRL as the most likely outcome following the panel.

Oppenheimer & Co. analyst Christopher Marai was a rare holdout, citing FDA satisfaction with the eteplirsen safety dataset and natural history control group as a potential upside and contending that broad FDA involvement, including Woodcock's participation, represented a "clear advantage" for eteplirsen compared to previous DMD applicants.

Amid a general sense of fatalism, two questions seemed to swirl around social media discussions of the adcom. Was the FDA's decision to accept the eteplirsen NDA rather than sending the company back to the starting blocks a missed opportunity for the agency, the company or both? And if the FDA openly stacks the deck against a sponsor in the run-up to an advisory committee meeting, does the ensuing discussion offer an opportunity to gather meaningful information or simply serve as a charade that wastes participant time and taxpayer dollars? Neither is likely to be addressed Monday in Hyattsville, Md.

###

CNY mom, sons to testify before FDA panel for approval of experimental drug [TOP](#)

Elizabeth Doran, Syracuse

Manlius mom Alison Dwyer Willis and her twin sons are scheduled to testify this afternoon before a federal advisory panel to urge approval of an experimental drug to treat Duchenne muscular dystrophy.

[Jack and Nolan Willis](#), 14, who are freshmen at Fayetteville-Manlius High School, have Duchenne muscular dystrophy, a genetic disorder where the muscles progressively degenerate and weaken. Most people with the disease die by age 30.

"We are making a plea for approval of the drug," said Alison Willis.

The boys have been part of a clinical trial for the past four years with the experimental drug eteplirsen, manufactured by [Sarepta Therapeutics Inc.](#) Sarepta is seeking accelerated approval for eteplirsen, which is designed to treat the disease. Currently, there are no Food and Drug Administration-approved treatments for the disease.

The drug has kept the boys' muscles stronger for longer, and helped stabilize their heart and respiratory function, Alison Willis said. "At their age, they would have seen much more marked deterioration without this drug," she said.

Duchenne muscular dystrophy is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. Symptoms appear in early childhood, usually between ages 3 and 5. The disease primarily affects boys.

The Willises are among hundreds of "patient advocates" attending the hearing, and have been selected along with others to testify at the Peripheral and Central Nervous System Drugs Advisory Committee meeting Monday at the Marriott in Hyattsville, MD. Each group is given three minutes to speak, Alison Willis said.

The public portion of the hearing starts at 2 p.m., although the hearing lasts all day.

[Jack and Nolan Willis](#) are among a dozen males with Duchenne muscular dystrophy who are part of the clinical trial, and Alison Willis said she believes 10 of those in the drug trial will be at the hearing.

Alison Willis said some critics have pointed to the fact that both of her sons stopped walking in 2012, while on the experimental drug. The critics say that's proof the drug doesn't work, she said.

But Alison Willis and others argue that losing the ability to walk is part of the disease. Even though the boys both use wheelchairs now, the drug has helped prevent their muscles from deteriorating more, and given them near-normal heart and respiratory functions, she said.

The Willis family wants to see others with the disease get the chance to use this drug, which will only happen if it gets approved by the FDA, Alison Willis said.

Jack Willis said he's ready for his testimony, and not afraid to speak in front of such a large group. "I'm not nervous," he said. "They're just people."

The panel's first hearing was postponed after a snowstorm in January, and many families have been waiting for this opportunity to advocate for the drug, Alison Willis said.

"This drug could save a whole population of children with DMD," she said. "And it's imperative that my boys stay on this drug or they will deteriorate. We don't want this drug to go away."

The panel is expected to make a recommendation by May 26 after taking in account FDA reviews, the company's data and public comments.

###

Sarepta Slammed by FDA, Stock Is Now Intriguing [TOP](#)

Andrew Bary, Barron's

Sarepta Therapeutics' [shares are down sharply](#) this morning, falling \$8, or 40%, to \$11.71, following the release this morning of a harsh assessment by the Food and Drug Administration of the company's novel treatment for Duchenne muscular dystrophy.

The FDA briefing document was prepared by the agency's neurology division ahead of an advisory committee hearing planned for Monday. The meeting, in Hyattsville, Md., just outside Washington D.C., could draw more than 1,000 people, including a huge contingent of Sarepta (ticker: [SRPT](#)) supporters from the DMD community.

It is unclear if the advisory committee will be asked to offer an opinion on whether the drug should be approved. In any event, the FDA is due to render a decision on whether to grant accelerated approval for the Sarepta drug, eteplirsen, by May 26. The new briefing document was compiled after a snowstorm in January resulted in the cancellation of a planned advisory committee hearing and also followed new clinical and other data provided by Sarepta.

Sarepta shares look inexpensive now, with the company's market value totaling \$600 million. But the odds of accelerated approval, which had been rising in recent weeks, have fallen sharply with the new briefing document, which is as negative and perhaps more so than the original one in January. The stock had doubled off its January low of \$10, hitting a recent high of \$22, after a group of 36 doctors involved in treating boys with DMD expressed strong support for eteplirsen approval. There also is widespread patient and political support for the drug.

[Barron's has been upbeat on Sarepta](#) and the prospects for eteplirsen in a series of stories in recent years, including a story that ran in last week's issue. There is huge revenue potential for a DMD drug. Eteplirsen, which treats a genetic mutation in about 13% of DMD cases, could have \$600 million of U.S. annual revenue potential and a family of DMD drugs could ultimately generate \$3 billion of annual sales.

The FDA countered nearly every argument that Sarepta has made for approval, including data on the production of dystrophin, the muscle protein missing in boys with DMD, and walking data from a small Phase 2 clinical trial involving 12 boys. The briefing document summary concluded that "Although FDA is prepared to be flexible with respect to a devastating disease with no treatment options, flexibility does not mean approving drugs for which substantial evidence of effectiveness has not been established." The FDA neurology division clearly is skeptical of eteplirsen's efficacy.

DMD is a fatal muscle-wasting disease affecting boys that puts them in wheelchairs by their early teens and usually leads to death by age 20 to 30. Eteplirsen is designed to stimulate the production in

muscle cells of the protein dystrophin, which is critical to muscle health. Sarepta offered quantitative evidence that the drug produced dystrophin and that 12 boys in a clinical trial fared better on a 6-minute walking test than an untreated group of boys who were evaluated in a separate study in Europe.

Leerink analysts wrote this morning in a client note that the briefing document “remains largely negative citing concerns with trial design, efficacy, dystrophin measurement methods, laboratory measurements and statistical analysis.” They are cautious on the stock.

The FDA attacked the dystrophin data, noting that after 3.5 years, the boys in the Sarepta study showed just 0.9% of the normal level of the protein based on muscle biopsy data, and that it probably would take a greater amount of dystrophin for clinical effectiveness.

One of Sarepta’s strongest arguments has been that 10 of the 12 boys in its study were walking after four years, compared with just one of 11 in the European study. The FDA wrote that on closer analysis, two of the boys in the European study “who were reported to have lost ambulation” actually could walk at least 10 meters. This makes the Sarepta comparison less compelling.

Like in the original briefing document, the FDA raised the issue of “whether there is convincing evidence that the clinical course of the 12 patients” in the Sarepta study “differs appreciably from the expected natural history of DMD.”

The [FDA advisory committee hearing](#) Monday promises to be a dramatic event and probably the most widely attended hearing ever. Sarepta and the FDA will present their cases to the committee, and a block of two-and-a-half hours is set aside for public comment. Many patients and family members of boys with DMD are expected to speak passionately in favor of the drug, arguing that the drug is slowing the progression of the disease and clearly showing a clinical benefit.

The FDA is under enormous patient and political pressure to approve the drug. Reflecting this, a senior FDA official, Janet Woodcock, the head the agency’s Center for Drug Evaluation and Research, will testify at the committee hearing.

If eteplirsen doesn’t get accelerated approval in May, it will dim but not kill the drug’s chances for approval. Sarepta now is conducting a confirmatory Phase 3 trial, and some results are expected next year or in 2018. If those results are positive, Sarepta could approach the FDA again and seek approval. Accelerated approval is granted in cases of a high unmet medical need and can be based on more limited clinical trials than are normally required for drug approval.

The long Sarepta saga continues and the prospects for eteplirsen approval clearly are diminished. At the current price, investors are putting low odds on approval. What’s the downside? If approval is denied in May, the stock could fall into the high single digits. If eteplirsen accelerated approval is granted, however, the stock could trade at \$60. The risk/reward is looking better now, but there is a lot of risk with Sarepta because it has no approved drug now and largely has staked its commercial future on eteplirsen and a group of similar drugs to treat DMD.

###

FDA chief lays out rationale for Duchenne drug to be granted temporary approval [TOP](#)

Don Seiffert, Boston Business Journal

Janet Woodcock, the Food and Drug Administration's director of drug evaluation, told panelists reviewing a potential drug for Duchenne muscular dystrophy this morning that there is a clear danger to patients in not approving a drug that works.

In comments before the advisory committee to review a drug developed by Cambridge-based [Sarepta Therapeutics](#) (Nasdaq: SRPT), Woodcock's comments will be seen as largely supportive of accelerated approval of the drug. She seemed to outline a rationale under which the drug could be given accelerated approval, despite much speculation on Wall Street to the contrary in the past three months. She told the panel and the audience of hundreds who packed into the room that just as there is a danger in approving a drug that does not work, "Often there is never consideration of another error — that of not approving a drug that works," she said.

Woodcock said there is "an inherent presumption" in the idea of accelerated approval of a drug that "more uncertainty is going to be tolerated, at least at the beginning."

She said her comments were meant to be a "framework" for the panel to consider the information that is being presented today by the company, by world-renowned experts in Duchenne muscular dystrophy, by patient advocates, and by the FDA scientists. She allowed that "it's possible to reach different conclusions about these comparisons" to patients who have been treated with the drug to what is known about patients who have not, seemingly allowing for the wide gap in interpretations of the data between Sarepta and the FDA.

She said "there is agreement that the drug does achieve primary pharmacodynamic effect," which is increasing a protein needed for muscle production known as dystrophin. The amount that it increased that protein was not as much as hoped, at least in the small study, but she acknowledged that there is evidence that even a small amount may help patients.

Woodcock's comments came at the end of a two-hour presentation by the company and top scientists that was mostly supportive of approval of the drug, but before the FDA's comments that are expected to be highly critical of it. While they do not ensure the panel will approve the drug — or that she will approve the drug regardless of the vote — her comments were perceived by many observers on Twitter as more positive toward the company than expected.

Earlier comments by the FDA's director of the Division of Neurology Products, [William Dunn](#) (a subordinate of Woodcock's) seemed to emphasize the need for "substantial" data needed for even accelerated approval. He said accelerated approval can't make up for bad or inconclusive data (the agency's main argument so far has been Sarepta's data is inconclusive), and even hinted that the company may have "misled" the agency into allowing a submission for approval of the drug.

In the end, it is Woodcock who will make the final approval decision on the drug, meaning that while she was speaking to the 10-member panel that will make the recommendation as to whether eteplirsen ought to be approved, she doesn't necessarily have to abide by that recommendation.

Patient testimony is expected to take up most of the afternoon, to be followed by the panel votes on seven key questions.

###

Does muscular dystrophy drug work? Advocates pack FDA meeting [TOP](#)

Maggie Fox, NBC

The video is distressing even though it's taken from too far away to see clearly — a boy trying to take a few steps and collapsing in a pile in the shiny hospital corridor.

"His quads just give out, giving him no time or warning to break his fall," says Christine McSherry, mother of a muscular dystrophy patient and one of the many advocates speaking out at a Food and Drug Administration hearing about an experimental new drug for muscular dystrophy, a genetic condition that cripples boys.

Patients, activists and advocates gave McSherry a standing ovation after her presentation at what, a few years ago, would have been a dry and quiet Food & Drug Administration hearing. Patients, advocates and others lined up outside the hearing at a hotel just outside Washington, D.C., hoping to grab an empty seat, craned to hear.

This hearing is just the latest to show the effects of the FDA's efforts to give patients a bigger voice in the drug approval process. This time, that patient voice has the help of several high-octane public relations firms and is encouraged by the success of a big PR effort to back the [controversial approval of Addyi](#), a female libido drug OK'd amid considerable media coverage last August.

FDA officials are worried about a repeat of accusations that they were pressured by the coverage.

This time, they say they'll listen to the patients, while not being unduly swayed by the emotional appeals of the parents, patients and advocates.

"It is not the volume of the message, but the content. We listen and listen closely," Dr. Billy Dunn, director of the FDA division of neurology products, said in opening the hearing.

The FDA is considering a drug aimed at just 13 percent of muscular dystrophy patients. It's a highly tailored therapy that uses a completely new approach to treating the condition.

Muscular dystrophy is a catchall term for a group of genetic diseases that gradually disable kids. Most patients are boys. Some die young as the muscles that control breathing break down, while others may live long lives with only moderate disability. There's no cure for any form and not even a real treatment, although steroids can help.

The drug in question is called eteplirsen. It's aimed at a mutation seen in a subset of children with Duchenne muscular dystrophy, a degenerative disease that causes muscles to break down because cells produce faulty versions of a protein called dystrophin.

Eteplirsen, made by a small company called Sarepta Therapeutics, uses an approach called RNA antisense to cause the body to "skip over" the mutation that causes the disease, as cells "read" the DNA to do their daily work.

The hope is that skipping over the mistake would help cells start making normal dystrophin again. But it's not clear it actually does that.

Sarepta's chief medical officer Dr. Edward Kaye says the company has shown this. "These data clearly indicate that eteplirsen is working as intended," Kaye told the packed-out hearing.

Dr. Jerry Mendell, who helped run the clinical trials of the drug at Nationwide Children's Hospital in Columbus, Ohio, says he's seen no evidence the drug has any side-effects and showed images of a 15-year-old boy he treated who walked in a marathon. "Usually boys this age with Duchenne muscular dystrophy don't walk," Mendell said.

"I can't see any grounds for withholding this drug for Duchenne muscular dystrophy boys."

But FDA officials say the evidence the company has presented is not clear at all. They're not sure that the 12 boys tested are producing dystrophin. They are also not fully convinced by videos that show the boys walking.

The boys were not treated in what's called a randomized trial — there were not untreated boys with similar backgrounds used to compare what happens when some get the drug and some do not. So the agency and its expert advisers have to just look at what happened before and after treatment, a notoriously unreliable way to assess how or whether a drug is actually working.

"The FDA is certainly keen on looking at the data in different ways," Dr. Ronald Farkas, who's helping lead the FDA team evaluating the drug, told the hearing.

Farkas, clearly aware that he was speaking to a hostile crowd, said repeatedly the FDA was not trying to keep a good drug off the market.

"I think that you haven't heard the whole story. But I really want to reassure everybody that I will remain open to what I hear from the community," he added. "I have made no final decision."

Farkas he said he and other experts cannot tell whether the boys tested were being helped by the drug. Different patients are affected differently by muscular dystrophy, he said.

Dr. Janet Woodcock, a senior FDA official, noted that the FDA does worry about approving a drug that doesn't work.

"There often is little consideration of another error — which is failing to approve a drug that actually works," she added. "But most of this consequence is borne by patients who have little say."

Advocates note there is nothing at all for muscular dystrophy patients.

"We fully understand that eteplirsen is not a cure and that it only slows progression of disease," said McSherry, whose Jett Foundation is named for her 20-year-old son who has muscular dystrophy.

"The collective evidence suggests to us that eteplirsen is having a real and concrete effect on disease."

And McSherry noted the extreme need. "Jett took his last step when he was 13," she said. Not only do patients then have to use wheelchairs, but this can over time affect their spines and their ability to breathe.

###

From: [Smith, Fallon](#)
To: [Califf, Robert](#); [Sherman, Rachel](#); [Kraus, Tom](#); [Sharp, Jeremy](#); [Cristinzio, Dayle](#); [Bolek, Michelle](#); [Shreeve, Chris](#); [Rawlings, Kimberly](#); [Woodcock, Janet](#); [Throckmorton, Douglas C](#); [Conover, Katie](#); [Young, Jason](#); [Rebello, Heidi](#); [Rodriguez, Jennifer](#); [Walsh, Sandy](#); [Kotz, Deborah](#); [Marchand, Heidi](#); [Quinn, Kathleen](#); [Scott, Meghan](#)
Subject: Eteplirsen Coverage: Med Page Today "Eteplirsen OK'd for Muscular Dystrophy"
Date: Monday, September 19, 2016 12:14:28 PM
Attachments: [image001.png](#)

[Eteplirsen OK'd for Muscular Dystrophy](#)

By: Kristina Fiore

After taking several additional months to make its decision, the FDA has overruled its advisory committee and approved eteplirsen (Exondys 51) to treat Duchenne muscular dystrophy (DMD), the agency announced.

The drug will be specifically indicated for patients who have a confirmed mutation of the dystrophin gene, which will make them more likely to respond to exon 51 skipping, the mechanism by which the drug works, the agency said. About 13% of the DMD population has this mutation.

The approval follows a grim picture painted by an agency advisory committee last April, which decided the data provided by drugmaker Sarepta Therapeutics didn't provide substantial evidence that the drug actually increased dystrophin levels.

But in a letter that accompanied the FDA approval press release, CDER director Janet Woodcock, MD, said the company has since provided additional data that provide "substantial evidence of dystrophin production, although the amount of dystrophin produced was only a small fraction of the normal level."

"The approval of Exondys 51 reflects FDA's ability to apply flexibility to address challenges we often see with rare, life-threatening diseases – while remaining within our statutory framework," Woodcock said in that letter. "In this case, flexibility is warranted because of the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a life-limiting disease of children."

"These factors, combined with the dystrophin production data – and the drug's low risk profile – led the Agency to approve the drug under the accelerated approval pathway," she said.

The FDA faced intense public pressure to approve eteplirsen, as heard in desperate pleas from patients, parents, and advocates during an unusually long public comment period at the April advisory committee meeting. The patient representative on the panel broke down in tears over concerns that the data were inadequate to support the magnitude of benefit reported by many patients, and one wheelchair-bound patient cursed loudly and ran his chair into several empty chairs before rolling out of the room.

Tensions were especially high, as another exon-skipping drug, drisapersen (Kyndrisa) was rejected by the agency last January. Drugmaker BioMarin subsequently shuttered the program in May.

Eteplirsen was supposed to be reviewed in November 2015, at the same time as drisapersen, but that hearing was delayed. Following the rescheduled April hearing, the agency extended the PDUFA date of eteplirsen indefinitely.

The drug was approved under the FDA's accelerated approval program, which allows for an approval decision to be made based solely on efficacy data from a surrogate endpoint -- in this case, dystrophin production -- that is "reasonably likely to predict a clinical benefit to patients," the agency said.

FDA will require Sarepta to conduct a clinical trial to test whether the drug can actually meet a clinical endpoint of preserving motor function.

Fallon Smith

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-8632
Fallon.Smith@fda.hhs.gov



From: [McCall, Jonathan *](#)
To: [Califf, Robert](#)
Cc: [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [Chasan-Sloan, Deborah \(FDA\)](#); [Kraus, Tom](#)
Subject: Eteplirsen decision memo and supporting materials for your review
Date: Thursday, September 15, 2016 4:56:02 PM
Attachments: [2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN\(occ\).doc](#)
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[Memo to File re Commissioner Decision 9-15-16_JMrs\(occ\)_CLEAN.doc](#)
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Hello Dr. Califf –

Here is the current version of the eteplirsen memo:

Here is the memo to file:

And here are the response cover notes:

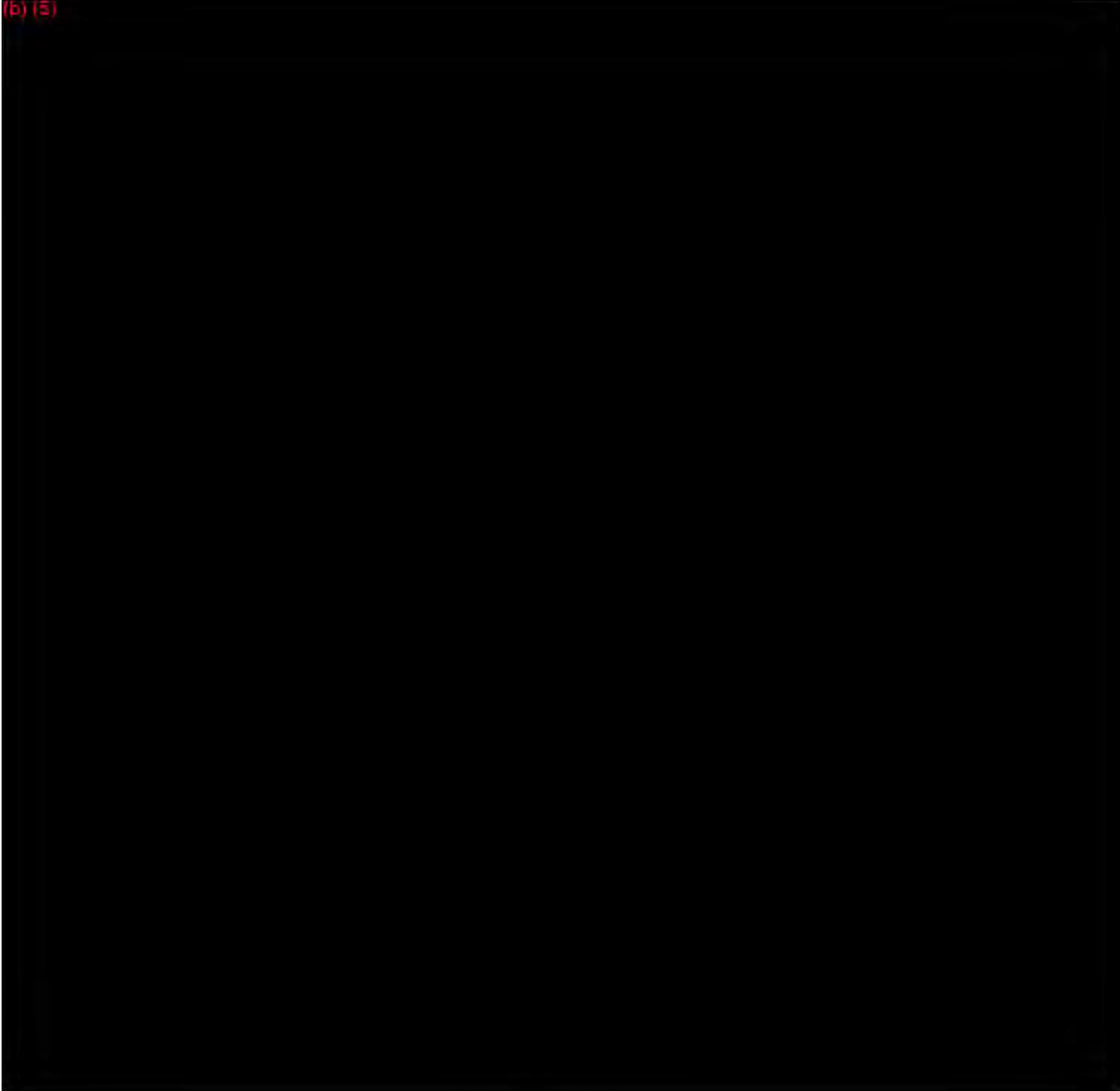
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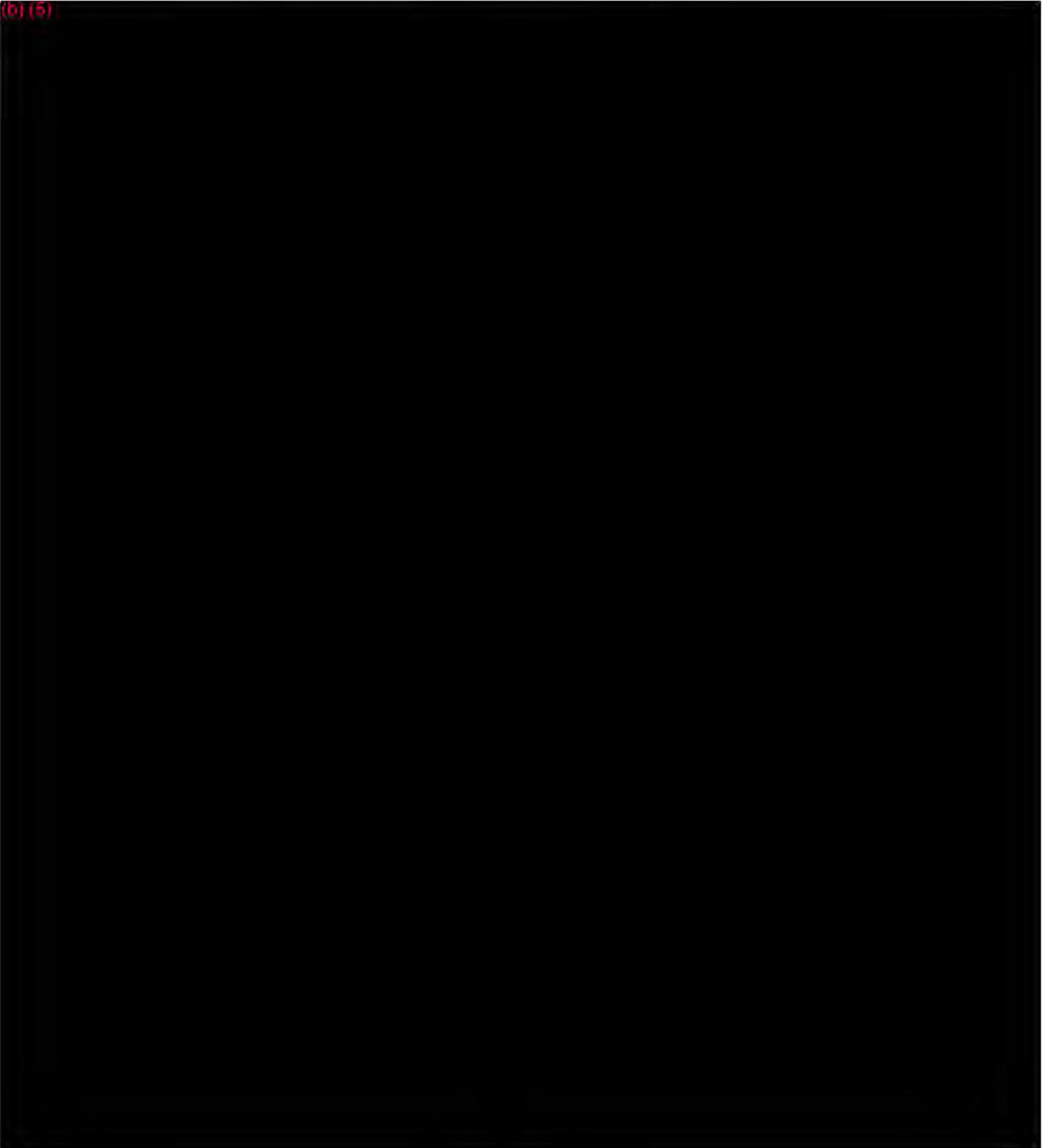
Jonathan

Scientific Dispute Regarding Approval of Sarepta Therapeutics' Eteplirsen – Commissioner's Decision

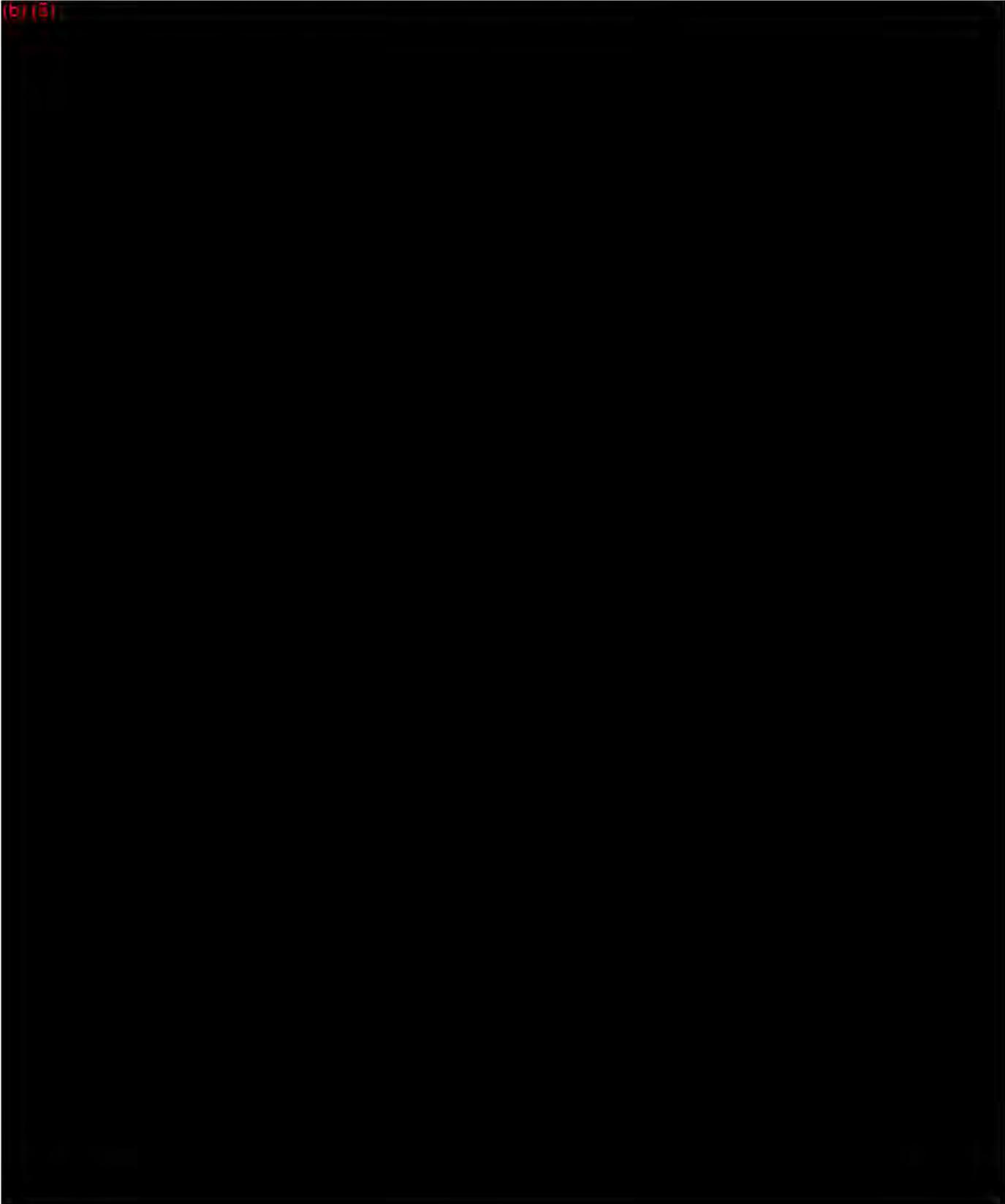
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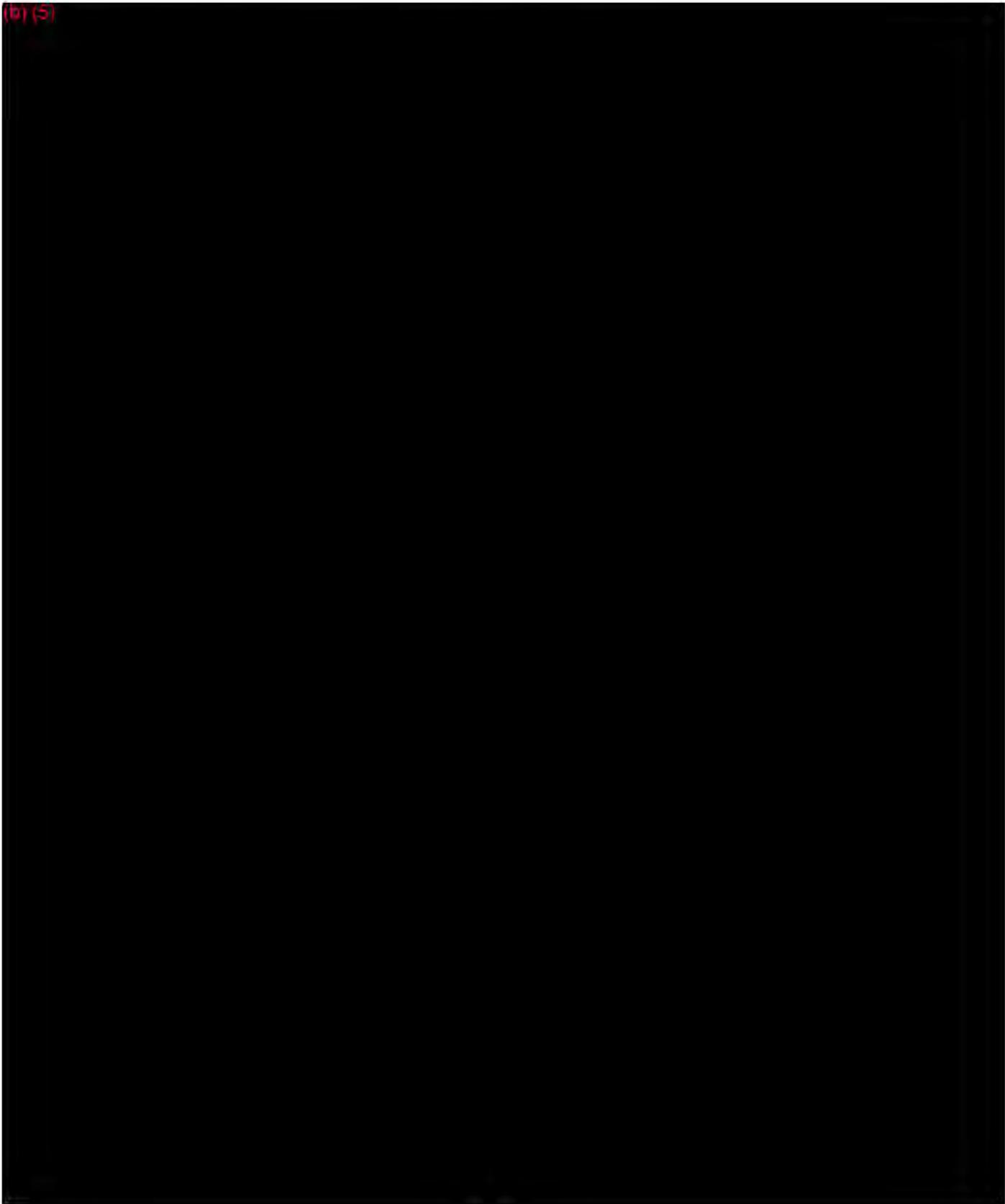
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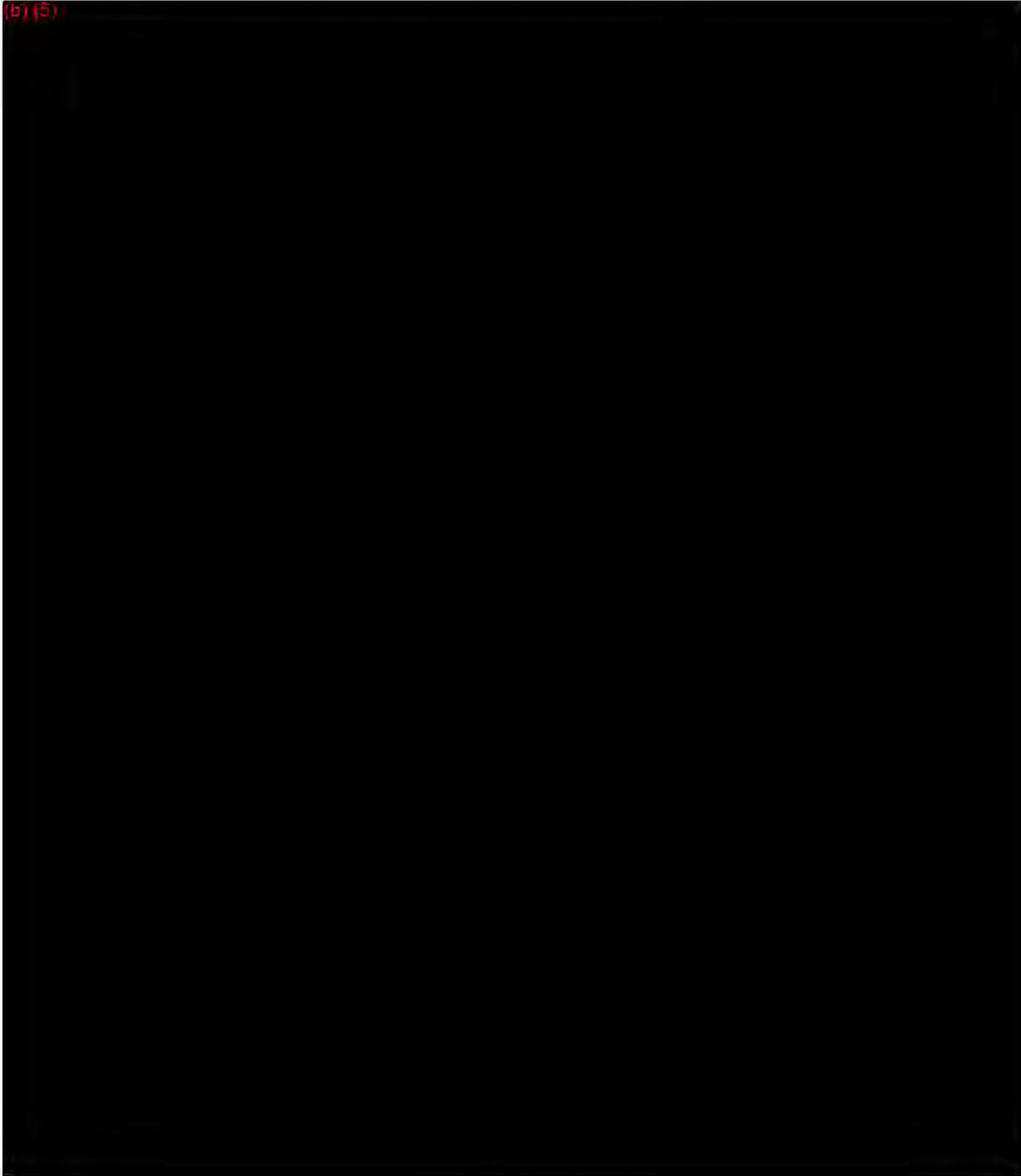
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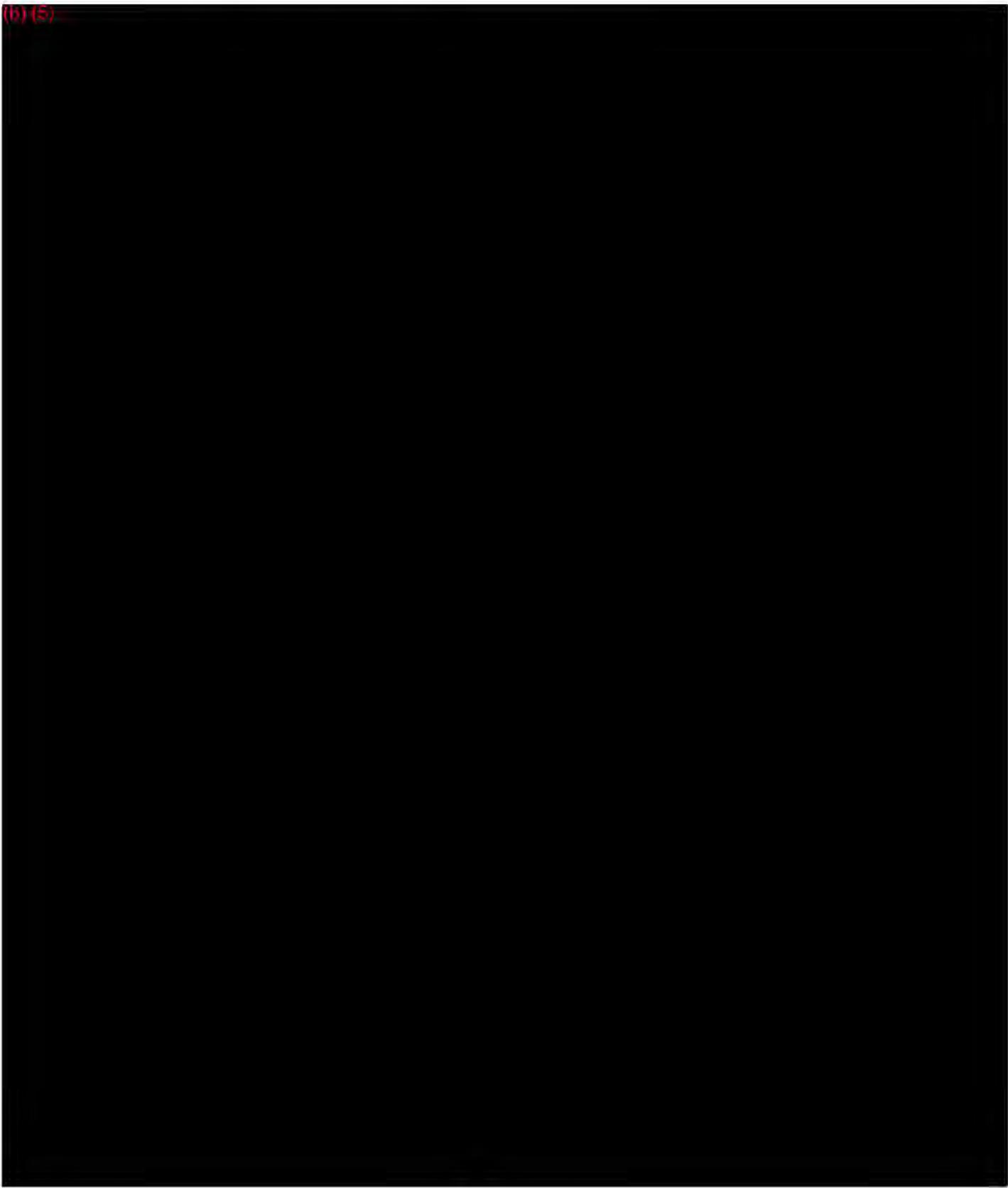
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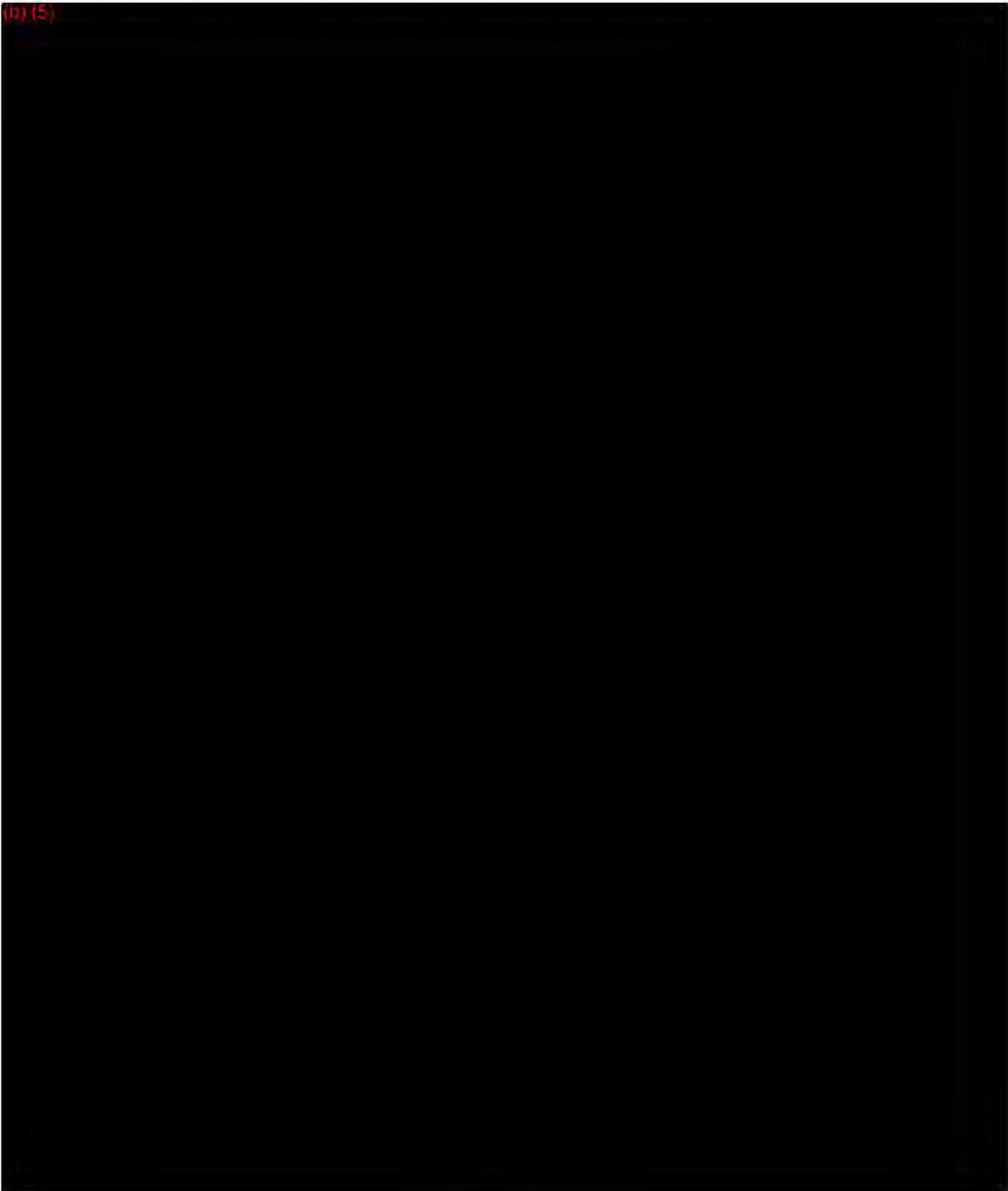
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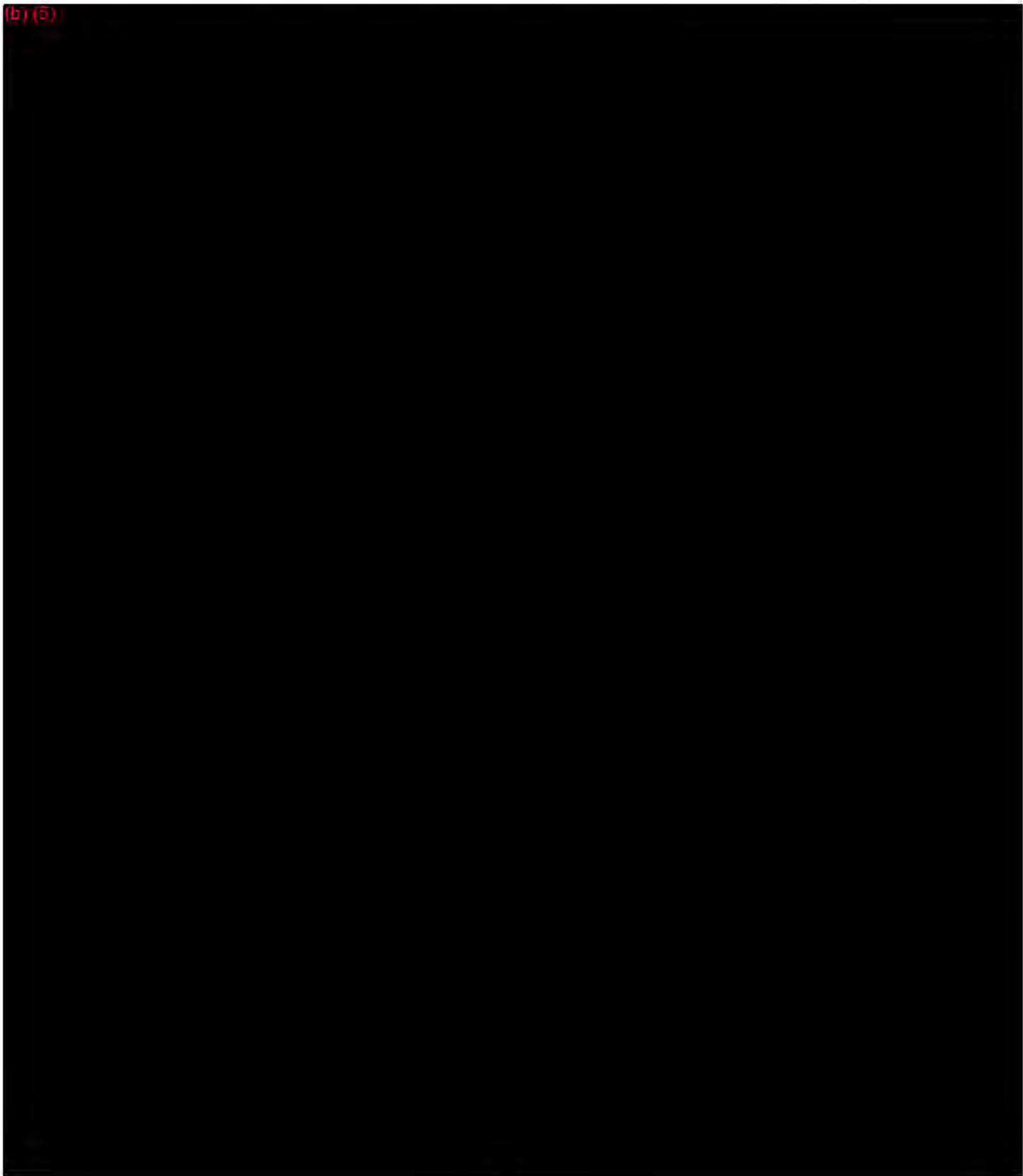
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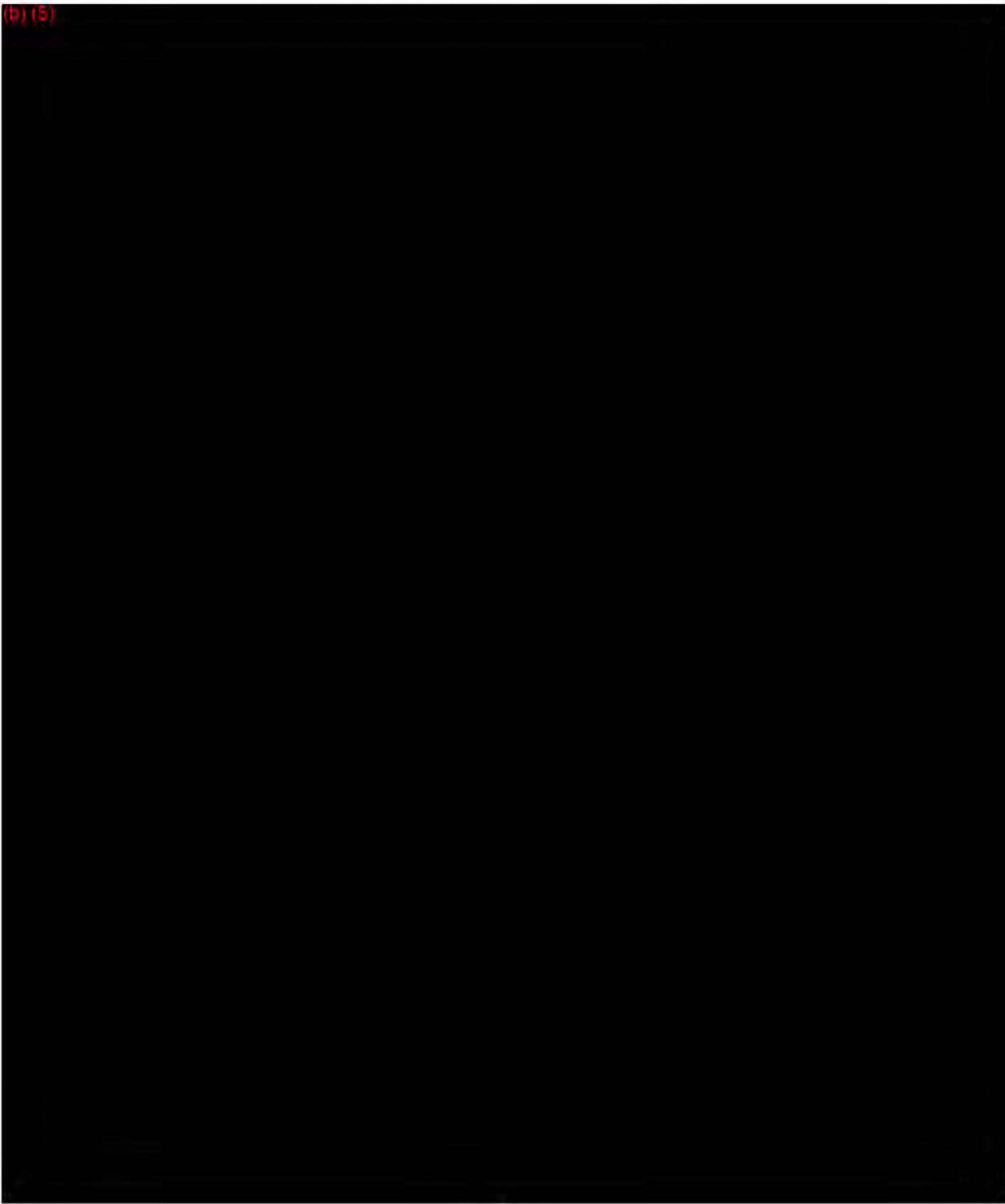
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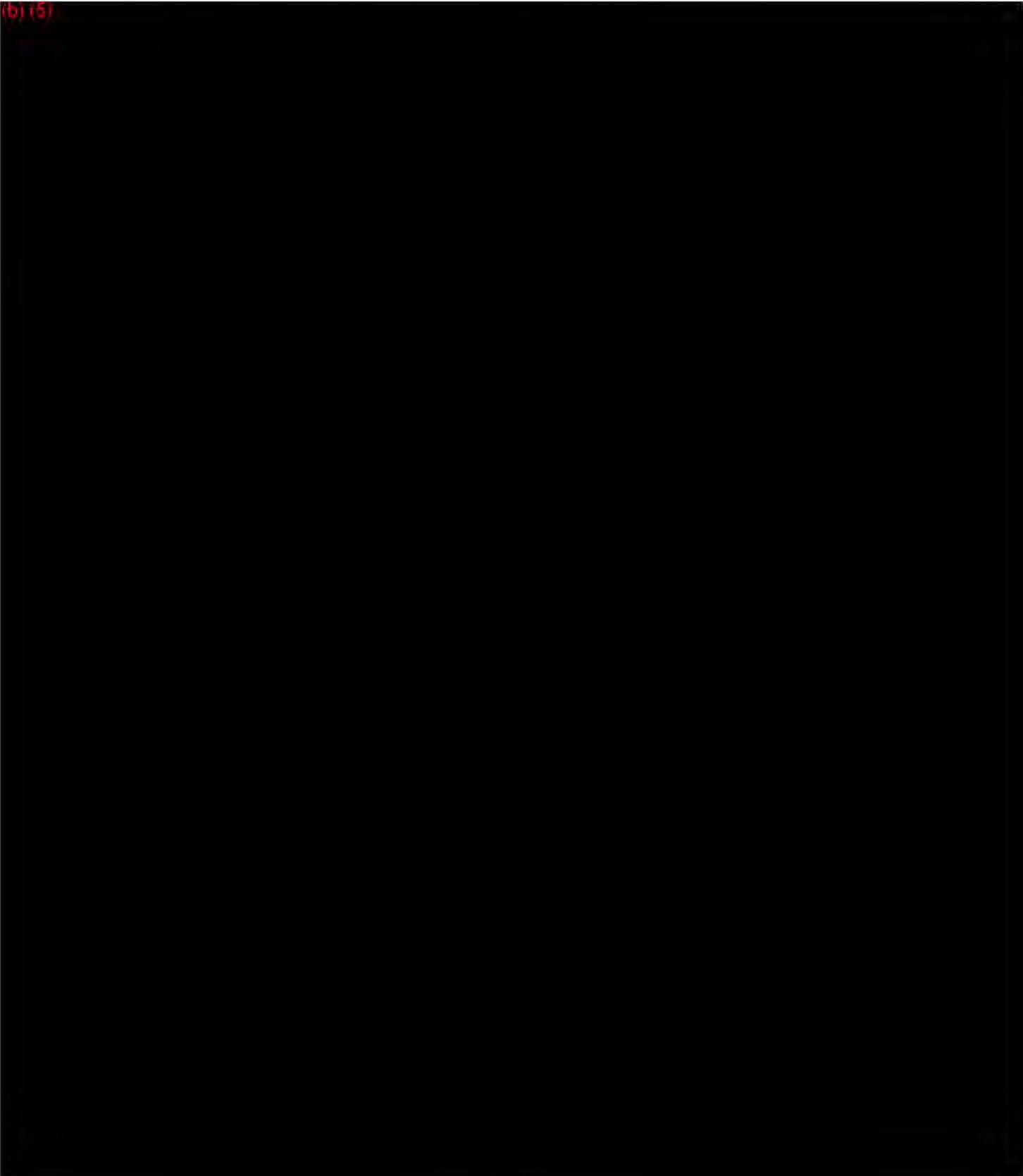
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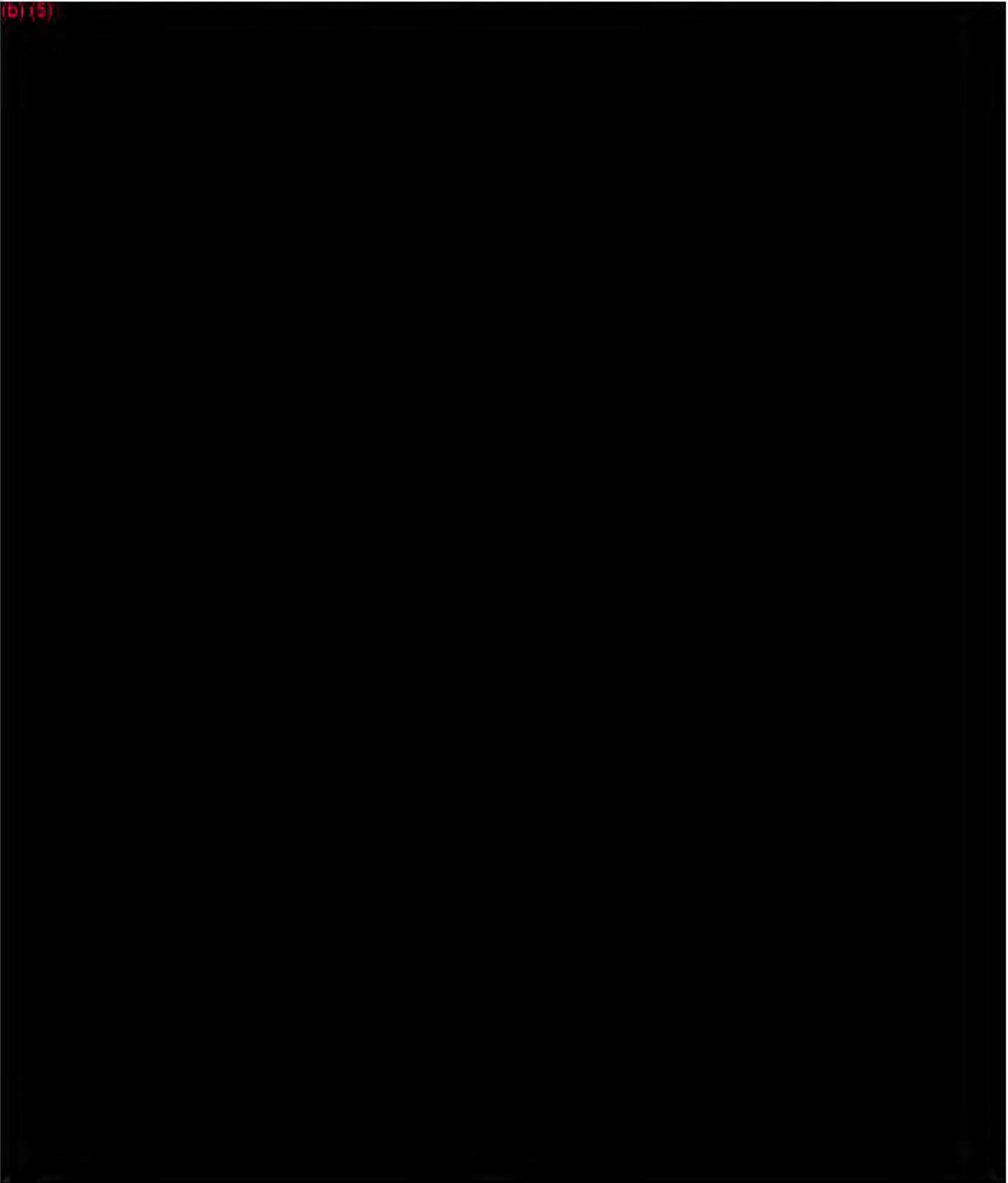
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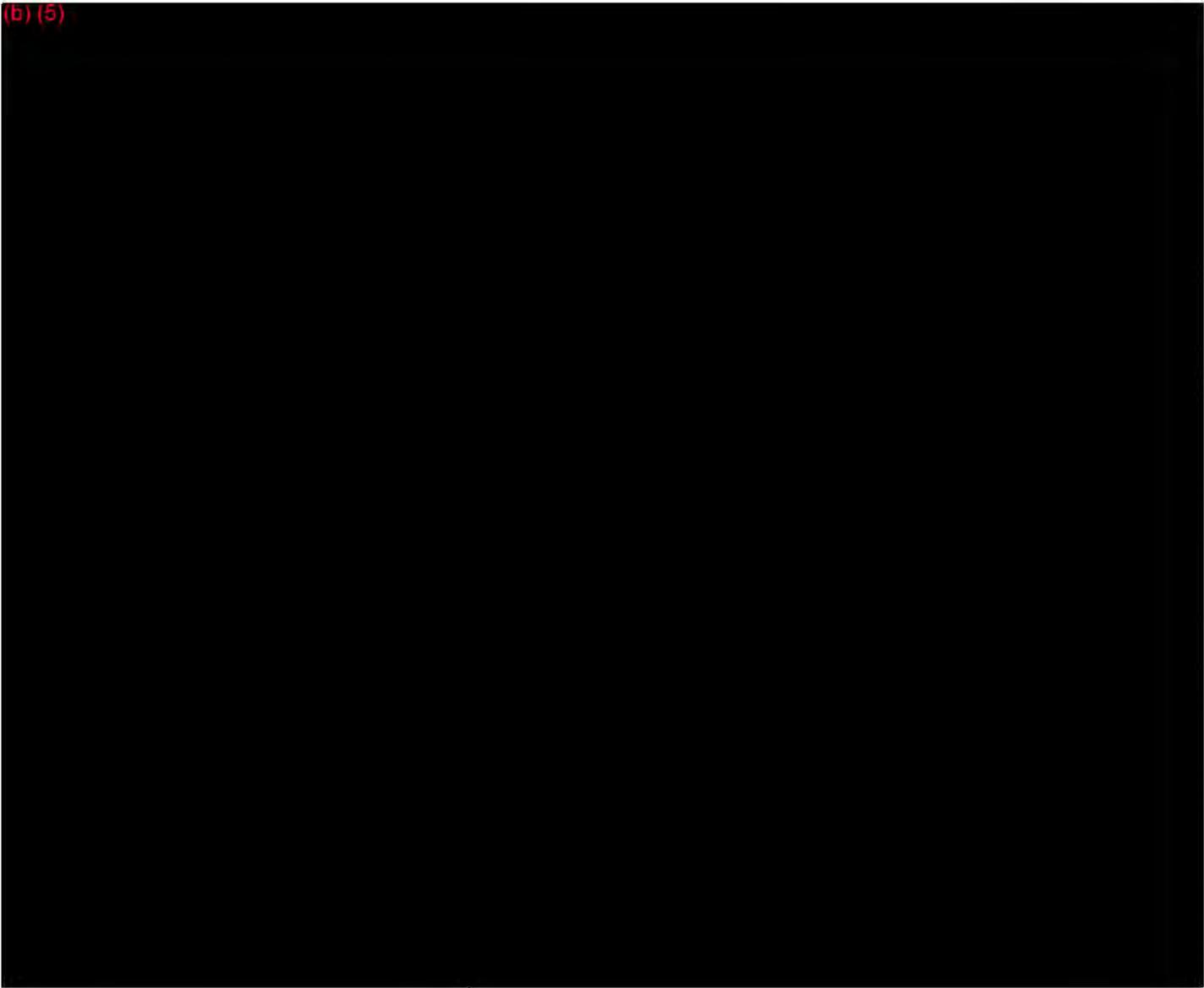
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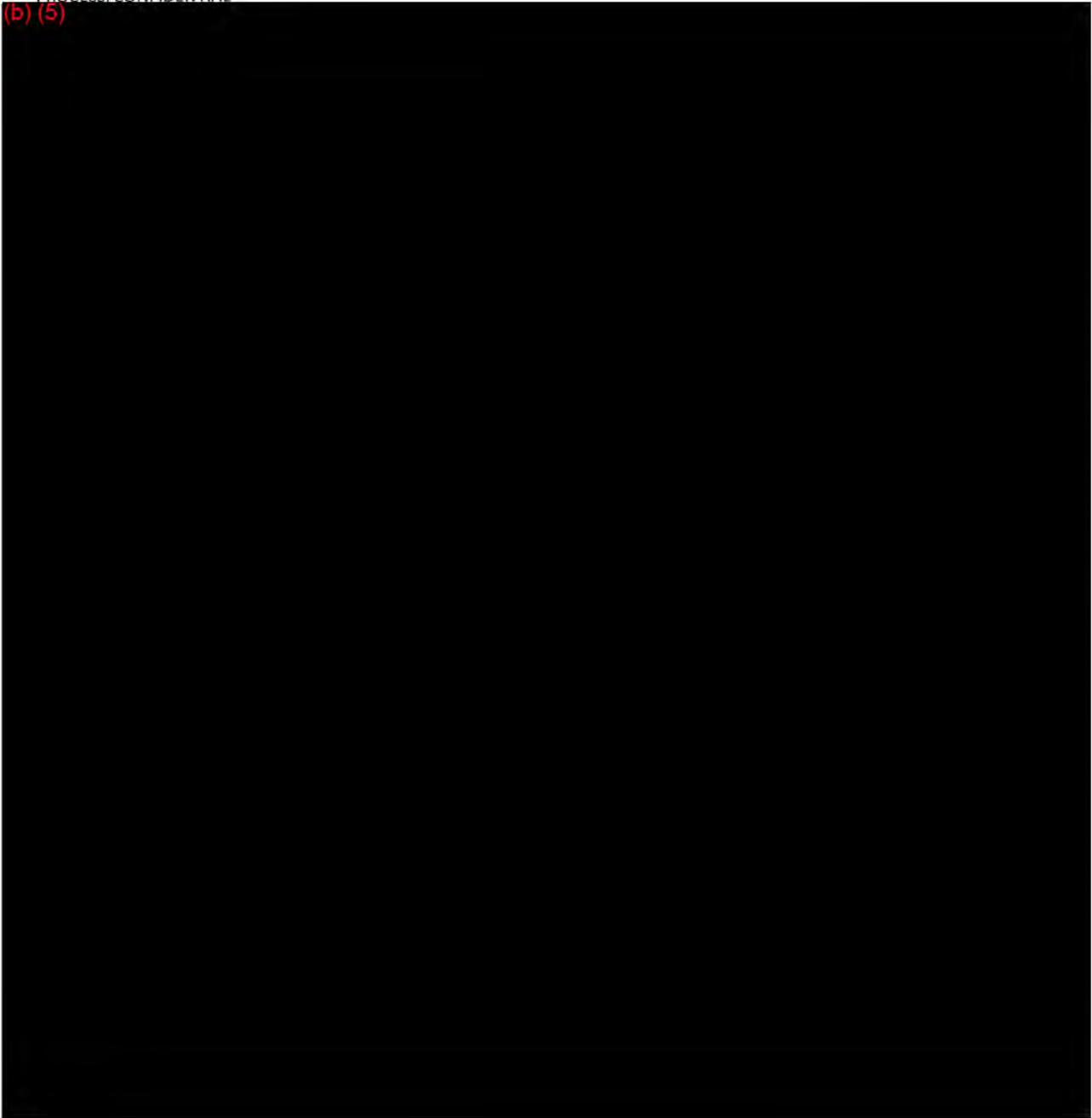
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**Scientific Dispute Regarding Approval of Sarepta Therapeutics'
Eteplirsen – Commissioner's Decision**

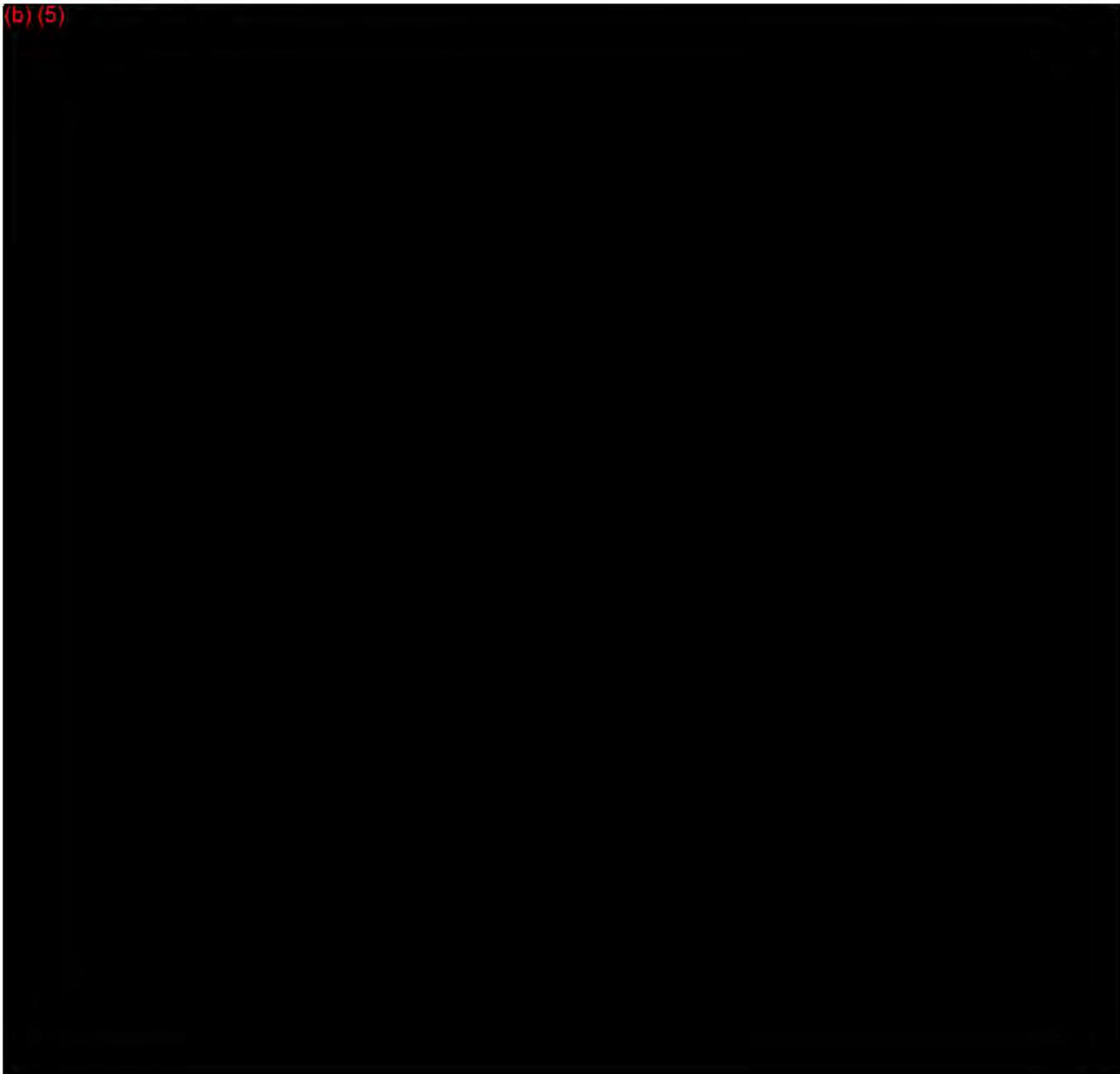
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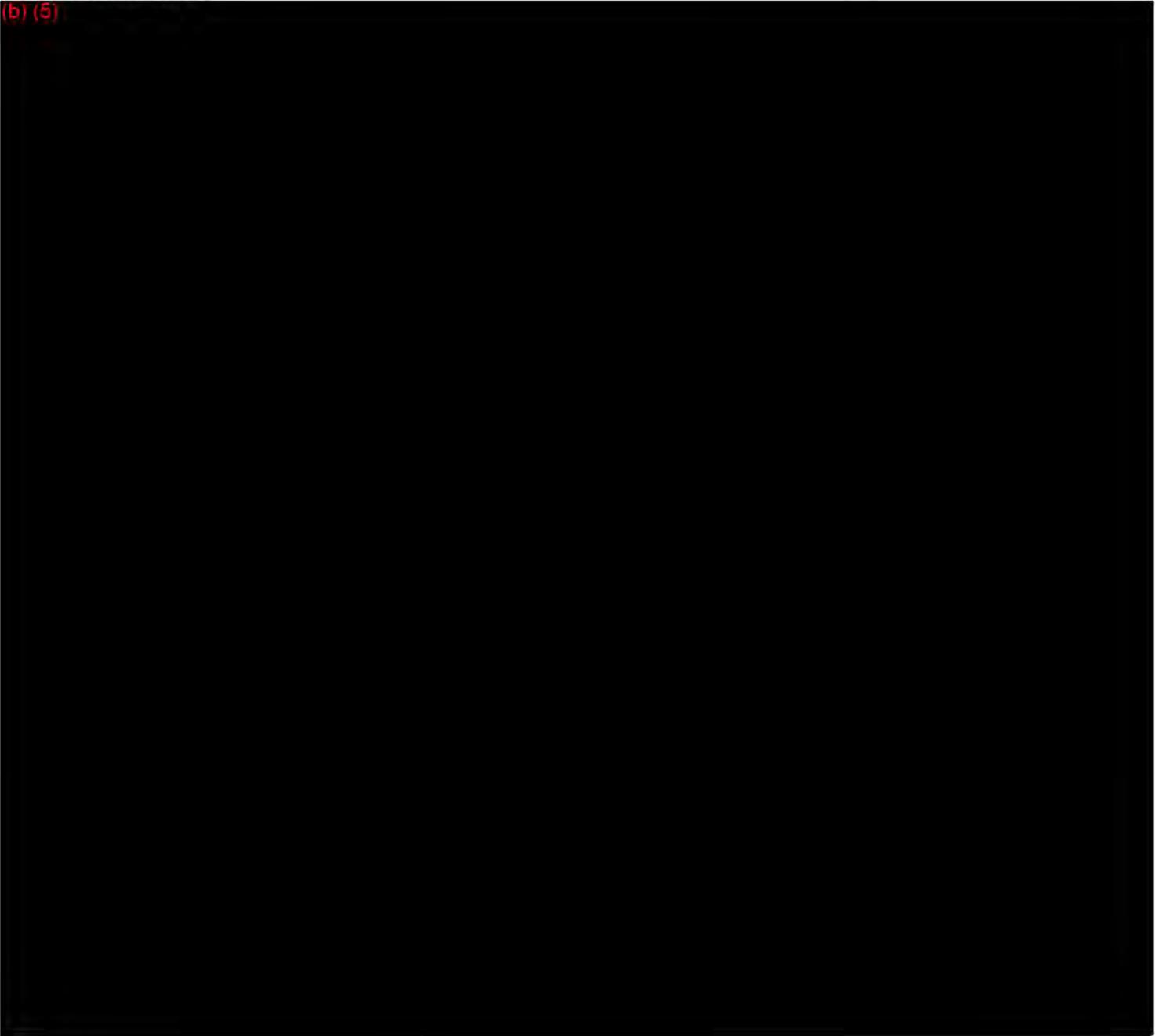
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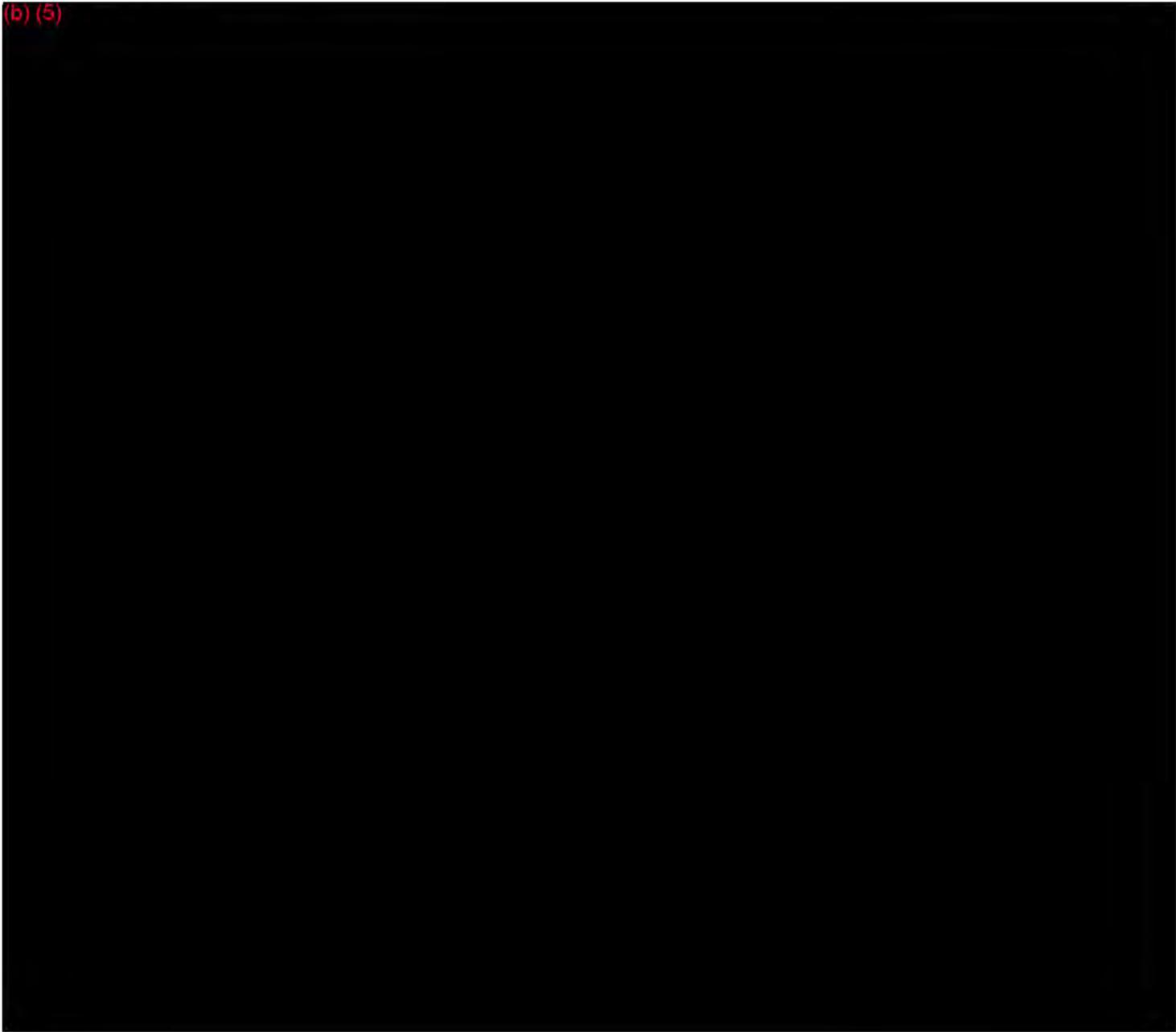
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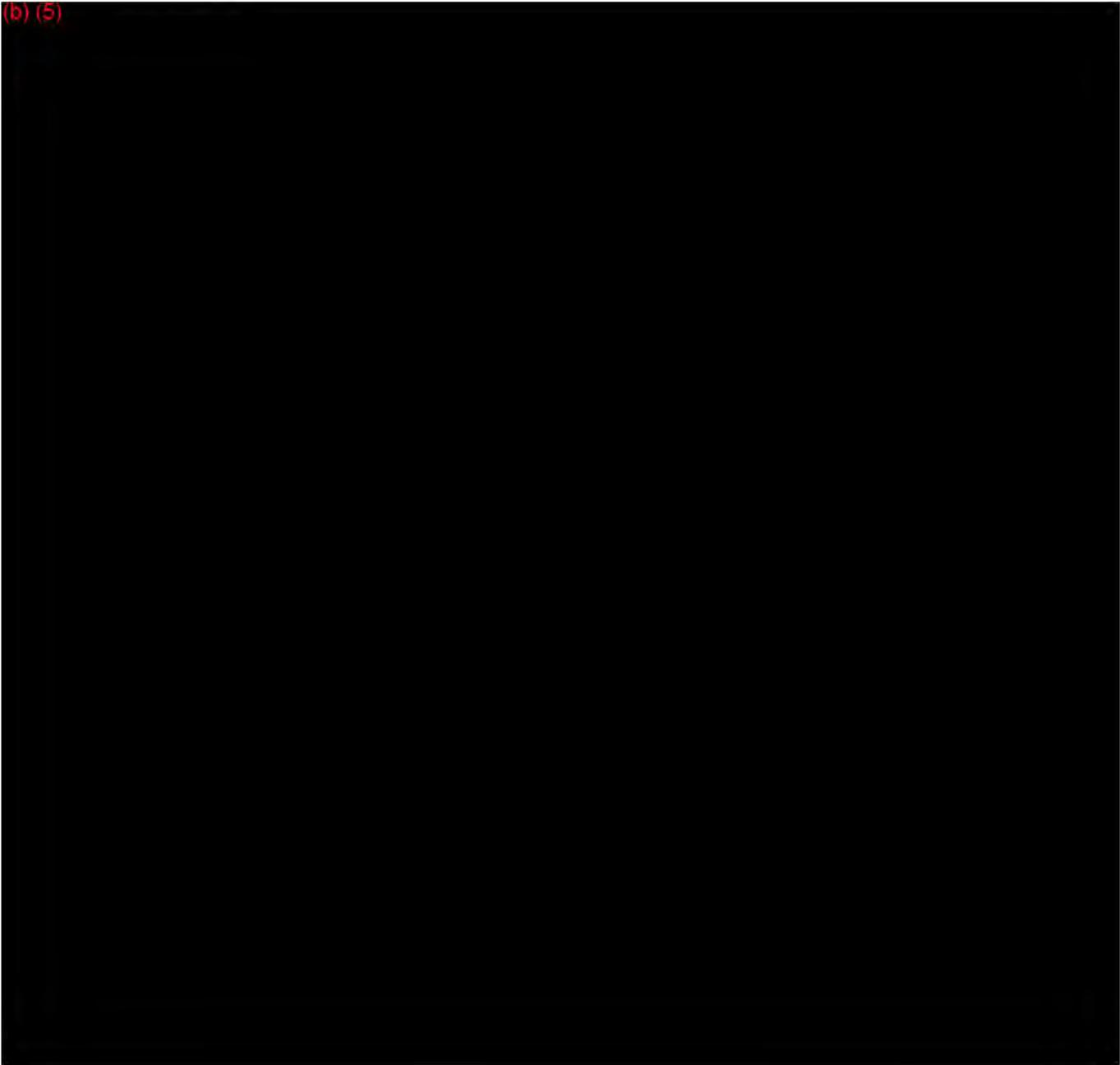
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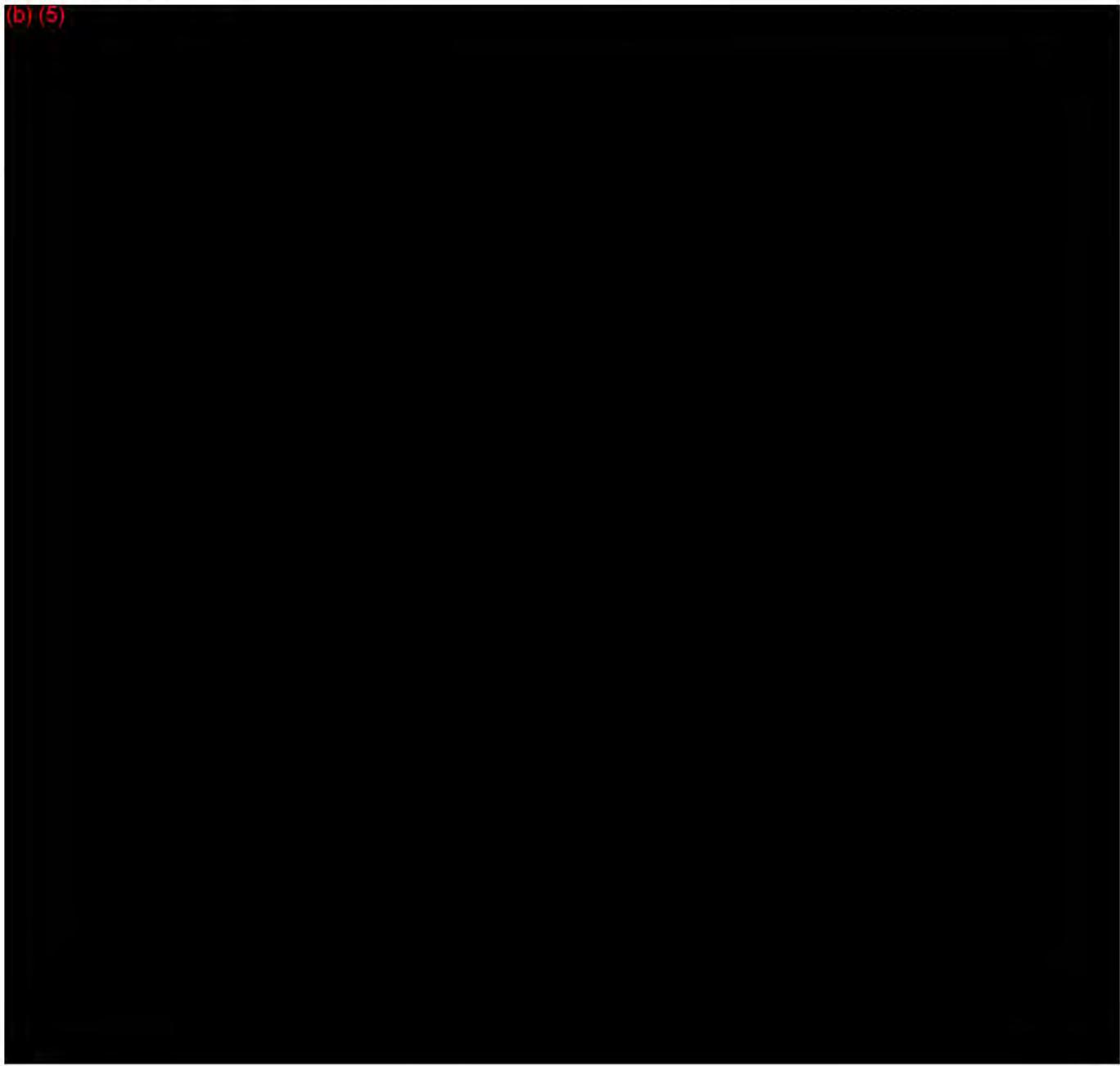
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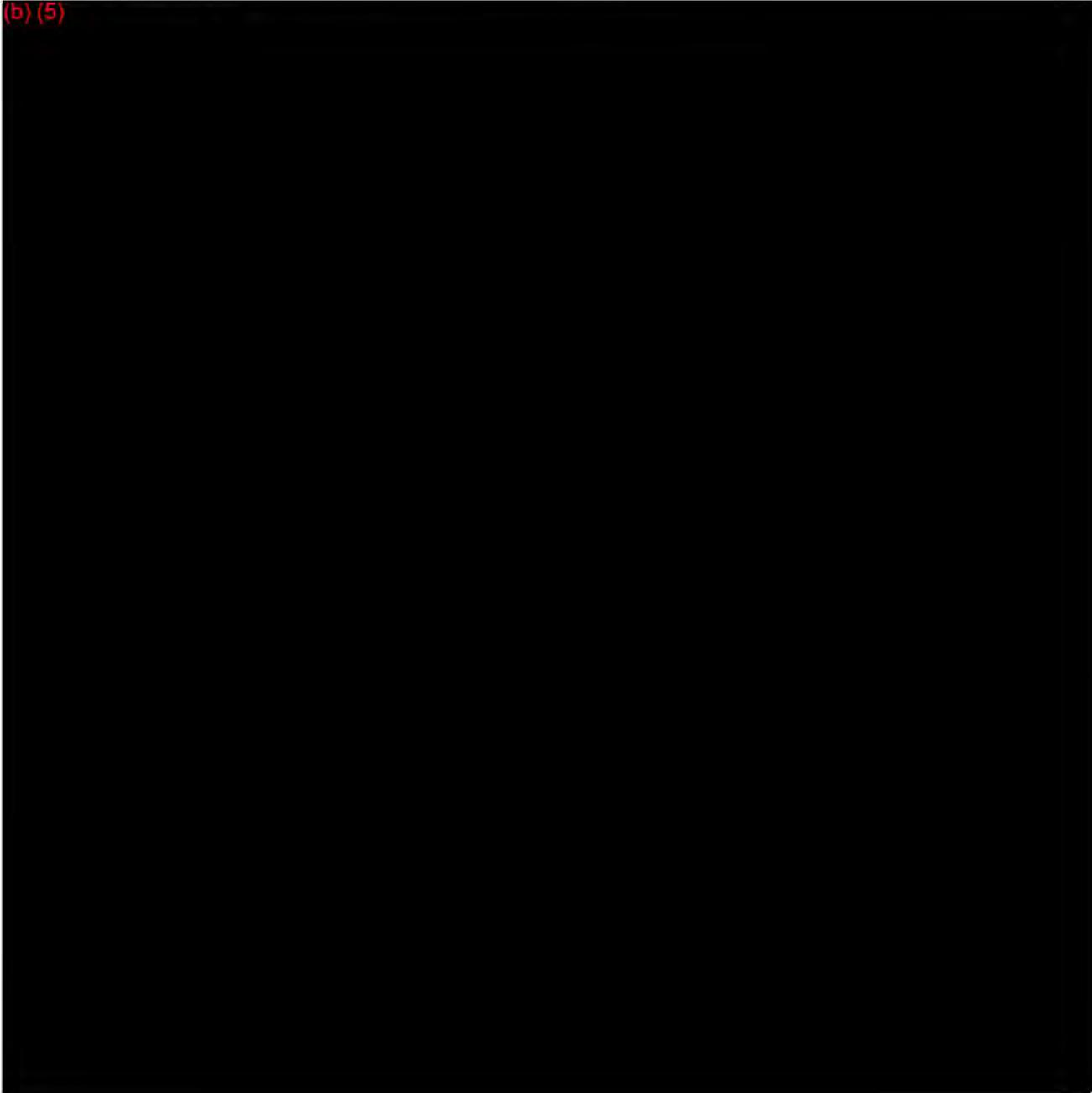
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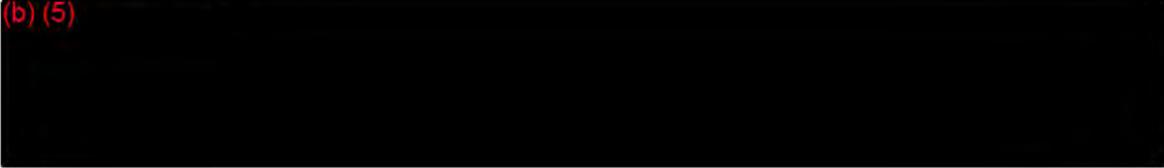


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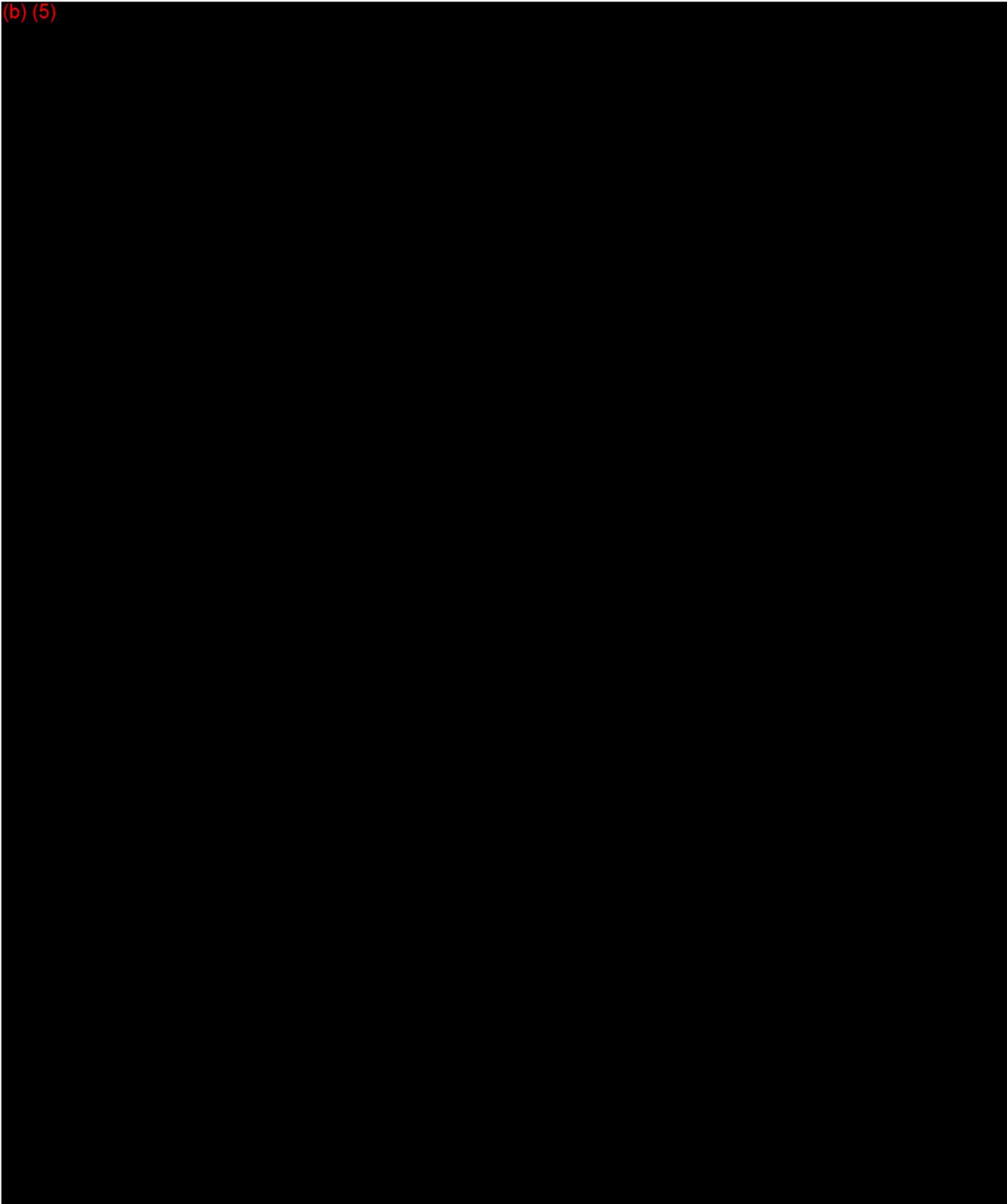


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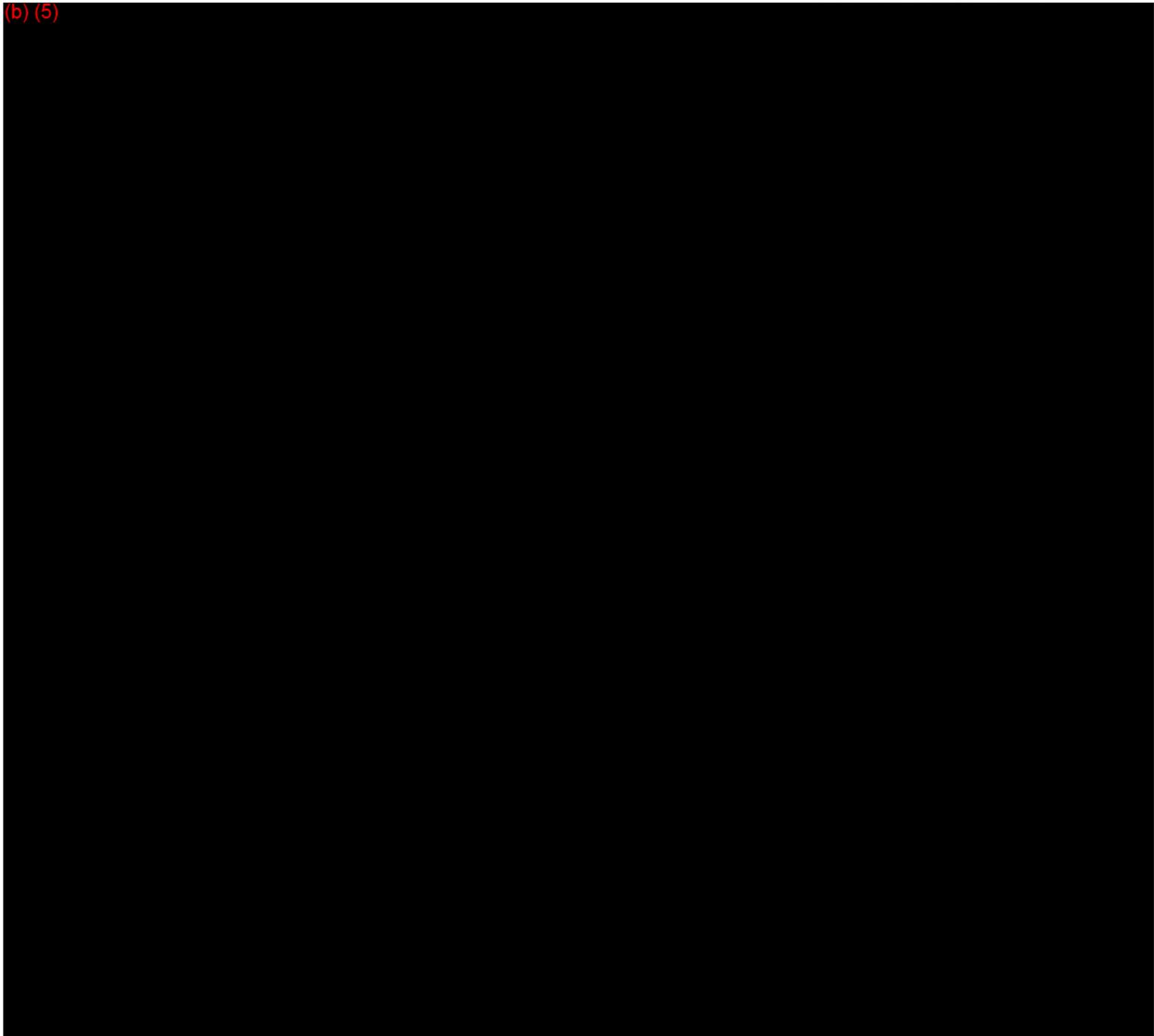
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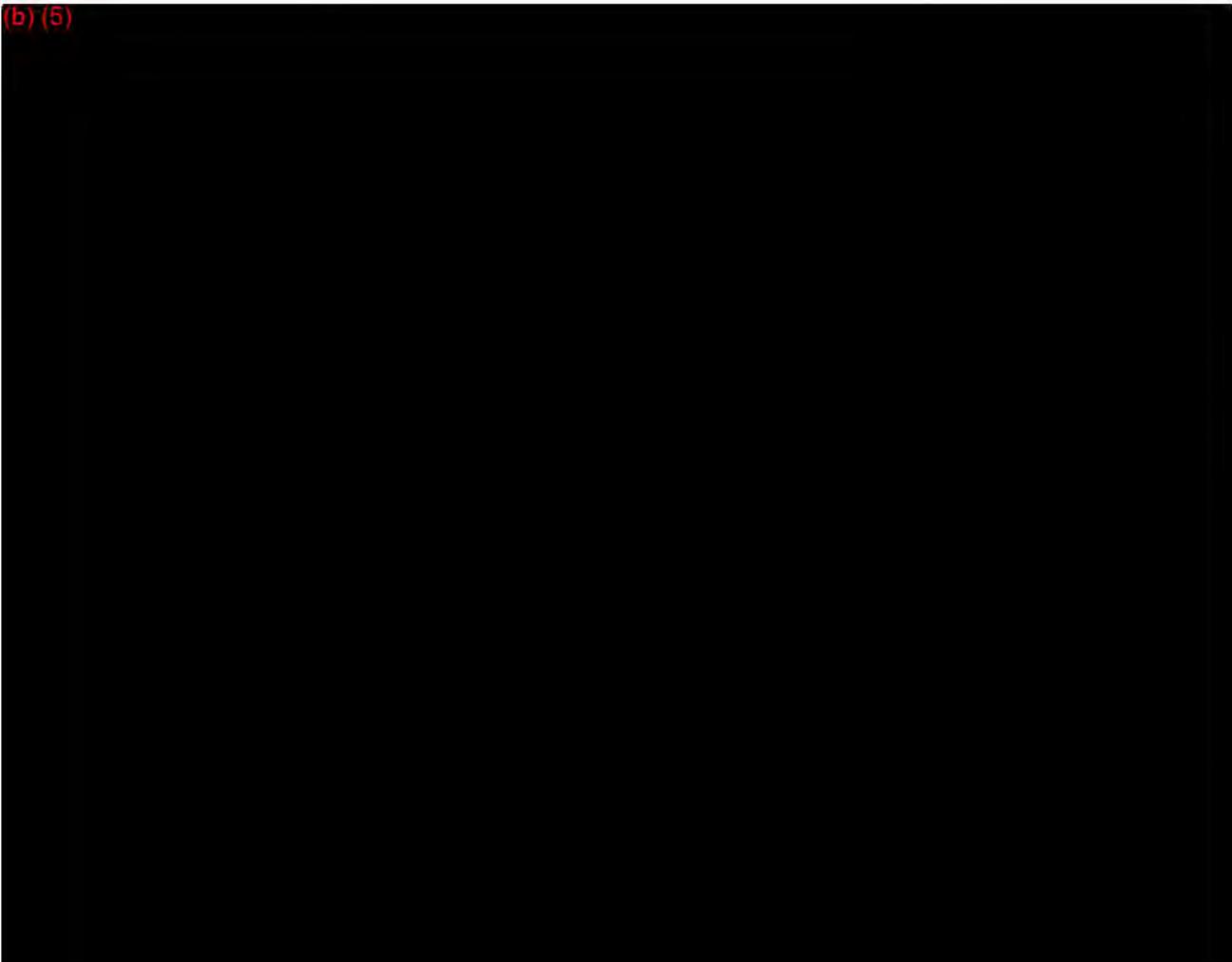
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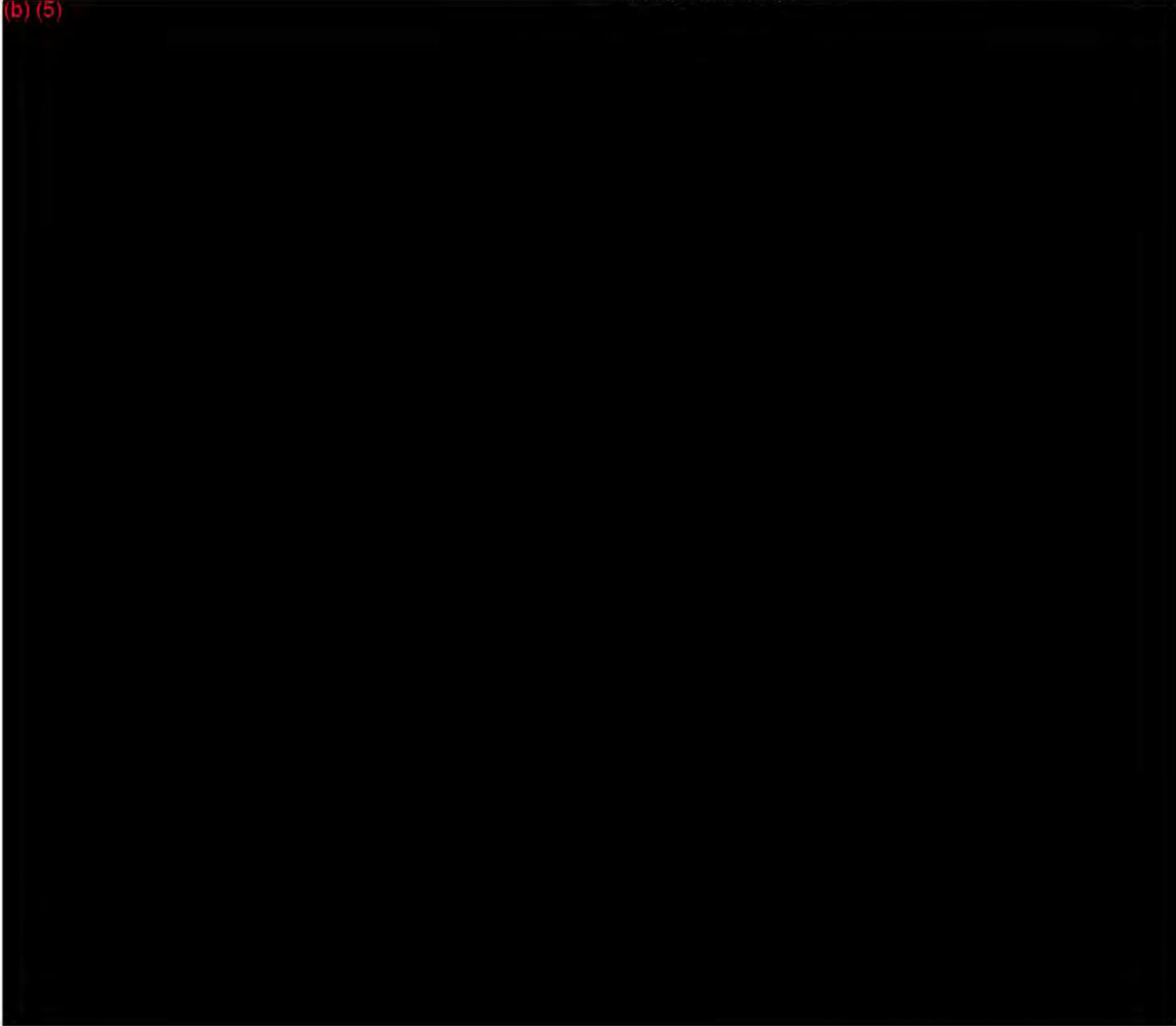
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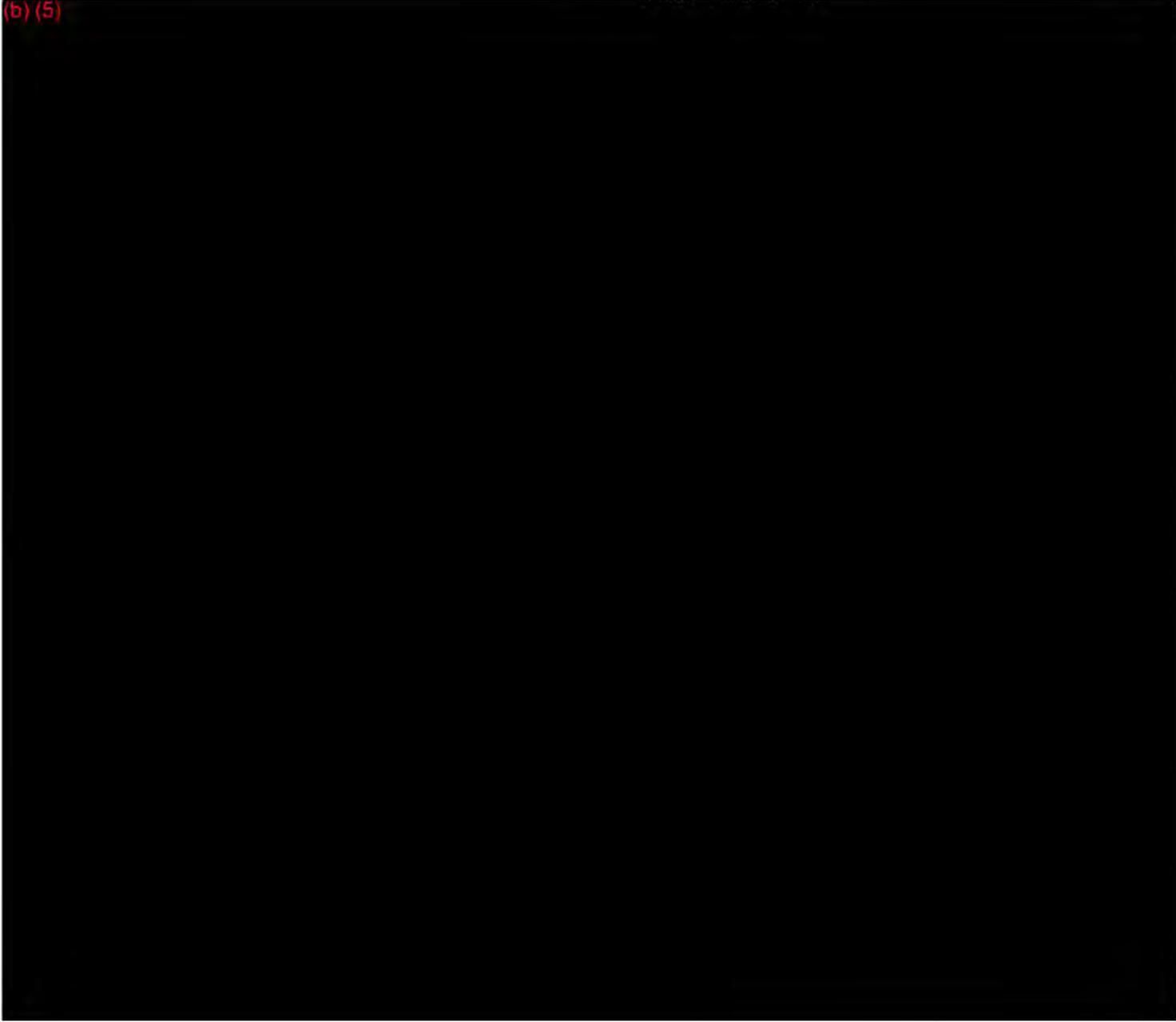
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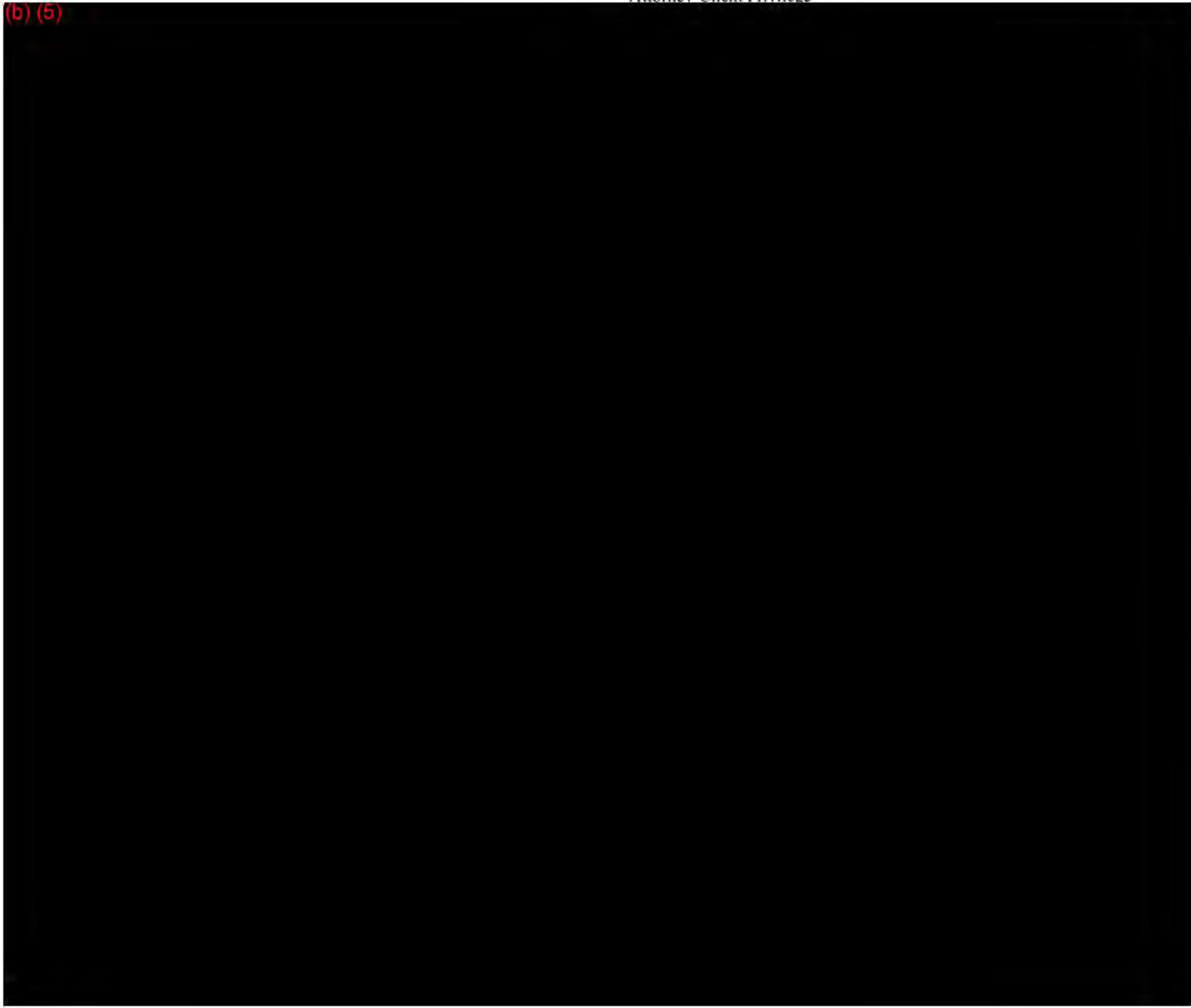
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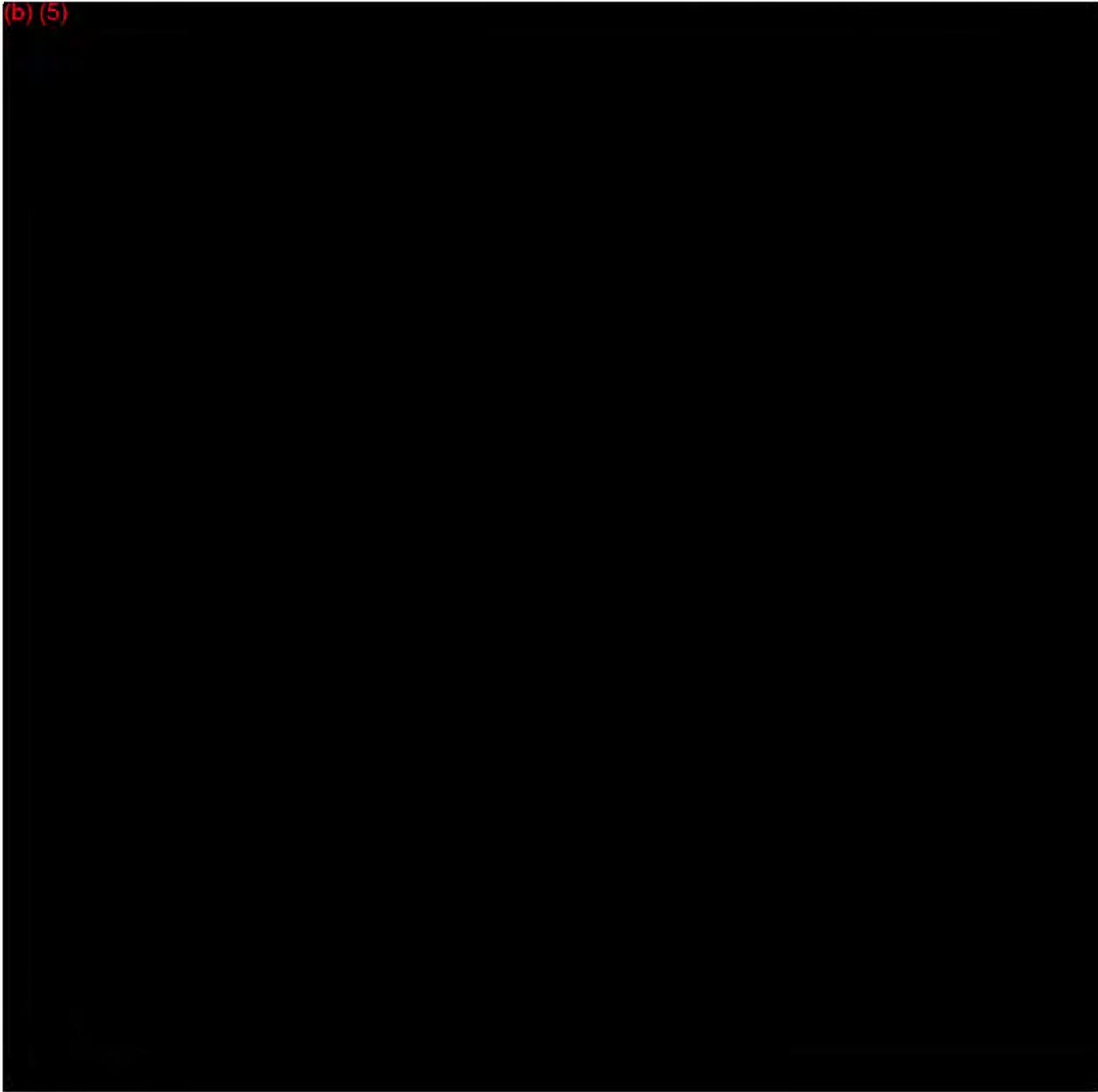
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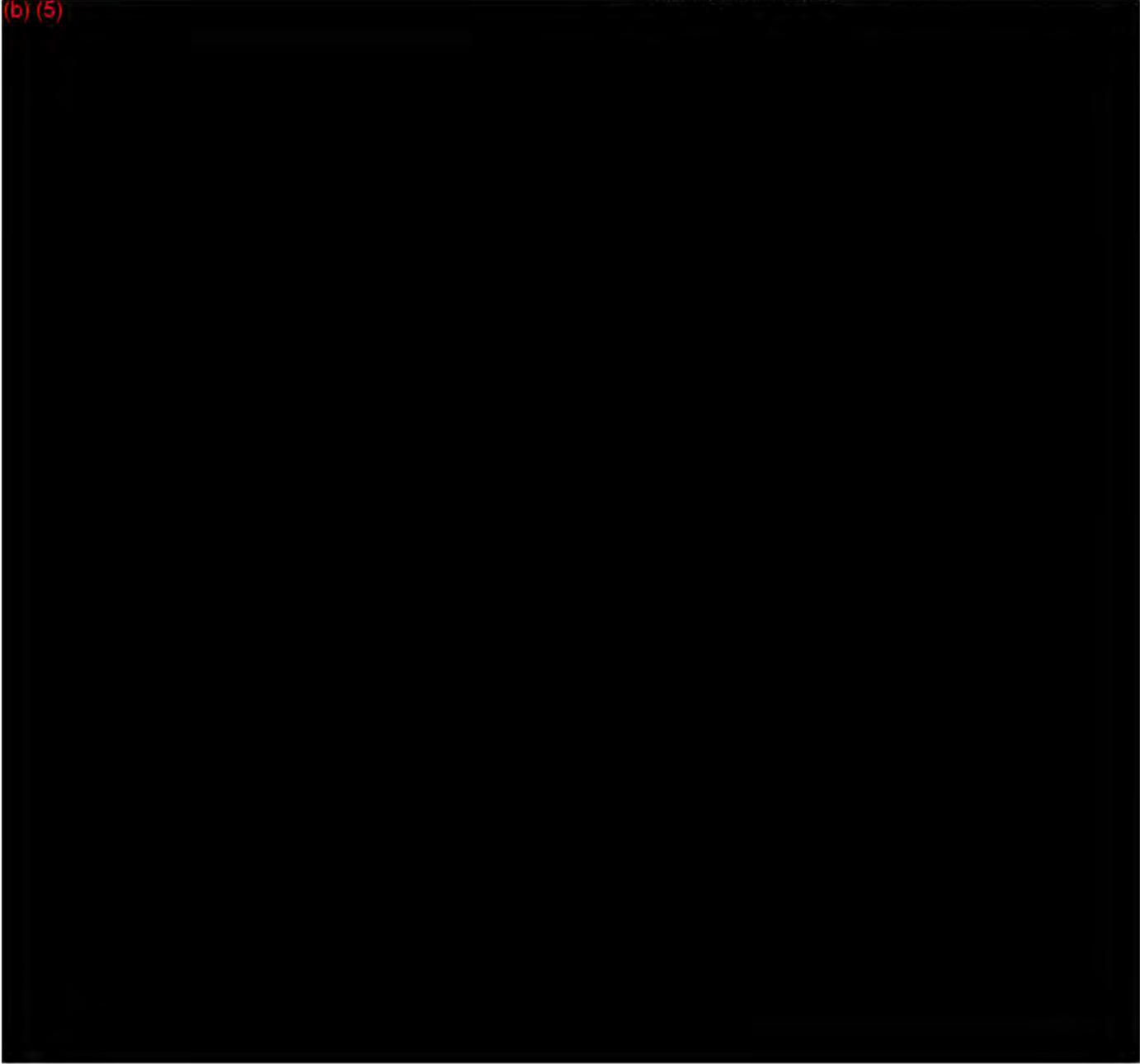
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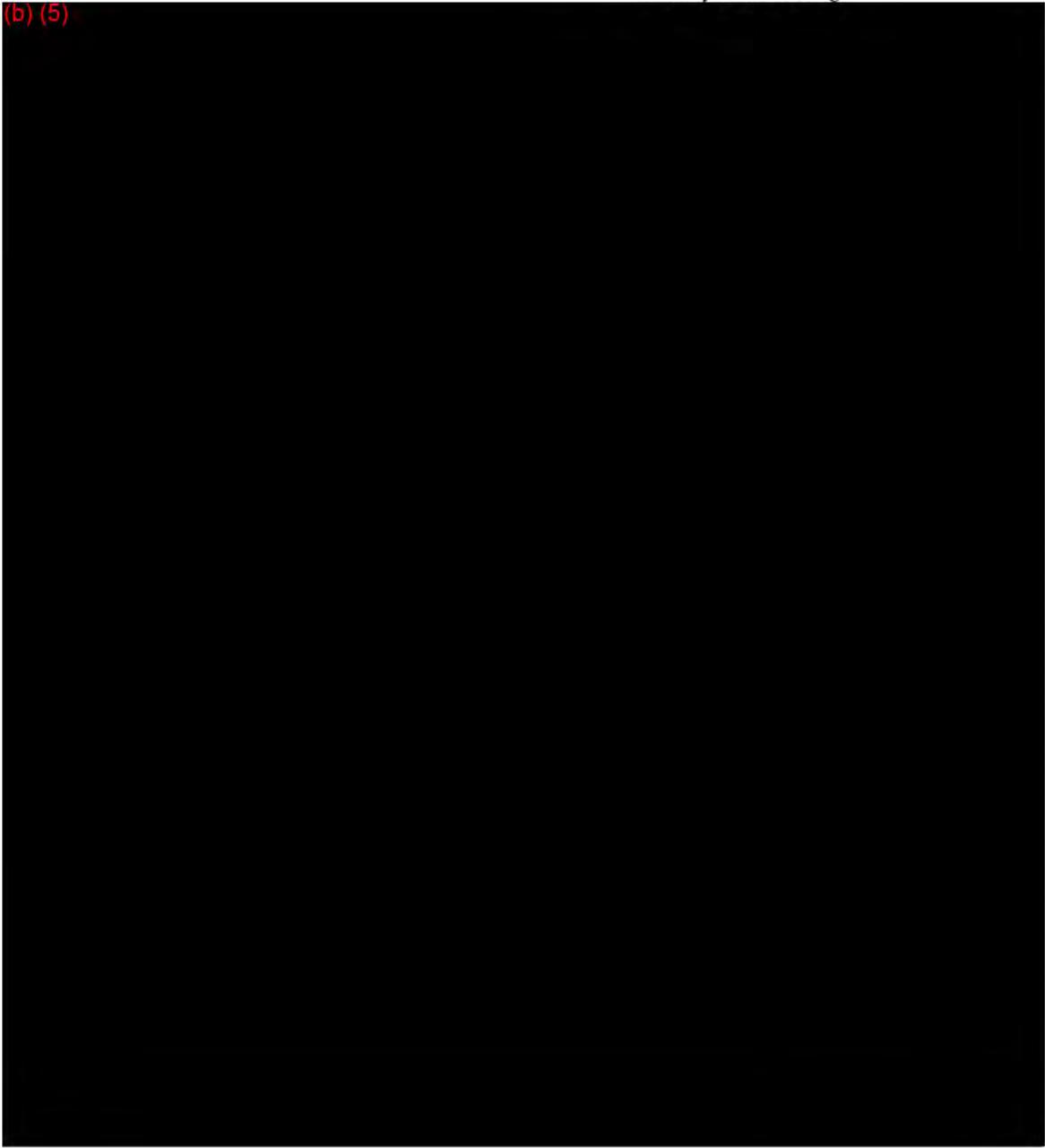
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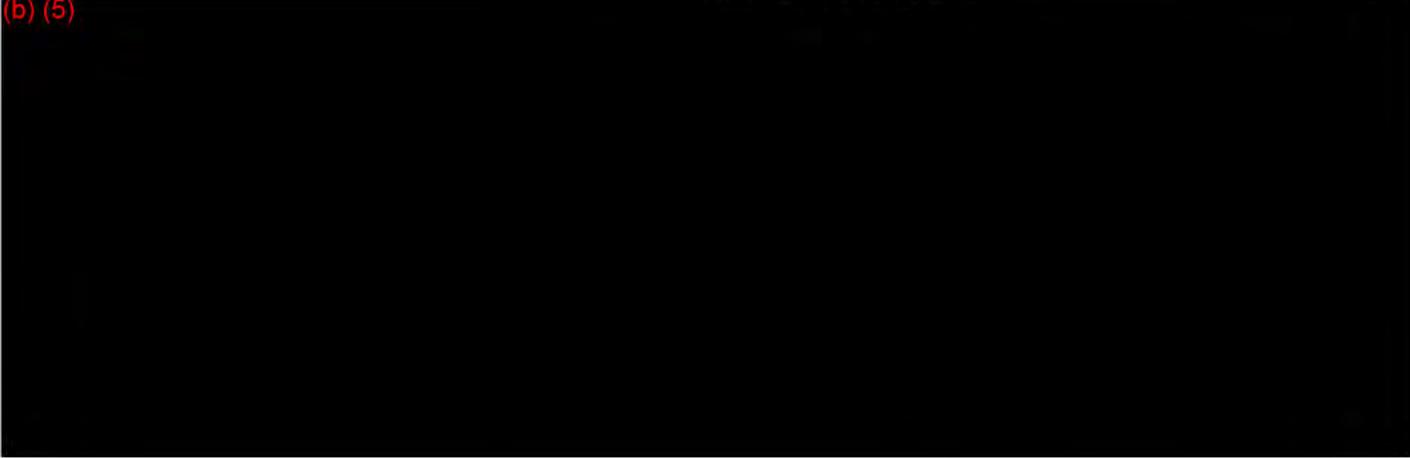
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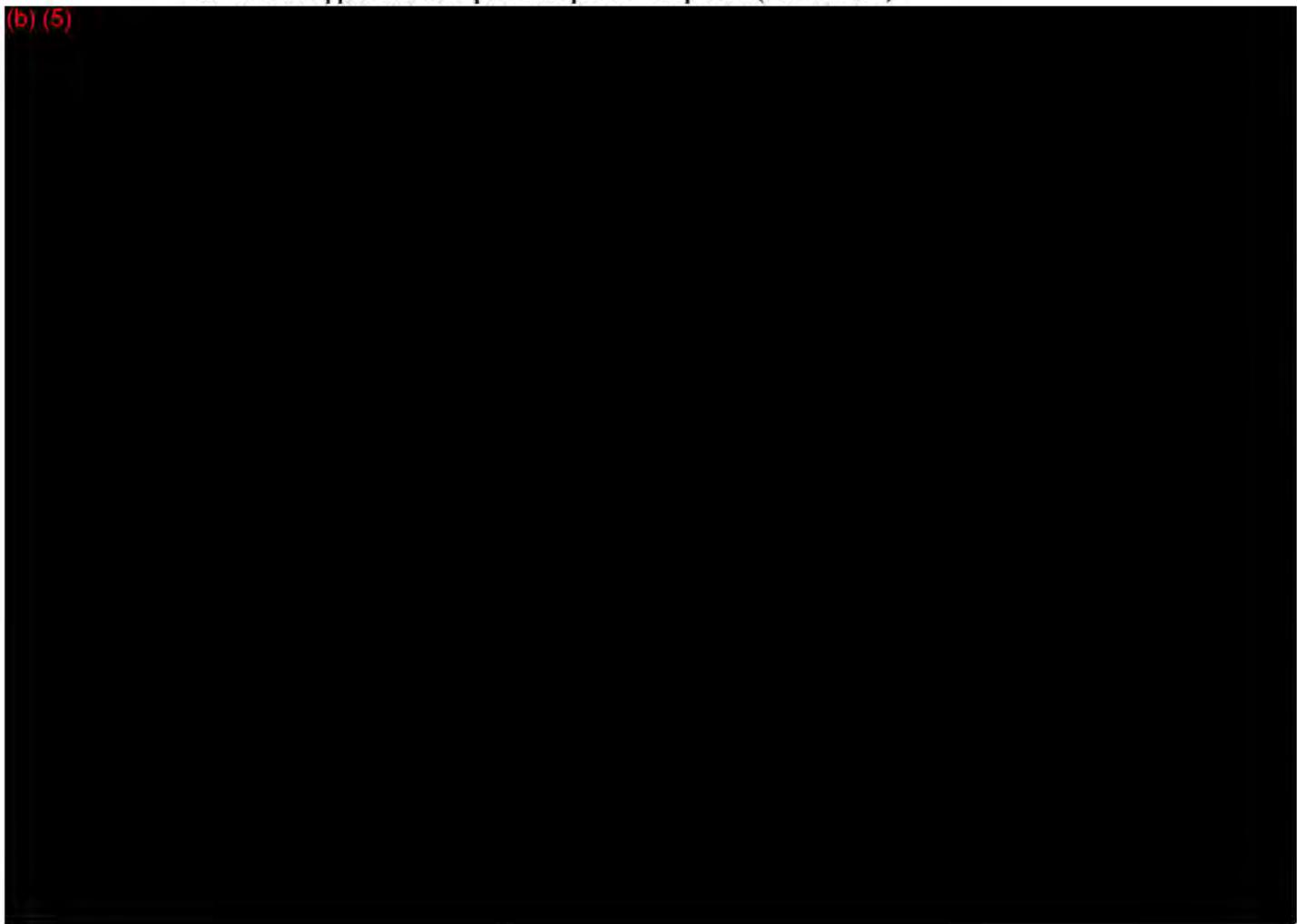
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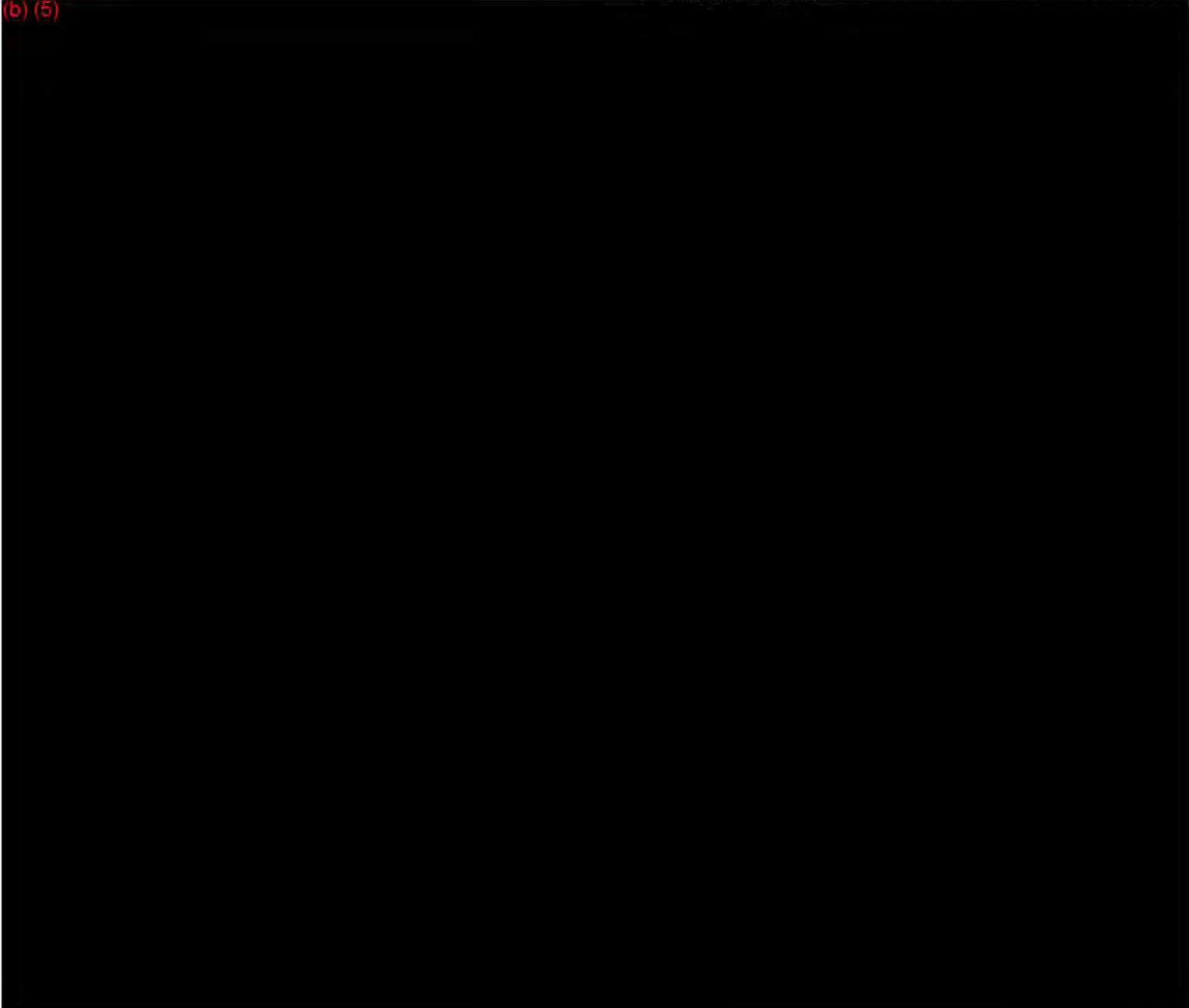
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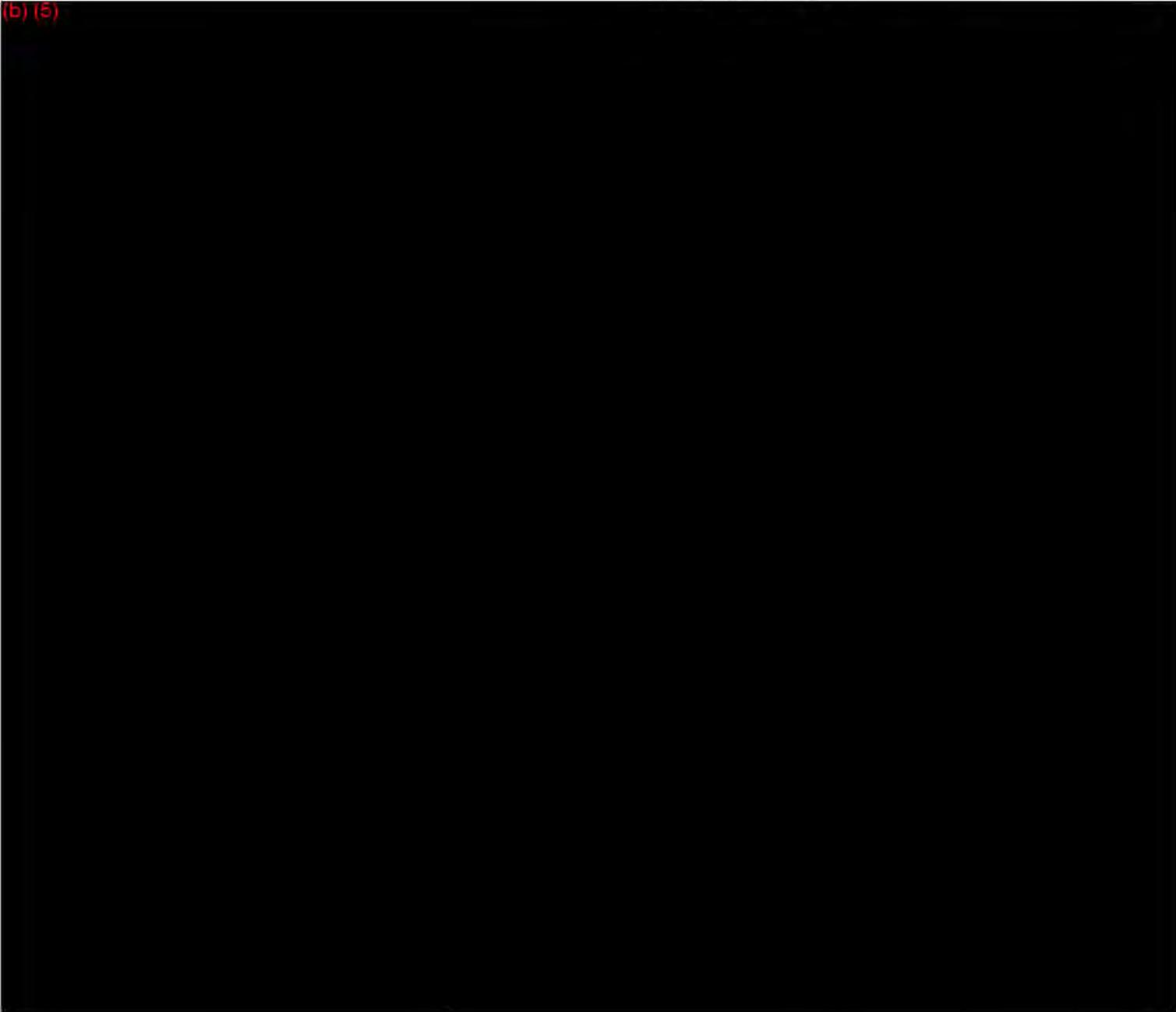
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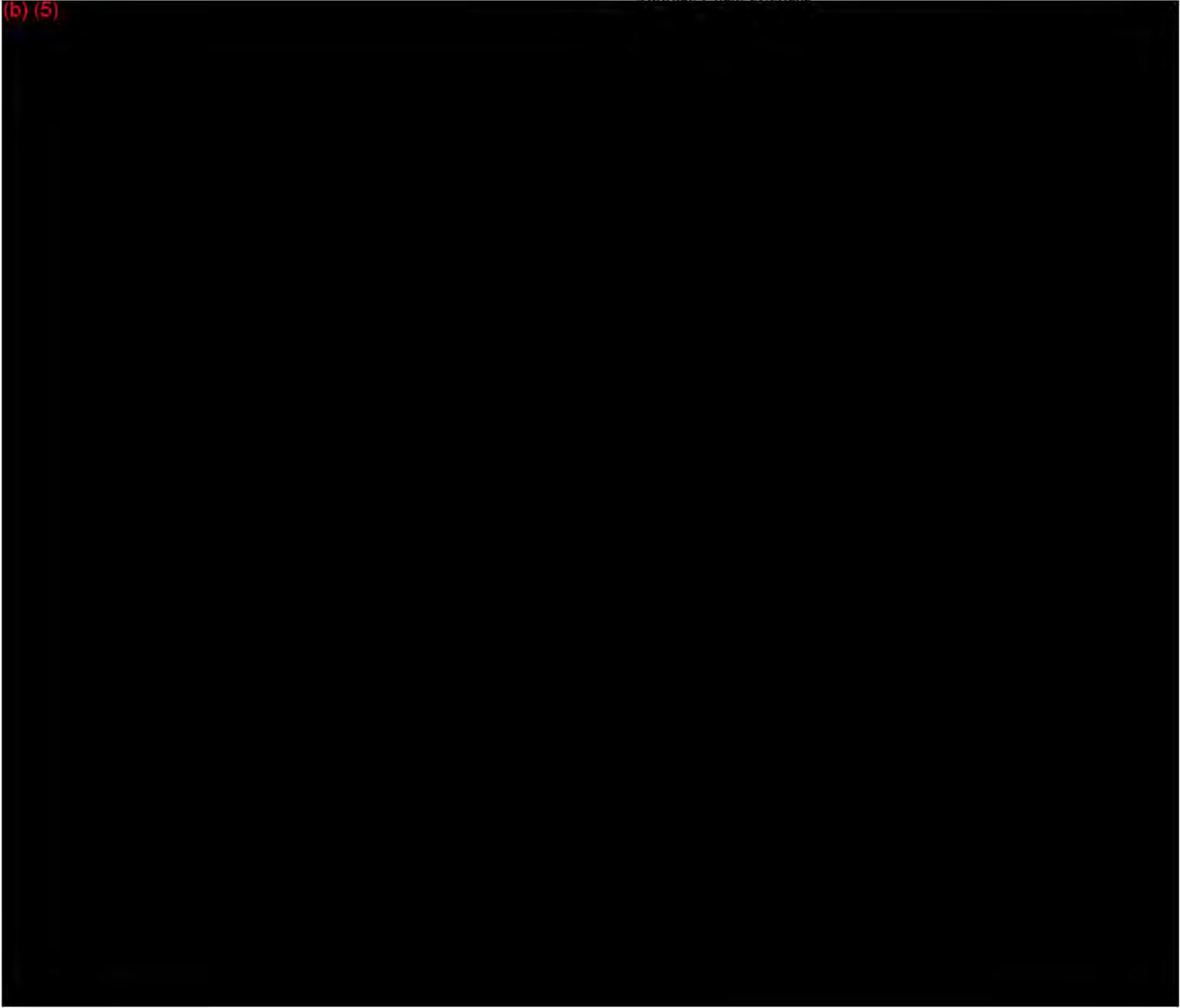


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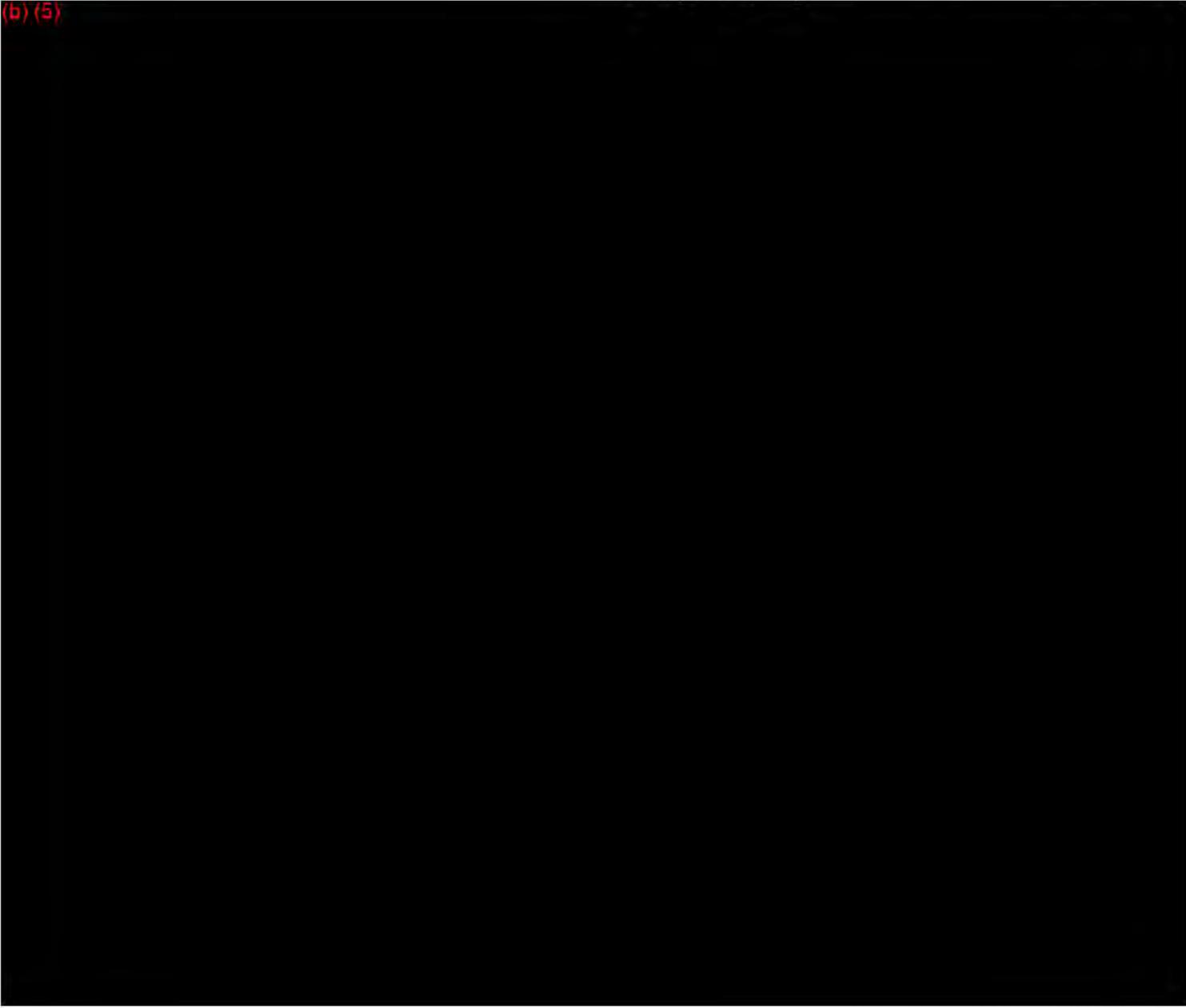
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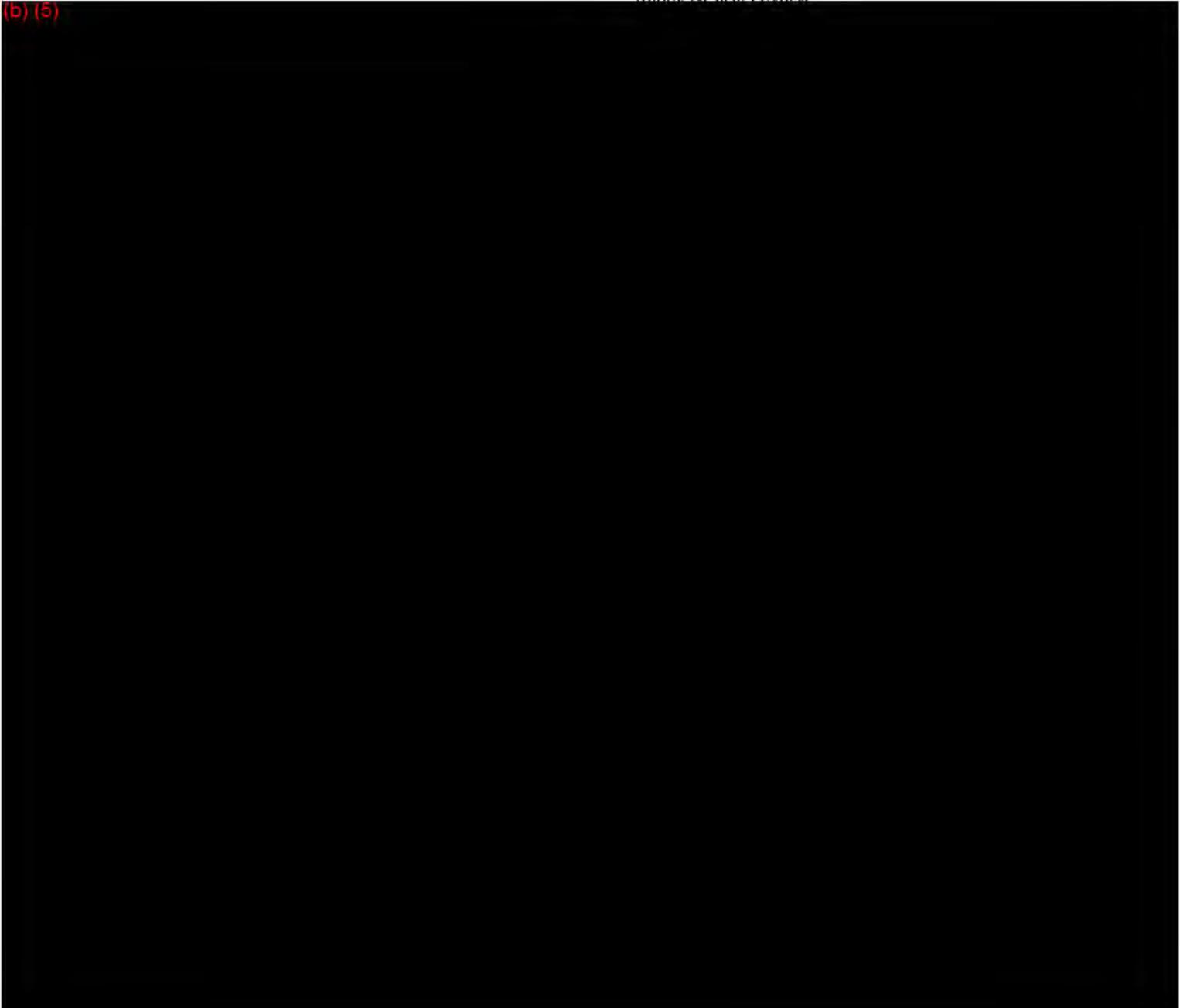


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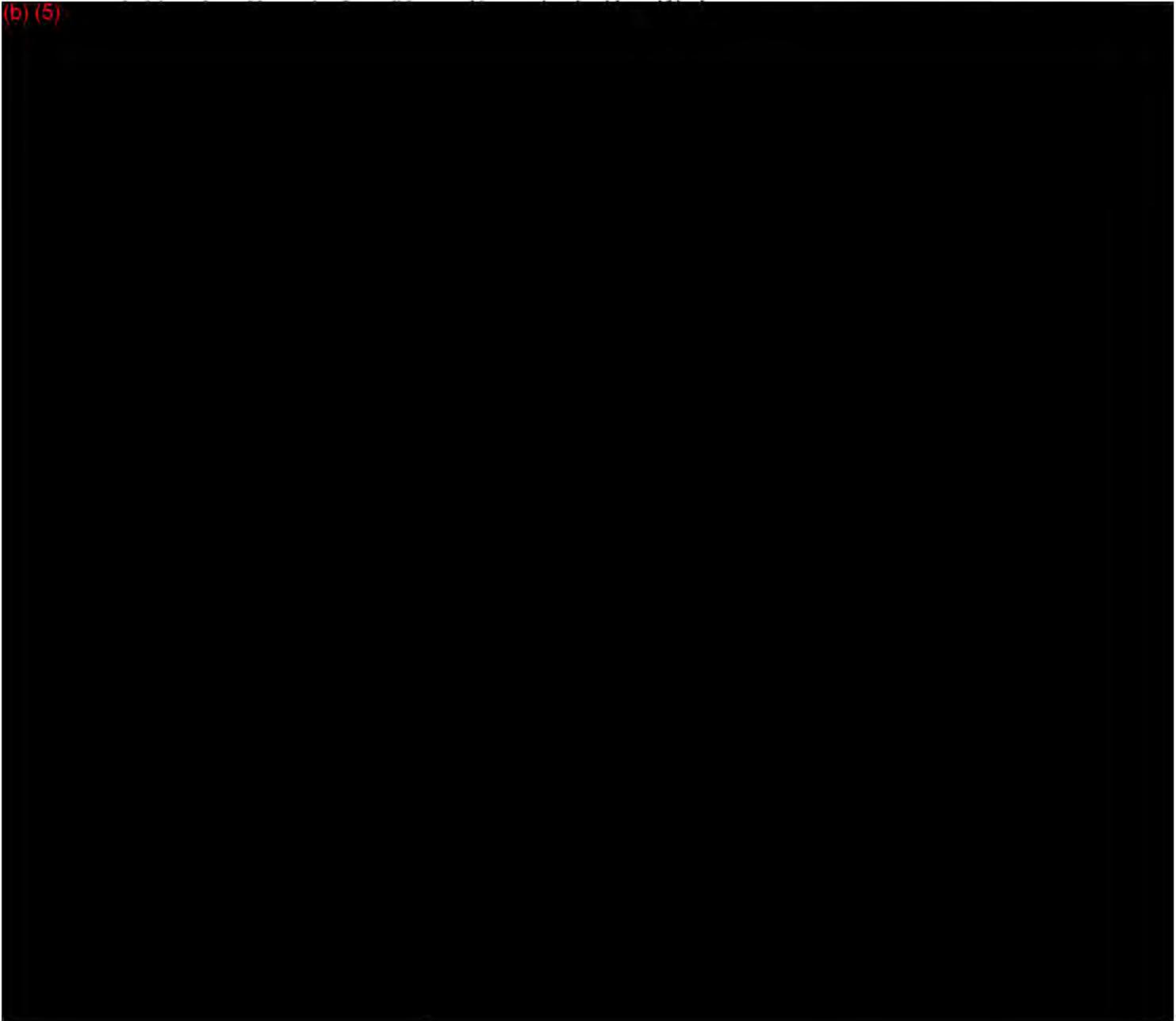
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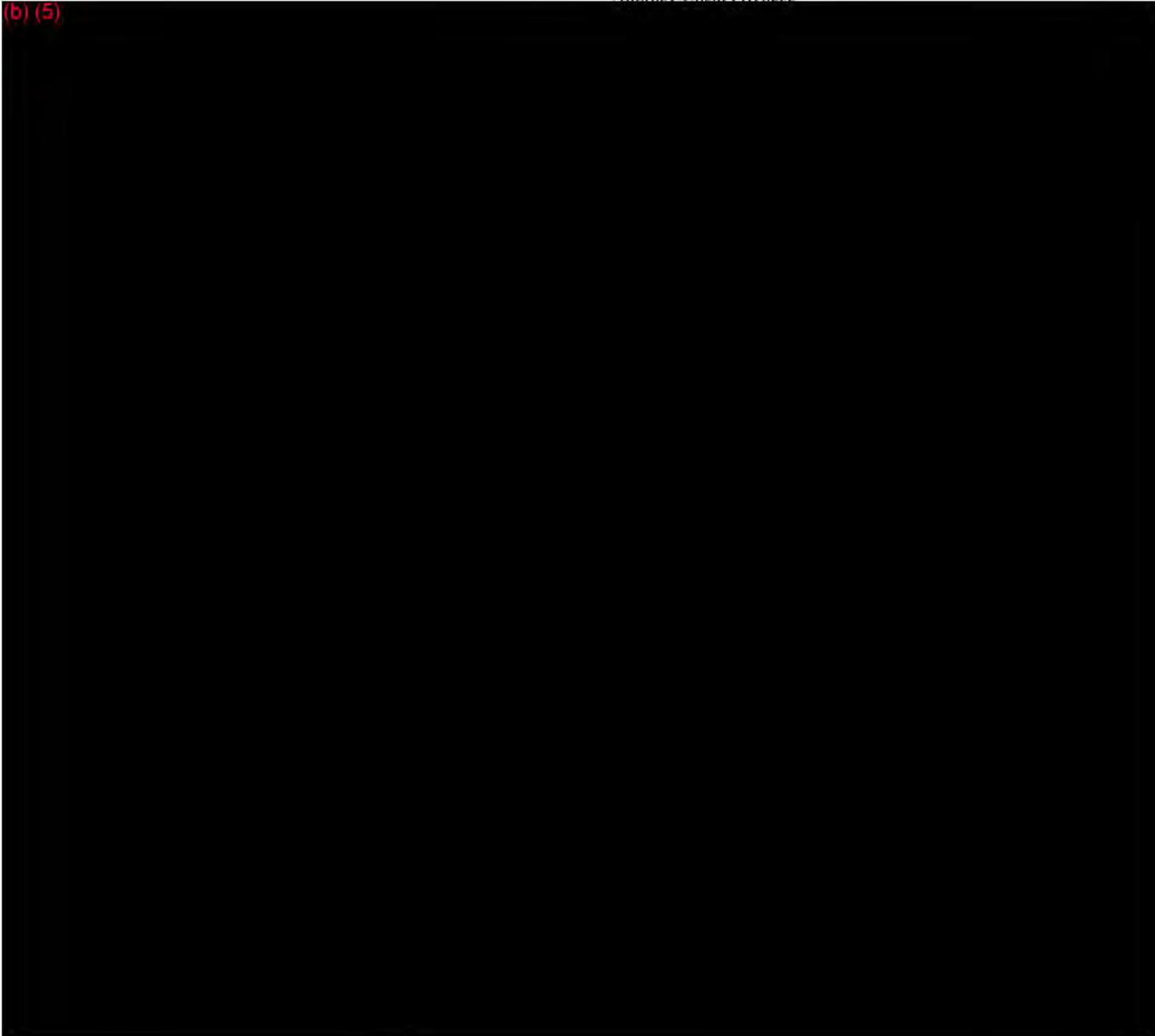


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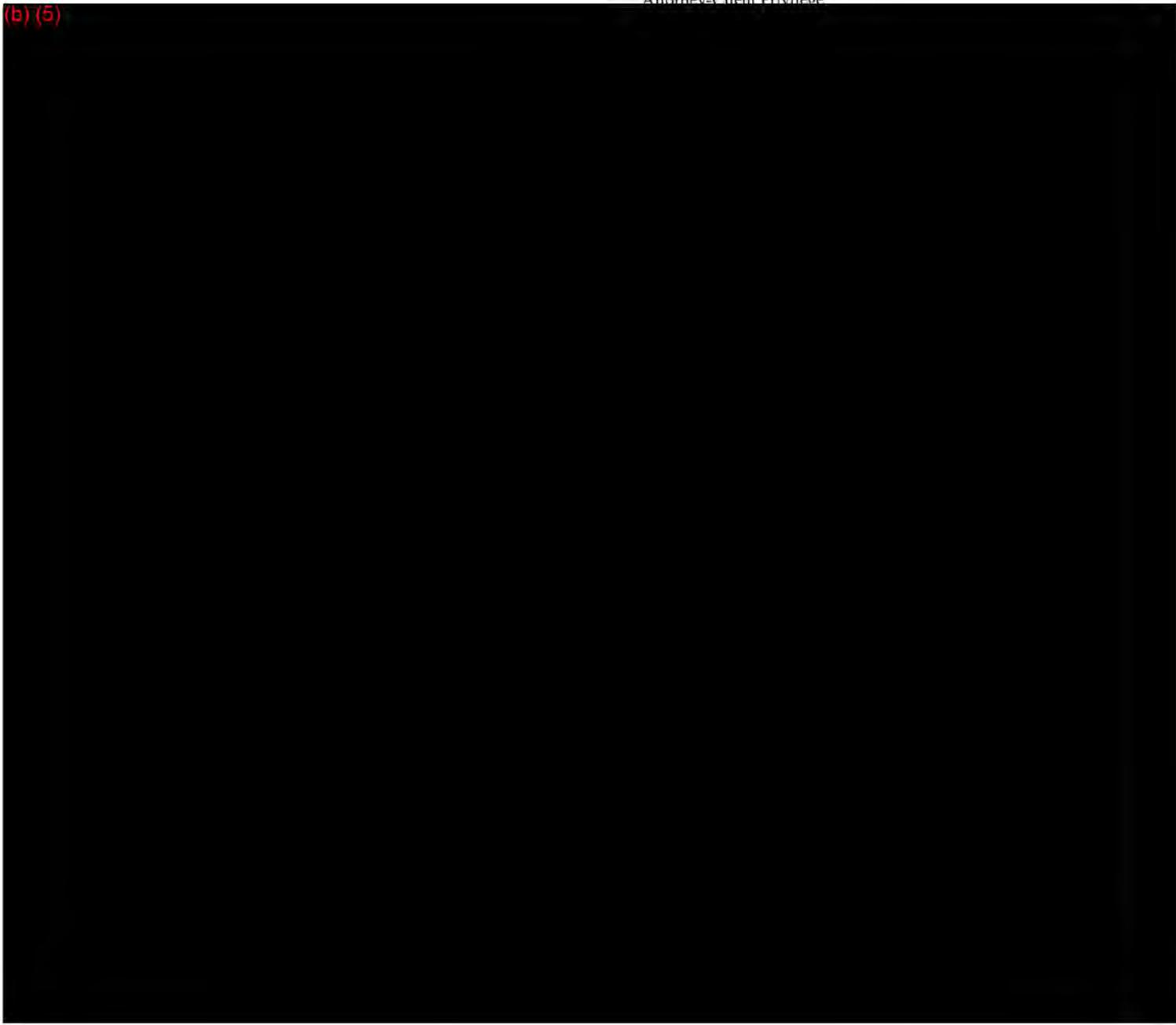


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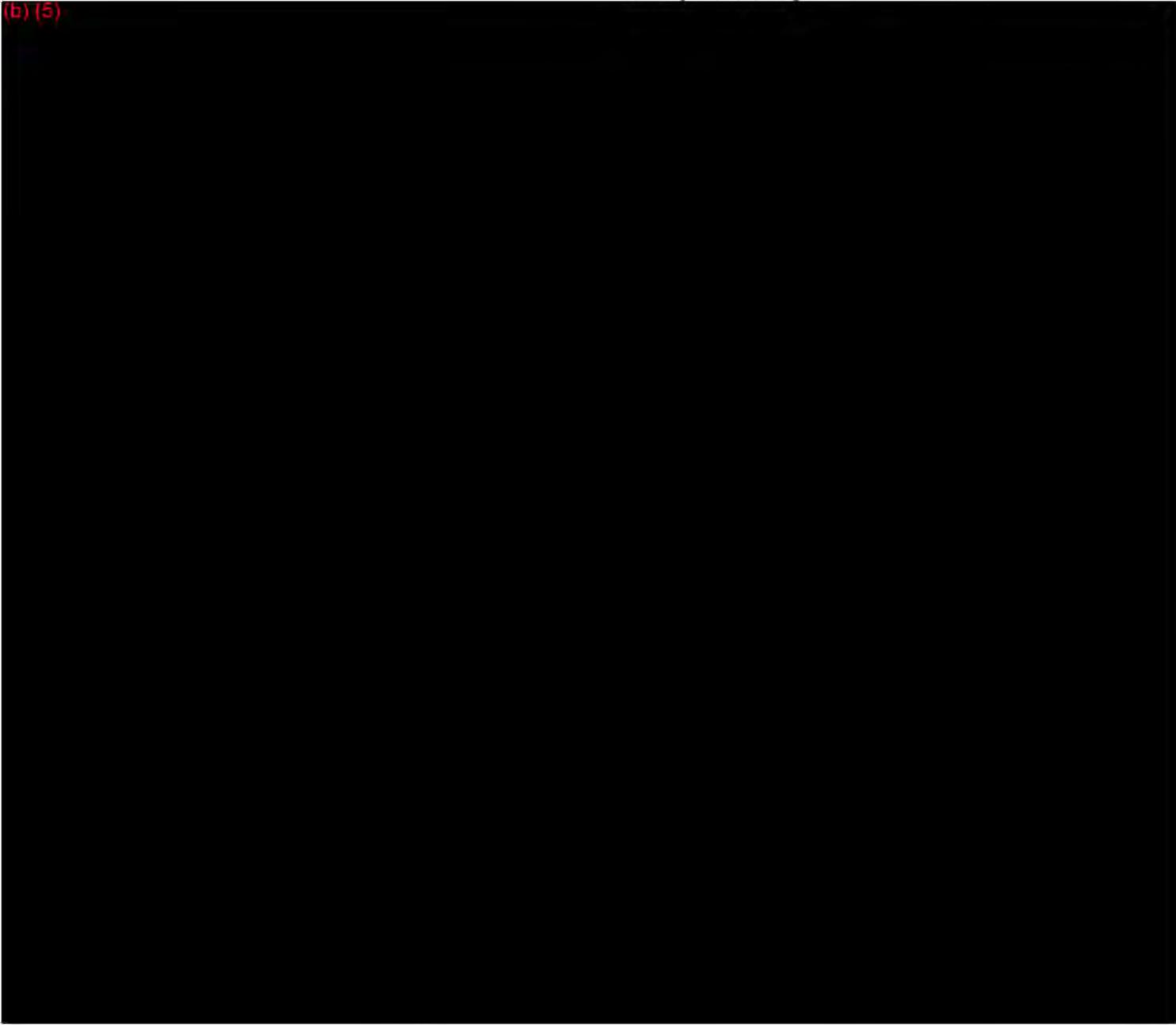
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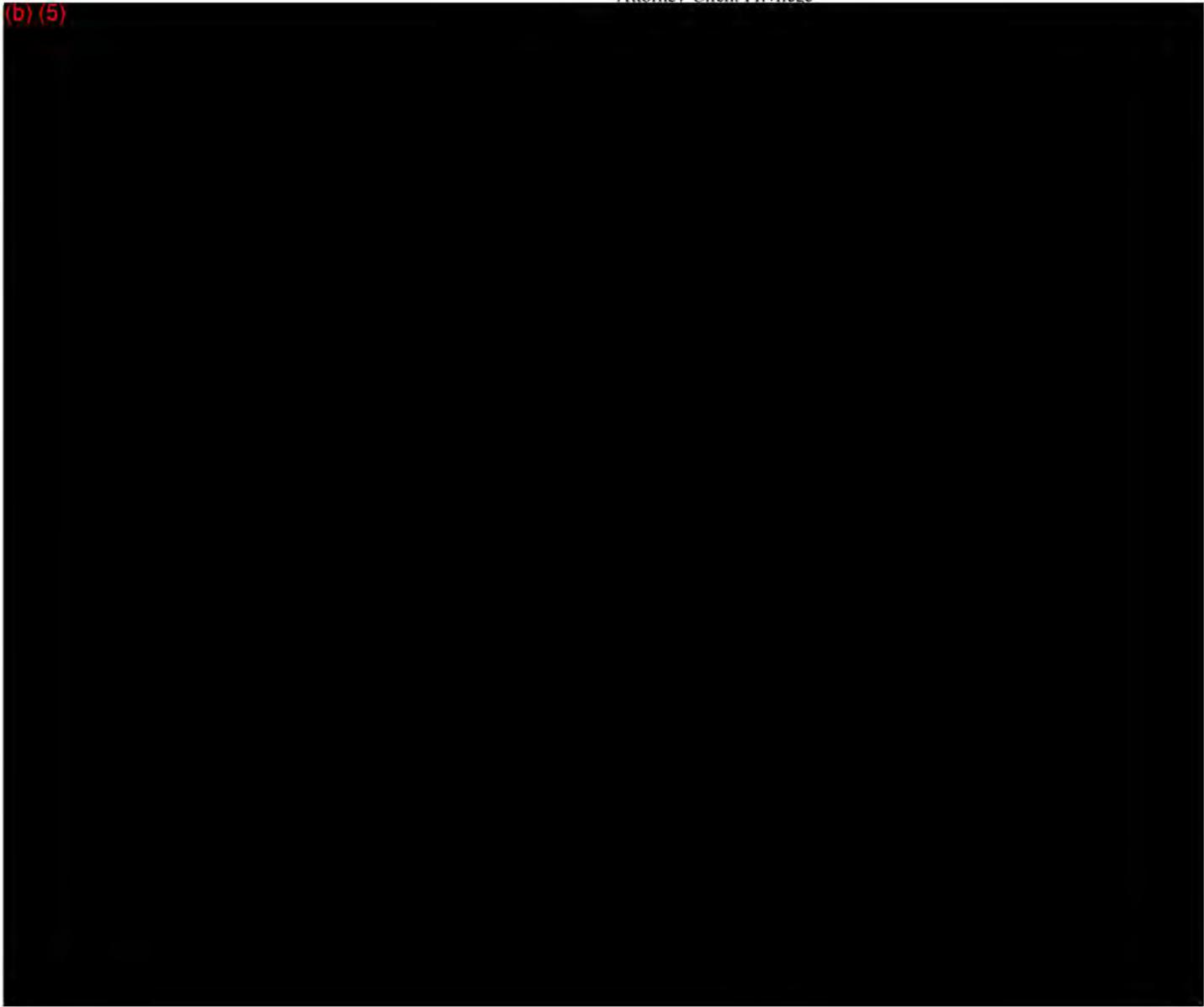


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From: [Quinn, Kathleen](#)
To: [Conover, Katie](#); [Califf, Robert](#)
Cc: [Kraus, Tom](#); [Dickinson, Elizabeth \(FDA\)](#); [Sharp, Jeremy](#)
Subject: Final Report
Date: Friday, September 23, 2016 2:34:33 PM
Attachments: [2016 eteplirsen coverage report-DMD.doc](#)
[DMD social media report 9_23.doc](#)
[image001.png](#)

All-

Attached you will find one (lengthy) report containing both stakeholder and media coverage and a second (due to formatting) on social media coverage. Please let me know if you have any questions or need anything more.

KKQ

From: Conover, Katie
Sent: Wednesday, September 21, 2016 3:42 PM
To: Califf, Robert
Cc: Kraus, Tom; Dickinson, Elizabeth (FDA); Quinn, Kathleen; Sharp, Jeremy
Subject: Final Report

Hello there –

Following up on our conversation regarding a final monitoring report of Monday's announcement... We are pulling together a very factual coverage report for delivery on Friday, which will allow us to look at trends throughout the week in traditional and social media, as well as among stakeholders.

Let us know if you have questions!

Katie and Kathleen

Katie Conover

Acting Associate Commissioner

Office of External Affairs

U.S. Food and Drug Administration

Tel: 240-402-2402 / Cell: 301-512-9120

priscilla.conover@fda.hhs.gov



**Primary Patient/Advocacy Organizations Coverage Report:
Eteplirsen for Duchenne Muscular Dystrophy Approval
(collected September 19-22, 2016)**

National Center for Health Research (NCHR):

- o NCHR President Diana Zuckerman issued a statement on NCHR's website: "[Statement of Dr Diana Zuckerman, President of the National Center for Health Research – FDA's Approval of Eteplirsen for Duchenne's Muscular Dystrophy.](#)" Key quotes excerpted below:
 - o "The internal documents released by the FDA today show that the FDA scientists in charge of reviewing the drug concluded that it should not be approved. They expressed concern that Dr. Janet Woodcock had decided FDA should approve the drug before she looked at the scientific evidence that the FDA had requested. Those scientists then asked FDA Commissioner Califf to reverse Dr. Woodcock's decision, but he denied that request."
 - o "This approval is an inevitable result of the FDA's recent slide toward faster approvals based on less and less scientific evidence."
 - o "This was a test for the new FDA Commissioner. I can't think of any other prescription drug approved on the basis of such a tiny number of patients and without a control group. The scientists agreed there was no clear evidence that the patients are benefitting from the drug. As such, the decision sets a dangerous precedent. The FDA made that approval decision based on a very small increase in the protein dystrophin, instead of basing it on health measures such as the boys' ability to walk."
 - o "This approval is an inevitable result of the FDA's recent slide toward faster approvals based on less and less scientific evidence."

- o NCHR posted *Washington Post* article on their website “[FDA grants accelerated approval to controversial muscular dystrophy drug](#),” which quotes Diana Zuckerman, NCHR President, as saying “If this drug can be approved under those conditions, is there any drug that FDA won’t approve?” said Diana Zuckerman, president of the National Center for Health Research, a nonprofit research organization. “This drug was based on the strong lobbying of patients and the company, and time will tell whether it will really help these boys or not, and that has always been the question.”

Parent Project Muscular Dystrophy (PPMD):

- o PPMD issued press release: “[PPMD Applauds FDA for Landmark Approval of First-Ever Disease-Modifying Drug to Treat Duchenne Muscular Dystrophy--Organization Will Continue to Support Patient Access and Drive Policies and Projects That Support Development and Approval of More Therapies](#),” which includes quote from PPMD President: “PPMD is thrilled that FDA has granted an Accelerated Approval to Exondys 51, a therapy with the potential to treat 13% of people living with Duchenne, marking the first-ever U.S. approval of a drug to treat this disease,” said PPMD Founding President and CEO Pat Furlong.”
- o PPMD’s President, Pat Furlong, issued blog [FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy](#). Excerpted quotes below:

§ “Today is a historic day for the entire Duchenne community. It is a first step. But a huge step forward. Exondys 51 could potentially help 13% of the Duchenne population. We know that it will take a combination of therapies to fully halt the progression of the disease. There are still many people with Duchenne who won’t benefit directly from Exondys 51. But, what everyone in this community will benefit from is today’s first Duchenne approval from the FDA. Today, progress has been made that we believe opens the door for the dozens of therapies moving through the clinical trial process. Therapies that will help other mutations, other exons. Therapies that will experiment with new technologies. Therapies that will benefit all people with Duchenne.”

§ “With today’s accelerated approval comes questions, many of which we are already exploring and working to get you answers. In fact, for the last couple of

weeks PPMD has been working with the team at Sarepta to schedule a webinar in the event of an approval that would dive deeper into what an accelerated approval means, labeling of Exondys 51, and what steps are being taken towards patient access and reimbursement. We hope to share the time and date of this webinar with you later this week.”

- o PPMD linked to [FDA Press Release](#) (click “Learn More”).

National Organization for Rare Disorders (NORD):

- o NORD issued press release “[FDA Approves Eteplirsen to Treat Duchenne Muscular Dystrophy](#),” which includes link to FDA press release.

CureDuchenne:

- o CureDuchenne issued press release “[CureDuchenne Celebrates FDA Approval of First Drug for Duchenne Muscular Dystrophy](#),” which quotes Debra Miller, Founder and CEO of CureDuchenne: “The first FDA-approved treatment for Duchenne is a landmark in our fight against this disease. It provides hope for all Duchenne families. Eteplirsen is a huge step forward in turning Duchenne muscular dystrophy from a fatal disease into a more manageable condition,” said Debra Miller, Founder and CEO of CureDuchenne. “Boys on eteplirsen have experienced improvements in quality of life that are amazing for a progressive disease that has remained without an approved drug for so long.”

Muscular Dystrophy Association (MDA):

- o MDA issued press release (via PR Newswire): “[MDA Celebrates FDA Accelerated Approval of Eteplirsen for Treatment of Duchenne Muscular Dystrophy--Approval expected to hasten development of treatments for DMD and related diseases](#),” which includes quote from MDA President and CEO, Steven M. Derks--"Today has been a long time in the making," said MDA President and CEO Steven M. Derks. "This is the

outcome MDA dreamed of 25 years ago when it was the first to invest in the breakthrough research that led to development of eteplirsen. Throughout this process we have seen the undeniable strength of our community to rally behind MDA's commitment to find treatments for our families. This is an important victory, and we are honored to stand shoulder-to-shoulder with everyone who has fought to make this day a reality."

- o MDA published a video (also on YouTube): "[Eteplirsen is Granted Accelerated Approval in US](#)," hosted by Lou Kunkel, Ph.D. Professor of Pediatrics and Genetics, Harvard Medical School, Initial fellowship from MDA led to his discovery of dystrophin gene; highlight key researchers in field in support of approval.

- o MDA published blog "[Eteplirsen Granted Approval for DMD: Turning Promise into Progress](#)," which includes quote from MDA President and CEO Steven M. Derks (mentioned above) and also a quote from Grace Pavlath, MDA senior vice president & scientific program director, stating "Approval of eteplirsen is not only a big win for the Duchenne community, but also the other rare diseases in MDA's program."... "Seeing this success will entice other companies to work on these diseases, which is going to lead to an expansion in the number of therapeutic options in the pipeline."

CureSMA:

- o CureSMA President Kenneth Hobby quoted in *Xconomy* press release "[After New Data, FDA Bucks Advisory Panel, Approves Sarepta's Duchenne Drug](#)." Mr. Hobby stated that "Whatever [the FDA does] there is going to set a precedent for other orphan therapeutics coming through," Hobby says. "It's going to have to be the benchmark for other diseases, like SMA."

Jett Foundation:

- o Jett Foundation issued statement (via PRNewswire) "[Jett Foundation Celebrates Major Milestone in Fight Against Duchenne Muscular Dystrophy](#)," which quotes Christine McSherry, Founder Jett Foundation: "The FDA approval of a therapy that treats

Duchenne is an event I once never imagined I would witness in Jett's lifetime," McSherry said. "Not only will eteplirsen's approval change the way every mom and dad reacts when they hear their child's diagnosis, it gives hope to an entire generation of children that they too may have the opportunity to live a fuller and more normal life, a life where they can be just like their peers for a little while longer. However, the weeks, months and years of unnecessary and burdensome regulatory barriers that eteplirsen faced came at a massive, and unacceptable, human cost to the Duchenne patient community."

- o Jett Foundation posted "thank you" letter on website, "[Jett Foundation's Response to the Duchenne Community on the Accelerated Approval of Eteplirsen](#)," which linked to [accelerated approval letter sent to Sarepta](#).

Key Patient Advocacy Reactions in Media

National Center for Health Research (NCHR):

- o NCHR President Diana Zuckerman quoted in *Washington Post* article "[FDA grants accelerated approval to controversial muscular dystrophy drug](#)": "If this drug can be approved under those conditions, is there any drug that FDA won't approve?" said Diana Zuckerman, president of the National Center for Health Research, a nonprofit research organization. "This drug was based on the strong lobbying of patients and the company, and time will tell whether it will really help these boys or not, and that has always been the question."
- o NCHR President Diana Zuckerman quoted in *STAT News Article* "[Tough as nails? Storm swirls around FDA drug cop who approved controversial drug](#)": "...it's not enough for the FDA to conclude that the Duchenne muscular dystrophy drug is safe. If it doesn't work, why should patients and insurers pay an estimated \$300,000 a year for it? "The bigger risk is not the safety of this particular drug," Zuckerman said. "The bigger risk for this drug is that the patients will end up not being helped, and in some cases, a family will go broke paying for a drug that doesn't work. And other families will feel terrible because they can't afford it."

- o NCHR President Diana Zuckerman quoted in *TheVillageSunTimes* article “[FDA Grants Accelerated Approval To Sarepta' Drug For Duchenne Muscular Dystrophy](#)”: “It sets a risky precedent if the FDA is going to start approving drugs that aren't compared to anything.”

Parent Project Muscular Dystrophy (PPMD):

- o Pat Furlong, President of PPMD, quoted in *iNewsToday* article, “[FDA Approves First Drug for Duchenne Muscular Dystrophy](#)” A new drug for the treatment of a rare and fatal muscle wasting disease, developed by West Australian researchers, has been approved by the US Food and Drug Administration. This acknowledges that the patient voice is important.”
- o Pat Furlong quoted in *MagSeriesUSA* article, “[FDA grants accelerated approval to Exondys 51 for Duchenne muscular dystrophy](#)”: “Pat Furlong, a patient advocate who lost two sons to the disease, called the announcement 'an extraordinary win'.”

CureDuchenne:

- o Debra Miller, President and CEO of CureDuchenne, quoted in *Forbes* article “[Sarepta Wins FDA Nod For Embattled DMD Drug -- But With A Catch](#)”: “The DMD community rejoiced in the hours following the approval. “The first FDA-approved treatment for Duchenne is a landmark in our fight against this disease. It provides hope for all Duchenne families. ...Boys on eteplirsen have experienced improvements in quality of life that are amazing for a progressive disease that has remained without an approved drug for so long.”
- o Debra Miller, President and CEO, CureDuchenne, quoted in *Pink Sheet* “[Eteplirsen Review Offers Lessons For FDA, Advocacy Groups, Industry](#)”: “in an interview that while she was not sure what impact the patient voice or public pressure had, she hopes the deciding factor in FDA's approval decision was a deep look at the patient population, recognizing that there are variables that need to be considered and the importance of looking at actual patients and how they are doing.”
- o Cure Duchenne press release featured in *Rare Disease Report*, “[CureDuchenne Applauds the FDA Following Eteplirsen Approval](#).”

- Cure Duchenne, Fight DMD, and Charley’s Fund, quoted in *Forbes* article “[Now That FDA Has Approved Muscular Dystrophy Drug Against Advisors' Recommendation, What's Next?](#)”

- Jenn McNary of Jett Foundation quoted in *NBC News* article “[FDA Approves Controversial Muscular Dystrophy Drug](#)”: "I can hardly breathe," Jenn McNary, mother of two boys with muscular dystrophy in Saxtons River, Vermont, said by email. "This is what success feels like. I can't wait to hug the boys."

- PPMD’s Pat Furlong and MDA’s Valerie Cwik, Exec VP and Chief Medical and Science Office, and Public Citizen’s Health Research Group’s Director Michael Carome were quoted in CNN article, “[First drug approved to treat rare form of muscular dystrophy](#)”:
 - o Pat Furlong, president and CEO of the advocacy group Parent Project Muscular Dystrophy, said the FDA made the right call in approving the drug. "This acknowledges that the patient voice is important."
 - o "It's a huge step forward," said Dr. Valerie Cwik, executive vice president and chief medical and scientific officer at the Muscular Dystrophy Association, which advocates on behalf of patients and their families. "It's a really, really big day for the Duchenne community."
 - o Overruling the advisory committee shows "a disturbing disregard for the agency's legal standards for approving new drugs," said Michael Carome, director of Public Citizen's Health Research Group, a nonprofit that studies drug safety. "In particular, such action eviscerates the agency's long-standing requirement that there be substantial evidence of effectiveness for new drugs — even drugs for serious rare diseases — before they are marketed."

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Media Coverage Report:

Eteplirsen for Duchenne Muscular Dystrophy

September 19-22

Drug Approval September 19, 2016

This document provides a sampling of the media from the September 19, 2016 approval of eteplirsen, manufactured by Sarepta. The drug is the first to be approved for Duchenne Muscular Dystrophy, which affects about 3,500 boys and men in the U.S.

The news was covered by more than 50 outlets across coverage from top-tier outlets, trade press, and local TV affiliates. Initial coverage primarily focused on the drug approval with general statements about the agency over-ruling its medical staffers and the independent advisory committee that met earlier this year and voted against approving the drug. Reporters referred to the drug approval “controversial” and “long awaited” and quoted from the press release specifying that the clinical benefit of the drug “has not been established.” Articles explained that the drug remains on the market conditionally and its long term approval depends on a follow-up clinical trial comparing the approved dose of the drug with a higher dose of the drug. Details of the clinical trial used to approve the drug were described with an emphasis on the small number of patients included and the lack of meaningful results. The articles briefly described the accelerated approval pathway process and quoted Janet Woodcock in describing the approval as exercising the agency’s “ability to apply flexibility to address challenges” seen with rare life-threatening diseases. Articles also touched on Congressional and public pressure asserted onto the agency.

Later in the day and in following days, news stories focused more on the internal disagreement within FDA based on information in the summary review documents that FDA posted describing the decisional memo, scientific appeal, scientific dispute process review and the Commissioner’s decision. Reporters quoted extensively from the memos written by Luciana Borio and Ellis Unger and explored several areas as a result, including the issue of FDA approval standards and potential precedent, the role and impact of the patient voice, Dr. Woodcock’s role in the review process, and Dr. Farkas’ departure, among others. Among the areas, several reporters noted the section in Borio’s memo that cited Woodcock’s testimony to the review board that Sarepta “needed to be capitalized” and commenting on the drug’s stock. Additionally, several articles noted that Dr. Califf focused on a procedural decision rather than taking a position on the science.

Diana Zuckerman, president of the National Center for Health Research, was quoted in a number of articles as opposing the approval, saying that the FDA “set a dangerous precedent” and

comparing it to the FDA’s recent approval of Addyi (flibanserin) for female sexual dysfunction. Many articles also quoted those who praised eteplirsen’s approval including Duchenne patient advocacy organizations and the parents of children with DMD. They said they had a “champion” in Woodcock. The New York Times called it a “vivid example of the growing power that patients and their advocates wield over the federal government’s evaluation of drugs.” Several articles also quoted external positions on the issue of the FDA’s approval standard and potential precedent of the action.

Several articles described Sarepta’s announcement of the cost of the drug, \$300,000 a year annually, and what that would mean for the company’s financial future. A handful of articles discussed the priority review voucher that Sarepta would be receiving. Matt Herper from Forbes described the priority review voucher as “a coupon forcing the FDA to speed up review of a drug that’s not innovative. The last such voucher netted \$330 million in an auction.”

In addition, two editorials in the Wall Street Journal and the Boston Globe featured the approval of eteplirsen, which are included in the clips below.

Sampling of coverage:

1. **Forbes**, “*Now That FDA Has Approved Muscular Dystrophy Drug Against Advisors’ Recommendation, What’s Next?*” [View Online](#) [See Full Text](#)
2. **Endpoints**, “*Senior FDA officials warned that approving \$300,000 Duchenne drug will lower agency standards*” [View Online](#) [See Full Text](#)
3. **STAT**, “*Behind the Sarepta drug approval was intense FDA bickering*” [View Online](#) [See Full Text](#)
4. **Bloomberg**, “*Sarepta Approval Hints at a Lighter-Touch FDA*” [View Online](#) [See Full Text](#)
5. **Forbes**, “*Sarepta Wins FDA Nod For Embattled DMD Drug -- But With A Catch*” [View Online](#) [See Full Text](#)
6. **MDA Release**, “*MDA Celebrates FDA Accelerated Approval of Eteplirsen for Treatment of Duchenne Muscular Dystrophy*” [View Online](#) [See Full Text](#)
7. **Inside Health Policy**, “*FDA Goes Against Advisory Committee, Approves Duchenne Drug*” [View Online](#) [See Full Text](#)

8. Med Page Today, "*Eteplirsen OK'd for Muscular Dystrophy*" [View Online](#) [See Full Text](#)
9. NBC News, "*FDA Approves Controversial Muscular Dystrophy Drug*" [View Online](#) [See Full Text](#)
10. Fierce Biotech, "*Sarepta skyrockets on long-awaited DMD approval from FDA*" [View Online](#) [See Full Text](#)
11. BioPharma Dive, "*Sarepta skyrockets as FDA approves DMD drug*" [View Online](#) [See Full Text](#)
12. RAPS, "*Sarepta Wins Controversial FDA Approval for First DMD Drug*" [View Online](#) [See Full Text](#)
13. The Washington Post, "*FDA grants accelerated approval to controversial muscular dystrophy drug*" [View Online](#) [See Full Text](#)
14. Tribune Live, "*FDA approves drug Exondys 51 to treat Duchenne muscular dystrophy*" [View Online](#) [See Full Text](#)
15. Politico, "*FDA approves muscular dystrophy drug pushed by lawmakers*" [View Online](#) [See Full Text](#)
16. WSJ, "*FDA Approves Sarepta's Muscular Dystrophy Drug*" [View Online](#) [See Full Text](#)
17. Reuters, "*Bowing to pressure, FDA approves Sarepta's Duchenne drug*" [View Online](#) [See Full Text](#)
18. Bloomberg, "*Sarepta Stock Rises to Highest Since 2013 as Drug Approved*" [View Online](#) [See Full Text](#)
19. CNBC, "*Sarepta shares leap 90% after FDA approves drug*" [View Online](#) [See Full Text](#)
20. Business Insider, "*Biotech stock explodes 73% after the FDA approves the first drug to treat a rare muscle disorder*" [View Online](#) [See Full Text](#)
21. Street Insider, "*FDA Approves Sarepta Therapeutics' (SRPT) Eteplirsen*" [View Online](#) [See Full Text](#)
22. STAT, "*FDA approves Sarepta's controversial drug for Duchenne muscular dystrophy*" [View Online](#) [See Full Text](#)

23. Boston Globe, “Sarepta is now one of the hottest stars in Kendall Square” [View Online](#)
[See Full Text](#)
 24. Politico, “FDA scientists worry director bowed to political, financial pressures in controversial drug approval” [See Full Text](#)
 25. Forbes, “Approving A Muscular Dystrophy Drug Ignites A Civil War At The FDA”
[View Online](#) [See Full Text](#)
 26. NY Times, “F.D.A. Approves Muscular Dystrophy Drug That Patients Lobbied For”
[View Online](#) [See Full Text](#)
 27. USA Today, “FDA approves first drug to treat rare form of muscular dystrophy”
[View Online](#) [See Full Text](#)
 28. Boston Globe, “Drug’s approval brings hope, and tough questions” [View Online](#) [See Full Text](#)
 29. The Wall Street Journal, “The Boys Who Beat the FDA” [View Online](#) [See Full Text](#)
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Now That FDA Has Approved Muscular Dystrophy Drug Against Advisors' Recommendation, What's Next? [TOP](#)

Rita Rubin, Forbes

The Twittersverse was abuzz Monday over the news that the Food and Drug Administration had approved the first drug that could possibly change the course of Duchenne muscular dystrophy, even though an FDA advisory committee had recommended against it.

“This is the day the Duchenne community has been waiting for,” tweeted [Cure Duchenne](#), an advocacy group.

“Thx to everyone that (sic) made this happen,” tweeted [Fight DMD](#), another advocacy group.

“Majorly HUGE historic moment!!!,” tweeted [Charley’s Fund](#), yet another such group.

Exondys 51, the brand name of the drug eteplirsen, is far from a cure for the universally fatal disease, abbreviated DMD. The FDA [approved it](#) only for boys (DMD rarely affects girls) with the most common type of DMD, seen in just about 13% of patients. And the agency granted approval only on the condition that manufacturer Sarepta Therapeutics of Cambridge, Mass., conduct a trial demonstrating eteplirsen actually improves patients’ muscle function, a conclusion that parents of boys who’ve received the drug as part of a research trial have already reached.

“We are grateful to the many patients and investigators who participated in Exondys 51’s clinical studies,” Dr. Edward Kaye, Sarepta’s interim CEO and chief medical officer, said in a [prepared statement](#). “Exondys 51 represents the culmination of many years of work across our entire organization and the Duchenne community to address a critical unmet need by bringing this novel medicine to patients.”

Sarepta is expected to discuss the cost of eteplirsen, administered as a weekly injection, at a conference call beginning at 4 p.m. Eastern time.

Not surprisingly, Exondys 51 will be very expensive. During the conference call, company officials said they expect the net annual cost of therapy to be \$300,000, which works out to approximately \$6,000 a week. They said that takes into account several factors: the weight-based dosing on the drug’s label; the typical expected age and weight of a patient over time, based on the clinical trial experience; the natural history of the disease and the expectation that boys in the real world will be diagnosed earlier and start therapy at a younger age than those in the clinical trial. A 2-milliliter vial will cost \$1,600, while a 10-milliliter vial will cost \$8,000.

I’ve heard that \$300,000-a-year figure before. Vertex Pharmaceuticals’ drug Kalydeco, which the [FDA approved](#) in January 2012 to treat the 4% of cystic fibrosis (CF) patients who have a particular mutation, reportedly costs at least that much, and critics have [questioned](#) the basis for such a high price. Like Exondys 51, Kalydeco is the first drug approved to treat the underlying cause of a fatal genetic disease, as opposed to just its symptoms. And also like Exondys 51, Kalydeco is supposed to be taken by patients for the rest of their lives. There is a big difference between the two drugs, however. In two clinical trials involving 213 patients, treatment with Kalydeco resulted in “significant and sustained improvement in lung function” compared to a placebo pill, according to the FDA. Clinical trial data for Exondys 51, on the other hand, have so far provided only a hint that the drug might improve muscle function in boys with DMD.

And yet, DMD patients and parents packed an 1 1/2-hour [meeting](#) April 25 to urge the FDA’s Peripheral and Central Nervous System Drugs Advisory Committee to recommend that the agency approve eteplirsen. Despite the advocates’ often heart-wrenching testimony, though, only three of the 13 panelists voted “yes” to the FDA’s question of whether Sarepta’s one study of 12 boys provided “substantial evidence that eteplirsen is effective for the treatment of DMD.” Seven voted “no,” and three abstained.

Although the FDA usually follows the advice of its advisory committees, the agency decided to approve eteplirsen via its accelerated approval pathway, which, as the agency describes it, “provides for the approval of drugs that treat serious or life-threatening diseases and generally provide a meaningful advantage over existing treatments.” As was the case with Sarepta and eteplirsen, manufacturers don’t necessarily have to demonstrate that drugs eligible for this program benefit patients, only that they have a favorable effect on a “surrogate endpoint.”

“Surrogate endpoints are used when the clinical outcomes might take a very long time to study or in cases where the clinical benefit of improving the surrogate endpoint, such as controlling blood pressure, is well understood,” according to an [explanation](#) the FDA posted in July.

DMD is associated with errors in the gene that carries the blueprint for dystrophin, one of a group of proteins that strengthen and protect muscle fibers. The FDA concluded that Sarepta’s data demonstrated an increase in dystrophin production that is “reasonably likely” to translate into improved muscle function in patients. Still, Sarepta needs to prove it, or else, the FDA says, it might withdraw approval.

That wouldn’t happen for at least five years or so, according to [letter](#) Dr. Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research, sent Monday to Shamim Ruff, senior vice president of regulatory affairs and quality at Sarepta. In the letter, Woodcock laid out the requirements for several postmarket trials of eteplirsen in patients and in rodents.

None of the patients in the postmarket clinical trial designed will be assigned to receive a placebo. As evidenced by testimony by dozens of patients and parents at the advisory committee meeting last spring, the DMD community is already convinced that eteplirsen works, so it likely would have been difficult to recruit volunteers for a study in which they might get a placebo and not the real drug.

Instead of comparing eteplirsen to a dummy injection, Sarepta is supposed to compare the approved weekly dosage of the drug to a “significantly higher” dose, such as one seven times greater. The company has four years in which to complete the trial and another six months after that to submit its final report.

Two rodent studies are supposed to assess whether eteplirsen increases the risk of cancer.

Some observers speculate that FDA decided to approve eteplirsen because the drug’s main critic, Dr. Ronald Farkas, left the agency this month. At the April advisory committee meeting, Farkas questioned the accuracy of the measurements of dystrophin in muscle biopsies from the 12 boys who’d received the drug. And, he noted at the meeting, Sarepta had measured dystrophin in most of the boys before they started treatment, so it wasn’t clear that the levels seen afterward were an effect of the drug. Plus, as the FDA noted in its approval letter to Sarepta, the boys’ dystrophin levels weren’t correlated to how well they could walk.

###

Senior FDA officials warned that approving \$300,000 Duchenne drug will lower agency standards [TOP](#)

John Carroll, Endpoints

In the end, Sarepta did many things wrong when it came to developing a new drug for Duchenne muscular dystrophy. But it got one very important part right. The biotech, with the support of a legion of advocates in the patient community, won over Janet Woodcock to their side early on.

The powerful CDER director pushed for an approval even in the face of a heated debate inside the FDA, as senior officials weighed in in opposition to her stand. The acting chief scientist at the agency, Luciana Borio, argued that an approval would lower the agency's standards and encourage other developers to pursue the same kind of lobbying campaigns employed at Sarepta. And she accused Sarepta of acting irresponsibly by knowingly pushing "misleading" information about the drug. Ellis Unger, director of the office of drug evaluation, scoffed at the data Sarepta offered, calling the drug a "scientifically elegant placebo."

But FDA Commissioner Robert Califf refused to overrule Woodcock's decision to OK eteplirsen, despite sharing some of the major objections raised by officials who opposed putting this drug on the market at Sarepta's price of \$300,000 a year.

[Califf's summary review](#) of the extraordinary showdown over eteplirsen point to problems that would have easily killed practically any other marketing application. But with the center director taking a passionate stand in favor of the drug, the commissioner says he decided that he would defer to Woodcock in view of his lack of technical expertise in the matter and a sufficient record of evidence to warrant its move into the market.

Both Unger and Borio opposed Woodcock's decision to grant an accelerated approval for eteplirsen, according to the September 16 memo from Califf as well as their own memos. Califf set out to determine if the FDA was significantly lowering the bar for an approval, but ultimately decided that Woodcock was pursuing a well established track record for being willing to take tough, ethical stands inside the agency, rather than buckling to a lobbying campaign.

According to Borio, who says that Woodcock was leaning toward an OK in 2014, an approval of this flawed application may set a dangerous precedent that will encourage desperate patients to mount a furious assault in favor of other drug approvals. Her position, outlined in the memo:

Granting accelerated approval here on the basis of the data submitted could make matters worse for patients with no existing meaningful therapies — both by discouraging others from developing effective therapies for DMD and by encouraging other developers to seek approval for serious conditions before they have invested the time and research necessary to establish whether a product is likely to confer clinical benefit. If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients.

Unger, who warned that the safety profile of eteplirsen is not yet known and that patients taking the drug could die from treatment, was scathing in his assessment of the therapy.

By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk. I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs – if not to patients, to society.

And the review documents included Woodcock’s extraordinary argument that Sarepta needed an accelerated approval to help its stock price, so it could fund additional work.

She opined that Sarepta in particular “needed to be capitalized.” She noted that the sponsor’s stock went down after the AC meeting and went up after FDA sent the June 3, 2016 letter. Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would “lapse into a position of” self-treatment.

Significant deficiencies in the eteplirsen program, says Califf, include a consensus that “the poor quality of many of the biopsies and the failure of the sponsor to implement a high-quality procedure for assay validation” made it impossible to consider much of the data in the application. They all agreed that the drug produced levels of dystrophin that were “small compared with expectations at the outset of trials in humans.”

Sarepta “touted” a study that used unreliable measures of the assay, leading the company to overstate protein expression in follow-up biopsies. That study was debunked by FDA experts, Califf says, and should be corrected or retracted. Borio was much more critical of Sarepta. Her memo states:

I would be remiss if I did not note that the sponsor has exhibited serious irresponsibility by playing a role in publishing and promoting selective data during the development of this product. Not only was there a misleading published article with respect to the results of Study 201/202147 –which has never been retracted—but Sarepta also issued a press release relying on the misleading article and its findings.

There is a distinct possibility, the FDA feels, that increasing the dose would provide enough dystrophin expression, the key biomarker for this disease, to make it work as hoped. But it’s only been tested in animals, never in humans — at least not yet.

And if Sarepta had done what the FDA was telling the company to do, says Califf, then they would probably already have enough compelling data in hand to make a decision based on the merits of the drug.

Woodcock actually decided in favor of an approval on May 4, after taking an “extensive and early involvement” on the drug, which raised concerns about interference with “the integrity of scientific reviews” at lower levels in the FDA. Woodcock completed her final memorandum before Unger had had a chance to complete his own.

Once she determined her position, Woodcock never budged. Ultimately, that was enough. Whatever else happens, Woodcock was proved right about Sarepta’s stock price. Shares are up 86% in mid-afternoon trading. In a call with analysts Monday afternoon, company officials say they will file for an early approval in Europe before the end of this year.

###

Behind the Sarepta drug approval was intense FDA bickering [TOP](#)

Ed Silverman, STAT

he run-up to Monday’s [approval of a Sarepta Therapeutics drug](#) to treat Duchenne muscular dystrophy was marked by unusual bickering inside the Food and Drug Administration, where debate over a key scientific question morphed into a formal dispute, and the head of the drug review division was accused of being too intensely involved in the process for evaluating the medicine.

Ultimately, the decision to greenlight the drug fell to the FDA Commissioner, Dr. Robert Califf. In a 13-page [memo](#) last Friday, he deferred to Dr. Janet Woodcock, the controversial head of the drug review division, who pushed hard to approve the Sarepta medication but clashed with other FDA officials along the way.

“The science is not in dispute beyond the usual types of disagreement that occur when experts review clinical evidence from different perspectives,” he wrote. “It is clear that Dr. Woodcock’s decision utilized the flexibility afforded under the relevant statutory provisions, including consideration of the life-threatening decisions of the disease and the lack of alternative treatments.”

Califf was compelled to chronicle his decision in response to a formal dispute that was filed by Dr. Ellis Unger, who reports to Woodcock, and disagreed with her decision to approve the drug and the way she went about advocating for approval. The Califf memo was one of several internal FDA documents involving the dispute and the fate of the Sarepta drug that were released Monday.

There is frequently disagreement among FDA staff over the extent to which clinical trial data should support the approval of a new medicine. But the intensity of the dispute surrounding the Sarepta drug underscores the stakes that were involved in this episode. Beyond this one drug, the discord among FDA officials illuminated a [wider debate](#) about the pressures the agency faces to endorse medicines from an increasingly aggressive patient population.

In his dispute, Unger identified four deviations from the usual typical decision-making process. He claimed Woodcock was involved in the early stages of the review; she had “extensive involvement” in planning and participating in an expert panel meeting last spring; she made an initial decision last May to approve the drug before the FDA review team completed a draft review memo; and she issued a final decision memo before Unger finalized his own memo.

Unger was not alone. In an [Aug. 8 memo](#) to Califf, Dr. Luciana Borio, the FDA acting chief scientist who convened the board that reviewed the dispute, wrote that “we fear that those actions could have chilled scientific debate within (the FDA Center for Drug Evaluation and Review) and reduced the level of participation by the review team during the final stages of the decision-making process.”

“Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Dr. Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages,” Borio wrote. And she noted that at least two staffers were leaving or were about to leave in response to the decision-making process “and the pressures exerted by outside forces.”

Indeed, the dispute centered primarily on a disagreement over whether the Sarepta drug, known as eteplirsen, would produce enough of a protein called dystrophin to generate a clinically meaningful benefit. Boys suffering from Duchenne have a mutation and lack the protein. Sarepta argued that a very small clinical trial demonstrated the drug helped enough boys based on various measures, including a six-minute walking test.

According to the memos, Woodcock acknowledged some issues with trial data submitted by the company to win approval, but she disagreed with Unger and other FDA staff about the extent to which boys treated with the medicine would experience a meaningful clinical benefit.

Their disagreement, however, also reflected a more fundamental debate over the stance the agency should take toward the Sarepta drug. Until now, the FDA had not approved a drug to treat Duchenne, prompting parents and some lawmakers to argue for [accelerated approval](#), a process that relies on surrogate endpoints instead of actual medical benefits to endorse a drug.

This has been a highly charged issue and has transformed the Sarepta drug into a litmus test for agency approval of new medicines, notably for diseases with unmet medical needs. Seen through

that prism, Unger maintained that approving the drug would be detrimental to the FDA approval process on a long-term basis.

“By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk,” he wrote in a July 18 dispute report. “I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs — if not to patients, to society.”

He added that approval “would send the signal that political pressure and even intimidation — not science — guide FDA decisions... A standard this low would undercut FDA’s ability to ensure that drugs that are approved are effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.”

According to Borio, both Unger and the members of the FDA review team told the dispute review board that Woodcock “seemed focused on the external pressures, from both patient advocacy groups and Congress, and that she frequently talked about the effects of a decision regarding eteplirsen in terms of overarching policy.”

Ultimately, the review board found that “Woodcock’s extensive, early involvement in the review process troubling. Indeed, her involvement here appears to have upended the typical review and decision-making process. Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages.”

###

Sarepta Approval Hints at a Lighter-Touch FDA [TOP](#)

Max Nisen, Bloomberg

One of the longest and most contentious biotech sagas in recent memory is finally over(ish).

The FDA on Monday granted accelerated approval to Sarepta's drug Exondys, which treats the rare muscle-wasting disease Duchenne Muscular Dystrophy (DMD). The drug could be available to patients before the end of the year. The approval is conditional and can be reversed if a more-rigorous new trial shows the drug doesn't work.

But for now the FDA's decision ends a years-long conflict between scientists and patients. The drug's doubters (yes, [including me](#)) had warned there was limited and flawed evidence the medicine worked. The drug's boosters cited a huge unmet need for such a treatment and enough evidence of its effectiveness to justify approving the drug for patients with no options.

Sarepta's One-Day Price Gain on Exondys Approval

86% (So Far)

The decision could have a major impact beyond DMD patients and Sarepta shareholders, who enjoyed an 86-percent price gain on the news. The market seems to take the drug's approval as evidence the FDA will err on the side of approval in such cases; the Nasdaq Biotech Index rose as much as 1 percent on Monday. Sarepta's fellow DMD drugmaker PTC Therapeutics rose 24 percent.

The approval suggests new medicines might get to market more quickly and on thinner trial results than investors have come to expect. It also bolsters faith that the kind of patient lobbying behind Exondys may be able to shift bureaucratic mountains.

Sarepta shares have been a roller coaster as sentiment about its DMD drug alternately soared and cratered repeatedly over the past year

In 2012 Congress gave the FDA extra tools [and a mandate](#) to get new drugs for deadly diseases to patients more quickly. The agency appears to be taking that seriously.

Scientists have not been impressed with Exondys. They produced a negative review of the drug in February that cratered Sarepta's shares and left many doubting the drug's chances. An FDA panel of experts [voted against](#) letting the drug hit the market. The FDA isn't bound to follow the vote of these panels, but usually does.

But Janet Woodcock, the head of the FDA's Center for Drug Evaluation and Research, overruled the scientists' objections and pushed for the drug's approval, eventually backed by FDA commissioner of food and drugs Robert Califf.

Depending on your point of view, this is either a tragic blow to scientific and statistical rigor, or a victory for patients over myopic bureaucrats with unrealistic expectations.

We'll have to see if this was a one-off -- a unique combination of dire patient need and overwhelming political pressure backing a drug of uncertain effectiveness -- or if there will be many more accelerated approvals based on less-than-ideal studies.

At the very least, Califf's support of Woodcock over the scientists seems like a meaningful hint of where the FDA is leaning under his leadership, which began in February.

There's no doubt the approval is a lifesaver for Sarepta. The company can now sell what will almost certainly be a very expensive drug. And if it follows the playbook other companies have, it is likely to sell more of its now-pricier shares to raise more cash. If the drug had been rejected, then the company's shares likely would have plummeted, and it may have had trouble raising

money to continue developing its drug -- something Woodcock worried about openly, [according to an FDA document](#).

At its second-quarter spending rate, Sarepta's cash reserves may have run out early next year without replenishment.

Without an approval for its DMD drug, Sarepta may have run into a cash crunch in the near future

Either way, a previously uncertain door to the market has been opened a crack, and a lot of biotechs are undoubtedly hoping they can squeeze through.

###

Sarepta Wins FDA Nod For Embattled DMD Drug -- But With A Catch [TOP](#)

Arlene Weintraub, Forbes

Just five days after its main nemesis at the FDA departed the agency, Sarepta Therapeutics has won a long-sought-after approval for eteplirsen, its drug to treat Duchenne muscular dystrophy (DMD). It's been a long, strange trip for the Cambridge, Mass.-based company, which has held strong support from the DMD community but endured everything from a freak snowstorm that delayed an FDA advisory committee review to the aforementioned critic, Ron Farkas, who seemed to be doing everything in his power to prevent eteplirsen from getting approved.

But despite the good news—which prompted Sarepta's shares to nearly double to \$54.30 on Monday—[the approval isn't entirely straightforward](#) for the drug, which will carry the trade name Exondys 51. In a statement, the FDA said it is requiring Sarepta to perform another clinical trial to prove the drug does what the company claims—namely that it improves motor function in DMD patients who have a particular mutation in a gene that produces dystrophin, a protein key in proper muscle function.

Exondys 51 was cleared for marketing under the FDA's accelerated approval process, which generally requires that companies provide additional proof of efficacy. If Sarepta's drug fails the trial, the FDA can withdraw the approval, the agency says. Sarepta has not yet responded to the FDA's approval notice.

In a [statement](#), Edward Kaye, M.D., Sarepta's interim chief executive officer and chief medical officer, said the approval “represents the culmination of many years of work across our entire organization and the Duchenne community to address a critical unmet need by bringing this novel medicine to patients.” The company did not provide details about additional trials, nor did it disclose pricing of the new drug, though it was planning a conference call for later in the afternoon, when those questions were bound to be asked.

Doubts that Sarepta would ever reach this milestone emerged in late January, when the FDA released briefing documents ahead of a scheduled advisory panel meeting on Exondys 51. The documents [blasted the company for basing its approval application on a trial with only 12 patients](#). To measure the drug's effect, the investigators performed a six-minute walk test on the trial participants, but the FDA advisors—led by Farkas—said the test revealed “no nominally significant difference” between patients taking a higher dose, a lower dose or a placebo.

Sarepta responded by releasing updated data showing that 10 of the patients who were taking the drug were still walking 216 weeks after their entry into the trial. Dozens of DMD patients, parents and physicians were set to travel to D.C. for the meeting when a massive snowstorm hit, delaying the gathering until late April.

After a day filled with emotional testimonies from patients and parents, the panel voted 7-6 against approval. The FDA doesn't have to follow the advice of its advisory panels, but it usually does. When it missed the scheduled May 26 deadline for approving Exondys 51, speculation that the drug was doomed soared. In June, the FDA asked for a bit more data on the small trial that had already been submitted, but after that, there was little news indicating what the future of the drug might be.

But then the news of Farkas' departure emerged on September 14, sending Sarepta's shares up 27% in a day.

Exondys 51 is based on a technology platform called “exon skipping,” which enables the production of a synthesized form of dystrophin that's designed to function like the original muscle-preserving protein.

The DMD community rejoiced in the hours following the approval. “The first FDA-approved treatment for Duchenne is a landmark in our fight against this disease. It provides hope for all Duchenne families,” said Debra Miller, founder and CEO of CureDuchenne, which provided early funding for the eteplirsen trials. “Boys on eteplirsen have experienced improvements in quality of life that are amazing for a progressive disease that has remained without an approved drug for so long.”

The next challenge for Sarepta will be completing a second trial of the drug that will satisfy the FDA. It won't be easy: DMD is a rare disease that affects 20,000 patients per year, most of them boys. And only about 13% of DMD patients have the mutation that Exondys 51 targets, according to Sarepta.

###

MDA Celebrates FDA Accelerated Approval of Eteplirsen for Treatment of Duchenne Muscular Dystrophy [TOP](#)

MDA

The Muscular Dystrophy Association today celebrated news of the U.S. Food and Drug Administration's [decision to grant accelerated approval for eteplirsen](#), the first disease-modifying drug to treat the most common childhood form of muscular dystrophy.

Accelerated approval of the drug, which will treat a subset of those living with Duchenne muscular dystrophy, is an important step forward in the development of therapies for neuromuscular diseases and marks an historic achievement for the entire DMD community.

Eteplirsen is Granted Accelerated Approval. See Full Story Here

"Today has been a long time in the making," said MDA President and CEO Steven M. Derks. "This is the outcome MDA dreamed of 25 years ago when it was the first to invest in the breakthrough research that led to development of eteplirsen. Throughout this process we have seen the undeniable strength of our community to rally behind MDA's commitment to find treatments for our families. This is an important victory, and we are honored to stand shoulder-to-shoulder with everyone who has fought to make this day a reality."

Approval to market eteplirsen was given to pharmaceutical company Sarepta Therapeutics. Eteplirsen will be the first disease-modifying drug on the market in the United States to treat DMD, and approximately 13 percent of DMD patients potentially may be eligible for treatment. Under the terms of the FDA's accelerated approval, Sarepta must conduct a clinical trial of eteplirsen to confirm clinical benefit.

The news comes following an historic turnout at the FDA's advisory committee hearing in April, which brought a record-breaking number of families, members of the medical community and supporters to Washington to testify on behalf of the DMD community in favor of treatment options for Duchenne.

MDA Executive Vice President and Chief Medical and Scientific Officer Valerie A. Cwik, M.D., provided compelling [oral testimony](#) at the hearing, in addition to other MDA appeals to the FDA, urging the agency to consider the totality of the data and utilize maximum regulatory flexibility in its review of the drug.

"For our families, therapy options can't come soon enough," Cwik said. "MDA is eager for this treatment to get into the hands of those whom it can help, forever grateful to our partners, supporters, and, most importantly, our families, who all helped turn hope into a treatment that can change the course of Duchenne. We fully expect this accelerated approval will be an

inspiration and a catalyst to more innovation and follow-on funding for drug development across the board."

MDA has invested more than \$200 million in DMD research and has been central to the development of the exon skipping approach from the beginning in the 1990s, having funded foundational work upon which the strategy was built as well as extensive research into the strategy since that time. MDA supported the early development of eteplirsen via funding to Steve Wilton, then at the University of Western Australia in Perth, who pioneered the exon skipping technique that allows eteplirsen to work.

This year, MDA already has committed more than \$17 million to research, as it takes a unique big-picture perspective across the spectrum of muscle-debilitating diseases that take away everyday abilities such as walking, talking and hugging. With the help of its supporters, MDA plans to double its research spend targeting treatments and clinical trials by the year 2020.

[WATCH: Eteplirsen is Granted Accelerated Approval in U.S.](#)

For more information and updates on eteplirsen and exon skipping, [click here](#).

###

FDA Goes Against Advisory Committee, Approves Duchenne Drug [TOP](#)

Erin Durkin, Inside Health Policy

FDA granted accelerated approval to a controversial Duchenne muscular dystrophy drug Monday (Sept. 19) after an emotional hearing in April where an advisory panel voted against approval of the drug causing a backlash from an audience of DMD patients, parents, doctors and advocates. Agency officials had left the door open in April to approve the drug based on testimony from patients and their parents, leading some to view the product as a test for how much flexibility FDA has to weigh patient testimony regarding medical need.

In a memo to FDA staff Monday, drug center chief Janet Woodcock said Sarepta Therapeutics submitted additional data after the advisory committee meeting.

The agency is requiring Sarepta Therapeutics to conduct a clinical trial to confirm the drug's clinical benefit. The study will assess whether Exondys 51 improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. "If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug," FDA said in a press release.

Woodcock said in April that it would be appropriate to consider patient testimony. "I think that's fair," Woodcock said. "The standard is adequate and well-controlled trials. That's in the statute. We are instructed in flexibility on how to interpret that based on medical need."

At the time, Billy Dunn, director of the Division of Neurology Product in FDA's drug center, also signaled the agency would seriously consider the patients' testimony.

“The emotion and passion in the room during the discussion is clear, and I mentioned at the beginning of the day that we listen and we listen carefully. While I recognize there's great concern about the discussion and the results of the votes, I assure we listened very carefully to some very meaningful testimony today. We've observed the panel be highly influenced by that testimony. I assure that we will take the information we learned here today under very serious consideration as we adjourn this meeting,” said Dunn.

FDA had delayed its decision on the drug in May, according to the drug maker Sarepta Therapeutics, while lawmakers questioned the agency over how it ran the advisory committee that voted against approval of the product.

GOP Sens. Ron Johnson (WI) and Dan Coats (IN) wrote to FDA that they were concerned with how the agency posed questions to the advisory committee, alleging the questions were framed in a way that made it difficult for members to vote in favor of the application being approved.

###

Eteplirsen OK'd for Muscular Dystrophy [TOP](#)

Kristina Fiore, Medpage Today

After taking several additional months to make its decision, the FDA has overruled its advisory committee and approved eteplirsen (Exondys 51) to treat Duchenne muscular dystrophy (DMD), [the agency announced](#).

The drug will be specifically indicated for patients who have a confirmed mutation of the dystrophin gene, which will make them more likely to respond to exon 51 skipping, the mechanism by which the drug works, the agency said. About 13% of the DMD population has this mutation.

The approval follows a grim picture painted by an agency advisory committee last April, which decided the data provided by drugmaker Sarepta Therapeutics didn't provide substantial evidence that the drug actually increased dystrophin levels.

But in a letter that accompanied the FDA approval press release, CDER director Janet Woodcock, MD, said the company has since provided additional data that provide "substantial evidence of dystrophin production, although the amount of dystrophin produced was only a small fraction of the normal level."

"The approval of Exondys 51 reflects FDA's ability to apply flexibility to address challenges we often see with rare, life-threatening diseases – while remaining within our statutory framework,"

Woodcock said in that letter. "In this case, flexibility is warranted because of the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a life-limiting disease of children."

"These factors, combined with the dystrophin production data – and the drug's low risk profile – led the Agency to approve the drug under the accelerated approval pathway," she said.

The FDA faced intense public pressure to approve eteplirsen, as heard in desperate pleas from patients, parents, and advocates during an unusually long public [comment period at the April advisory committee meeting](#). The patient representative on the panel broke down in tears over concerns that the data were inadequate to support the magnitude of benefit reported by many patients, and one wheelchair-bound patient cursed loudly and ran his chair into several empty chairs before rolling out of the room.

Tensions were especially high, as another exon-skipping drug, drisapersen (Kyndrisa) was [rejected by the agency last January](#). Drugmaker BioMarin subsequently shuttered the program in May.

Eteplirsen was supposed to be reviewed in November 2015, at the same time as drisapersen, but that [hearing was delayed](#). Following the rescheduled April hearing, the agency extended the PDUFA date of eteplirsen indefinitely.

The drug was approved under the FDA's accelerated approval program, which allows for an approval decision to be made based solely on efficacy data from a surrogate endpoint -- in this case, dystrophin production -- that is "reasonably likely to predict a clinical benefit to patients," the agency said.

FDA will require Sarepta to conduct a clinical trial to test whether the drug can actually meet a clinical endpoint of preserving motor function.

###

FDA Approves Controversial Muscular Dystrophy Drug [TOP](#)

Maggie Fox, NBC

The Food and Drug Administration approved a controversial muscular dystrophy drug Monday, ignoring the advice of its advisers and delighting families and advocates who had campaigned hard for its approval.

The company that makes the drug, called eteplirsen, says it will charge \$300,000 a year for treatment.

The drug is designed for children with a genetic mutation that causes some cases of Duchenne muscular dystrophy, the most common type of [muscular dystrophy](#) — a degenerative disease that causes muscles to break down because cells produce faulty versions of a protein called dystrophin, or none at all.

Studies of the drug cannot show whether it actually helped patients, but the FDA says the company can study it more and report back.

The disease affects more boys than girls and symptoms usually show up when kids are between 3 and 5. Right now there's no treatment, and patients almost always die young.

FDA's panel of expert advisers recommended against the drug's approval after an emotional, packed meeting in which children with muscular dystrophy pleaded for the drug's approval and doctors debated whether the drug helped everyone.

"I can hardly breathe," Jenn McNary, mother of two boys with muscular dystrophy in Saxtons River, Vermont, said by email.

"This is what success feels like. I can't wait to hug the boys."

And several FDA scientists fought hard to prevent its approval.

"FDA should never mislead patients by granting even accelerated approval to products that are not shown to offer the prospect of meaningful benefit to patients."

"By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk," Dr. Ellis Unger, acting director of FDA's Office of New Drugs, wrote in [a memo released online](#).

"Eteplirsen's risks are certain, whereas its efficacy is not," he added, noting that the drug will be delivered by a semi-permanent catheter that could make kids vulnerable to infections.

"FDA should never mislead patients by granting even accelerated approval to products that are not shown to offer the prospect of meaningful benefit to patients under the appropriate regulatory and scientific standard," said Dr. Luciana Borio, acting deputy chief scientist at the FDA.

The agency gave itself extra time to decide. But expectations about approval soared last week when one key FDA critic of the drug, Ronald Farkas, [left the agency last week](#).

Farkas has been the target of social media attacks by advocates for the drug who have accused him of holding up approval.

It's an unusual decision and the FDA says it's not clear whether the drug has actually helped any of the patients who have tried it.

"Patients with a particular type of Duchenne muscular dystrophy will now have access to an approved treatment for this rare and devastating disease."

"A clinical benefit of Exondys 51, including improved motor function, has not been established. In making this decision, the FDA considered the potential risks associated with the drug, the life-threatening and debilitating nature of the disease for these children and the lack of available therapy," the agency said.

The FDA says it's hoping for more information about how and whether eteplirsen works. It's designed to help only about 13 percent of Duchenne muscular dystrophy patients.

"Patients with a particular type of Duchenne muscular dystrophy will now have access to an approved treatment for this rare and devastating disease," said Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research.

"In rare diseases, new drug development is especially challenging due to the small numbers of people affected by each disease and the lack of medical understanding of many disorders," Woodcock added in a statement.

"Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval."

FDA Commissioner Dr. Robert Califf backed Woodcock over the objections of others at the FDA.

"I do not find that she deviated from her responsibilities as Center Director, nor do I find that she succumbed to pressure from the patient community, the public, the press or others," he wrote in the FDA memo, which detailed the arguments for and against approval.

"This is what success feels like."

"Exondys 51 was approved under the accelerated approval pathway, which provides for the approval of drugs that treat serious or life-threatening diseases and generally provide a meaningful advantage over existing treatments," the FDA said.

The drug's maker, Sarepta Therapeutics, will be required to gather more information on patients who try it.

###

Sarepta skyrockets on long-awaited DMD approval from FDA [TOP](#)

Stacy Lawrence, Fierce Biotech

Sarepta Therapeutics (\$SRPT) was up by about 75% in early trading on news that its Duchenne muscular dystrophy (DMD) treatment Exondys 51 (eteplirsen) has been approved by the U.S. Food and Drug Administration. The controversial drug faced multiple delays with the agency along the way due to efficacy concerns.

Shares quickly fell back to a gain of around 50% only to surge again as investors digested the terms of the [FDA's accelerated approval](#), which requires a confirmatory clinical trial to demonstrate efficacy. The agency is requiring an additional two-year randomized, controlled trial of eteplirsen; it's slated to be dose-ranging from the approved dose of 30 mg/kg weekly up to a much higher dosage of 30 mg/kg daily.

The injection is approved specifically for DMD patients with a mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13% of the population.

The confirmatory trial will be in that specific population with a primary endpoint based on the North Star Ambulatory Assessment, with a secondary endpoint of dystrophin levels as a percent of normal as determined by a tissue biopsy.

The FDA concluded that the existing data based on skeletal muscle biopsy demonstrated an increase in dystrophin production; it then said this is "reasonably likely to predict clinical benefit in some patients." But it added decisively that any clinical benefit, including improved motor function, has not been established.

"Patients with a particular type of Duchenne muscular dystrophy will now have access to an approved treatment for this rare and devastating disease," said Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, in a statement. "In rare diseases, new drug development is especially challenging due to the small numbers of people affected by each disease and the lack of medical understanding of many disorders."

She added, "Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval."

Sarepta is slated to submit a draft protocol for the upcoming trial in October with a final protocol submission due in April 2017. The trial is slated to complete in November 2020 with final data due by May 2021, according to the [approval letter](#).

The rare genetic disorder DMD is characterized by progressive muscle deterioration and weakness; it occurs in one out of about every 3,600 male infants worldwide. DMD patients are typically wheelchair-bound by their early teens and often die in their 20s or 30s.

The accelerated approval process was beset by [myriad delays](#) throughout this year as the FDA weighed how to proceed with this potential treatment that lacked compelling efficacy data, but seems to offer some potential in this terrible disease that previously had no approved treatment.

###

Sarepta skyrockets as FDA approves DMD drug [TOP](#)

Ned Pagliarulo and Lisa LaMotta, BioPharma Dive

Dive Brief:

- Sarepta Therapeutics on Monday [won](#) conditional approval from the Food and Drug Administration for its Duchenne muscular dystrophy (DMD) treatment, after a months-long delay left the company and DMD patients in regulatory limbo.
- Sarepta will be required to carry out a clinical trial to confirm the drug's clinical benefit, and the Food and Drug Administration made clear a failure to verify efficacy could lead the regulator to withdraw approval for the treatment.
- Shares in Sarepta skyrocketed by over 90% at one point Monday morning, as the FDA's decision resolved a long-standing question of whether the company would be sent back to the drawing board. The drug, now known as Exondys 51 (eteplirsen), is the first approved treatment for DMD.

Dive Insight:

The FDA has signed off on approval of Sarepta's DMD drug after several years of back and forth with the community. While the drug did pass muster for a conditional approval, the decision is a contentious one. Regulators had been originally expected to make a decision on the drug in May.

Advocates for the community have been particularly outspoken and criticized the FDA for passing over drugs from several other companies, including PTC Therapeutics and BioMarin. An advisory committee to the FDA voted against approval of eteplirsen earlier this year, raising further ire from the community.

The regulatory agency and its experts have long claimed that while the unmet need is very high in this case, the drug candidates in development have not shown strong efficacy.

DMD is a genetic disease that affects young boys, many of which die before reaching adulthood. The disease is characterized by muscle wasting and most of these boys lose the ability to walk and eventually succumb to respiratory failure. Advocacy groups — composed largely of parents of the children — have been major supporters of DMD developers and clinical trials seeking to test disease-modifying drugs.

Several companies have pulled out of the space after the FDA made clear there was no path forward for approval for their drugs. BioMarin was forced to announced this spring that it would end pursuit of approval of its drug, Kyndrisa (drisapersen).

###

Sarepta Wins Controversial FDA Approval for First DMD Drug [TOP](#)

Zachary Brennan, RAPS

The US Food and Drug Administration (FDA) on Monday approved Sarepta Therapeutics' first drug to treat patients with Duchenne muscular dystrophy (DMD), a rare genetic disorder that causes progressive muscle deterioration and weakness in young children.

The approval is highly controversial after a [FDA advisory committee voted against approval](#) in April as the outside experts said there was not substantial evidence that the drug is effective in providing clinical benefit, which is the standard for traditional approval. Before that vote and afterwards, the DMD patient community protested vigorously.

DMD, occurring in about one out of every 3,600 male infants worldwide, is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. The first symptoms are usually seen between the ages of three and five, and worsen over time.

The agency said that following the hearing, Sarepta submitted additional data “showing substantial evidence of dystrophin production, although the amount of dystrophin produced was only a small fraction of the normal level.”

The injection, known as Exondys 51 (eteplirsen), is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, who constitute approximately 13% of the population with DMD. Sarepta said late Monday that the average cost per patient will be \$300,000.

Ultimately, the new injection, known as Exondys 51, was approved under FDA's accelerated approval program, reserved for drugs to treat serious or life-threatening diseases, and where there is a lack of available therapy.

“Based on the data submitted by the applicant, the Agency has concluded that there is a statistically significant increase in dystrophin production in indicated patients who are exposed to the drug that meets this requirement,” FDA said Monday.

Disagreement

That approval followed a contentious scientific disagreement inside of FDA pitting Janet Woodcock, director of the Center for Drug Evaluation and Research (who was in favor of approval) against Ellis Unger, director of the Office of Drug Evaluation.

The fight boiled down to what should be considered a "statistically significant increase in dystrophin, the surrogate endpoint," and, according to Unger, whether "an exceptionally small magnitude" implies clinical benefit, according to the [126-page approval letter](#).

"This decision could be precedent setting with respect to accelerated approval, i.e., where the bar should be set for changes in a pharmacodynamic biomarker that are deemed 'reasonably likely to predict clinical benefit.' Moreover, to my knowledge, this could be the first time a Center Director has overruled a review team (and an advisory committee) on a question of whether effectiveness has been demonstrated," Unger wrote in an email to Woodcock.

In his appeal of Woodcock's decision to override the advisory committee's vote and other reviewers' qualms with the the application, Unger noted that the position of the review team in the Division of Neurology Products, the Office of Biometrics, the Office of Clinical Pharmacology, the Office of Drug Evaluation-I, and the Office of New Drugs "(verbal acknowledgement from Dr. John Jenkins) is that the applicant has not provided evidence that this drug is effective at the dose studied."

However, FDA Commissioner Robert Califf noted in his letter on the dispute that he deferred to Woodcock on the approval decision.

New Trial

Moving forward, FDA said it is requiring Sarepta (company's stock increased in value by more than 80% as of Monday morning and the company also won a rare pediatric priority review voucher as a result of the approval, which it says it will sell) to conduct a clinical trial to show that the drug preserves motor function, with eteplirsen being compared to placebo.

The required study is designed to assess whether Exondys 51 improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. If the trial fails to verify clinical benefit, FDA said it “may initiate proceedings to withdraw approval of the drug.

“In this case, flexibility is warranted because of the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a life-limiting disease of children. These factors, combined with the dystrophin production data – and the drug’s low risk profile – led the Agency to approve the drug under the accelerated approval pathway,” FDA said.

###

FDA grants accelerated approval to controversial muscular dystrophy drug [TOP](#)

Carolyn Y. Johnson, The Washington Post

After months of advocacy and speculation, the Food and Drug Administration today granted accelerated approval to the first treatment for a rare form of muscular dystrophy. The decision pitted the passionate testimony of patients and families against an FDA [advisory committee](#) and internal reviewers who weren't convinced the drug worked.

The approval of Sarepta Therapeutics' drug, eteplirsen, was a huge, emotionally fraught victory for families with Duchenne muscular dystrophy -- one of the most vocal and involved patient communities since the days when HIV patients pushed the agency to approve more drugs. The approval specifies that the clinical benefit of the drug "has not been established" and is contingent on a follow-up clinical trial. The process has been closely watched by parents, patient advocates and biotech investors, and has been seen as an important test case for the effort to integrate the patients' point of view more deeply into the approval process.

"Obviously it's a big relief, and it may have come just in time to help save some of these young boys' lives, which is so important," said Christine McSherry, whose adult son Jett has been taking the drug in a safety study. "But it wasn't timely enough," she added, referring to the months families spent in limbo.

Duchenne muscular dystrophy is a devastating, invariably fatal disease that affects between 9,000 and 12,000 boys in the United States. Boys with the disease grow progressively weaker, becoming reliant on a wheelchair in their teens and dying in their 20s or 30s.

The news was cheered by parents and advocates, including Terri Ellsworth, whose said she was stunned, happy and relieved. Her 15-year-old son, Billy, has been participating in a clinical trial for the drug and hadn't heard the news before he left for school. She planned to visit him at school to surprise him with the good news.

"I did fear that if this didn't get approval, pharmaceuticals would pull out of research, because it's just such a tough, complex disease," Ellsworth said. "I know this drug works, and I know there's still naysayers out there who say it doesn't. I'm still hurt by the people who use the term 'measly and pathetic data' – that's my son."

Sarepta said the average cost for a year of the drug would be \$300,000 per year. The company plans to offer financial assistance to help uninsured or underinsured patients pay for the drug. A research note by Ritu Baral, a managing director at Cowen and Co., estimated peak sales of \$400 million in the U.S.

The agency usually follows the recommendation of its advisers, whose [split vote against approval](#) was met with angry outbursts at the conclusion of a long and contentious meeting in April. The FDA missed its initial deadline to decide on whether to approve the drug and requested more data from the company, fueling a rollercoaster of rumors about whether the drug would ultimately be approved.

“In rare diseases, new drug development is especially challenging due to the small numbers of people affected by each disease and the lack of medical understanding of many disorders. Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval,” Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research said in a statement.

The study supporting approval was a small trial with a dozen boys who carry a gene mutation that occurs in 13 percent of the 9,000 to 12,000 boys in the U.S. with Duchenne. FDA deemed that the trial did not show improvement on a walking test, but did show a measurable increase in dystrophin, the protein that is missing in the disease in some patients. There was significant dispute internally at the FDA over whether that increase was likely to be a predictor of a clinical benefit. [Internal documents](#) released show that, in an unusual move, Woodcock's decision was appealed and the commissioner Robert Califf ultimately sided with Woodcock's decision to grant accelerated approval.

"I find no basis for a view that Dr. Woodcock was unduly influenced by involvement with the patient community or other external pressures, and note that our understanding about how to include patients in the regulatory process is evolving," Califf wrote, in regard to the scientific dispute over whether the drug should be approved. "In addition, serious shortcomings present in the eteplirsen development program should not be allowed to establish a broad precedent for therapeutic development in rare diseases."

But critics of the decision worry that the approval of a drug -- when internal scientists and an external advisory committee have found the evidence unconvincing -- could be a slippery slope.

"If this drug can be approved under those conditions, is there any drug that FDA won't approve?" said Diana Zuckerman, president of the National Center for Health Research, a nonprofit research organization. "This drug was based on the strong lobbying of patients and the company, and time will tell whether it will really help these boys or not, and that has always been the question."

At a meeting in April, the agency walked a difficult high-wire act, visibly struggling to strike the balance between respecting the views of parents and boys who attributed their health to the drugs while also pointing out that the data showed scant evidence of the positive effects reported.

Woodcock attended the entire meeting and made remarks at the beginning warning the advisory committee to beware of the possibility of making what's called a "type 2" error -- the possible harms that could come from not approving a drug that is effective.

"I was about 50-50 as to whether they would approve this or not," said [Louis Kunkel, a Harvard geneticist](#) who is credited with discovering the gene behind Duchenne. "It's a great sign to the Duchenne community that the FDA is willing to listen to them."

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Kunkel, who is an outside consultant to Sarepta, said he believes the FDA did the right thing by putting a condition on the approval that the company undertake another clinical trial.

Kunkel said it was clear that the boys who received eteplirsen were producing some dystrophin, an essential protein involved in muscle function that boys with Duchenne lack.

"It wasn't very much, but it was something," Kunkel said. "[Eteplirsen] has no negative effects. It has no downside. So why not give it to these kids and do further follow up?"

He said Monday's approval "sets the stage" for additional drugs that are coming down the pipe. But he also added that it could be difficult to ask patients to participate in a placebo-controlled trial now that an approved Duchenne drug is on the market. "They're not going to go for that," he said.

Brady Dennis contributed to this report.

###

FDA approves drug Exondys 51 to treat Duchenne muscular dystrophy [TOP](#)

Wes Venteicher, TribLive

The Food and Drug Administration granted accelerated approval Monday for a drug to treat a variant of Duchenne muscular dystrophy, prompting celebration among families affected by the rare disease while raising questions about the regulator's standards of evidence.

Accelerated approval provides a pathway for patients, including 15-year-old Billy Ellsworth of Coraopolis, to get the drug while Massachusetts-based Sarepta Therapeutics continues testing in broader clinical trials.

The agency approved the drug, called Exondys 51, or eteplirsen, after an advisory committee recommended in April against approving it. A majority of committee members said Sarepta had not gathered enough evidence in a 12-person clinical trial to support approval.

Ellsworth is one of the boys in the trial. He testified in favor of the drug at the committee's hearing, and his mother, Terri Ellsworth, has advocated for approval. The family credits weekly doses of eteplirsen with slowing the progress of the disease. Ellsworth learned of the FDA's decision at work Monday morning.

“I'm still in shock. I'm stunned,” she said when reached by phone. “It was the right call as far as I'm concerned.”

The decision will allow boys not in the trial to start getting eteplirsen, she said. It also means that the Ellsworths will have to start paying for the drug, which she expects to cost at least \$300,000 per year. During the clinical trial phase, the family did not have to pay for the treatments. Terri said she hopes the family's insurance will cover the drug.

Duchenne inhibits the body's ability to produce the protein dystrophin, which muscles require to function. Most people with the disease lose the ability to walk by their teenage years.

As it progresses, the disease impedes the function of organs, including the heart, until it kills most people who have it in their 20s or 30s. There are no approved treatments for the disorder.

Eteplirsen appears to help the body produce dystrophin. The boys in the trial started treatment between the ages of 7 and 13, and after five years, 10 of them could still walk, according to a Sarepta-funded study published in 2014. Billy is able to walk today.

The trial had no control group to compare results to, so researchers compared the participants' conditions to those of boys with the disease who received treatment at two European medical centers.

The lack of a control group and other elements of the small study raised doubts among members of the advisory committee at the FDA that the drug was effective. Seven committee members voted against approval, three voted for it, and three abstained.

Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, in an FDA statement released Monday cited the difficulties of gathering high-quality evidence for treatment of the rare disease.

Duchenne primarily affects males, occurring in about one in 3,500 to 6,000 newborn boys around the world, according to the Centers for Disease Control and Prevention.

“In rare diseases, new drug development is especially challenging due to the small numbers of people affected by each disease and the lack of medical understanding of many disorders,”

Woodcock said in the statement. “Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval.”

The agency's decision to approve the drug without more robust evidence could set a precedent, said Dr. Michael Carome, director of the health research group at Washington, D.C.-based policy group Public Citizen.

“Such action eviscerates the agency's long-standing requirement that there be substantial evidence of effectiveness for new drugs — even drugs for serious rare diseases — before they are marketed,” Carome said in a statement.

The FDA is requiring Sarepta to conduct a better trial, and if the company fails to show clinical benefit, the accelerated approval could be withdrawn, according to the agency's statement.

The agency had planned to announce in May whether it would grant approval, but it delayed, requesting more information in June from Sarepta.

Eteplirsen treats the most common form of the disorder, which affects about 13 percent of boys with the disease. Certain genetic mutations related to Duchenne, including the mutation in the most common form of the disease, delete exons, which are involved in dystrophin production. The treatment targets the specific exon affected by the genetic mutation.

###

FDA approves muscular dystrophy drug pushed by lawmakers [TOP](#)

Sarah Karlin-Smith, Politico

FDA granted [accelerated approval](#) to Sarepta's Duchenne muscular dystrophy treatment this morning, following months of political pressure by lawmakers and patient advocates.

FDA's drug center Director Janet Woodcock, with the support of Commissioner Robert Califf, overruled the drug's review team, which had raised concerns about the drug's effectiveness, according to documents posted on FDA's website. Ellis Unger, the director of the Office of Drug Evaluation I and FDA's chairman of the scientific dispute process review board, also recommended against approval.

The agency's green light makes eteplirsen the first drug approved for the rare genetic disease that often causes death in patients' 20s or 30s.

The approval follows a [negative review from a FDA advisory committee](#) meeting for the drug in April, when agency advisers said Sarepta had not provided "substantial evidence" that the drug effectively treats the disease. FDA's own briefing documents issued ahead of the panel indicated the agency also was not convinced the drug warranted approval.

The FDA's accelerated approval means it concluded eteplirsen is reasonably likely to improve patients' lives or longevity. Sarepta will have to conduct an additional clinical trial as a condition of full approval to confirm the drug's clinical benefit. If that fails, FDA can withdraw the drug's approval.

More than 100 members of Congress have pushed FDA to approve the drug, delivering floor speeches and writing op-eds. FDA appropriations bills passed by House and Senate committees in the spring also included report language reminding the agency it has "the tools, authorities and latitude necessary" to approve rare-disease treatments like drugs for Duchenne as fast as possible.

###

FDA Approves Sarepta's Muscular Dystrophy Drug [TOP](#)

Tom Burton, WSJ

The U.S. Food and Drug Administration on Monday gave accelerated approval to the first drug for the crippling disease Duchenne muscular dystrophy, from [Sarepta Therapeutics Inc.](#), after sharp disagreements within the agency.

The circumstances of the approval at the agency were highly unusual, and included sharp internal protests that were ultimately resolved by FDA Commissioner Dr. Robert M. Califf.

An advisory committee to the FDA [in April voted 7-3](#), with 3 abstentions, that the data for the drug weren't enough for agency approval. Specifically, they focused on the fact that the company's hope for approval largely was based on a [single study of 12 patients](#).

Sarepta officials said Monday that the drug's cost would be based on the patient's weight. For the average-size child, the company said, the annual cost would be \$300,000.

On Monday, Sarepta shares surged 74% to \$48.94 after hitting an earlier high of \$56.18, its highest point since March 2002. The stock in April fell as low as \$8 after the FDA panel failed to back the drug, but the price had been rising in recent weeks amid optimism for FDA approval. The gains Monday valued the company at \$2.3 billion.

Duchenne is progressive, severely crippling illness that afflicts male children. It is estimated that it affects about 1 in 3,500 boys world-wide. It destroys muscles and frequently kills patients by the time they are in their 30s.

At the FDA panel hearing, many parents gave often-emotional testimony about how—despite the scientific data—they were convinced that their own children had benefited from taking the drug.

By late May, Sarepta had announced that the FDA [wouldn't make a decision](#) by the deadline and that it would work with the agency in its examination of the data. Before that panel meeting,

FDA staffers had indicated they were “prepared to be flexible with respect to a devastating illness with no treatment options.”

An incident at the advisory committee meeting presaged what became an unusually contentious process within the FDA. At the meeting, Dr. Janet Woodcock, director of the FDA’s center for drugs, signaled a complex decision lay ahead and said the agency had “flexibility and that’s where we should take the views of the community into account.” Several doctors who had heard the evidence expressed skepticism then and since that the FDA decision should be anything other than a strict consideration of the very limited evidence.

The agency’s staffers who had studied that evidence concluded that the small study’s design “did not provide interpretable evidence of benefit.”

Ultimately, Dr. Woodcock, a controversial figure within the FDA whom some prominent critics say tends to lean in industry’s direction, decided to approve the drug. Dr. Ellis Unger, a senior physician in the drug division, objected to her decision and filed a protest that reached Dr. Califf, the commissioner.

Dr. Califf, in a decision dated Friday, wrote that he had reviewed the evidence and that his “decision following this review is to defer to Dr. Woodcock’s judgment and authority” to make the decision to approve the drug. The FDA’s acting chief scientist and chair of an FDA committee that resolves internal disputes, concluded the opposite: Dr. Luciana Borio said, according to a memo from Dr. Califf, that she “does not believe the available data and information support accelerated approval of” the drug, which is called eteplirsen.

The approval also comes a week after the FDA confirmed that Dr. Ronald Farkas, who led the FDA review team that evaluated Sarepta’s data, had left the agency.

The FDA said it wouldn’t make any of its staff available for interviews. The decision prompted different reactions from the medical community.

Michael A Carome, director of the Public Citizen Health Research Group, said, “The decision by Dr. Woodcock to approve eteplirsen, against the strong objections of FDA experts who reviewed the drug and the advice of its advisory committee, represents a disturbing disregard for the agency’s legal standards for approving new drugs. In particular, such action eviscerates the FDA’s longstanding requirement that there be substantial evidence of effectiveness for new drugs—even drugs for serious rare diseases—before they are marketed.”

Steven M. Derks, president of the Muscular Dystrophy Association, said, “This is the outcome MDA dreamed of 25 years ago when it was the first to invest in the breakthrough research that led to development of eteplirsen.”

###

Bowing to pressure, FDA approves Sarepta's Duchenne drug [TOP](#)

Toni Clarke, Reuters

Bowing to pressure from patient advocates, the U.S. Food and Drug Administration on Monday approved a treatment for Duchenne muscular dystrophy even though an outside panel of experts and the agency's own reviewers questioned the drug's efficacy.

The FDA's lead reviewer, Dr. Ronald Farkas, recently quit the agency after issuing a scathing report criticizing the quality of the data presented by Sarepta Therapeutics Inc, developer of the drug Exondys 51, known also as eteplirsen.

Sarepta's stock nearly doubled to \$56.18 on news of the decision.

Farkas's departure highlighted sharp divisions within the agency. He and other scientists were opposed by Dr. Janet Woodcock, the agency's powerful head of pharmaceuticals, who argued for approval, according to a summary of the dispute.

ADVERTISING

In an email to staff on Monday, Woodcock said the approval "reflects FDA's ability to apply flexibility to address challenges we often see with rare, life-threatening diseases - while remaining within our statutory framework."

The drug treats a subset of patients with Duchenne muscular dystrophy, a rare, progressive genetic disorder that hampers muscle movement, eventually killing most sufferers by age 30. The subset includes about 13 percent of all DMD patients, or some 1,300 to 1,900 patients in the United States.

FDA scientists, including Dr. Ellis Unger, director of the drug evaluations division overseeing the product, appealed Woodcock's planned decision to an internal disputes board, according to a publicly available summary of the dispute written by FDA Commissioner Robert Califf on Sept. 16.

The agency's acting chief scientist, Dr. Luciana Borio, also did not believe Sarepta's data supported approval, Califf's summary stated.

Nonetheless, Califf decided to "defer to Dr. Woodcock's judgment and authority to make the decision."

"I find no basis for a view that Dr. Woodcock was unduly influenced by involvement with the patient community or other external pressures," he wrote.

He added, however, that "serious shortcomings present in the eteplirsen development program should not be allowed to establish a broad precedent for therapeutic development in rare diseases."

Simos Simeonidis, an analyst at RBC Capital Markets, described the approval as "one of the most perplexing regulatory decisions in recent history."

The FDA approved Sarepta's drug under its so-called "accelerated" approval pathway in which a product is approved based on data believed to predict a clinical benefit. That benefit must be proven by the company in a subsequent clinical trial.

"It will be years before we find out the outcome of that trial," Simeonidis said, adding that Sarepta "now becomes one of the most attractive mergers and acquisitions targets in biopharma."

PATIENT ADVOCATE PRESSURE

This is the second time in just over a year that the FDA has bowed to patient pressure to approve a drug despite scant scientific evidence showing it worked.

Last August the agency approved Addyi, a pill to boost libido in women with low sexual desire. A coalition of women's groups backed by the manufacturer, Sprout Pharmaceuticals, packed an advisory committee meeting with women who testified to their desperate need for the pill.

Woodcock said at the time that the agency was "committed to supporting the development of safe and effective treatments for female sexual dysfunction." The drug carries a boxed warning saying it can cause fainting and extremely low blood pressure and that it should not be used with alcohol.

Analysts said the approval of Exondys 51 bodes well for similar approvals elsewhere in the world. Tim Lugo, an analyst with William Blair, estimated the drug will generate global peak annual sales of close to \$2 billion.

The FDA also granted Sarepta a rare pediatric disease voucher representing a commitment by the FDA to review a new drug developed by Sarepta within six months rather than the standard 10 months or more.

The voucher can be sold to another company. Michelle Gilson, an analyst at Oppenheimer, estimates the voucher could be worth roughly \$350 million, which could be used to fund the launch of the drug.

BioMarin Pharmaceutical Inc's Kyndrisa, designed to address the same subset of patients as eteplirsen, was rejected by the FDA in January.

###

Sarepta Stock Rises to Highest Since 2013 as Drug Approved [TOP](#)

Anna Edney, Bloomberg

Sarepta Therapeutics Inc. won U.S. approval for its drug to treat Duchenne muscular dystrophy, a victory for young patients with a form of the deadly muscle disease and their parents after a long and disputed regulatory review.

The stock rose 74 percent to \$48.94, the highest closing price since October 2013. The gain gives Cambridge, Massachusetts-based Sarepta a market value of \$2.34 billion, and the positive news from the Food and Drug Administration could make it a much more appetizing -- and expensive -- takeover target.

The drug, which will be sold as Exondys 51, is the first therapy approved for Duchenne muscular dystrophy, or DMD, a genetic disease that mainly affects young boys. It will have a net price of \$300,000 a year, Sarepta said on a conference call Monday. adding that it wasn't sure exactly how many patients would qualify for use of the therapy.

Sarepta Interim CEO Edward Kaye said the price of the drug was "in the middle of the range" for rare disease treatments, which are developed for a small handful of patients. Kaye said the company also factored in its research costs as well as the expense of future drug trials.

"Given the sensitivity to pricing we have tried to be what we think is very reasonable given all of the costs for this," he said on the call.

Approval Process

Following months of uncertainty -- including a rejection by a panel of outside advisers in April and an internal dispute over clearing the treatment for sale -- the FDA decided to approve it under its "accelerated approval" program, which can make drugs available for sale if they show signs they might help patients while more study is conducted.

"Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval," Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, said in a statement. Future trials will run for two years, Sarepta said on the conference call.

Sarepta's stock has oscillated widely over the past year over the fate of experimental treatment, also called eteplirsen. The FDA decision sent shares of other rare-disease drug developers higher, including PTC Therapeutics Inc., up 21 percent, and Amicus Therapeutics Inc., up 5 percent.

Sarepta said in June that the FDA had asked for data from patient biopsies obtained in an ongoing study of the drug that was intended to confirm its benefit after it reached the market, raising hopes that the therapy had a chance of approval. The request was a rare step by the agency, which has given more weight to patient perspectives even when clinical trials don't conclusively show benefit.

'Shaking and Quivering'

For parents of children with DMD who worked hard to get a treatment approved, the FDA's decision is a major achievement.

"I'm standing here shaking and quivering," said Terri Ellsworth, the mother of a 15-year-old boy who is among 12 children enrolled in a Sarepta drug trial. "It means so much for the muscular dystrophy world."

"All of our hard work has paid off, writing the FDA and writing to everyone," Ellsworth said. "I can't say enough how much your voice matters, and I will do it again and again so more research can go forward."

Patients with DMD lack a protein, called dystrophin, that keeps muscles intact. They quickly lose strength, robbing them of the ability to walk, stand and breathe. Sufferers often die by age 25, usually from lung disorders, according to the National Institutes of Health.

FDA Split

The Exondys 51 review caused a split within the FDA that went all the way to Commissioner Robert Califf, who sided with Woodcock to approve the drug. Ellis Unger, a top FDA reviewer, wanted to reject the treatment.

"Patient-focused drug development is about listening to patient perspectives about what matters to them; it is not about basing drug approvals on anecdotal testimony that is not corroborated by data," Unger wrote in a July 15 memo posted on FDA's website.

"If we were to approve eteplirsen without substantial evidence of effectiveness, or on the basis of a surrogate endpoint with a trivial treatment effect, we would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients, in essence, allowing marketing based on desperation, patient lobbying, and the desire and need of hope," Unger continued.

Califf countered that Woodcock has a “well-documented history of not bowing to such influences.” He said overturning Woodcock’s decision to approve Exondys 51 would be an “exceedingly rare” move and he deferred to Woodcock’s judgment given he doesn’t have technical expertise beyond hers or that of Unger, her subordinate.

‘Amazed’

The ruling and the way it was made could have implications well beyond Sarepta, potentially easing the requirements for medicines that treat patients with rare conditions who have no other options, said Sam Fazeli, an analyst with Bloomberg Intelligence in London.

“I am amazed after all that has happened,” Fazeli said. “This does mean that the FDA may be more lenient on very rare diseases such as DMD with no drug options at all.”

Experimental Duchenne drugs have had a tough history at the FDA. This year, the agency rejected two other experimental therapies, one from BioMarin Pharmaceutical Inc. and the other from PTC. Sarepta is also studying at least nine other drugs to treat various forms of DMD.

Closely held Marathon Pharmaceuticals LLC submitted an application to the FDA on June 14 seeking approval of its DMD drug, called deflazacort.

“Change usually happens from a champion or an individual who is willing to think outside the box,” Debra Miller, head of advocacy group CureDuchenne. said. “We had a champion in Janet Woodcock who was able to see beyond the numbers on the paper and actually see the patients who were involved, and understand the benefits.”

###

Sarepta shares leap 90% after FDA approves drug [TOP](#)

Evelyn Cheng, CNBC

Shares of [Sarepta Therapeutics](#) briefly surged more than 90 percent Monday after the Food and Drug Administration approved the company's muscular dystrophy drug eteplirsen.

The drug is the first approved to treat patients with Duchenne muscular dystrophy, a rare, genetic muscle-wasting disease, and was given accelerated approval, the FDA said.

Earlier, the stock climbed about 11 percent before trading was temporarily halted. It closed Monday's session up nearly 74 percent.

Recently, the stock changed hands up 60 percent, or a 21 percent gain for the year so far.

###

Biotech stock explodes 73% after the FDA approves the first drug to treat a rare muscle disorder [TOP](#)

Akin Oyedele, Business Insider

Sarepta Therapeutics shares spiked by as much as 86% in trading on Monday after the US Food and Drug Administration said it approved a key drug.

The FDA green-lighted Exondys 51 (eteplirsen), the first approved drug to treat patients with Duchenne muscular dystrophy (DMD), it said in a [statement](#).

DMD is a rare disorder in males caused by the absence of dystrophin, a protein that helps keep muscle cells intact.

It causes gradual but severe damage while limiting movement. Patients could need wheelchairs in their early teens, and could die by the time they are in their 30s.

"The FDA has concluded that the data submitted by the applicant demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in some patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping," the statement said.

The FDA confirmed last week that Ronald Farkas, a staffer who opposed the drug partly because of its small 12-patient clinical trial, had left the agency, [Stat News](#) reported. Sarepta shares soared then, as Farkas' departure was seen by investors to pave the way for approval.

Advocacy groups had pressured the FDA to endorse the drug, following the rejection of two treatments from other companies, Stat News noted.

"Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval," said Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, in the statement.

Sarepta shares were briefly halted for volatility after the spike on Monday.

###

FDA Approves Sarepta Therapeutics' (SRPT) Eteplirsen [TOP](#)

Street Insider

The U.S. Food and Drug Administration today approved Sarepta Therapeutics' (Nasdaq: [SRPT](#)) Exondys 51 (eteplirsen) injection, the first drug approved to treat patients with Duchenne

muscular dystrophy (DMD). Exondys 51 is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13 percent of the population with DMD.

“Patients with a particular type of Duchenne muscular dystrophy will now have access to an approved treatment for this rare and devastating disease,” said Janet Woodcock, M.D., director of the FDA’s Center for Drug Evaluation and Research. “In rare diseases, new drug development is especially challenging due to the small numbers of people affected by each disease and the lack of medical understanding of many disorders. Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval.”

DMD is a rare genetic disorder characterized by progressive muscle deterioration and weakness. It is the most common type of muscular dystrophy. DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. The first symptoms are usually seen between three and five years of age, and worsen over time. The disease often occurs in people without a known family history of the condition and primarily affects boys, but in rare cases it can affect girls. DMD occurs in about one out of every 3,600 male infants worldwide.

People with DMD progressively lose the ability to perform activities independently and often require use of a wheelchair by their early teens. As the disease progresses, life-threatening heart and respiratory conditions can occur. Patients typically succumb to the disease in their 20s or 30s; however, disease severity and life expectancy vary.

Exondys 51 was approved under the accelerated approval pathway, which provides for the approval of drugs that treat serious or life-threatening diseases and generally provide a meaningful advantage over existing treatments. Approval under this pathway can be based on adequate and well-controlled studies showing the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit to patients (how a patient feels or functions or whether they survive). This pathway provides earlier patient access to promising new drugs while the company conducts clinical trials to verify the predicted clinical benefit.

The accelerated approval of Exondys 51 is based on the surrogate endpoint of dystrophin increase in skeletal muscle observed in some Exondys 51-treated patients. The FDA has concluded that the data submitted by the applicant demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in some patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. A clinical benefit of Exondys 51, including improved motor function, has not been established. In making this decision, the FDA considered the potential risks associated with the drug, the life-threatening and debilitating nature of the disease for these children and the lack of available therapy.

Under the accelerated approval provisions, the FDA is requiring Sarepta Therapeutics to conduct a clinical trial to confirm the drug's clinical benefit. The required study is designed to assess whether Exondys 51 improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug.

The most common side effects reported by participants taking Exondys 51 in the clinical trials were balance disorder and vomiting.

The FDA granted Exondys 51 fast track designation, which is a designation to facilitate the development and expedite the review of drugs that are intended to treat serious conditions and that demonstrate the potential to address an unmet medical need. It was also granted priority review and orphan drug designation. Priority review status is granted to applications for drugs that, if approved, would be a significant improvement in safety or effectiveness in the treatment of a serious condition. Orphan drug designation provides incentives such as clinical trial tax credits, user fee waiver and eligibility for orphan drug exclusivity to assist and encourage the development of drugs for rare diseases.

The manufacturer received a rare pediatric disease priority review voucher, which comes from a program intended to encourage development of new drugs and biologics for the prevention and treatment of rare pediatric diseases. This is the seventh rare pediatric disease priority review voucher issued by the FDA since the program began.

Exondys 51 is made by Sarepta Therapeutics (Nasdaq: [SRPT](#)) of Cambridge, Massachusetts.

###

FDA approves Sarepta's controversial drug for Duchenne muscular dystrophy [TOP](#)

Ed Silverman, STAT

The Food and Drug Administration on Monday [approved](#) a controversial drug to treat Duchenne muscular dystrophy, a rare disease that confines boys to wheelchairs and condemns them to an early death.

The decision came after months of protracted debate about whether drug maker Sarepta Therapeutics had provided enough evidence to demonstrate that its medication, called eteplirsen, had a meaningful impact on patients. Sarepta said the drug would be priced at about \$300,000 a year in the US.

In reaching its decision, the agency essentially overruled its own medical staffers, who earlier this year [questioned](#) the effectiveness of the drug, which was tested in a small clinical trial. The wrangling raised still larger questions about standards for approving a drug, especially when it's intended for patients with a rare and deadly disease and no other treatment options.

“In rare diseases, new drug development is especially challenging due to the small numbers of people affected by each disease and the lack of medical understanding of many disorders,” said Dr. Janet Woodcock, who heads the agency division that reviews medicines, in a [statement](#).

As a condition of the approval, Sarepta will have to conduct a two-year, randomized controlled trial to verify the clinical benefit of the drug. The purpose is to determine whether the drug actually improves motor functions. If the trial fails, the FDA could move to withdraw approval.

The approval delighted a frazzled, but vociferous community of parents, whose determined lobbying efforts were reminiscent of the movement three decades ago to force regulators to greenlight AIDS treatments. And the FDA endorsement also jazzed investors, who sent Sarepta shares soaring, while breathing new life into still other companies that are investigating Duchenne treatments. Sarepta stock was up 80 percent in afternoon trading.

“This is huge. It’s going to give all of us some hope. But it’s also a bit surreal, after all the ups and downs we’ve been through,” said Debra Miller of CureDuchenne, an advocacy group that raises money to invest in drug makers, including Sarepta, that are developing products to combat DMD.

The fate of the Sarepta drug has been closely watched as a [litmus test](#) for an intensifying struggle between the FDA and patient groups that want the agency to take a more expansive view toward approving medicines for unmet medical needs. In this instance, patient advocates hoped the FDA would use the accelerated approval process to endorse eteplirsen. This approach relies on a substitute outcome in a clinical trial to suggest a drug may have, but does not guarantee, a benefit.

It was a long and complicated road, however, to this moment, as the FDA and Sarepta [squabbled repeatedly](#) over several technical, but significant details.

A key issue was whether the drug can sufficiently produce higher levels of a protein called dystrophin. Without this protein, muscle fibers degenerate and voluntary movement becomes impossible. The FDA also raised doubts about the results of a small, 12-patient clinical trial that Sarepta relied on to make its case, as well as the viability of six-minute walking tests that trial participants underwent. Moreover, the company failed to conduct a larger trial involving the use of a placebo, as the FDA had requested.

In light of these concerns, an FDA advisory panel in April [voted](#) that the drug should not be approved and, by a narrow margin, also agreed that the drug does not appear to be effective. Those decisions were made at a day-long meeting that was punctuated by a parade of emotional pleas from parents and children, some of whom appeared in wheelchairs.

Despite the outcome, the agency appeared to signal that parents should not lose hope. In remarks designed to appease the crowd, Janet Woodcock, who heads the agency division that approves drugs, said that “It’s possible to reach different conclusions based on the data presented today ... Failing to approve a drug that actually works in devastating diseases — these consequences are extreme.”

And so, the FDA made an [unexpected request](#) for Sarepta to provide more data about muscle biopsies from 13 boys who participated in an ongoing trial in order to determine the extent to which the medicine may produce dystrophin. The move suggested that the FDA tried to find other ways to approve the drugs.

###

Sarepta is now one of the hottest stars in Kendall Square [TOP](#)

Robert Weisman, Boston Globe

In an e-mail announcing that Cambridge-based [Sarepta Therapeutics](#) will be allowed to market the drug, called eteplirsen, the FDA’s Janet Woodcock [said](#) the ruling showed the agency’s “ability to apply flexibility to address challenges we often see with rare, life-threatening diseases — while remaining within our statutory framework.” Put more plainly, regulators decided it was worth taking a chance on eteplirsen, even though only 12 patients were enrolled in Sarepta’s clinical trial; a study that an independent advisory panel – and even some FDA staffers — found woefully inadequate.

The drug produces a crucial protein needed for muscle movement that’s lacking in a subset of Duchenne patients, but there was [disagreement within the agency](#) about whether it’s enough to make a difference. Dr. Ronald Farkas, the FDA’s top drug reviewer, and a critic of Sarepta’s data, [recently quit](#), and Woodcock — director of the [Center for Drug Evaluation and Research](#) — faced [an internal backlash](#). An independent FDA advisory panel also was not convinced of the drug’s effectiveness. Following an April hearing in a crowded Maryland hotel ballroom, the panel narrowly voted to recommend against its approval, despite [emotional testimony from patients and their families](#). Richard P. Hoffmann, a pharmacist named to the committee to represent consumers, ended up abstaining. “I was just basically torn between my mind and my heart,” he said.

That’s the crux of the dilemma facing the FDA. It’s supposed to only allow the sale of medicines that have been clinically proven to work, and don’t cause harm. If regulators were to be unduly swayed by anecdotal evidence and heartfelt pleas, drug companies could come to rely on armies of patient advocates to overcome spotty trial results. But if the approval process is completely dehumanized, the agency could be viewed as unwilling to put patients’ lives over strict adherence to bureaucracy.

“The FDA needs to take a step back and re-evaluate how it’s going to do this going forward,” says [Harry Glorikian](#), a health care consultant based in Lexington. “Historically, we’ve let science and data drive our decisions when it comes to therapeutics.”

The eteplirsen decision came with a large asterisk — Sarepta has to conduct a two-year study to better show whether the drug helps maintain or improve mobility — but its entry into the marketplace represents a major victory for the patient advocacy movement, and is bound to encourage more such engagement in the drug-approval process. Based on the infighting that went on over the Duchenne treatment, that’s going to be challenging for the FDA. It has to find a balance between public opinion and what’s truly in the public interest.

###

FDA scientists worry director bowed to political, financial pressures in controversial drug approval [TOP](#)

Sarah Karlin-Smith, Politico

FDA's decision to approve a controversial Duchenne muscular dystrophy drug this week has raised questions within the agency about whether its top drug regulator pushed too aggressively to greenlight an unproven treatment - for a rare disease that kills young people and stirs strong emotions.

[Internal documents](#) detailing FDA's decision to ultimately approve the drug for types of Duchenne reveal that critics within the agency saw FDA's Drug Center Director Janet Woodcock as too influenced by patient advocates, who mounted an aggressive campaign for approval despite shaky evidence of the treatment's benefits.

Some worried that Woodcock let politics and public pressure - and even the drug company's financial considerations - influence the approval Monday of a \$300,000-per-year drug based on questionable science.

An independent advisory committee and the FDA's own review team recommended both recommended against approval for the drug, eteplirsen, in part because of perceived flaws in the clinical trials.

The application's main clinical trial involved only 12 patients, who for much of the trial knew they were on experimental drug. There was no control group on a placebo. FDA's reviewers said that design left the trial open to bias and made it difficult to analyze the drug's benefits. And the agency cited other quality control issues.

Despite those red flags, Woodcock granted the drug accelerated approval with the support of FDA Commissioner Robert Califf. Both were among the agency staff who acknowledged flaws in the data.

The FDA released a statement to POLITICO defending Woodcock's overall actions as appropriate. It was the subject of an internal review - which criticized her. Related documents including agency staff criticism of the process were publicly posted Monday.

The approval of eteplirsen came a year after FDA was widely criticized for approving a female libido drug that many scientists believed wasn't up to agency standards, but like the Duchenne drug was the subject of a sustained inside the Beltway advocacy campaign. And the FDA's decision on Duchenne comes as the Hill has been working toward a major biomedical innovation package - drawing on the House-passed CURES ACT - meant to speed the development of innovative treatments.

Duchenne patients had been advocating for the drug's approval for years and saw the FDA decision as a major victory. Duchenne cripples and then kills people, usually by their 30s, and there is no effective treatment. But critics pointed to the quality around the science.

The FDA "has rarely if ever approved a drug on less evidence than that provided by Sarepta," [wrote](#) Rachel Sachs of the Washington University School of Law.

FDA documents, which the agency posted on Monday, show some staffers believe Woodcock may have decided to approve eteplirsen even before the FDA received an application - and that she took unusual steps to influence FDA staff doing the review.

An internal FDA board, which oversees "serious scientific disputes" within the agency, raised concerns about Woodcock's "extensive and early involvement in the review process" of the drug, saying it went against typical FDA processes. Further, the board said, Woodcock told the FDA's new drug division in May that she planned to approve the drug. That was even before the head of FDA's new drug office finalized his recommendation to reject the drug.

"Rather than ensuring that the scientific reviews started at the bottom of the chain of command, Dr. Woodcock made clear from her position at the top that she was pushing for a particular outcome from the very early stages," the dispute review board said. "Review teams should have the opportunity to conduct their reviews without preemption by the Center Director." Woodcock directed the drug review office to join her in meetings with patient advocacy groups anywhere from six to 12 times, the documents said. The reviewers described the meetings as "intense," "personal" and "intimidating."

Woodcock's extensive involvement in the drug's review "could have chilled scientific debate with [FDA's drug center] and reduce the level of participation by the review team during the final stages of the decision-making process," the dispute review board said.

The documents also indicate Woodcock's concern for Sarepta's financial well-being if the drug wasn't approved, which experts say is out of the scope of FDA's reviews. Woodcock told the dispute resolution board that Sarepta "needed to be capitalized," noting that the sponsor's stock went down after independent agency advisers recommended against the

drug's approval in April. She cautioned that if the company didn't receive accelerated approval it would have insufficient funding to study the drug and other similar products, and that patients would abandon hope for development of new treatments.

In his memo supporting Woodcock's decision, Califf said he was troubled by Woodcock's statements suggesting the company's financial well-being affected her decision to approve the drug. But he said after discussing it with Woodcock, he was satisfied her decision was based on a scientific evaluation of the evidence.

"It strikes me as unusual that the agency would be worried about the financial health of the company, at least that it would be documented in this way," said Patti Zettler, a former FDA associate chief counsel now at the University of Georgia.

In response to questions, FDA emphasized to POLITICO that Woodcock's decision was based on "the scientific evidence." FDA also cited a memo from acting chief scientist Luciana Borio, who oversaw the internal dispute process, that said Woodcock considered all relevant evidence. The agency said it is important to include patient perspective to understand their view of a drug's benefit and risks.

FDA also defended Woodcock's interactions with staffers reviewing the drug application. It cited Califf's memo, which said her involvement "fits within her longstanding management approach and interest in complex, difficult issues."

Woodcock's justification to the review board appeared to reference recent encouragement from lawmakers to speed the approval of rare disease treatments. House and Senate appropriators this year instructed the FDA that it has "the tools, authorities and latitude necessary" to approve treatments like those for Duchenne as fast as possible.

"Given the deficiencies that have been identified in the development program, my conclusion ... represent[s] the greatest flexibility possible for FDA while remaining within its statutory framework," Woodcock said.

But safety advocates, who worry about politics tainting FDA decision-making, say they see similarities between the Duchenne drug and the approval of the so-called female Viagra drug, filbanserin. FDA had rejected filbanserin twice because it found the slim benefits didn't outweigh safety concerns but ultimately approved it last year amid public pressure.

"Companies are very smart and they see how this battle was won by Sarepta," said Diana Zuckerman, president of the National Center for Health Research. "What Sarepta did was just a more extreme version of filbanserin."

FDA documents showed some within the agency worried about setting a precedent with the Duchenne drug.

Ellis Unger, director of one of FDA's new drug division, told the dispute board that Woodcock "seemed focused on the external pressure, from both patient advocacy groups and Congress." He worried that greenlighting the drug would usher in an era of approvals based on emotion.

Unger wrote that if FDA approved the drug based on available data, "We would quickly find ourselves in the position of having to approve a myriad of ineffective treatments for groups of desperate patients."

Woodcock criticized agency reviewers for downplaying and undercutting the views of patient advocates. In a memo included in the posted review documents, Califf acknowledged "the strain created by political and public pressure" to approve the drug, but he defended Woodcock's "well-documented history of not bowing to such influences."

"I do not find that she deviated from her responsibilities as center director, nor do I find that she succumbed to pressure from the patient community, the public the press or others," Califf said. He also said he didn't find her involvement in the review atypical or that her conduct was in conflict with her job requirements.

Serapta now must conduct a clinical trial to verify that the drug provides patients with a clinical benefit - that it either improves or extends their lives. That was not demonstrated in earlier research which focused in part on a potentially beneficial response from increasing a missing protein in those patients. If the follow up study fails, FDA can withdraw its approval. The study is not expected to be completed until November 2020.

Califf said the agency's decision on eteplirsen won't set the pace for FDA's approval. "Serious shortcoming present in the eteplirsen development program should not be allowed to establish a broad precedent for therapeutic development in rare disease," Califf wrote.

###

To sway drug approval, patient advocates turn up the heat on the FDA [TOP](#)

Matthew Herper, Forbes

Yesterday, the Food and Drug Administration made history, approving a drug to treat Duchenne muscular dystrophy that works by targeting the genetic mutation at the root of the disease.

The decision was unique for reasons that were not just scientific. Janet Woodcock, the director of the FDA's Center for Drug Evaluation and Research overruled the protests of her own staff to approve the drug. One of her division's top officials appealed the ruling, and the agency's chief scientist largely backed his conclusions, saying that "by any meaningful objective standard" the medicine is unlikely to improve patients. But the FDA's commissioner, Robert Califf, decided not to overturn Woodcock's decision, citing Woodcock's long record of independence and arguing that her differences with other FDA scientists were a matter of honest scientific disagreement, and the decision was within Woodcock's authority.

In this Friday, June 5, 2015 photo, 10-year-old Gabe Griffin sits in a train on a playground in Birmingham, Ala. Griffin suffers from Duchenne Muscular Dystrophy, a rare muscular degenerative disease that gradually and then rapidly leads to incapacitation before ultimately to an early death. A new Alabama law passed during the 2015 legislative session seeks to allow

terminally ill patients to try drugs that have passed the first clinical trial but that haven't been approved by the U.S. Food and Drug Administration. (AP Photo/Brynn Anderson)

The news is an unmitigated win for Sarepta Therapeutics, the biotechnology company that developed the drug, now known as Exondys 51 or, generically, eteplirsen. Sarepta shares increased 74% to almost \$49, giving the company a market capitalization of \$2.5 billion. Last night, on a conference call with investors, the company said that it expected to charge \$300,000 per patient per year for Exondys 51, with the exact dosage being determined by weight. The company, which might have folded with a rejection, will now have money to fully test Exondys and other, similar drugs for Duchenne.

For patients with Duchenne, the approval is also a victory. Patient advocates campaigned hard for Exondys to be approved, with many attending an expert panel the FDA convened in April. At the time, the outside experts convened by the FDA voted 7-6 to recommend the FDA should not approve Exondys.

“The moment I saw eteplirsen received approval, I broke down, I cried,” says Josh Argall, a network technician whose 15-year-old son has Duchenne caused by the gene Exondys 51 targets. “When my son was diagnosed 12 years ago a lot went through my mind that I wouldn't be able to do with him. I felt as though some of our future was taken away. Today, it was given back and man, I couldn't be more thankful.”

But for the FDA, the decision represents a civil war that could have unknown reverberations. Ronald Farkas, the FDA reviewer was charged with reviewing the Exondys new drug application, has already left the agency to take a job in industry. The contention between Woodcock and Ellis Unger, who is in charge of reviews of heart, kidney, neurology, and psychiatric drugs, are sharp.

And some outside experts are already arguing that Unger was right. Eric Topol, chief academic officer at Scripps Research Institute in La Jolla, Calif., says the decision is “compromising reasonable approval standards.” Walid Gellad, an associate professor of medicine at the University of Pittsburgh who frequently serves on FDA panels tweeted: “Let me summarize: a drug the FDA says has no clinical benefit will cost four times as much as a drug that cures hepatitis C.”

The approval of Exondys is called an accelerated approval, meaning that the FDA has the option of withdrawing it if specific future studies don't prove out the drug's benefit. Topol says he wishes that Congress had instead created a conditional approval, where the drug would be automatically withdrawn unless studies show it really works.

From the start, the Sarepta story has been a strange case. It was incredibly expensive to make – in small batches probably costing \$100,000 per patient, analysts say – and the company was

strapped for cash. So it did a small study of 14 patients. Two of those patients were not evaluable, but in the rest something surprising seemed to happen: those that got Exondys 51 from the start of the study seemed to do much better than those who had a delayed start on the drug. More enticingly, the boys (because the genetic defect that causes Duchenne is on the X chromosome, it is a disease of boys) seemed to be showing marked increases in dystrophin, the protein that is missing in the disease.

Based on these results, Sarepta filed with the FDA. It was likely the smallest pivotal study in FDA's modern history. The FDA now says that it implored Sarepta to run a placebo-controlled study with more patients, but the company argued that it would be impossible to get Duchenne patients to enroll given the already positive results. But under the FDA's reviewers – in particular Farkas — did not believe the study results. They said the differences between boys who got the drug at the beginning of the trial and those that had to wait could be due to chance, as could what advocates said was the overall tendency of all the boys to do better than expected.

Worse, the FDA had issues with the way Sarepta had tested dystrophin. After the FDA's April advisory committee voted that the drug should not be approved, the FDA and Sarepta agreed to look at one more set of data points: samples would be taken from patients to see if their dystrophin levels increased after 48 weeks of treatment. It was possible to get data from 12 of those patients. When the dystrophin data were produced the FDA would make a decision within four days, per an agreement made by Woodcock and agreed to by Unger.

But when the data came in on June 27, they disappointed even Woodcock, according to a review of the facts presented by Luciana Borio, the FDA's Acting Chief Scientist. The data showed an increase of only 0.28% of normal levels, which was, on average, a tripling of dystrophin levels for these boys. But Unger and the reviewers argued that, based on comparisons of different types of muscular dystrophy, an increase beyond 10% of normal would be needed to have a clinical impact on muscular dystrophy symptoms.

Unger wanted to ask Sarepta to test the current dose of Exondys 51 against a much more frequent dose of the drug before approving the medicine. If the more frequent dose was more effective, the drug could then be approved. Woodcock, despite the disappointing data, wanted to grant accelerated approval right away.

“By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk,” Unger wrote in his protest. “I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs – if not to patients, to society.”

The FDA is not supposed to concern itself with the cost of a drug. But both Unger and Woodcock were. Unger was worried about the unknown risks of the drug, as well as the risks to boys who might get injection ports while they were also on immune-suppressing steroids, raising

the risk of injection. Woodcock was worried about the cost to Sarepta.

Woodcock, according to Borio, argued that if the drug were not approved, Sarepta would see its stock price crash and probably go out of business. It was probably true. Brian Skorney at R.W. Baird, an analyst who has gotten the Sarepta story very much right, estimates Sarepta would have needed \$400 million to complete the study, yet would have had only a \$250 million market cap on rejection – meaning it couldn't raise the money it needed if the FDA rejected it. It's also not a reason to approve a drug.

At the end of the day, Woodcock, Unger, Borio and Califf all wound up agreeing on many key points: that Sarepta's studies were flawed and difficult to interpret; that early versions of the Sarepta data as released were misleading; that both the FDA and Sarepta stumbled at multiple points along the way; and that, at the end of the day, Sarepta's drug showed only a minimal amount of dystrophin was produced. The disagreement is on one point: was this tiny increase in dystrophin enough to merit approving the drug, even on a conditional basis?

Woodcock decided the answer was yes, and, for the first time in her eight-and-a-half-year term as director of the FDA's drug division, overruled her scientists and decided to approve the drug, saying that she wanted to use "the greatest flexibility possible for FDA while remaining within its statutory framework."

Borio, the FDA's Acting Chief Scientist, sided with Unger. "By any meaningful objective standard, however, the overall evidence derived from eteplirsen's limited clinical development program does not support that the levels of dystrophin produced by eteplirsen at the doses studied are reasonably likely to provide a clinical benefit."

But the final decision sat with Robert Califf, the FDA Commissioner who, as an academic researcher, made a career of pushing companies to do bigger, more rigorous data. At the end of the day, he declined to make his own judgment on the merits of Sarepta's data. He simply decided that Woodcock had not overstepped her authority and that he, a political appointee, was not going to take another gigantic step by overruling the FDA staff.

Califf's memo asserts that this decision should not be seen as precedent. But it will. Companies will spend more on lobbying, and more on supporting patient groups as a result. They will also try to push through drugs with minimal data. The decision also will demoralize FDA staff – imagine being told your boss could push you around even more. It would have been better if he had grappled with the data instead of throwing up his hands and standing on procedure.

Those fear that the FDA has been lowering the bar dramatically in recent years, will hate the Exondys approval. One critic told me: "This isn't even science!" The FDA has approved a drug, essentially, on a minimal efficacy data from 12 patients and safety data from a larger dataset. But this was always a tough decision, because this was exactly the kind of case that accelerated

approval was designed for: A death sentence with no options. It's wrong for the FDA to approve a drug without evidence it works, but it's also paternalistic to say boys with Duchenne and their families shouldn't be able to take risks they dearly want to take.

At least this decision sets up a clear path for testing whether Exondys works: A more frequent dose (the FDA suggests daily dosing) should clearly outperform the currently approved dose, or the FDA will yank the drug. The agency, after taking such a big risk, will have to follow through on yanking the drug if that trial, due in 2020, is not positive. That gives Sarepta, or whoever buys it, three years to marshal its evidence.

The lobbying floodgates were already opened by a far worse decision: The FDA's approval of Addyi, a drug to treat female sexual dysfunction that had little evidence of efficacy. Its maker, Sprout Pharmaceuticals, created a campaign that presented the approval of the drug as a feminist issue, and the drug got approved. That's a far cry from giving a shot at a longer life to dying boys.

But Exondys should represent the absolute minimum in terms of the data required to get a new medicine to market. And in the future, we need to find ways to communicate the FDA's concerns about an experimental medicine to the public, not just to a drugmaker behind closed doors.

And Congress should now stop mucking with the FDA approval process for a while. In an effort to speed up the bureaucracy, legislators have layered breakthrough designations on priority reviews on fast tracks (all seek to declare some drug reviews special), while adding vouchers and other measures aimed to incentivize drug development. In addition to the hundreds of millions in annual sales Sarepta will get for selling its \$300,000 drug, it will also get a priority review voucher for developing a rare pediatric drug. This is a coupon forcing the FDA to speed up review of a drug that's not innovative. The last such voucher netted \$330 million in an auction. Given that the FDA brass all agreed Sarepta had touted study results that were misleading, does the company really deserve what's essentially an extra year of sales?

Legislation under consideration aims to add more such incentives. It's time to put on the brakes. There's no argument now: the FDA is bending over backward to make sure that patients have access to medicines, using the maximum flexibility of the law. In an agency driven by precedent, this decision will matter. Already, medicines are usually approved in America before they're approved anywhere else. It's time to pause before the bar is lowered any further.

###

F.D.A. Approves Muscular Dystrophy Drug That Patients Lobbied For [TOP](#)

Sabrina Tavernise, NY Times

WASHINGTON — The [Food and Drug Administration approved](#) the first drug to treat patients with the most common childhood form of [muscular dystrophy](#), a vivid example of the growing power that patients and their advocates wield over the federal government’s evaluation of drugs.

The agency’s approval [went against the recommendation](#) of its experts. The main clinical trial of the drug was small, involving only 12 boys with the disease known as [Duchenne muscular dystrophy](#), and did not have an adequate control group of boys who had the disease but did not take the drug. A group of independent experts convened by the agency this spring said there was not enough evidence that it was effective.

But the vote was close. Large and impassioned groups of patients, including boys in wheelchairs, and their advocates, weighed in. The muscular dystrophy community is well organized and has lobbied for years to win approval for the drug, getting members of Congress to write letters to the agency.

A decision on the drug [had been delayed for months](#). The approval was so controversial that [F.D.A.](#) employees fought over it, a dispute that was taken to the agency’s commissioner, Dr. Robert M. Califf, who [ultimately decided that it would stand](#).

The approval delighted the drug’s advocates and sent the share price of the drug’s maker, [Sarepta Therapeutics](#), soaring. But it was taken as a deeply troubling sign among drug policy experts who believe the F.D.A. has been far too influenced by patient advocates and drug companies, and has allowed the delicate balance in drug approvals to tilt toward speedy decisions based on preliminary data and away from more conclusive evidence of effectiveness and safety.

“The agency has set a dangerous precedent,” said Diana Zuckerman, president of the National Center for Health Research in Washington. “To prove something works, you have to compare it to something else — a placebo or a treatment. They didn’t do that.”

About 9,000 to 12,000 Americans, virtually all boys, are estimated to have Duchenne muscular dystrophy. Because of rare genetic mutations, people with the disease make little or no dystrophin, a protein that acts as a shock absorber to protect muscles from deterioration. Boys with Duchenne typically need wheelchairs by their teens and die by their late 20s.

The drug, eteplirsen, uses a technology [called exon skipping](#) that seeks to partly correct the genetic defect, allowing muscle cells to produce a somewhat functional form of dystrophin. The drug is applicable to only about 13 percent of Duchenne patients. Other exon-skipping drugs are being developed for patients with different mutations.

Sarepta said the average cost of eteplirsen for a patient would be about \$300,000 a year. That is double the cost of most new [cancer](#) drugs, according to Dr. Zuckerman.

The drug received accelerated approval, which is reserved for medicines that treat serious diseases and address an “unmet medical need.” The agency defines that as “a condition whose treatment or diagnosis is not addressed adequately by available therapy.”

But even as it approved the drug, the agency also required the company to conduct another clinical trial to confirm the drug's effectiveness. If the drug maker fails to prove it, the agency said it may "initiate proceedings to withdraw approval."

During a heated public meeting in April, experts voted 7 to 3, with three abstentions, that the clinical data did not meet the F.D.A. requirements for well-controlled studies necessary for approval. The agency had urged Sarepta, which is based in Cambridge, Mass., to do a larger study with a placebo control to better determine whether the drug worked.

But the company argued that doing so would be unethical and impractical, since early hints of effectiveness meant that parents would no longer enroll their sons in a trial where they might not get the drug. Instead, Sarepta compared the data from the 12 boys in the trial to historical data from patients in Italy and Belgium who were as closely matched as possible in disease characteristics.

Now the company will have to conduct another trial. But Dr. Zuckerman argued that it is more difficult to enroll patients after a drug had been approved, because families will not want to take a chance that their son would be in a placebo group.

Dr. Janet Woodcock, director of the F.D.A.'s Center for Drug Evaluation and Research, said in a statement, "We eagerly await learning more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval."

###

FDA approves first drug to treat rare form of muscular dystrophy [TOP](#)

Liz Szabo, USA Today

The Food and Drug Administration on Monday approved the first drug to treat Duchenne muscular dystrophy, a rare and lethal muscle weakening disorder that affects about 15,000 Americans. The approval of the drug, which will sell for \$300,000 a year, has been controversial.

The FDA's [approval](#) of the drug, Exondys 51, also known generically as eteplirsen, came over the objections of its own advisory committee, which voted not to approve the medication [earlier](#) this year. Patients and their families had lobbied hard for the drug, made by Sarepta Therapeutics of Cambridge, Mass., noting that people with the disease have few treatment options.

Exondys 51 doesn't cure Duchenne muscular dystrophy and will only help a minority of patients. It is designed for the 13% of patients with a particular genetic mutation that prevents them from making dystrophin, a key protein that keeps muscles intact. Without that protein, muscles weaken so much that children are unable to walk and must use wheelchairs by the time they're teens.

Eventually, the disease can fatally weaken the heart and muscles needed to breathe. Patients often die in their 20s or 30s.

The FDA's decision speeds up the approval process for Exondys 51, allowing it onto the market based on preliminary data that suggest the drug will strengthen children's muscles, even though the company has not yet produced clear proof that the medication will delay paralysis or improve symptoms.

In clinical trials, some patients treated with Exondys 51 had more dystrophin in their skeletal muscles, which people use to move their arms and legs. The FDA will require Sarepta to launch another clinical trial to show whether it actually improves patients' symptoms. If the drug doesn't help, the FDA could withdraw approval.

Sarepta's stock price jumped 90% Monday after the approval was announced. The company's stock also got a bounce last week after the FDA confirmed a staff member who had been critical of the drug, Dr. Ronald Farkas, had [left the agency](#) for another job.

Farkas had expressed doubts about the drug's effectiveness during a review of Exondys 51 earlier this year.

Duchenne muscular dystrophy primarily occurs in boys and affects about one out of every 3,600 baby boys worldwide, according to the FDA. It's "an X-linked recessive inheritance pattern and is passed on by the mother, who is referred to as a carrier of the gene," according to the Muscular Dystrophy Association.

The disease is so rare that the FDA considers it an "orphan disease," or one that isn't common enough to attract many drug developers. The FDA encourages companies to develop drugs for orphan diseases by giving them special tax credits and extending the amount of time that companies are able to sell them exclusively, without generic competition.

Pat Furlong, president and CEO of the advocacy group Parent Project Muscular Dystrophy, said the FDA made the right call in approving the drug. "This acknowledges that the patient voice is important," Furlong said.

Advocates say they hope the approval will be the first of many.

"It's a huge step forward," said Dr. Valerie Cwik, executive vice president and chief medical and scientific officer at the Muscular Dystrophy Association, which advocates on behalf of patients and their families. "It's a really, really big day for the Duchenne community."

Developing a drug for rare diseases like this is complicated by the "small numbers of people affected by each disease and the lack of medical understanding of many disorders," said Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research. "Accelerated approval makes this drug available to patients based on initial data, but we eagerly await learning

more about the efficacy of this drug through a confirmatory clinical trial that the company must conduct after approval.”

The most common side effects from Exondys 51 include vomiting and problems with balance.

Some health advocates criticized the FDA’s decision.

Overruling the advisory committee shows “a disturbing disregard for the agency’s legal standards for approving new drugs,” said Michael Carome, director of Public Citizen’s Health Research Group, a non-profit that studies drug safety. “In particular, such action eviscerates the agency’s long-standing requirement that there be substantial evidence of effectiveness for new drugs — even drugs for serious rare diseases — before they are marketed.”

Diana Zuckerman, president of the National Center for Health Research, a non-profit research group, noted that the Exondys 51 clinical trial was poorly done. Doctors leading the trial didn’t compare patients who received the drug with a “control group” of untreated patients.

“It sets a dangerous precedent if the FDA is going to start approving drugs that aren’t compared to anything,” Zuckerman said. “Why would a company choose to do a careful, well-designed study that might show that its product isn’t particularly safe or effective if it can get away with doing a tiny, poorly designed study with ambiguous results?”

But Laura McLinn, an Indiana mother whose 7-year-old son has Duchenne muscular dystrophy, was in tears Monday when she heard the news of the drug’s approval. Although her son isn’t eligible to take Exondys 51, because his disease is caused by a different mutation, McLinn said she hopes the approval will speed the development of another drug in Sarepta’s pipeline, which could help her son. She hopes he could enter a clinical trial by the end of the year.

“I’m really overwhelmed,” McLinn said. “We’ve been waiting a long time to hear this.”

The news of FDA approval for Sarepta’s drug follows the agency’s rejection of another highly touted treatment for Duchenne. In January, the agency ended months of uncertainty about the drug Kyndrisa after a panel of advisers found that the drug’s effectiveness in trials did not conclusively show improved walking ability in patients. BioMarin Pharmaceuticals has since announced it was abandoning development of Kyndrisa.

###

Drug’s approval brings hope, and tough questions [TOP](#)

John Boal, Boston Globe

Monday’s [approval](#) of the first drug to treat the underlying cause of [Duchenne muscular dystrophy](#) offers hope to young patients handed a cruel sentence — almost certain death before their 25th birthday. But the impact of the [Food and Drug Administration’s](#) decision will extend beyond boys who suffer from a form of the disease — fewer than 2,000 in the United States —

and raises complicated questions about the role patient advocacy should play in a regulatory process rooted in science.

In an e-mail announcing that Cambridge-based [Sarepta Therapeutics](#) will be allowed to market the drug, called eteplirsen, the FDA's Janet Woodcock [said](#) the ruling showed the agency's "ability to apply flexibility to address challenges we often see with rare, life-threatening diseases — while remaining within our statutory framework." Put more plainly, regulators decided it was worth taking a chance on eteplirsen, even though only 12 patients were enrolled in Sarepta's clinical trial; a study that an independent advisory panel — and even some FDA staffers — found woefully inadequate.

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The drug produces a crucial protein needed for muscle movement that's lacking in a subset of Duchenne patients, but there was [disagreement within the agency](#) about whether it's enough to make a difference. Dr. Ronald Farkas, the FDA's top drug reviewer, and a critic of Sarepta's data, [recently quit](#), and Woodcock — director of the [Center for Drug Evaluation and Research](#) — faced [an internal backlash](#). An independent FDA advisory panel also was not convinced of the drug's effectiveness. Following an April hearing in a crowded Maryland hotel ballroom, the panel narrowly voted to recommend against its approval, despite [emotional testimony from patients and their families](#). Richard P. Hoffmann, a pharmacist named to the committee to represent consumers, ended up abstaining. "I was just basically torn between my mind and my heart," he said.

That's the crux of the dilemma facing the FDA. It's supposed to only allow the sale of medicines that have been clinically proven to work, and don't cause harm. If regulators were to be unduly swayed by anecdotal evidence and heartfelt pleas, drug companies could come to rely on armies of patient advocates to overcome spotty trial results. But if the approval process is completely dehumanized, the agency could be viewed as unwilling to put patients' lives over strict adherence to bureaucracy.

"The FDA needs to take a step back and re-evaluate how it's going to do this going forward," says [Harry Glorikian](#), a health care consultant based in Lexington. "Historically, we've let science and data drive our decisions when it comes to therapeutics."

The eteplirsen decision came with a large asterisk — Sarepta has to conduct a two-year study to better show whether the drug helps maintain or improve mobility — but its entry into the marketplace represents a major victory for the patient advocacy movement, and is bound to encourage more such engagement in the drug-approval process. Based on the infighting that went on over the Duchenne treatment, that's going to be challenging for the FDA. It has to find a balance between public opinion and what's truly in the public interest.

####

The Boys Who Beat the FDA [TOP](#)

Opinion, The Wall Street Journal

Miracles happen. The Food and Drug Administration on Monday approved a drug for muscular dystrophy after months of delay and bureaucratic infighting. This is a triumph for scientific innovation, and for young men who will live better and more independently—if the bureaucracy doesn't strike back.

FDA announced accelerated approval for eteplirsen by [Sarepta Therapeutics SRPT -3.30 %](#) more than 100 days after the agency's legally mandated decision date. The therapy is the first for Duchenne muscular dystrophy patients, typically boys who lose the ability to walk around age 12 before heart or respiratory failure in their 20s. Ten of 12 boys in a clinical trial still walk after four years on eteplirsen—nearly two football fields farther than a control group.

Agency documents released Monday reveal a protracted fight over the drug between Janet Woodcock, head of FDA's drug evaluation center, and various reviewers. As early as May 4 Dr. Woodcock planned to overrule the agency's review, which Duchenne experts and clinicians had picked apart as error-ridden and scientifically questionable. But a division director filed a complaint under an FDA process for handling disputes, a proceeding we first reported. ("[Heart of Bureaucratic Darkness](#)," Aug. 10)

The FDA decision paper is a tour of toxic bureaucratic politics: The complaint charged Dr. Woodcock with the mortal sin of meeting with patients and families too often and attending a contentious committee meeting. Another charge is that Dr. Woodcock once mentioned that destroying Sarepta might preclude later innovations, which is obvious and irrelevant to approval.

The criticism is even less believable given that the sticking point was whether the drug produced protein at a level that was "reasonably likely to predict a clinical benefit." The drug has already produced reasonable results in some boys. Dr. Woodcock seems to be the only employee who noticed that a 2012 law directs FDA to exercise broad flexibility in approving first-in-class drugs for rare diseases.

Dr. Woodcock also deserves credit for political bravery because her boss, FDA Commissioner Robert Califf, announced that he would "defer to Dr. Woodcock's judgment" without taking a position himself. There's a profile in non-courage.

FDA's report notes that members of the review team plan to leave the agency due to concerns about decision-making and "pressures exerted by outside forces," presumably those meddling patients who dared to say the drug worked. The agency confirmed to us last week that the neurology division's clinical team leader, Ronald Farkas, no longer works at FDA, and he will not be missed.

Even with “accelerated” approval, Sarepta must now conduct a double-blind, randomized trial to confirm its initial findings, or FDA could pull the drug. Some patients will receive the recommended dose and others will be infused with more. Yet it isn’t clear who would sign up for a clinical trial when the treatment is on the market, and this could be an opening for more FDA sabotage.

Sarepta is enrolling a placebo trial to certify later versions of the drug, which use the same “exon-skipping” technology to jump over different genetic code. Infusing a child’s muscles with saline is not ethical, but this protocol is the only way to move new iterations through a recalcitrant FDA.

A Duchenne boy’s veins often weaken so that a port must be inserted into his body, but we’ve heard the ports are banned in this study on ethical grounds. That means a child whose veins are deteriorating will be pricked as many times as it takes to start treatment—six, seven needles. How is this more moral?

If the grimness of placebo trials sounds abstract, ask Mitch and Mindy Leffler. In 2011 their then-8-year-old son Aidan started a trial for a drug called drisapersen, which FDA later rejected. The Lefflers, who have two other children, flew or drove from their home near Seattle to Vancouver, B.C. once a week for two years, the first 48 weeks of which Aidan received dummy treatment. Aidan is now 13 and in an eteplirsen trial. He still walks.

There will be more Duchenne drama, and some bubbled up Monday afternoon on the not-so-breaking news that drug innovation is expensive: Eteplirsen, now known as Exondys 51, will be priced based on a child’s weight and cost about \$300,000 a year for the average patient. The drug is expensive to manufacture but years of government delay have no doubt added to the cost.

Congress allowed for accelerated approval precisely to advance treatments for patients with no other options. But FDA reviewers hate the process because it reduces their life-and-death political control. Sarepta’s victory is a sign that death by bureaucracy isn’t inevitable.

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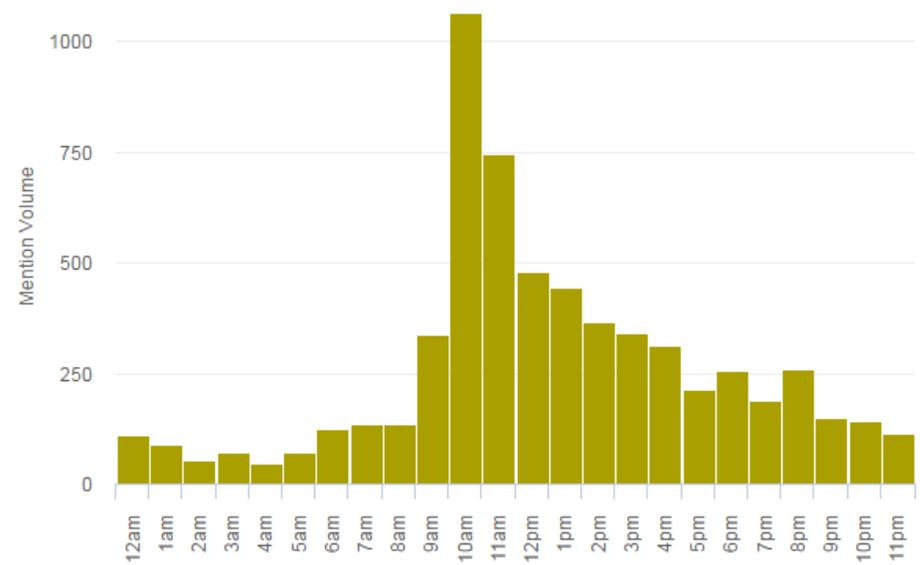
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WebMD @WebMD	1333200
ABC News @abcnews	1163010
Clay Matthews III @ClayMatthews52	994064
NYT Health @NYTHealth	941163
WSJ Health News @WSJhealth	555682
The Boston Globe @BostonGlobe	527092



Financial Times @FinancialTimes

Headlines from the FT. Follow us on @FT for news stories, features and updates. Our customer service team is @FTcare.

Follow @FinancialTimes

Location

Greater London, United Kingdom

Latest mention of: Duchenne (DMD)

Financial Times @FinancialTimes

Sarepta shares surge 90% on FDA approval on.ft.com/2cLhRqJ

PREVIOUS REPORTS

DMD Social Media 9/20 A.M. Report

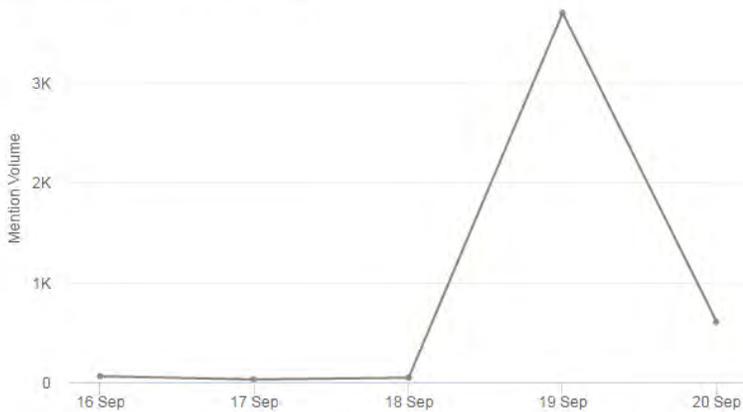
25M+ reach for topic (FDA/DMD) on Twitter

Key Insights | Duchenne (DMD) | Sep 16, 2016 - Sep 20, 2016

Total Mentions 4431 <small>▲ 351% Previous Period: 983</small>	Unique Authors 2832 <small>▲ 416% Previous Period: 549</small>	Trending Topics <ol style="list-style-type: none"> Sarepta Therapeutics' Exondys 51 approved a controversial FDA approves Sarepta's Duchenne drug 	Top News Stories <ol style="list-style-type: none"> Isle of Capri, GM and Halliburton climb... Reuters Health News Summary Business Highlights
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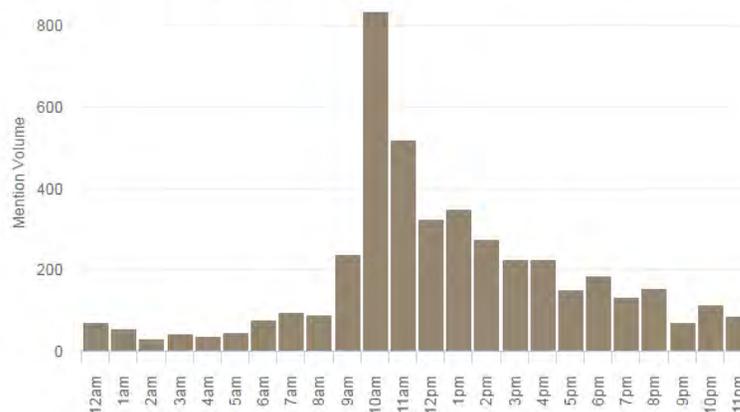
Mentions Over Time by Day

Duchenne (DMD) | Sep 16, 2016 - Sep 20, 2016



Mentions by Hour of Day

Duchenne (DMD) | Sep 16, 2016 - Sep 20, 2016



Twitter Insights | Duchenne (DMD) | Sep 16, 2016 - Sep 20, 2016

Top Stories	TWEETS	RETWEETS	ALL TWEETS	IMPRESSIONS	Top Hashtags	TWEETS	RETWEETS	ALL TWEETS	IMPRESSIONS
fda.gov/NewsEvents/Newsroom...	96	109	205	642402	#duchenne	75	158	233	610195
fda.gov/NewsEvents/Newsroom...	58	105	163	546596	#dmd	97	102	199	835894
reuters.com/article/us-sarepta-fd...	149	0	149	541503	#fda	117	70	187	1087649
scientificamerican.com/article/fd...	43	86	129	3989073	#eteplirsen	70	104	174	677064
statnews.com/pharmalot/2016/0...	48	73	121	624137	#sarepta	100	36	136	369678
accessdata.fda.gov/drugsatfda_...	18	94	112	943512	#pharma	28	67	95	659703
cnbc.com/2016/09/19/sarepta-th...	85	2	87	315545	#health	53	1	54	242579
bloomberg.com/news/articles/20...	65	16	81	241147	#biotech	40	11	51	174725
webmd.com/children/news/2016...	71	5	76	563827	#news	46	3	49	172660
statnews.com/pharmalot/2016/0...	23	21	44	158628	#muscular dystrophy	18	23	41	651109

Top Tweeters | Sep 16, 2016 - Sep 20, 2016

USERNAME	FOLLOWERS
FT Financial Times @FinancialTimes 5360296	
CNBC @CNBC 2422065	
SA Scientific Am... @sciam 1675271	
BI Business Ins... @businessins... 1635460	
WebMD @WebMD 1333200	
ABC News @abcnews 1163010	
Clay Matthe... @ClayMatthe... 994064	
NYT Health @NYTHealth 941163	
WSJ Health ... @WSJhealth 555682	
The Boston ... @BostonGlobe 527092	

FT Financial Times @FinancialTimes
Headlines from the FT. Follow us on @FT for news stories, features and updates. Our customer service team is @FTcare.
[Follow @FinancialTimes](#)

Location: Greater London, United Kingdom

Latest mention of: Duchenne (DMD)
[Financial Times @FinancialTimes](#) Sarepta shares surge 90% on FDA approval on.ft.com/2cLhRqJ

Top News Authors | Sep 16, 2016 - Sep 20, 2016

AUTHOR NAME	SITE	MENTIONS	TOTAL
Reuters	www.dailymail.co.uk	2	64
Associated Press	www.dailymail.co.uk	4	64
Rachel Wong	www.smh.com.au	1	60
Chronicle News Services	www.sfgate.com	1	59
newsfeeds@nzherald.co.nz	www.nzherald.co.nz	3	59
By The Associated Press	www.chron.com	1	58
Rachel Wong	www.theage.com.au	1	58
newsfeedback@fool.com (Todd Campbell)	www.fool.com	2	58
Associated Press	www.bostonherald.com	1	56
Todd Campbell	www.foxbusiness.com	1	56
Total for top authors		17	

DMD Social Media 9/19 P.M. report
15M+ reach for topic (FDA/DMD) on Twitter

Key Insights | Duchenne (DMD) | Sep 19, 2016

Total Mentions

1066
▲ 6563%
Previous Period: 16

Unique Authors

761
▲ 7510%
Previous Period: 10

Trending Topics

1. drug to treat Duchenne muscular dystro...
2. treat Duchenne muscular dystrophy
3. Sarepta drug

Top News Stories

1. FDA tentatively approves 1st drug for ...
2. Twitter to lay off some employees at de...
3. BRIEF-GoPro announces pricing of Her...

Mentions Over Time by Day

Mentions by Hour of Day | Duchenne (DMD) | Sep 19, 2016

DMD Social Meida 9/19 A.M. report

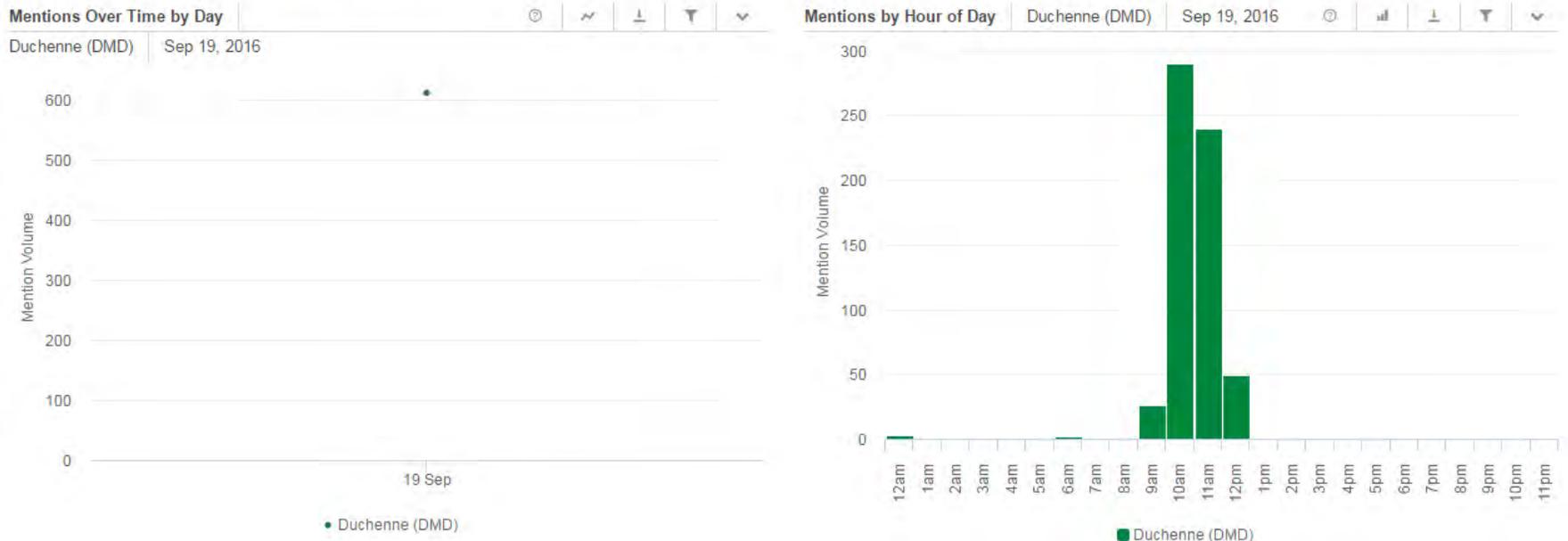
14M+ reach for topic (FDA/DMD) on Twitter

Total Mentions up 7550%

Unique Authors up 6786%

Key Insights | Duchenne (DMD) | Sep 19, 2016

Total Mentions 612 ▲ 7550% Previous Period: 8	Unique Authors 482 ▲ 6786% Previous Period: 7	Trending Topics 1. Duchenne Muscular Dystrophy drug 2. Sarepta's keenly watched muscle 3. 13 percent	Top News Stories 1. FDA grants accelerated approval to con... 2. BRIEF-Monte dei Paschi ends session ... 3. Phone game Pokemon GO distracts dri...
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Tweets from the Hill

Dan Donovan @RepDanDonovan · 6m
Happy to hear @US_FDA approved #DuchenneMuscularDystrophy treatment!
@PietrosFight

Rep. Erik Paulsen @RepErikPaulsen · 2h
Glad @US_FDA approved first drug treatment for Duchenne muscular dystrophy. I sent them letter in July urging an expedited approval process

Additional Tweets of Note

[The Boston Globe](#) @BostonGlobe [13 minutes ago](#)

As condition of FDA's approval of Sarepta drug, company will conduct two-year randomized controlled trial bos.gl/XLARdII

[Kimberly Leonard](#) @leonardkl [2h2 hours ago](#)

FDA has fast-tracked a drug to treat Duchenne muscular dystrophy: [http://www.usnews.com/news/articles/2016-09-19/fda-fast-tracks-drug-for-duchenne-muscular-dystrophy?src=usn_tw ...](http://www.usnews.com/news/articles/2016-09-19/fda-fast-tracks-drug-for-duchenne-muscular-dystrophy?src=usn_tw...) #DMD

[Medscape](#) @Medscape [1h1 hour ago](#)

NEWS ALERT: FDA grants accelerated approval for eteplirsen, first drug approved for DMD patients.

[Forbes](#) @Forbes [38 minutes ago](#)

Sarepta has won a long-sought-after approval for its drug to treat DMD, but with a catch: on.forbes.com/6015B7dOF <https://t.co/MXz1gxzC3O>

[Laura Helbling](#) @Laura_H [2m2 minutes ago](#)

Per Sarepta **eteplirsen** summary review, Commissioner Califf deferred to CDER Director Woodcock's judgment. - http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf ...

[C. Michael Gibson MD](#) @CMichaelGibson [7m7 minutes ago](#)

Wow #Eteplirsen approved by FDA http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/206488Orig1s000ltr.pdf ...

[Adam Feuerstein](#) [Verified account](#) @adamfeuerstein [14m14 minutes ago](#)

And there it is.... \$SRPT **eteplirsen** approved. FDA letter → http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/206488Orig1s000ltr.pdf ...

[Donna Young](#) @DonnaYoungDC [8m8 minutes ago](#)

Donna Young Retweeted Donna Young

#FDA PR & letter for \$SRPT #eteplirsen <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm> ...

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/206488Orig1s000ltr.pdf ... #Duchenne #DMD #biotech

[Michael McCaughan](#) @RPMReportMike [12m12 minutes ago](#)

Eteplirsen approval letter signed by CDER Director Woodcock. Decision was appealed to Califf, who deferred to Woodcock. Unger appealed.

David Maizenberg @biologypartners 43s44 seconds ago

FDA approves Sarepta's **Eteplirsen**. Stock skyrockets. DMD families celebrate. Statisticians frown. Many essays will b written about this saga

Marilynn Marchione **Verified account** @MMarchioneAP 1m1 minute ago

A win for rare disease advocates: #FDA approves 1st Duchenne #musculardystrophy drug, \$SRPT Sarepta's **eteplirsen** <http://tinyurl.com/zboal5z>

Kim McCleary @KimTweetsDC 19m19 minutes ago

#FDA will require #Sarepta to conduct addl study to confirm clinical benefit of **#eteplirsen**.

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm> ... #Duchenne #DMD

From: [Sherman, Rachel](#)
To: [Davies, Kathleen](#); [Soreth, Janice M](#)
Cc: [Califf, Robert](#); [McCall, Jonathan *](#)
Subject: FW: Can you send me the latest version of Rob's appeal memo?
Date: Thursday, September 08, 2016 4:40:31 PM
Attachments: [2016_Sept_08_Eteplirsen_JM_CLEAN-COMMENTED.doc](#)
[2016_Sept_08_Eteplirsen_JM_TRACKED.doc](#)
[Cover note_Sept-8-2016_JM_CLEAN.doc](#)
[Cover note_Sept-8-2016_JM_TRACKED.doc](#)

Hi guys,

I offered the two of you up as judicious, careful, ex (or semi ex) CDER readers. Please review and see if anything pops out at you.

If possible tonight or early tomorrow. Let me know if you want to discuss. And thank you!!

Rachel

PS Please see Jonathan's request below. Needless to say, I have not been good about version control (although I have tried).....

From: McCall, Jonathan *
Sent: Thursday, September 08, 2016 4:36 PM
To: Sherman, Rachel
Subject: RE: Can you send me the latest version of Rob's appeal memo?

You bet. This is a tidied version (clean and tracked) that I put together this afternoon; I'm also including the cover letter.

One request: if you make changes, can you make them to the tracked version? I'll take that and re-create a clean/commented version for tomorrow.

Thanks!

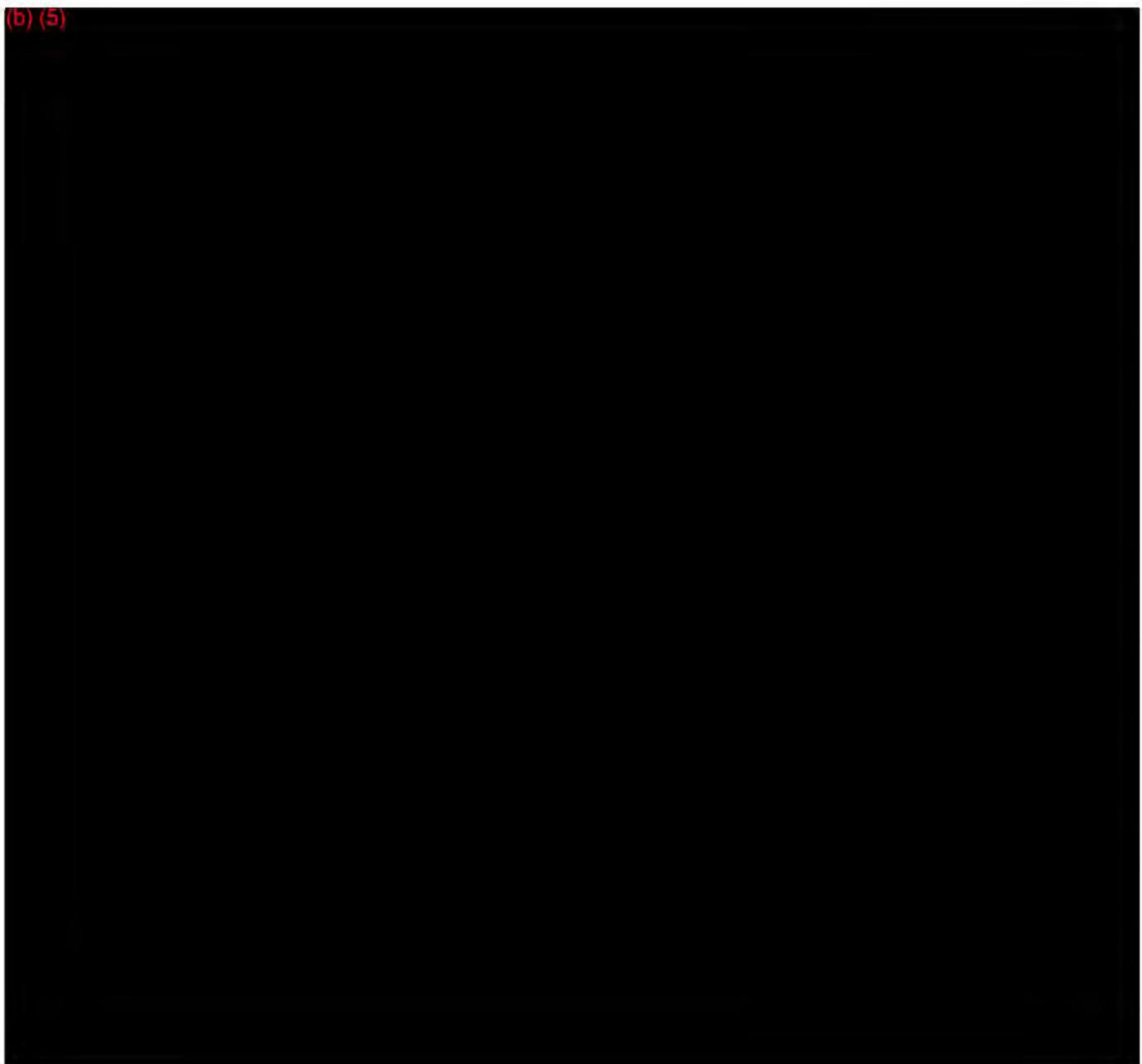
--

J

From: Sherman, Rachel
Sent: Thursday, September 08, 2016 4:32 PM
To: McCall, Jonathan *
Subject: Can you send me the latest version of Rob's appeal memo?

Thanks!

(b) (5)



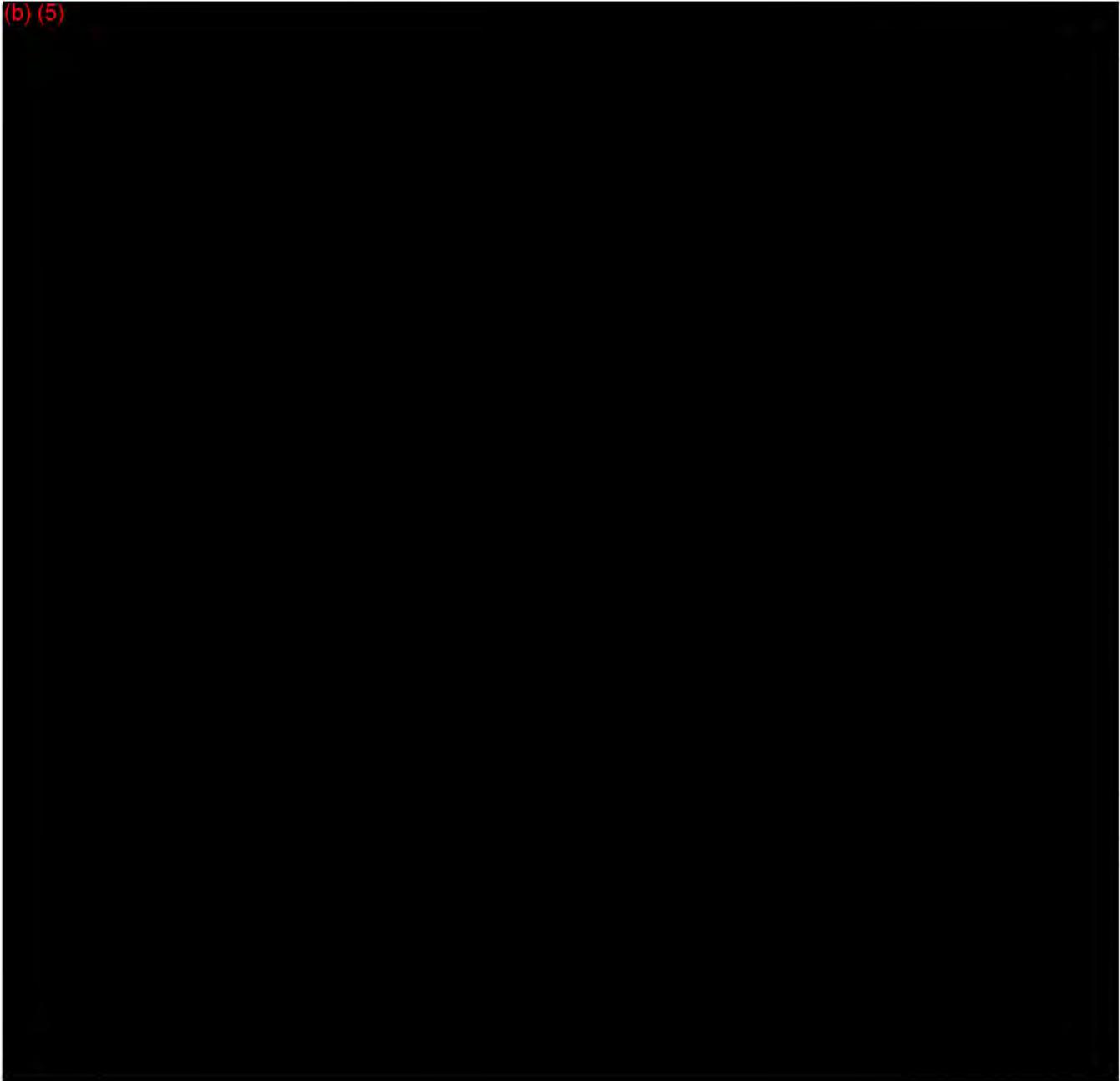
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(b) (5)



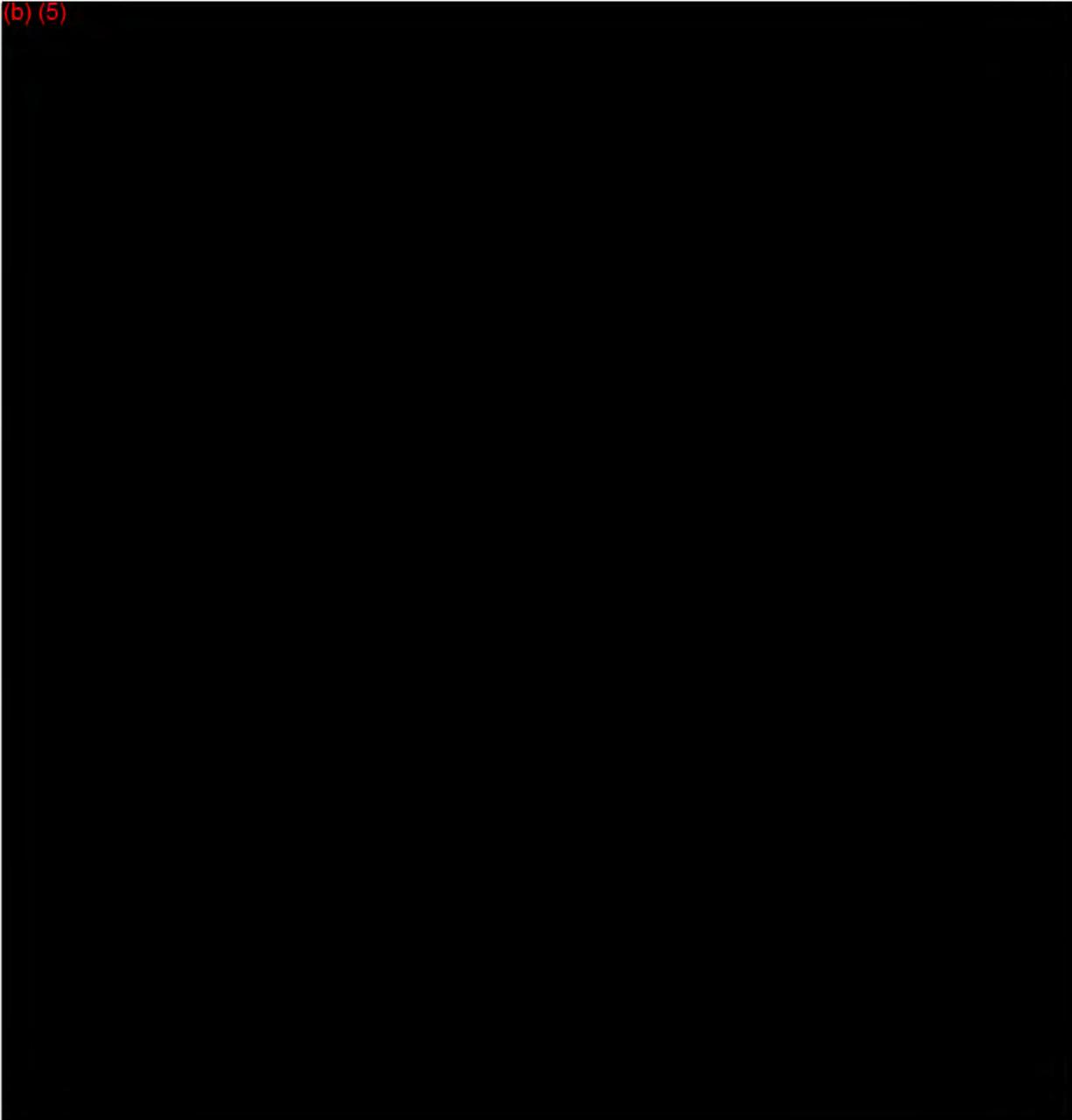
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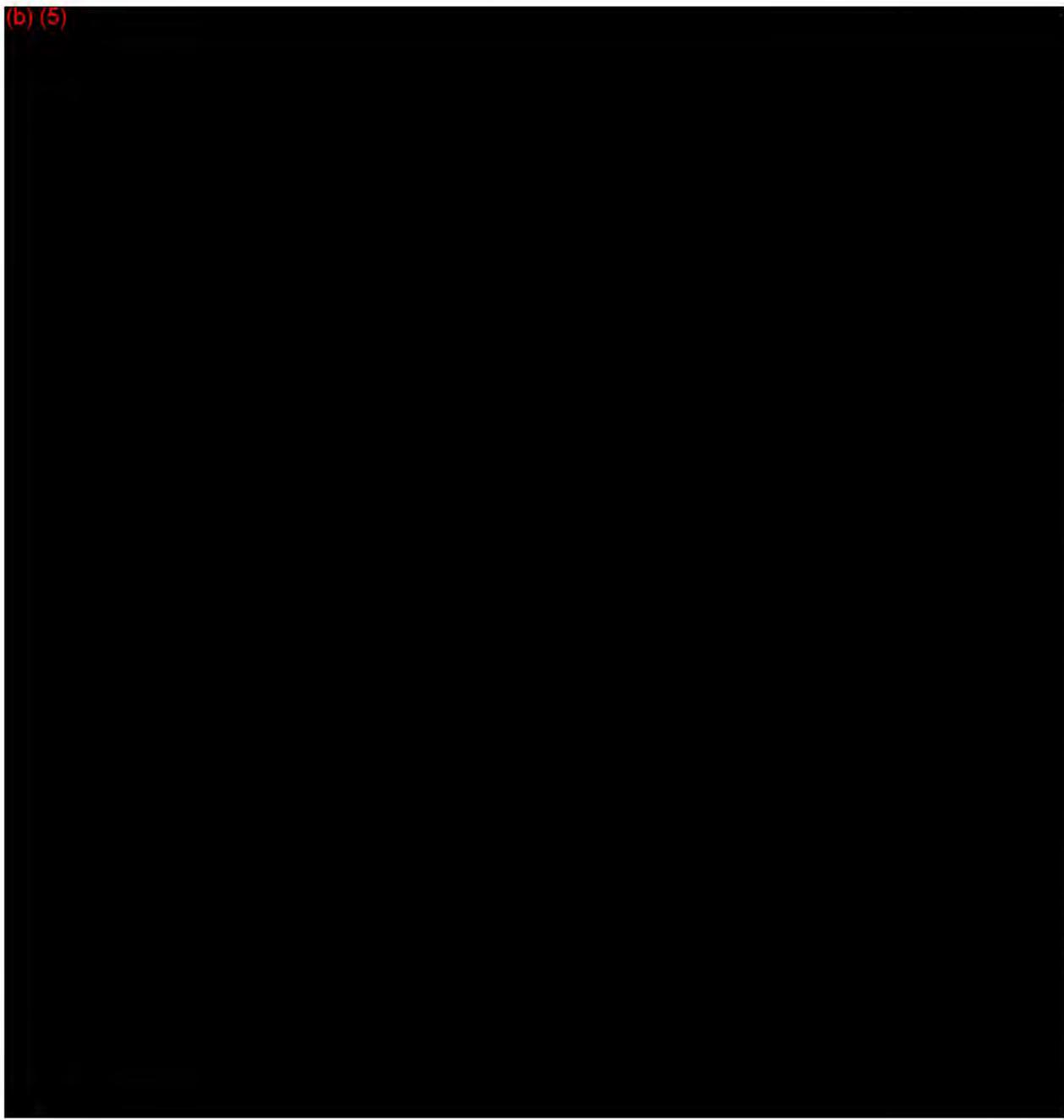
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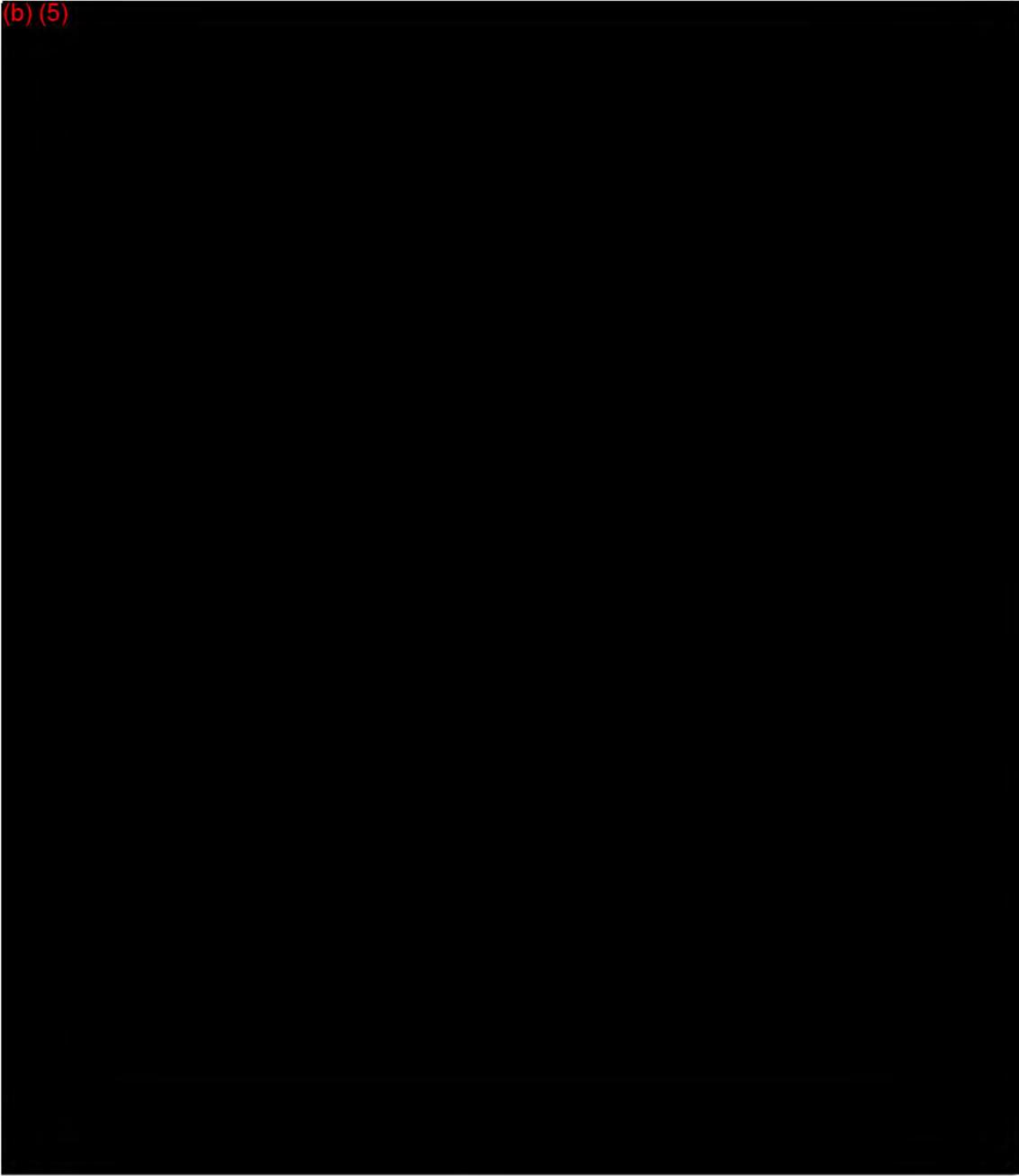
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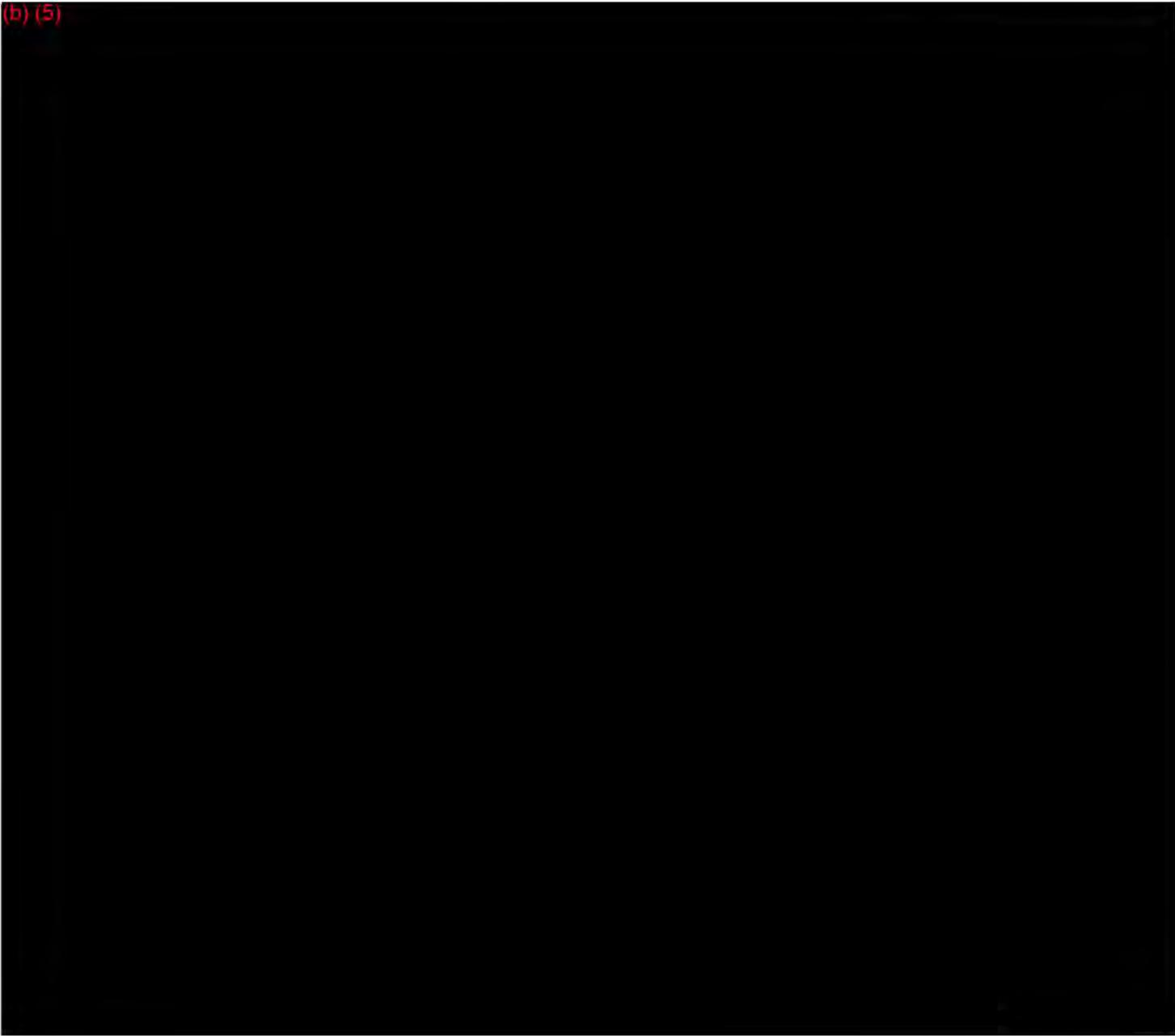
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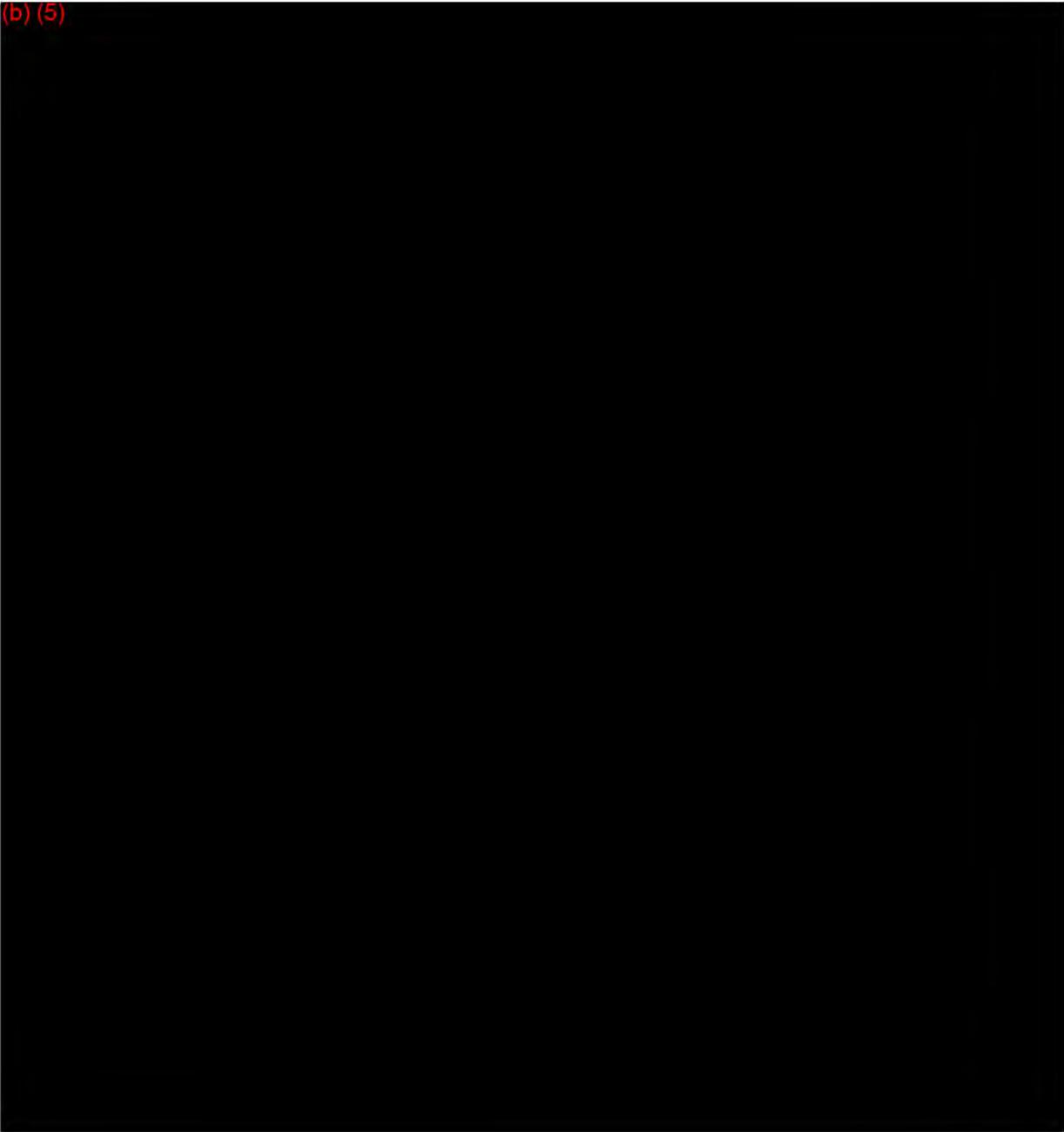
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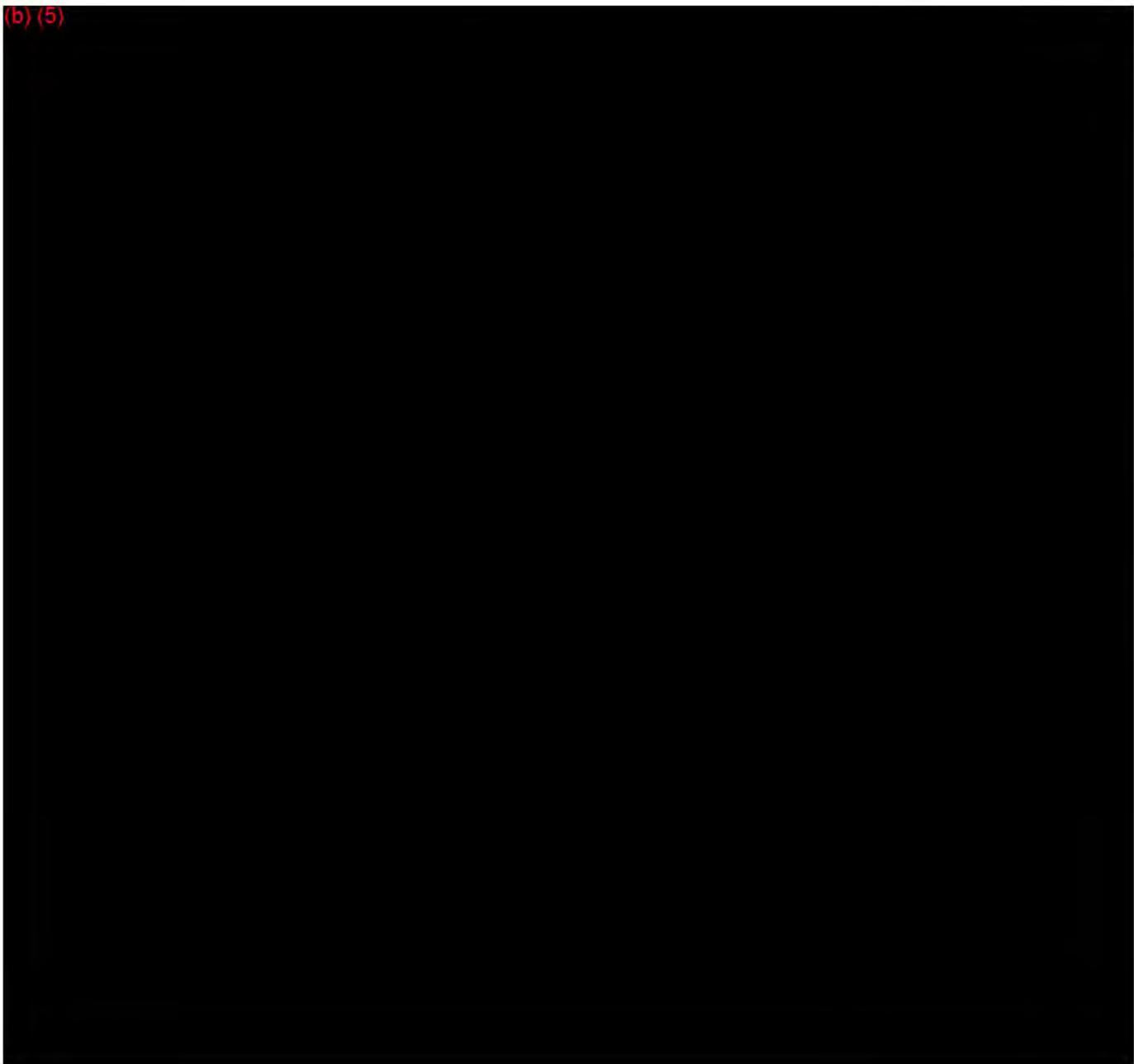
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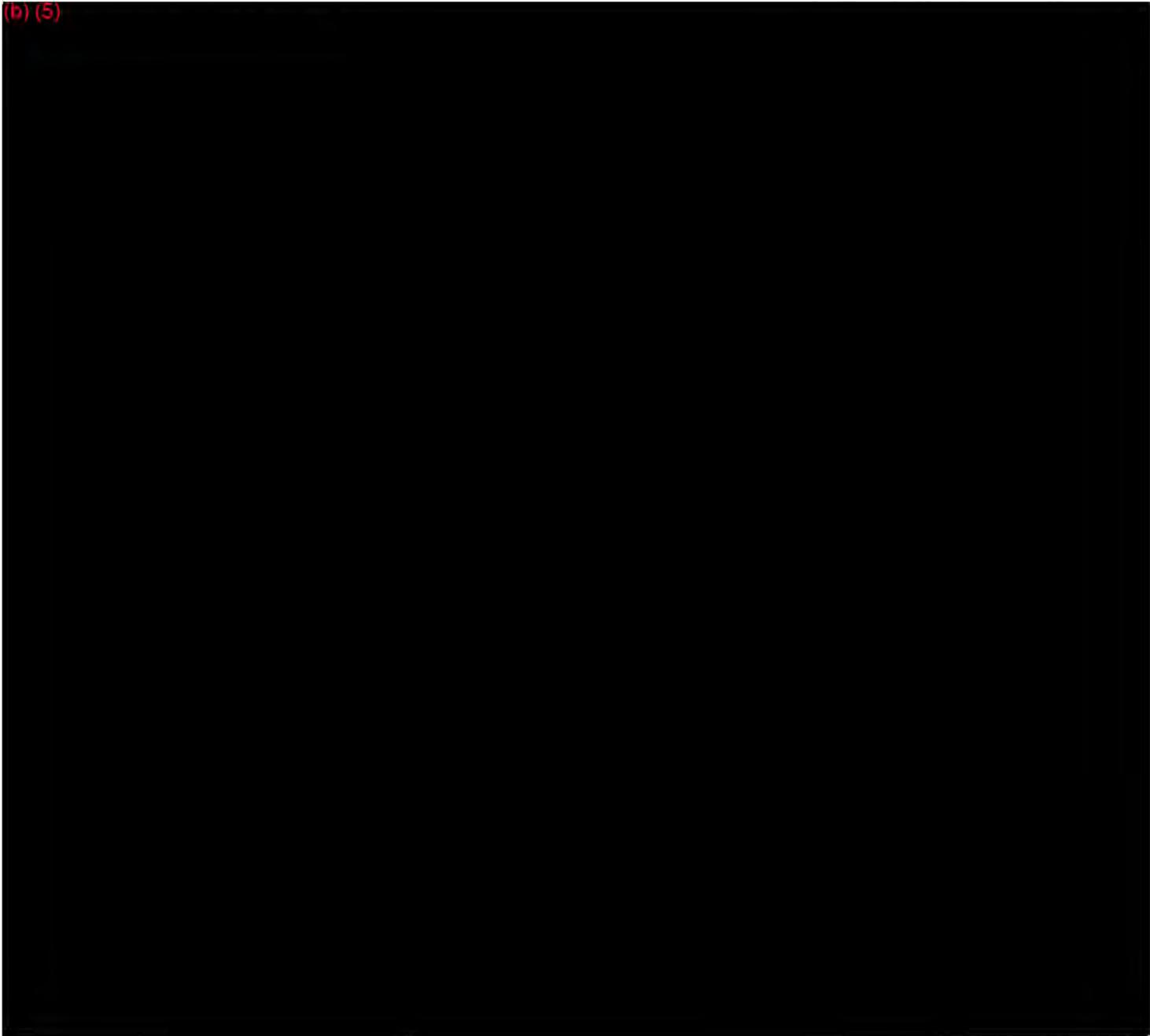
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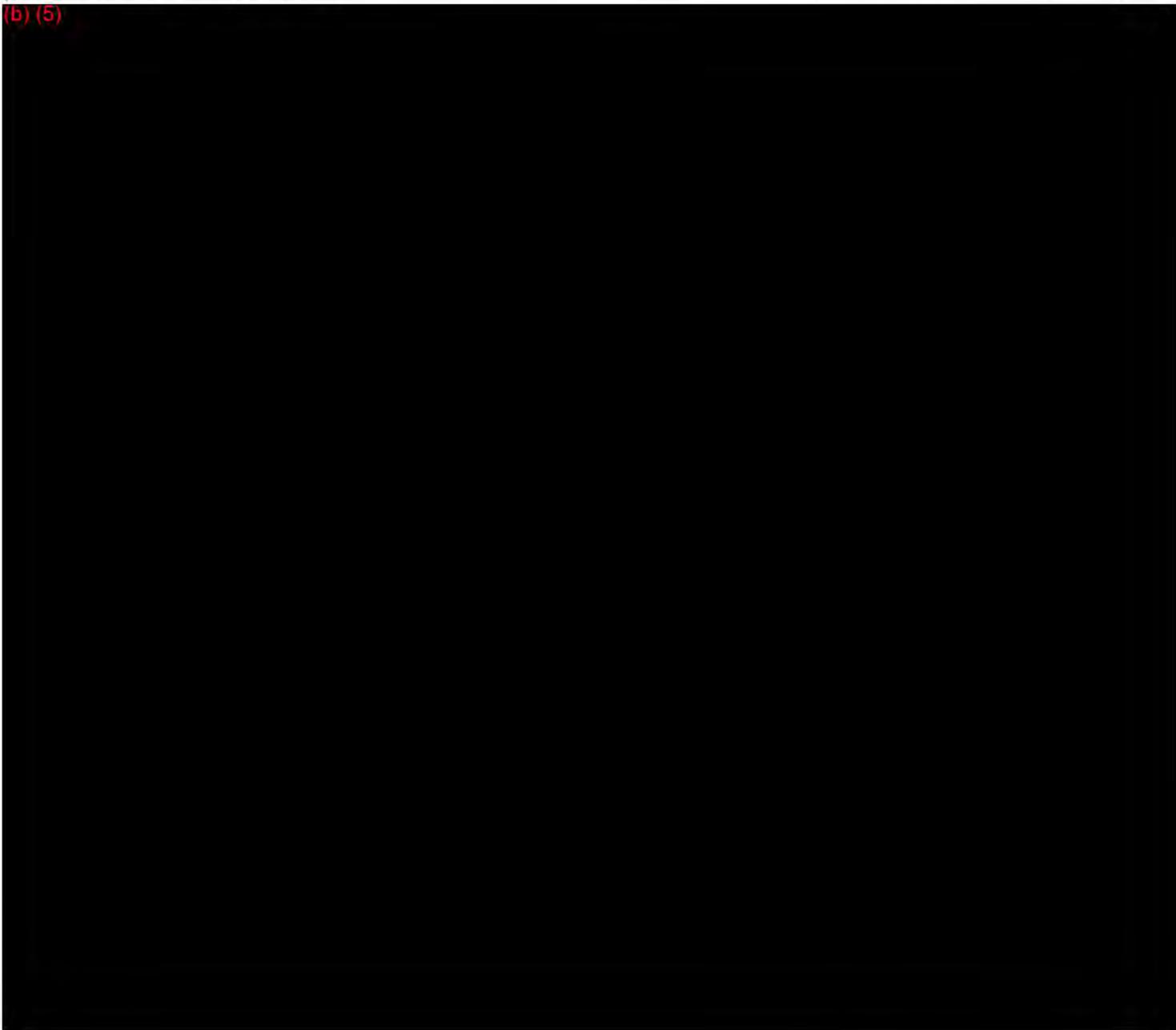
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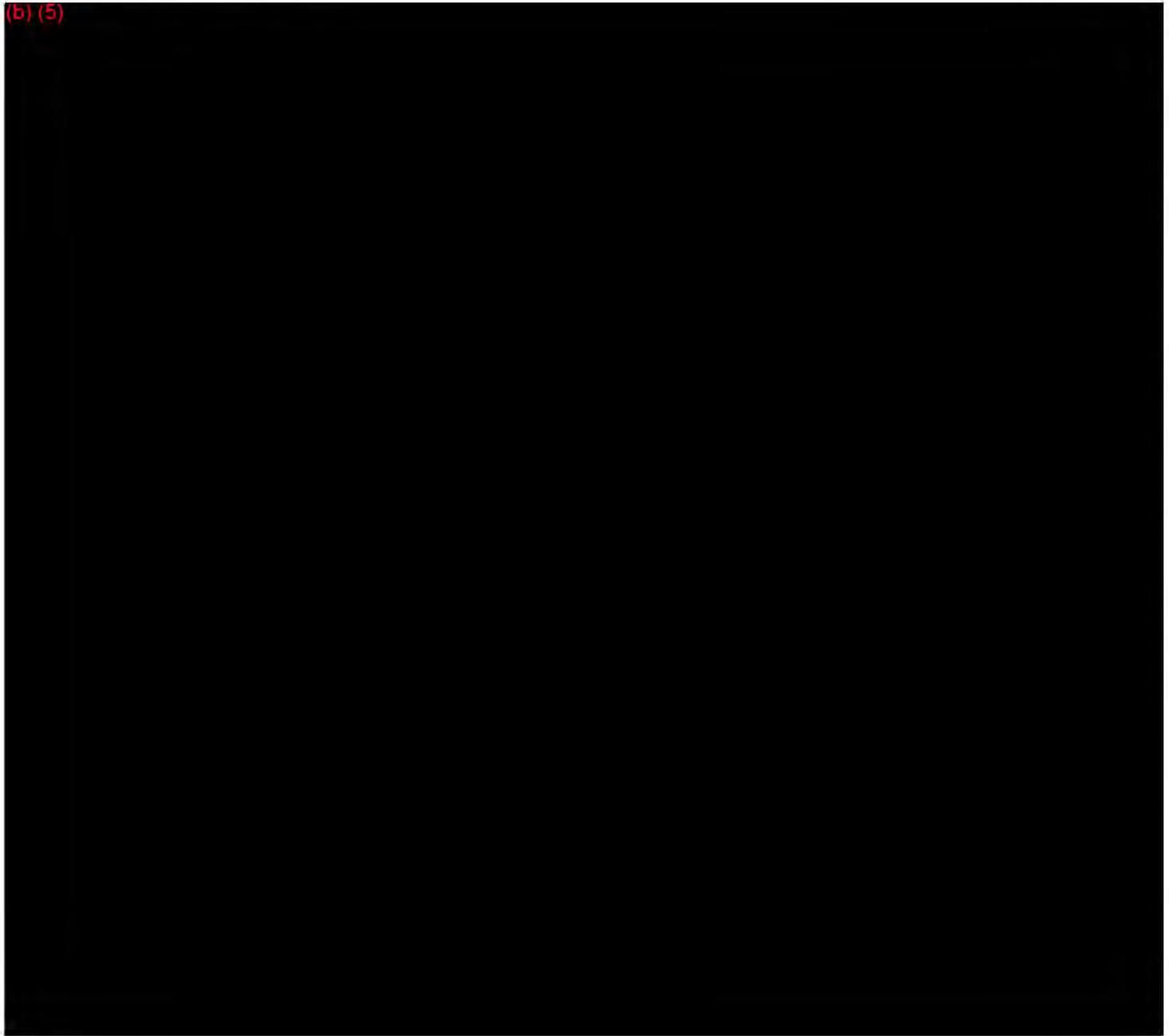
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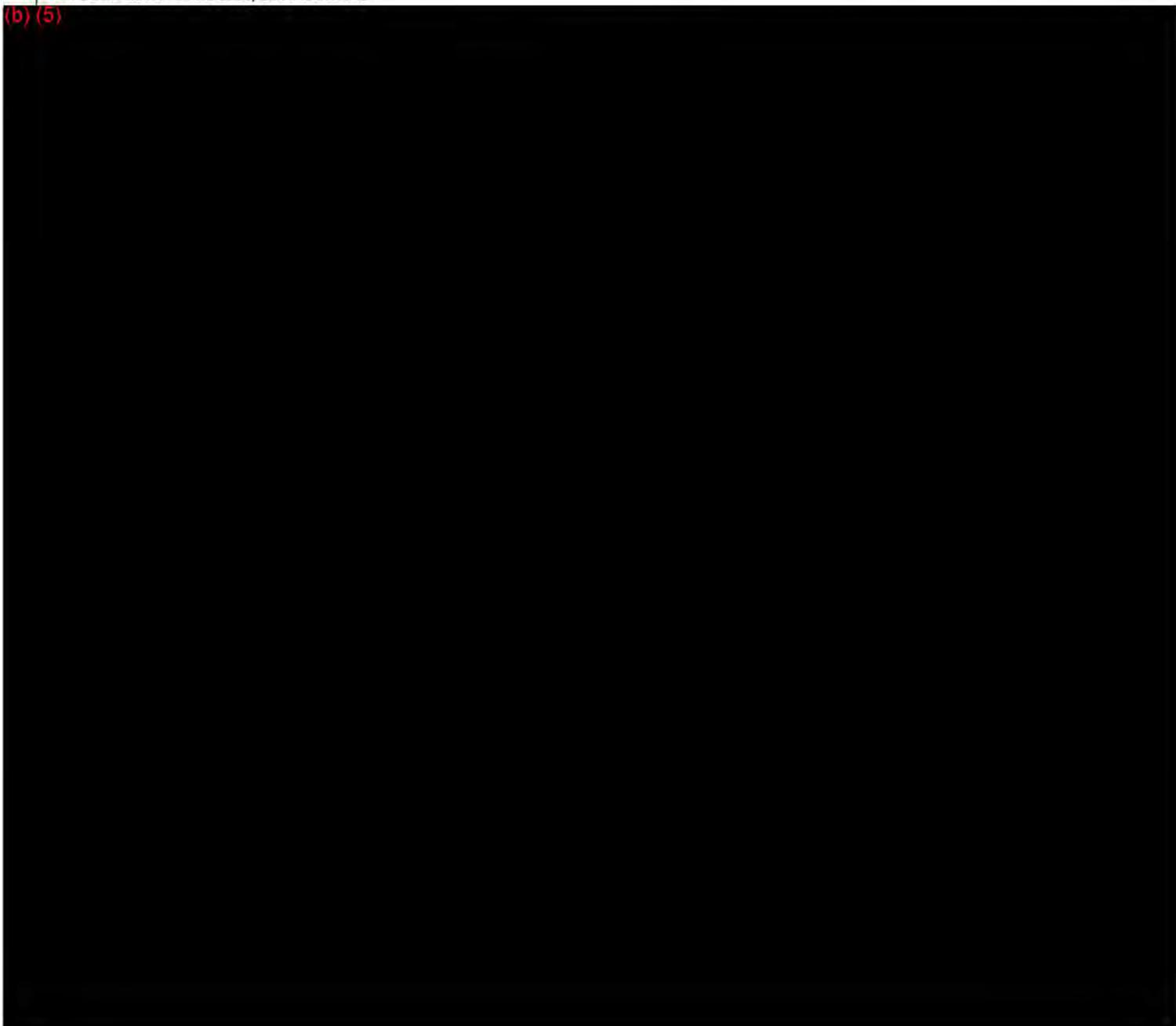
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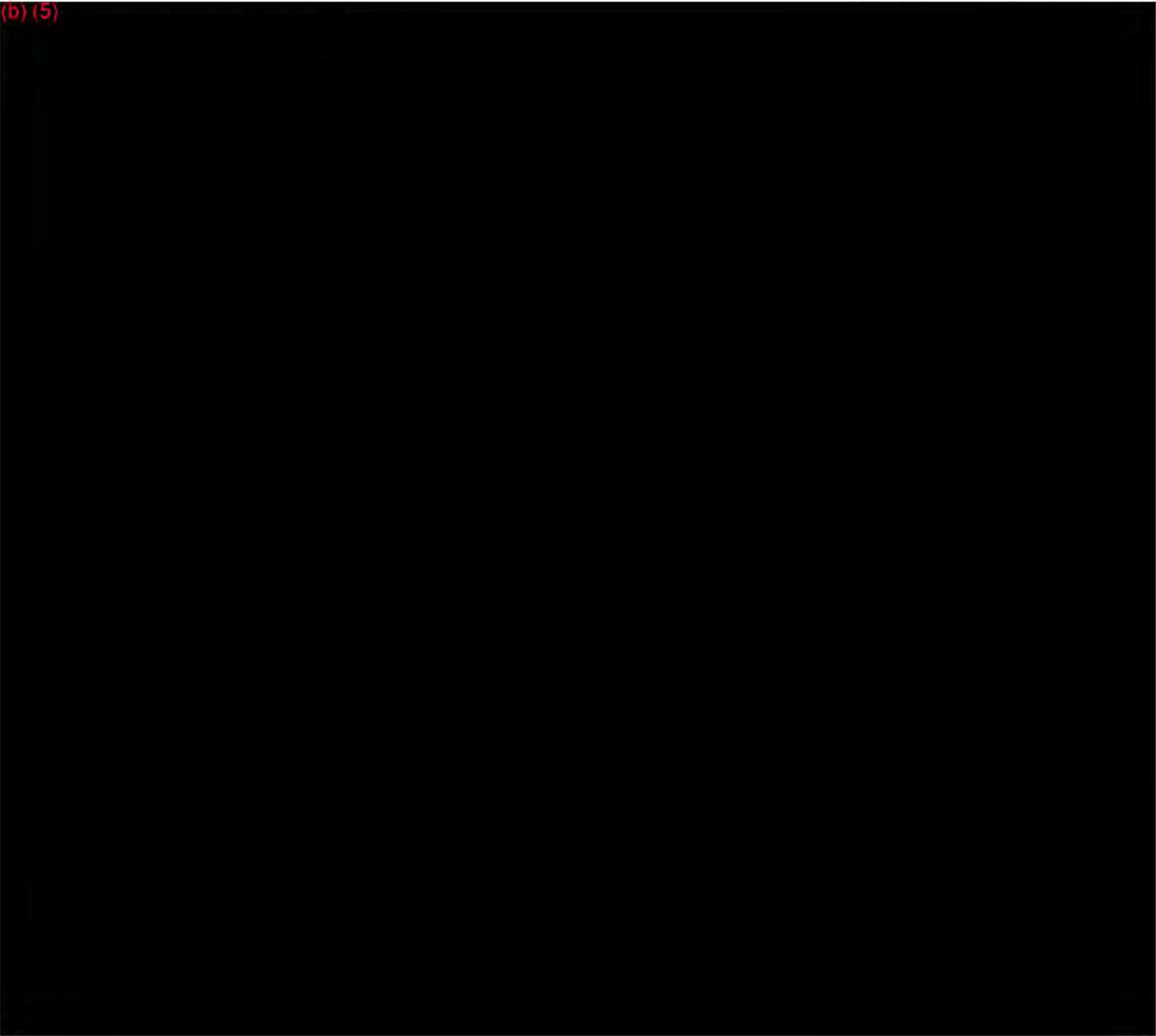
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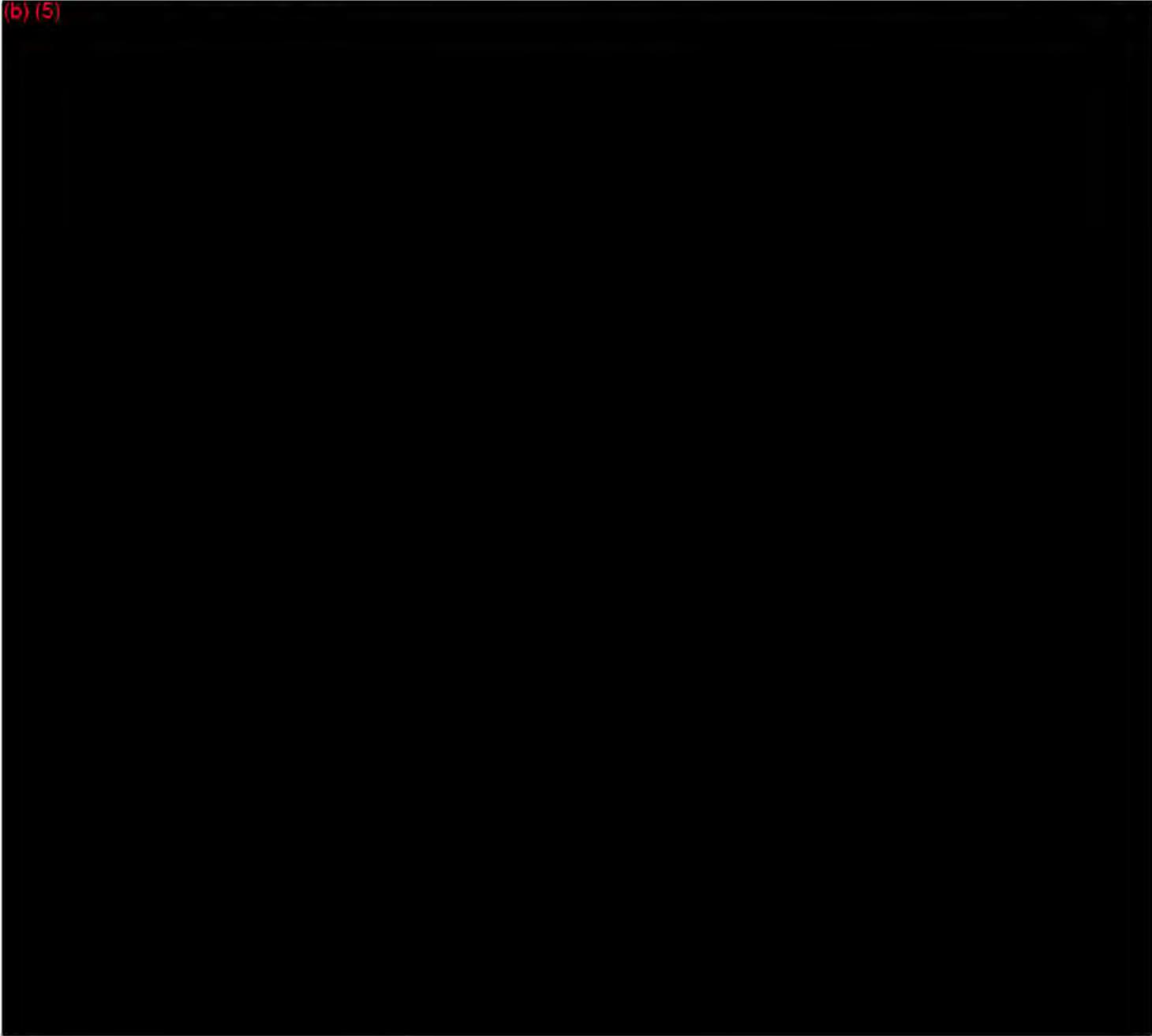
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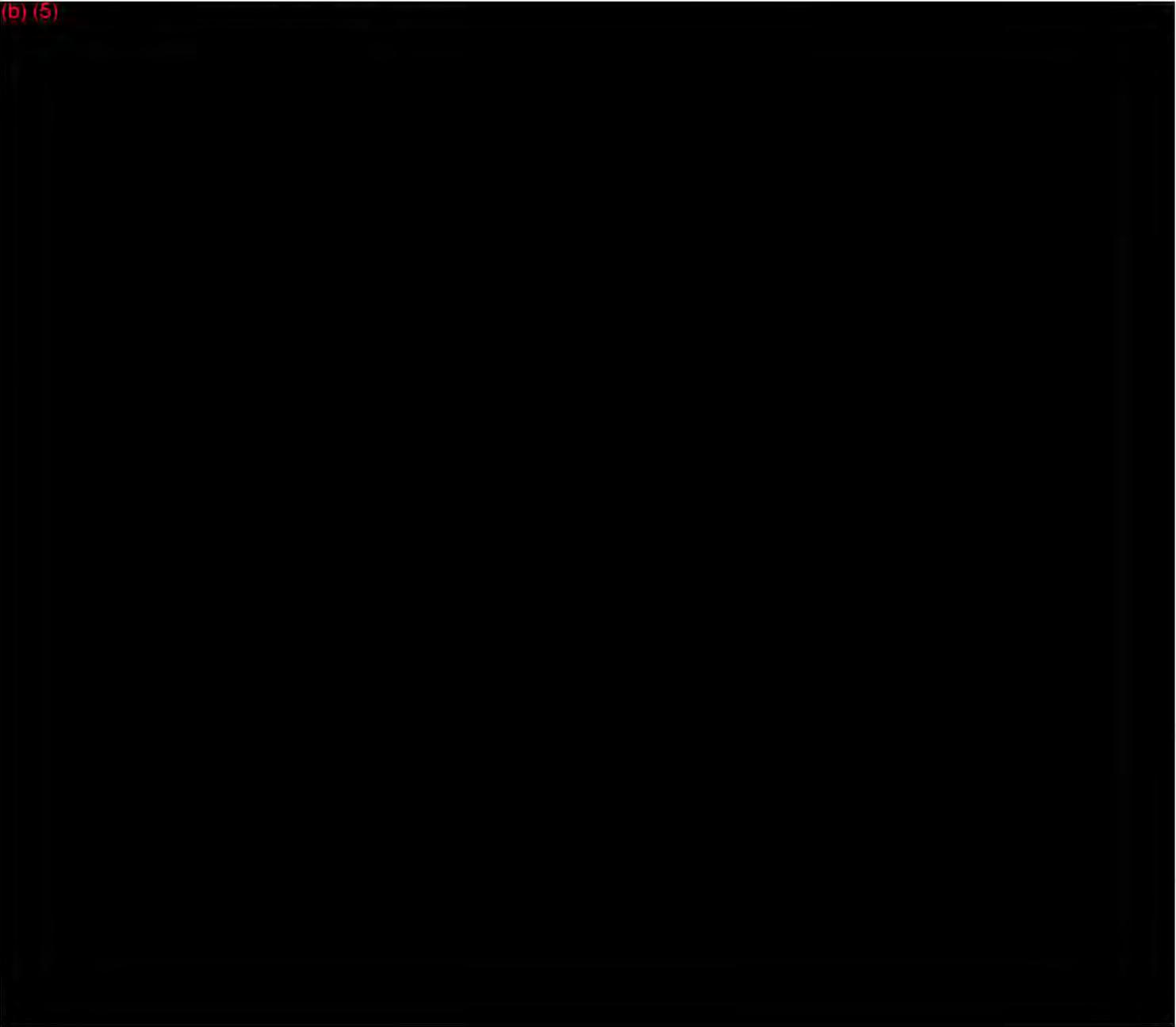
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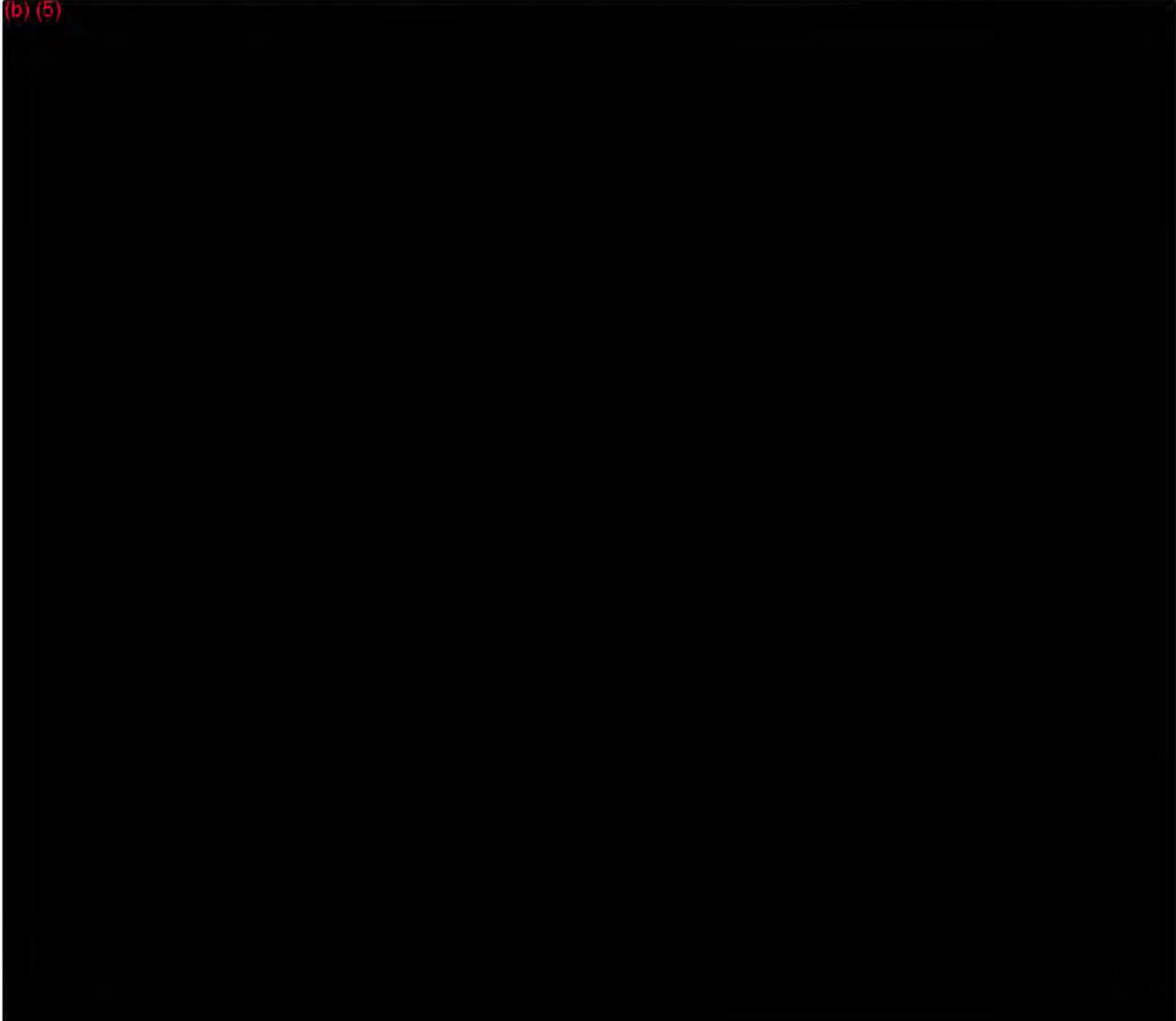
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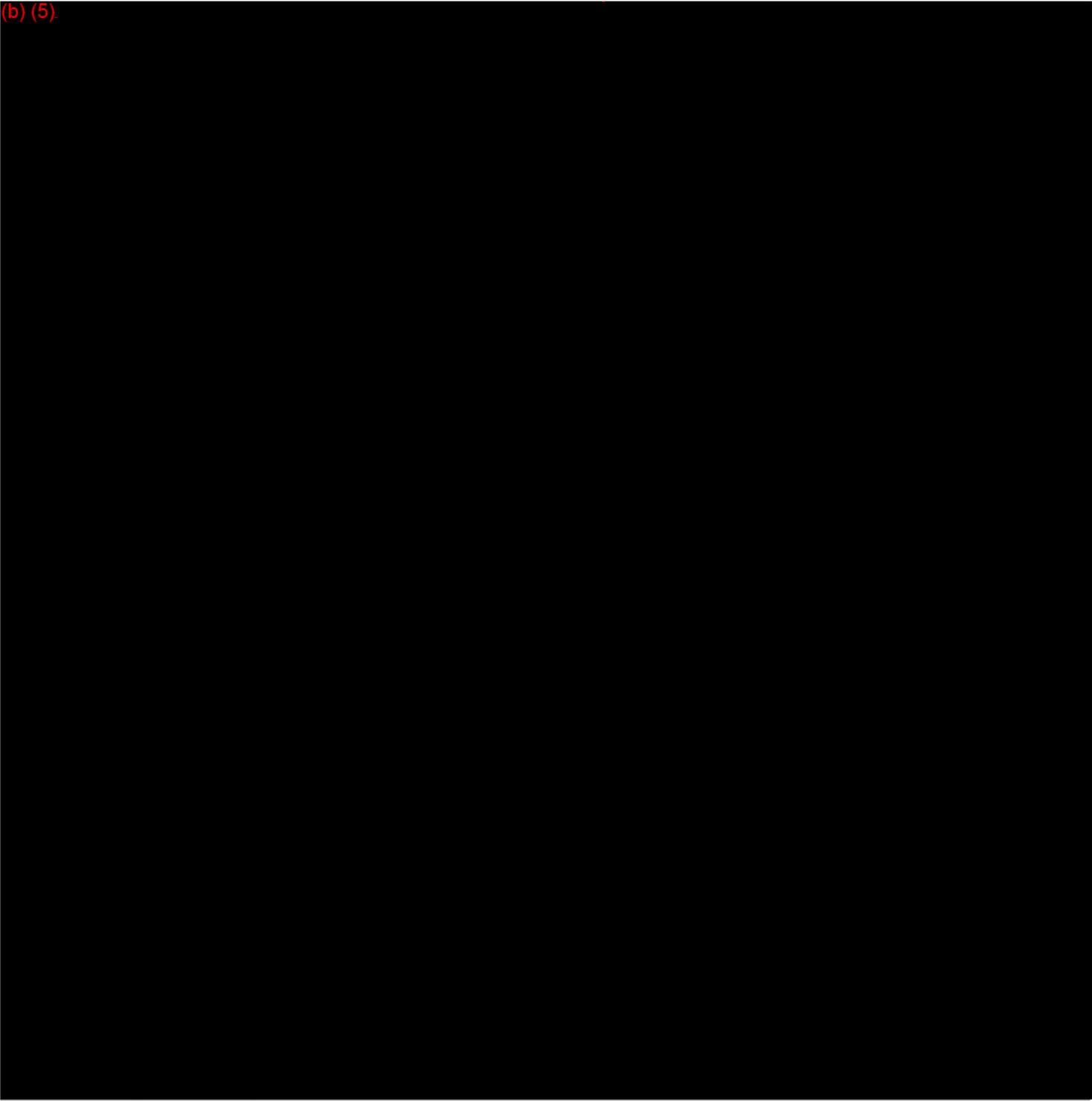
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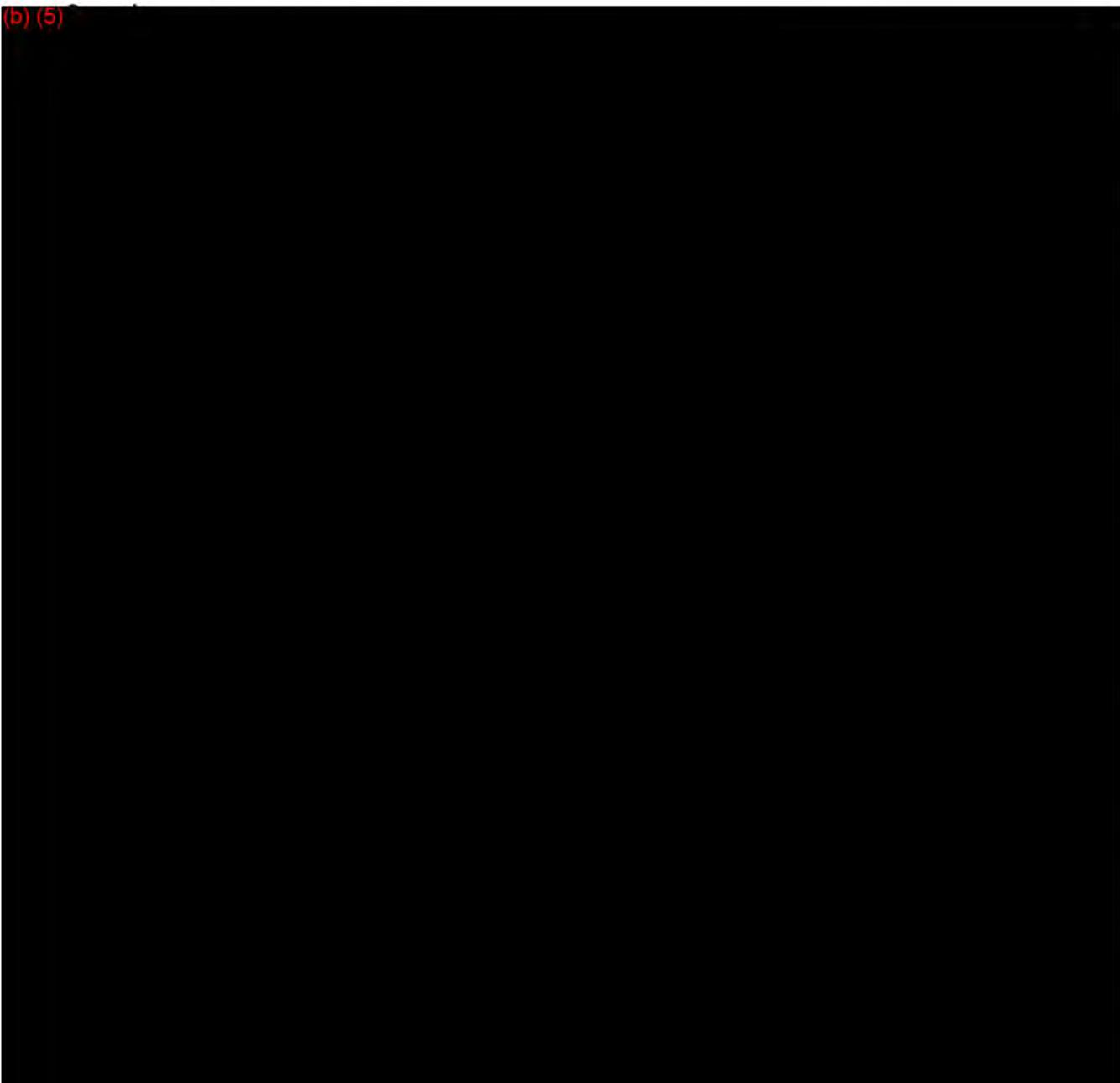
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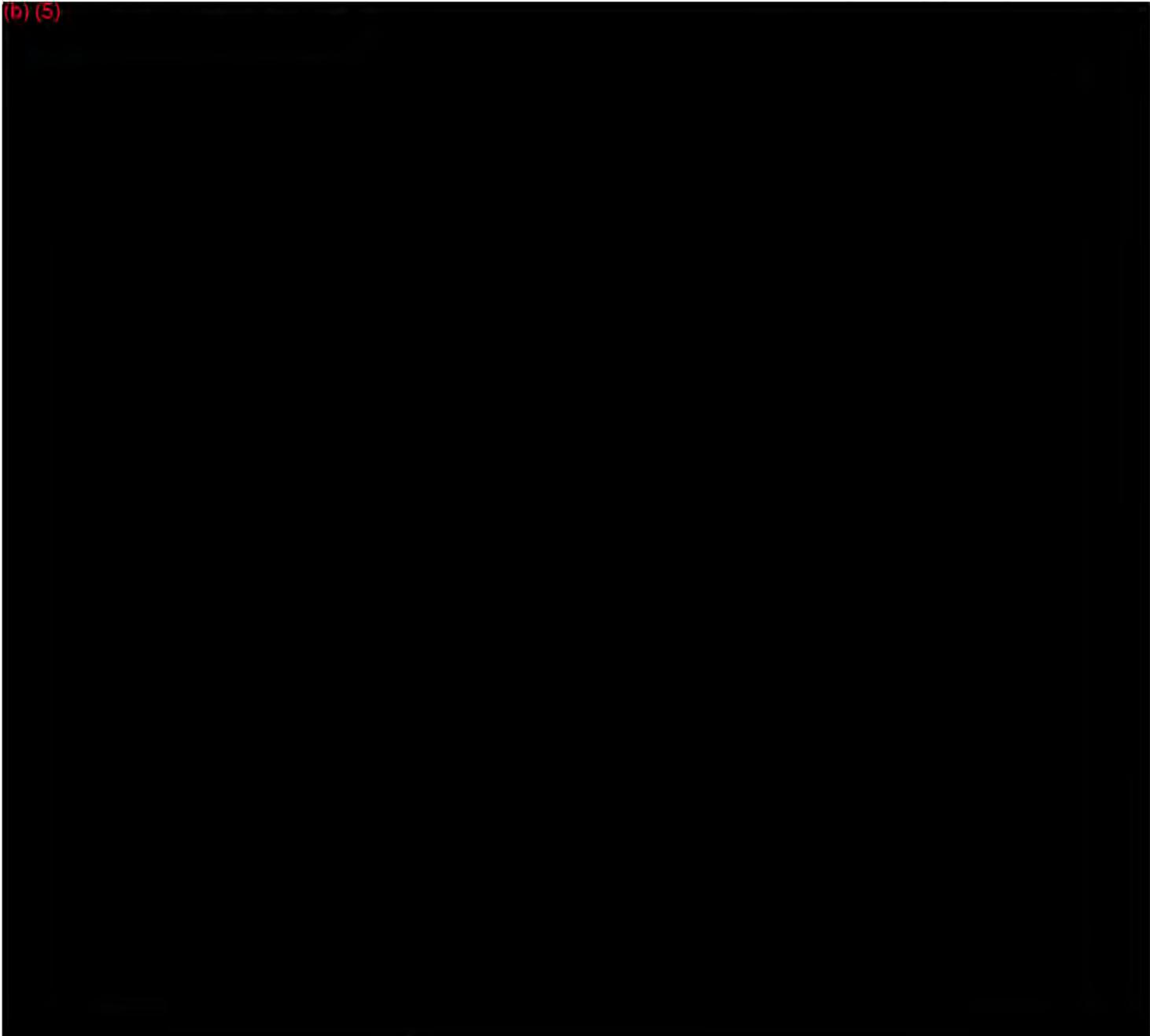
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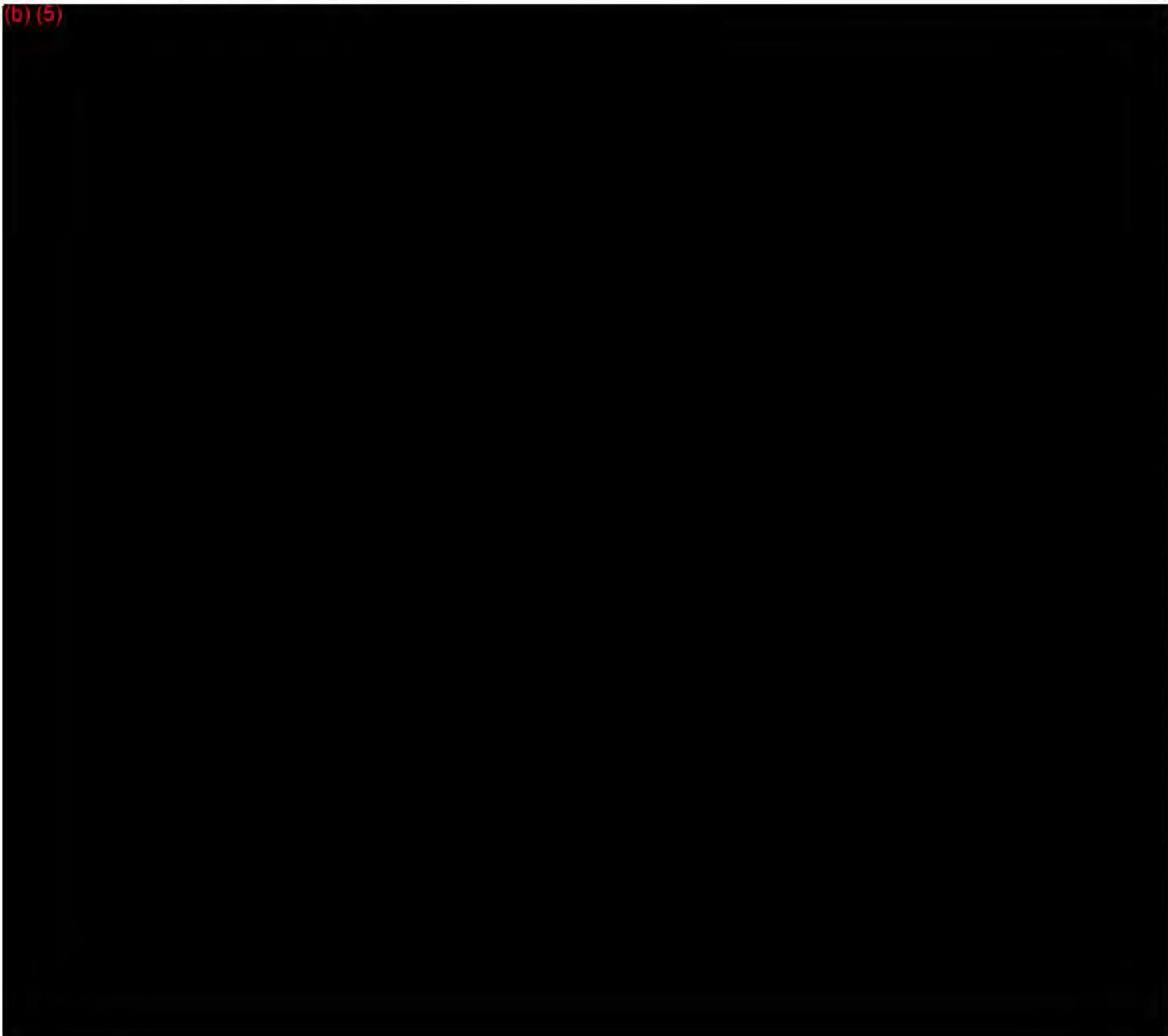
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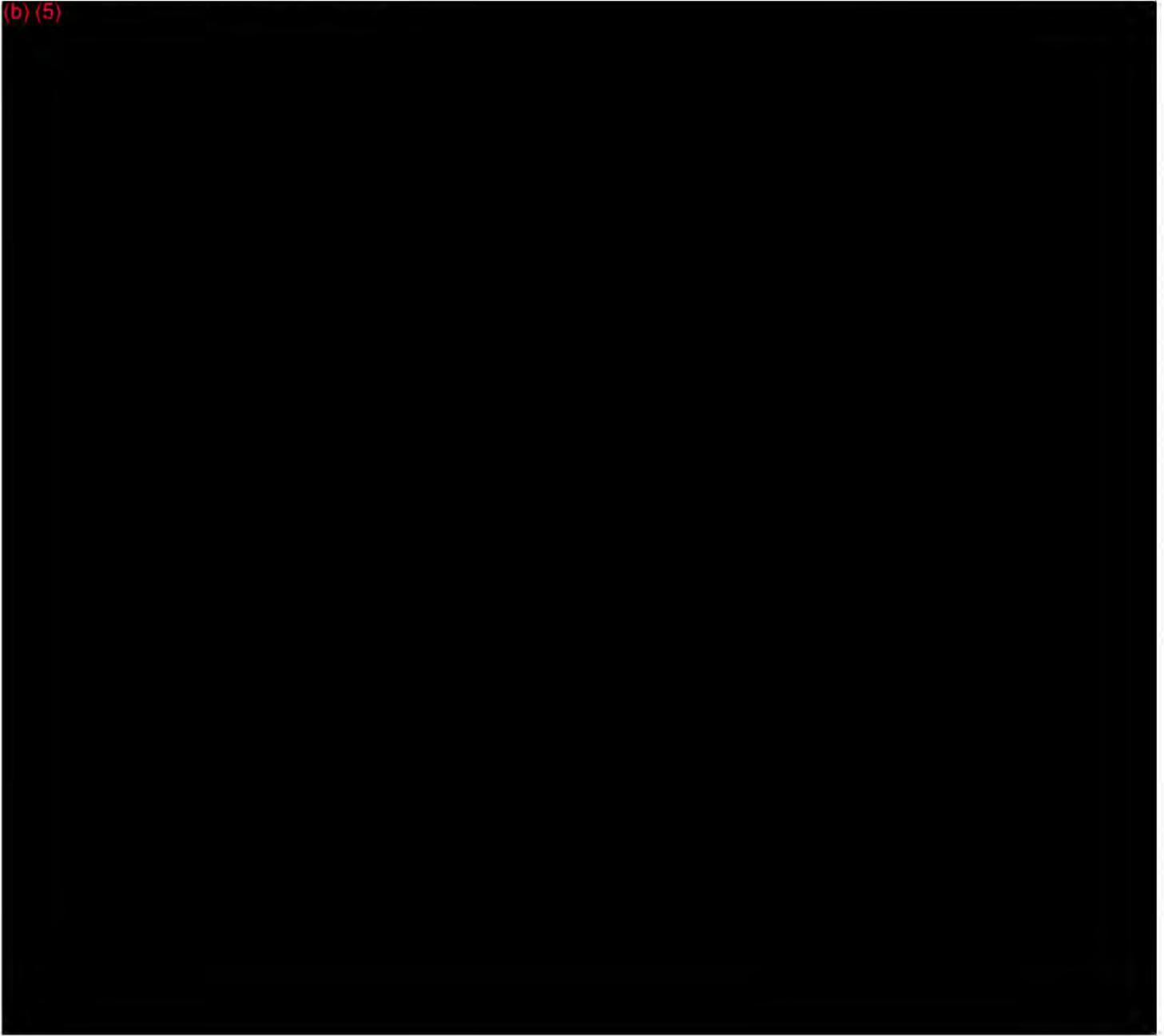
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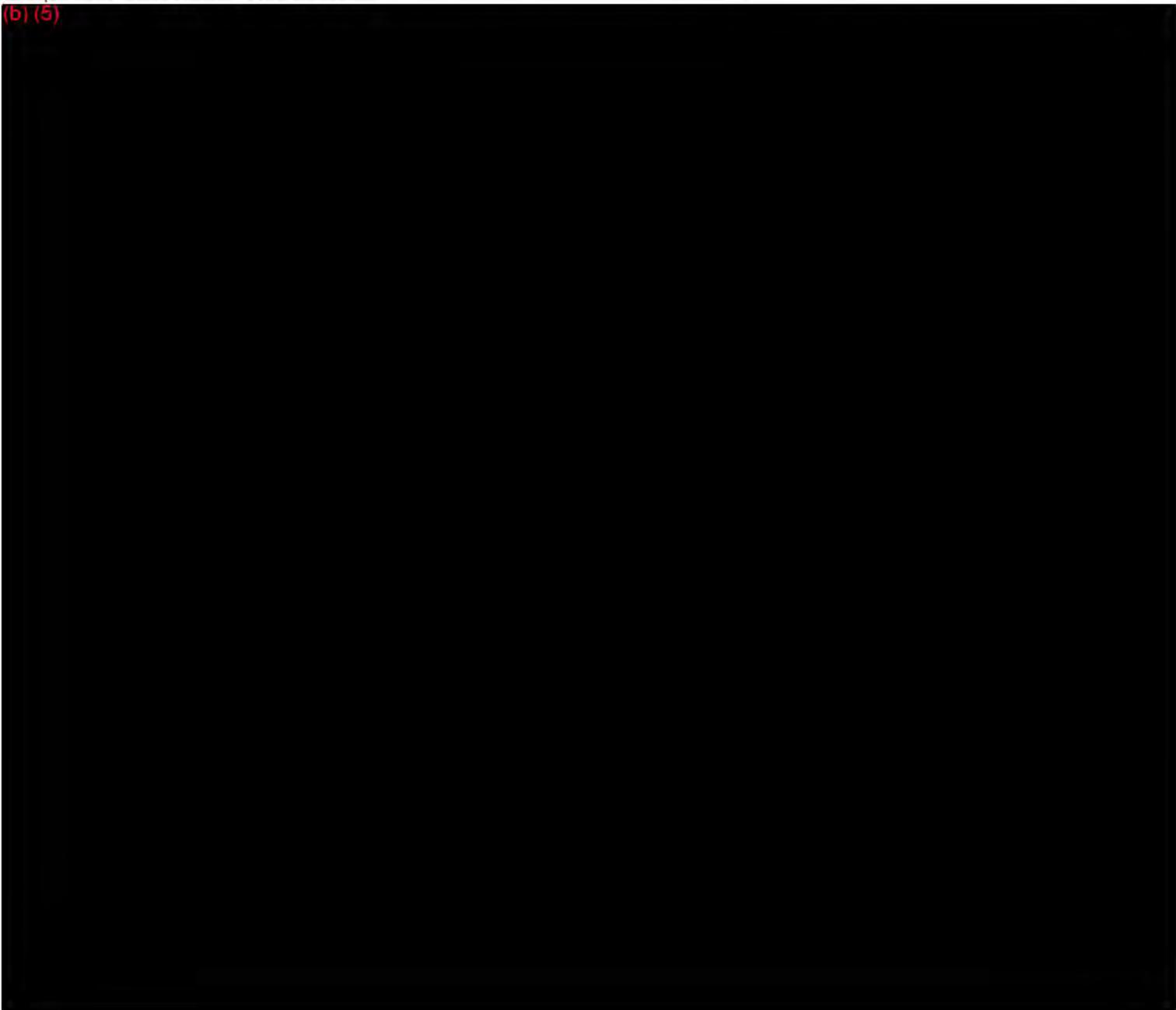
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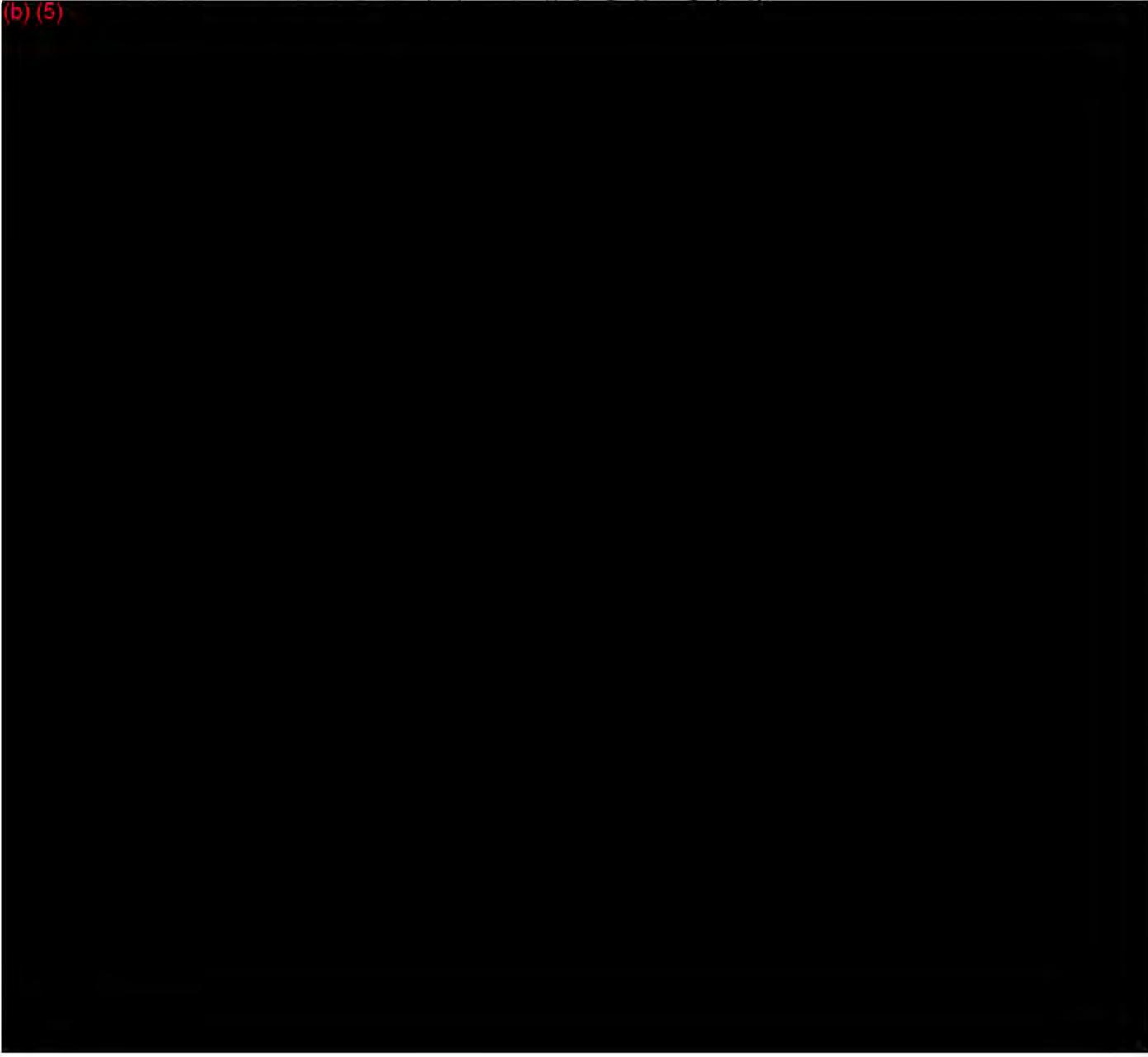
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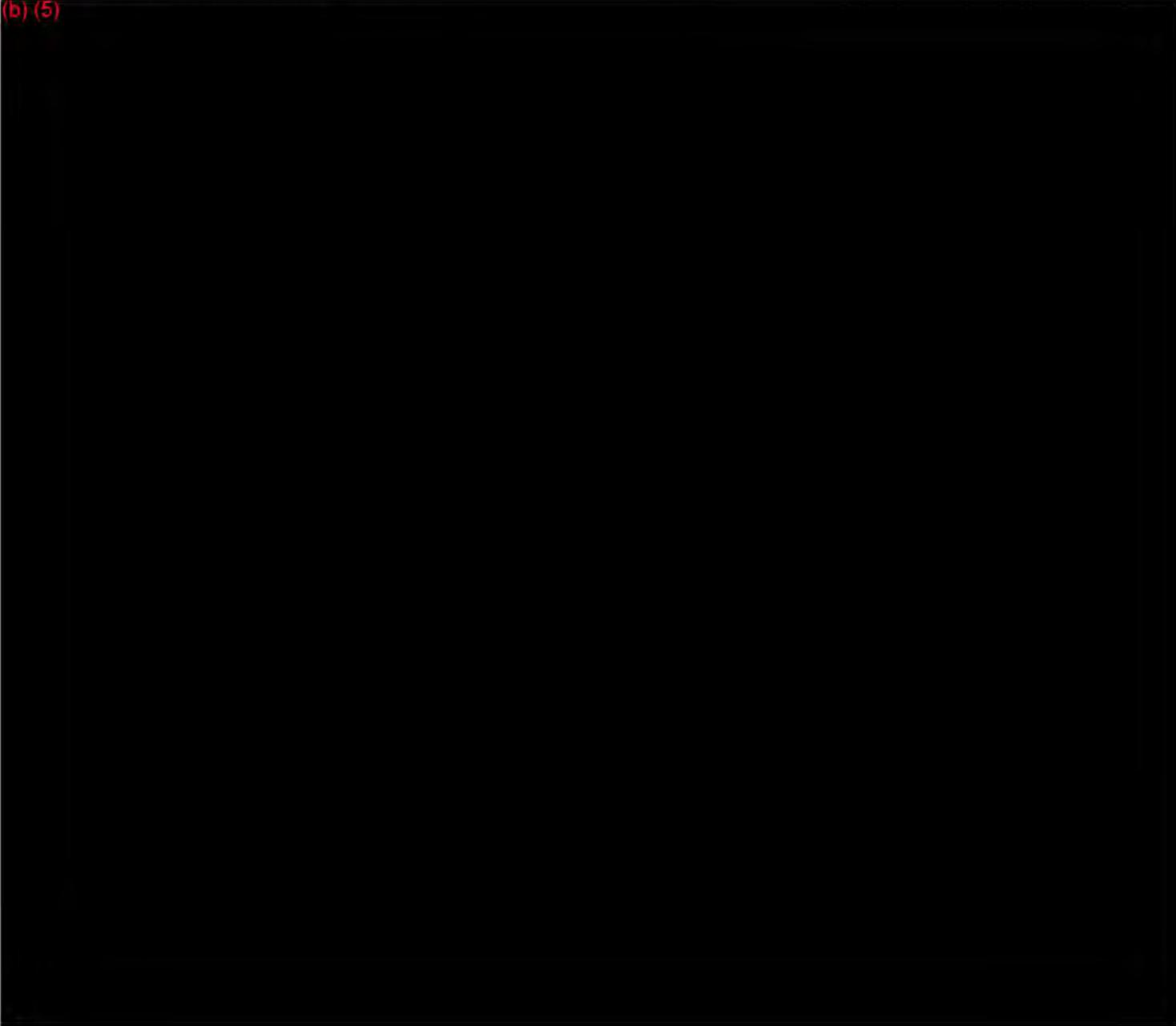
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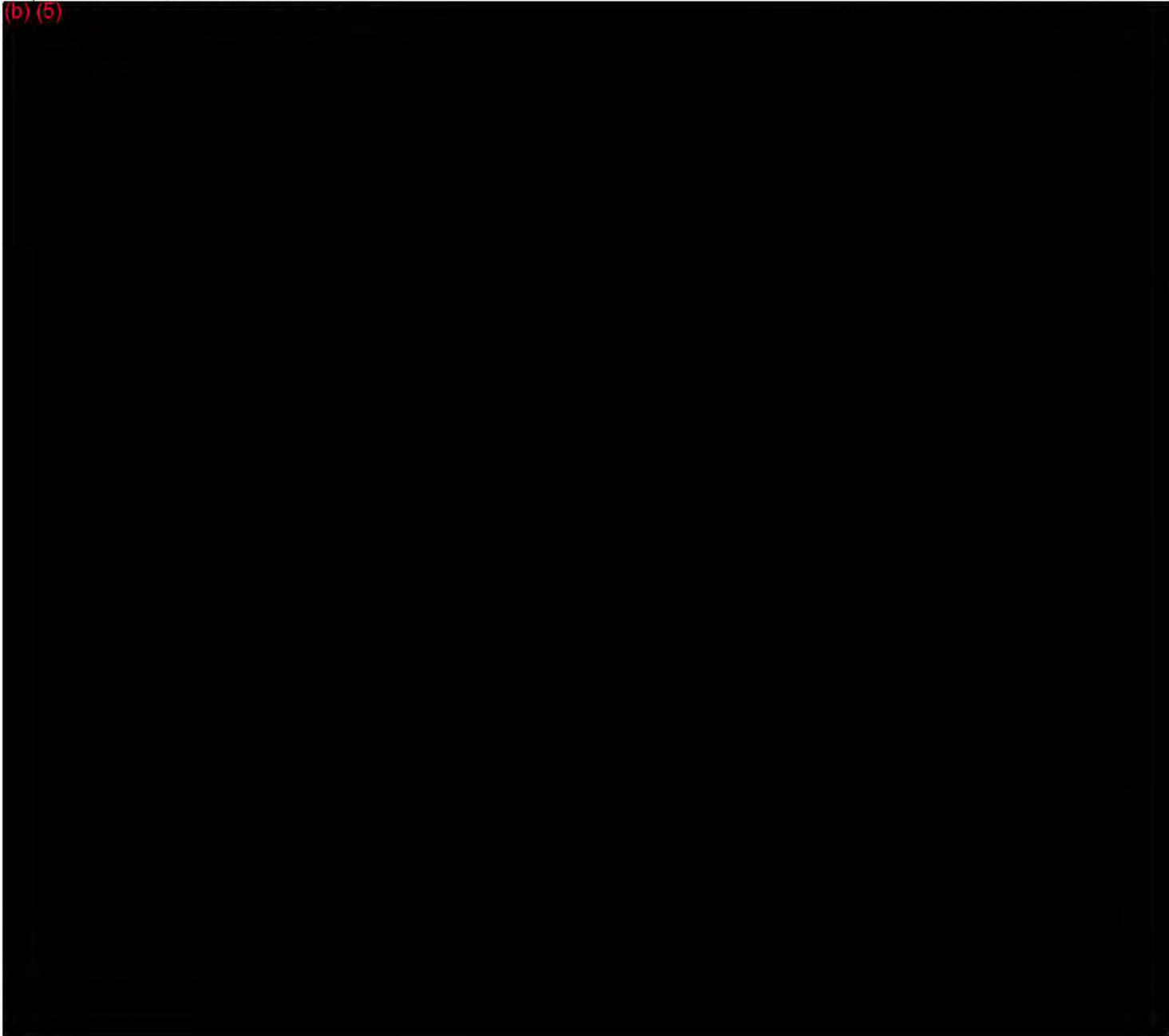
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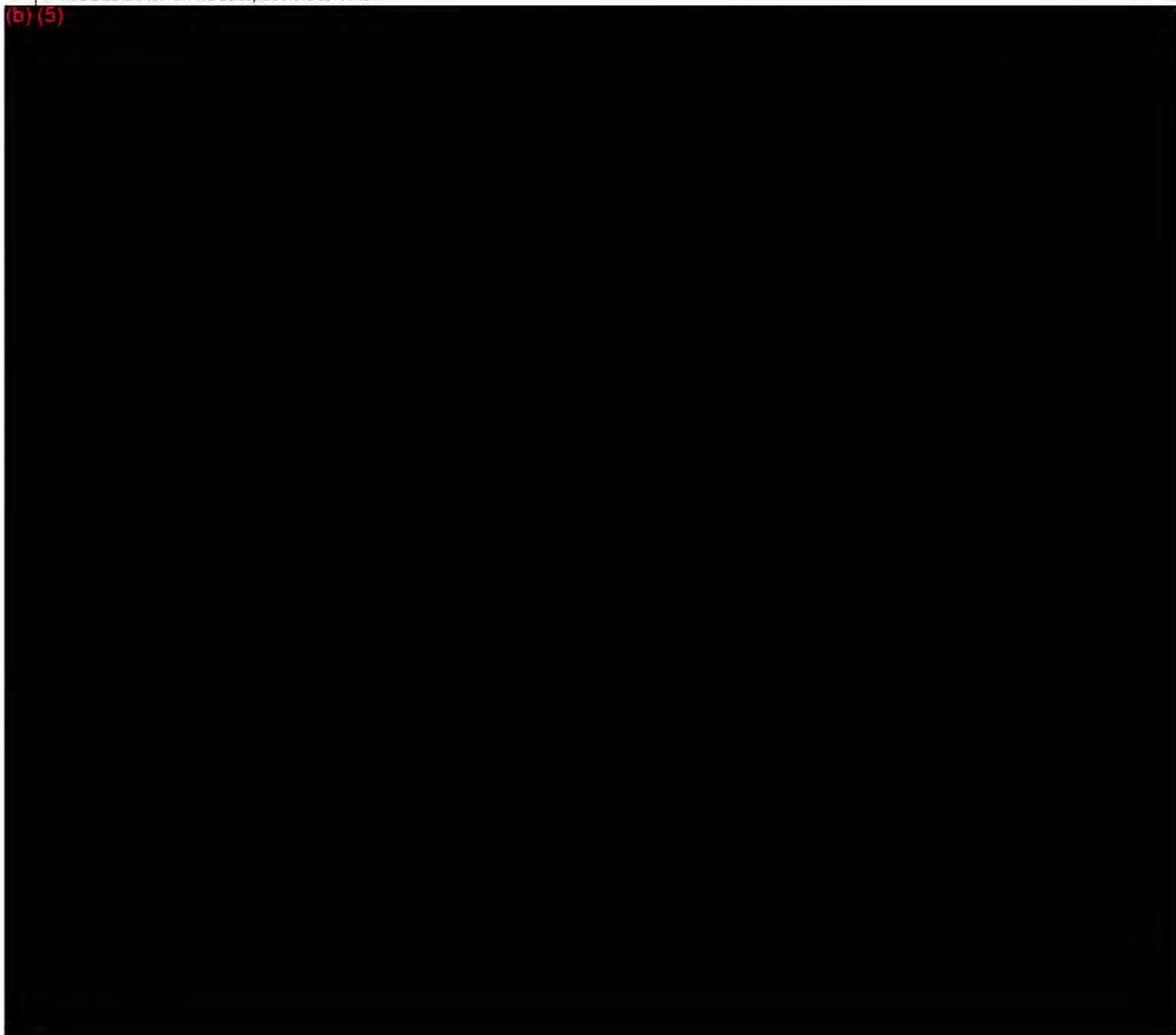
(b) (5)



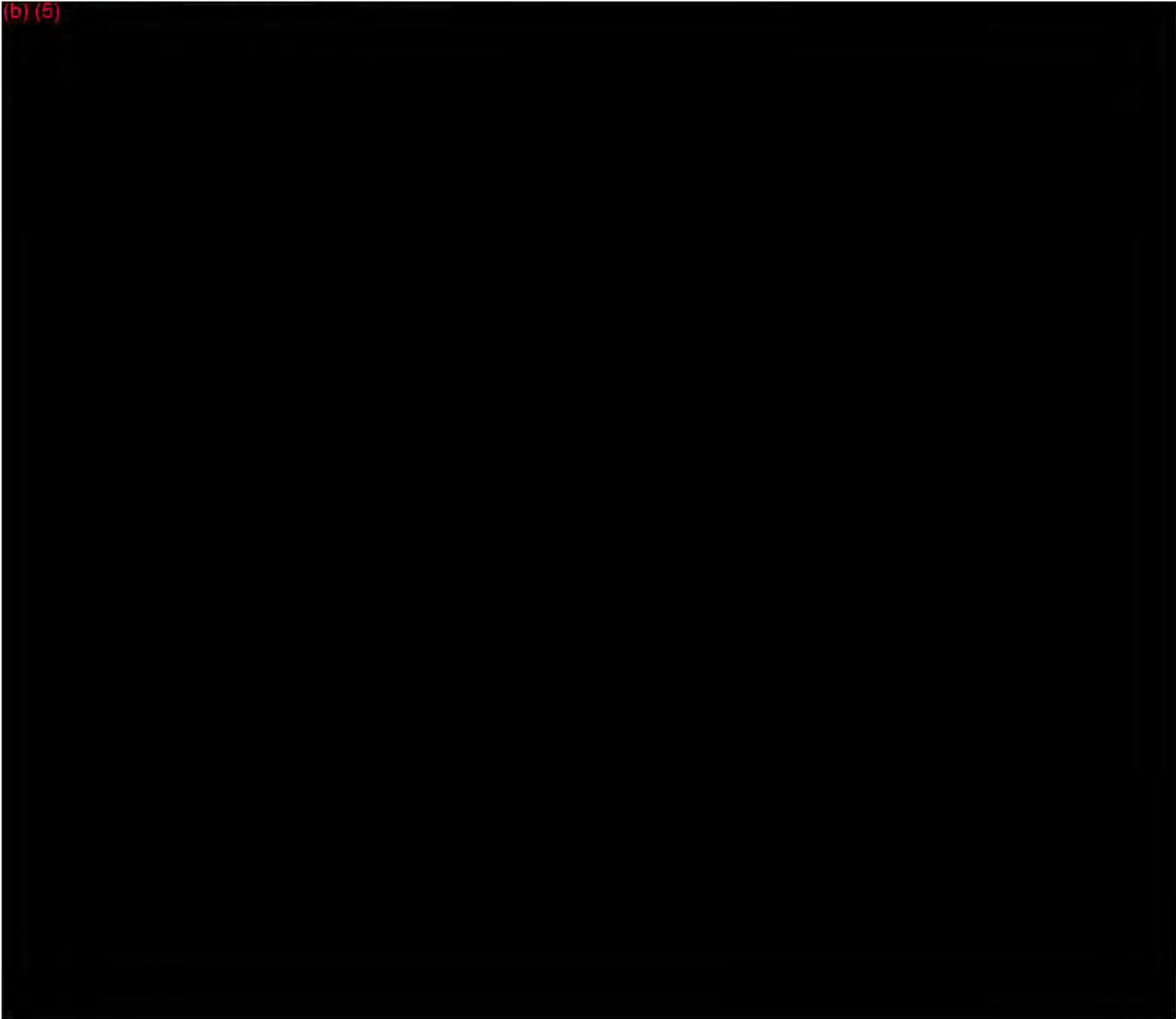
(b) (5)



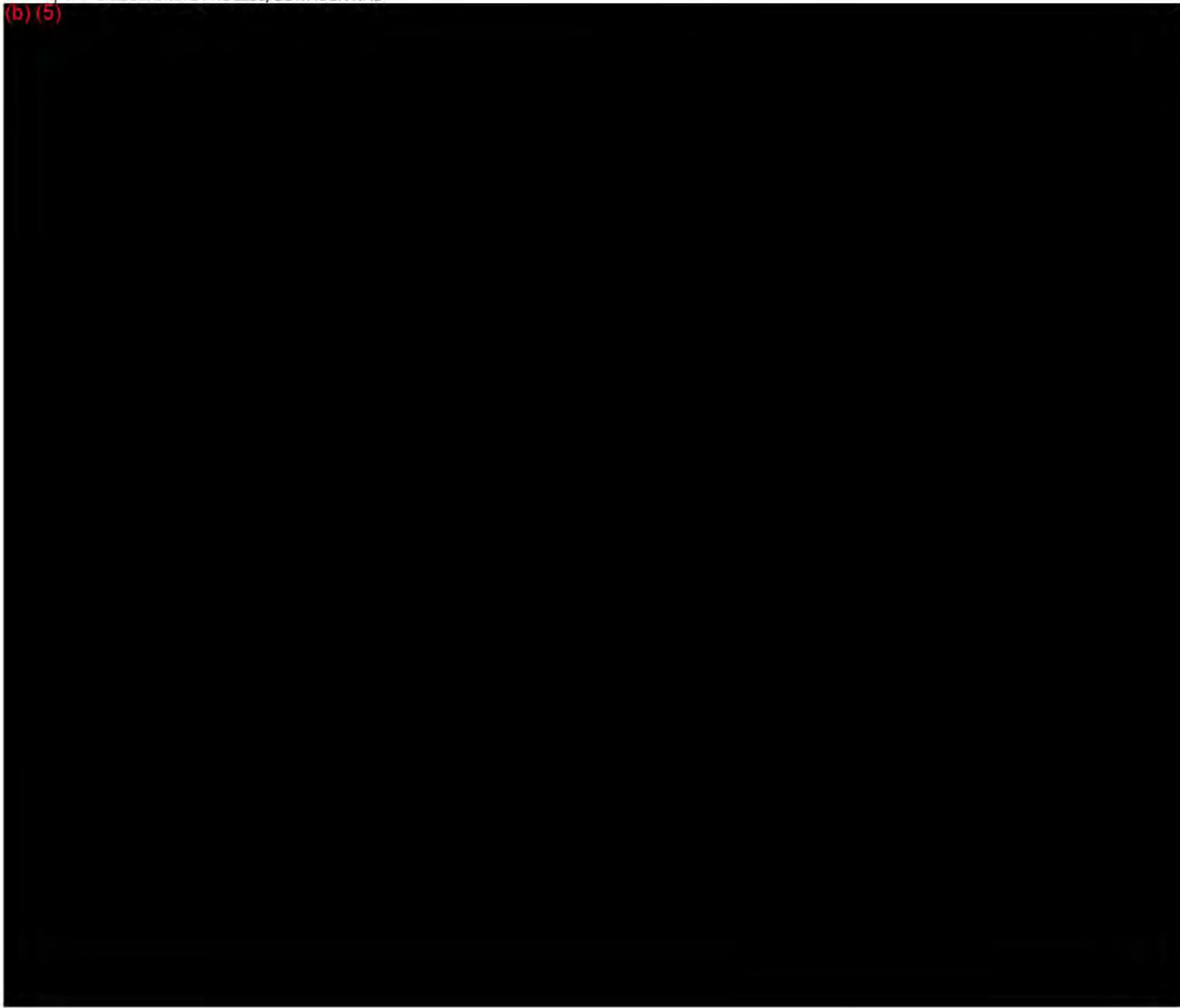
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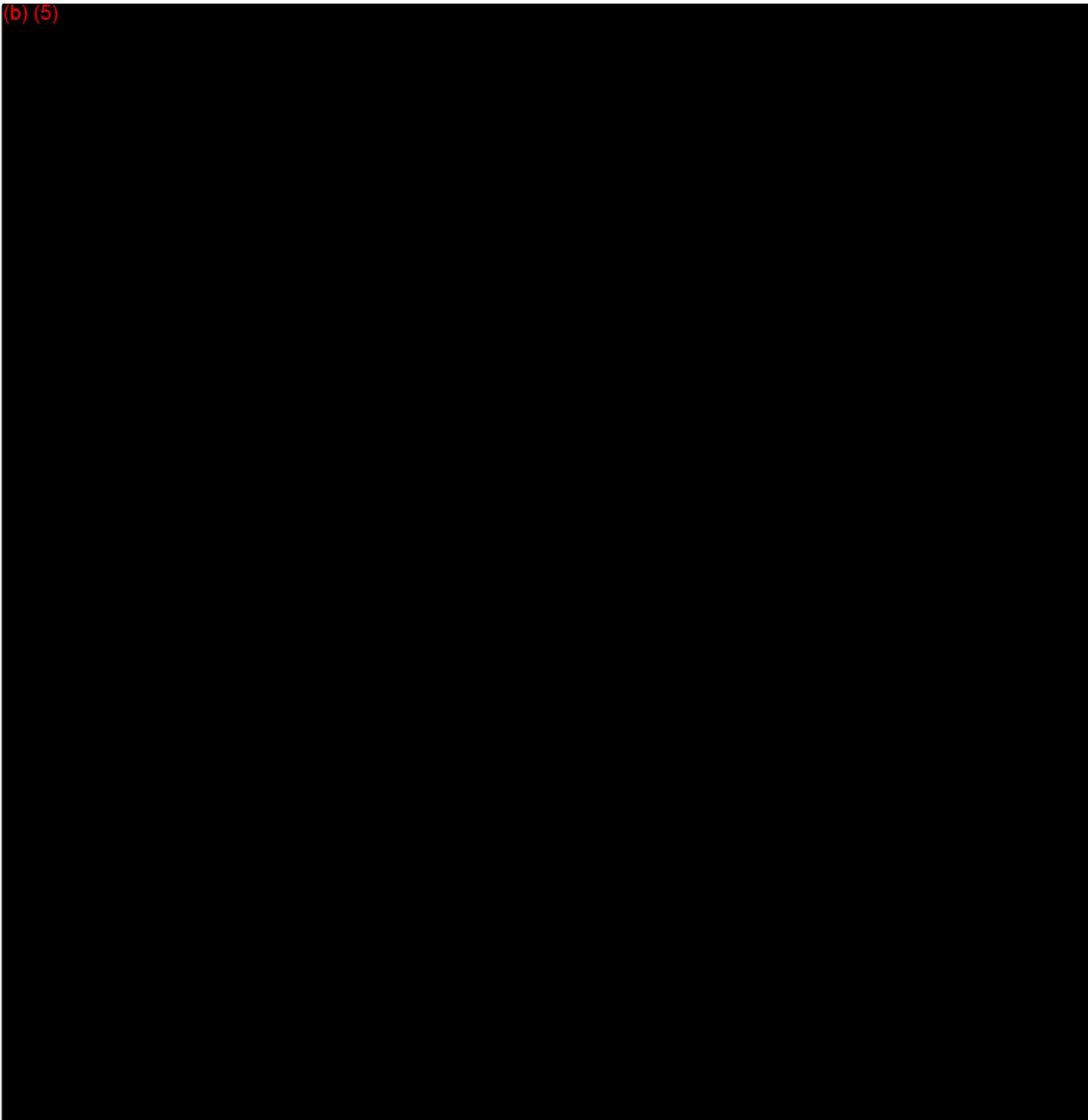
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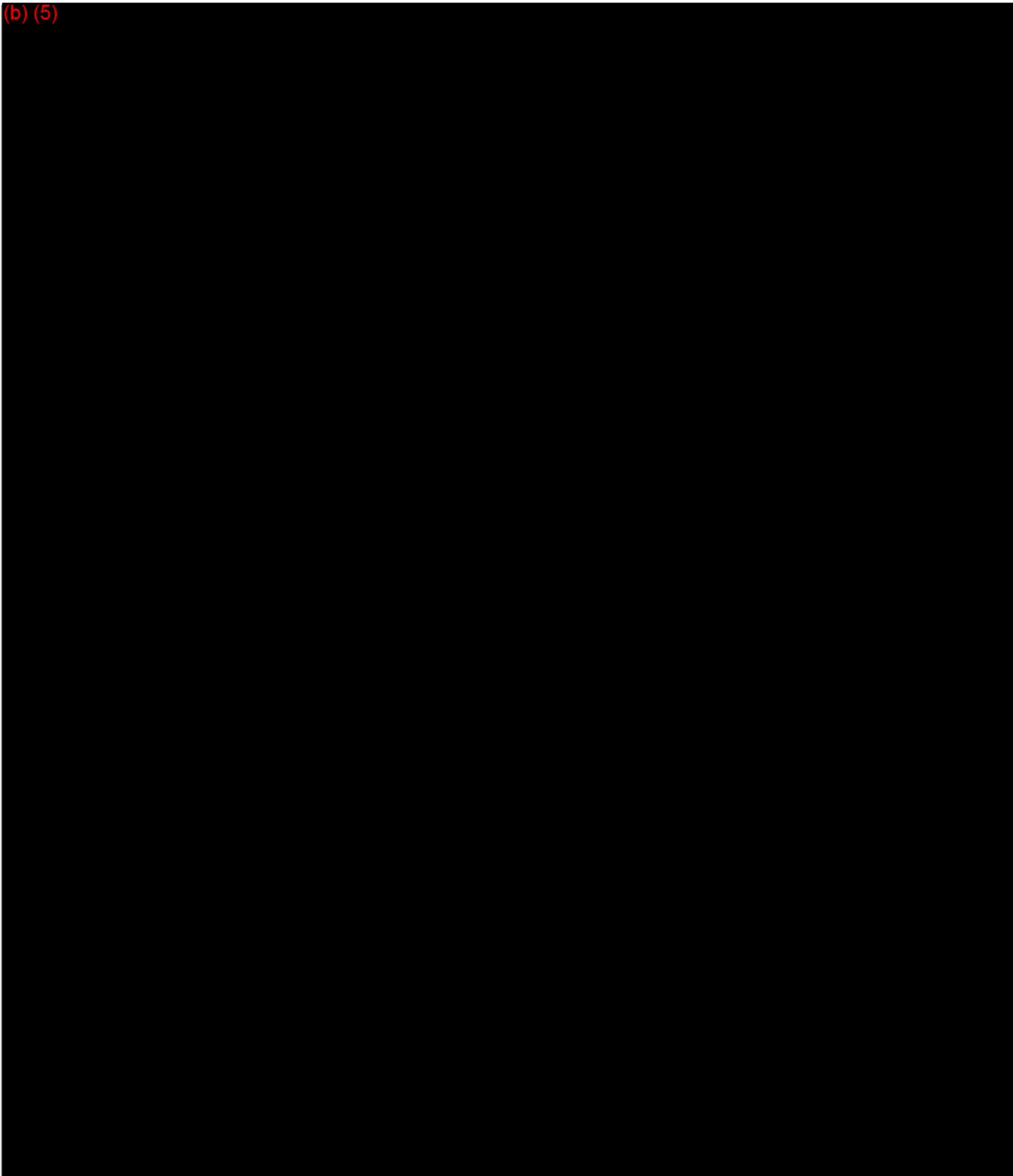
(b) (5)



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(b) (5)



(b) (5)

From: [Sherman Rachel](#)
To: [Califf Robert](#)
Subject: FW: CDER Trade Press News Update September 30, 2016
Date: Friday, September 30, 2016 9:30:41 AM
Attachments: [image002.png](#)
[image003.png](#)
[image004.png](#)
[image005.png](#)
[image006.png](#)
[image008.png](#)
[image010.png](#)
[image011.png](#)

FYI **(b) (6)** is a close friend of Bob's.

From: CDER Trade Press
Sent: Friday, September 30, 2016 9:20 AM
To: CDER Trade Press
Subject: CDER Trade Press News Update September 30, 2016



Today's Headlines (click to go directly to the article):

(The Pink Sheet – NOTE: Informa publications including, the Pink, Tan, and Gold Sheets along with the RPM Report and Scrip Regulatory Affairs significantly changed their format. Those publications are now all included under the “Pink Sheet” banner)

[The Eteplirsen Approval: Former FDA Officials Weigh In On The Science](#)

[Priority Review Voucher Program For Rare Pediatric Diseases Extended As FDA Lowers Fee](#)

(Regulatory Focus)

[Priority Review Voucher Fees to Decline in FY 2017](#)

(FDA News)

[Pharmaceutical Industry Seeks Faster Track for Antimicrobial Susceptibility Tests](#)

(Inside Health Policy)

[House Speaker, Senate Majority Leader Want 'Cures' Passed In November](#)

(FDA Webview)

[Court Allowing FDA to Regulate Medical Practice: Attorneys](#)

[FDA Clinical Hold on Alcobra ADHD Trial](#)

[Comments on Quality Metrics Technical Guidance](#)

(BioCentury Extra)

[GOP leaders pushing for 21st Century Cures Act](#)

[House passes bill to extend voucher program](#)

[Senate right-to-try bill derailed](#)

**If you are unable to access a link within an article, please respond to this email, and we will provide you the text of the linked article.*

The Eteplirsen Approval: Former FDA Officials Weigh In On The Science

- 29 Sep 2016
- **Opinion**

Ramsey Baghdadi [@Ramsey_Baghdadi](#) ramsey.baghdadi@previsionpolicy.com

Executive Summary

A former CDER director, office director, division director, and supervisory reviewer agreed to comment for the record on the merits of the science that formed the basis of FDA's accelerated approval of the Duchenne Muscular Dystrophy therapy *Exondys 51*.

FDA's decision to grant accelerated approval to Sarepta's DMD drug *Exondys 51* (eteplirsen) has generated divergent opinions on what the approval means to the agency standards for approval and to the relationships between the different review levels within the Center for Drug Evaluation and Research.

Patient Advocacy With FDA Review Staff Will Be Tougher Post-Sarepta

By Cole Werble 23 Sep 2016

Efforts by CDER management to encourage more interaction between patients and FDA reviewers may be part of the collateral damage from the difficult FDA review of Sarepta's *Exondys 51*. The hopes of parents of boys with DMD pushed the regulatory flexibility by CDER management on this application – but may end up limiting the willingness of FDA reviewers to...

[Read the full article here](#)

Eteplirsen Review Offers Lessons For FDA, Advocacy Groups, Industry

By Sue Sutter 21 Sep 2016

Agency reviewers believed the line between patient input and external intimidation had been crossed; early data from the Sarepta muscular dystrophy drug's flawed development program stoked patient community expectations and made regulatory review difficult.

[Read the full article here](#)

Further coverage of those issues can be found in the sidebars, but behind them all is the important fundamental assessment on the quality of the science: do the data in the eteplirsen application support accelerated approval?

To bring in knowledgeable observations on the interpretation of the science behind the *Exondys 51* accelerated approval, we asked four former senior FDA officials to comment on the review. These are experts removed from direct involvement in the internal debates on the Sarepta application but experienced in the hard work of FDA regulatory science:

- Former Center for Drug Evaluation & Research Director Carl Peck
- Former Division of Neuropharmacology Drug Products Director Paul Leber
- Former Office of Drug Evaluation II Director Robert Meyer
- Former Supervisory Medical Reviewer Thomas Garvey

After a review of the [documents and scientific arguments](#) released by FDA at the time of approval, all four agreed to have their remarks published in their entirety for the record.

Carl Peck

Former CDER Director

Chairman & Founder, NDA Partners

First of all, this is regulation at its best. We have really competent people in FDA, all who understand the science and all who care about the patients. This is all legal, there is no malfeasance or anything like it. We are so lucky to have a transparent process here.

Second, there has been a concern expressed about a center director who gets involved in the review process. Again, that's regulation at its best. You don't want a center director who doesn't know or care about the science or a center director who doesn't care about the review. Remember, the authority to approve drugs resides with the HHS Secretary, that is delegated to the FDA Commissioner who in turn delegates it to the center director, who in turn delegates it to the office and division directors. During my time as center director, I personally reviewed and signed at least three NDAs. There is nothing unusual about this.

Looking through the summary review, these documents are really informative and powerful. The key issue that emerges is the meaning of the biomarker that they selected [dystrophin production]. The question is, is it going to benefit patients? The answer to that question is not entirely clear. As you read through the documents, Janet and Unger agree on a lot of things. The disagreement is over whether the evidence fits into the accelerated approval regulation. That is a judgment call, plain and simple.

My personal view is that Janet made the right decision. Because it's the decision I would have made.

My personal view is that Janet made the right decision. From the information that I have seen, that is the decision I would have made.

The idea that it weakens the standard I don't believe is true. A lot of these issues first evolved during the AIDS crisis that I, along with former Commissioner Frank Young and then David Kessler were thrust into. We wanted to have rules and good science that also gave these young men opportunity for relief and who were otherwise guaranteed a fatal outcome.

My conclusion on the Sarepta decision is not a feeling. It's the result of an analysis of the publicly available evidence. The basic approval criterion that we're used to for standard drugs is based on frequentist statistics – the P value gives you a very simplistic yes or no answer that can be misleading. Is it greater than 0.05 or less than 0.05? It formally excludes all other information or evidence. Lots of things happen in clinical trials and there is a lot of information to consider.

Although a formal Bayesian analysis that considers all available data was not undertaken in this instance, implicitly or intuitively, that is what Janet applied to this.

Am I convinced by the muscle data? No, not by itself. But by the totality of evidence? Yes.

What I think is in play here is the philosophical framework that each has brought to bear on the evidence and accelerated approval. Strong personalities stake out positions and sometimes it's hard to move them.

Paul Leber

Former Division of Neuropharmacological Drug Products Director

Director, Neuro-Pharm Group, LLC

Section 21 CFR 314.510 of FDA's regulations state that "FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint

that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit.”

Dr. Woodcock, who held signatory authority for the Exondys 51 (eteplirsen) NDA, concluded (see her Center Director Decisional Memo) (1) “...that there is evidence from adequate and well-controlled trials, and supportive evidence, that exposure to eteplirsen increases dystrophin protein production in muscle cells” and (2) “... that both the biochemical data and the clinical data lead me to conclude that an “increase in dystrophin production” is reasonably likely to predict clinical benefit in DMD.”

Viewed from a strictly scientific perspective, however, the evidence cited to justify the marketing of eteplirsen is quite weak, perhaps even grossly inadequate.

Accordingly, FDA’s decision to approve eteplirsen for marketing appears on its face to conform fully with the requirements of existing federal drug regulatory law and regulation.

Viewed from a strictly scientific perspective, however, the evidence cited to justify the marketing of eteplirsen is quite weak, perhaps even grossly inadequate. At the crux of the problem is the ill-conceived notion that an individual can determine in any substantively meaningful way whether an un-validated surrogate is likely to predict anything, let alone a drug effect. A belief, no matter how strongly held, is not scientific evidence. To meaningfully evaluate the predictive power of a surrogate one needs to determine whether, and if so, how a change in the surrogate is related to a change in the clinical status of patients over the full range of outcome states that are of potential clinical interest.

The scientific limitations of un-validated surrogates are well known; in 1992, when the accelerated approval rule was first published for comment, I submitted a formal comment to the administrative file of the pending regulation urging that it not be adopted.

I suspect the rule survives because it provides a way for the FDA to be flexible in its evaluation of “promising drugs” intended for the treatment of serious and life-threatening illness.

For the record, what I know of the eteplirsen derives from a cursory read of several documents explicating the views of FDA officials who were involved in an extensive and protracted internal debate concerning the ‘approvability’ of Sarepta’s NDA.

Robert Meyer

Former Office of Drug Evaluation II Director

Director, Virginia Center for Translational & Regulatory Sciences at UVA School of Medicine

Focusing on the science of it over the process, from my point of view, I would characterize the database provided by the company to FDA as interesting and I would see there might be some evidence of an effect, but I would not see that there was a basis for approval based on substantial evidence.

To be honest, I had more concerns on the safety side than expressed in the FDA documents. Based on the small number of patients studied, there is only about a 1 in 20 chance of seeing an event from a safety perspective, meaning even something occurring at a rate of 1 out of 100 patients exposed can’t be excluded. While no important signal was seen with eteplirsen, when you look at the predicate drug, Biomarin’s drisapersen, which was not approved, it had some pretty serious side effects from a safety perspective.

I had more concerns on the safety side than expressed in the FDA documents.

On efficacy, what puzzled me is that the treatment of dystrophin production as a valid surrogate seems less credible when viewed in context the Biomarin drug, and that did not seem to be incorporated into the review decision. Biomarin conducted a pretty substantial, rigorous, well-controlled trial so they did some pretty substantial work on this. In essence, the Biomarin program more robust and despite them showing some pharmacodynamic improvement on dystrophin and early function, the larger, longer trials failed.

One other thing to consider is the confirmatory data. If, for instance, the main trial to confirm the subpart H is a dose-response design without a placebo (and the Western Blots did not show a dose-response) the failure to show a difference between the regular dose and high arm could mean neither worked, the trial failed or both worked equally – and you won't know.

I think the decision reflects a tension between the staff within the center and Dr. Woodcock. She talked about the FDA's longstanding concern about never approving drugs that end up to be ineffective. She's expressed concern about denying drugs when the risk is the other way – not approving drugs that may be effective. That's a legitimate point of view, particularly for a very dire disease with no effective therapies. And the ultimate authority to approve drugs rests with the HHS Secretary and is delegated down the chain. She has the perfect right to intercede, but it is highly unusual.

Besides the internal staff, Janet did get to speak to the advisory committee directly and make these points to them. And still, they mostly recommended against it by a slim majority. So, she's not just acting against the decisions of the people in the review division, but also against the recommendation of the advisory committee.

The closest parallel to this kind of decision is oncology. Sarepta did show four patients who are substantially out on treatment, who would have been predicted to have lost ambulatory function, but who have not. Most cancers at a late stage never see a regression, so if you see evidence of regression even in a small number of patients in an uncontrolled sample, that can be compelling.

So maybe this accelerated approval decision is not unprecedented, but the politics here seem pretty rare.

Tom Garvey

Former Supervisory FDA Medical Reviewer, Division of Cardio-Renal Drug Products

Founder, Garvey Associates, Inc.

Eteplirsen, a drug with a novel mechanism involving eliding translation of a mutated, dysfunctional exon, is aimed at Duchenne's Muscular Dystrophy (DMD), an inborn, X-linked genetic error resulting in inexorably progressive muscle wasting and death usually before the fourth decade for which no significantly effective therapy exists currently. Sarepta Therapeutics developed eteplirsen with considerable FDA input, and, seeking "accelerated approval" to market the drug, submitted a new drug application (NDA) to FDA on June 26, 2015.

Even without access to the primary data and other key information, it seems clear, on the basis of assessments by experienced and competent FDA reviewers and supervisors, that although the drug appears to be safe, the data submitted in the eteplirsen NDA do not meet the Agency's current evidentiary standards for effectiveness and, hence, the drug does not qualify for any sort of approval. As an aside, that this is the case appears to have been obvious very quickly after submission and raises the question of why there was not a refusal-to-file (RTF). There was no RTF, apparently, and, hence, FDA agreed to review the NDA indicating that the possibility of approval was entertained by somebody high enough in the FDA hierarchy to ensure filing.

By law, regulations and precedent, the eteplirsen NDA is not approvable. Yet, Janet Woodcock has asserted that regardless of the eteplirsen NDA's glaring deficiencies (even though the drug was developed with FDA's vigorous assistance) that the drug, is approvable for marketing.

I think that what Dr. Woodcock may really mean is that FDA's handling of drugs like eteplirsen for indications like DMD must change.

I think that what Dr. Woodcock may really mean is that FDA's handling of drugs like eteplirsen for indications like DMD must change. I am quite sure that FDA has been considering how to modify evidentiary standards for approval of drugs like eteplirsen, recognizing that recent advances in science and medicine are rapidly producing new knowledge and therapeutic approaches to previously intractable disease/conditions that may not fit well into the current regulatory framework. Beyond the thorny legal and epistemological issues, individualized or personalized medicine, to some extent driven by fast moving advances in understanding and manipulation of the genome and epigenome as well, have resulted in a new world of therapeutic endeavor and this must be considered.

This is not an easy problem. FDA's pace in dealing with such matters is typically and, perhaps, reasonably, glacial. It is possible, however, to accelerate the process.

Because of its many "warts," the eteplirsen NDA may not have been the best choice to prod FDA into action, but I suspect that Dr. Woodcock decided that something had to happen. Overall, I think the situation is not unusual in that FDA has, in the past responded to real-world situations (e.g., the need for HIV/AIDS drugs) of a sort that could only be encountered by FDA, by moving regulatory science forward to better serve and protect the public.

A positive aspect of the furor over eteplirsen is FDA's exemplary and laudable willingness to allow the public almost complete access to the intra-mural goings on.

From the editors of the RPM Report

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Priority Review Voucher Program For Rare Pediatric Diseases Extended As FDA Lowers Fee

- 29 Sep 2016

- **Analysis**

-

Derrick Gingery [@dgingery derrick.gingery@informa.com](mailto:dgingery@informa.com)

Executive Summary

Next fiscal year will be a good one to redeem a voucher, and probably to qualify for one as well.

FDA review costs are decreasing, which has pushed down the cost to redeem a priority review voucher.

The voucher redemption user fee will be \$2.71m in FY 2017, the agency said in a Federal Register [notice](#) scheduled to be published Sept. 30. It is about \$21,000 less than the FY 2016 fee of \$2.73m.

The announcement comes a day after Congress voted a second time to prevent the rare pediatric disease priority review voucher program from expiring. As part of the Continuing Resolution that will fund the government through Dec. 9, Congress included a provision extending the voucher program until the same day.

When Congress returns after the presidential election, they will address the federal budget for fiscal year 2017 and likely a longer extension of the voucher program.

The fee applies to the tropical disease as well as the rare pediatric disease priority review voucher.

Both programs allow a voucher holder to receive a priority review for any application they choose.

FDA is allowed by law to set a separate fee for priority review voucher redemption that is based on the difference between the average cost of a standard and priority NDA review.

FDA said in the notice that it used FY 2015 data to determine the FY 2017 voucher fee. The cost of a standard NDA/BLA review was \$3.98m and a priority review \$6.64m. The difference between those plus a multiplier to adjust for cost increases in FY 2016 resulted in the final rate.

Last year's voucher fee used standard and priority review costs that were slightly higher: \$3.99m and \$6.66m, respectively (*see graphic*).

Source: Federal Register notices

FDA changed its formula for calculating priority review costs beginning for FY 2013. The result was costs that were much lower than under the previous calculation. (Also see "[FDA Priority Review Costs Remain Stable While Voucher Fee Ticks Up](#)" - Pink Sheet, 1 Sep, 2014.)

FDA is giving industry several fee breaks in FY 2017. Prescription drug user fees will decrease significantly because the agency had to rebate fees it had collected above what was appropriated by Congress.

The application fee dropped more than 14% compared to the FY 2016 rate. (Also see "[PDUFA Fees Forced Down For FY 2017 Due To Refund Provision](#)" - Pink Sheet, 27 Jul, 2016.)

Congress Saves Program Twice

With industry celebrating the fee decrease, stakeholders are joining to rejoice in the rare pediatric disease voucher program's continuation, even if it is temporary.

It has proven popular since its creation in 2012. More pediatric vouchers have been issued to date than tropical disease vouchers, despite the tropical disease program existing much longer. (Also see "[Tracking The Priority Review Vouchers](#)" - Pink Sheet, 27 Jul, 2016.)

The most recent award went to [Sarepta Therapeutics Inc.](#), following FDA's approval of its Duchenne muscular dystrophy treatment *Exondys 51* (eteplirsen).

Among the benefits of the voucher is that it can be sold to another company. Sarepta expects to sell its voucher, which could command hundreds of millions of dollars. (Also see "[Duchenne Surprise: Sarepta Prices Exondys 51 Below Expectations](#)" - Scrip, 19 Sep, 2016.)

Industry and rare disease advocates mobilized in recent weeks to ensure the program was extended beyond its Oct. 1 expiration.

Their lobbying was so effective that Congress actually passed two bills saving the program. A stand-alone bill, the [Advancing Hope Act](#), was headed to President Obama on Sept. 27. It would extend the program through Dec. 31.

But it was muted when Congress passed a continuing resolution funding the government for another three months that Obama signed on Sept. 29.

A provision within that bill extended the program until Dec. 9.

It seems that stakeholders were hedging against a CR not passing and the government shutting down. But the move also illustrates the influence the rare disease and industry lobbies have on Capitol Hill.

Rare disease groups have been pushing for an extension as part of the 21st Century Cures legislation, but when it became clear that bill would not gain any attention prior to the deadline, they moved to the CR and stand-alone options. (Also see "[Pediatric Rare Disease Voucher Program Faces Expiration](#)" - Pink Sheet, 10 Sep, 2016.)

The experience also may be indicative of FDA's lack of influence on the Hill in this instance. Agency officials have made clear on several occasions that they do not like the voucher program because it directs additional resources toward applications that may not necessarily deserve it. (Also see "[Review Voucher Program For Rare Pediatric Diseases Should Not Be Reauthorized, US FDA Says](#)" - Pink Sheet, 3 Mar, 2016.)

Incidentally, Senate Majority Leader Mitch McConnell, R-Ky., said in a Sept. 29 press conference his top priorities for the lame-duck session are funding the government and the Cures legislation.

Cures is intended to help push innovative drugs to the market faster and includes additional research funding for NIH, as well as precision medicine and the Cancer Moonshot initiatives. It also includes some FDA policy changes, but no new

money as of yet. (Also see "[FDA Wouldn't Get Funding Boost As Part Of Senate GOP Innovation Bill](#)" - Pink Sheet, 9 Mar, 2016.)

No New Vouchers Appear Affected

Even though the program survived, there does not appear to be any NDAs that would have suffered had the extension not passed.

Of the user fee goal dates between Sept. 30 and Dec. 9, none appear to fit the criteria for a rare pediatric disease voucher.

The designation process for potential voucher eligibility will continue as well, which also should benefit future sponsors.

A designation is not required to receive a voucher, but it can expedite the process.

FDA's Office of Orphan Products Development, which administers the program, also reviews orphan product designation requests. Its workload has forced it to extend its goals for completing reviews. (Also see "[Orphan Designation Requests To Get Slower Reviews](#)" - Pink Sheet, 10 May, 2016.)

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Priority Review Voucher Fees to Decline in FY 2017

Posted 29 September 2016 By [Zachary Brennan](#)

The US Food and Drug Administration (FDA) on Thursday unveiled the new user fee rates for the tropical disease and rare pediatric disease priority review voucher (PRV) programs. The additional fees necessary to use the vouchers for both programs are set to decline by about \$20,000 when compared to last year.

Tropical Disease Priority Review Voucher User Fee	
Year	Voucher Fee
FY 2011	\$4,582,000
FY 2012	\$5,280,000
FY 2013	\$3,559,000
FY 2014	\$2,325,000
FY 2015	\$2,562,000
FY 2016	\$2,727,000
FY 2017	\$2,706,000

Rare Pediatric Disease Priority Review Voucher User Fee	
Year	Voucher Fee
FY 2014	\$2,325,000
FY 2015	\$2,562,000
FY 2016	\$2,727,000
FY 2017	\$2,706,000

The new rate is based on FDA's estimate that the cost of a standard review for new molecular entity (NME) new drug applications (NDAs) and biologic license applications (BLAs) will be about \$3,977,000, while the cost of a priority review for NME NDAs and BLAs is about \$6,642,000, meaning the agency thinks such costs will be slightly less in FY 2017 than FY 2016.

FDA's estimates are based on the costs FDA saw in FY 2015 when it reviewed 56 NDAs and BLAs. The total cost to review the 56 applications in FY 2015 (32 NME NDAs with clinical data and 24 BLAs) was \$289,352,000, according to FDA.

Eleven PRVs have been [awarded so far](#) (including the [latest to Sarepta](#)) and five have been sold (including the [one Gilead bought in 2016](#)), with one selling for \$350 million in August 2015 to AbbVie.

The rare pediatric disease and tropical disease PRV fees established in the new fee schedule must be paid for any application that is received on or after 1 October 2016, and must be paid in addition to any [other fee due under the Prescription Drug User Fee Act \(PDUFA\)](#).

In addition to the fee announcement, Congress this week [passed a short-term extension](#) to the pediatric PRV program so that it would not sunset at the end of September. Negotiations for another extension are ongoing.

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FDANEWS

Pharmaceutical Industry Seeks Faster Track for Antimicrobial Susceptibility Tests

Drug manufacturers are pressing for faster approval of antimicrobial susceptibility tests, because without them, physicians are reluctant to prescribe new antibiotic drugs, even when they have received FDA approval.

The tests are not only used to drive individual patient treatment decisions toward the most effective therapies, but can also provide summary data for empirical use of broad-spectrum antibiotics and formulary decisions, and can help track the development of resistant strains of bacteria.

At an FDA workshop, representatives from the industry called for simultaneous approvals, or the creation of an expedited regulatory pathway for the devices — similar to what has already been done with the Fast Track designation in drug development.

The GAIN Act, passed by Congress in 2014, authorizes prioritized review and marketing exclusivity for qualified antibiotic drug applications. But in the clinical setting, physicians are wary to prescribe the new antibiotic treatments without the results of a related test, which can take years to develop and commercialize.

The FDA recently published a draft guidance encouraging coordinated development of the drugs and tests, including early and frequent communication with both CDER and CDRH. The agency stressed that it was pursuing coordinated development, not co-development, and that the process would not be similar to the approval of in vitro companion diagnostic tests.

Clearance of ASTs, categorized as Class II devices, would still have to come after the approval of an NDA. The FDA will continue to make its review decisions independently.

“CDRH can communicate with CDER and review the 510(k) submission during the NDA review process, to maximize the likelihood that AST device clearance can occur either coincident with or shortly after drug approval,” according to the draft guidance. The FDA is accepting public comments until Nov. 21.

At the workshop, representatives from the agency said pharmaceutical companies and device manufacturers could present

early, pre-submission coordinated development plans for FDA review and comment free of charge, and encouraged joint meetings between CDER and CDRH reviewers and members from both industry firms.

“We’re only doing part of the job in addressing an unmet need,” said Kevin Krause, director and head of microbiology at Achaogen. “It is only partially helpful to bring a drug to market faster when we don’t have AST available at the same time.”

Clearance of an AST, especially complex automated versions, can sometimes take months or years after an NDA approval, Krause said, and companies may still need up to a year after receiving clearance to commercialize the test, further delaying widespread use of the antibiotic.

The draft guidance can be read here: www.fdanews.com/09-29-16-FDADraftGuidanceASTs.pdf. — Conor Hale

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House Speaker, Senate Majority Leader Want 'Cures' Passed In November

September 29, 2016

Senate Majority Leader Mitch McConnell (R-KY) and House Speaker Paul Ryan (R-WI) said Thursday (Sept. 29) they want to complete work on the 21st Century Cures Act in the lame-duck session, coming after leaders of the Senate health and House Energy & Commerce committees released statements this week saying they are working towards an agreement. As talks continue, a source says new language addressing restrictions on generic drug makers getting drug samples has been floated as a funding offset.

“My own personal priorities are funding the government and the 21st Century Cures bill, which I think could end up being the most significant piece of legislation we pass in the whole Congress,” said McConnell at a press conference. “The president is interested in it -- Precision Medicine. The vice president is interested in it -- Cancer Moonshot. I’m interested in it -- regenerative medicine. There are a lot of us who are deeply invested in that and I think that will be a top priority in the Senate in the lame duck, as well as funding the government.”

McConnell said President Obama, Vice President Joe Biden and Ryan want to move forward with the legislation this year.

Senate health committee ranking Democrat Patty Murray (D-WA) joined Chairman Lamar Alexander (R-TN) in pushing for movement on the Senate version of the 21st Century Cures Act in a statement Wednesday (Sept. 28), saying both lawmakers are committed to getting a result this year that would lead to lifesaving medical breakthroughs. The joint statement says the Senate version of the bill would focus on providing support for Cancer Moonshot and precision medicine initiatives.

House E&C lawmakers additionally released a statement saying they were committed to getting the bill signed into law this fall.

“We have been working hard for months, and we will continue to work toward an agreement that can pass both chambers and be signed by the president. And the good news is that we are on the cusp of something special,” said Chairman Fred Upton (R-MI), ranking Democrat Frank Pallone, Jr. (NJ), Rep. Diana DeGette (D-CO) and health subcommittee Chairman Joseph Pitts (R-PA) and ranking Democrat Gene Green (TX).

The House-passed bill, one of Upton's legislative priorities, has stalled despite repeated efforts by Upton to move the legislation.

Concerns about increased funding for the National Institutes of Health have been cited as a major stumbling block by Democrats, given that [many offsets for the House version of the bill have since been used for other bills](#).

Earlier this month Murray [told IHP that NIH funding is](#) "the one thing that is critically important" for Democrats. Negotiations on NIH funding are ongoing between Alexander and Murray, an congressional aide recently said.

A source told *IHP* lawmakers are eyeing an offset that would prevent brand pharmaceutical companies from barring generic makers access to samples of drugs, however the source clarified that the language is not identical to Senate and House bills aimed at addressing the same issue. The two pending bills, the Creating and Restoring Equal Access to Equivalent Samples Act and the Fair Access for Safe and Timely Generics Act, aim to allow generic manufacturers to sue brand-name manufacturers for injunctive relief if they restrict samples of a branded product.

The White House declined to comment when asked about the discussions. -- David Lim (dlim@iwppnews.com) ([Return to Top](#))



Court Allowing FDA to Regulate Medical Practice: Attorneys

09/29/2016

A 9th Circuit Court of Appeals decision appears to "impermissibly grant FDA authority to regulate the practice of medicine and to further muddy the regulatory morass governing off-label use of products," according to attorneys **Anne Walsh** and **Andrew Hull** (Hyman, Phelps & McNamara). Writing in their firm's *FDA Law Blog*, the two [discuss](#) the felony conviction and 48-month imprisonment of a Nevada urologist for conspiracy to commit adulteration under the Federal Food, Drug, and Cosmetic Act (FFDCA).

Complaints by the doctor's medical assistants to the state medical board that he was reusing single-use needle guides in multiple invasive prostate procedures led FDA's Office of Criminal Investigations (OCI) to open an investigation.

The post says that the relevant section of the act discusses adulteration of items that are "held for sale" and the doctor argued that the needle guides were not held for sale because he never transferred their ownership to the patients, instead simply using them in treating patients. The district federal court rejected this argument as did the appeals court.

On appeal, the doctor also claimed that his reuse of single-use needle guides was an allowable off-label use of a medical device.

"Although the outcome ... may have been appropriate based on the egregious nature of ... the conduct, the decision unfortunately clouds, rather than clarifies, important issues," the attorneys write. "There can be no dispute that Congress did not intend FDA to regulate the practice of medicine via the FFDCA."

They note that other remedies are available to deal with such behavior either through state medical board or malpractice suits. However, they say, "the Ninth Circuit holding criminalizes the doctor's practice of medicine via a logically tortuous path by characterizing his use of a device in treating patients as a commercial act (holding for sale). And the court left open questions such as whether a physician's use of a device in the provision of free medical services or the use of general office equipment to treat a patient would be covered. The court also dismissed [the doctor's] contention that his actions constituted permissible off-label use under the FFDCA."

They report that the appeals court opinion said that while a doctor may exercise professional judgment in the off-label use of unadulterated products, nothing in the FFDCA or caselaw suggests that the use of adulterated products is ever permissible. "This less-than-clear explanation carries a strong risk of being taken out of context," Walsh and Hull write. "The court's 'bright-line' rule prohibiting the use of adulterated products fails to consider the nuances of the FFDCA, which considers a

device adulterated if it has a new intended use for which it is required to have, but lacks, pre-market approval. What the court should have clarified is that its holding is limited to products that are adulterated ... because they were held under insanitary conditions, which is what was charged here, and not because they were being used off-label (single use versus reuse).”

In passing, the attorneys also reference the recent media and congressional interest in OCI’s work and ask whether its involvement in this case, which they say may have been more appropriately adjudicated by the state medical board and medical malpractice suits, is another example of misplaced OCI attention.

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FDA Clinical Hold on Alcobra ADHD Trial

09/29/2016

FDA has placed a clinical hold on an Alcobra Ltd. clinical trial called MEASURE that is evaluating its investigational drug MDX (metadoxine) extended release for treating adult patients with attention deficit hyperactivity disorder. Alcobra says it has not yet received written notice of the clinical hold from the agency, however, based on verbal communications, the hold is due to adverse neurological findings in a pre-clinical study. “The FDA notification was not based on clinical safety data observed in the ongoing MEASURE study, which has enrolled nearly 500 subjects, or previous clinical studies involving MDX,” it says.

In contrast to available treatments, MDX is not a stimulant and shows no signs of abuse or addiction, Alcobra says. “It has a differentiated mechanism of action that targets neither dopamine nor norepinephrine,” the company says. “Our two Phase II placebo-controlled studies showed significant clinical improvement in clinical symptoms with high response rates and a rapid onset of action. The trials also demonstrated favorable tolerability.”

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Comments on Quality Metrics Technical Guidance

09/29/2016

Pharmaceutical Research and Manufacturers of America says in a comment [letter](#) on an FDA draft guidance on quality metrics technical conformance that it commends the agency’s innovative vision to harness its new authorities under the FDA Safety and Innovation Act to use quality metrics reporting in risk-based scheduling of drug manufacturing establishments. The trade association says that to date industry has devoted considerable time determining how quality metrics can be defined and used by industry and FDA to transform regulation of drug manufacturing quality. The letter offers general comments on:

- relationship of the quality metrics technical conformance guide to the request for quality metrics draft guidance;
- continued alignment and collaboration across FDA;
- IT infrastructure and validation; and
- data security and confidentiality.

The group also provided specific technical comments.

Baxter [asks](#) for an opportunity to evaluate the potential to harmonize this draft with the CDRH metrics effort since it appears that both programs are trying to accomplish similar results. It also asks for a single document clarifying all definitions.

The International Society for Pharmaceutical Engineering [says](#) that additional detail and clarity as discussed in its specific comments would be beneficial in areas such as technical specifications, definitions, and format for XML data submission.

Sanofi’s [letter](#) says it understands that FDA plans to issue revised draft guidance on submission of quality metrics data and asks that, as needed, the technical conformance guide be amended to reflect the contents of the revised draft comments and then be released again for public comment.

Finally, the Parenteral Drug Association (PDA) [suggests](#) that to streamline implementation and maximize learning, FDA “provide a pilot or ‘sandbox’ where companies could make example submissions and receive FDA feedback on whether the response meets expectations. PDA further recommends FDA engage in collaborative dialog on preparing the validation rules for these data sets rather than waiting to disclose the rules once finalized.”

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GOP leaders pushing for 21st Century Cures Act

Passing the 21st Century Cures Act during the lame duck session of Congress following the elections is a high priority, Senate Majority Leader Mitch McConnell (R-Ky.) and House Speaker Paul Ryan (R-Wis.) each said Thursday. The House passed a version of the bill ([H.R. 6](#)) in July 2015, but the Senate has not passed companion legislation ([see BioCentury, April 18](#)).

Briefing reporters, McConnell said he has two priorities for the lame duck session: “funding the government and the 21st Century Cures bill, which I think could end up being the most significant piece of legislation we pass in the whole Congress.” McConnell noted that President Obama favors the bill because it would fund the Precision Medicine Initiative and Vice President Biden supports it because it would fund the Cancer Moonshot Initiative.

McConnell added that he favors its enactment because of his interest in regenerative medicine. He is pushing to incorporate the Reliable and Effective Growth for Regenerative Health Options that Improve Wellness (REGROW) Act ([S. 2689](#)) into the Senate version of 21st Century Cures legislation. REGROW would create a pathway for FDA to conditionally approve cellular therapies based on “preliminary clinical evidence of safety, and a reasonable expectation of effectiveness, without initiation” of Phase III trials.

Ryan told reporters the 21st Century Cures Act is one of several bills already passed by the House that could also be passed by the Senate in the lame duck session. In a statement Wednesday, Senate Health, Education, Labor and Pensions Committee Chairman Lamar Alexander (R-Tenn.) and the committee’s ranking Democrat Patty Murray (D-Wash.) said they are continuing to work on a Senate version of the bill, and are “committed to getting a result this year that will lead to lifesaving medical breakthroughs and advance President Obama’s Precision Medicine Initiative and Vice President Biden’s Cancer Moonshot.”

Despite the expressions of support, enactment in the current session of Congress is far from certain. Since the House passed H.R. 6, its budget offsets were reallocated by Congress for other purposes. ([Return to Top](#))

House passes bill to extend voucher program

The U.S. House of Representatives passed an amended version of the Advancing Hope Act ([S. 1878](#)) that would extend the Rare Pediatric Disease Priority Review Voucher program until YE16. The U.S. Senate passed the bill unanimously last week. The voucher program is scheduled to sunset Oct. 1 ([see BioCentury Extra, Sept. 23](#)). ([Return to Top](#))

Senate right-to-try bill derailed

On Wednesday, U.S. Senate Minority Leader Harry Reid (D-Nev.) derailed an effort to enact the Trickett Wendler Right to

Try Act of 2016 ([S. 2912](#)) by unanimous consent.

The bill's sponsor, Sen. Ron Johnson (R-Wis.), had sought to bypass a committee vote. Reid [said](#) he objected because "major players in this haven't had an opportunity to tell us what's wrong with this bill."

Similar legislation is pending in the House, but it is unlikely that either bill will be enacted in the current session of Congress. ([Return to Top](#))

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From: [Salerno, Mary Jo](#)
To: [FDA Senior Executives](#); [OC-Executive Secretariat](#)
Cc: [FDA Senior Executive Assistants](#); [OC OEA OMA-Press](#); [FDA - Information Advisories](#); [CDER EXSEC](#); [Bernstein, Jessica](#); [Mfum-Gyau, Akua](#)
Subject: FW: CONFIDENTIAL: Information Advisory (IA) - FDA to Announce a Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to Discuss Eteplirsen to Treat Duchenne Muscular Dystrophy
Date: Wednesday, December 16, 2015 10:01:34 AM
Attachments: [IA Public Mtg PCNS AC Eteplirsen to Treat Duchenne Muscular Dystrophy Final to HHS 12 15 15.doc](#)

Good morning.

The attached Information Advisory was sent to the Department.

From: Salerno, Mary Jo
Sent: Wednesday, December 16, 2015 10:00 AM
To: Swenson-O'Brien, Alicia J (OS) (Alicia.Swenson-OBrien@hhs.gov); Valverde, Madhura (OS); Hall, Bill (OS); Horowitz, David J (OS); Pakulis, Averil (OS); Clark, Robert J (OS) (Robert.Clark@hhs.gov)
Subject: CONFIDENTIAL: Information Advisory (IA) - FDA to Announce a Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to Discuss Eteplirsen to Treat Duchenne Muscular Dystrophy

Good morning.

Please see the attached IA concerning an upcoming FR notice: FDA to Announce a Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to Discuss Eteplirsen to Treat Duchenne Muscular Dystrophy.

Best regards,

Mary Jo

Mary Jo Salerno, MPH, CPH
Policy Analyst
Office of the Commissioner
Office of the Executive Secretariat
MaryJo.Salerno@fda.hhs.gov
(240) 402-0420

DATE: December 16, 2015

INFORMATION ADVISORY
(CONFIDENTIAL)

SUBJECT/LEAD COMPONENT: FDA to Announce a Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to Discuss Eteplirsen to Treat Duchenne Muscular Dystrophy

WHY THIS INFORMATION IS IMPORTANT FOR THE SECRETARY: On or about December 17, FDA will announce a meeting of the Peripheral and Central Nervous System

(PCNS) Drugs Advisory Committee. The Committee will meet on January 22, 2016, to discuss a new drug application (NDA) for eteplirsen injection to treat Duchenne muscular dystrophy (DMD) in patients who have a specific mutation of the DMD gene. Eteplirsen is sponsored by Sarepta Therapeutics, Inc., and is one of two DMD drugs currently in development. On November 24, the PCNS met to discuss an NDA for drisapersen, a different drug developed to treat the same population of DMD patients, and Committee members agreed that the efficacy data for the drug were weak and inconsistent and that additional studies would be needed to attempt to identify a group of patients that would benefit from treatment with drisapersen. There is an active community of advocates for research on muscular dystrophy that includes parents of children with DMD. Advocates are well-informed about drugs in development for DMD and will be interested in the outcome of this meeting to discuss eteplirsen. FDA expects the meeting announcement will be of interest to patients with DMD and their families, advocacy groups, industry, health care professionals (including neurologists and therapists working with people with DMD), researchers, and those working in regulatory science, and Congress. FDA will include the meeting information in the weekly tip sheet sent to reporters on the FDA media list, but will not issue a press release. The meeting is expected to garner adequate press coverage such that, after the meeting, a press release will not be necessary to disseminate the results of the meeting to the community.

SUMMARY OF ISSUE, BACKGROUND, AND DEPARTMENT RESPONSE/ACTIONS:

- DMD is a rare genetic disease. In the United States, the prevalence of DMD at birth is about 1 in 3,500 to 1 in 6,000 males. DMD typically manifests in early childhood and progresses to loss of ambulation and death in young adulthood. DMD is caused by mutations in a gene on the X chromosome that encodes for the dystrophin protein, which imparts structural stability to membranes of muscle fiber cells. People with DMD produce little or no functional dystrophin.
- Current treatment for DMD includes corticosteroids, which may prolong function and survival by several years, and supportive care (e.g., physical therapy, mechanical supports, orthopedic surgery, and assisted ventilation). Eteplirsen targets a specific mutation that affects approximately 13 percent of patients with DMD.
- FDA granted orphan drug designation to eteplirsen because it is intended for the treatment of a rare disease. As such, Sarepta Therapeutics, Inc. is eligible for certain financial incentives, as well as other incentives to advance scientific development. Eteplirsen has also been granted fast-track designation because it is intended to treat a serious medical condition and address an unmet medical need. In addition, the NDA has been granted a priority review, indicating FDA's goal to take action on the application within 6 months. FDA accepted Sarepta's NDA under "rolling review," indicating that FDA was able to review completed portions of the NDA as they were submitted.
- In October 2014, FDA issued a "Duchenne Muscular Dystrophy Statement" that described guidance FDA provided about additional data needed to determine whether eteplirsen is effective. The statement also acknowledged the importance of FDA's actions to the DMD community.
- This PCNS meeting will discuss the NDA for eteplirsen, review safety and efficacy data

(including clinical trial results and the benefit-risk profile of the product), and comment on whether adequate data have been submitted to support approval.

- FDA continues to work to assist sponsors in clinical development of drugs for the treatment of DMD. For example, in June 2015, FDA released a draft guidance entitled “Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment.” One advocacy group, Parent Project Muscular Dystrophy, submitted a draft guidance to FDA that contributed to the Agency’s draft guidance.
- Parent Project Muscular Dystrophy and other advocacy organizations have contacted members of Congress, including ranking majority and minority members of the Senate Committee on Health, Education, Labor, and Pensions, urging them to support specific bills that would accelerate the pace of drug development and review for rare diseases, including DMD.

CONTACTS: Alicia Swenson-O’Brien, OS/ES, (202) 205-9953; Mary Jo Salerno, FDA/OES, (240) 402-0420; Jessica Bernstein, CDER/DEO, (240) 402-0524

DATE: December 16, 2015

INFORMATION ADVISORY
(CONFIDENTIAL)

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From: [Moran, Kristy](#)
To: [FDA Senior Executives](#); [OC-Executive Secretariat](#)
Cc: [FDA Senior Executive Assistants](#); [FDA - Information Advisories](#); [OC OEA OMA-Press](#); [Sullivan, Diane](#); [Bernstein, Jessica](#); [Unger, Ellis](#); [CDER EXSEC](#)
Subject: FW: Confidential: Information Advisory (IA) - FDA to Announce a Rescheduled Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to Discuss Eteplirsen to Treat Duchenne Muscular Dystrophy
Date: Thursday, March 10, 2016 3:06:30 PM
Attachments: [AC Public Mtg Eteplirsen to Treat DMD FINAL.doc](#)

This Information Advisory was sent to the Department.

From: Moran, Kristy
Sent: Thursday, March 10, 2016 3:03 PM
To: Swenson-O'Brien, Alicia J (OS); Hall, Bill (OS); Horowitz, David J (OS); Pakulis, Averi (OS); Clark, Robert J (OS)
Subject: Confidential: Information Advisory (IA) - FDA to Announce a Rescheduled Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to Discuss Eteplirsen to Treat Duchenne Muscular Dystrophy

Good afternoon,

Please see the attached Information Advisory, FDA to Announce a Rescheduled Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to Discuss Eteplirsen to Treat Duchenne Muscular Dystrophy

Best regards,
Kristy Moran
Policy Analyst
FDA/OC/OES

DATE: March 10, 2016

INFORMATION ADVISORY
(CONFIDENTIAL)

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patients. Committee members agreed that the efficacy data for the drug were weak and inconsistent and that additional studies would be needed to attempt to identify a group of patients that would benefit from treatment with drisapersen. There is an active community of advocates for research on muscular dystrophy that includes parents of children with DMD. Advocates are well-informed about drugs in development for DMD and will be interested in the outcome of this meeting to discuss eteplirsen. One advocacy group, Parent Project Muscular Dystrophy, submitted draft guidance to FDA that contributed to the Agency's draft guidance on developing drugs for this rare disease. FDA expects the meeting announcement will be of interest to patients with DMD and their families, advocacy groups, industry, health care professionals (including neurologists and therapists working with people with DMD), researchers, those working in regulatory science, and Congress. FDA will include the meeting information in the weekly tip sheet sent to reporters on the FDA media list, but will not issue a press release. It is expected that a large number of media representatives will attend and FDA expects substantial press coverage of the results.

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From: [Watson, Sharron](#)
To: [Califf, Robert](#); [Roth, Deborah](#)
Subject: FW: issue papers for tomorrow's prep sessions
Date: Monday, October 19, 2015 5:19:47 PM
Attachments: [ALS - GM604.docx](#)
[Duchenne Muscular Dystrophy.docx](#)
Importance: High

FYI

From: Alexander, Uchenna
Sent: Monday, October 19, 2015 5:05 PM
To: Watson, Sharron
Subject: issue papers for tomorrow's prep sessions
Importance: High

Hi Sharron,

I just received the attached two issue papers, which will be topics during Dr. Califf's review session tomorrow. Please pass them along as you are able.

Thanks, and sorry for the lateness of this request,
Uchenna

Uchenna Alexander
Congressional Affairs Specialist
OC/OPPLA/OL
301-796-9125

Duchenne Muscular Dystrophy (DMD)

Key Messages

Key Message #1: FDA recognizes the unmet medical need that exists in patients with DMD, the devastating nature of the disease for patients and their families and the urgency to make new treatments available.

Key Message #2: FDA values the effort and comprehensive insight provided by Parent Project Muscular Dystrophy (PPMD) in their proposed guidance; this type of engagement between stakeholders and FDA is an example of how early input from patients and caregivers can often contribute to drug development.

Key Message #3: Peripheral and Central Nervous System Drugs Advisory Committee will be holding a meeting at the FDA on November 24, 2015, to discuss new drug application (NDA) 206031, drisapersen solution for injection, sponsored by BioMarin Pharmaceutical Inc., for the treatment of patients with Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing.

Questions and Answers

1. What is Duchenne Muscular Dystrophy?

- Duchenne muscular dystrophy is a form of muscular dystrophy.
- Duchenne muscular dystrophy is caused by a defective gene for dystrophin (a protein in the muscles).
- However, it often occurs in people without a known family history of the condition.
- Because of the way the disease is inherited, it usually affects boys. Very rarely, a girl can be affected by the disease.
- Duchenne muscular dystrophy occurs in about 1 out of every 3,600 male infants. Because this is an inherited disorder, risks include a family history of Duchenne muscular dystrophy.

2. Are there any FDA-approved drug treatments for this condition?

- There is no known cure for Duchenne muscular dystrophy and the FDA has not approved any drugs for its treatment.

- Therapies used by specialists in this disease include corticosteroids, which appear to delay, but not prevent, muscle degeneration, and other supportive care that is critical for preserving function and quality of life as long as possible.

Background

- Duchenne muscular dystrophy (DMD) is a rare genetic disorder characterized by progressive muscle degeneration and weakness.
 - DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact.
 - The most prominent pathology in dystrophinopathies is degeneration of skeletal and cardiac muscle leading to progressive loss of muscle function, respiratory and cardiac failure, and premature death.
 - Symptom onset is in early childhood, usually between ages 3 and 5 years.
 - The disease primarily affects males, but in rare cases can also affect females.
- During a public-private policy forum for DMD on December 12, 2013, FDA agreed that Parent Project Muscular Dystrophy (PPMD) and other interested parties in the DMD community could submit for FDA consideration a proposal for a draft guidance for industry on developing drugs for DMD.
 - PPMD submitted a proposed draft guidance to FDA on June 25, 2014.
 - The submission of a proposed draft guidance for a rare disease by a patient advocacy group was unprecedented to our knowledge.
 - FDA posted the document to seek public comment.
- Having considered the proposed draft guidance from PPMD, public comments received, as well as FDA's current thinking on the topic, FDA wrote a draft guidance, intended to assist sponsors in the clinical development of drugs for the treatment of DMD and related dystrophinopathies.
 - The purpose of this draft guidance is to assist drug companies and researchers in the clinical development of drugs to treat DMD. It covers important clinical considerations sponsors (such as drug manufacturers) should consider when conducting clinical trials, such as study populations, safety considerations and study design.
 - This draft guidance addresses FDA's current thinking regarding the clinical development program and clinical trial designs for drugs to treat dystrophinopathies.
 - The draft guidance is intended to serve as a focus for continued discussion with sponsors and researchers about drugs to treat DMD.

Source: KMQA for DMD draft guidance, updated 5/26/15; Federal Register Notice posted 10/15/15:
<https://www.federalregister.gov/articles/2015/10/15/2015-26162/peripheral-and-central-nervous-system-drugs-advisory-committee-notice-of-meeting>

Reorganized/streamlined by: S.Horowitz, OL, 10/14/15

Amyotrophic Lateral Sclerosis (ALS)

Key Messages

Key Message #1: FDA recognizes the critical unmet medical need for new, effective treatments for amyotrophic lateral sclerosis (ALS).

Key Message #2: We are committed to working with drug companies and the ALS community to facilitate development and approval of drugs to treat this devastating disease.

Key Message #3: FDA is prepared to use all expedited development and approval pathways available to us to further this mutual goal.

Questions and Answers

1. What is the status of GM604?

- Confidentiality laws prohibit FDA from disclosing information about products that are under development, unless that information was first made public by the manufacturer.
- As noted in our statement of April 17, 2015, however, we have called upon Genervon to release all data from their trial to allow a more informed discussion of the trial findings among ALS stakeholders.
- This data would provide the strongest basis for assessing safety and efficacy of GM604.

2. Are there any FDA approved drugs to treat ALS?

- Nuedexta (combination of dextromethorphan and quinidine) was approved in 2010 for the treatment of pseudobulbar affect, a symptom that some ALS patients develop.
- However, we know it has been many years since a drug that prolongs survival in ALS has been discovered and we understand the frustration felt by patients and their families.

Background

Talking points:

- We at the FDA recognize the urgency to identify effective treatments for patients with ALS. The FDA is actively engaged with multiple drug companies that are developing new drugs for ALS.

- The many negative studies in this area have been disappointing, but we are encouraged that multiple drug companies have interest in this area. In the past few years there have been a number of important discoveries about the specific genes that cause ALS in some patients. Knowing the genes that cause the disease may help in finding drugs that will be effective.
- Senior officials from the FDA's Center for Drug Evaluation and Research are deeply committed to this area of drug development and have been meeting regularly with ALS advocates to discuss this devastating disease. There have been multiple meetings between FDA and ALS advocates in the past year.
- It is FDA's job to make sure drugs work for the intended condition. While we know patients with devastating diseases are willing to accept risk of adverse drug effects, we need to make sure we have sound scientific data that shows a drug will be effective to treat a disease. We understand that even a small benefit is valuable for ALS patients.
- We stand ready to expeditiously review data that might show a drug is effective for ALS. We consider all the ways a drug might work – from prolonging life to increasing strength to decreasing symptoms.

FDA Statement on GM604:

- FDA recognizes the critical unmet medical need for new, effective treatments for amyotrophic lateral sclerosis (ALS). We are committed to working with drug companies and the ALS community to facilitate development and approval of drugs to treat this devastating disease. FDA is prepared to use all expedited development and approval pathways available to us to further this mutual goal.
- FDA knows that ALS patients, their families, and others in the ALS community are concerned about the status of Genervon's experimental drug, GM604, for the treatment of ALS. However, FDA is prohibited by law, under usual circumstances, from releasing confidential information about experimental drugs, including GM604.
- We call upon Genervon to release all the data from their recently completed trial in order to allow a more informed discussion of the trial findings among ALS stakeholders. Such a release should include the pre-specified clinical outcome measures as assessed by change from baseline observations that were taken just prior to randomization to drug or placebo. Such data provide the strongest basis to assess for drug-related changes in efficacy and safety parameters.
- FDA will continue to provide detailed advice and support to Genervon as they pursue further study of GM604 to determine if it is safe and effective to treat ALS. We remain committed to working with the ALS community to find effective treatments for this disease.

Source: FDA Statement on GM604: <http://www.fda.gov/Drugs/DrugSafety/ucm443242.htm>, Talking Points for Dr. Woodcock for 10/21/15 interview with HBO/VICE

Reorganized/streamlined by: S.Horowitz, OL, 10/19/15

From: [Sherman, Rachel](#)
To: [Califf, Robert](#)
Subject: Fwd: CDER Trade Press News Update December 29, 2016
Date: Thursday, December 29, 2016 9:31:03 AM
Attachments: [image003.png](#)
[image008.png](#)
[image006.png](#)
[image007.png](#)
[image005.png](#)

Were you briefed on the clin pharm biosims guidance before it was published?

From: CDER Trade Press <CDERTradePress@fda.hhs.gov>
Date: December 29, 2016 at 5:30:58 AM MST
To: CDER Trade Press <CDERTradePress@fda.hhs.gov>
Subject: CDER Trade Press News Update December 29, 2016



Today's Headlines (click to go directly to the article):

(The Pink Sheet)

[Biosimilars Get Bespoke Service: EMA To Pilot Tailored Scientific Advice](#)

[Biosimilars: FDA Closes Out 2016 With Clinical Pharmacology Guidance](#)

[Exondys Approval: Measured Efficacy Outcomes Vs. Patient 'Anecdotes'](#)

[Eteplirsen Approval Reflected FDA's Conflict On Accelerated Approval – Former Sarepta CEO](#)

(The Rose Sheet)

[FDA Warnings Slow, But Anti-Aging Claims Remain Class Action Targets](#)

(FDA News)

[FDA Tweaks Guidance on Clinical Pharmacology Data for Demonstrating Biosimilarity](#)

[FDA Clarifies Botanical Drug Considerations for Combination Drugs](#)

[FDA Hands Aplicare Warning Letter Over Sterility Controls, Off-Label Promotion](#)

[Sanofi Sues Novo Nordisk Over Misleading Claims of Lantus, Toujeo Coverage](#)

(Inside Health Policy)

[Jenkins: FDA Approving More Drugs, And Faster, Since PDUFA Start](#)

**If you are unable to access a link within an article, please respond to this email, and we will provide you the text of the linked article.*



Biosimilars Get Bespoke Service: EMA To Pilot Tailored Scientific Advice

- 28 Dec 2016
- News

[Vibha Sharma @ScripRegVibhavibha.sharma@informa.com](mailto:Vibha.Sharma@ScripRegVibhavibha.sharma@informa.com)

Executive Summary

Quality data will be focus of 'extra advice' offered by European Medicines Agency's pilot, which will suggest directions for sponsors' next steps but stop short of formal data evaluation.

The European Medicines Agency will start offering tailored scientific advice for a limited number of biosimilars as part of a pilot to be launched in February next year.

The pilot has been devised in response to a demand from companies who are looking "for this extra advice, specifically for biosimilars," the EMA told the Pink Sheet. The US Food and Drug Administration already offers biosimilar sponsors a similar possibility. (Also see "[Biosimilars Will Get PDUFA-Style Reviews Under New User Fee Plan](#)" - Pink Sheet, 28 Sep, 2016.)

The EMA pilot will specifically deal with scientific advice relating to quality aspects. According to the agency, companies will be able to provide quality data and get extended advice that will help them plan future product development and prepare better for a marketing authorization

submission.

EMA does not see this as advanced data assessment, as companies will only get additional advice to help them better plan their product's continuing development for next steps, such as those pertaining to quality, non-clinical, clinical aspects, the spokesperson added.

The tailored approach will be different from the EMA's current scientific advice procedure, as this does not involve a formal assessment of data. Under the tailored approach, advice will be given on the basis of the data submitted by companies. Specifically, the EMA will carry out an in-depth review of the quality, analytical and functional data available, which will allow for more tailored recommendations on the studies/tests that should be carried out in the next step of the development. This will allow companies to make a more informed decision on their development strategy once sufficient quality data has been accumulated.

Resource Intensive

Providing such tailored scientific advice will be resource intensive for the assessors and members of the EMA's scientific advice working party (SAWP). "This pilot should help us to judge how much additional effort is required and where," the agency spokesperson said.

The fee will be the standard fee for a scientific advice procedure including quality, non-clinical and clinical questions.

To ensure that the agency is not overburdened with requests, the pilot is planned to run until six scientific advice requests have been completed, with no more than one scientific advice request accepted per month. The pilot will help the agency test the added value and feasibility of providing such a service on a permanent basis in the future. "We would explore the experience of both parties (industry and regulators) before deciding to continue/modify/not use the approach," the EMA spokesperson said.

The pilot will be open to all companies seeking scientific advice for the development of any type of biosimilar. Companies wanting to participate in the pilot will have a pre-submission meeting, during which the suitability of their data package will be reviewed. The SAWP will need an extra month on top of the normal scientific advice timelines to review the requests accepted in the pilot.

The EMA currently has 17 biosimilar products under evaluation. (Also see "[Blockbuster Competitors Figure Large Among Biosimilars Under Review in EU](#)" - Pink Sheet, 21 Dec, 2016.)

From the editors of Scrip Regulatory Affairs.

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Biosimilars: FDA Closes Out 2016 With Clinical

Pharmacology Guidance

- 28 Dec 2016

- **News**

[Sue Sutter @PinkSheetSuttersue.sutter@informa.com](mailto:Sue.Sutter@PinkSheetSuttersue.sutter@informa.com)

Executive Summary

While industry awaits US FDA guidance on interchangeability, agency finalizes document on clinical pharmacology data to support a demonstration of biosimilarity – years ahead of May 2019 target date in commitment letter for user fee program's renewal.

The US FDA got one of its commitments under the Biosimilar User Fee Act (BsUFA) reauthorization agreement out of the way almost two-and-a-half years early with its Dec. 28 release of a final guidance on clinical pharmacology data to support a demonstration of biosimilarity.

The document is intended to assist sponsors in determining the clinical pharmacology data necessary for evaluation of a proposed biosimilar.

Changes reflected in the final guidance document are for clarity and not substantive, FDA said.

The [final guidance](#) largely tracks the [draft version](#) released in May 2014, although the agency made a number of revisions, including changes in the language used to describe four possible outcomes for the analytical comparisons of a proposed biosimilar to a reference product.

After reviewing public comments on the draft guidance "and in light of increased regulatory experience and the evolution of the science in biosimilar product development and evaluation, FDA has finalized that guidance with certain changes," the agency said in a [Federal Register notice](#) slated for Dec. 29 publication. "These changes are for clarity, however, and are not substantive."

Target Date May 2019

The clinical pharmacology document was probably one of easier biosimilar guidances for the agency to deliver to industry and other stakeholders, which have been champing at the bit particularly for draft guidance on interchangeability and final documents addressing nonproprietary naming and labeling.

Nevertheless, it allows the agency to tick off another item on its list of tasks necessary to implement the Biologics Price Competition and Innovation Act, which created the 351(k) biosimilar pathway.

Under the BsUFA II commitment letter negotiated with industry, the agency agreed to target dates

for some long-awaited guidance documents on biosimilar development. However, the nearest term target was for two draft guidance documents – on interchangeability, and statistical considerations for analytic similarity data – by Dec. 31, 2017.

Revised draft or final guidance on clinical pharmacology data was not due until May 31, 2019. This was the same timeframe established for revised draft or final guidance on nonproprietary naming of biological products and biosimilar labeling. (Also see "[Biosimilar User Fee Agreement Puts FDA On Hook For Delayed Guidances](#)" - Pink Sheet, 22 Sep, 2016.)

The clinical pharmacology document could be part of a year-end push at the agency to get guidance documents out the door ahead of the change in presidential administration coming in mid-January.

"We would like to get the remaining guidances that are kind of pending out as soon as possible." – CDER's Woodcock

In remarks at the FDA/CMS Summit in Washington, DC on Dec. 14, Center for Drug Evaluation and Research Director Janet Woodcock was asked about the chances that the biosimilar interchangeability guidance would be released before 2017.

"It is seeming less likely as we get more toward the end of the year," she said. "We would like to get the remaining guidances that are kind of pending out as soon as possible. But obviously, we only have a few weeks left."

505(b)(2) Language Stricken From Guidance

As in the draft version, the final guidance discusses overarching concepts related to clinical pharmacology testing for biosimilar products, approaches for developing the appropriate clinical pharmacology database, and the use of modeling and simulation for designing clinical trials.

One change from the draft version is found in the document's introduction. The draft had stated that some of the scientific principles described in the guidance "may also be informative for the development of certain biological products under section 505(b)(2)" of the Food, Drug and Cosmetic Act. However, the draft noted that "no particular relationship between the standards for approval" under 505(b)(2) and 351(k) was implied.

FDA has historically regulated certain types of protein products, such as insulin and human growth hormone, as new drug applications (NDAs) under Section 505. However, in March 2020 such products will be deemed to be licensed as biologic license applications (BLAs) under the Public Health Service Act.

The agency's March draft guidance on implementation of the "transition provisions" drew sharp complaints from industry stakeholders, who said it could create a blackout period for new applications lasting several years. (Also see "[FDA Biologic Transition Plan Creates 'Dead Zone' For Applications, Sponsors Fear](#)" - Pink Sheet, 23 May, 2016.)

Although the language related to 505(b)(2) NDAs has been removed in the final version of the clinical pharmacology guidance, the Federal Register notice announcing the document's availability reiterates that the scientific principles may also be informative for the development of certain biological products under 505(b)(2).

Four Outcomes Get Name Changes

The final guidance discusses the role of clinical pharmacology data in building upon a foundation of comparative analytical data in the stepwise approach to demonstrating biosimilarity.

Clinical pharmacology studies "are normally a critical part of demonstrating biosimilarity by supporting a demonstration that there are no clinically meaningful differences between the proposed biosimilar product and the reference product," the guidance states.

FDA retained the concept of the four-tier hierarchy despite some objections from industry.

"These clinical pharmacology studies may address residual uncertainties that remain after the analytical evaluation, can add to the totality of the evidence supporting a demonstration of biosimilarity, and can guide both the need for and design of subsequent clinical testing to support a demonstration of no clinically meaningful differences in the overall demonstration of biosimilarity."

One of the most apparent changes in the final guidance is not specific to clinical pharmacology data but, rather, to FDA's terminology for the four outcomes that can result from the comparative analytical characterization. (Also see "[Biosimilar Draft Guidance Outlines Three-Arm Bridging Studies For Non-U.S. Products](#)" - Pink Sheet, 13 May, 2014.)

While the definitions for each of these outcomes remained largely intact, FDA refined the nomenclature in the final guidance(see chart).

Terminology On Analytical Characterization Assessment Outcomes	
Draft Guidance	Final Guidance
Not similar	Insufficient analytical similarity
Similar	Analytical similarity with residual uncertainty
Highly similar	Tentative analytical similarity
Highly similar with fingerprint-like similarity	Fingerprint-like analytical similarity

The final guidance emphasizes that these assessments occur within a development-phase continuum "and with the understanding that FDA does not make the ultimate determination that the proposed biosimilar product is highly similar to the US-licensed reference product until the time of licensure."

"The outcome of the comparative analytical characterization should inform the next steps in the demonstration of biosimilarity," the guidance states.

FDA retained the concept of the four-tier hierarchy despite some objections from industry.

In comments on the draft, the Pharmaceutical Research and Manufacturers of America asserted the hierarchy is beyond the scope of the draft guidance and should be removed. Alternatively, it urged FDA to clarify the meaning of the categories and explain how the agency intends to use them.

In separate comments, the Biotechnology Innovation Organization asserted that more clarification was needed in the type or scope of information needed to differentiate among the categories and said the agency should include limiting principles around certain scenarios.

New Language On Assays And Study Materials

Language regarding general pharmacokinetic (PK) assay considerations has been revised to state that sponsors should design or choose an assay based on a thorough understanding "to the extent that the mechanism of action is known for the reference product."

"An assay producing concentration data that correlate to the pharmacological/[pharmacodynamic] activity is preferred," the final guidance states. "The same assay should be used for measuring concentrations of the proposed biosimilar product and the reference product and validated for use with both products. Analytical assays should have design and performance parameters that are consistent with current industry best practices."

Clinical pharmacology studies of the proposed biosimilar should be performed using materials from the final manufacturing process.

The final guidance also reflects new language related to the materials used in clinical pharmacology studies.

"All clinical pharmacology studies of the proposed biosimilar product should be performed using materials from the final manufacturing process expected to be used for the marketed product if approval is granted," the guidance states.

"The relevance of data submitted from studies using materials from different manufacturing processes may need to be adequately justified, for example, by establishing an analytical and PK bridge to the to-be-marketed product."

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Exondys Approval: Measured Efficacy

Outcomes Vs. Patient 'Anecdotes'

- 28 Dec 2016

- Analysis

[Sue Sutter @PinkSheetSuttersue.sutter@informa.com](mailto:Sue.Sutter@PinkSheetSuttersue.sutter@informa.com)

Executive Summary

Pink Sheet's Drug Review Profile looks at US FDA clinical memos opposing approval of Sarepta's Duchenne muscular dystrophy drug eteplirsen, revealing challenges patient advocates and agency face in transforming patient experiences into hard data that can be used for approvals.

Patient advocates played a very visible role in FDA's review of [Sarepta Therapeutics Inc.'s Exondys 51](#) (eteplirsen) for Duchenne muscular dystrophy, but agency documents show just how difficult it can be for patient testimonials and caregiver surveys to sway FDA scientific staff when they believe the underlying clinical trial data fall short.

Agency reviewers could not reconcile what they saw as a disconnect between the clinical trial participants' experiences on eteplirsen versus the measured efficacy outcomes from those studies.

Clinical reviewers could not reconcile the disconnect between trial participants' experiences on eteplirsen versus the measured efficacy outcomes from those studies.

Center for Drug Evaluation and Research (CDER) Director Janet Woodcock ultimately made the accelerated approval decision, finding that the small amount of dystrophin produced by the drug was reasonably likely to predict clinical benefit. Her decision was backed by FDA Commissioner Robert Califf, who said he found no evidence that she was unduly influenced by the patient community or other external pressures. (Also see "[Sarepta's Eteplirsen Approved After Contentious Internal Debate](#)" - Pink Sheet, 19 Sep, 2016.)

While the highly vocal Duchenne patient community ultimately got what it wanted – market access to the first drug approved for patients with an exon 51-skipping DMD gene – the controversial approval reflects the challenges patient advocates, as well as FDA reviewers, will continue to face in the move toward better integration of the patient voice in the drug development and approval process.

While reviewers may pay heed to patient and caregiver testimony and survey data on outcomes and quality-of-life improvements, clinical efficacy data still reign supreme, even when regulatory flexibility is encouraged in the context of rare diseases.

'Flexibility' Does Not Trump 'Substantial Evidence'

"I have considered this issue from the perspective of applying 'flexibility' as described" by the FDA Safety and Innovation Act of 2012, clinical reviewer Christopher Breder said in a May 9 review. "The flexibility does not mean that the threshold for substantial evidence is lowered."

"I believe that considerable flexibility was afforded the application through the review team accepting studies that were not formally powered, by considering data where the standards of execution were evolving even through the review cycle, and by considering the patient and family testimony from the advisory committee," Breder said. "Despite these considerations, I still do not consider the threshold for substantial evidence to have been met."

Sarepta's former CEO Chris Garabedian has also suggested that the drama surrounding the approval of eteplirsen reflects a fundamental tension at FDA about the role of accelerated approval. (Also see "[Eteplirsen Approval Reflected FDA's Conflict On Accelerated Approval – Former Sarepta CEO](#)" - Pink Sheet, 28 Dec, 2016.)

In a July 16 decisional memo recommending a complete response letter, Office of Drug Evaluation I Director Ellis Unger said the agency takes seriously the patient perspective and the congressional mandate to be flexible.

"But patient-focused drug development is about listening to patient perspectives about what matters to them," Unger said. "It is not about basing drug approvals on anecdotal testimony that is not corroborated by data."

The eteplirsen experience highlights the importance of FDA's commitments in the negotiated agreement reauthorizing the Prescription Drug User Fee Act to develop guidance on methods for collecting and analyzing survey data and patient-reported outcomes in a way that they can be used to support regulatory decision-making.

Approval Rested On Biomarker Data

The disagreement between Woodcock and other CDER staff over the interpretation of the eteplirsen efficacy data has become well known since FDA released senior leaders' decisional memos at the time of the drug's approval in September (*see box*).

Reviewers in the agency's Division of Neurology Products, as well as senior staff within CDER, found no evidence that eteplirsen demonstrated an improvement on clinical endpoints in Study 201/202, the 12-patient, historically controlled Phase I/II study that served as the basis for the NDA submission.

The reviewers also found the dystrophin biomarker data from 201/202 either unreliable or unpersuasive. Although muscle biopsy data from an ongoing trial, Study 301, submitted late in the review showed a statistically significant increase in dystrophin levels, the magnitude of effect was small and inadequate to conclude that it was reasonably likely to predict clinical benefit, reviewers said.

In contrast, Woodcock said the Study 301 interim data, combined with 180-week data from Study 202, supported the finding of substantial evidence of increased dystrophin production with eteplirsen. She further concluded that low-level increases in dystrophin production are reasonably likely to predict clinical benefit. (Also see "[Accelerated Approval After Eteplirsen: A Lowered Bar Or A Unique Event?](#)" - Pink Sheet, 20 Sep, 2016.)

While Woodcock acknowledged that results of the six-minute walk test in Study 202 did not show a strong correlation with dystrophin levels, her analysis of North Star Ambulatory Assessment (NSAA) results in boys who were still ambulatory found that higher dystrophin levels were correlated with a lower rate of decline.

Furthermore, accelerated approval represented an appropriate exercise of regulatory flexibility given the life-threatening nature of the disease, lack of other available therapies and the drug's good safety profile, she said.

Unger appealed Woodcock's decision, and the dispute ultimately landed on Califf's desk. (*See timeline sidebar*)

Patient Experiences Aired At AdComm

While the review division's opinions of the efficacy evidence became publicly clear through the advisory committee review, it has been less obvious how patient and caregiver testimony during that meeting, and other input from the DMD community, factored into reviewers' recommendations for regulatory action.

DMD patients, caregivers and other advocates were a force to be reckoned with during the eteplirsen review. In his formal appeal of Woodcock's decision, Unger reported receiving 2,792 emails urging approval, some of which contained profane language. He also noted that more than 50 individuals registered to speak at the April advisory committee meeting.

At that meeting, Sarepta handed over 10 minutes of its presentation time to Christine McSherry, executive director of the Jett Foundation, marking what is believed to be the first time a patient group has been allowed to speak during the sponsor's presentation. (Also see "[Duchenne Group's Presentation Is Milestone For Patient Involvement](#)" - Pink Sheet, 2 May, 2016.)

McSherry presented data on activities of daily living collected through semi-structured interviews with eight of 12 boys who participated in Study 201/202 and had been receiving eteplirsen for three years. The group also interviewed three eteplirsen-treated boys from a separate study, 204.

Eteplirsen-treated patients and their caregivers reported a decrease in spontaneous falls and an increased ability to walk after fracture, McSherry said. In addition, levels of fatigue declined or stabilized, and non-ambulatory patients were better able to maintain activities of daily living, she said.

During the meeting's open public hearing, Pat Furlong, president and CEO of Parent Project

Muscular Dystrophy (PPMD), presented results from the group's benefit/risk preference study on incremental benefit, which found that for parents of boys with DMD the overwhelming priority is to slow disease progression.

PPMD has been actively involved in trying to establish regulatory guideposts for DMD drug development. In June 2014, the group submitted for FDA consideration a proposed guidance that emphasized the importance of formal patient preference collection methods and included recommendations on clinical trial design, outcome measures and biomarkers. The agency embraced many of the patient group's recommendations in a draft guidance it published a year later. (Also see "[Duchenne Muscular Dystrophy: FDA Supports Broader Outcome Measures, Biomarkers](#)" - Pink Sheet, 10 Jun, 2015.)

Testimonies Of Improved Function ...

FDA clinical review documents focus primarily on the clinical trial efficacy and safety evidence and dystrophin data, with only brief mention of patient input received during the review.

While the review team considered the experiences reported by patients and their caretakers, and in some cases even found the patient testimony to be supportive evidence of benefit, it was not enough to overcome weaknesses in the eteplirsen clinical efficacy data resulting, in part, from the drug's troubled development program.

Among the clinical review team, Cross-Discipline Team Leader Ronald Farkas' May 19 memo contains the most discussion of patient testimony and input FDA received in writing and during the advisory committee open public hearing, which lasted more than two-and-a-half hours. (*See reviewers sidebar*)

Farkas, who has since left the agency for a job in private industry, listed the names of open public hearing speakers and a short summary of each individual's or group's comments.

Among these were patient and caregiver testimonials that the clinical course of eteplirsen-treated patients differs from the natural history of DMD, with the following benefits: maintenance of walking ability, fewer falls, increased strength, more stamina, regained or increased activities of daily living, stabilized cardiac and pulmonary function, and improved quality of life.

"I myself have great difficulties reconciling the testimonies with the study results." – FDA's Bastings

"The patient testimonies were very moving, and uniformly supportive of eteplirsen, indicating in multiple cases improvement of the patients' condition," Eric Bastings, deputy director of the Division of Neurology Products, said in a July 15 review.

"Although many of the members of the advisory committee were as moved by the testimonies as I was, several members noted the disconnect between the testimonies and clinical outcome results, including the invited member who had Duchenne muscular dystrophy," Bastings said. "I myself have great difficulties reconciling the testimonies with the study results."

... Not Borne Out By Trial Data

No eteplirsen-treated patient experienced a sustained functional improvement in the outcome measures that were assessed in Study 202, particularly the NSAA, "which is a rather comprehensive measure of mobility and transfers," Bastings noted.

"It is quite clear that eteplirsen does not have a dramatic effect, or even a moderate to large effect on disease progression in Duchenne muscular dystrophy. In fact, there is no clinical evidence of efficacy from Study 201/202," he said.

While it is possible that lower magnitude differences could be identified on outcome measures in future trials, Bastings voiced "very serious doubts" that a historical control study would be capable of picking up such differences.

Unger also addressed the testimony and other input received at the advisory committee's open public hearing, which included remarks from 10 of the 12 patients in Study 202.

"The testimonies of these patients were quite consistent and remarkably positive: all were convinced that eteplirsen had made a substantial positive impact on their physical performance, improving numerous aspects of their lives," Unger said. "It was noteworthy that a number of individuals who were in Study 201/202 reported improvement in physical function with eteplirsen treatment."

"The review team did not find any patients in Study 201/202 with consistent improvement in physical performance as assessed by formal testing." – FDA's Unger

"Importantly however, despite the claims of improvement made at the microphone at the advisory committee meeting, the review team did not find any patients in Study 201/202 with consistent improvement in physical performance as assessed by formal testing (6-minute walk, rise time, NSAA, 10-meter run)," Unger said. "These tests have shown moderate to extreme declines in physical function for all patients."

Consequently, the review team, as well as many of the advisory committee members, "were unable to reconcile the patient testimonies with the data collected by the applicant: the testimonies spoke of improvement; the data showed progressive worsening."

"Despite considerable pressure from the DMD patient community and many well-intentioned members of the public who have lobbied on their behalf, I am unable to reach the conclusion that the applicant has provided substantial evidence to support either conventional or accelerated approval of eteplirsen for the treatment of DMD," Unger said. "This view is in agreement with the unanimous opinions of members of the review team from the Division of Neurology Products, the clinical pharmacology review team, and the biostatistics review team."

Instead of conducting a new trial exploring higher eteplirsen doses, Sarepta "chose instead to

trumpet the preliminary findings from their 12-patient Phase I/II study, convincing many in the DMD community that the drug was highly effective, and unleashing a public media campaign (with support of many politicians) to approve the drug," Unger said. "The reality is that FDA is a science-based organization. We do not – and should not – make approval decisions based on patient anecdotes or campaigns through social media."

What's On The Regulatory Horizon For Patient Input?

The need to move from sharing patient anecdotes to scientifically grounded collection and analysis of patient-centered data is at the heart of FDA commitments under the PDUFA VI agreement negotiated with industry.

The agency has agreed to develop a series of guidance documents on approaches and methods to bridge from initial patient-focused drug development meetings under PDUFA V to fit-for-purpose tools to collect meaningful patient and caregiver input for use in regulatory decision-making.

Establishing a more concrete scientific framework around the collection and analysis of patient- and caregiver-reported experiences could not only improve the prospects for drug approval when the clinical efficacy data are less than robust, it also should aid in clinical trial design by ensuring that sponsors build in outcomes that the patient community cares most about.

There also will soon be a brighter light shining on FDA's use of patient experience data in regulatory decision-making.

Under the recently enacted 21st Century Cures legislation, FDA must make a public statement about any patient experience data or related information submitted and reviewed as part of an application. (Also see "[21st Century Cures Revisions Tell FDA To Highlight 'Patient Experience Data'](#)" - Pink Sheet, 27 Nov, 2016.) The new law also includes requirements for FDA guidance on collection of patient experience data, including how the agency plans to use such data when evaluating the risks and benefits of a drug.

"When you know the disease and you know the progression of the disease, it became very apparent these boys were acting much differently than what you would think." – Jett Foundation's McSherry

The statutory provisions should help address some patient groups' calls for increased transparency into how FDA uses patient preference data in the drug review process. (Also see "[Patient-Driven Drug Development Requires New Transparency Policies](#)" - Pink Sheet, 11 Nov, 2016.)

In a recent interview, Annie Kennedy, PPMD's senior vice president for legislation and public policy, said the group does not know how its patient preference data were used by FDA during the eteplirsen review or whether the group is developing research tools and data that are useful to the agency.

Nevertheless, the advocacy efforts around eteplirsen's approval seem likely to ensure that the

patient voice finds its way into the review process, particularly when the pre-specified clinical efficacy outcomes data look equivocal.

At the recent FDA/CMS Summit, Jett Foundation's McSherry took umbrage at the suggestion that the patient community had too much influence in the approval of eteplirsen when some say there is no evidence the drug is efficacious.

"Parents and patients need to be taken into consideration, they need their viewpoints to be heard," she said. "Oftentimes and in this case especially, it was hard, I think, for the company ... to identify what type of endpoint they were going to see during the trial."

"They identified a clinical endpoint that looked like it was slowing the progression of the disease down," McSherry said. "It didn't maybe look very impressive if you didn't know the disease. When you know the disease and you know the progression of the disease, it became very apparent these boys were acting much differently than what you would think."

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Eteplirsen Approval Reflected FDA's Conflict On Accelerated Approval – Former Sarepta CEO

- 28 Dec 2016

- News

[Sue Sutter @PinkSheetSuttersue.sutter@informa.com](mailto:Sue.Sutter@PinkSheetSuttersue.sutter@informa.com)

Executive Summary

There is anxiety within the US agency over use of the pathway amid the prospect for confirmatory trials to fail, former CEO Garabedian says at FDA/CMS Summit.

The regulatory review of [Sarepta Therapeutics Inc.](#)'s Duchenne muscular dystrophy drug *Exondys 51* (eteplirsen) highlighted FDA staff's conflicted feelings about the accelerated approval pathway, the company's former CEO said Dec. 14.

"I think it's fair to say that there are probably some within the FDA who see the accelerated approval pathway as a bit of a headache," Chris Garabedian said at the FDA/CMS Summit in Washington, DC.

Garabedian suggested there is an inherent conflict between the "reasonably likely to predict clinical benefit" standard for accelerated approval, and the statutory requirement for sponsors to demonstrate substantial evidence of efficacy. "There's an irreconcilable conflict in those two

statements," he asserted, noting that FDA has said "we're not going to lower our standards for accelerated approval."

Garabedian also suggested that a lot of the agency's anxiety around accelerated approval stems from the potential for confirmatory trials to fail.

Additional Eteplirsen Coverage

The Pink Sheet has provided extensive coverage of the controversial approval of Sarepta's DMD drug, including most recently a deep dive into its journey through FDA as the December feature in our monthly Drug Review Profile series:

- (Also see "[Exondys Approval: Measured Efficacy Outcomes Vs. Patient 'Anecdotes'](#)" - Pink Sheet, 28 Dec, 2016.)
- (Also see "[Exondys 51 Clinical Development Timeline](#)" - Pink Sheet, 28 Dec, 2016.)
- (Also see "[Exondys 51 Reviewers](#)" - Pink Sheet, 28 Dec, 2016.)

"If the new data comes out and doesn't support it, we're going to have a bigger problem if we try to pull a drug from the market that you're hearing a parent say is working for their child," Garabedian said.

The former Sarepta exec said the eteplirsen experience shows that FDA and sponsors need to figure out where accelerated approval fits into the development paradigm for rare diseases, where patients are few, endpoints are novel and natural history data are lacking.

Weighing Accelerated Approval Vs. Placebo Controls

Garabedian's remarks came during a panel discussion on FDA and patient advocacy in the wake of the eteplirsen approval.

FDA granted accelerated approval to eteplirsen in September. The controversial decision to approve was made by Center for Drug Evaluation and Research Director Janet Woodcock, who overruled the objections of review staff and other senior CDER officials. Woodcock concluded that the small amount of dystrophin produced by eteplirsen was reasonably likely to predict a clinical benefit under the accelerated approval standard, and FDA Commissioner Robert Califf deferred to her decision. (Also see "[Sarepta's Eteplirsen Approved After Contentious Internal Debate](#)" - Pink Sheet, 19 Sep, 2016.)

Internal agency documents show that while Woodcock viewed eteplirsen's approval as an exercise of the flexibility envisioned for the accelerated approval pathway, other agency officials saw it as a lowering of the efficacy bar and a threat to the substantial evidence standard. (Also see "[Accelerated Approval After Eteplirsen: A Lowered Bar Or A Unique Event?](#)" - Pink Sheet, 20 Sep, 2016.)

Garabedian was CEO of Sarepta from January 2011 until his resignation March 2015. His ouster

largely was seen as an effort by the company to smooth both its strained relations with FDA and the regulatory pathway for eteplirsen. (Also see "[Hoping To Smooth Relations With FDA, Sarepta Moves On From CEO Garabedian](#)" - Pink Sheet, 1 Apr, 2015.)

Those strained relations resulted, in part, from differences in how FDA and Sarepta viewed the advice the agency gave to the company, and in the company's public disclosures about its data and interactions with FDA.

"The issue is you need to resolve are you going to consider this for accelerated approval or not, and if you're not should you shift to a placebo-controlled study?" – Former Sarepta CEO Garabedian

Garabedian said it was a "misnomer" that FDA told Sarepta to do a placebo-controlled trial and that the company refused. "You have to do what FDA asks, it's their choice," he said. "They gave us guidance at the end of the day to please do an open-label study."

Internal review documents show that while FDA repeatedly encouraged Sarepta to conduct a placebo-controlled trial, the agency ultimately agreed to other study designs, such as a historically controlled trial, in light of concerns expressed by the company and patient community that a placebo-controlled trial would not be feasible. (Also see "[Exondys 51's Development: Was Placebo-Controlled Trial Possible?](#)" - Pink Sheet, 16 Nov, 2016.)

"Now the reason that was such a controversial decision was you can't on the one hand say we'll consider accelerated approval and your drug could be on the market next year, and we want you to do a placebo-controlled study," Garabedian said.

"No one was debating the fact that no one is going to stay in a placebo-controlled study when you've got a terminal, progressive, irreversible condition and you don't even know if your drug is working. You're going to drop out and then you have no data," Garabedian said. "So even FDA wasn't contesting that."

"The issue is you need to resolve are you going to consider this for accelerated approval or not, and if you're not should you shift to a placebo-controlled study?"

No Lowering Of The Bar

Garabedian also rejected any suggestion that the eteplirsen approval would lower the bar for other drugs. "I think from a program standpoint we raised the bar," Garabedian said, describing the eteplirsen clinical program as the most rigorous ever conducted for a Duchenne drug.

His comments seemingly stand in stark contrast with the views of agency staff, including Woodcock and Califf. In internal memos and public statements, FDA officials have described the eteplirsen development program as seriously flawed and one that should not serve as a model for other drugs. (Also see "[No More Sarepta-Like Development, FDA Officials Say](#)" - Pink Sheet, 20 Oct, 2016.)

With its accelerated approval of eteplirsen, FDA "did differentiate, they didn't lower the standards," Garabedian said.

He pointed to the agency's decision on two other Duchenne drugs that predated the eteplirsen approval: a complete response letter for [BioMarin Pharmaceutical Inc.](#)'s *Kyndrisa* (drisapersen) and a refuse-to-file decision for [PTC Therapeutics Inc.](#)'s *Translarna* (ataluren).

"They said no to another drug with a similar mechanism because the data wasn't there," Garabedian said. "They said refuse to file to another drug that was dystrophin producing. I don't think if you talk to those companies they would say they lowered their standard." ([Return to Top](#))



FDA Warnings Slow, But Anti-Aging Claims Remain Class Action Targets

- 28 Dec 2016
- **Analysis**

[Ryan Nelson ryan.nelson@informa.com](mailto:ryan.nelson@informa.com)

Executive Summary

The online universe is abuzz with complaints about 2016, with some ready to dub the year "worst ever." It certainly was a rough one for anti-aging skin-care marketers, and while FDA's warning letter activity has declined of late, consumer lawsuits continue to file challenging companies' clock-reversing promises.

FDA warning letters to skin-care players may be scarcer in the new year, compared with 2016, but firms continue to be at risk of consumers taking claims enforcement into their own hands with false-advertising class actions.

Based on information available on its website, FDA has not issued a warning letter for unapproved drug claims on an anti-aging product since October 18, making the past two months the longest warning letter-free stretch for cosmetics since they began issuing regularly in March, totaling close to 30 for 2016 overall.

FDA officials noted in exchanges with lawmakers this year that the unprecedented number of

warning letters reflected an agency initiative launched in late 2015 to rein in cosmetic claims. (Also see "[FDA Divulges Cosmetics Enforcement Data, Notes Hair Loss As 'Serious' AE](#)" - Rose Sheet, 3 Nov, 2016.)

The agency and its district offices may be focusing resources elsewhere in 2017. Marketers of e-cigarettes, for example, increasingly are being hit with warning letters under an FDA final rule that went into effect in August, extending the agency's regulatory authority to cover all electronic nicotine delivery systems.

Super-premium Adore CELLMAX products do not contain an exclusive active ingredient, but rather feature Mibelle Biochemistry's PhytoCellTec apple stem cells preparation, which has not been shown in clinical testing to provide anti-aging benefits by protecting human skin stem cells, plaintiffs assert.

Consumer class actions for alleged false advertising and other violations are known to piggyback on FDA warning letters, so it's possible that suits against anti-aging cosmetic brands will drop off if the agency's attention shifts to other regulated product categories.

However, recently filed complaints in federal courts signal that plaintiffs do not necessarily need cues from FDA to challenge cosmetic product claims perceived as excessive, unsubstantiated and potentially misleading.

Sunday Riley Modern Skincare, LLC has been targeted with one such suit in New York's Southern District, which seeks class action certification and a jury trial.

Filed Dec. 2 by plaintiffs Helena Armstrong and Lynn Moore, residents of New York and California, respectively, the complaint alleges that, "like a modern-day snake oil salesman," *Sunday Riley* "preys on consumers' fundamental fear of aging" by deceptively marketing its Bionic Anti-Aging Cream as capable of impacting skin's physical structure and function.

For example, the company has claimed via labeling, its website and other promotional materials that the product contains ingredients that "activate your body's ability to extend the lifespan of our cells (true anti-aging!) and repair and restore collagen."

According to the firm, use of the Bionic cream helps to "regenerate skin while you are sleeping" and combat skin aging that results from pollution exposure, the complaint notes.

Such statements are similar to many highlighted in FDA warning letters in 2016, though Sunday Riley was not a recipient itself.

Plaintiffs in the case say the company lacks scientific support for its claims, which induce hoodwinked consumers to purchase the cream at an "exorbitant" price, believing they are buying a product that performs at drug strength.

The 1.7-oz. Bionic product, previously sold through Sephora.com and other online retail platforms for \$125, appears to be largely unavailable now.

In their complaint, the plaintiffs demonstrate a firm grasp on the types of claims that FDA deems excessive for cosmetic products and note important distinctions that differentiate Sunday Riley's claims on other offerings from those targeted in the suit.

They point out that the defendant promotes other products in its portfolio as delivering "results [that] are purely cosmetic by using phrases such as 'the appearance of wrinkles,' 'the visible signs of aging' and 'healthy-looking complexion.'"

The emphasis on aesthetic qualities, rather than structure/function effects, aligns such claims with the cosmetic definition enshrined in the Federal Food, Drug and Cosmetic Act, they suggest.

Sunday Riley's marketing for the Bionic cream, on the other hand, renders its product an unapproved drug, according to the complaint.

The New York Southern District Court may be reluctant to tackle the question of whether the defendant's product is lawfully marketed under FDA regs, which the company could assert is the agency's primary jurisdiction.

However, such arguments are not foolproof in the current legal climate and in some cases succeed only in delaying litigation while FDA is given the opportunity to weigh in, an exercise that rarely yields a response of pivotal substance. (Also see "[Supreme Court Turns Down Athena v. Allergan: 'Torrent' Of Suits To Come?](#)" - Rose Sheet, 30 Jun, 2015.)

Plaintiffs seek an injunctive order, compensatory and other damages, and attorneys' fees and costs.

PhytoCellTec-Based Line Challenged

In another proposed class action filed Sept. 29 in the US District Court for the Central District of California, plaintiff Lisa Mollicone alleges that **Universal Handicraft, Inc.** is in violation of false advertising and consumer protection laws due to misleading claims on its *Adore* CELLMAX line.

The claims in question mainly relate to the company's "proven Plant Stem Cell formula" and the anti-aging effects that it says are achievable from product use.

CELLMAX offerings sell at super-premium price points – around \$750 for an Elite Facial Serum and \$850 for a Superior Supplement Facial Thermal Mask – with bold assertions about "halting" the aging process.

But plaintiffs contend that such products cannot possibly perform as advertised and in reality are "simple and low-cost" formulas that feature not an exclusive, "breakthrough" active compound as touted, but rather the widely used *PhytoCellTec* Malus Domestica from **Mibelle Biochemistry**.

Johnson & Johnson successfully blocked class certification in 2013 in a suit challenging its *Neutrogena* Rapid Wrinkle Repair claims, which the plaintiff alleged conveyed a message "that

the products can effectuate an impossible result.”

Mibelle says its patented liposomal preparation of apple stem cells “has been shown to protect skin stem cells while also delaying the senescence of hair follicles.” Launched in 2008, the active made waves in the cosmetics sector as the first ingredient to emerge based on plant stem cells, according to the Swiss firm. (Also see "[Mibelle Looks To Maintain Momentum In Plant Stem Cells](#)" - Rose Sheet, 30 Apr, 2012.)

However, from plaintiff Mollicone’s perspective, “all credible evidence shows that Defendants’ claims about plant stem cells in the Adore products and their ability to interact with human skin stem cells to provide anti-aging benefits are false and deceptive.”

She points to statements from scientific experts, as well as reported admissions from Mibelle’s Research Director Daniel Schmid, which cast doubt on the capacity of plant stem-cell treatments to benefit human skin. At the least, certain promising in vitro test results need to be confirmed by clinical trials, experts suggest.

Further, she holds that the processing and production methods used to turn out Adore CELLMAX products void any benefits that potentially could be derived from living plant stem cells.

“The totality of evidence shows that the plant stem cells in cosmeceutical products are not effective at providing anti-aging benefits and thus the Adore products are likely to mislead reasonable consumers,” the plaintiff says.

Universal Handicraft/Adore Cosmetics has eluded FDA’s notice, but Mollicone notes that warning letters from the agency have taken other companies to task for claims about the PhytoCellTec ingredient’s potential impact on skin. (Also see "[FDA Warning Cites Ageless Derma’s Anti-Wrinkle, Brightening Claims](#)" - Rose Sheet, 9 May, 2016.)

She suggests that in addition to being fraudulently advertised, the Adore products are misbranded and therefore in violation of state food and drug statutes, including California’s Sherman Law.

The plaintiff seeks restitution, damages and injunctive relief on behalf of herself and similarly situated consumers nationwide, with five classes proposed in total.

Plaintiffs Face Significant Hurdles

Skin-care brands may take some comfort from trends suggesting that suits disputing anti-aging claims – compared with other popular targets for the plaintiffs’ bar, such as “natural” claims on cosmetic products – seem to be even more challenging to litigate, particularly when it comes to winning class certification.

Certification often hinges on plaintiffs demonstrating commonality and typicality across all members of a proposed class in terms of the way they interpreted marketing claims at issue and their product experiences in light of expectations established by such claims.

In instances where courts determine that plaintiff claims must be evaluated on an individual basis to assess the particulars of each purchaser's case, certification is routinely denied.

For example, [Johnson & Johnson](#) successfully blocked class certification in 2013 in a suit challenging its *Neutrogena* Rapid Wrinkle Repair claims, which the plaintiff alleged conveyed a message "that the products can effectuate an impossible result." (Also see "[J&J Skin Care Continues Apace With 'Rapid' Products, '1 Week' Claims](#)" - Rose Sheet, 22 Jul, 2016.)

In its order denying class certification, California's Central District Court specifically noted that "in this case, there are significant individualized questions as to whether the product worked as advertised for each individual class member."

Plaintiffs contesting **Avon Products, Inc.**'s wrinkle-reversing and collagen-rebuilding claims for *Anew* anti-aging skin-care products were denied class certification in September 2015, with New York's Southern District Court ruling that they had not met certification thresholds for predominance and ascertainability. (Also see "[Avon Beats Class Bid In Suit Challenging Anti-Aging Claims; Appeal Filed](#)" - Rose Sheet, 20 Oct, 2015.)

Reportedly, the plaintiffs are seeking a reversal of the decision from the US Court of Appeals for the Second Circuit.

The Estee Lauder Companies, Inc. defeated a suit alleging that its namesake brand's *Advanced Night Repair* products were promoted deceptively not by squashing the plaintiff's class certification bid, but by arguing that she missed her legal window for notifying Lauder about the problem.

New York's Eastern District Court dismissed her breach of warranty claims, agreeing that the 30 months that elapsed between the plaintiff's purchase of *Advanced Night Repair* items and her complaint to the company constituted an "unreasonable" lag under state law. The decision led to the case's dismissal in September 2015.

[\(Return to Top\)](#)



FDA Tweaks Guidance on Clinical Pharmacology Data for Demonstrating Biosimilarity

The FDA has made modest changes to its guidance on clinical pharmacology testing for biosimilars.

The guidance — released on Wednesday — finalizes a draft version published in May 2014 that detailed the pharmacokinetic (PK) and pharmacodynamic (PD) data needed to show biosimilarity.

The final guidance expands on the previous version by providing additional details on: the assessment of PD biomarkers; the integrity of bioanalytical methods in PK and PD studies; the development of PK and PD data; and the populations for PK and PD studies.

When determining which PD biomarkers to use to measure the response of a biosimilar, the FDA advised sponsors to consider the time it takes to return to baseline with the discontinuation of dosing. They should also consider the PD biomarker's analytical validity.

The agency clarified that sponsors should take into account the relevance of the biomarker to the mechanism of action of the reference drug only to the extent that the mechanism of action is understood. The rest of the considerations for biomarkers remain unchanged from the draft guidance.

As sponsors develop biosimilars, the FDA continues to recommend that they engage in a stepwise assessment of biosimilarity to evaluate the pharmacodynamic studies used for demonstrating a high level of similarity to the reference drug, but the agency's four assessment categories have been renamed.

Without changing the criteria for each assessment category, the FDA is now suggesting that biosimilarity be assessed on a four-point sliding scale that starts with "insufficient analytical similarity," moving up to "analytical similarity with residual uncertainty;" "tentative analytical similarity;" and "fingerprint-like analytical similarity." Sponsors should no longer use the previous categories, which included: not similar, similar, highly similar and highly similar with fingerprint-like similarity ([DID, May 14, 2014](#)).

On the integrity of bioanalytical methods used for PK and PD studies, sponsors are given clarifications on the agency's preferred assays, with the FDA recommending that they use an assay that produces concentration data correlated to the reference drug's pharmacological activity. This assay should be validated for use in the reference product and biosimilar to measure their concentrations. All analytical assays should meet performance parameters consistent with industry best practices.

Additionally, the final guidance reminds sponsors that PK and PD studies should be conducted using the materials from the manufacturing process they expect to use when marketing the biosimilar. Data using alternative materials may need an adequate justification, such as an analytical bridge.

As far as selecting the appropriate study population for the PK and PD studies, the FDA is now advising sponsors to rely on a population outside the reference drug's typical patient population if that group is better suited to detect differences between the biosimilar and reference drug.

Read the final guidance here: www.fdanews.com/12-28-16-BiosimilarityGuidance.pdf. — José Vasquez ([Return to Top](#))

FDA Clarifies Botanical Drug Considerations for Combination Drugs

The FDA updated its guidance for botanical drug development to include recommendations for navigating combination drug regulations, with possible criteria for receiving a waiver.

While current fixed-dose drug combination regulations require demonstrating the contribution of each active ingredient to overall safety and efficacy, the FDA said it recognizes that meeting that requirement with each raw botanical ingredient may not be feasible.

Whether that regulation applies to a specific botanical drug product depends on the type of mixture: for example, a product derived from a single plant source would not be considered a combination, because the entire botanical mixture is considered to be the active ingredient.

The guidance refers to a separate rule proposed in December of last year. The FDA suggested waiving the requirements in certain situations: for example, botanical drug products composed of multiple raw materials in fixed ratios — such as multiple parts of the same plant, or combinations of different plant species — could be considered for a waiver, as long as there is previous human experience for clinical use of the combination.

Since that rule has yet to be finalized, the FDA recommends that sponsors discuss approaches for each drug candidate with reviewers early. The agency also suggested holding pre-NDA meetings at least two months ahead of submissions, to allow time to respond to feedback.

This week's final guidance is largely unchanged from a 2015 draft, which suggested using multiple batches of the botanical drug in late-phase studies to examine any changes in chemical composition or treatment effect, due to natural variations in raw materials or changes in agricultural methods. The FDA also said that bridging studies may be needed to explore any uncertainty regarding different batches ([DID, Aug. 17, 2015](#)).

The final guidance is available here: www.fdanews.com/12-28-16-FDABotanicalDrugGuidance.pdf.
— Conor Hale ([Return to Top](#))

FDA Hands Aplicare Warning Letter Over Sterility Controls, Off-Label Promotion

Aplicare landed an FDA warning letter after an inspection uncovered four significant GMP violations involving sterility controls and marketing claims for unapproved uses.

FDA investigators found Aplicare neglected to implement adequate microbial controls for its povidone-iodine drugs and failed to validate its sterilization process, which resulted in the contamination of the company's povidone-iodine solution, ointment and gel.

Aplicare also failed to use air filtration systems in its manufacturing areas to maintain the appropriate air quality and cleanliness for drug production, the FDA said, calling the conditions "inadequate" to ensure sterility and protect drugs from contamination.

The company's failure to designate areas for the production of povidone-iodine further exposed its drugs to the risk of contamination. Furthermore, the firm's lack of written procedures for stability tests raised concerns about its povidone-iodine drug products meeting sterility specifications, the agency said.

On the company's website, the FDA discovered that the company markets four of its povidone-iodine products as antimicrobials, although the products did not contain antifungal active ingredients to support such claims.

In response to these observations, Aplicare said it would revalidate its sterilization process for povidone-iodine products, but the FDA deemed that measure inadequate given that the company previously attempted to take this corrective action and failed to provide scientific justification that its process is capable of robustly rendering products sterile.

The FDA asked the company to describe any improvements to its manufacturing operation that will establish a high level of sterility assurance. Additionally, the FDA urged the company to hire a GMP consultant to assist with meeting compliance standards.

Read the warning letter here: www.fdanews.com/12-27-16-AppicarePharma.pdf. — Derek Major ([Return to Top](#))

Sanofi Sues Novo Nordisk Over Misleading Claims of Lantus, Toujeo Coverage

Sanofi alleges Novo Nordisk engaged in a national advertising campaign that falsely claimed access to Sanofi's diabetes therapies Lantus and Toujeo would be restricted next year.

In a five-count complaint, Sanofi accuses Novo Nordisk of running an advertisement intended to switch patients from Lantus and Toujeo to Novo's long-acting insulin Tresiba by misrepresenting the continued availability of the drugs following their removal from CVS's formulary.

The advertisement in dispute states that, effective Jan. 1, 2017, "Lantus and Toujeo will be blocked." Sanofi c

From: [Health News Daily](#)
To: [Califf, Robert](#)
Subject: Health News Daily | Today's News & Analysis
Date: Tuesday, January 19, 2016 4:42:47 AM



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Prescription Pharmaceutical News from "The Pink Sheet" DAILY

BioMarin's Drisapersen 'Compete Response' Shows FDA Flexibility Still Limited FDA wants another clinical trial for Duchenne muscular dystrophy treatment; focus moves to Sarepta's candidate, which gets committee review next week.



Consumer Health and Personal Care News from "The Tan Sheet" and "The Rose Sheet"

P&G Asks For Higher Class Action Floor In Align Class Certification Appeal Procter & Gamble petitions the Supreme Court to overturn a decision giving class action certification to a complaint alleging the firm deceived consumers with its "snake oil" Align probiotic. If the court overturns the lower court, the action could make class action certifications more difficult.

Medical Device News from "The Gray Sheet"

CDRH Prioritizes Leveraging Real-World And Patient-Preference Data, Enhancing Quality In its 2016-2017 strategic priorities, the device center lays out specific goals for putting more emphasis on real-world postmarket data to support regulatory decisions, making better use of patient-preference input, and enhancing quality at CDRH and in industry. Topping FDA's list: gaining access to 25 million electronic patient records with device identification from global registries, insurance claims data and

electronic health records, and expanding that number to 100 million by the end of 2017 to support premarket and postmarket decisions.

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From: [Califf, Robert](#)
To: [Dunn, Billy](#); [Choy, Fannie \(Yuet\)](#); [Kelley, Laurie](#); [Paine, Rainer](#); [Mentari, Evelyn](#); [Yasuda, Sally](#); [Rogers, Hobart](#); [Bhattaram, Atul](#); [Grimstein, Christian](#); [Krudys, Kevin](#); [Sabarinath, Sreedharan](#); [Mehta, Mehul U](#); [Massie, Tristan](#); [Jin, Kun](#); [Hung, Hsien Ming J](#); [Fisher, J Edward](#); [Freed, Lois M](#); [Brown, Paul C](#); [Lynch, Patrick](#); [Cooper, Monica](#); [Chelliah, Mariappan](#); [Miller, Denise](#); [Gieser, Gerlie](#); [Kim, Erin](#); [Thakur, Aditi](#); [Woody, Dahlia](#); [Wilson, Wendy](#); [Heimann, Martha R](#); [Srinivasachar, Kasturi](#); [Alfaro, Cara](#); [Thompson, Susan \(CDER\)](#); [Ayalew, Kassa](#); [Pohlman, Janice](#); [Williams, LaKisha](#); [Patague, Yolanda](#); [Cuff, Althea](#); [Hadwiger, Michael](#); [Moukhtara, Aline](#); [Fienkeng, Mathilda](#); [Howard, Corwin](#); [Morris, Chad \(John\)](#); [White, Lolita](#); [Bridges, Todd](#); [Pratt, Robert](#); [Wilkins Parker, Jamie](#); [Peters, Tracy](#); [Rusinowitz, Martin](#); [Klein, Michael](#); [Walsh, Sandy](#); [Chew, Catherine](#); [Diggs, Felicia](#); [Locicero, Colleen L](#); [Unger, Ellis](#); [Temple, Robert](#); [Ware, Jacqueline H](#); [Hughes, Alice](#); [Kozauer, Nicholas](#); [Bastings, Eric](#); [CDER-OND-120-ALL](#)
Cc: [Jenkins, John K](#); [Stein, Peter](#); [Moscicki, Richard](#); [Woodcock, Janet](#)
Subject: RE: Approval of Spinraza (nusinersen) for spinal muscular atrophy
Date: Saturday, December 24, 2016 7:31:55 AM

Exciting news, and done the right way. Happy holidays.

rmc

Robert M Califf MD
Commissioner of Food and Drugs

From: Dunn, Billy
Sent: Friday, December 23, 2016 4:16 PM
To: Choy, Fannie (Yuet); Kelley, Laurie; Paine, Rainer; Mentari, Evelyn; Yasuda, Sally; Rogers, Hobart; Bhattaram, Atul; Grimstein, Christian; Krudys, Kevin; Sabarinath, Sreedharan; Mehta, Mehul U; Massie, Tristan; Jin, Kun; Hung, Hsien Ming J; Fisher, J Edward; Freed, Lois M; Brown, Paul C; Lynch, Patrick; Cooper, Monica; Chelliah, Mariappan; Miller, Denise; Gieser, Gerlie; Kim, Erin; Thakur, Aditi; Woody, Dahlia; Wilson, Wendy; Heimann, Martha R; Srinivasachar, Kasturi; Alfaro, Cara; Thompson, Susan (CDER); Ayalew, Kassa; Pohlman, Janice; Williams, LaKisha; Patague, Yolanda; Cuff, Althea; Hadwiger, Michael; Moukhtara, Aline; Fienkeng, Mathilda; Howard, Corwin; Morris, Chad (John); White, Lolita; Bridges, Todd; Pratt, Robert; Wilkins Parker, Jamie; Peters, Tracy; Rusinowitz, Martin; Klein, Michael; Walsh, Sandy; Chew, Catherine; Diggs, Felicia; Locicero, Colleen L; Unger, Ellis; Temple, Robert; Ware, Jacqueline H; Hughes, Alice; Kozauer, Nicholas; Bastings, Eric; CDER-OND-120-ALL
Cc: Jenkins, John K; Stein, Peter; Moscicki, Richard; Woodcock, Janet; Califf, Robert
Subject: Approval of Spinraza (nusinersen) for spinal muscular atrophy

Today, Spinraza (nusinersen) was approved for the treatment of spinal muscular atrophy (SMA). Many of you are aware of this, but for those that are not, this is the first treatment ever approved for this often fatal genetic disease. The infantile-onset form of this disease is the most common genetic cause of infant mortality. With the ever increasing focus on needed treatments for rare diseases, this is an example of a clear success in this area.

Nusinersen is an antisense oligonucleotide that is designed to promote production of functional survival motor neuron (SMN) protein, the protein that is necessary for motor neuron survival and is lacking in patients with SMA due to a deletion of the SMN1 gene that is normally responsible for the production of SMN protein. The similar SMN2 gene is naturally able to produce a small amount of SMN protein but it is insufficient for normal function. The variability of how much SMN protein SMN2 produces is tied to the heterogeneity of disease severity seen in SMA. Nusinersen binds to SMN2 pre-mRNA and promotes the production of full-length functional SMA protein by including the otherwise lacking exon 7 in the mRNA transcript (the key difference in SMN1 and SMN2 is this lack of exon 7). The specificity of this approach is indicative of the increasing sophistication that a detailed understanding of disease pathophysiology brings to drug development.

In brief, the results of a controlled study in infantile-onset SMA demonstrated highly significant ($p < 0.0001$) effects on motor milestone achievement (40% vs. none) supported by consistent sensitivity analyses. A motor abilities/function scale for infants with neuromuscular disease showed substantial numerical differences between groups for meaningful improvement and worsening (63% vs. 3% and 4% vs. 40%, respectively). Open-label data suggesting that some patients achieved milestones such as the ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected considering the number of SMN2 gene copies of patients enrolled in the studies, are supportive of these results.

There are many interesting aspects to this application and I invite you to peruse the various reviews, but I want to highlight three especially important things about this application.

First, we played a crucial role in leading the sponsor to an interpretable result as rapidly as possible. The sponsor had a meeting with us to present the results of an open-label cohort of SMA patients that were compared to natural history. Although the sponsor argued that this was sufficient evidence, the numbers were very small, and we noted that the sponsor had an ongoing controlled study (the study that ended up being the primary basis of this approval) that was designed to look at mortality in an interim analysis but that analysis would not occur for quite some time. We pointed out to the sponsor that an interim analysis based on function could be done much sooner if the sponsor's assertions about the effect of the drug were true and that we would see such an analysis as a crucial part of a marketing application. After some further discussion, the sponsor agreed with this approach and we began a period of intense review of the sponsor's plans for an interim analysis of function. We were involved in great detail in the design of this analysis and this work was done very quickly, allowing the sponsor to move forward rapidly with the analysis that ultimately showed the benefit of the drug. This represented a great deal of work for the folks involved, but it paid off in our familiarity with the analysis at the time of submission.

Next, many are aware of the speed with which we reviewed this application. This application was reviewed under the expedited review principles associated with a product that represents a breakthrough in its therapeutic area. Expedited review is essentially a super-priority review for breakthrough products that attempts to take action before a priority review deadline. Not only did we accomplish that, but we beat the priority review deadline in historic fashion, reviewing and acting on this application in only 90 days. Note also that this was for an NME. This is a truly remarkable feat. It is completely accurate, with no hyperbole involved, to recognize that to accomplish this review in this amount of time required an extraordinary and superhuman effort on the part of the review team. Great personal sacrifices were made by our team members. These sacrifices are not the norm, nor should they be, and we are now better prepared for the occurrence of any future expedited review that comes our way. I deeply appreciate the commitment our team members made to this review and I am humbled by their efforts.

Finally, very importantly, and directly related to the previous point, I want to highlight and thank the review team. Without the efforts I described above, we would not be taking this action today. That is a direct reflection of the commitment our team members made to this review. In no particular

order whatsoever, the nusinersen review team included Fannie Choy, Laurie Kelley, Rainer Paine, Evelyn Mentari, Sally Jo Yasuda, Bart Rogers, Atul Bhattaram, Christian Grimstein, Kevin Krudys, Sreedharan Sabarinath, Mehul Mehta, Tristan Massie, Kun Jin, Hsien Ming Hung, Ed Fisher, Lois Freed, Paul Brown, Patrick Lynch, Monica Cooper, Mariappan Chelliah, Denise Miller, Gerlie Gieser, Erin Kim, Aditi Thakur, Dahlia Woody, Wendy Wilson-Lee, Martha Heimann, Kasturi Srinivasachar, Cara Alfaro, Susan Thompson, Kassa Ayalew, Janice Pohlman, Lakisha Williams, Yolanda Patague, Althea Cuff, Michael Hadwiger, Aline Moukhtara, Mathilda Fienkeng, Corwin Howard, John Morris, Lolita White, Todd Bridges, Bob Pratt, Jamie Wilkins Parker, Tracy Peters, Marty Rusinowitz, Michael Klein, Sandy Walsh, Cat Chew, Felicia Diggs, Colleen Locicero, Ellis Unger, Bob Temple, Jackie Ware, Alice Hughes, Nick Kozauer, and Eric Bastings. Please forgive me if I have inadvertently left anyone off this list.

I leave you with a link to a story about the first infantile-onset patient to receive nusinersen. Upon diagnosis, her parents were told by her neurologist to expect her death by the time she was 2 years old. She began treatment with nusinersen in 2013 at age 7 months. She is now 4 years old.

<https://med.stanford.edu/news/all-news/2016/12/stanford-patient-is-first-infant-to-receive-lifesaving-drug.html>

Again, my thanks to the nusinersen review team, and, indeed, to all the wonderful employees of DNP and FDA committed to the development of safe and effective treatments for the incredible range of neurological diseases, so very many of which continue to await the arrival of their first approved therapy. Without you, the effort would be doomed. With you, continued progress will be made, one drug at a time.

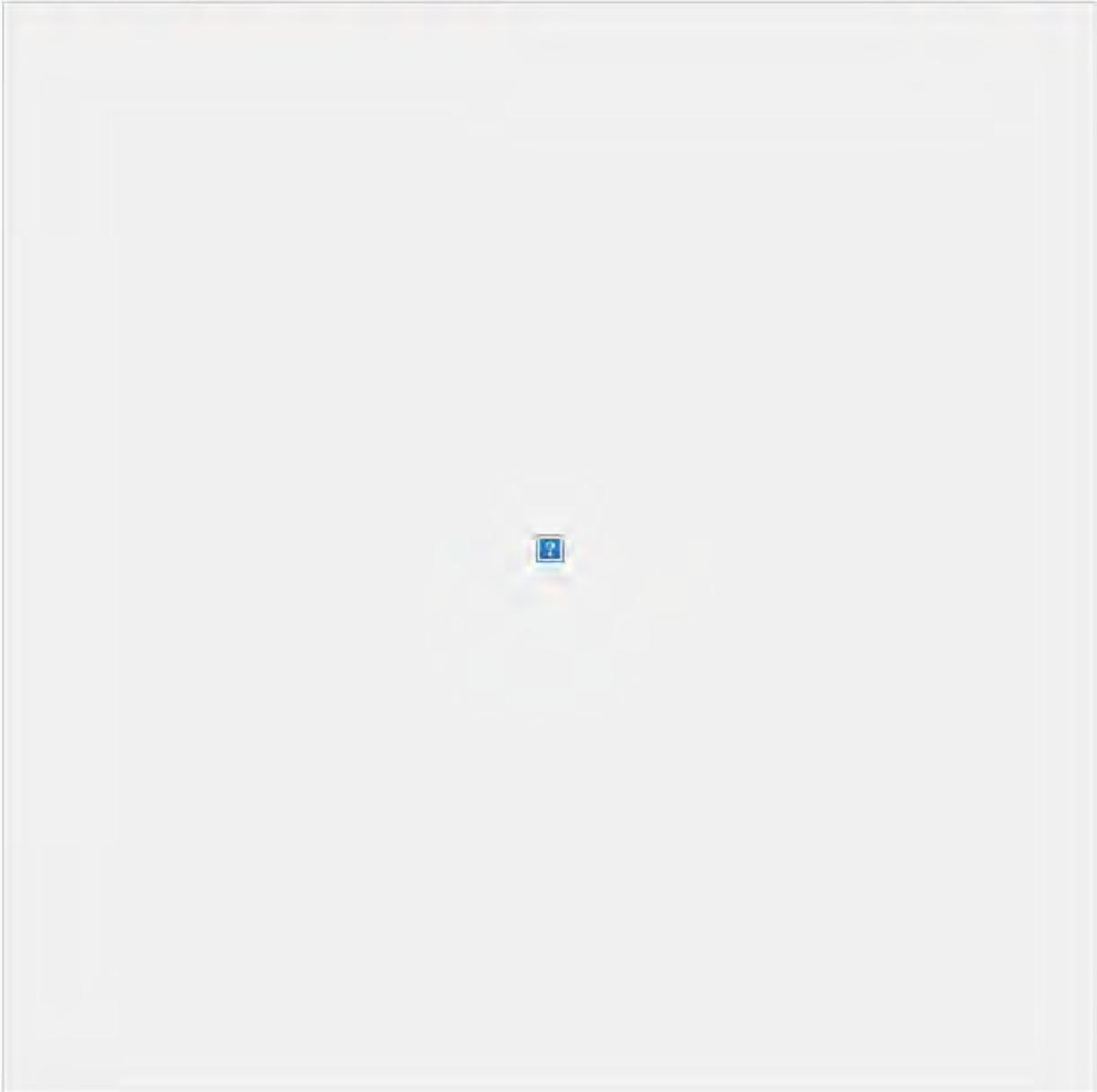
I wish each of you a joyous holiday season.

Billy

From: [NORD](#)
To: [Califf, Robert](#)
Subject: NORD eNews August 2015
Date: Wednesday, August 26, 2015 3:55:52 PM

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[Register by August 28th for Early Bird Savings for NORD Summit](#)



More than 500 people from around the world are expected to attend and will learn from some of the most powerful and inspiring voices in rare diseases. Our annual Rare Diseases and Orphan Products Breakthrough Summit (Oct. 21-22) is the largest multi-stakeholder event of its kind. Register by this Friday to receive Early Bird rates. [More](#).

Sean Hepburn Ferrer Raises Awareness in New PSA



Actress Audrey Hepburn died of a rare form of cancer and her son, Sean Hepburn Ferrer, works with NORD, EURORDIS and the organizations specific to her disease – pseudomyxoma peritonei – to promote rare disease awareness. A new PSA that Sean created with NORD has just been released, marking the 200-day countdown to Rare Disease Day 2016. [View the PSA](#).

NORD Advocates for Rare Disease Research in NIH Strategic Plan

In comments submitted to the National Institutes of Health (NIH) for the NIH strategic plan, NORD talks about the importance of programs for rare diseases, including those for undiagnosed patients. [Read letter](#) from NORD President and CEO Peter L. Saltonstall.

Read other recent [policy statements and letters](#) from NORD.

Rare Action Road Tour: Addressing Issues at the State Level

Associate Director of State Policy, Tim Boyd, spent part of the summer driving across the country to meet with NORD's State Ambassadors and discuss issues we will be addressing at the state level through our Rare Action Network™. [Read Tim's blog posts](#) and meet some of the State Ambassadors. ([Learn more about NORD's Rare Action Network™](#).)



New NORD Educational Resources and Collaborations

NORD to be "Voice of the Community" in Rare Disease Report

Through a new editorial collaboration with Rare Disease Communications, NORD will provide a "Voice of the Community" column for each issue of *Rare Disease Report* and corresponding pages on the [Rare Disease Report website](#). NORD will provide expertise and resources, including news from its 230+ member organizations and other rare disease partners. [More](#).

New Video Promotes Awareness of Rare Movement Disorder



NORD's new video released this week provides information about a rare medical condition known as [neurogenic orthostatic hypotension \(nOH\)](#). The video features patient testimonials, medical experts and NORD resources, including a Patient Assistance Program. [More](#).

Giving Spotlight: Paula Mann Donates to NORD

"I believe in your mission and am honored to make this donation on behalf of our son," says Paula Mann about her donation to NORD in honor of her son, Garrett. Paula was recently awarded the Mike Lellyo Award by her employer, Novartis Oncology, which includes choosing a charitable organization where Novartis makes a donation. [Read Paula and her family's story.](#)

Garrett Mann



Policy News

NORD Files Amicus Brief to Protect Drug Development Incentives in the Orphan Drug Act

NORD has filed an amicus brief in the D.C. Circuit of the U.S. Court of Appeals, stating that a recent Food and Drug Administration (FDA) decision has the potential to impede the development of new treatments to help patients with rare diseases. [More](#).

FDA News

New FDA Guidance: Common Issues in Orphan Drug Development

The FDA has released a draft guidance intended to help drug-makers tackle common issues encountered in the development of drugs to treat rare diseases. [More](#).

In related news, the FDA launched a new guidance document [search tool](#) that makes it easier to

find specific documents that explain the agency's thinking on a particular subject.

Patient-Focused Drug Development Meeting: Nontuberculous Mycobacterial (NTM) Lung Infections

This public meeting on October 15 will focus on obtaining patients' perspectives on the impact of NTM lung infections on daily life and patient views on treatment approaches. [More](#).

Registration for Patient and Consumer Groups to Attend Medical Device Meeting

Beginning this fall, FDA will host meetings with representatives of patient and consumer groups to discuss the reauthorization of the Medical Device User Fee Amendments (MDUFA). Registration is now open for a meeting to take place on Sept. 15. [More](#).

Recent Drug Approvals

Kyprolis (carfilzomib) has been approved to treat patients with multiple myeloma who have received at least two prior therapies, including treatment with Velcade (bortezomib) and an immunomodulatory therapy. Kyprolis is marketed by Onyx Pharmaceuticals. [Read the press release](#).

Recent Orphan Drug Designations

- Immunomedics for veltuzumab, a humanized anti-CD20 antibody, for treatment immune thrombocytopenia
- Insys Therapeutics, Inc. for its pharmaceutical cannabidiol for treatment of infantile spasms
- NanoSmart Pharmaceuticals, Inc. for a formulation of dactinomycin to treat Ewing's sarcoma
- ZIOPHARM Oncology, Inc. for Ad-RTS-hIL-12 + veledimex to treat malignant glioma
- Pfizer Inc. for its autoimmune candidate drug GL-2045 to treat chronic inflammatory demyelinating polyneuropathy
- Veloxis Pharmaceuticals for Envarsus XR for prophylaxis of organ rejection in patients who convert from immediate-release tacrolimus
- Hybrigenics for inecalcitol for the treatment of acute myeloid leukemia
- ASLAN Pharmaceuticals for varlitinib to treat cholangiocarcinoma
- Seres Therapeutics for SER-109 to treat recurrent *C. difficile* infection
- Boehringer Ingelheim for afatinib (Gilotrif) to treat squamous cell lung carcinoma in patients whose disease has progressed after chemotherapy

Recent Rare Pediatric Disease Designations

- BioMarin Pharmaceutical Inc. for drisapersen to treat Duchenne muscular dystrophy patients who are amenable to exon 51 skipping treatment
- Santhera Pharmaceuticals for idebenone for the treatment of Duchenne muscular dystrophy

Recent Breakthrough Therapy Designations

- Progenics Pharmaceuticals for Azedra, a treatment for pheochromocytoma and paraganglioma
- Exelixis for cabozantinib (Cometriq) for treatment of patients with advanced renal cell carcinoma following one prior therapy

Recent Fast Track Designations

- Omeros Corporation for OMS721 for the treatment of atypical hemolytic uremic syndrome
- GW Pharmaceuticals plc for an intravenous form of cannabidiol to treat neonatal hypoxic-

ischemic encephalopathy

- Corbus Pharmaceuticals Holdings, Inc. for Resunab to treat systemic sclerosis (scleroderma)

NIH News

NIH Proposes Web-Based Resource for Youth About Clinical Research

NIH has proposed a web-based resource to help young people make informed decisions about clinical research and to increase motivation to participate in pediatric clinical trials. Read the [Federal Register notice](#).

NORD Welcomes New Member Organizations

NORD is happy to welcome the following new Member Organizations. Learn more about the benefits of NORD membership [here](#).

- [A Cure In Sight](#): Raising awareness of ocular melanoma and helping to find and pay for treatment
- [Child Growth Foundation](#): A leading UK charity focused on children's growth and endocrine issues
- [ISMRD](#): An international advocacy organization for those affected by glycoprotein storage diseases
- [SBS Cure Project](#): Seeking a cure for short bowel syndrome
- [The Oley Foundation](#): Enriching the lives of those requiring home IV and tube feeding

News from NORD Member Organizations

Alport Syndrome Foundation (ASF)

The Paul Silver Tribute Award for Alport syndrome kidney patients (ages 16 to 22 years old) is aimed at enriching the lives of young patients by helping support education, complete a project, or pursue an activity that will enhance the applicant's life. Awards will be granted for a maximum of \$1,000 and applications are due November 2. [More](#).

Cornelia de Lange Syndrome (CdLS) Foundation, Inc.

The CdLS Foundation has announced its 2015 Small Research Grants program recipients. Funding is being awarded to researchers at Kennedy Krieger/Johns Hopkins Institute, Children's Hospital of Philadelphia, and the University of Utah. [More](#).

cureCADASIL Association

The Association has announced a new global registry -- the cureCADASIL Family Registry -- to facilitate the sharing of information among families and with researchers to gain a better understanding of this rare disease and to accelerate research. [More](#).

Cystinosis Research Network

The Cystinosis Research Network hosted an innovative art exhibit -- titled "Dream, Achieve, Inspire" -- at its recent annual conference in Chicago. The exhibit featured the work of cystinosis patients, and art pieces now will be exhibited at cystinosis gatherings around the world.

Cystinosis Research Network



Cystinosis Research Network at the annual conference in Chicago

Morgan Learn Vaughn Fund

A podcast series, "Speaking of NEC", has been developed by the MLV Fund to highlight current prevention, diagnosis and treatment strategies for necrotizing enterocolitis (NEC), and the search for a cure. The series features one-on-one conversations with NEC medical experts. [More.](#)

National Adrenal Diseases Foundation (NADF)

The NADF has joined the Autoimmune Research Network (ARNet) in order to boost autoimmunity research. The first goal of ARNet is to reduce the time it takes to diagnose Addison's disease. Researchers will be able to use ARNet to find out how many people are qualified to participate in their medical research projects. A survey is posted that should take about 15 minutes to complete. [More.](#)

Vestibular Disorders Association (VEDA)

The Louisiana State University Health Sciences Center, in cooperation with VEDA, is conducting a survey to assess physician knowledge of, and experience with, diagnosing vestibular disorders. [More.](#)

NORD Welcomes New Corporate Council Members

NORD is delighted to welcome the following new members to our Corporate Council. Learn about the Corporate Council and the benefits of membership [here](#).

- [Achillion Pharmaceuticals](#): Achillion is advancing a platform of complement factor D inhibitors for the treatment of complement-related diseases.
- [Invitae](#): Invitae is a genetic information company whose mission is to bring genetic information into mainstream medical practice, specializing in genetic diagnostics for hereditary disorders.
- [Mallinckrodt Pharmaceuticals](#): Mallinckrodt Pharmaceuticals is a global specialty biopharmaceutical company.

Provider Resources

AAN and AANEM Guideline on Facioscapulohumeral Muscular Dystrophy (FSHD)

The American Academy of Neurology (AAN) and the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) have published a guideline on the evaluation, diagnosis, and

management of FSHD. This condition can be confused with other neuromuscular disorders (such as other muscular dystrophies or polymyositis), leading to an inaccurate diagnosis and, sometimes, to unnecessary treatment. [Read the full guideline.](#)

ACMG Releases New Scope of Practice Document for the Specialty of Medical Genetics

In an effort to clearly define the changing role of the specialty of medical genetics and the distinction between medical geneticists and other genetics healthcare professionals, the American College of Medical Genetics and Genomics (ACMG) has released a new "Scope of Practice of the Specialty of Medical Genetics" document. [More.](#)

Treatment

Basket Study Documents Preliminary Efficacy of Vemurafenib in Nonmelanoma Cancers

A basket study is a new clinical trial design that explores responses to drugs based on specific mutations in patients' tumors rather than where their cancer originated. Vemurafenib is known to be an effective treatment for BRAFV600-mutated melanoma. This new study found that this medication may also be effective in treating non-small cell lung cancer as well as Erdheim-Chester disease and Langerhans cell histiocytosis. Basket studies may greatly increase the number of patients eligible to receive certain drugs. [More.](#)

Medical Foods May Cause Harm if Not Properly Managed

Researchers have reported that patients with methylmalonic acidemia (MMA) on restricted protein diets and taking medical foods had four or five times the recommended amounts of leucine, which could have a negative effect on growth and development. In a study of patients with cobalamin C type combined MMA and hyper-homocysteinemia, failure to properly process vitamin B12 results in a different form of MMA that clinically looks different and requires different management. [More.](#)

Pediatric Pain Management

The FDA recently approved the use of OxyContin in children ages 11 to 16 with severe pain, but care of pediatric patients treated with this medication should be properly coordinated by a health care team experienced in opioid treatment. [More.](#)

International News

Japan Launches Initiative on Rare and Undiagnosed Diseases (IRUD)

The Japan Agency for Medical Research and Development has launched IRUD so patients with undiagnosed conditions can be referred to a centralized network of specialists for genome analysis. [More.](#)

Upcoming Meetings and Webcasts

Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC)

The ACHDNC meeting will take place on August 27-28 in Rockville, MD. [More.](#)

Development of Standards for NGS Testing - Clinical Validity and Utility

The American Society of Human Genetics is conducting this webinar on September 1 from 1:00-2:30 pm EDT to discuss scientific and clinical issues relevant to development of community-wide standards for next-generation sequencing (NGS) genetic tests. [More](#).

Miscellaneous

Patient Advocacy Leadership (PAL) Awards

Genzyme has announced the fifth annual PAL Awards program for non-profit organizations that serve the lysosomal storage disorder patient community. Proposals can now be submitted in any language. The focus of the PAL program this year is on collaboration and only projects that involve a collaboration of two or more organizations will be accepted. A total of \$50,000 will be awarded. Applications are due September 30. [More](#).

UNITY-GC Survey: Understanding Needs in Teens and Young Adults with Genetic Conditions

The purpose of the survey, designed by family leaders in the Western States Genetic Services Collaborative, is to learn about health needs of teens and young adults as they transition to adult health care services. [More](#).

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From: [Dickinson, Elizabeth \(FDA\)](#)
To: [Kraus, Tom](#); [Sherman, Rachel](#); [Conover, Katie](#); [Califf, Robert](#)
Cc: [Chasan-Sloan, Deborah \(FDA\)](#)
Subject: Pink Sheet
Date: Friday, September 16, 2016 8:19:38 AM

FDA Neurology Clinical Team Leader Departure May Be Mountain Disguised As Molehill

Executive Summary

Attention to the departure of neurology reviewer Ron Farkas from FDA has focused on what it means for Sarepta's eteplirsen application, but there are larger regulatory environment issues that deserve more scrutiny.

Like most controversies today, it started with a tweet.

“Seems like Ron Farkas is no longer at the [@US_FDA](#) cc [\\$SRPT](#)” Jenn McNary, one of the most active Duchenne Muscular Dystrophy patient advocates and a mother of a son with DMD, wrote on Sept. 13 using the stock ticker symbol for [Sarepta Therapeutics Inc.](#), the sponsor of eteplirsen.

The reaction on social media was fast and furious: reporters and investors attempted to confirm with FDA and Parexel – the rumored new employer of Farkas – that the reviewer had indeed left the agency.

Farkas *was* Division of Neurology Products clinical team leader who conducted the review of Sarepta's DMD drug eteplirsen. His review was overwhelmingly negative and concluded that not only was there not substantial evidence of an effect from eteplirsen but there was no evidence at all. (Also see "[Sarepta, FDA And The Dangers Of Strong Early Results](#)" - Pink Sheet, 2 May, 2016.)

McNary's tweet in turn led to Wall Street speculation and stories confirming Farkas had left FDA and that it was a positive development – if not confirmation – that eteplirsen will get accelerated approval. The application has survived bumps at FDA but remains a possibility for an accelerated approval.

But reading the tea leaves of the Farkas departure solely as another piece in the up-or-down decision on the Sarepta drug misses a potentially broader significance to the event. There are other messages and reverberations that may last longer.

Personal Enmity Towards Reviewers

The first is the personalization of enmity toward an FDA reviewer. Farkas was

painted as enemy number one for what some believed was an obstructionist position on the eteplirsen application for a deadly disease in young boys. Farkas has been negative on other recent applications. He reviewed [BioMarin Pharmaceutical Inc.](#)'s DMD drug drisapersen that was rejected by FDA and probably had an important role in FDA's decision to refuse-to-file [PTC Therapeutics Inc.](#)'s application for ataluren.

Farkas also was negative on Merck's sleep drug suvorexant that led to a big write-up in the *New Yorker* titled "[The Big Sleep.](#)" But that's not always the case. He supported approval of Vanda's non-24 sleep drug tasimelteon for the blind that was approved by FDA.

Removing emotion from the case of eteplirsen, Farkas applied the FDA's long-established regulatory standards to the review and made it very clear that the application fell well short of the threshold for approval in his opinion as primary reviewer.

Tough standards come into conflict with applications for life-threatening conditions at FDA: it is part of the territory.

For many reasons, though, the eteplirsen application reached an almost unprecedented level of political and patient sensitivity. Therefore, Farkas' position as lead reviewer and regulatory determination were magnified. What reviewer will want to take on an application like eteplirsen in the future?

Not Farkas' Call To Make

Lost in the focus on Farkas is the fact that Division Director Billy Dunn and Deputy Director Eric Bastings both expressed the same position as Farkas regarding the eteplirsen application. Office of Drug Evaluation 1 Director Ellis Unger appeared to be of the same mind as well given some of his comments at the panel meeting, but it was less clear.

And if an unprecedented level of regulatory flexibility were to be applied to the filing in order to reach an approval decision, it will be done by several layers above Farkas – that was always going to be the case.

The final sign off decision will fall to Unger or could escalate – unlikely but possible in this unusual case – to CDER Director Janet Woodcock, who opened the door for an accelerated approval pathway for eteplirsen during her presentation at the eteplirsen panel review.

Put another way, it was not Farkas' call to make despite the perception that he was the implacable roadblock to the application.

Bolstering Review Morale

The second issue: this is what the start of a decline of a peak approval climate looks like. Anyone who watched the April 25 advisory committee review of eteplirsen or who has followed Sarepta can tell you this was a brutal review. And the pressure on the neurology division to approve an application for DMD – particularly eteplirsen – has not been lost on other reviewers in different divisions.

In other words, everybody is watching this application but FDA reviewers are watching the eteplirsen outcome too.

If a myth or storyline develops that Farkas left FDA because management overruled him due to external pressure, that would create a significant problem for FDA internally. Senior FDA officials have worked tirelessly and successfully to remove that distraction and create an almost peerless period of pro-innovation, approvals, cutting edge regulatory science and efficiency.

The risk is that others could follow Farkas out the door, or worse stay on at the agency demoralized and perhaps resentful and fretful of being overridden from management above.

Impossible? No. That is what happened in the nadir of the FDA drug approval process four decades ago – two decades before Woodcock even joined the agency. A general perception first within FDA and then generally in the public of too much bending in favor of applications and industry-bias by FDA managers led to a general collapse of morale and Congressional hearings.

Preventing A Toxic Review Climate

Sarepta has collected many Congressional supporters for its application. So a negative response from Capitol Hill to an eteplirsen approval is not likely. What is dangerous is a sense at the working review levels that management is pushing too hard for approvals. That story – true or false – can be toxic to the NDA review environment.

The Neurology Division's portfolio of diseases includes some of the most high-profile diseases for which there is major unmet need: Alzheimer's, Parkinson's disease, Huntington's disease, multiple sclerosis, epilepsy, migraine, muscular dystrophy, ALS, narcolepsy.

Now that division has lost a senior reviewer at a time when FDA is having great difficulty recruiting young neurologists to staff the division. CDER Director Janet

Woodcock has publicly lamented the fact that newly minted neurologists out of medical school can make as much as an FDA Center Director.

The truth is no one at this point know why Farkas left. His departure and the eteplirsen review may be completely unrelated or a direct cause and effect. But keep watching to see if something bigger may be brewing here.

From the editors of the RPM Report

From: [Chasan-Sloan, Deborah \(FDA\)](#)
To: [McCall, Jonathan *](#); [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#)
Cc: [Califf, Robert](#); [Kraus, Tom](#); [Conover, Katie](#); [Rodriguez, Jennifer](#); [Evans, Dana](#)
Subject: RE: Appeal documents
Date: Friday, September 09, 2016 3:52:18 PM
Attachments: [2016_Sept_09_Eteplirsen_CLEAN-COMMENTED\(occ\).doc](#)

I've added some comments and minor edits to the "clean-commented" version of the memo (attached). Nothing further from me on the cover letter (and Liz is on leave today, with sporadic email access).

From: McCall, Jonathan *
Sent: Friday, September 09, 2016 9:57 AM
To: Sherman, Rachel; Dickinson, Elizabeth (FDA)
Cc: Califf, Robert; Kraus, Tom; Chasan-Sloan, Deborah (FDA); Conover, Katie; Rodriguez, Jennifer; Evans, Dana
Subject: RE: Appeal documents

Hello all –

I am attaching tracked and clean versions of the memo and cover letter that incorporate all changes and comments received to date.

The "clean-commented" versions have all changes accepted; the only remaining comments are those that appear to still require a decision or resolution.

There are several places in the memo where some edits to the wording have been flagged for attention. These have comments attached and are also highlighted.

Please let me know if you have any questions!

Best,

Jonathan

From: Sherman, Rachel
Sent: Thursday, September 08, 2016 12:26 PM
To: Dickinson, Elizabeth (FDA); McCall, Jonathan *
Cc: Califf, Robert; Kraus, Tom; Chasan-Sloan, Deborah (FDA); Conover, Katie; Rodriguez, Jennifer; Evans, Dana
Subject: RE: Appeal documents

Hi all,

I think we are at risk for serious version control problems. Does the following sound right? All documents need an owner and all comments and revisions will be sent to the owner.

Jen will own all comms docs.

Jonathan will own Rob's memo and cover email.

Labeling and letters are owned by the division; I can be the primary point of contact to return all comments to the division (unless no one trusts me – this would be understandable – in which case I will ask Jonathan for help).

Alternatively, I can assign a project manager.

Thoughts?

Thanks!

Rachel

From: Dickinson, Elizabeth (FDA)
Sent: Thursday, September 08, 2016 11:23 AM
To: Sherman, Rachel; McCall, Jonathan *
Cc: Califf, Robert; Kraus, Tom; Chasan-Sloan, Deborah (FDA); Conover, Katie; Rodriguez, Jennifer; Evans, Dana
Subject: RE: Appeal documents

I believe the comms materials are still undergoing significant revisions, so I would hold off a bit on adding those to the packet.

From: Sherman, Rachel
Sent: Thursday, September 08, 2016 10:53 AM
To: McCall, Jonathan *
Cc: Califf, Robert; Dickinson, Elizabeth (FDA); Kraus, Tom; Chasan-Sloan, Deborah (FDA); Conover, Katie; Rodriguez, Jennifer; Evans, Dana
Subject: RE: Appeal documents

This looks right to me and you are correct – we have not yet received draft labeling or the letter.

Thanks!

From: McCall, Jonathan *
Sent: Thursday, September 08, 2016 10:09 AM
To: Sherman, Rachel
Cc: Califf, Robert; Dickinson, Elizabeth (FDA); Kraus, Tom; Chasan-Sloan, Deborah (FDA); Conover, Katie; Rodriguez, Jennifer; Evans, Dana
Subject: RE: Appeal documents

Hi Rachel –

Will do. Just in the interest of avoiding any potential version control issues, here's a quick inventory of what I have at present:

- The latest version of the response document, with Dr. Califf's edits, received 7:42 this

morning. I'll clean up this version today.

- The PR and KMQA documents, received from Jennifer Rodriguez on Monday (9/5) morning. I'm happy to look at these if someone wants me to, but so far have not done so.
- The Sunday (9/4) version of the cover letter from Dr. Califf.
- Haven't seen draft approval/labeling yet, to my knowledge.

Please let me know if I need to await a more up-to-date version of anything, but these are all the latest versions of the respective documents that I have in my files.

Thanks!

--

J

From: Sherman, Rachel

Sent: Thursday, September 08, 2016 9:39 AM

To: McCall, Jonathan *

Cc: Califf, Robert; Dickinson, Elizabeth (FDA); Kraus, Tom; Chasan-Sloan, Deborah (FDA); Conover, Katie; Rodriguez, Jennifer; Evans, Dana

Subject: Appeal documents

Hi Jonathan,

As we discussed yesterday, tomorrow could you send Rob (for the weekend) the most current versions of:

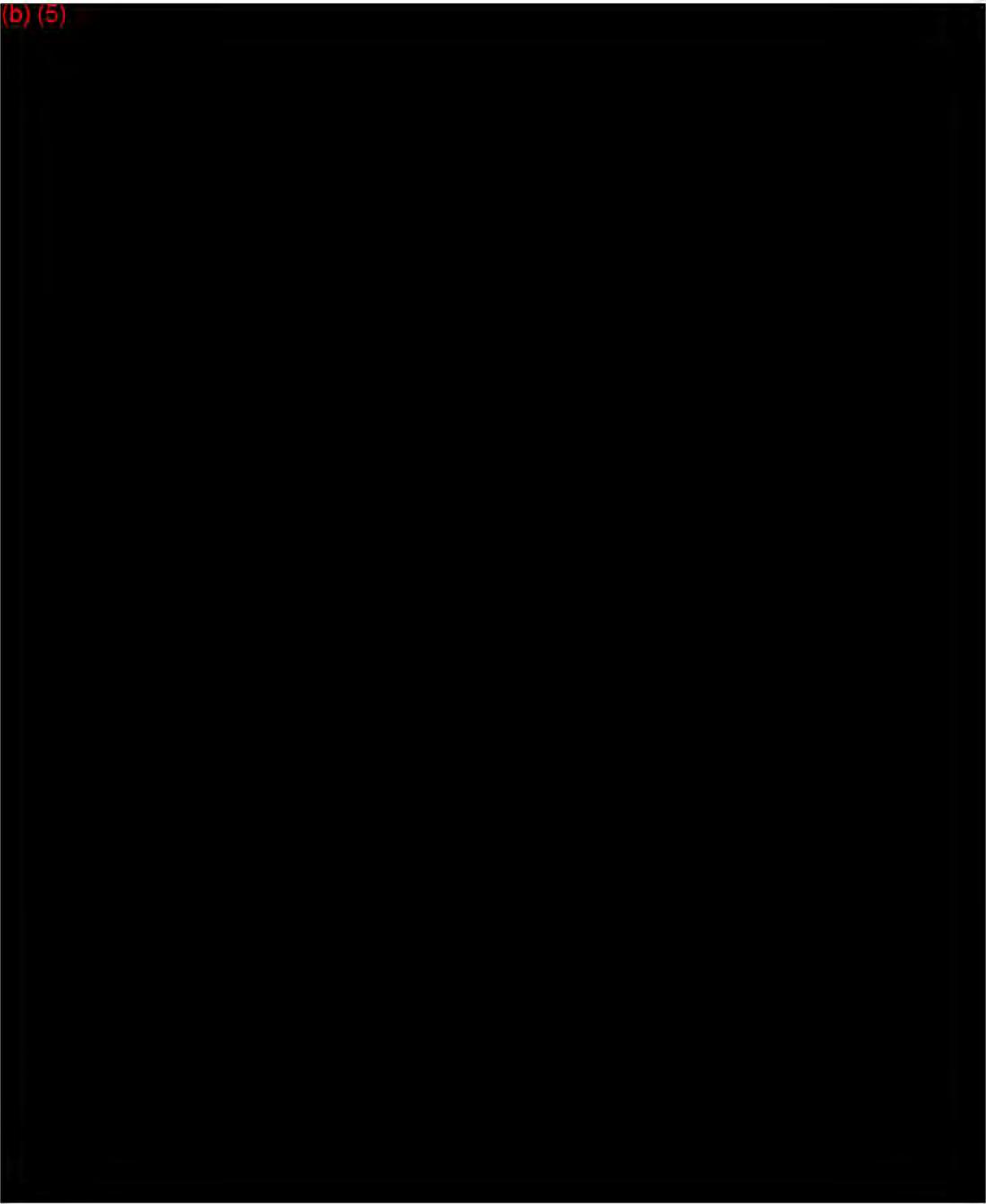
- Memo (with my two questions)
- 2 comms docs
- Cover email
- If we have, the draft approval letter and labeling

Please copy this group. We will keep this separate from the weekly homework.

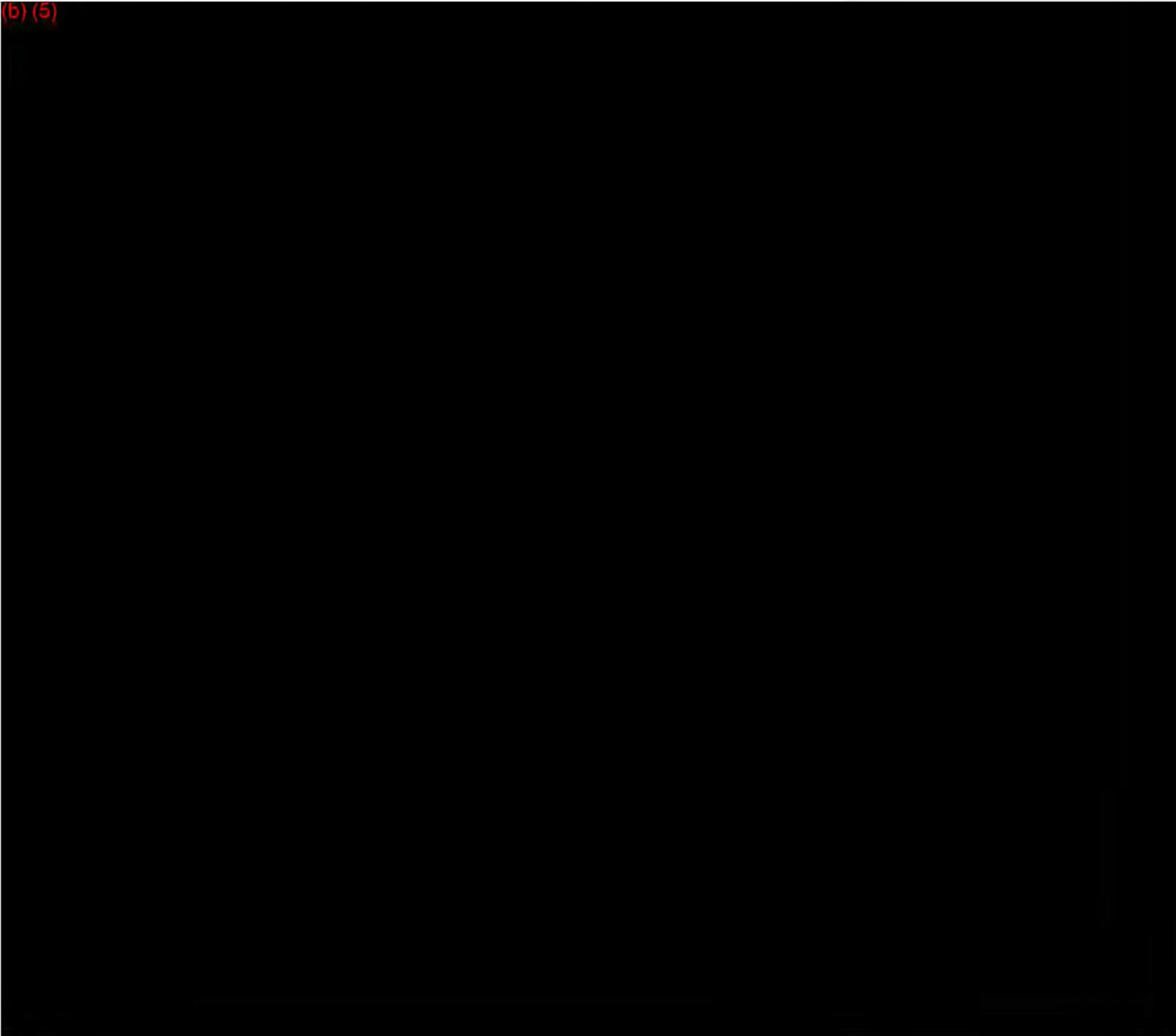
Thanks much!

Rachel

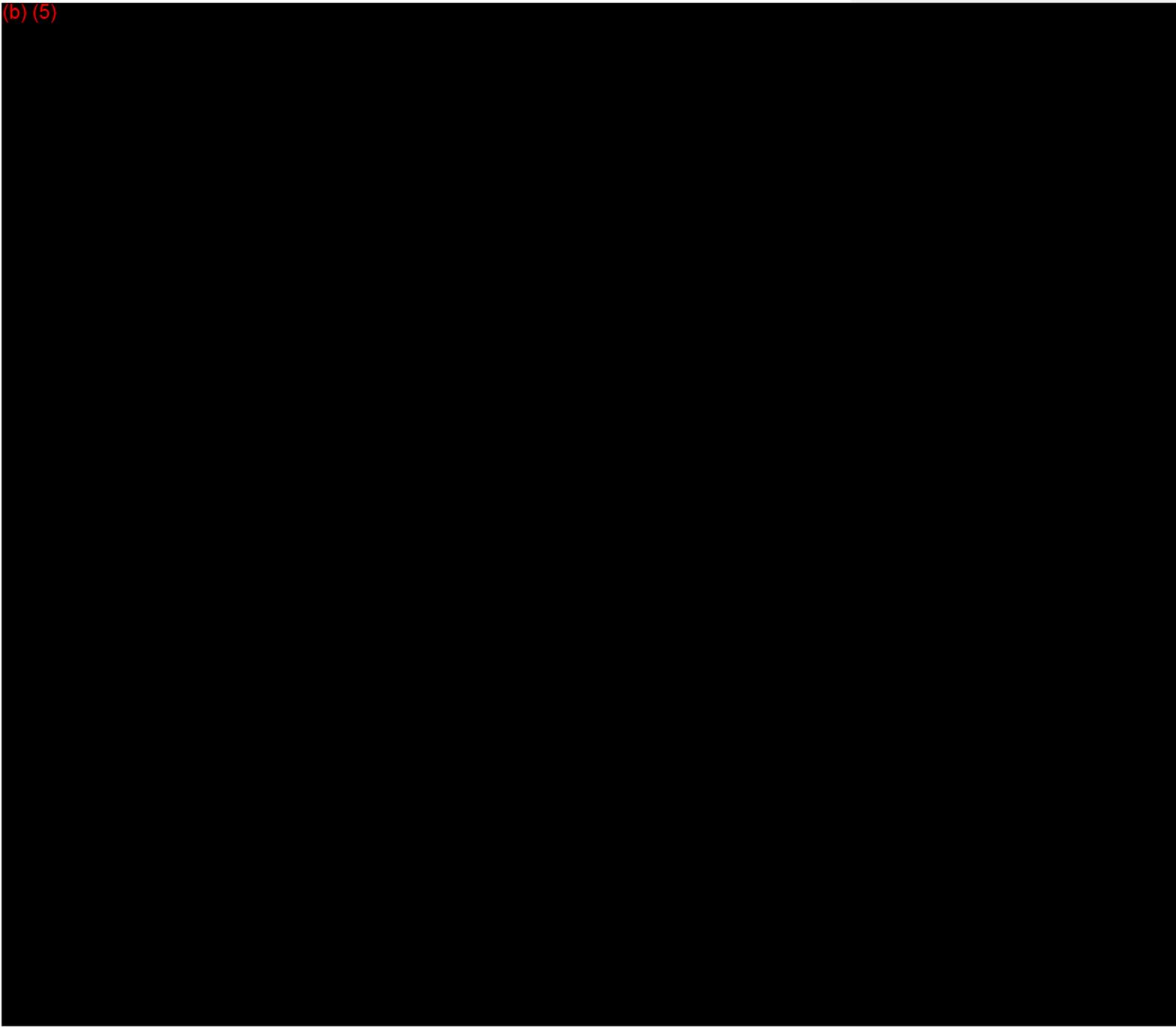
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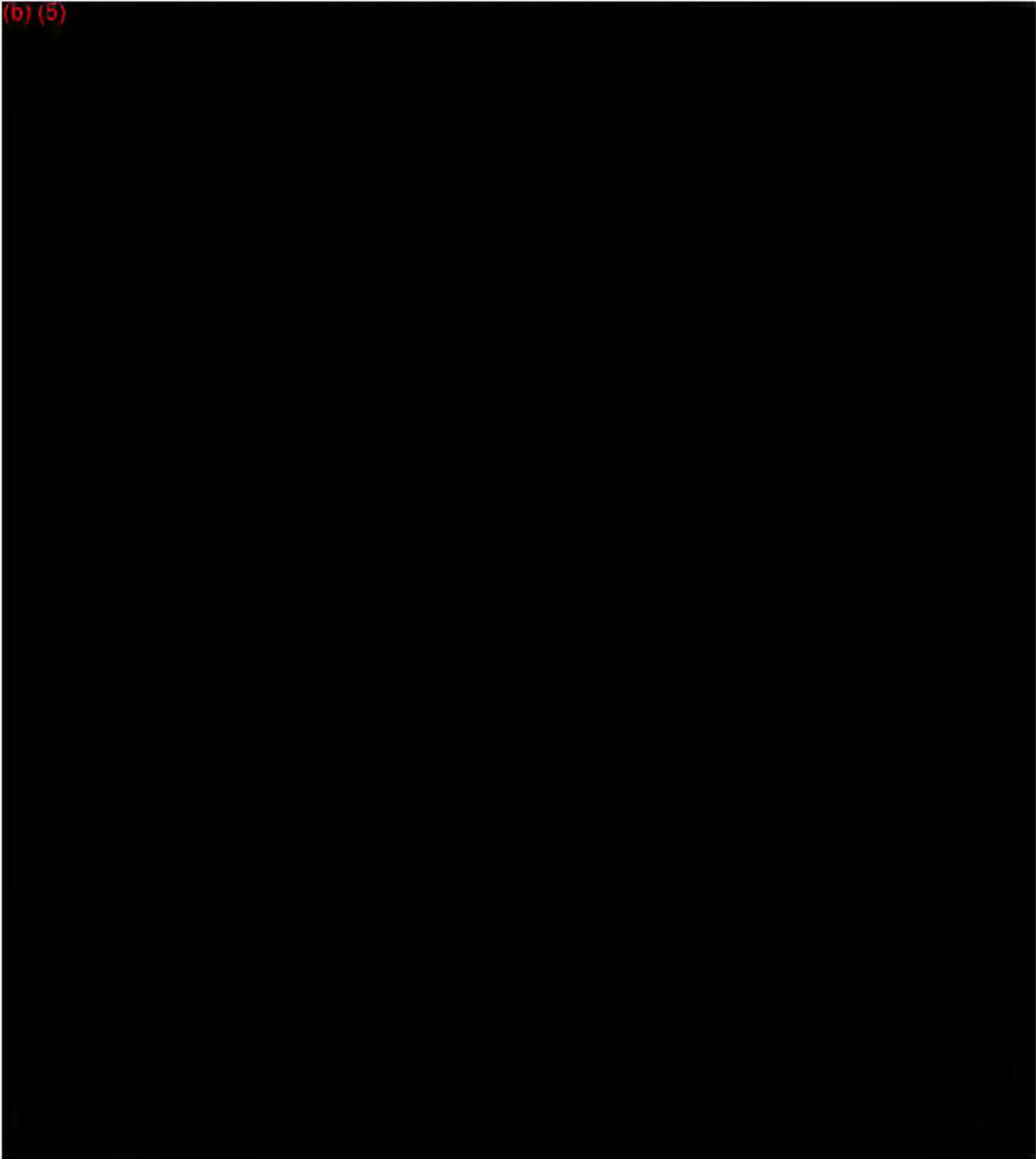
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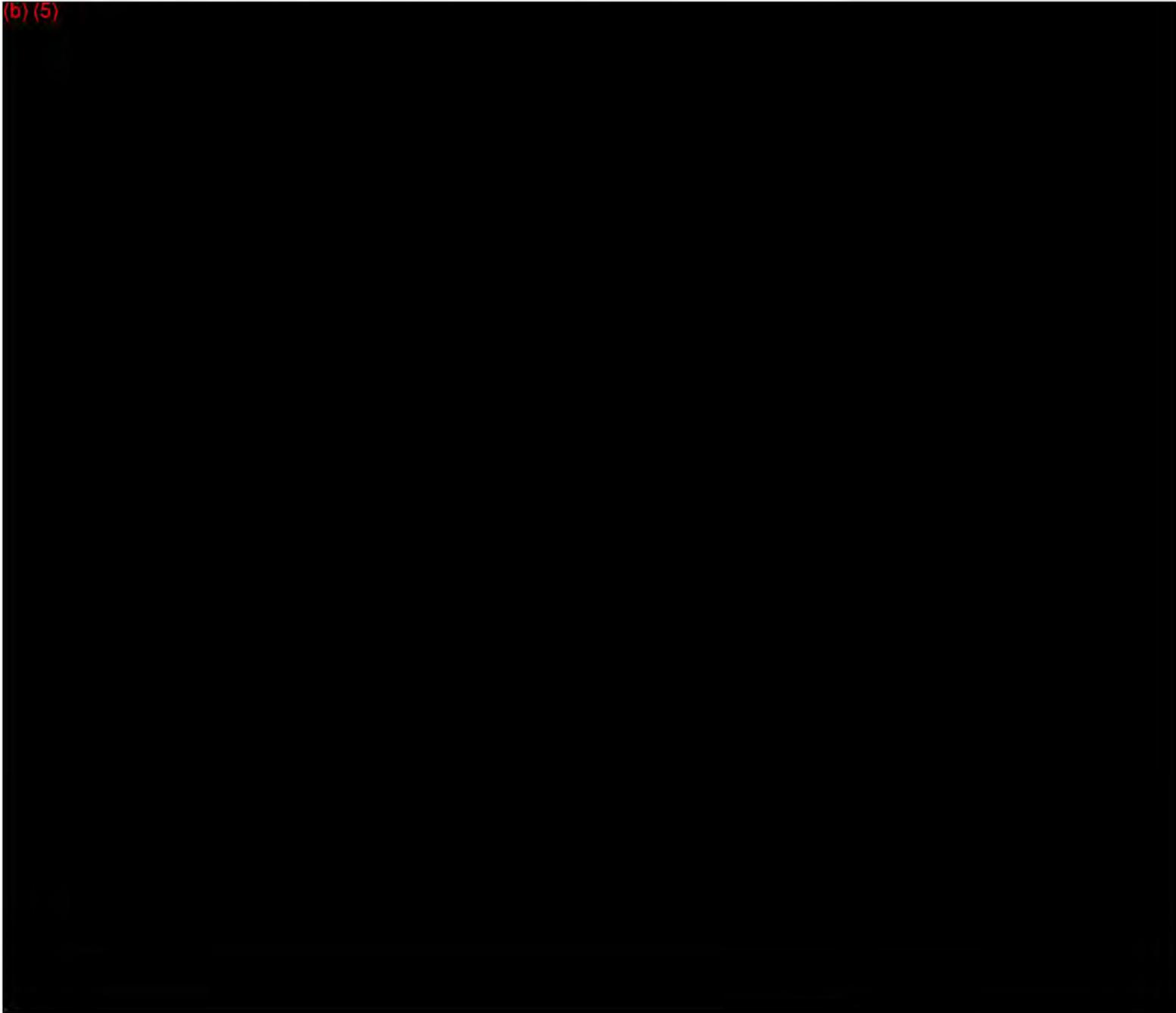
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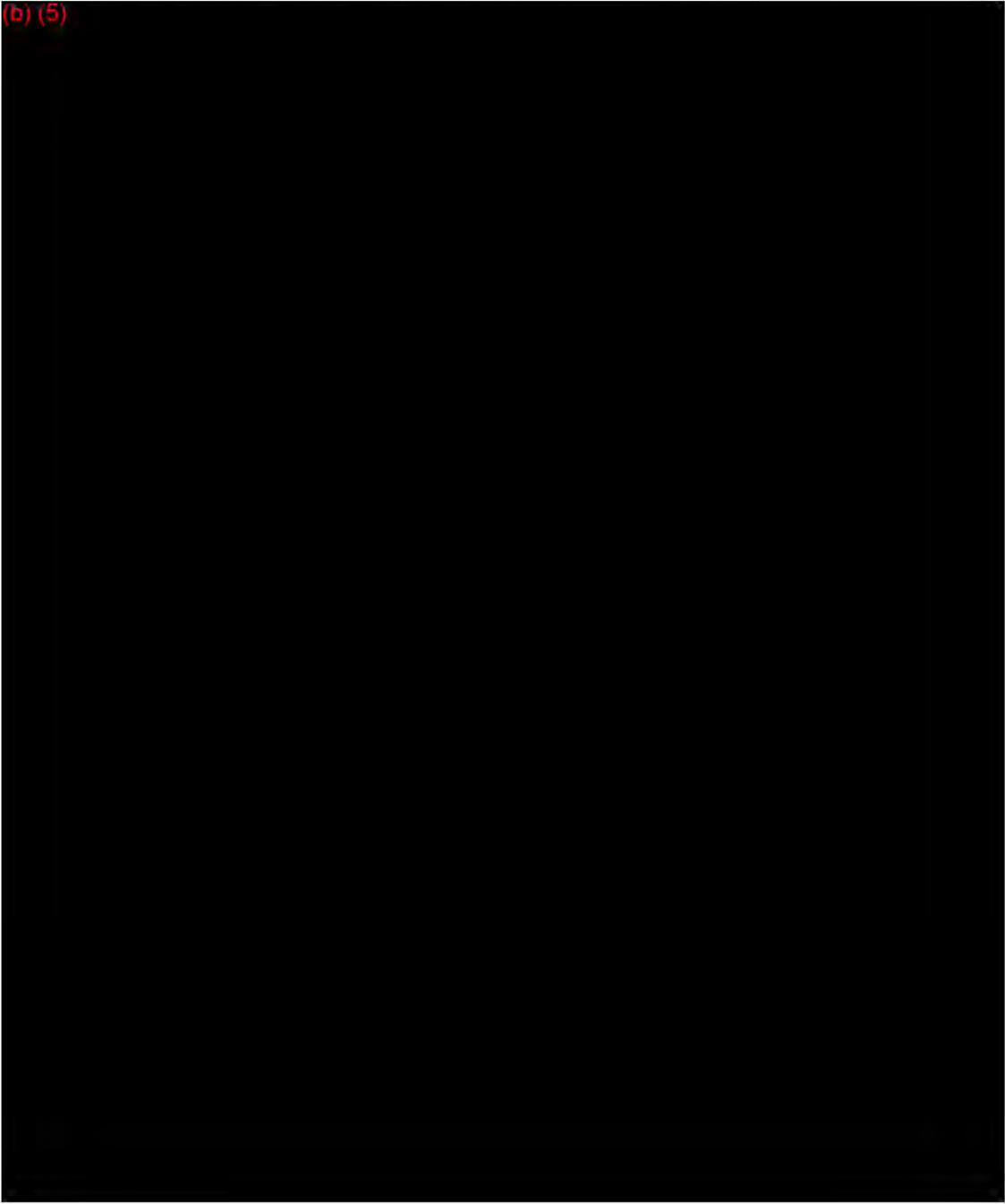
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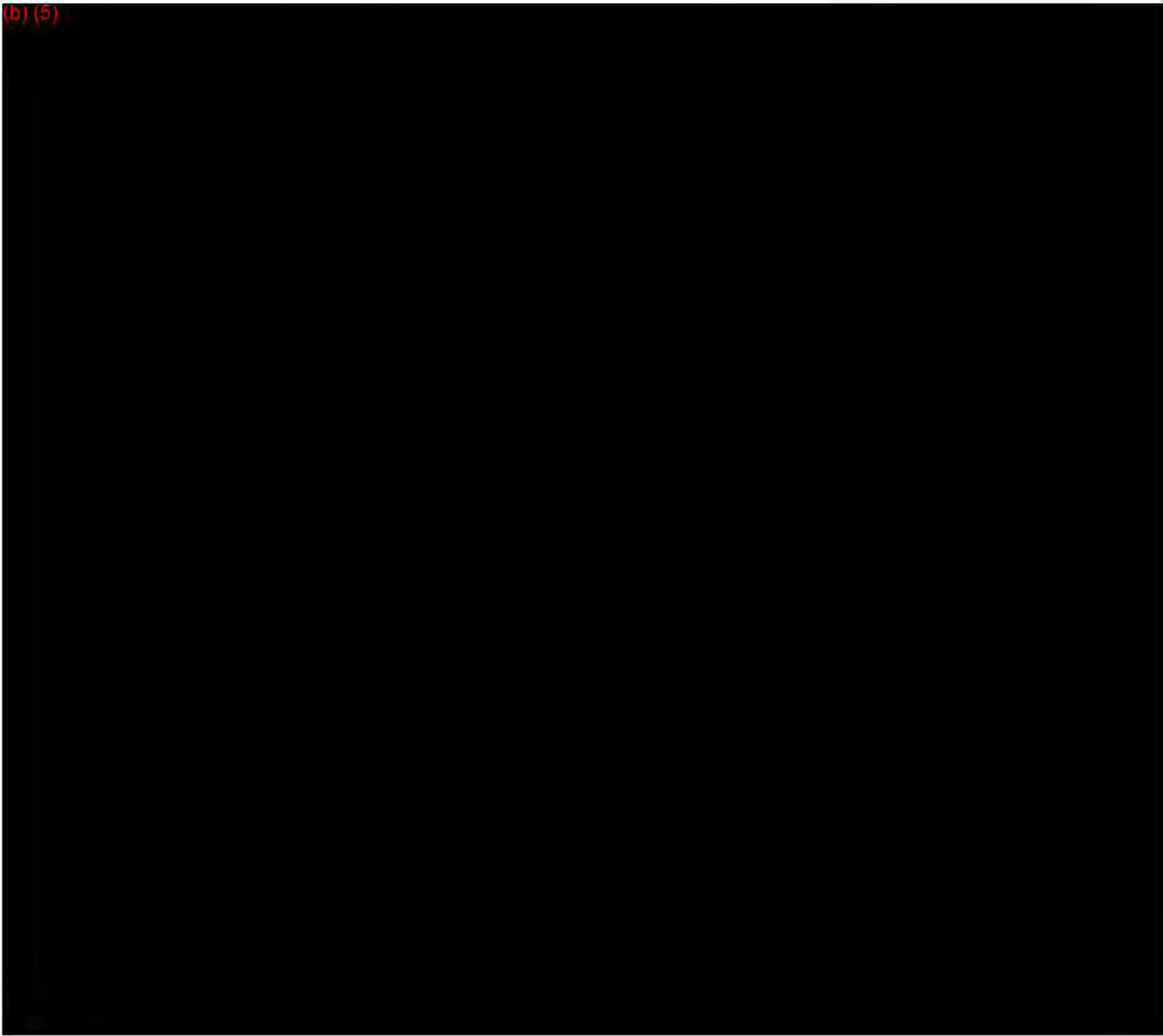
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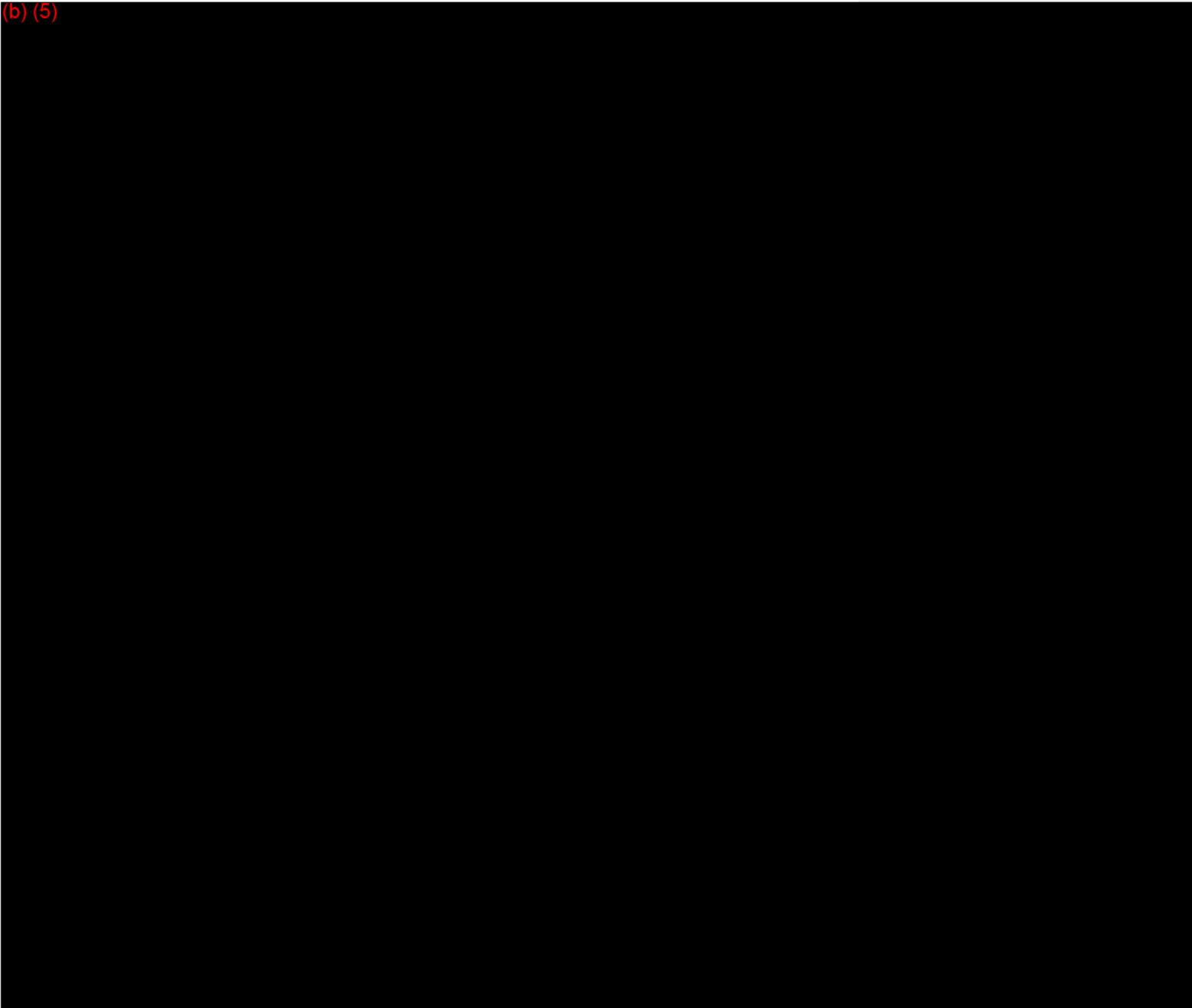
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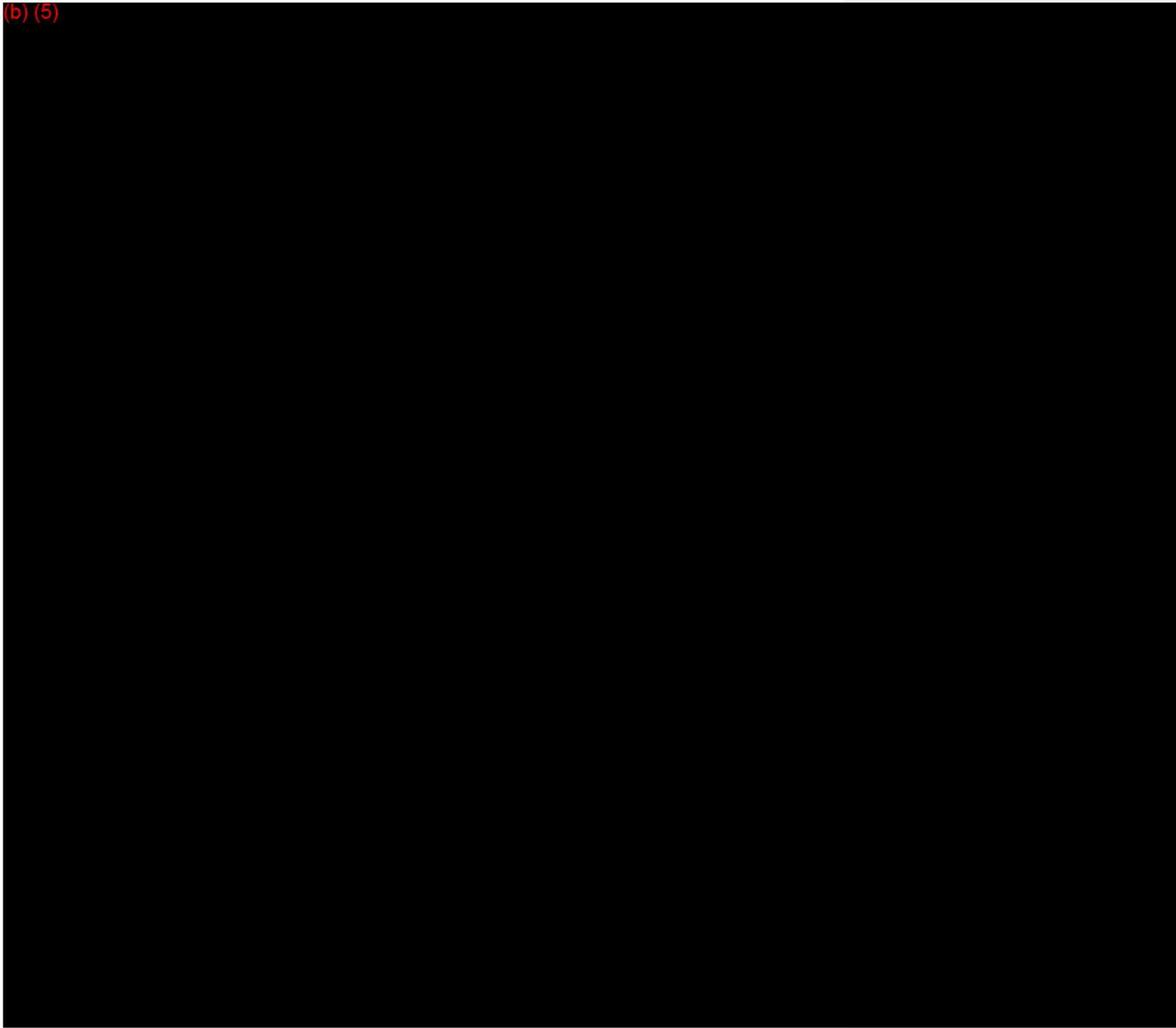
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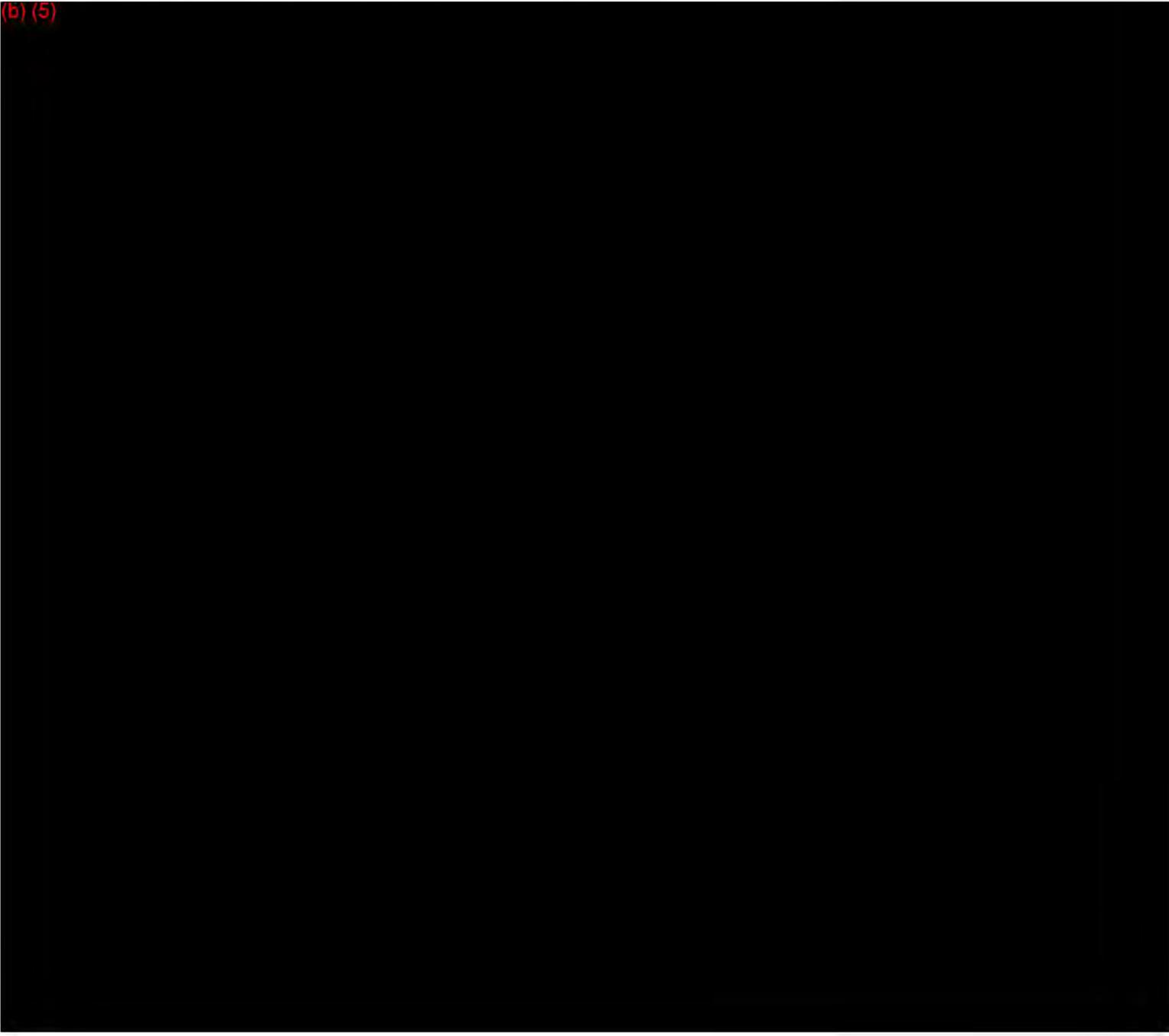
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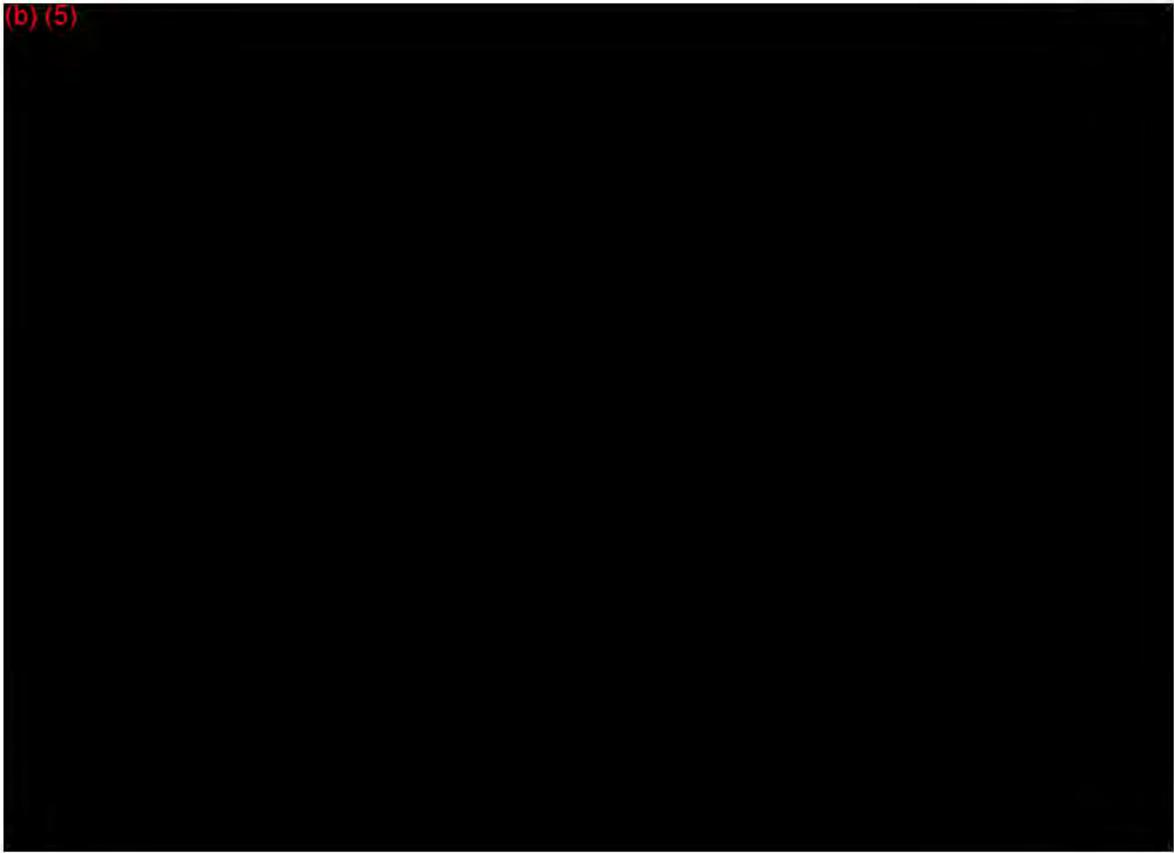
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From: [Soreth, Janice M](#)
To: [Sherman, Rachel](#); [Davies, Kathleen](#)
Cc: [Califf, Robert](#); [McCall, Jonathan *](#)
Subject: RE: Can you send me the latest version of Rob's appeal memo?
Date: Thursday, September 08, 2016 9:02:41 PM
Attachments: [2016_Sept_08_Eteplirsen_JM_TRACKED_js.doc](#)

Dear All,

I share Kathleen's overall view. And I've made a few comments with suggested changes.

Thanks for the opportunity to review.

Janice

From: Sherman, Rachel
Sent: Thursday, September 08, 2016 6:15 PM
To: Davies, Kathleen; Soreth, Janice M
Cc: Califf, Robert; McCall, Jonathan *
Subject: RE: Can you send me the latest version of Rob's appeal memo?

Hi Kathleen,

Thanks so much for the rapid review and clearly articulated assessment.

Rachel

From: Davies, Kathleen
Sent: Thursday, September 08, 2016 6:13 PM
To: Sherman, Rachel; Soreth, Janice M
Cc: Califf, Robert; McCall, Jonathan *
Subject: RE: Can you send me the latest version of Rob's appeal memo?

Hi All,

I read it and nothing pops out at me. It appropriately acknowledges each side of the appeal and clearly articulates the role of the Commissioner in the appeal/dispute process and a decision based upon that role.

Kathleen

From: Sherman, Rachel
Sent: Thursday, September 08, 2016 4:41 PM
To: Davies, Kathleen; Soreth, Janice M
Cc: Califf, Robert; McCall, Jonathan *
Subject: FW: Can you send me the latest version of Rob's appeal memo?

Hi guys,

I offered the two of you up as judicious, careful, ex (or semi ex) CDER readers. Please review and see if anything pops out at you.

If possible tonight or early tomorrow. Let me know if you want to discuss. And thank you!!

Rachel

PS Please see Jonathan's request below. Needless to say, I have not been good about version control (although I have tried).....

From: McCall, Jonathan *
Sent: Thursday, September 08, 2016 4:36 PM
To: Sherman, Rachel
Subject: RE: Can you send me the latest version of Rob's appeal memo?

You bet. This is a tidied version (clean and tracked) that I put together this afternoon; I'm also including the cover letter.

One request: if you make changes, can you make them to the tracked version? I'll take that and re-create a clean/commented version for tomorrow.

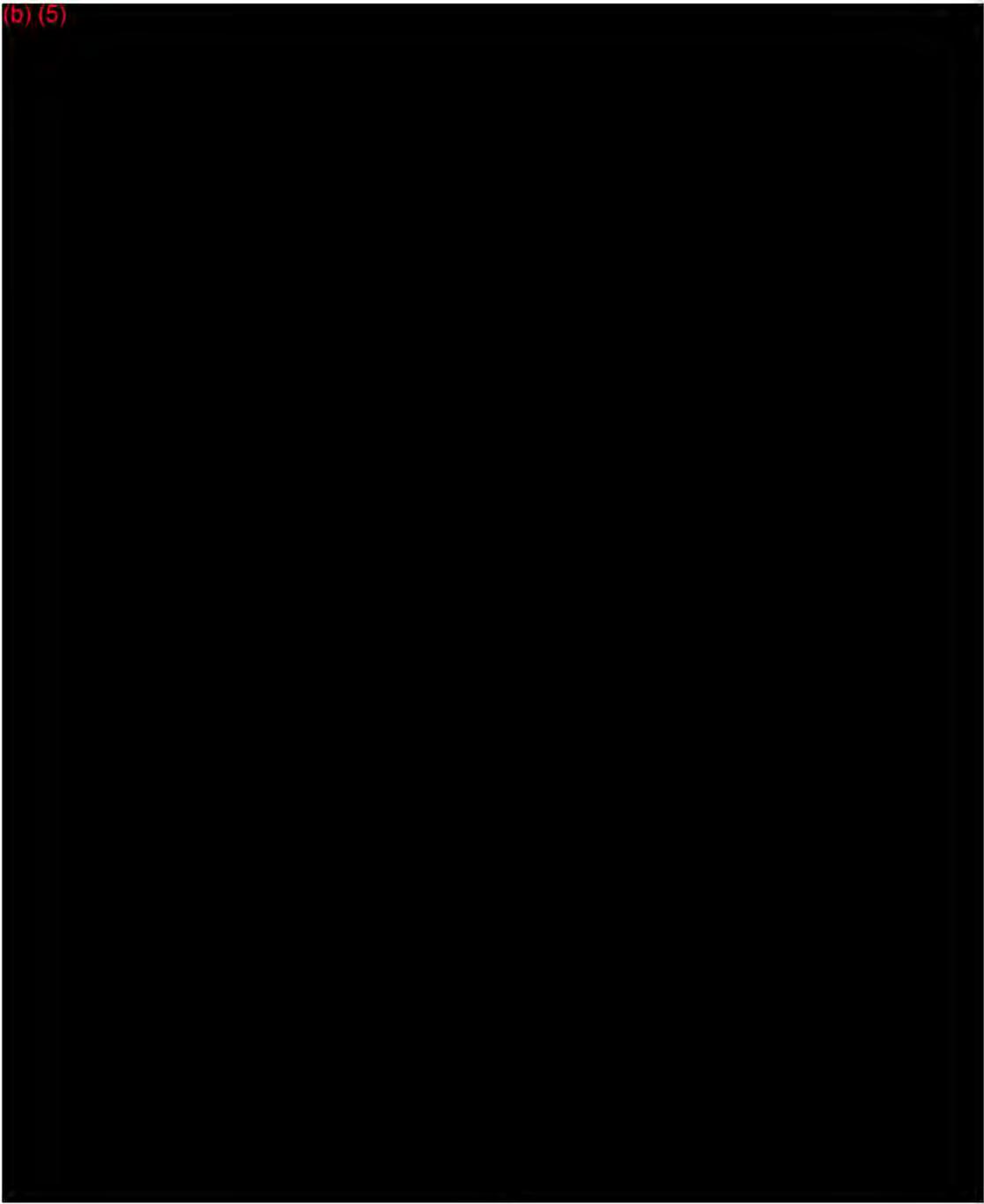
Thanks!

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J

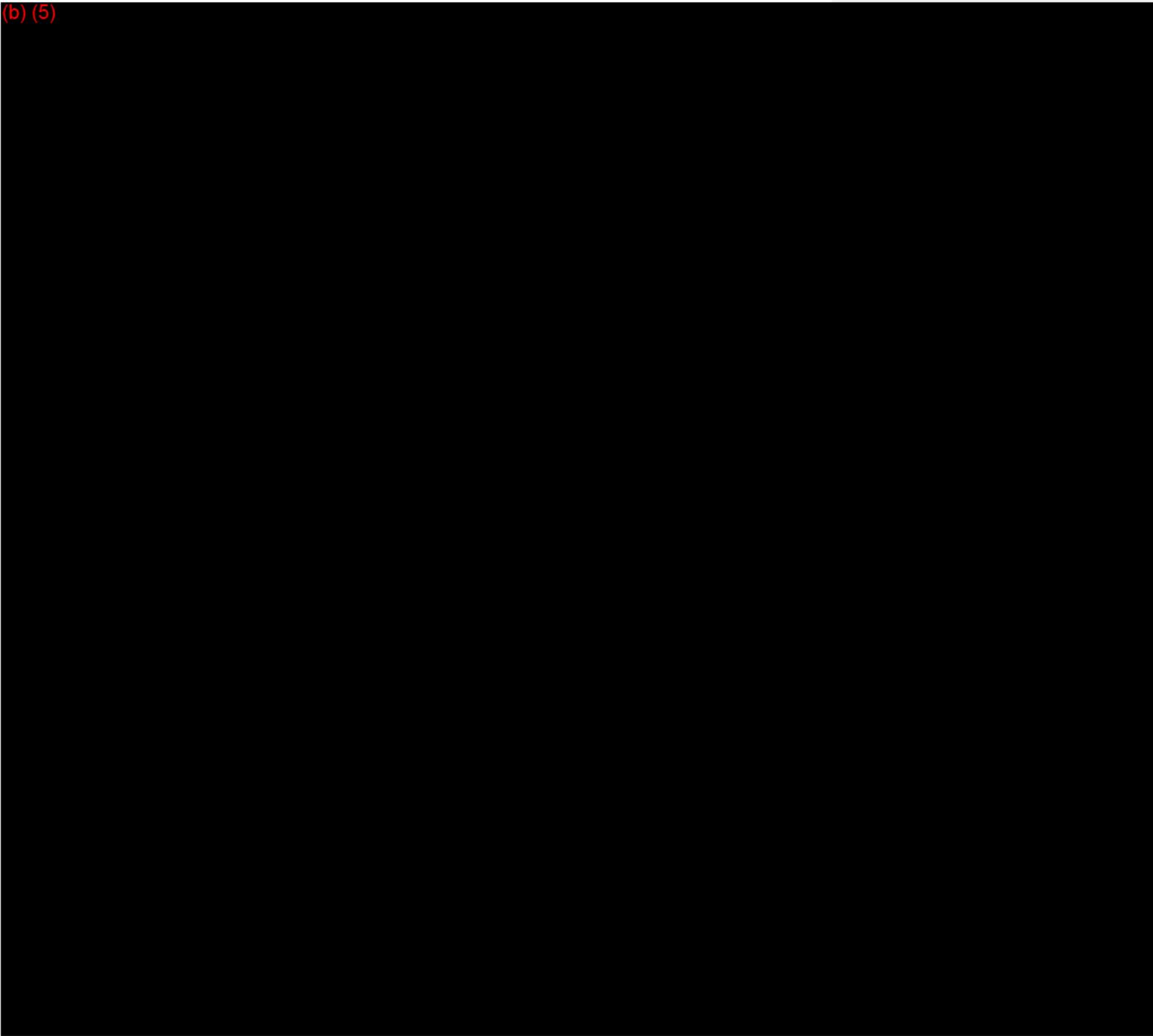
From: Sherman, Rachel
Sent: Thursday, September 08, 2016 4:32 PM
To: McCall, Jonathan *
Subject: Can you send me the latest version of Rob's appeal memo?

Thanks!

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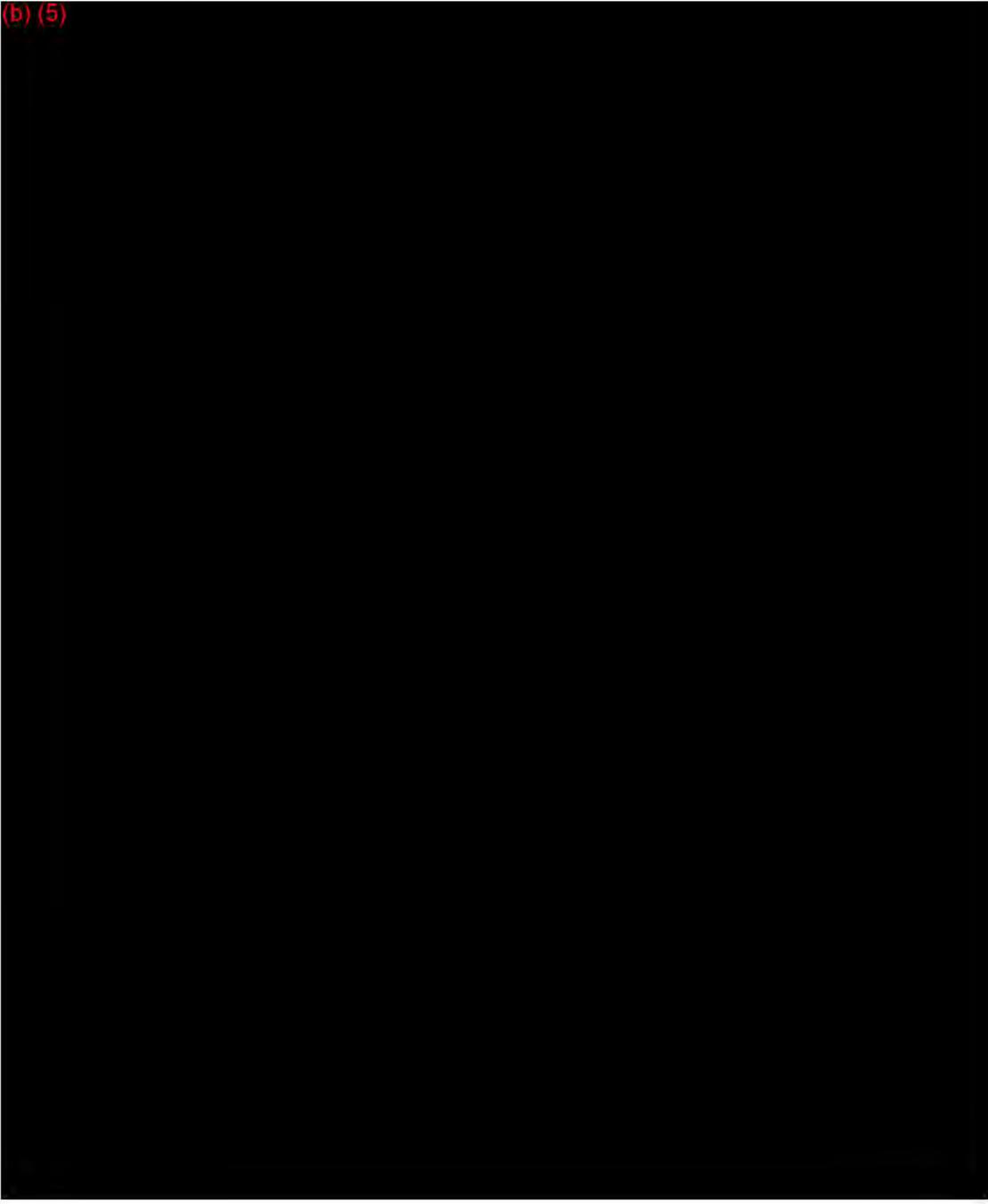
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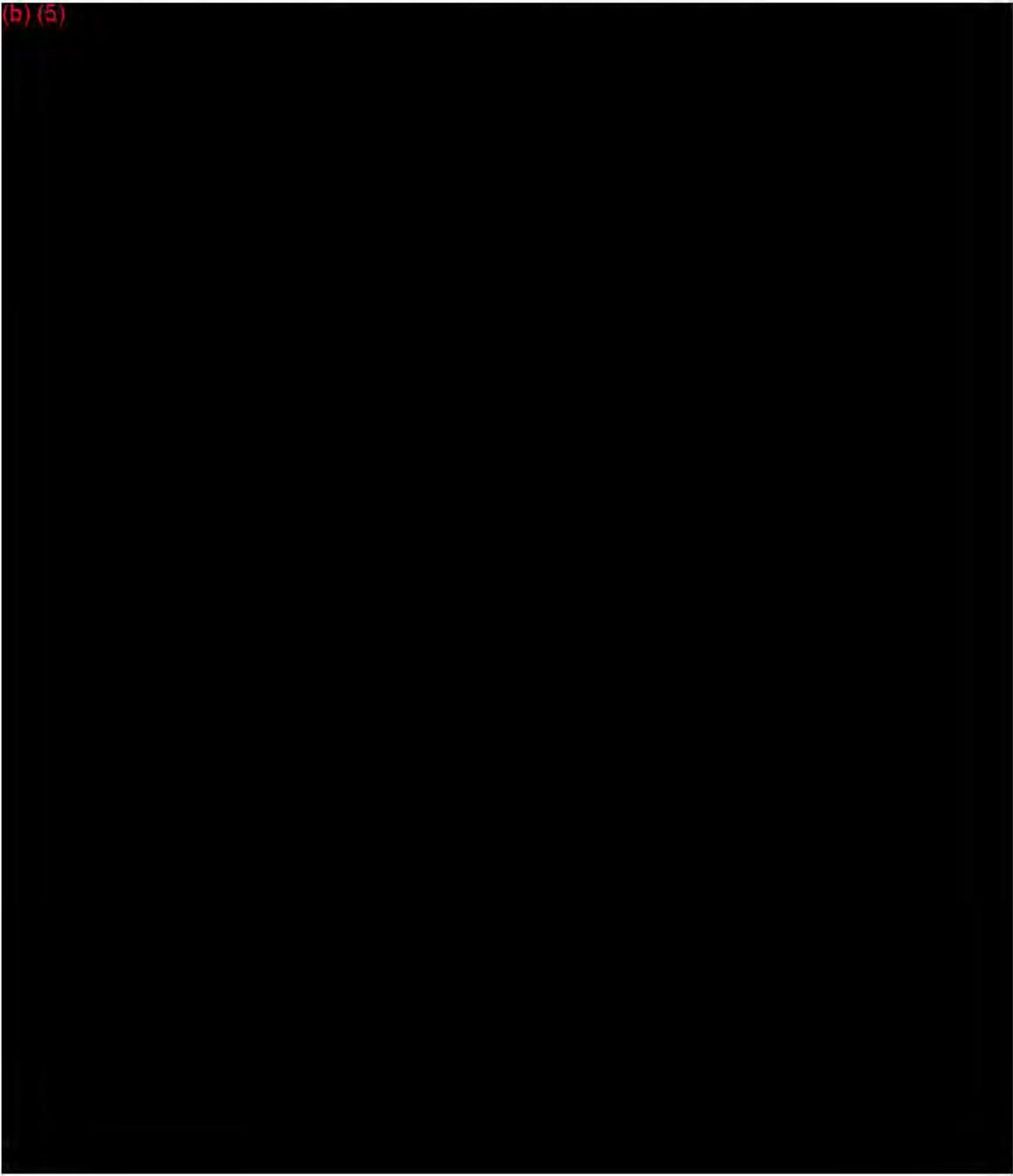
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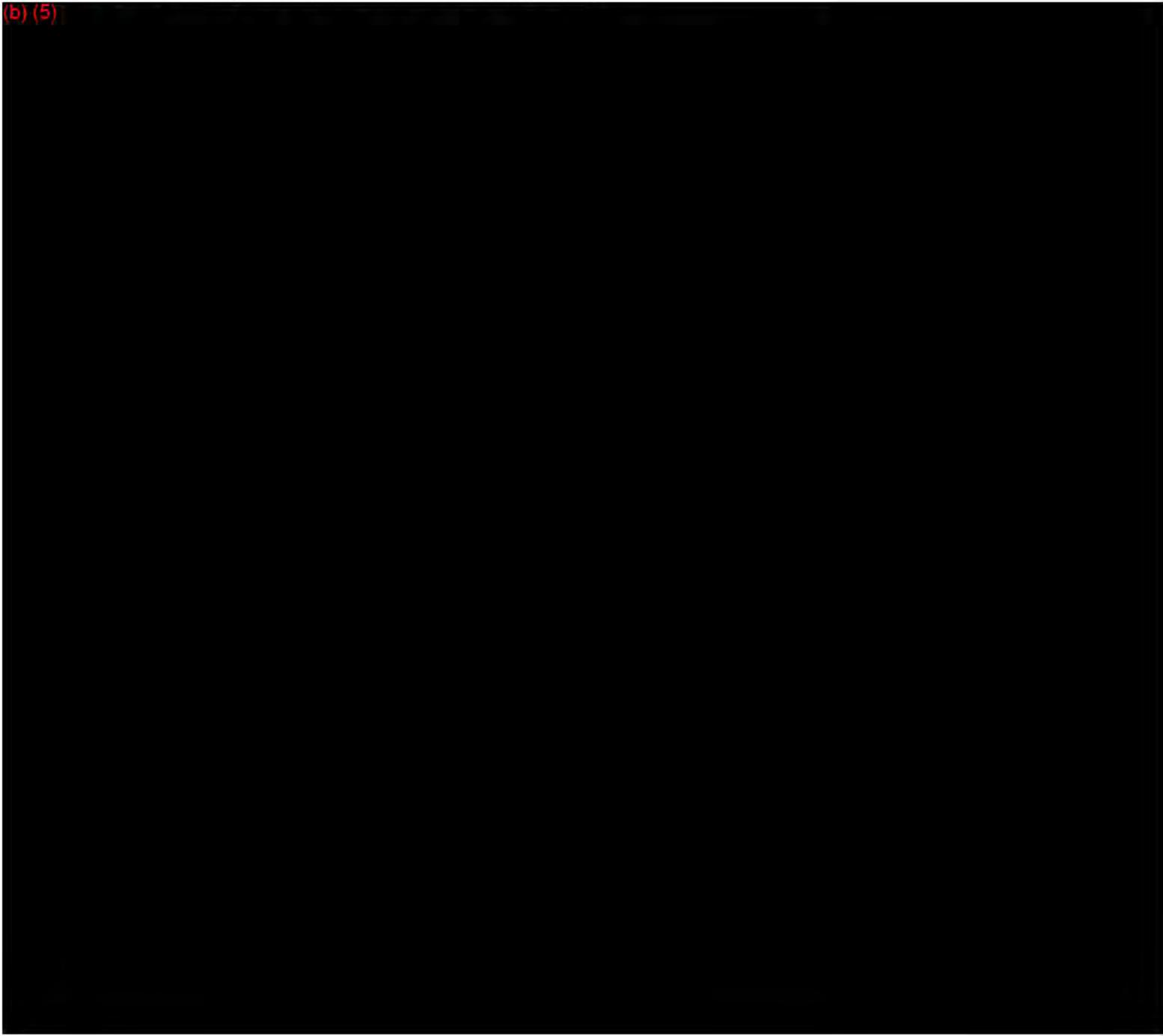
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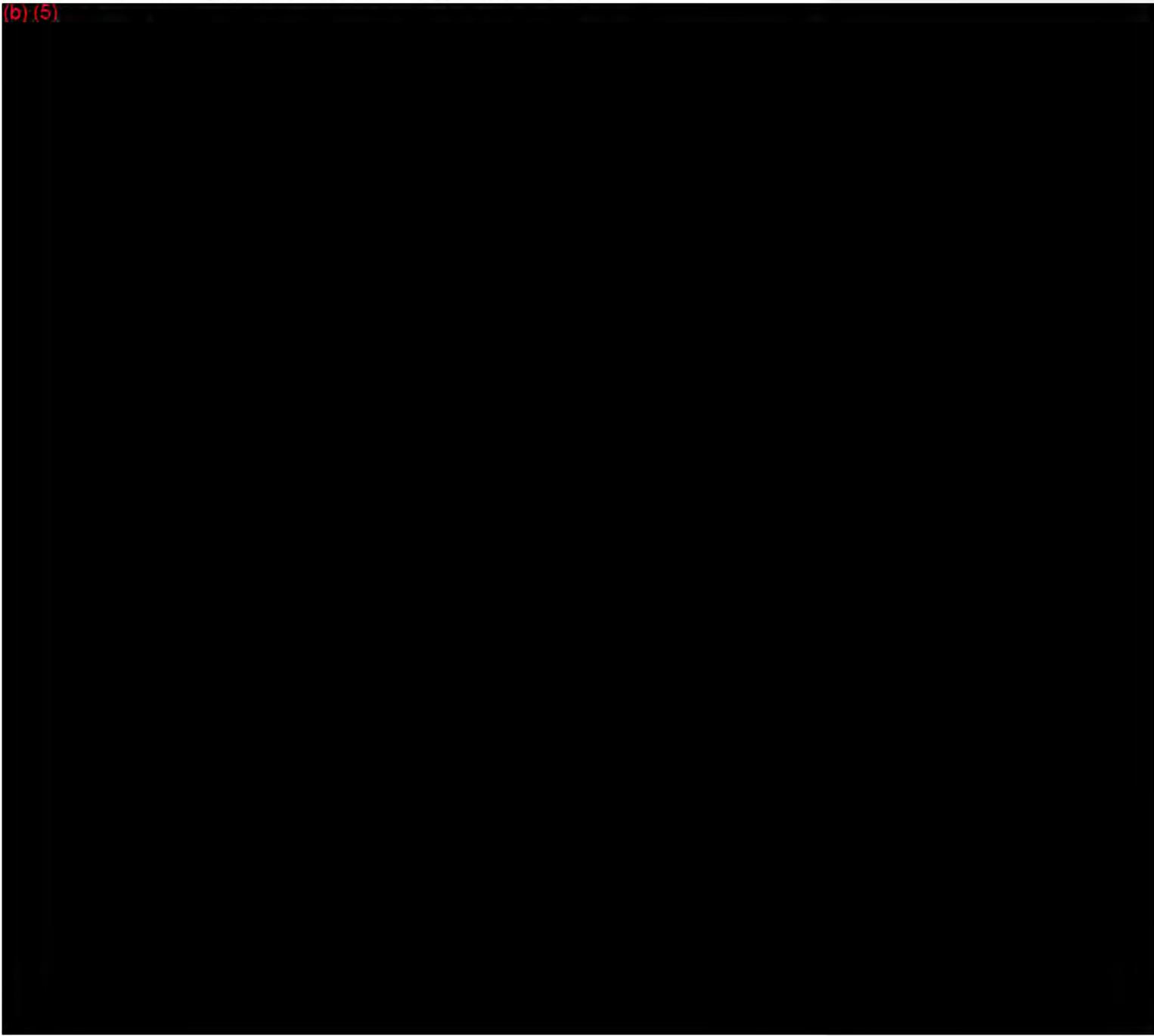
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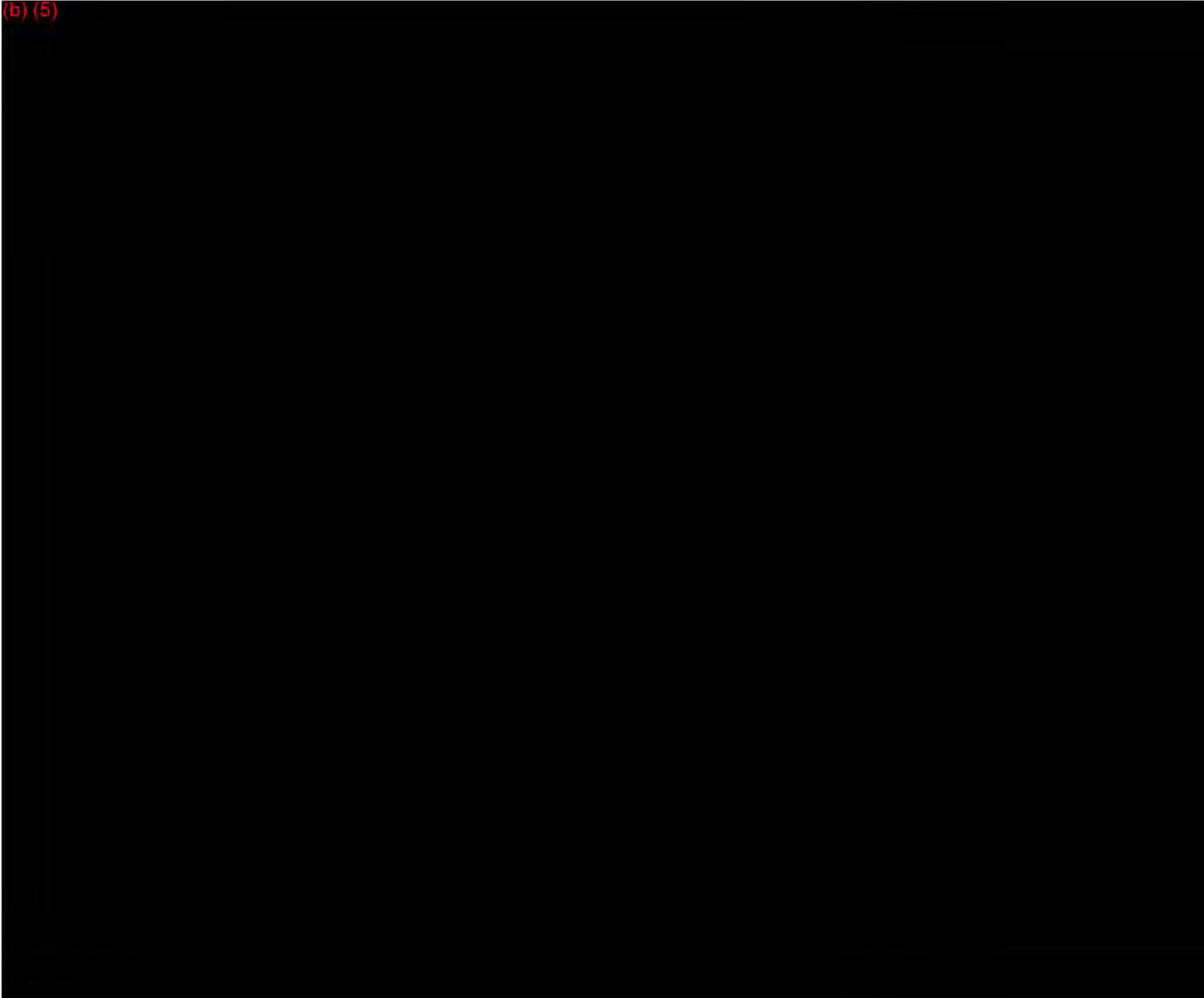
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From: [Smith, Fallon](#)
To: [Califf, Robert](#); [Sherman, Rachel](#); [Kraus, Tom](#); [Sharp, Jeremy](#); [Cristinzio, Dayle](#); [Bolek, Michelle](#); [Shreeve, Chris](#); [Rawlings, Kimberly](#); [Woodcock, Janet](#); [Throckmorton, Douglas C](#); [Conover, Katie](#); [Young, Jason](#); [Rebello, Heidi](#); [Rodriguez, Jennifer](#); [Walsh, Sandy](#); [Kotz, Deborah](#); [Marchand, Heidi](#); [Quinn, Kathleen](#); [Scott, Meghan](#)
Subject: RE: Eteplirsen Coverage: BioPharma Dive and Regulatory Focus
Date: Monday, September 19, 2016 11:44:52 AM
Attachments: [image001.png](#)

BioPharma: [Sarepta skyrockets as FDA approves DMD drug](#)

By: Ned Pagliarulo and Lisa LaMotta

Dive Brief:

Sarepta Therapeutics on Monday won conditional approval from the Food and Drug Administration for its Duchenne muscular dystrophy (DMD) treatment, after a months-long delay left the company and DMD patients in regulatory limbo.

Sarepta will be required to carry out a clinical trial to confirm the drug's clinical benefit, and the Food and Drug Administration made clear a failure to verify efficacy could lead the regulator to withdraw approval for the treatment.

Shares in Sarepta skyrocketed by over 90% at one point Monday morning, as the FDA's decision resolved a long-standing question of whether the company would be sent back to the drawing board. The drug, now known as Exondys 51 (eteplirsen), is the first approved treatment for DMD.

Dive Insight:

The FDA has signed off on approval of Sarepta's DMD drug after several years of back and forth with the community. While the drug did pass muster for a conditional approval, the decision is a contentious one. Regulators had been originally expected to make a decision on the drug in May.

Advocates for the community have been particularly outspoken and criticized the FDA for passing over drugs from several other companies, including PTC Therapeutics and BioMarin. An advisory committee to the FDA voted against approval of eteplirsen earlier this year, raising further ire from the community.

The regulatory agency and its experts have long claimed that while the unmet need is very high in this case, the drug candidates in development have not shown strong efficacy.

DMD is a genetic disease that affects young boys, many of which die before reaching adulthood. The disease is characterized by muscle wasting and most of these boys lose the ability to walk and eventually succumb to respiratory failure. Advocacy groups — composed largely of parents of the children — have been major supporters of DMD developers and clinical trials seeking to test disease-modifying drugs.

Several companies have pulled out of the space after the FDA made clear there was no path forward for approval for their drugs. BioMarin was forced to announced this spring that it would end pursuit of approval of its drug, Kyndrisa (drisapersen).

###

RAPS: Sarepta Wins Controversial FDA Approval for First DMD Drug

By: Zachary Brennan

The US Food and Drug Administration (FDA) on Monday approved Sarepta Therapeutics' first drug to treat patients with Duchenne muscular dystrophy (DMD), a rare genetic disorder that causes progressive muscle deterioration and weakness in young children.

The approval is highly controversial after a FDA advisory committee voted against approval in April as the outside experts said there was not substantial evidence that the drug is effective in providing clinical benefit, which is the standard for traditional approval. Before that vote and afterwards, the DMD patient community protested vigorously.

DMD, occurring in about one out of every 3,600 male infants worldwide, is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. The first symptoms are usually seen between the ages of three and five, and worsen over time.

The agency said that following the hearing, Sarepta submitted additional data "showing substantial evidence of dystrophin production, although the amount of dystrophin produced was only a small fraction of the normal level."

The injection, known as Exondys 51 (eteplirsen), is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, who constitute approximately 13 percent of the population with DMD.

Ultimately, the new injection, known as Exondys 51, was approved under FDA's accelerated approval program, reserved for drugs to treat serious or life-threatening diseases, and where there is a lack of available therapy.

"Based on the data submitted by the applicant, the Agency has concluded that there is a statistically significant increase in dystrophin production in indicated patients who are exposed to the drug that meets this requirement," FDA said Monday.

That approval followed a contentious scientific disagreement among FDA, with some saying the "statistically significant increase in dystrophin, the surrogate endpoint, of an exceptionally small magnitude does not imply clinical benefit," according to the 126-page approval letter.

Moving forward, FDA said it is requiring Sarepta (company's stock increased in value by more than 80% as of Monday morning and the company also won a rare pediatric priority review voucher as a result of the approval) to conduct a clinical trial to show that the drug preserves motor function, with eteplirsen being compared to placebo.

The required study is designed to assess whether Exondys 51 improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. If the trial

fails to verify clinical benefit, FDA said it “may initiate proceedings to withdraw approval of the drug.

“In this case, flexibility is warranted because of the life-threatening nature of the disease; the lack of available therapy; the fact that the intended population is a small subset of an already rare disease; and the fact that this is a life-limiting disease of children. These factors, combined with the dystrophin production data – and the drug’s low risk profile – led the Agency to approve the drug under the accelerated approval pathway,” FDA said.

Fallon Smith

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-8632
Fallon.Smith@fda.hhs.gov



From: [McCall, Jonathan *](#)
To: [Chasan-Sloan, Deborah \(FDA\)](#); [Califf, Robert](#)
Cc: [Sherman, Rachel](#); [Dickinson, Elizabeth \(FDA\)](#); [Kraus, Tom](#); [Conover, Katie](#); [Rodriguez, Jennifer](#)
Subject: RE: Eteplirsen decision memo and supporting materials for your review
Date: Friday, September 16, 2016 10:40:35 AM
Attachments: [Memo-to-file_9-16-2016_JM_CLEAN.doc](#)
[Memo-to-file_9-16-2016_JM_TRACKED.doc](#)

Hello all –

Here are tracked and clean versions of the memo to file. I've tried to regularize the formatting and make clear the separations between statements and responses.

This draft represents a merged version that combined edits from the 10:36 PM 9/15 version from Liz, the version attached to the email below, and incorporates Liz' emailed edits. Please let me know if I missed anything!

Thanks!

--

Jonathan

From: Chasan-Sloan, Deborah (FDA)
Sent: Friday, September 16, 2016 12:38 AM
To: Califf, Robert; McCall, Jonathan *
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Kraus, Tom; Conover, Katie; Rodriguez, Jennifer
Subject: RE: Eteplirsen decision memo and supporting materials for your review

Please see some additional suggested edits to the memo to file attached. Note that this version doesn't contain the edits that Liz forwarded yesterday at 10:36 pm regarding the (b) (5) .” On the attached, I've flagged the two places where those edits need to be input on this draft. Jonathan, if it's not clear what the edits are from Liz's email yesterday, please let me know.

<< File: 20160915 Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN_rmc(occ).doc >>

From: Califf, Robert
Sent: Thursday, September 15, 2016 9:16 PM
To: McCall, Jonathan *

FDAOC0003594

Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom; Conover, Katie; Rodriguez, Jennifer
Subject: RE: Eteplirsen decision memo and supporting materials for your review

<< File: 20160915 Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN_rmc.doc >>

Comments added. Hopefully this will do it. Should be easy for you to check out.

rmc

From: McCall, Jonathan *
Sent: Thursday, September 15, 2016 4:56 PM
To: Califf, Robert
Cc: Sherman, Rachel; Dickinson, Elizabeth (FDA); Chasan-Sloan, Deborah (FDA); Kraus, Tom
Subject: Eteplirsen decision memo and supporting materials for your review

Hello Dr. Califf –

Here is the current version of the eteplirsen memo:

<< File: 2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ).doc >> << File: 2016_Sept_012_R2_Eteplirsen_CLEAN Borio_rmc_JM-CLEAN(occ)_Commented.doc >>

Here is the memo to file:

<< File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_CLEAN.doc >> << File: Memo to File re Commissioner Decision_9-15-16_JMrs(occ)_COMMENTED.doc >>

And here are the response cover notes:

<< File: 20160915 response notesrs_JM_CLEAN.doc >> << File: 20160915 response notesrs_JM_TRACKED.doc >>

Thanks!

--

Jonathan

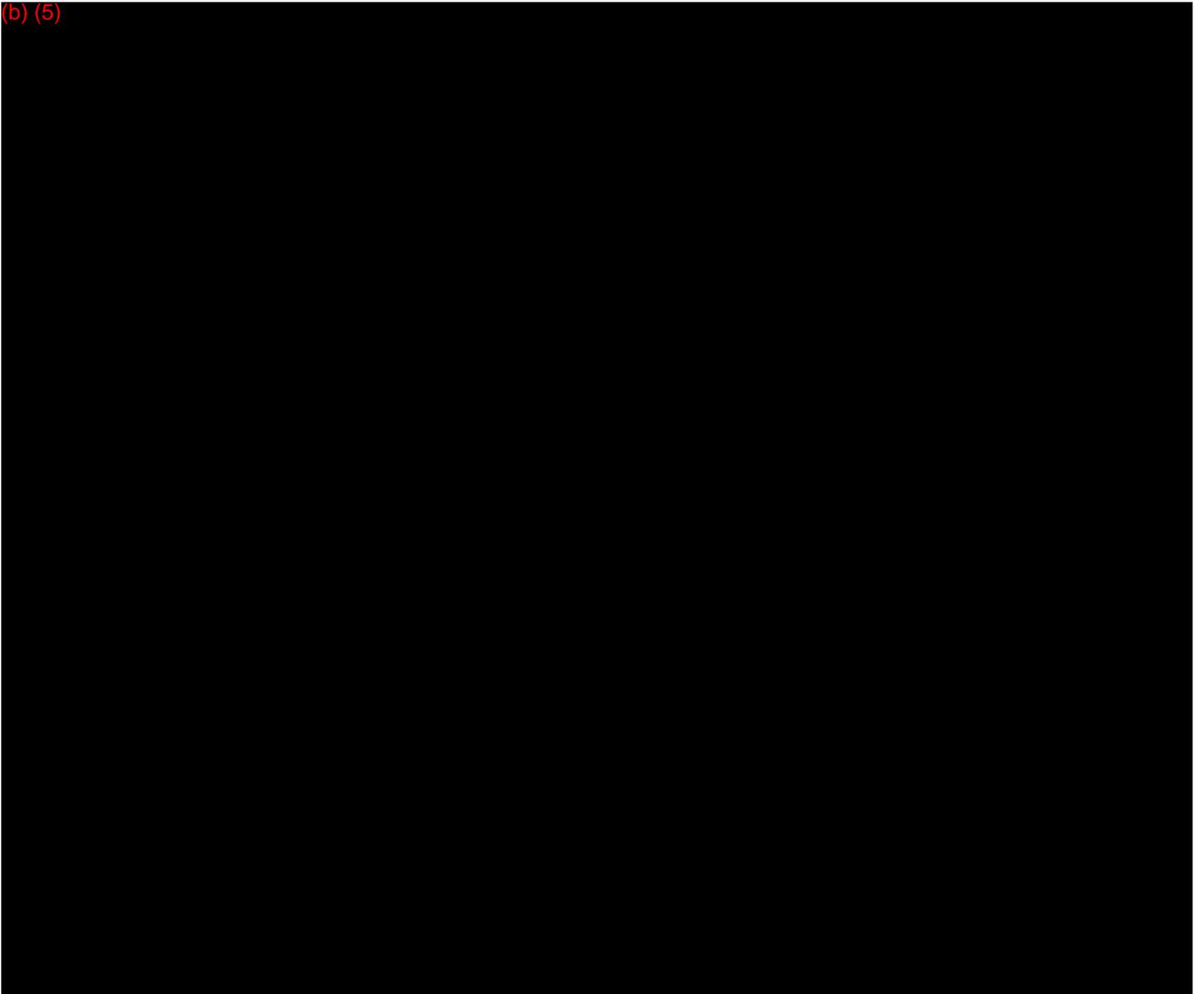
MEMO TO FILE

FROM: Robert Califf, M.D., Commissioner of Food and Drugs

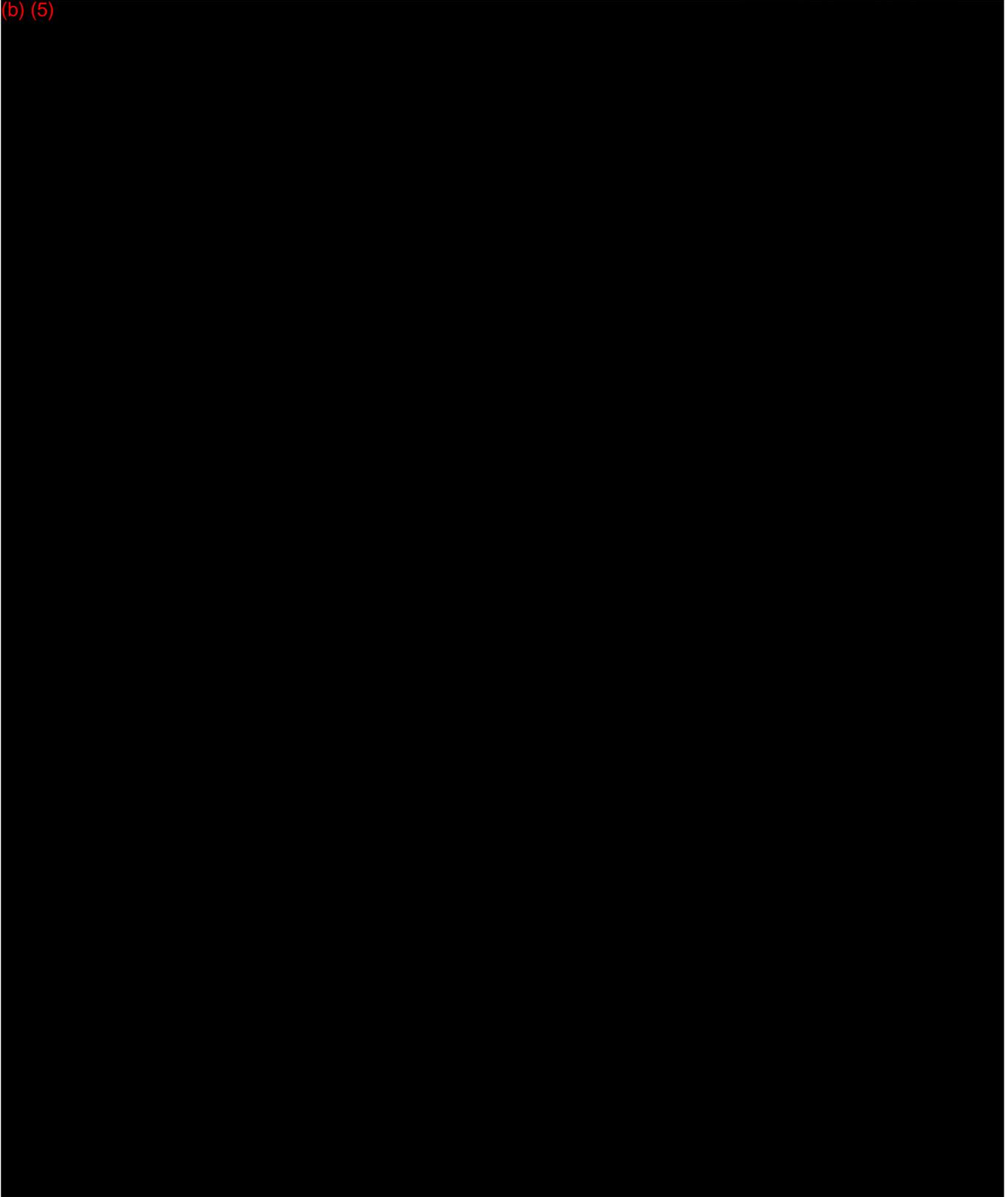
DATE:

RE: Process for Commissioner’s Decision about the Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics’ Eteplirsen (NDA 206488)

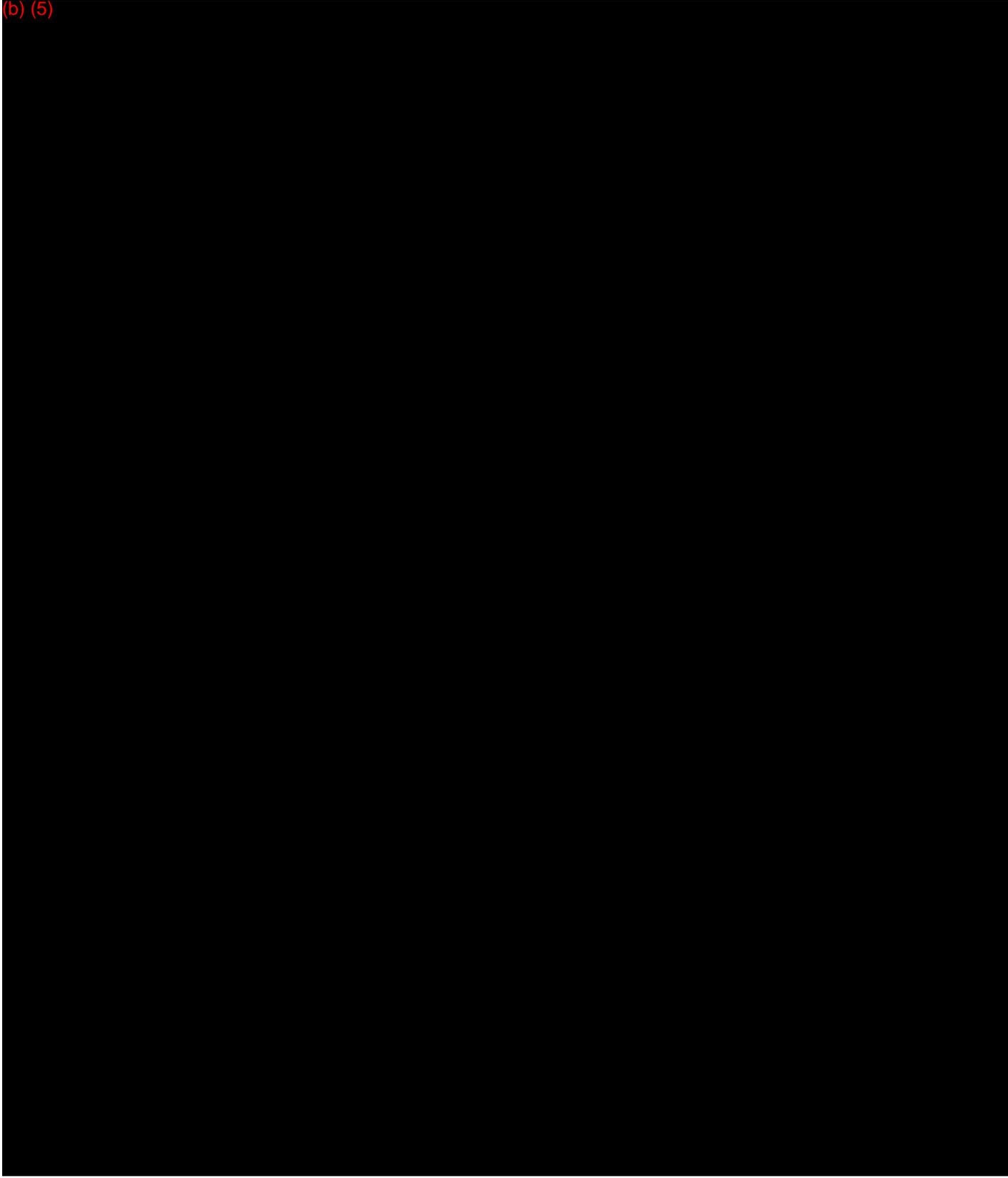
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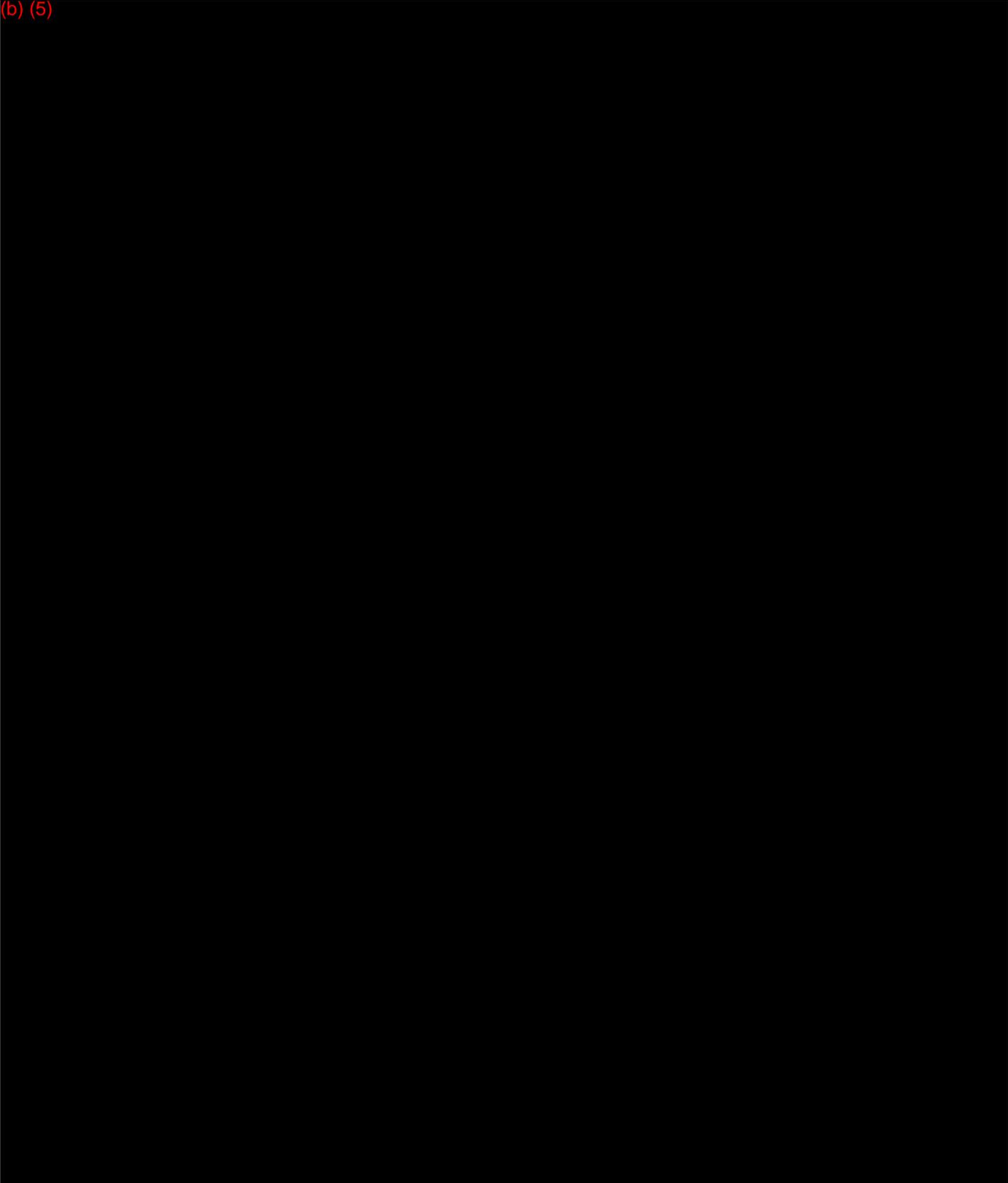
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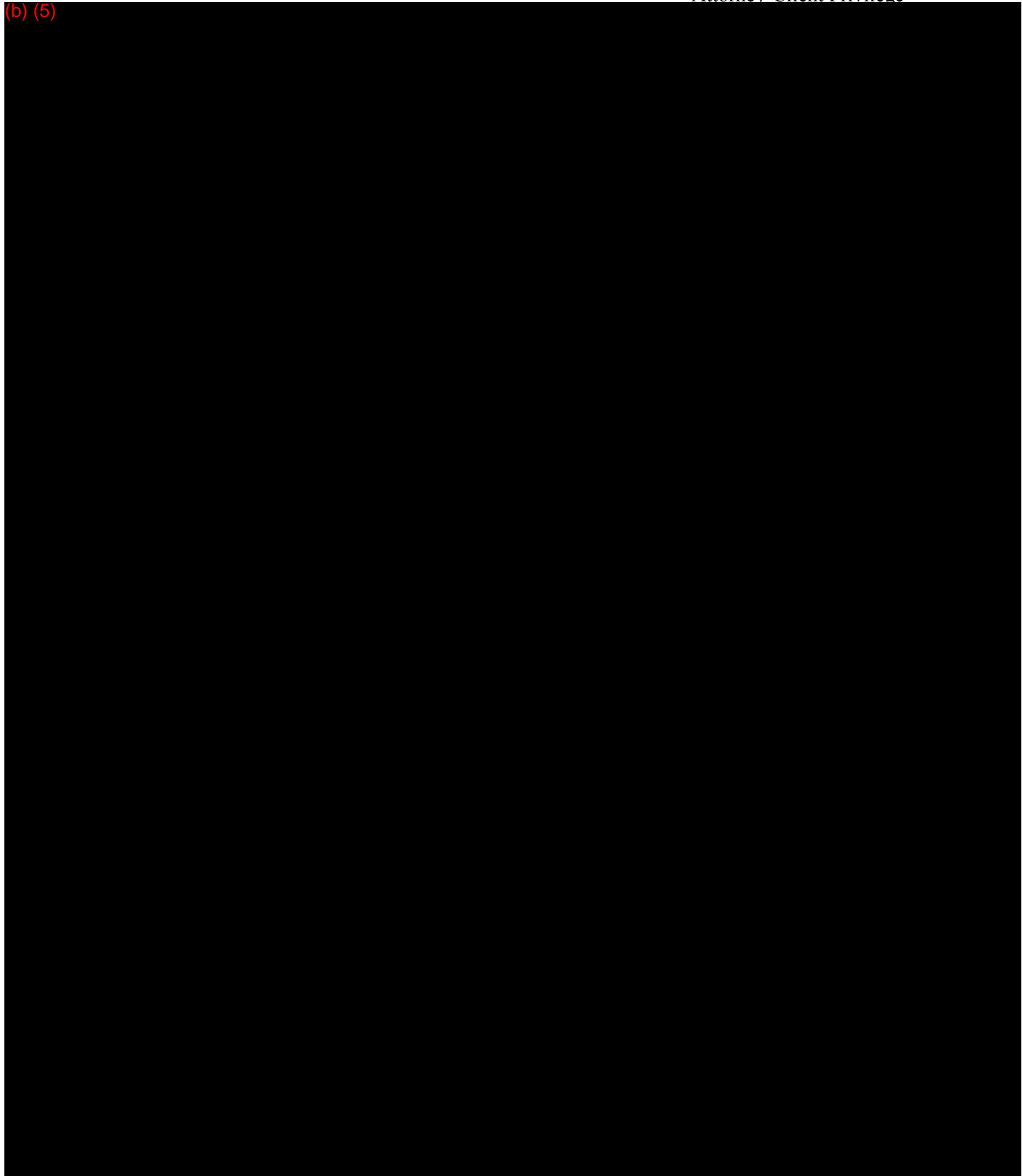
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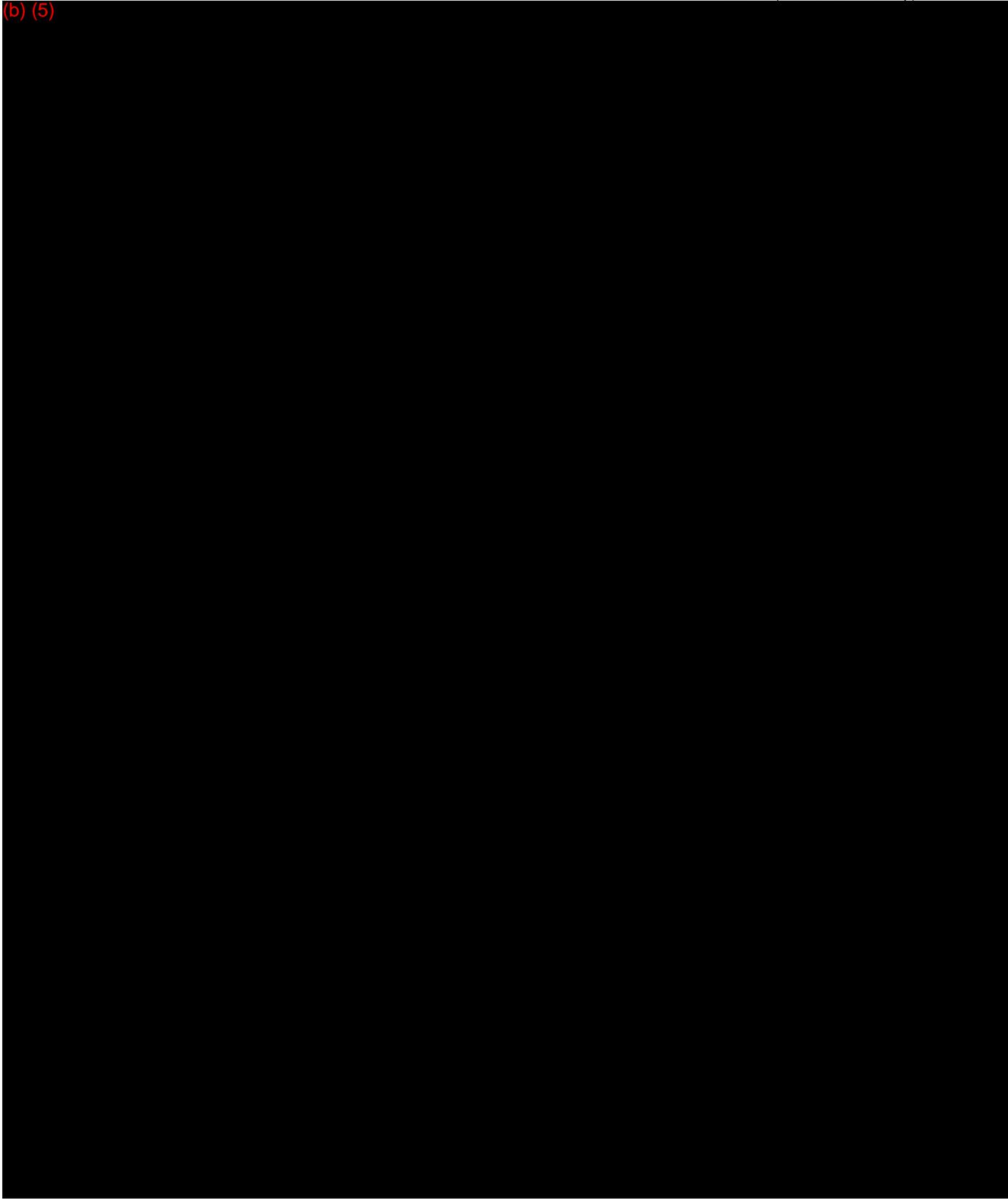
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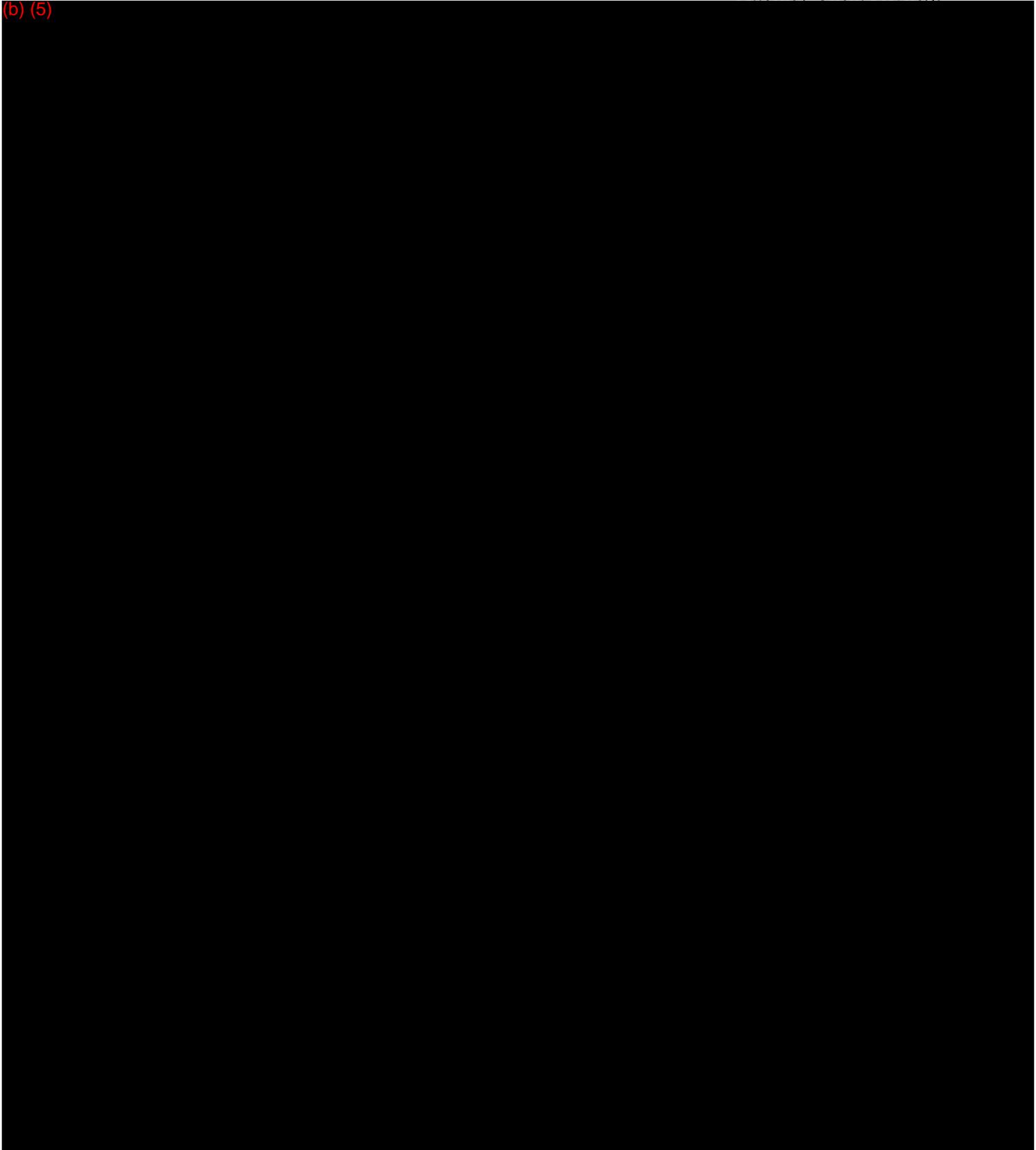
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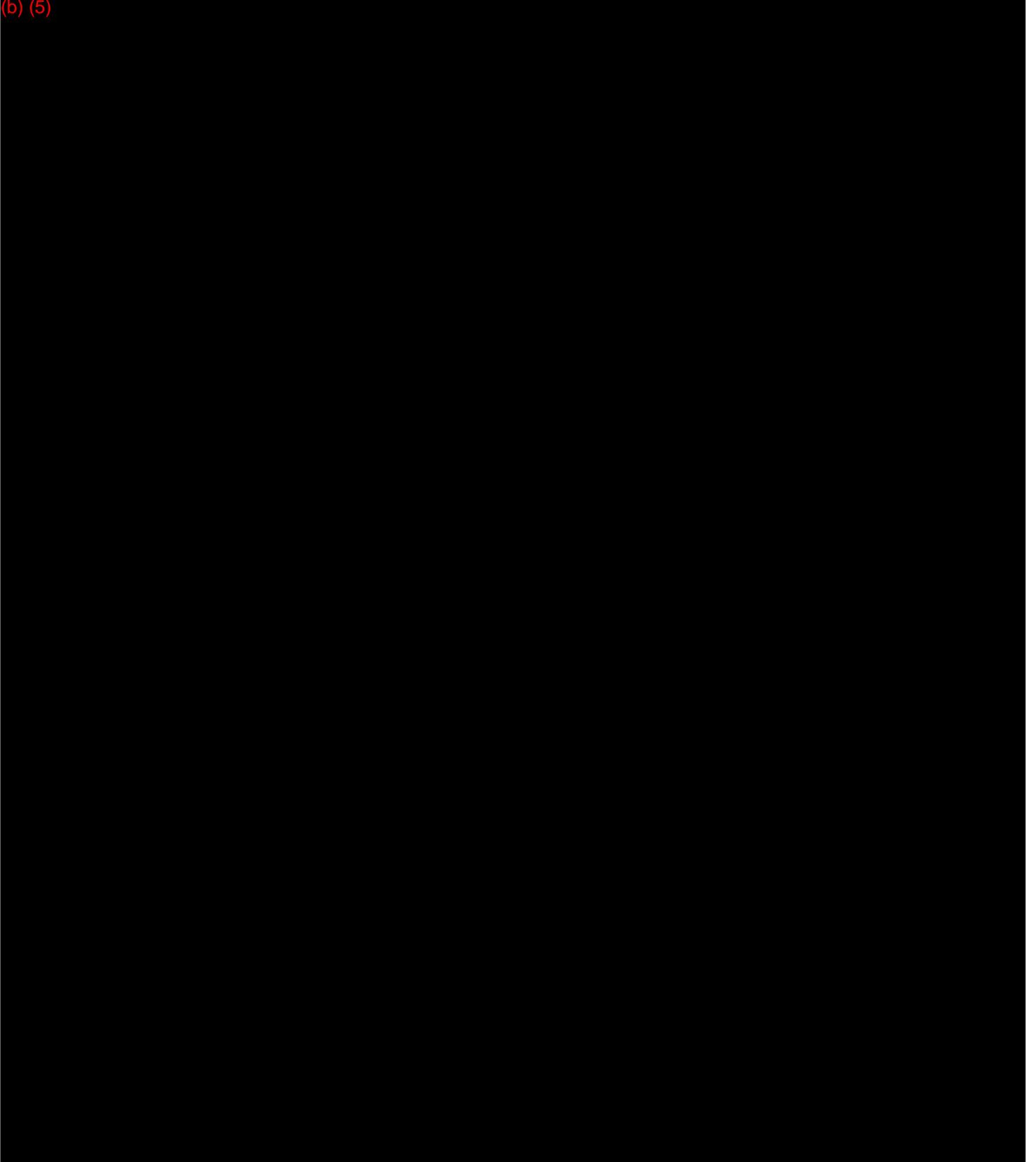
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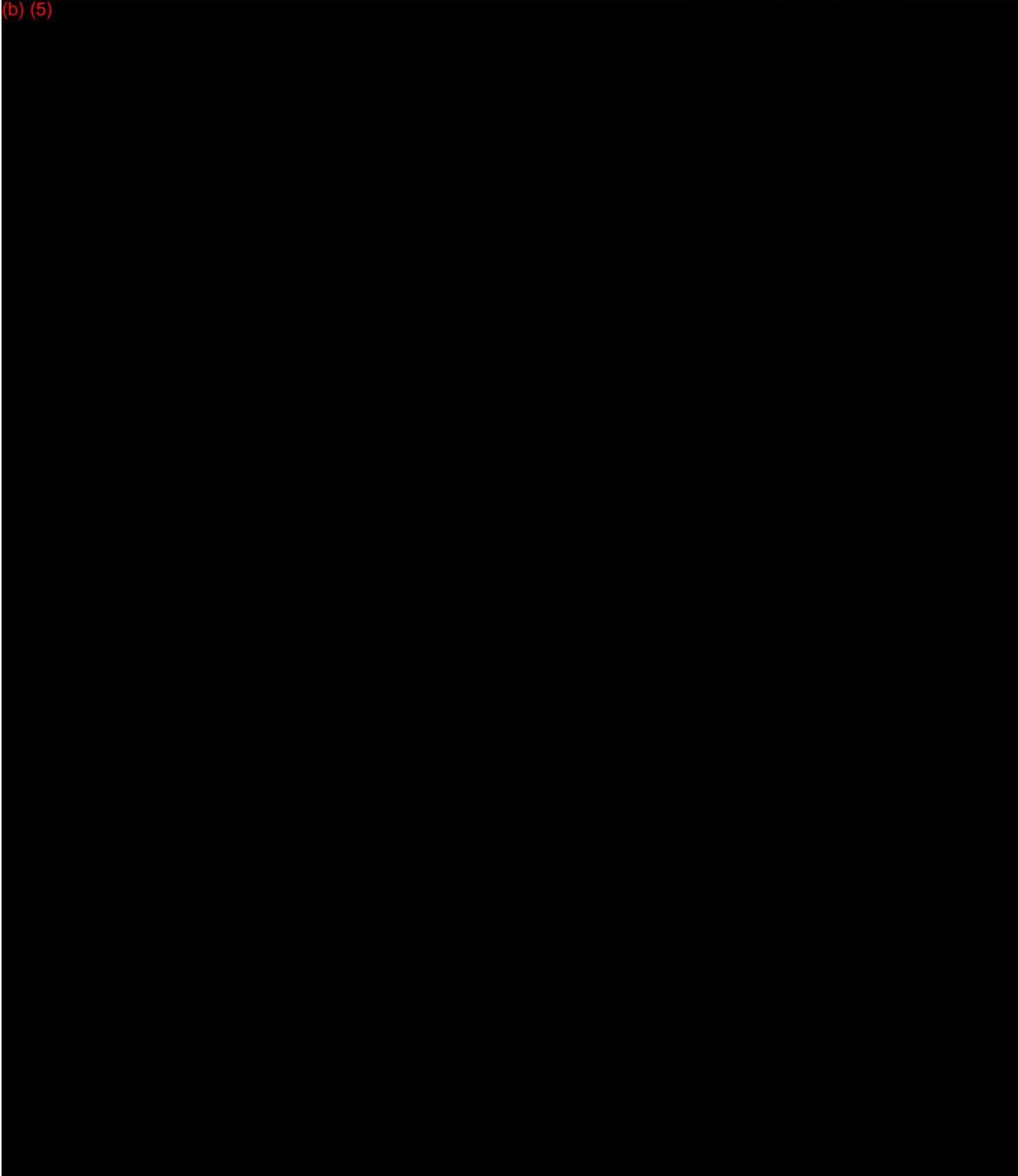
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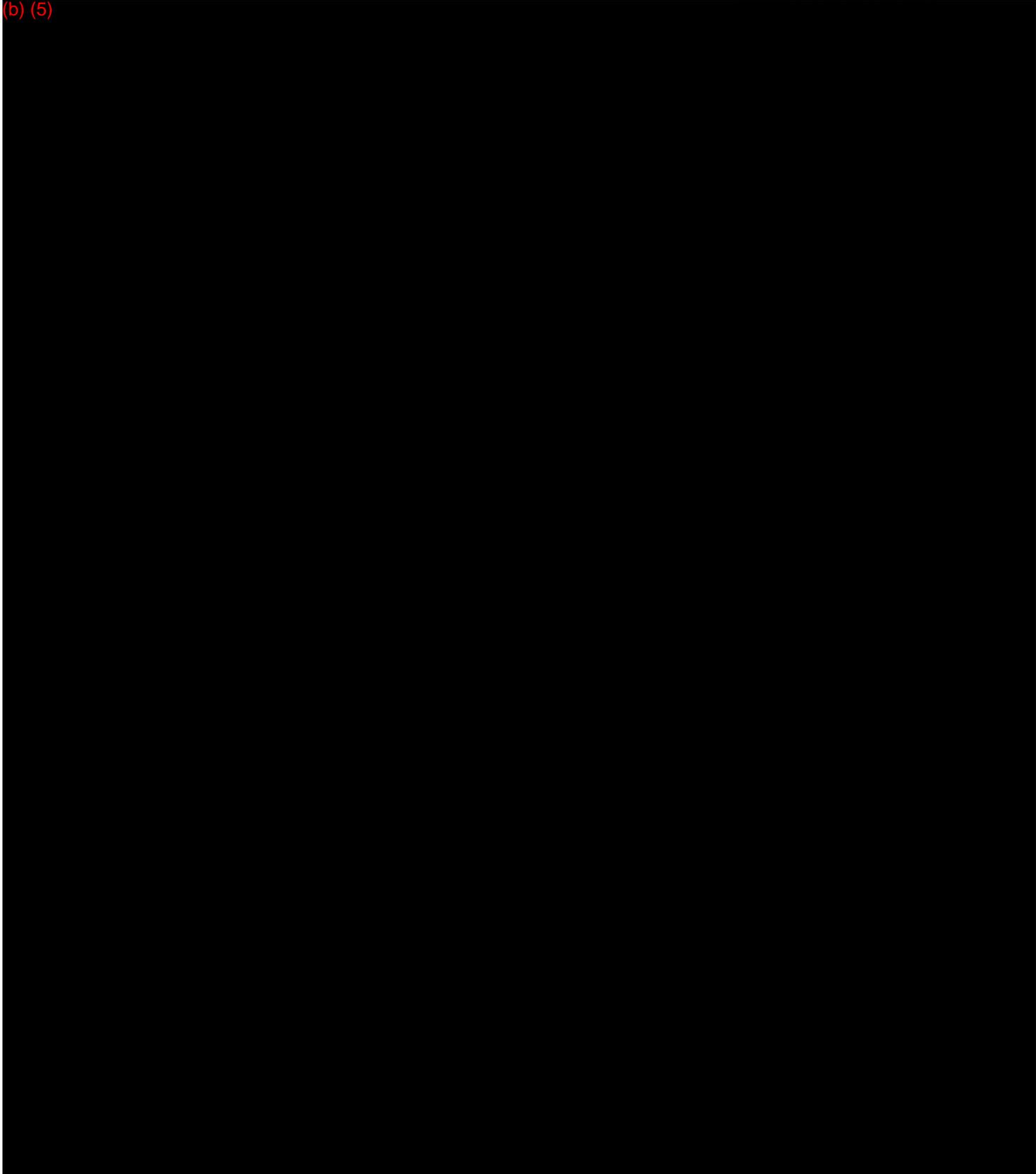
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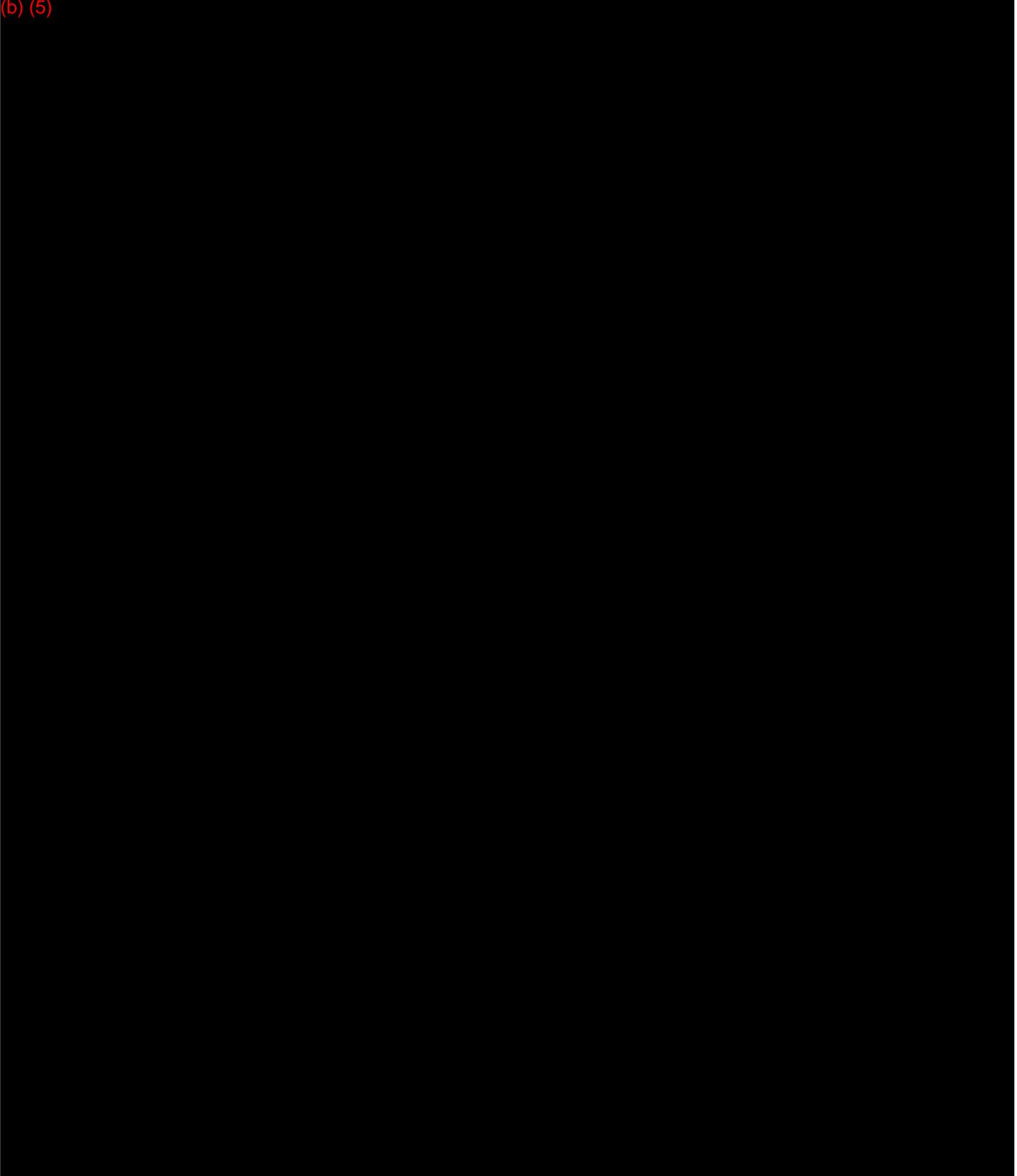
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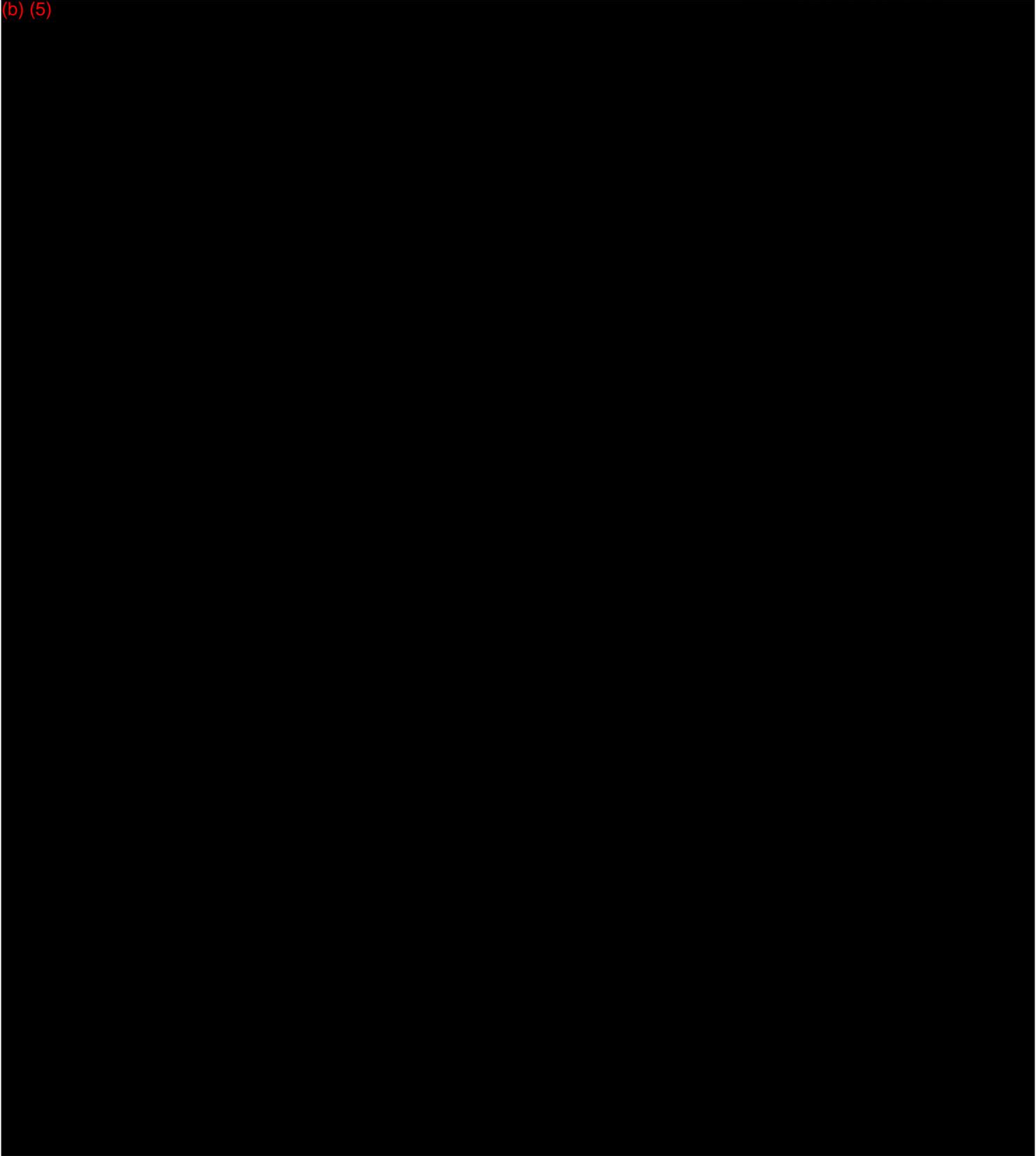


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MEMO TO FILE

FROM: Robert Califf, M.D., Commissioner of Food and Drugs

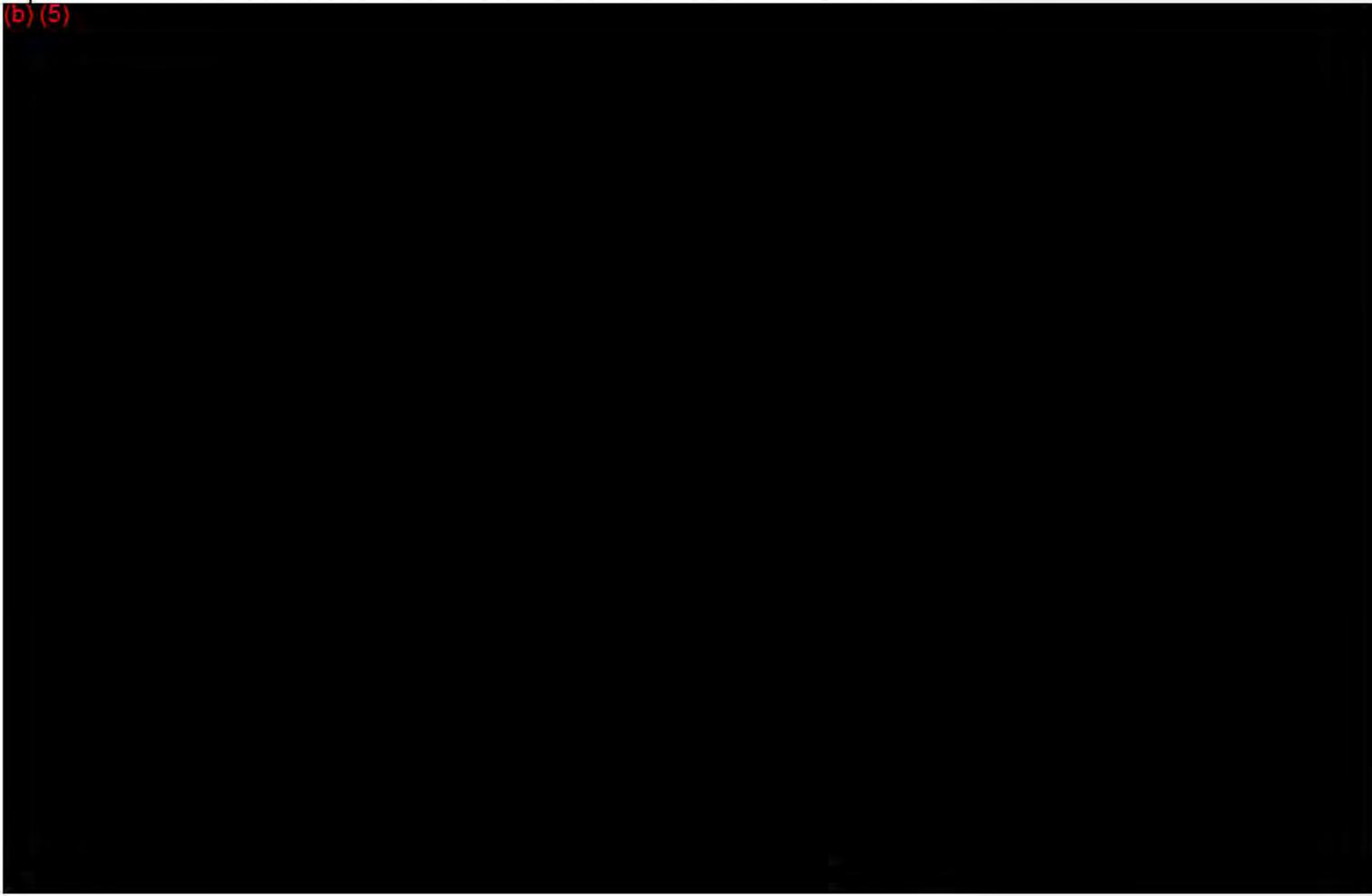
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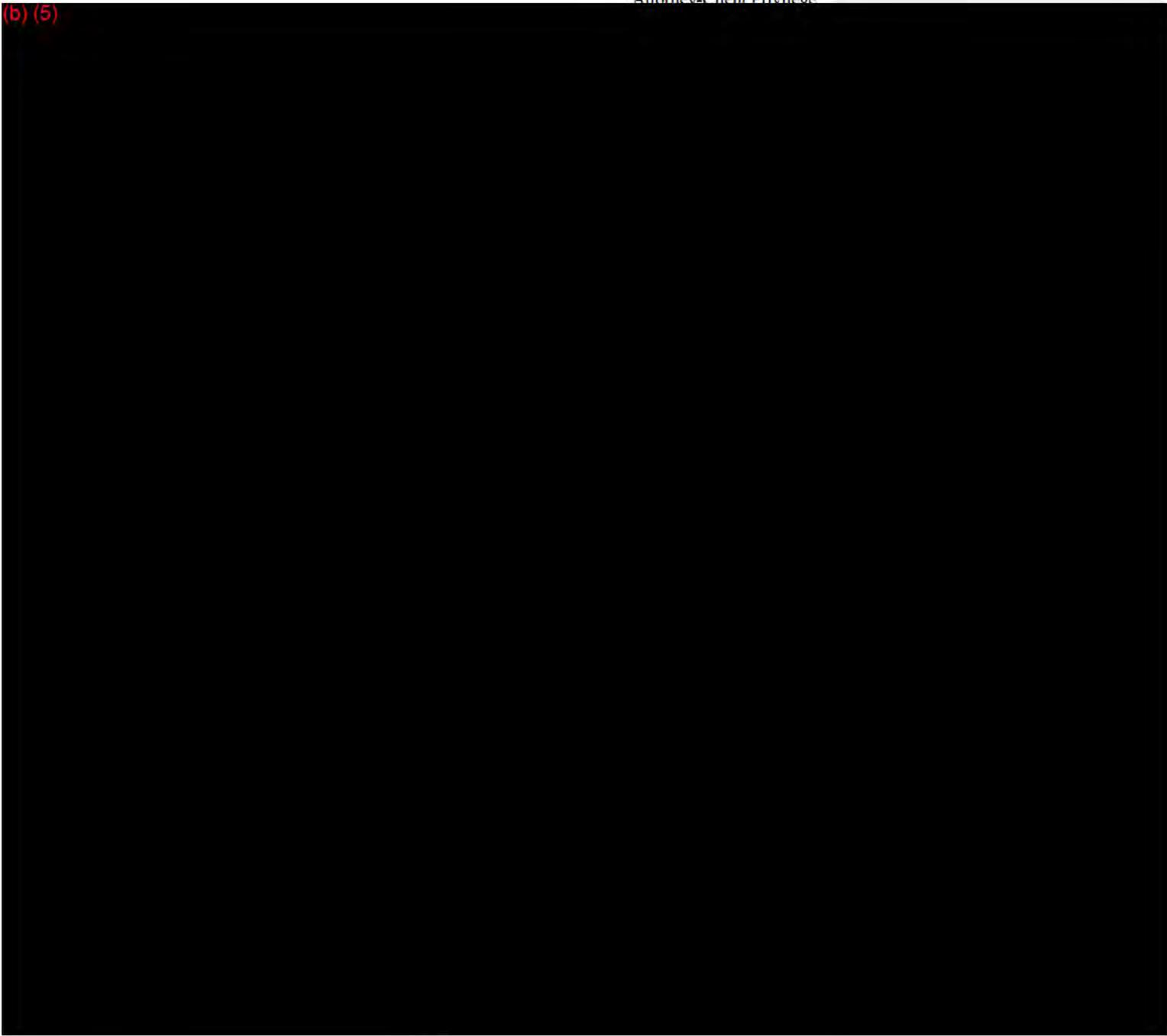
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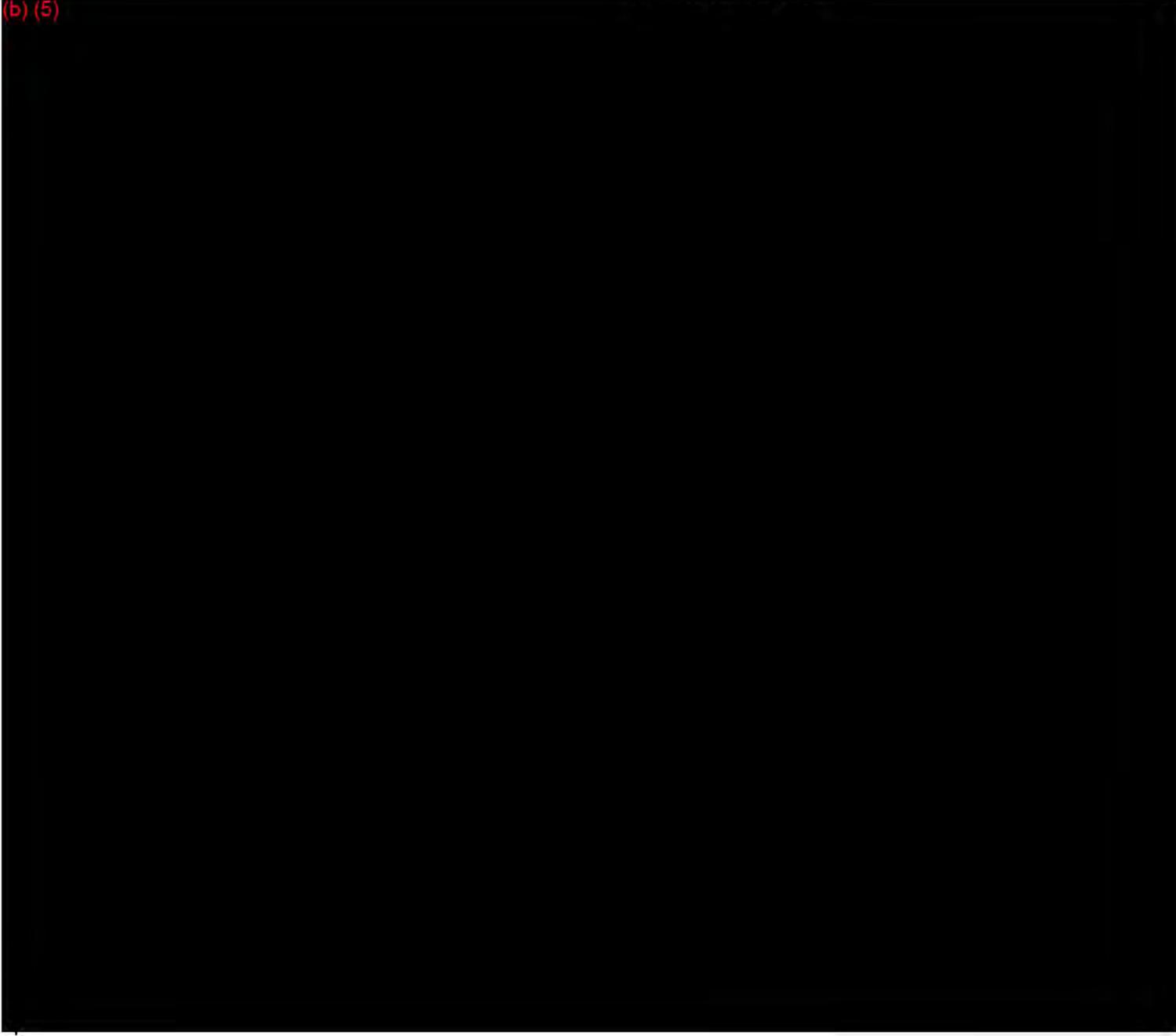


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Deliberative Process Privilege
Attorney-Client Privilege

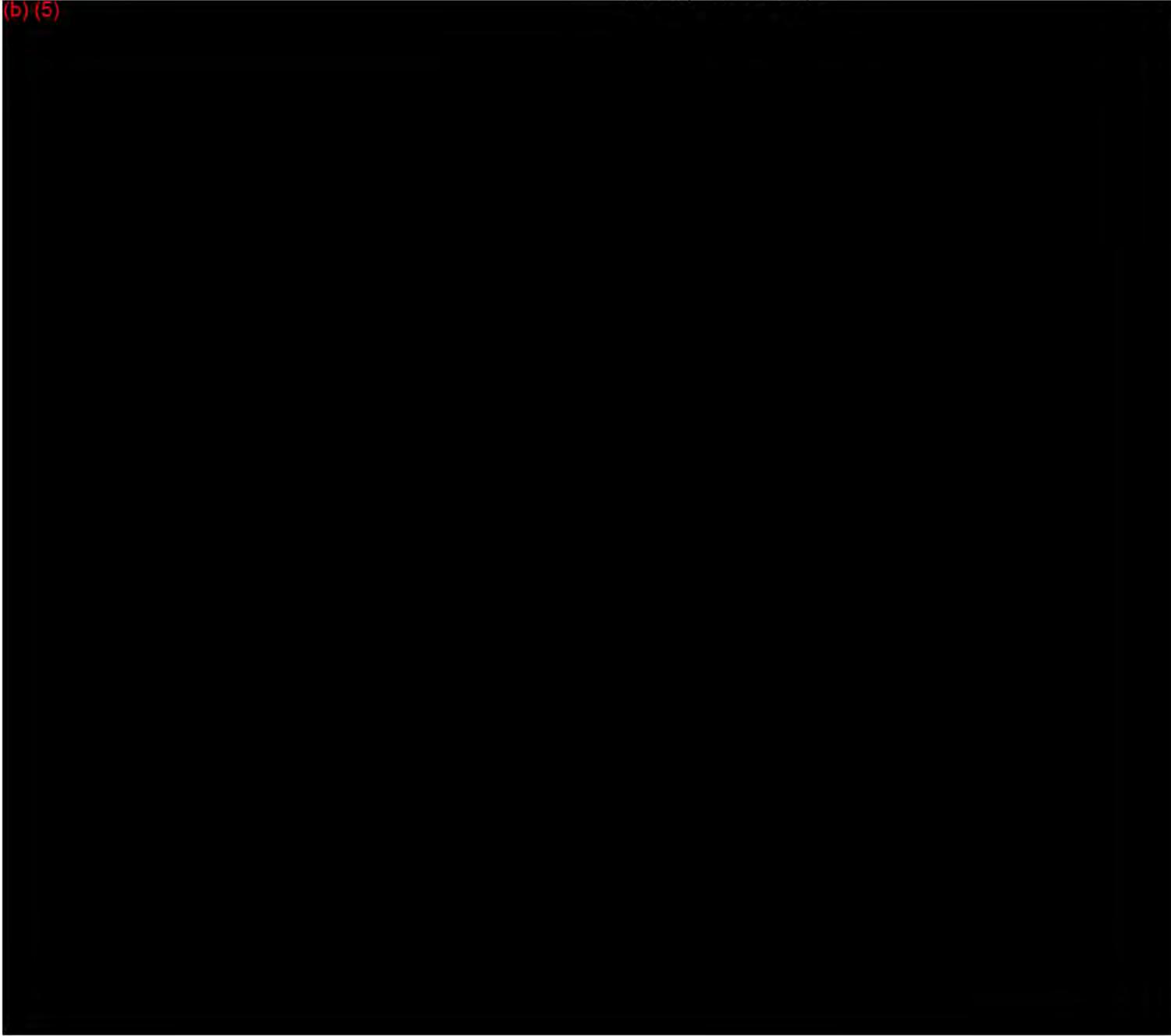
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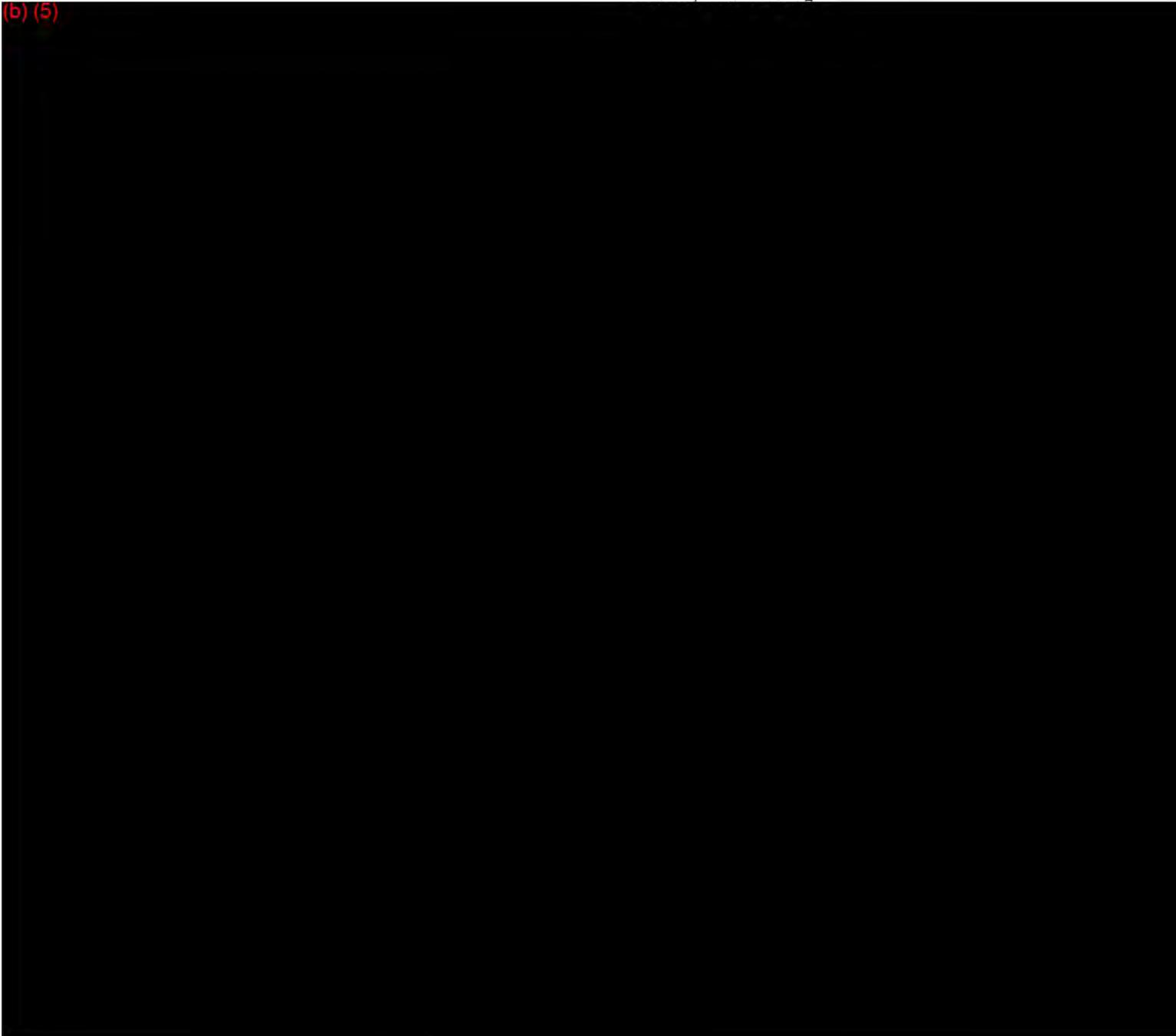
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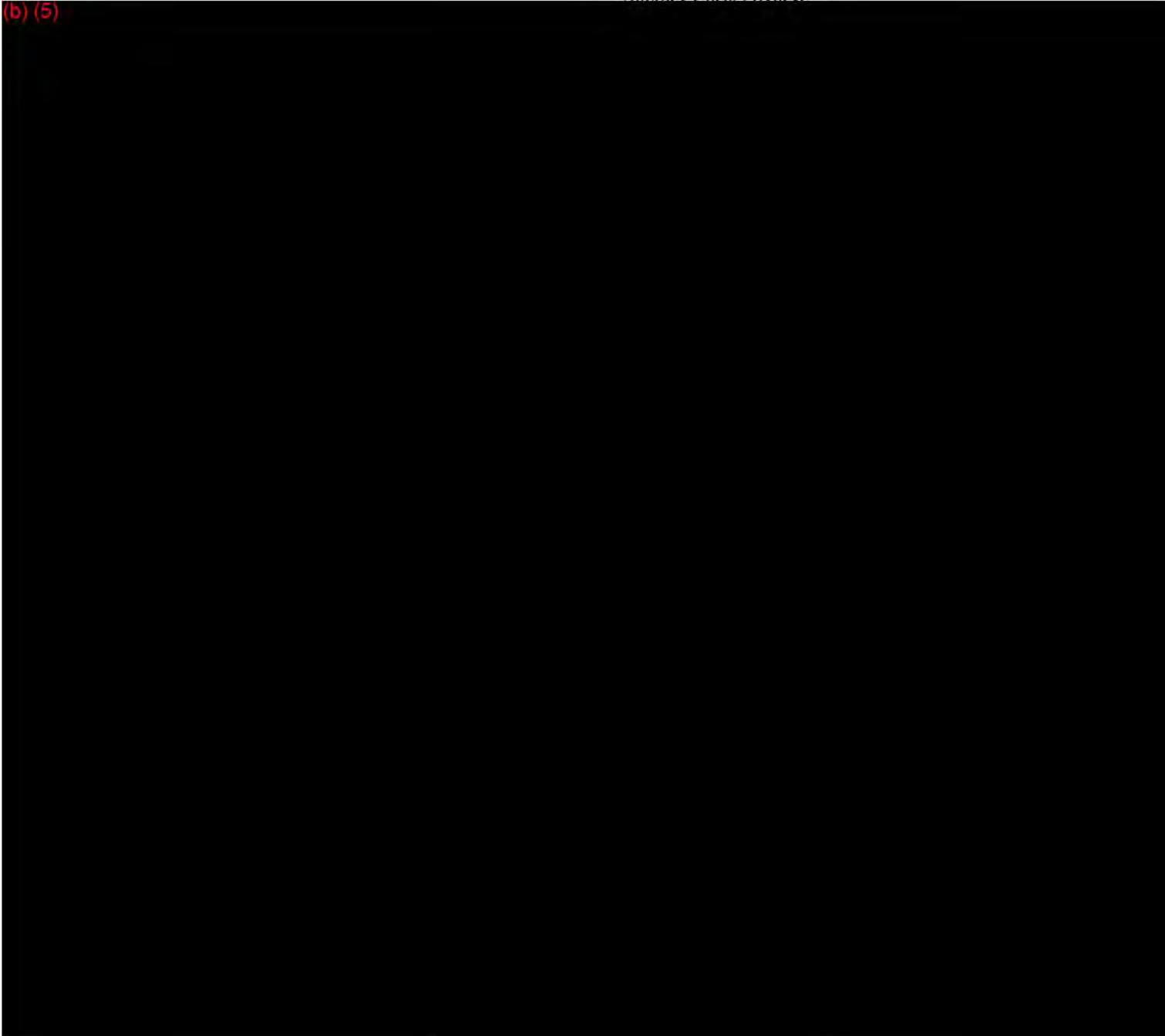
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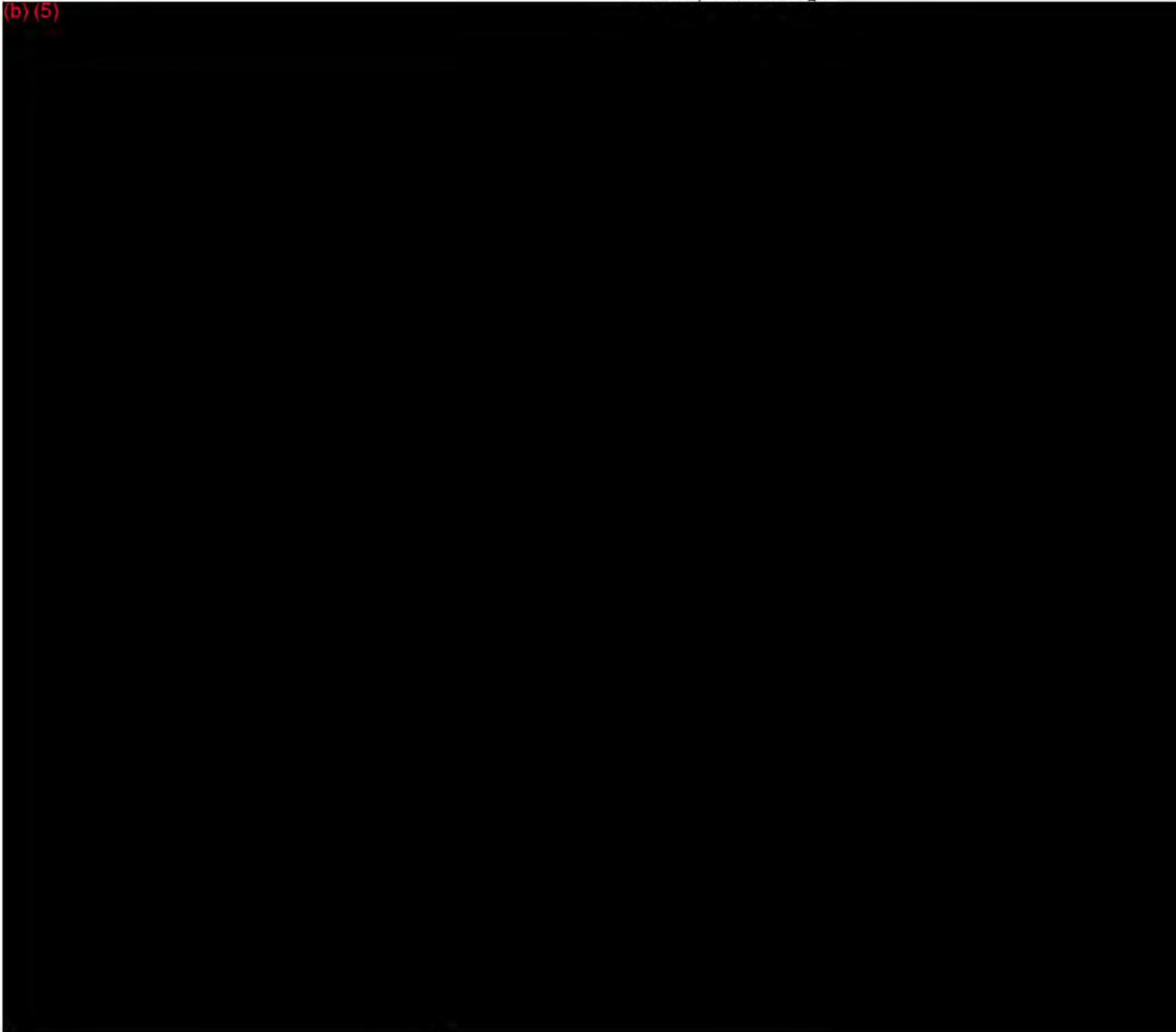
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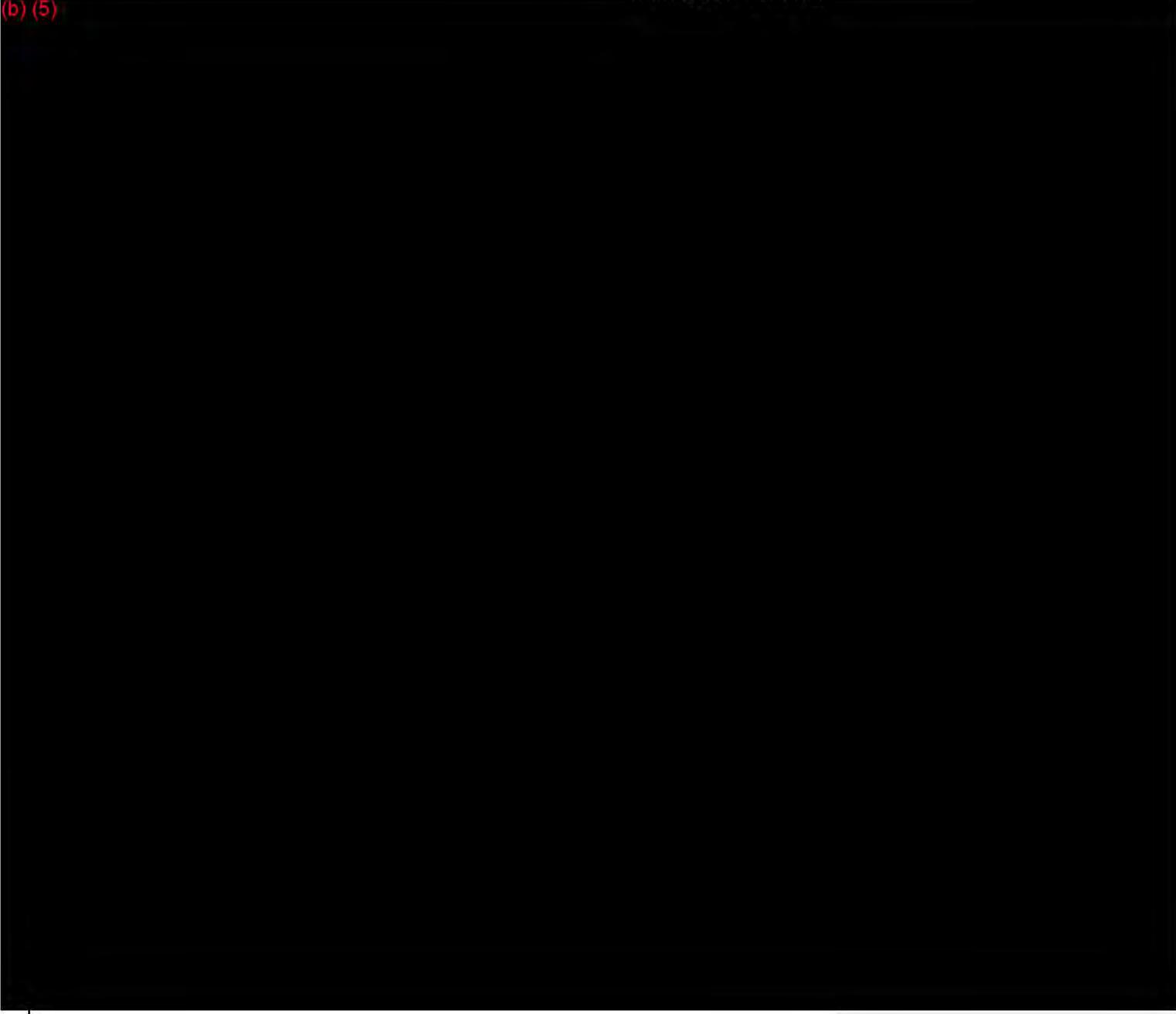
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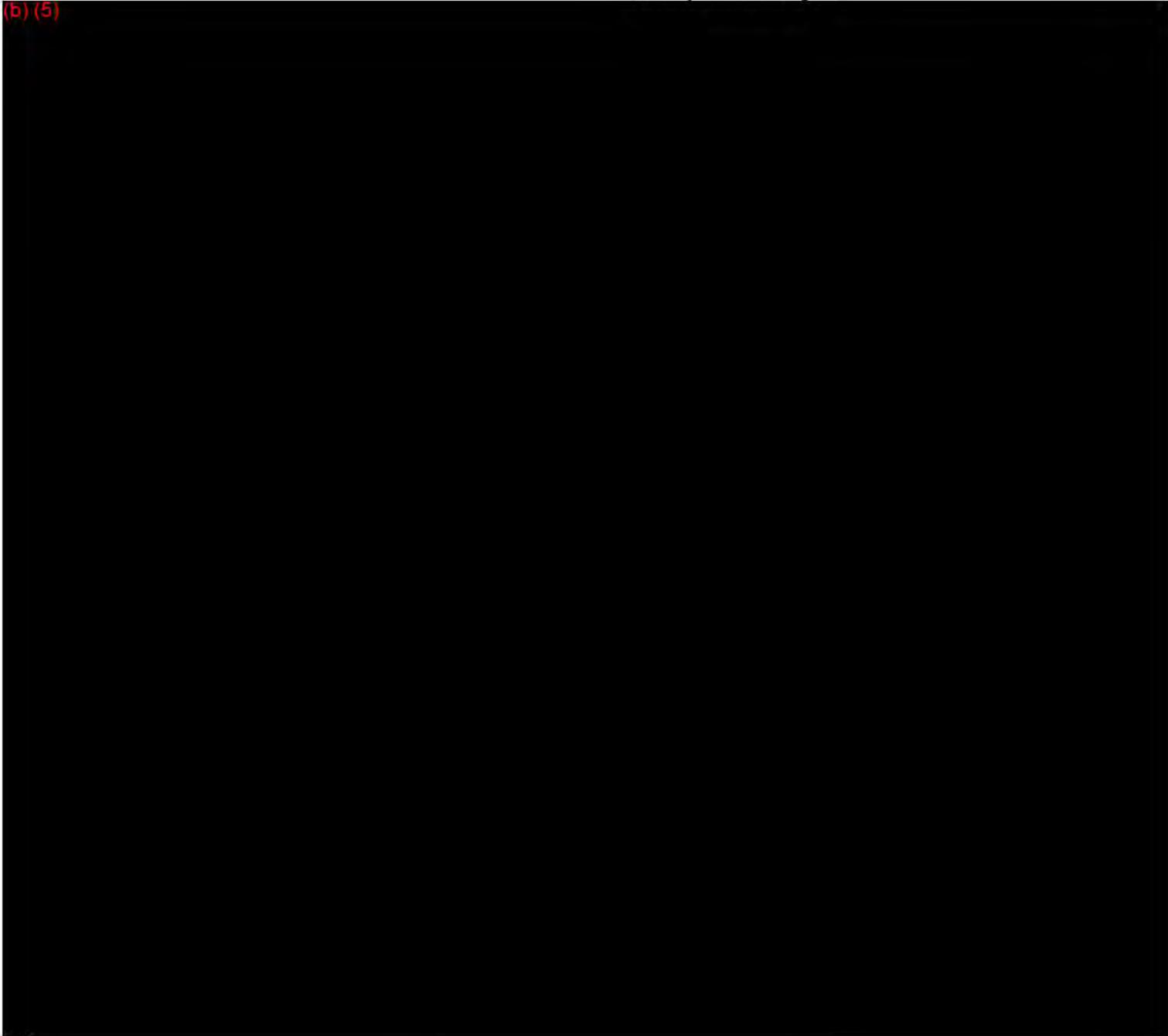
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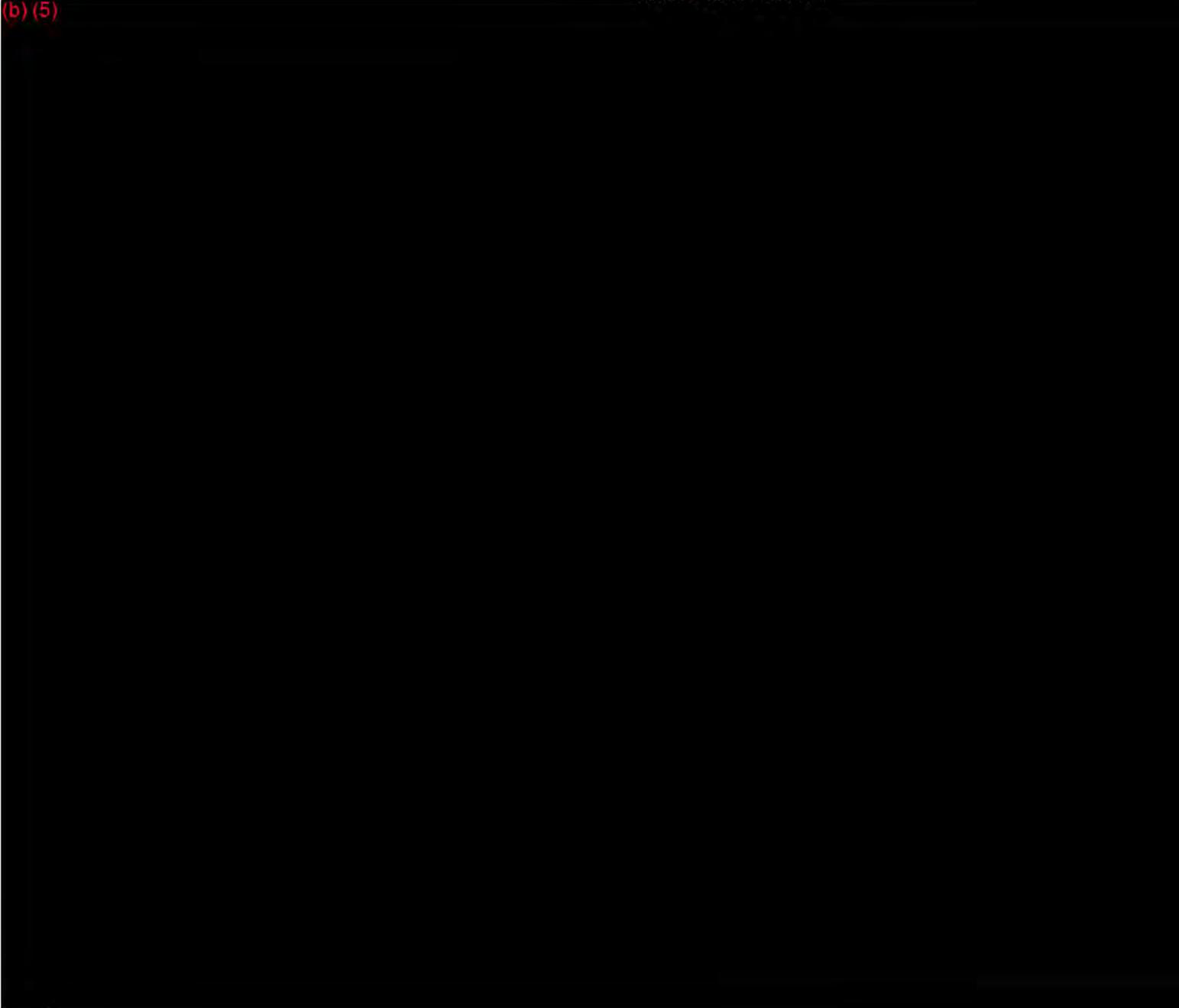
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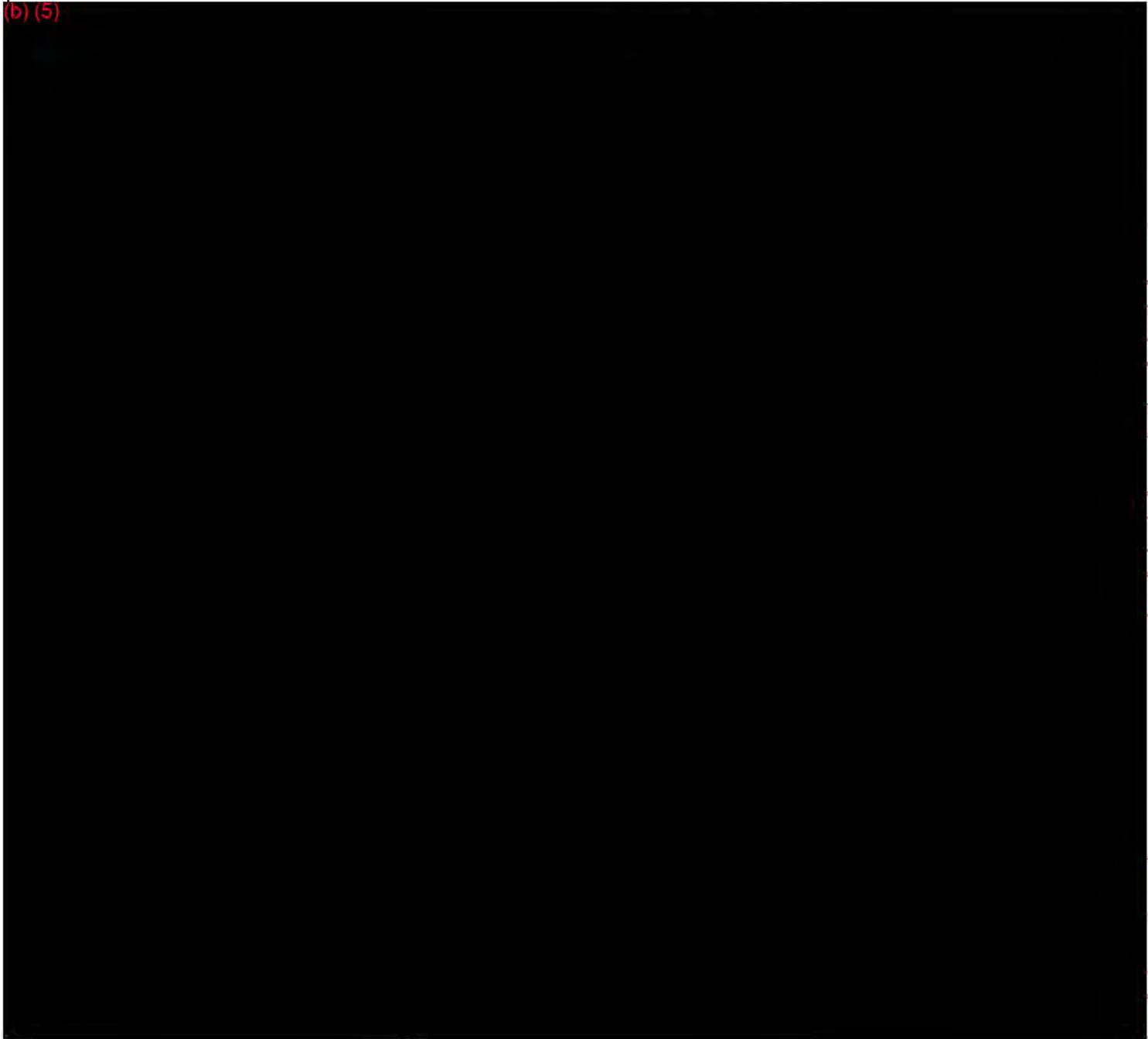


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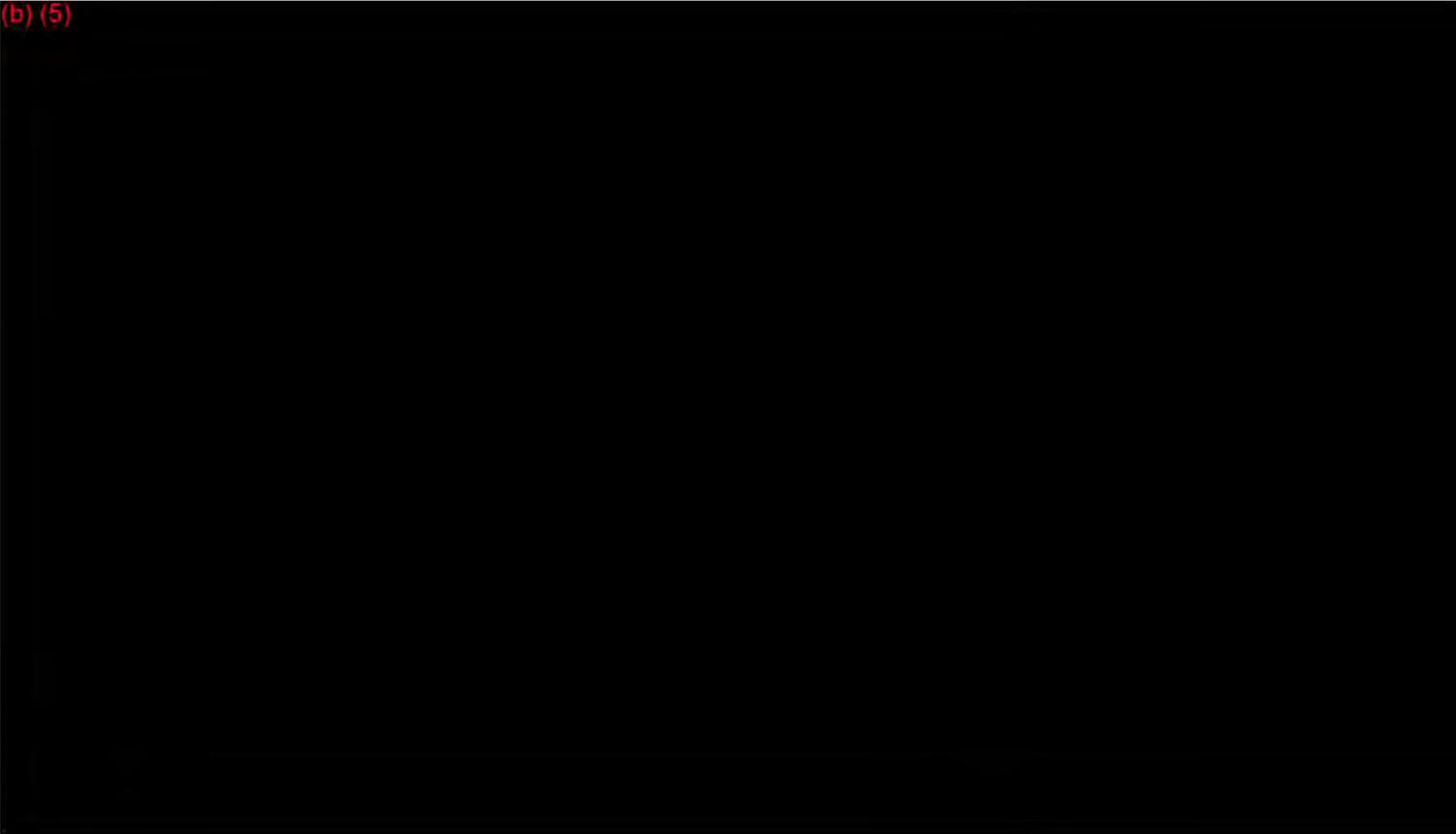


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Attorney-Client Privilege

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From: [Chasan-Sloan, Deborah \(FDA\)](#)
To: [Califf, Robert](#); [Sherman, Rachel](#)
Cc: [McCall, Jonathan *](#)
Subject: RE: Slight change of plans
Date: Tuesday, August 23, 2016 12:31:08 PM
Attachments: [Eteplirsen_combined-comments_8-18-2016_reorganized_and_adopts_someRSOCCRCcomments_SEMI_CLEANrscm_rmcrs+OCCv3\(occ edits\).doc](#)

I added a few comments (highlighted in green) based on the points Rachel raised regarding the role you are playing in this decision. For example, (b) (5)

(b) (5)

I also added some edits/citations in redline at the bottom of page 2 in response to Rachel's question to me.

I'll sit tight until there's a revised draft ready for further review.

Deborah

From: Califf, Robert
Sent: Tuesday, August 23, 2016 6:29 AM
To: Sherman, Rachel; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: RE: Slight change of plans

Thanks for looking again. Let me get through the meetings with Janet and Ellis, and I'll take another look tonight.

rmc

From: Sherman, Rachel
Sent: Monday, August 22, 2016 8:42 PM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: Slight change of plans

Hi,

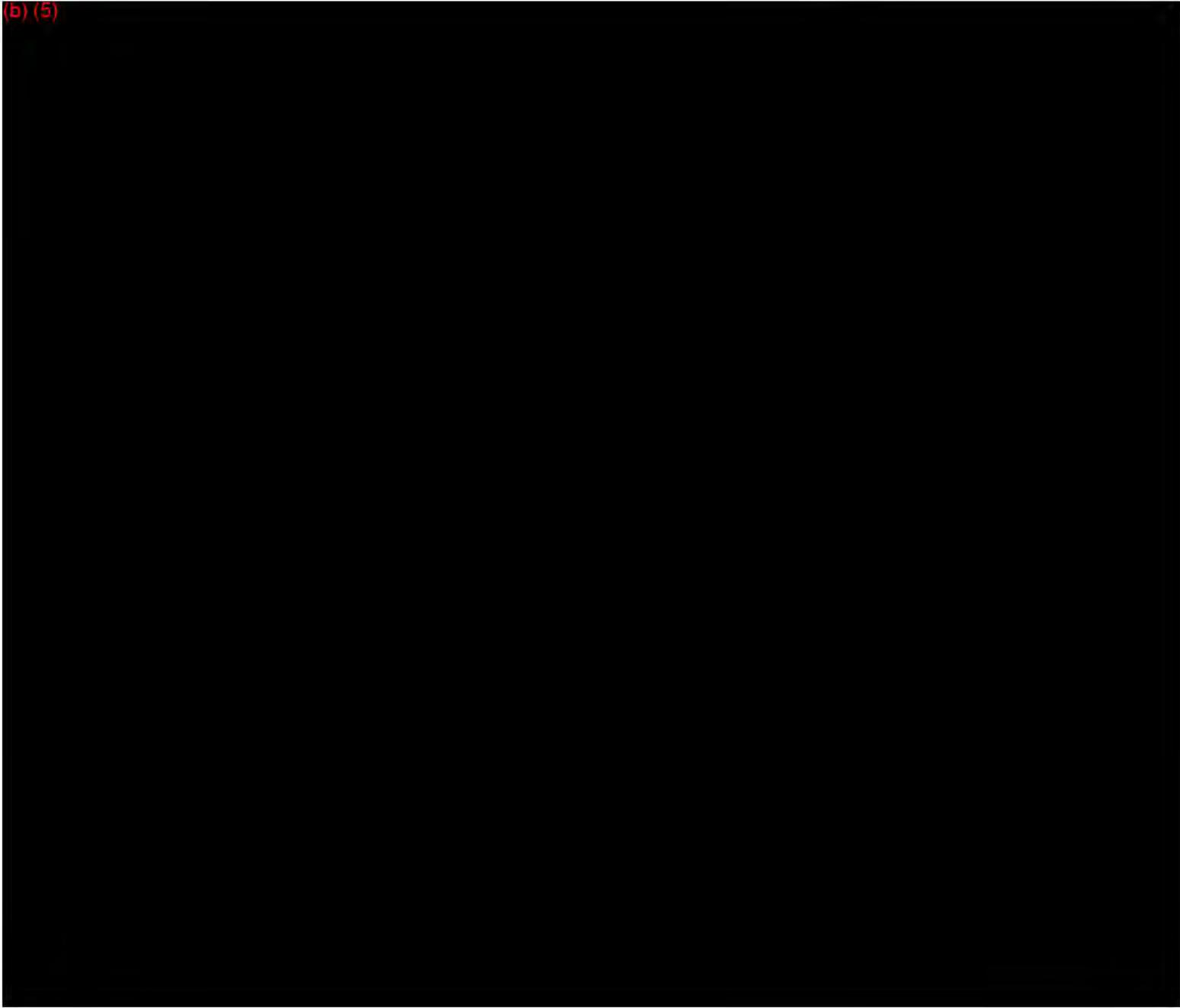
Based on a conversation with Rob this evening, I inserted a few more comments – trying to emphasize the uncertainty and that Rob's fundamental decision is that he is not going to overrule Janet (at least that's how I understand his position).

Rob – please let us know if you want Deborah to look or you want to look first.

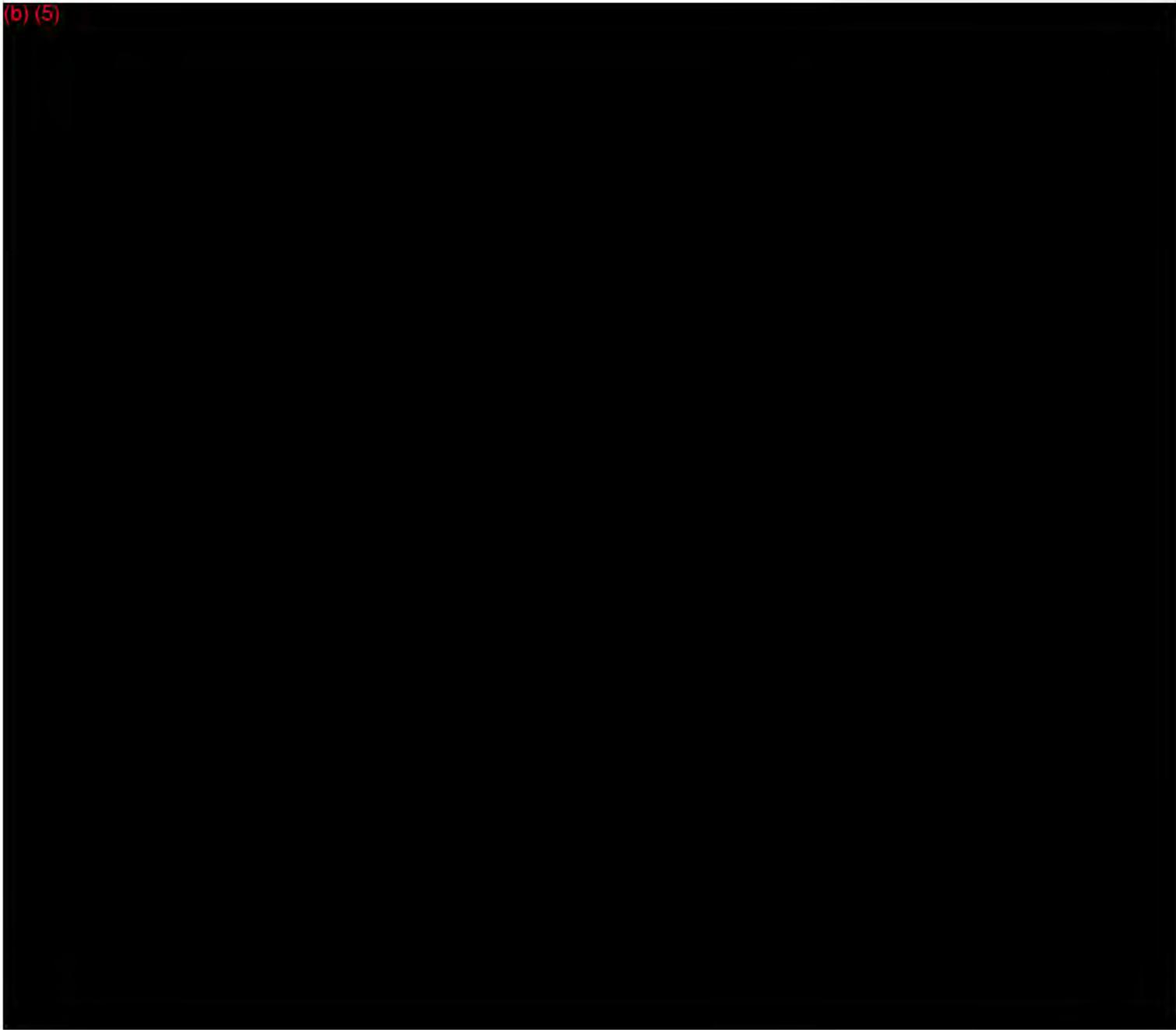
I think Jonathan may be able to help by consolidating your conclusions in a more prominent space. I have highlighted the two places that seem buried. The last is right at the end so it is more obvious.

Rachel

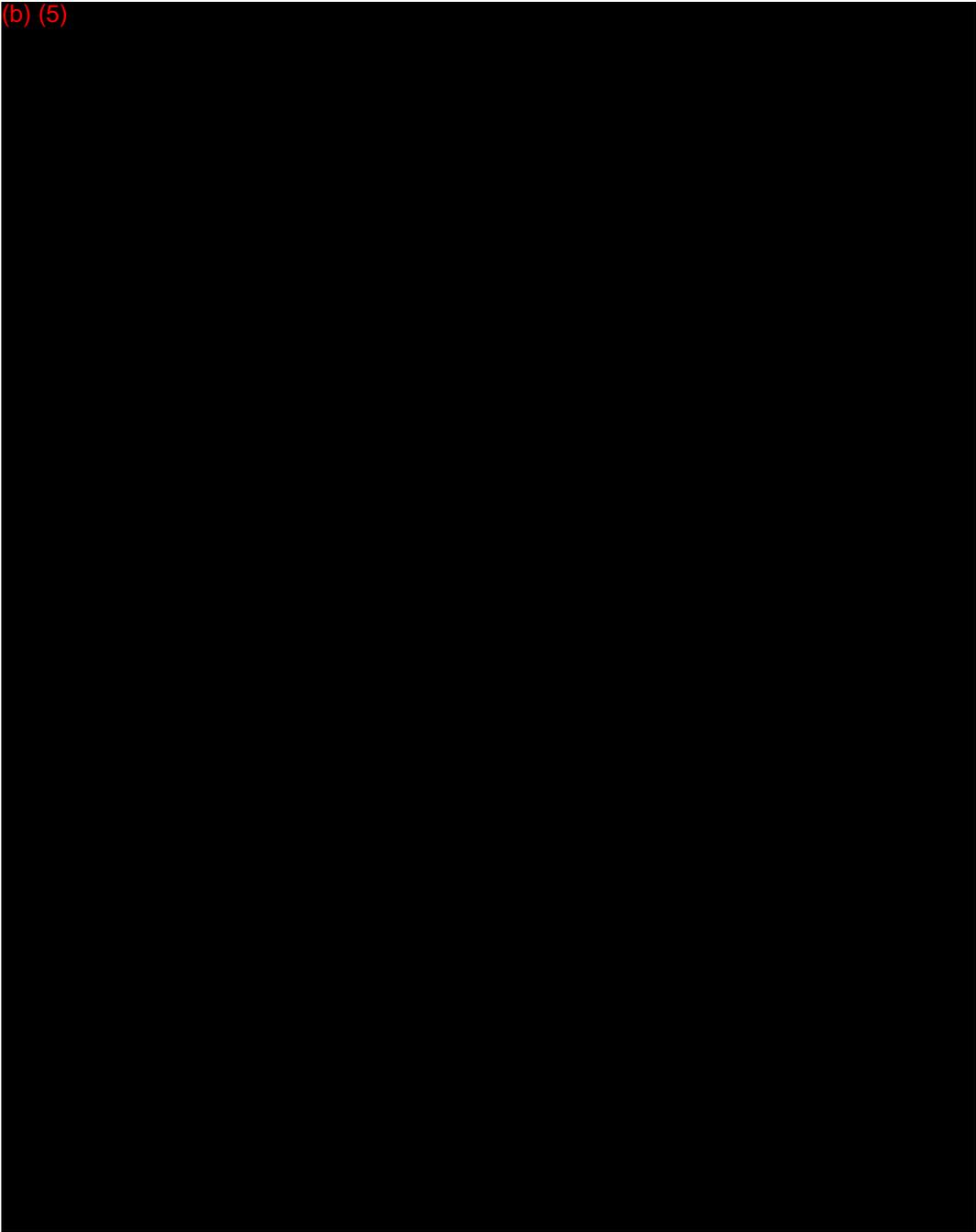
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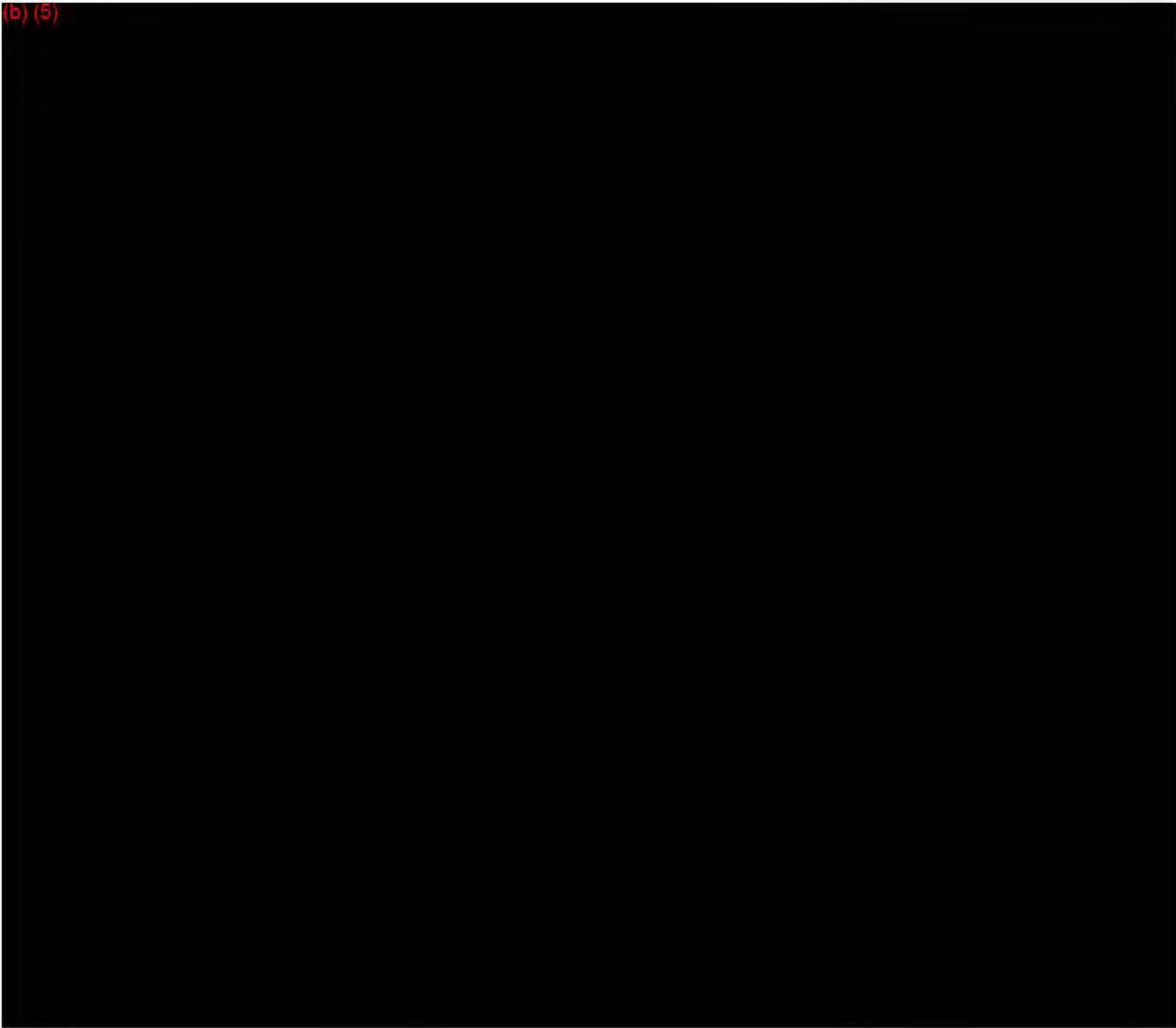
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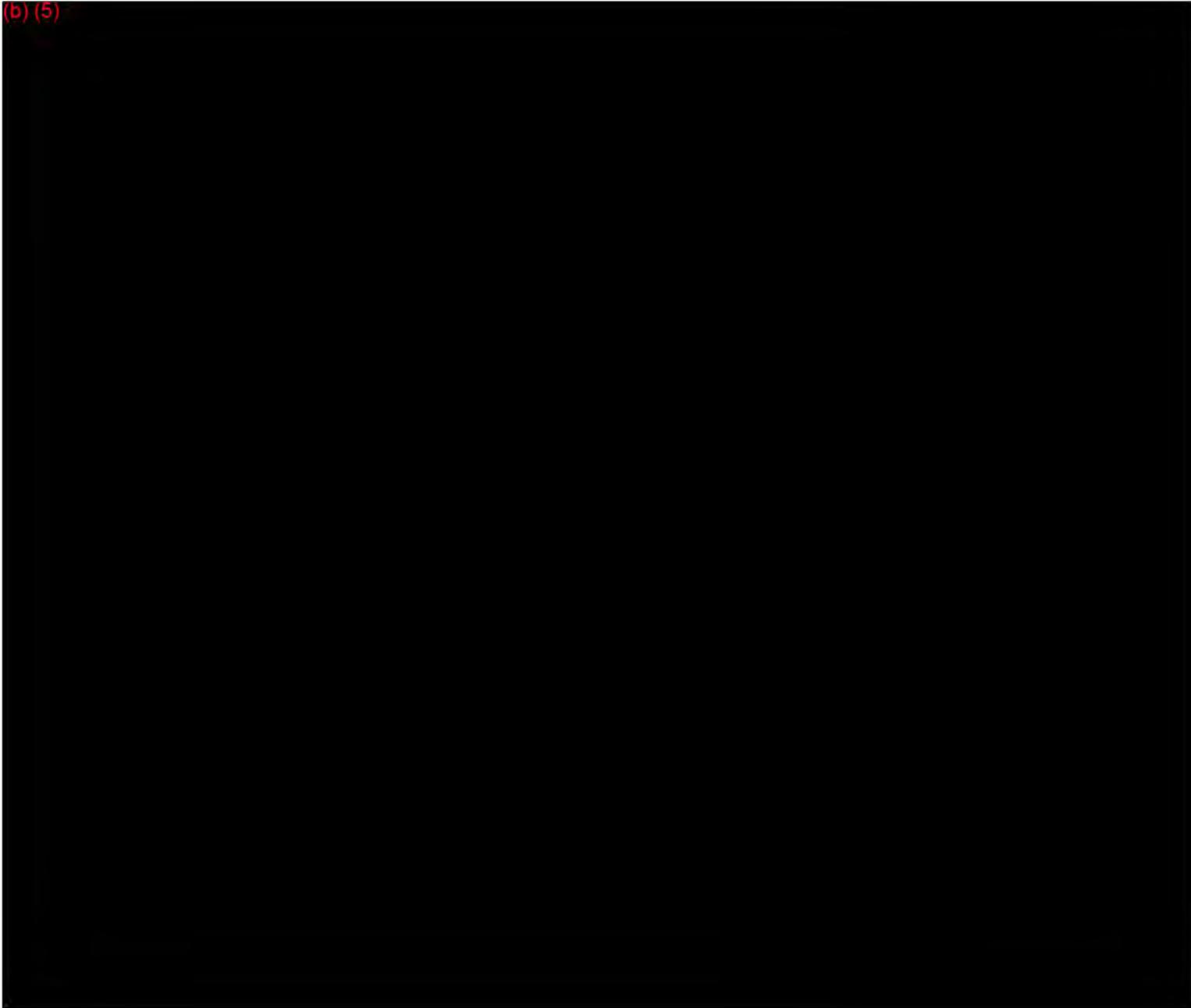
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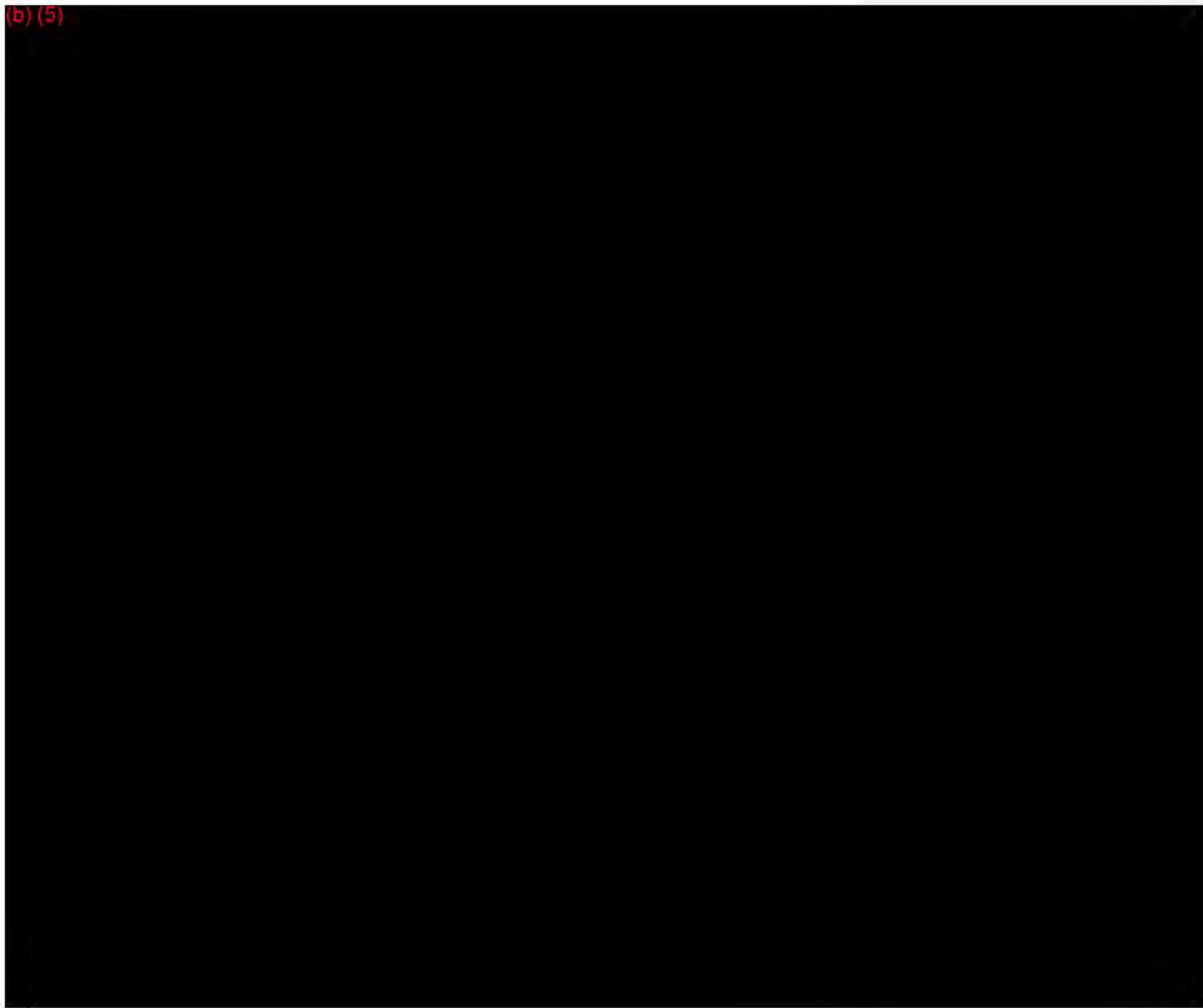
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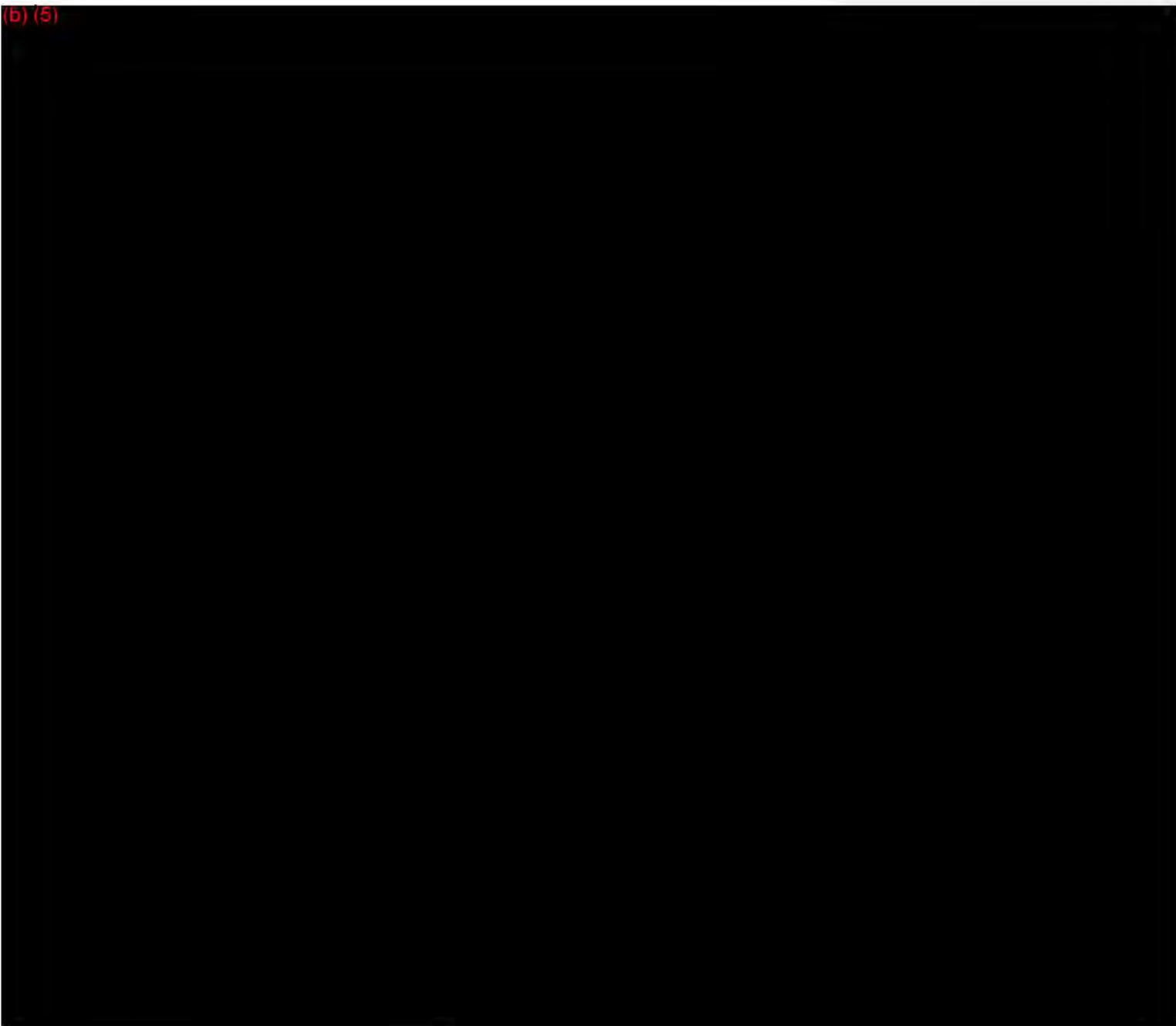
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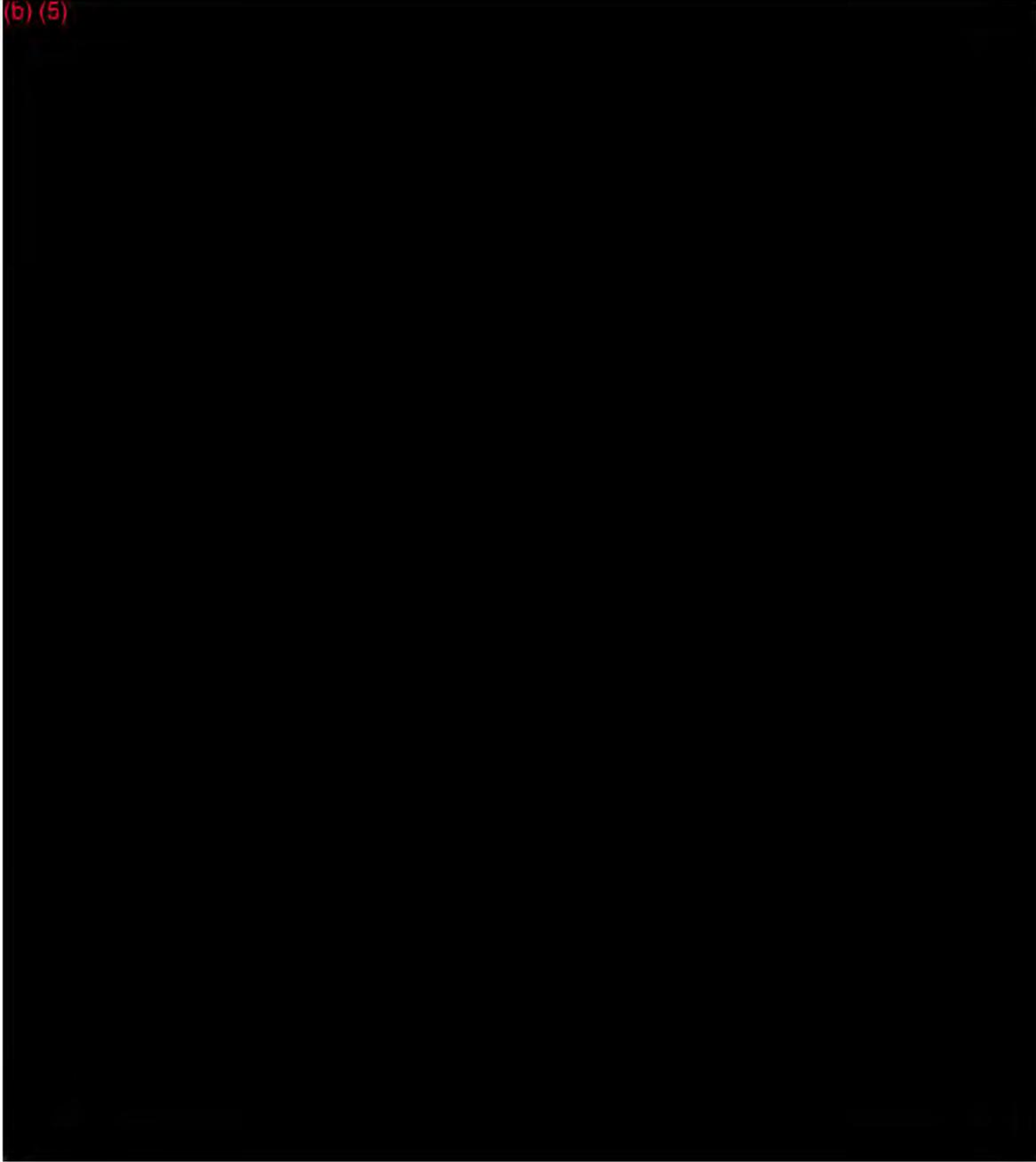
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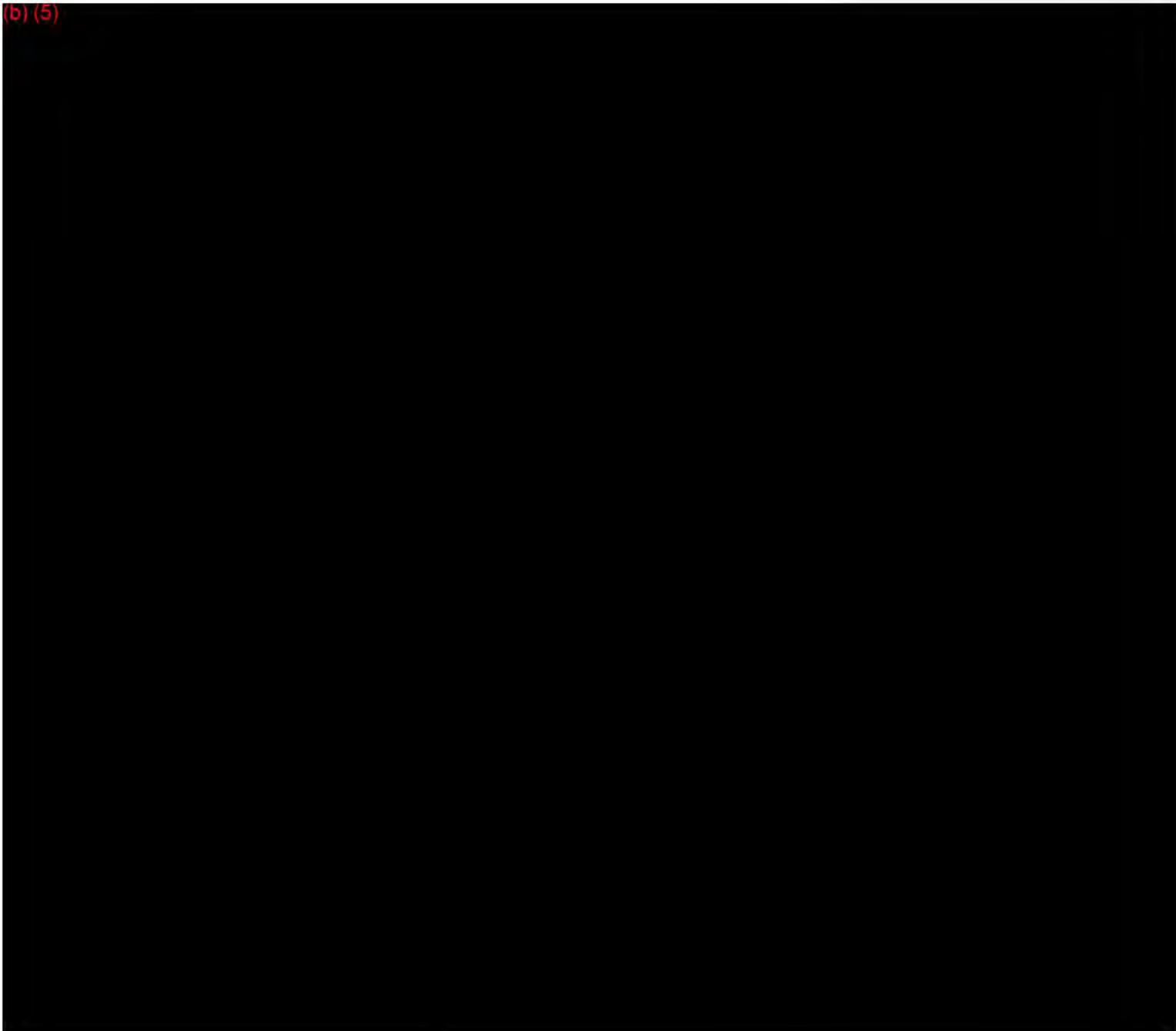
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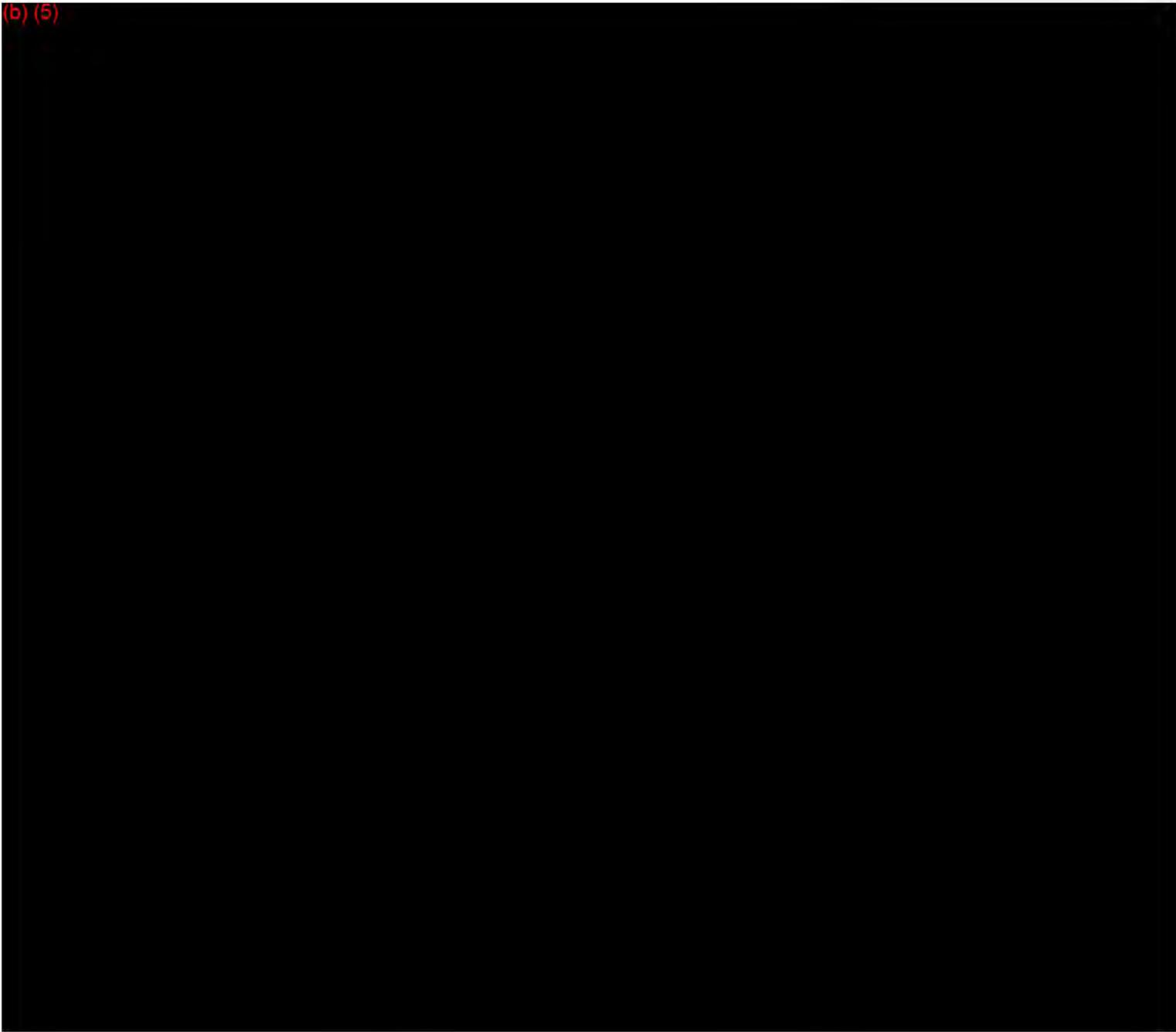
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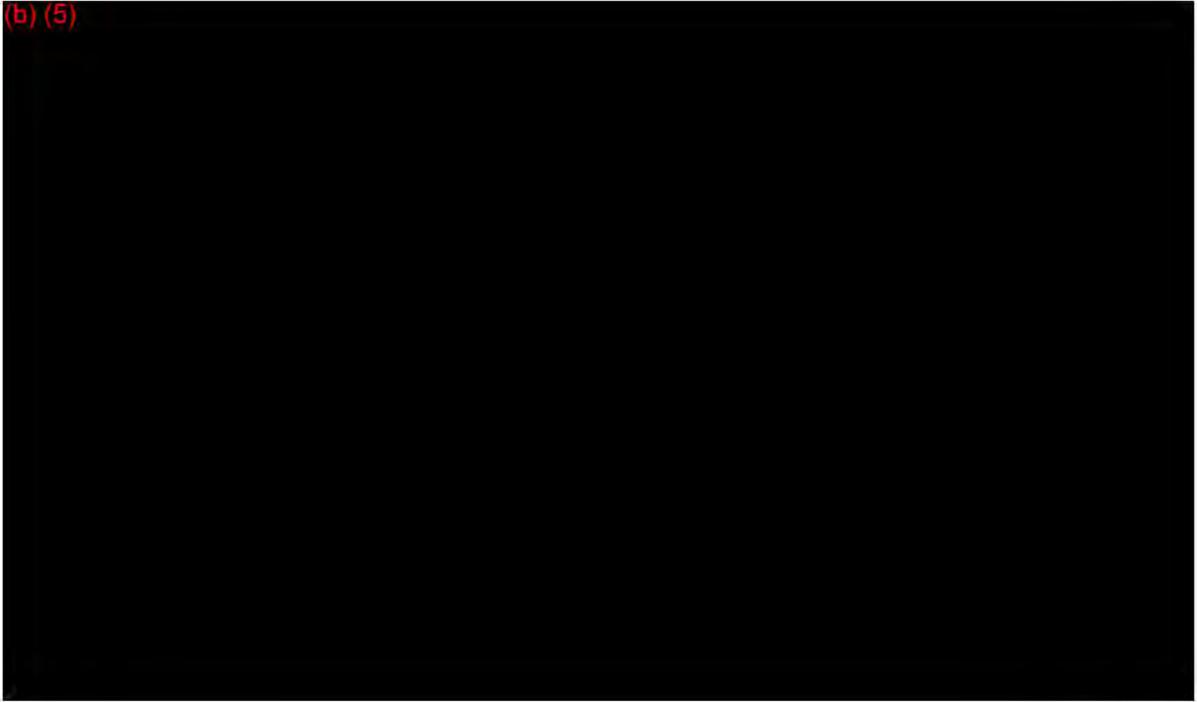
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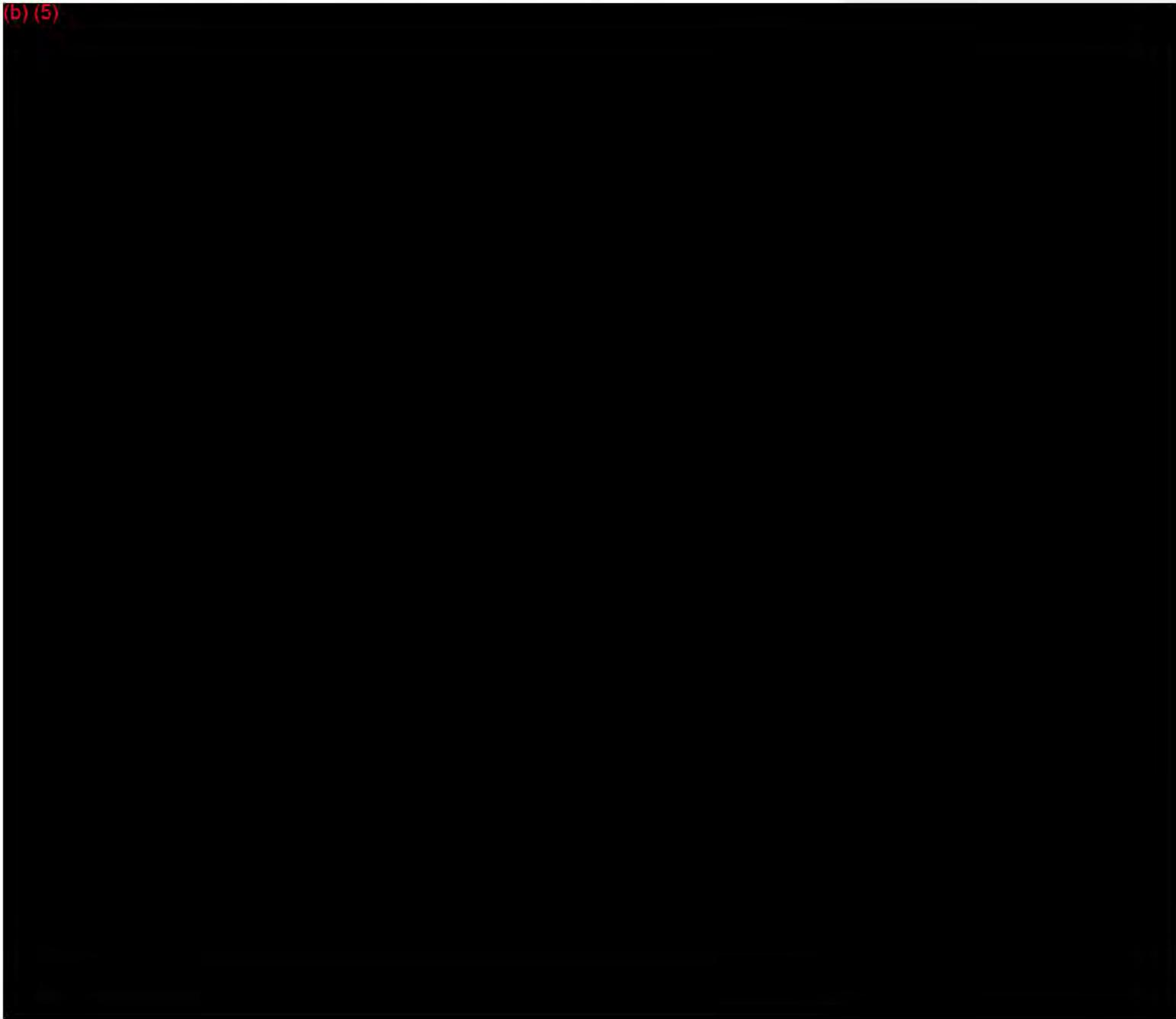
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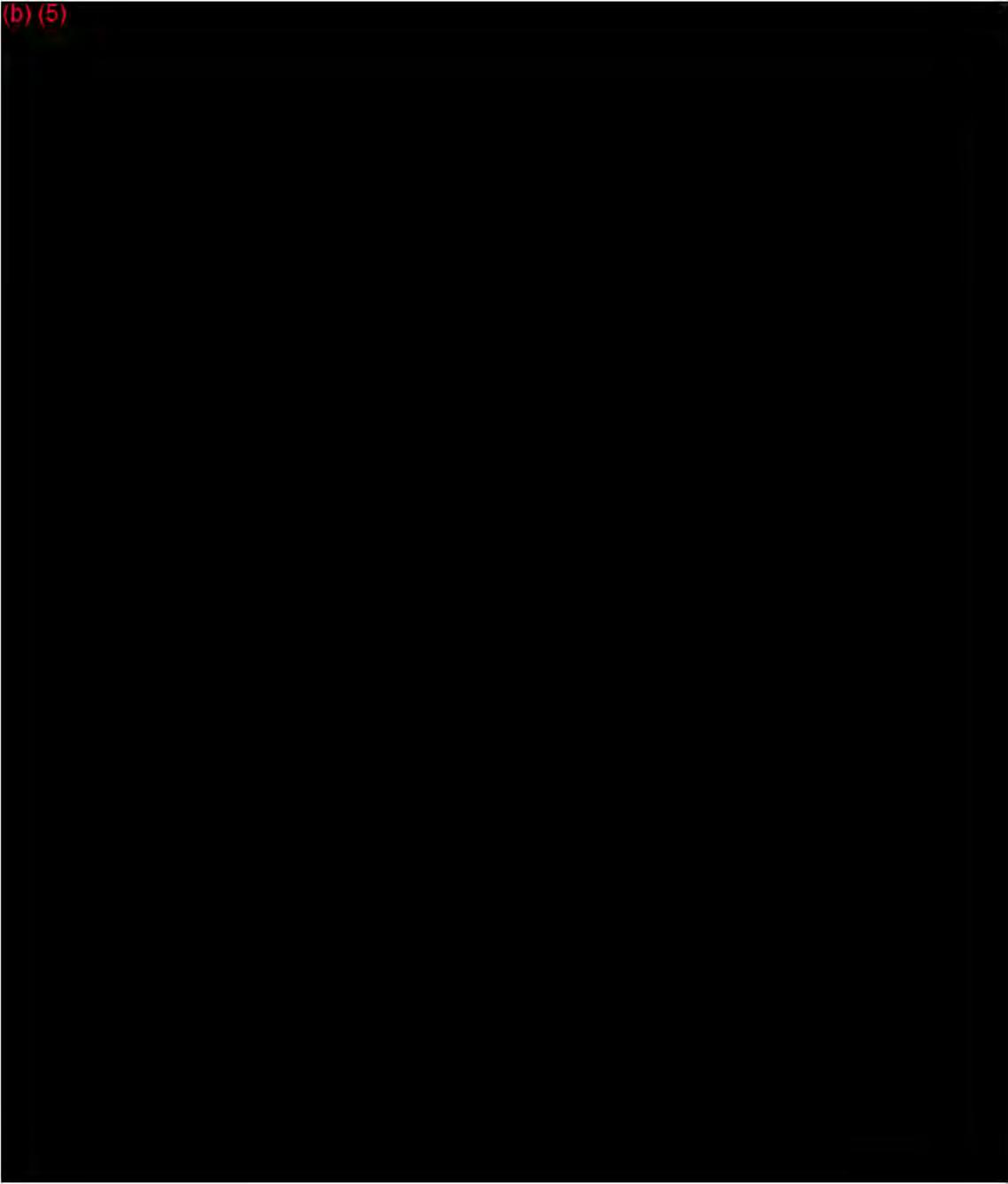
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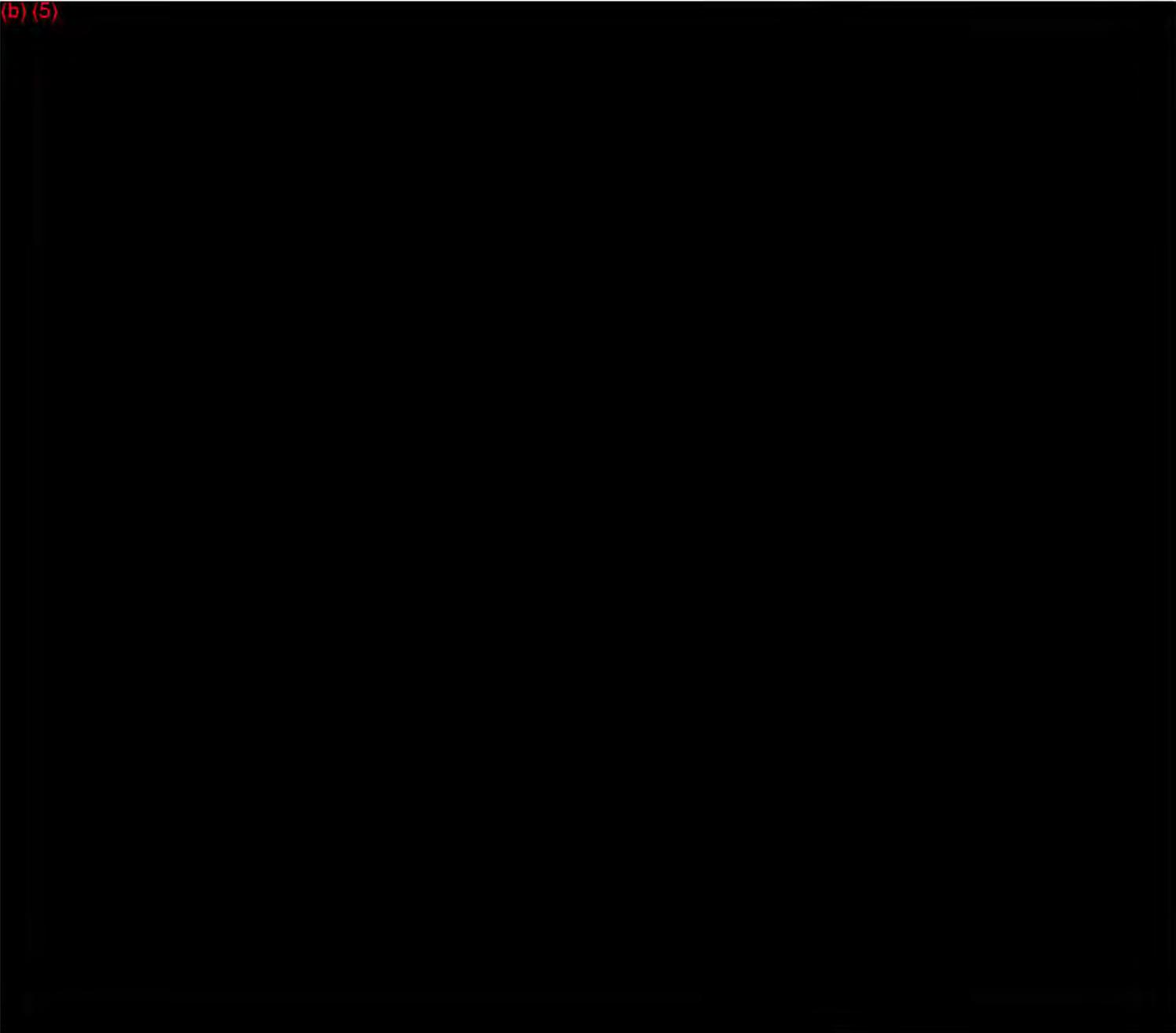
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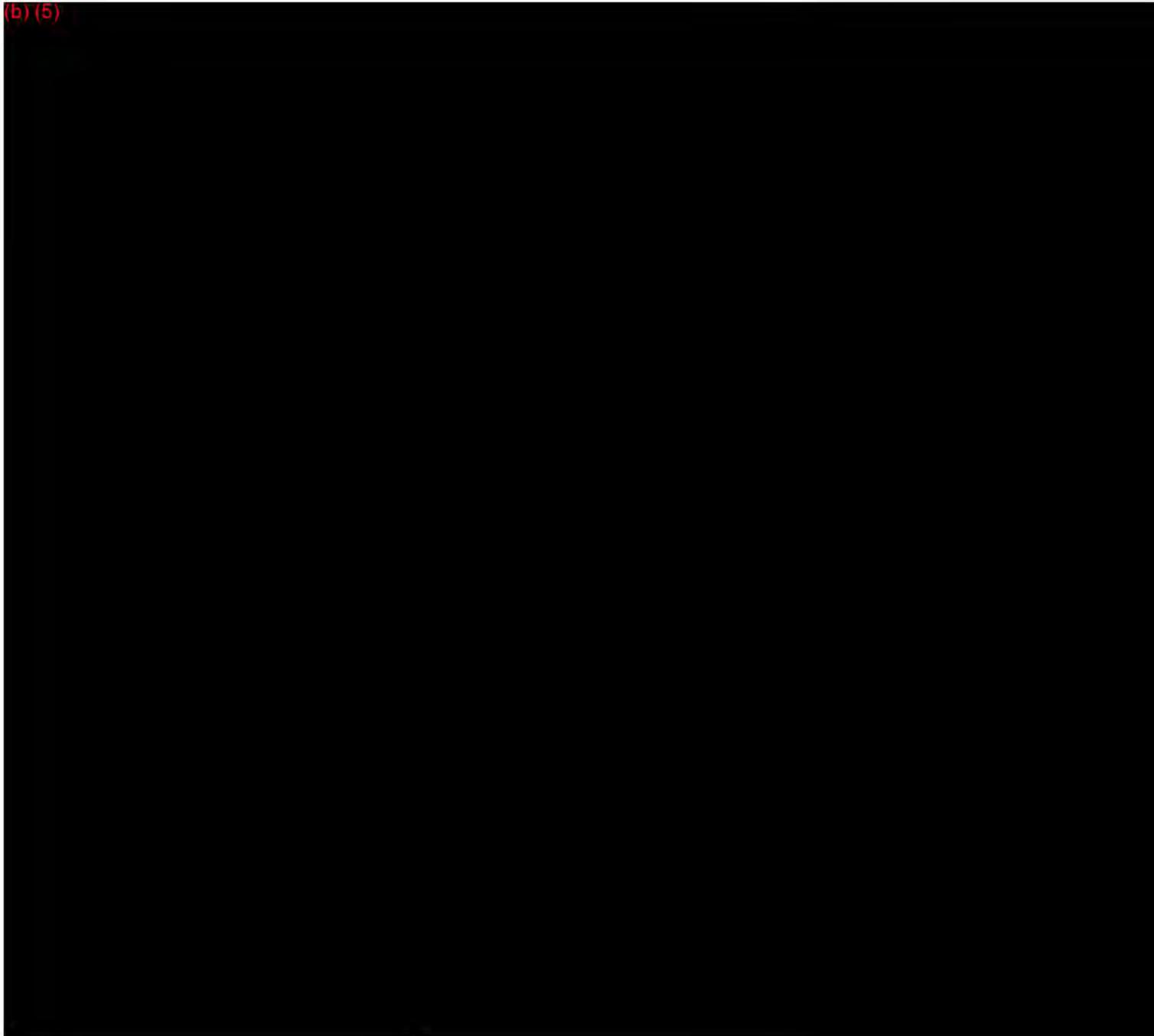
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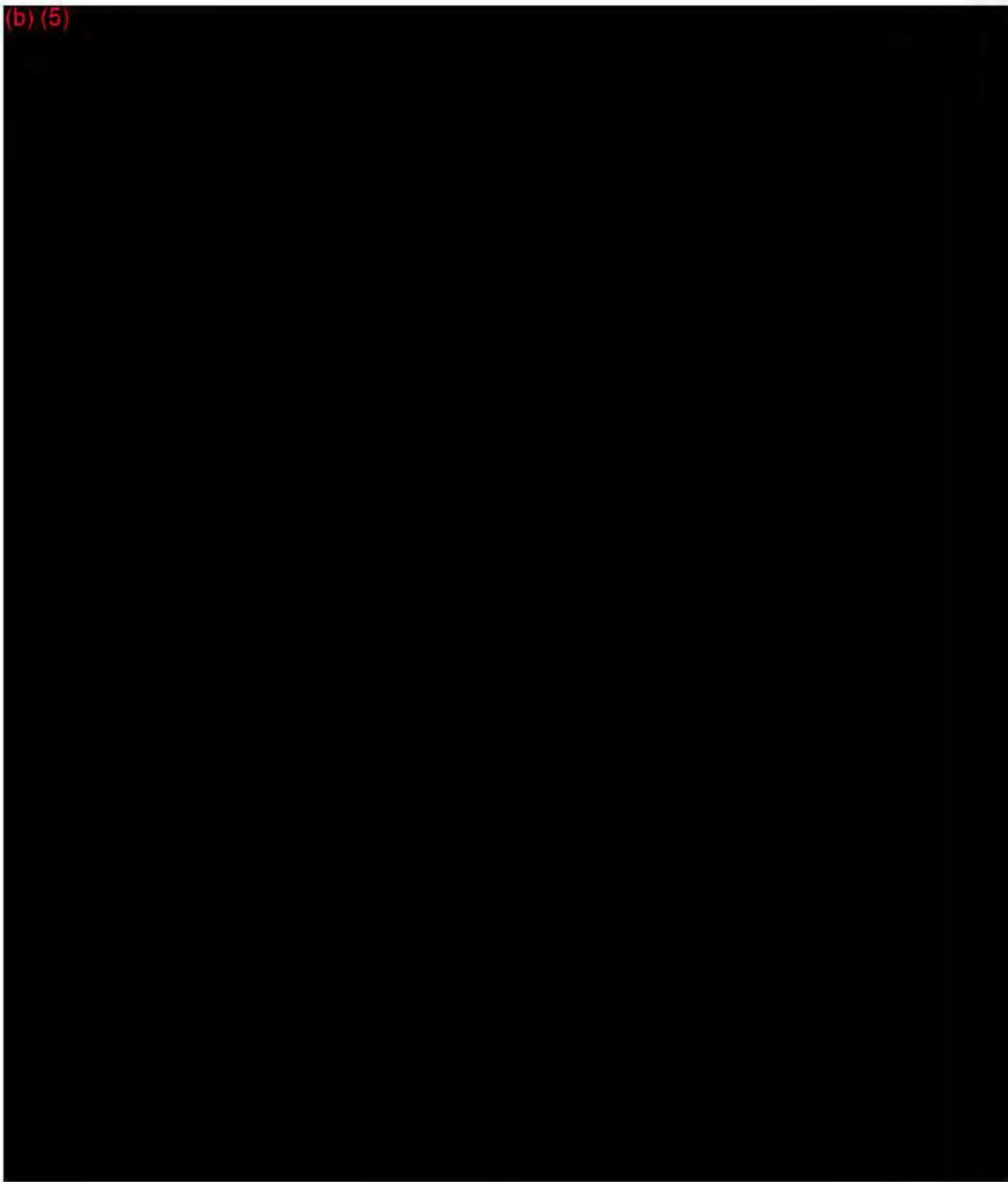
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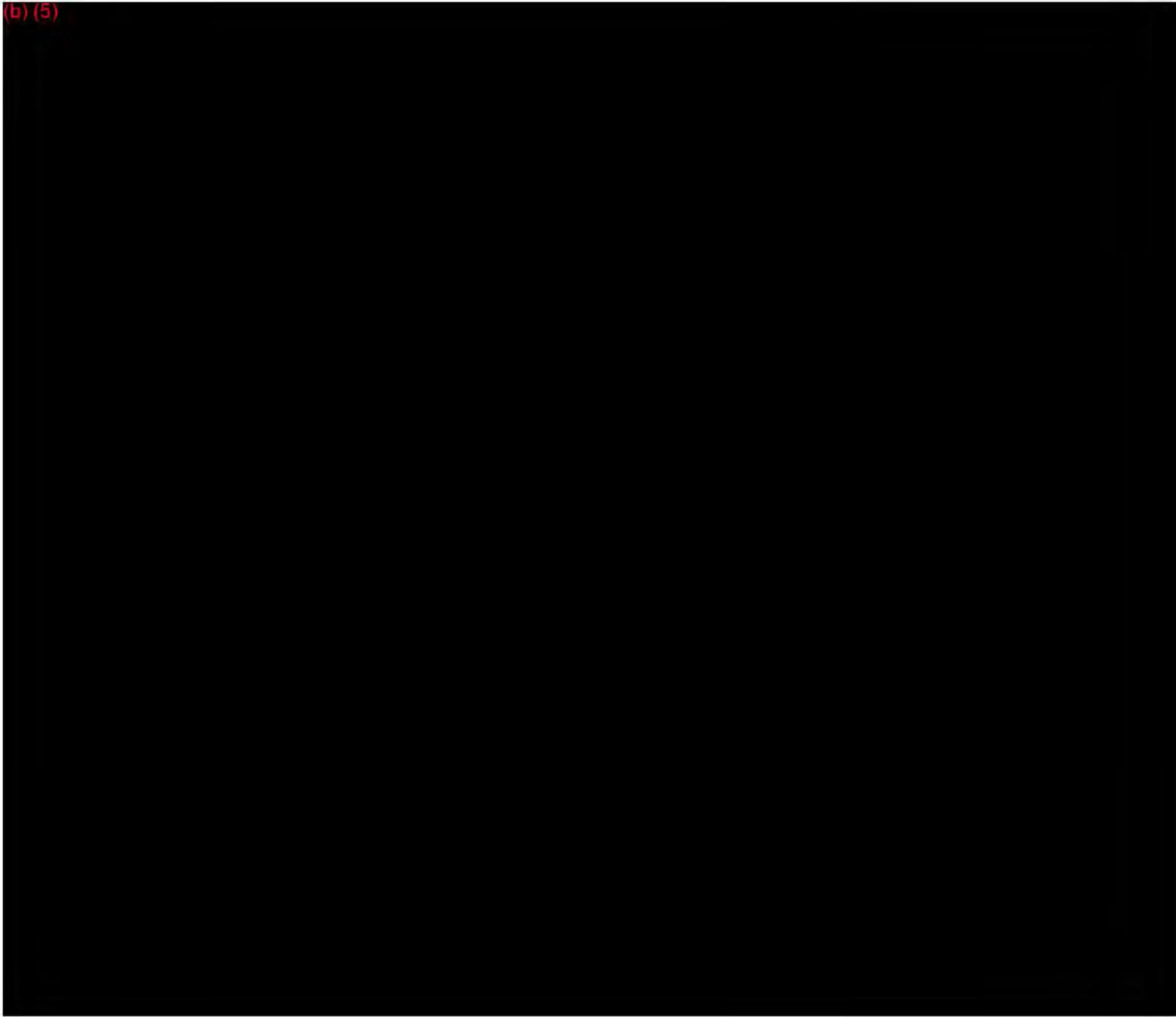
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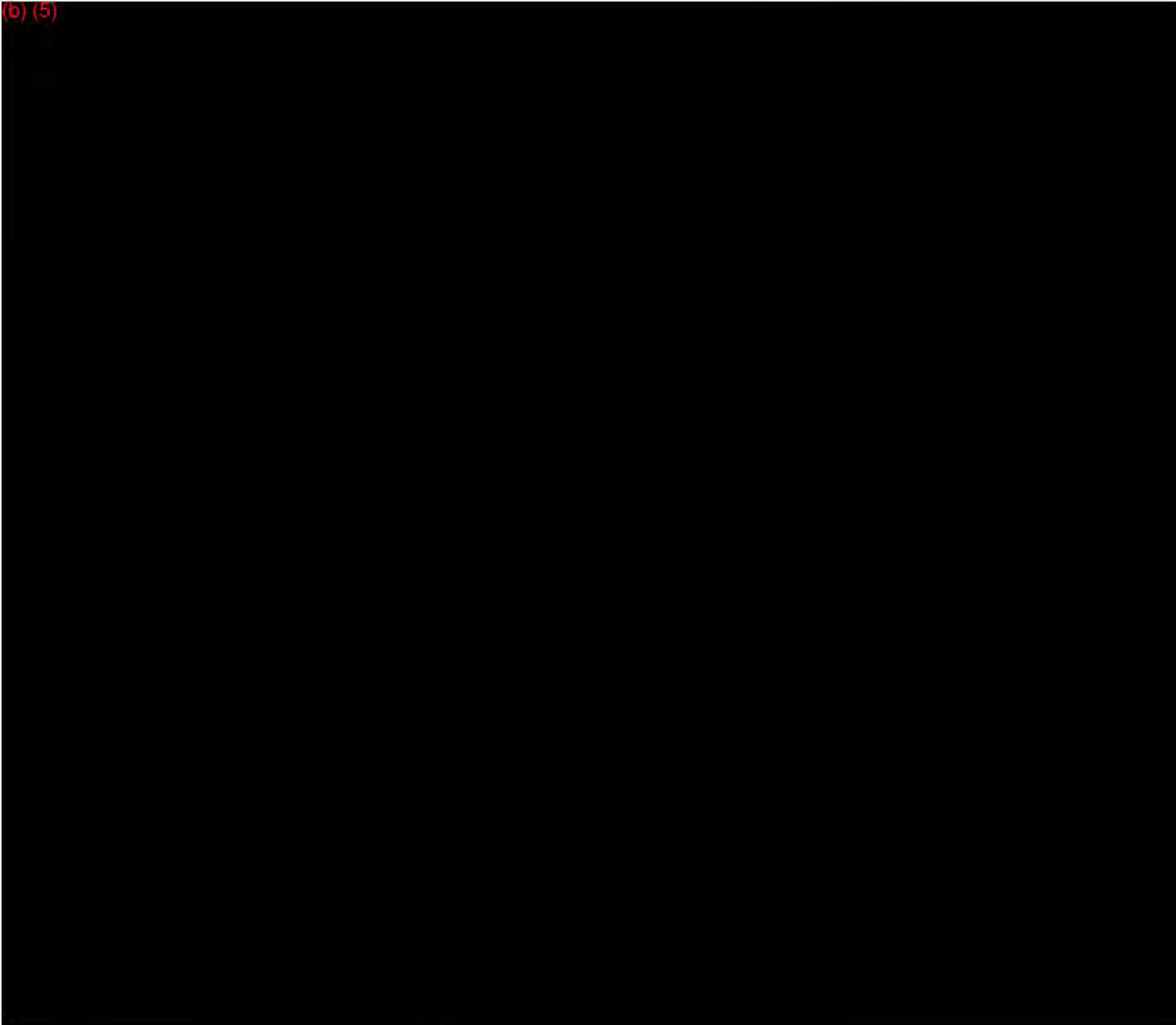
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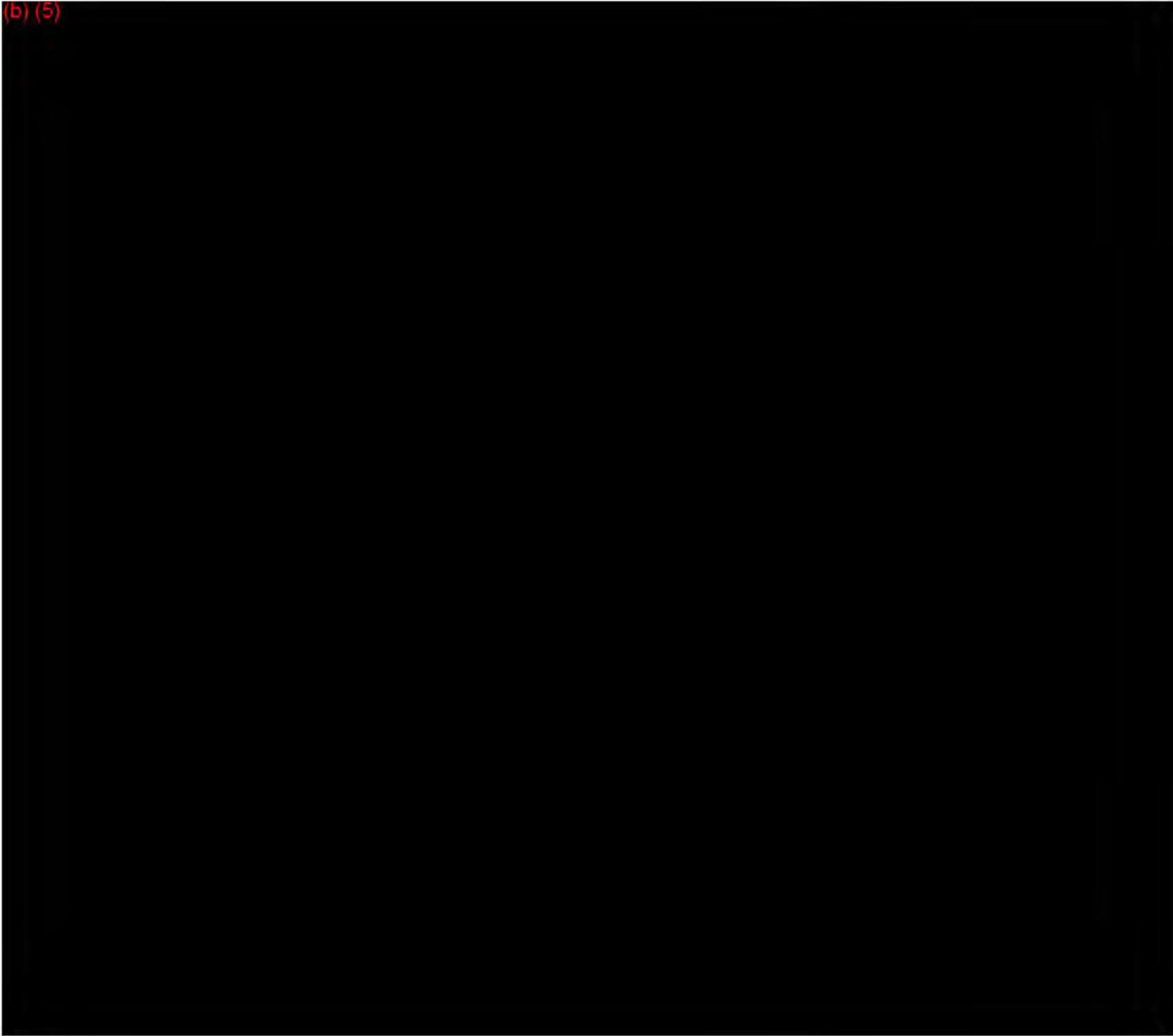
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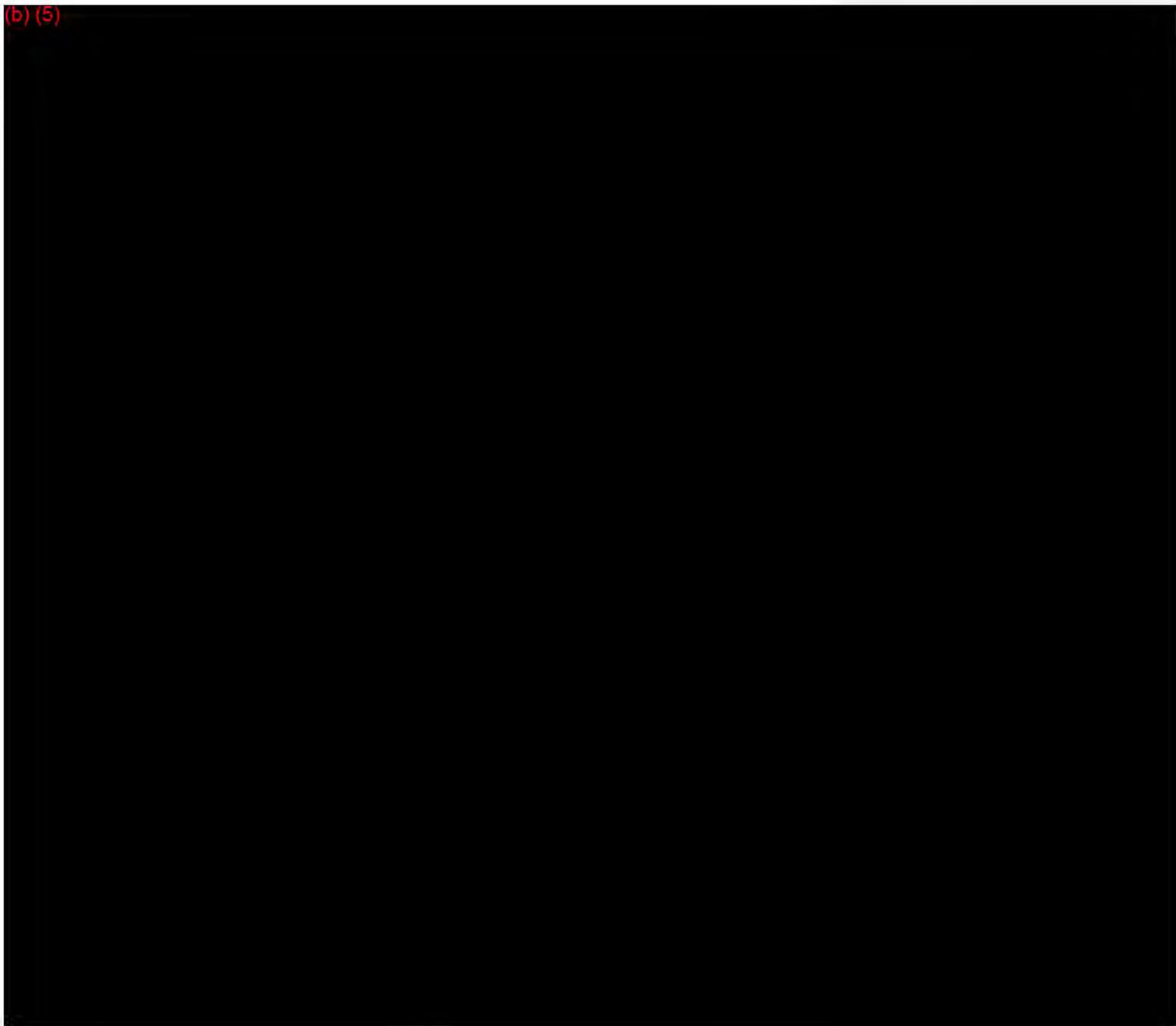
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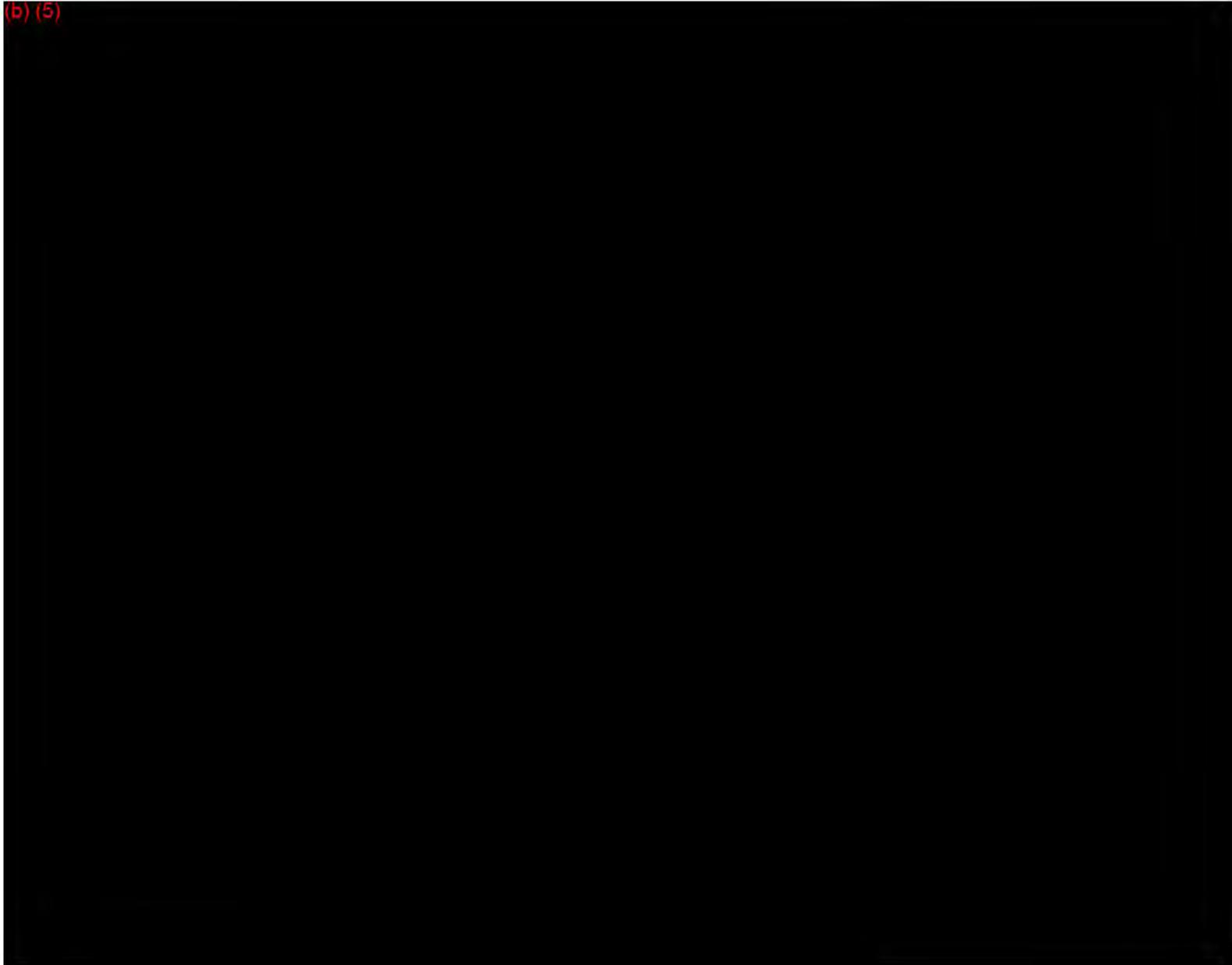
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From: [McCall, Jonathan *](#)
To: [Califf, Robert](#); [Sherman, Rachel](#)
Subject: RE: Slight change of plans
Date: Wednesday, August 24, 2016 11:10:03 AM
Attachments: [Eteplirsen_combined_8-24-2016_TRACKED.doc](#)
[Eteplirsen_combined_8-24-2016_CLEAN-COMMENTED.doc](#)

Here are tracked and clean versions of the current doc, with Deborah's notes and changes merged in. Clean version maintains all comments.

Thanks!

--
J

From: Califf, Robert
Sent: Wednesday, August 24, 2016 7:44 AM
To: Sherman, Rachel; McCall, Jonathan *
Subject: RE: Slight change of plans

I agree. Can y'all make sure Deborah's comments are added. I think she commented on the previous version in her email yesterday. I think I've got it and will have a new draft by end of day.

rmc

From: Sherman, Rachel
Sent: Tuesday, August 23, 2016 12:21 PM
To: Califf, Robert; McCall, Jonathan *
Subject: RE: Slight change of plans

I think this looks really good! It certainly addresses my major concerns.

We should probably wait to see what Rob might want to add after today's meetings.

I think it works better without the numbering, for what it's worth.

Thanks!!

From: McCall, Jonathan * <Jonathan.McCall@fda.hhs.gov>
Date: August 23, 2016 at 12:00:34 PM EDT
To: Sherman, Rachel <Rachel.Sherman@fda.hhs.gov>, Califf, Robert <RMC1@fda.hhs.gov>
Subject: RE: Slight change of plans

Hello all –

I've reformatted, dropping the outline approach and opting for headers and subheaders. I've consolidated some concluding elements (have included notes where I did this) in the hopes of clearly demarcating thematic sections and conclusions specific to those sections.

I've eschewed using numbering for the headers, but we can certainly add those if people feel that they're useful. Headings are currently linked in the document for easier navigation.

Happy to refine further on this approach, or try something else entirely.

Thanks!

--
J

From: Sherman, Rachel
Sent: Monday, August 22, 2016 8:42 PM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: Slight change of plans

Hi,

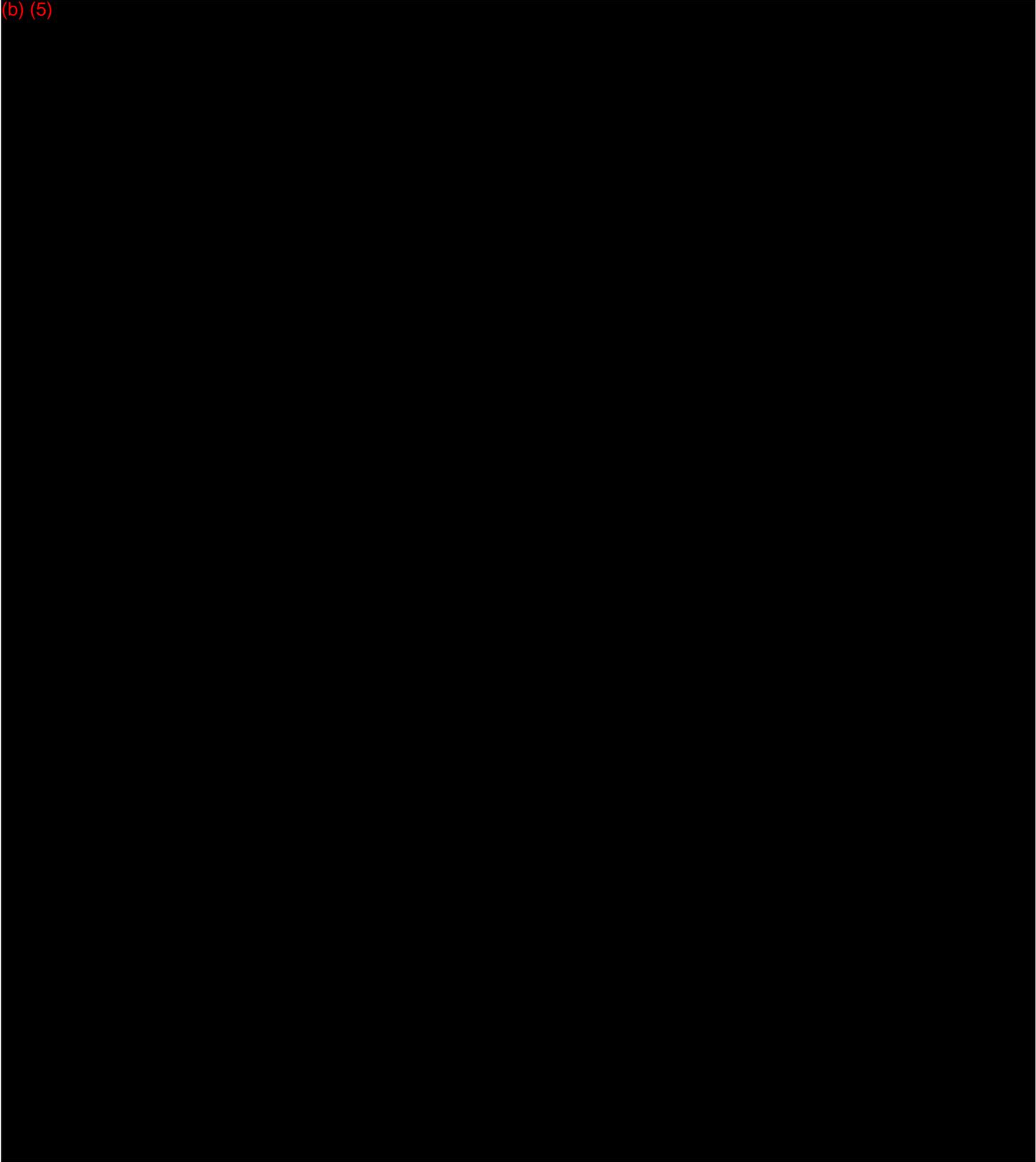
Based on a conversation with Rob this evening, I inserted a few more comments – trying to emphasize the uncertainty and that Rob's fundamental decision is that he is not going to overrule Janet (at least that's how I understand his position).

Rob – please let us know if you want Deborah to look or you want to look first.

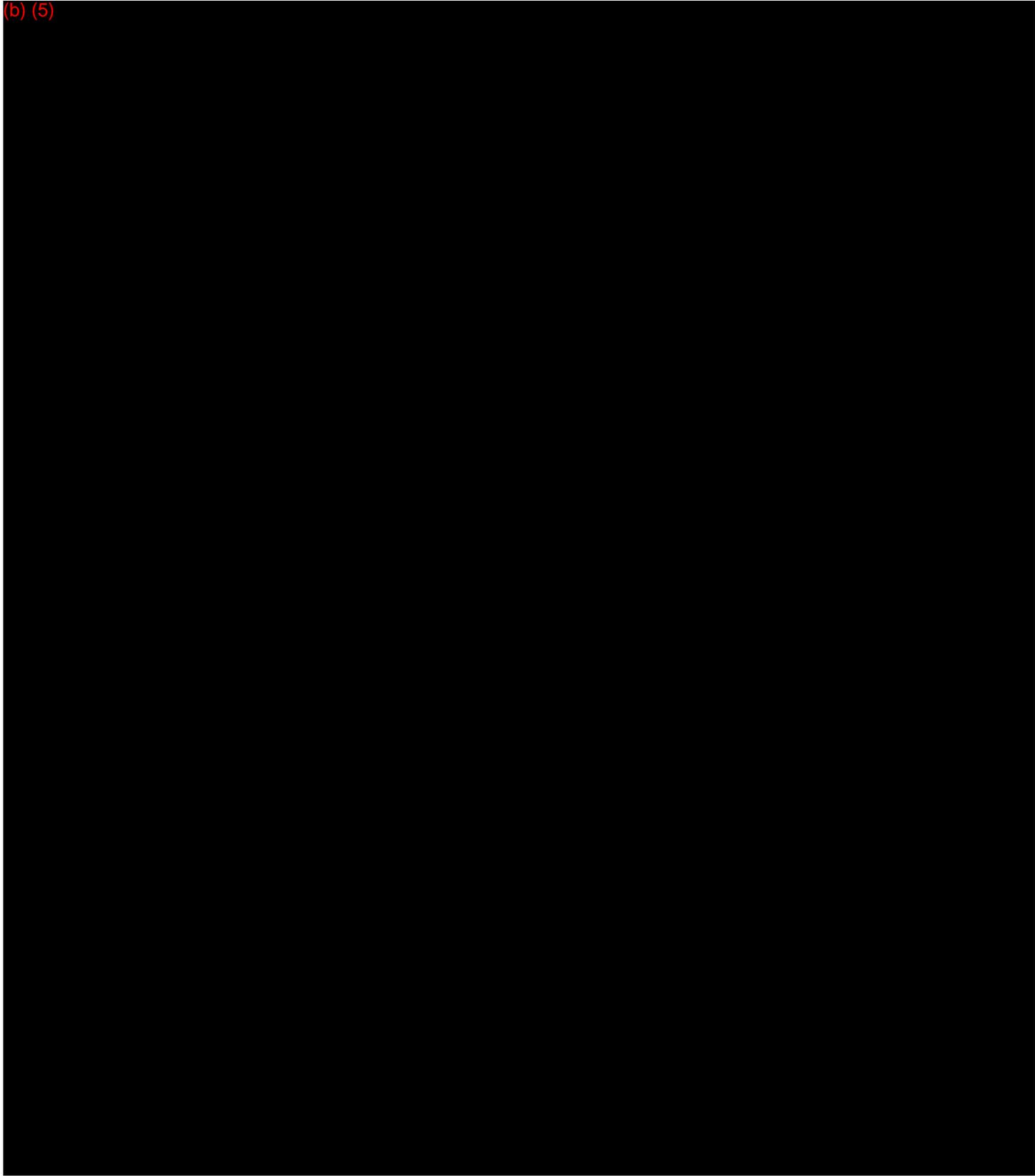
I think Jonathan may be able to help by consolidating your conclusions in a more prominent space. I have highlighted the two places that seem buried. The last is right at the end so it is more obvious.

Rachel

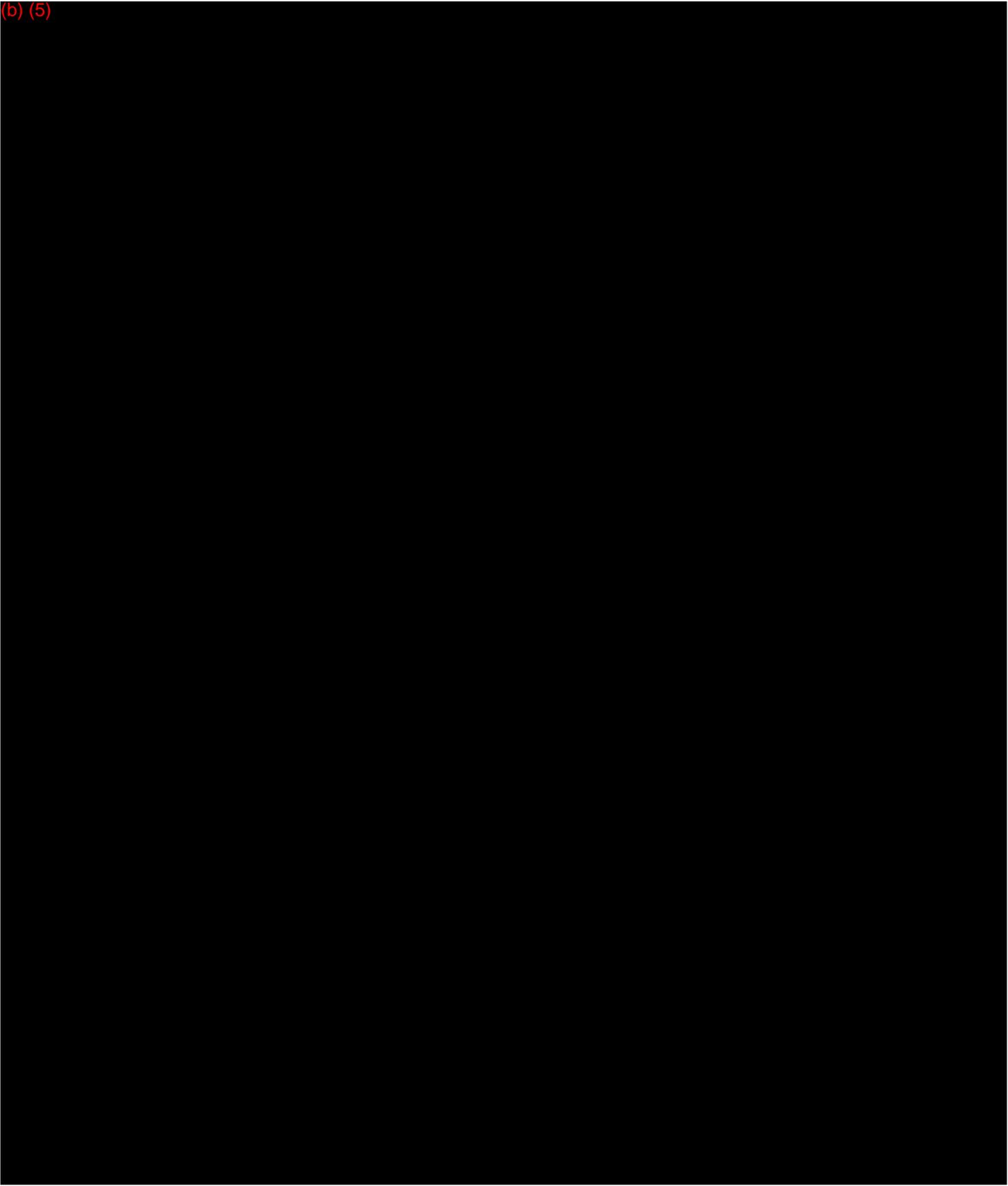
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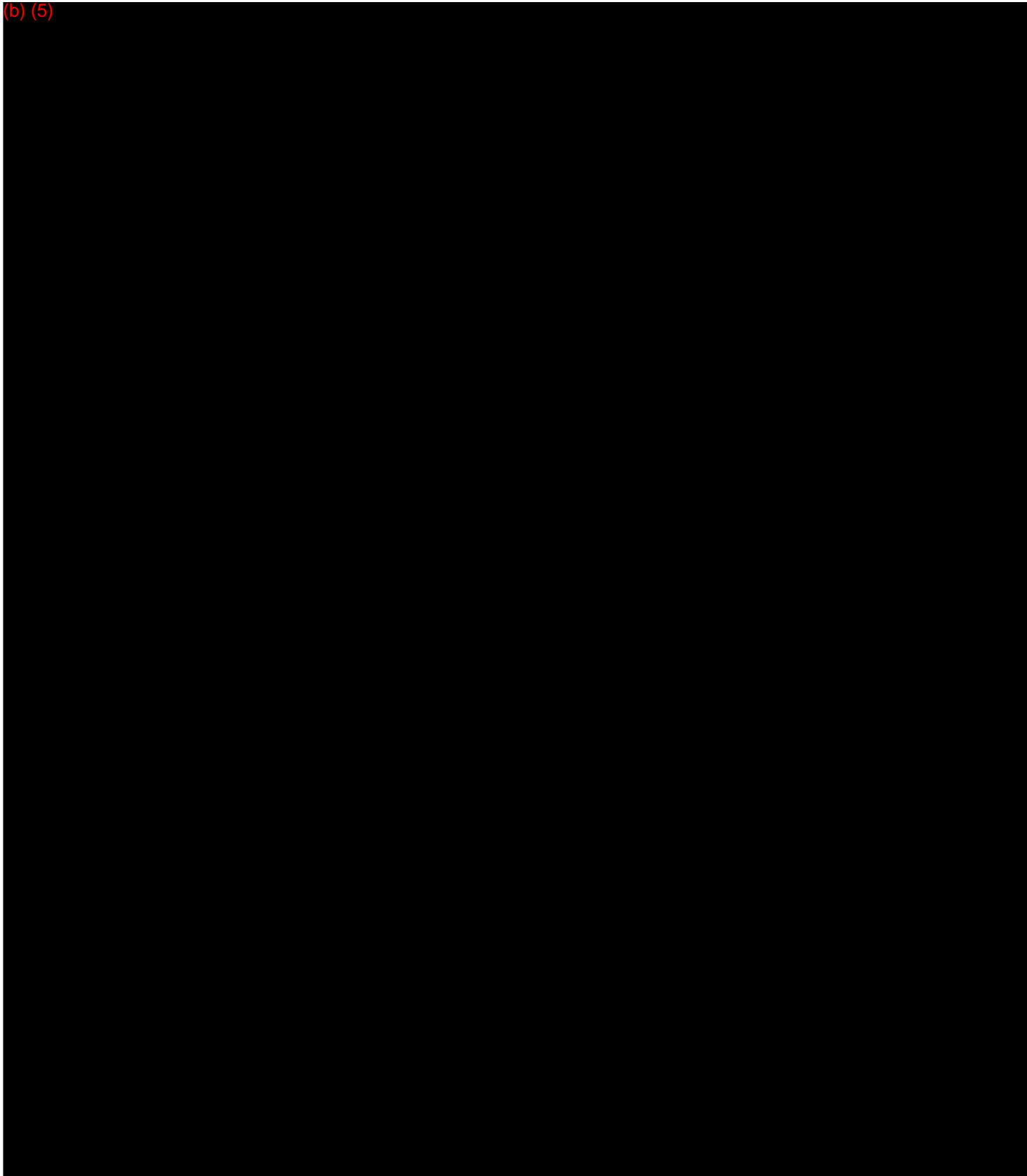
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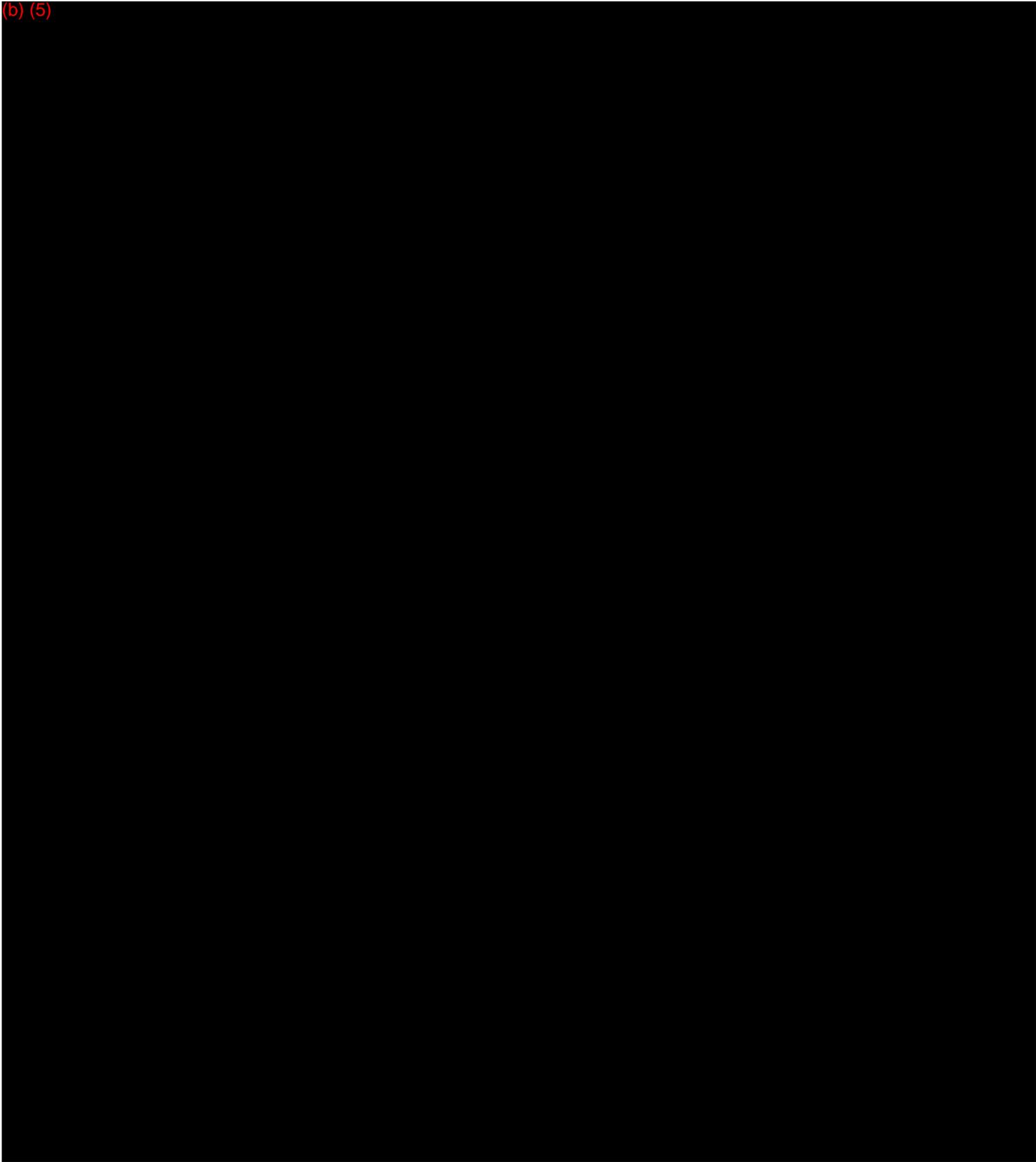
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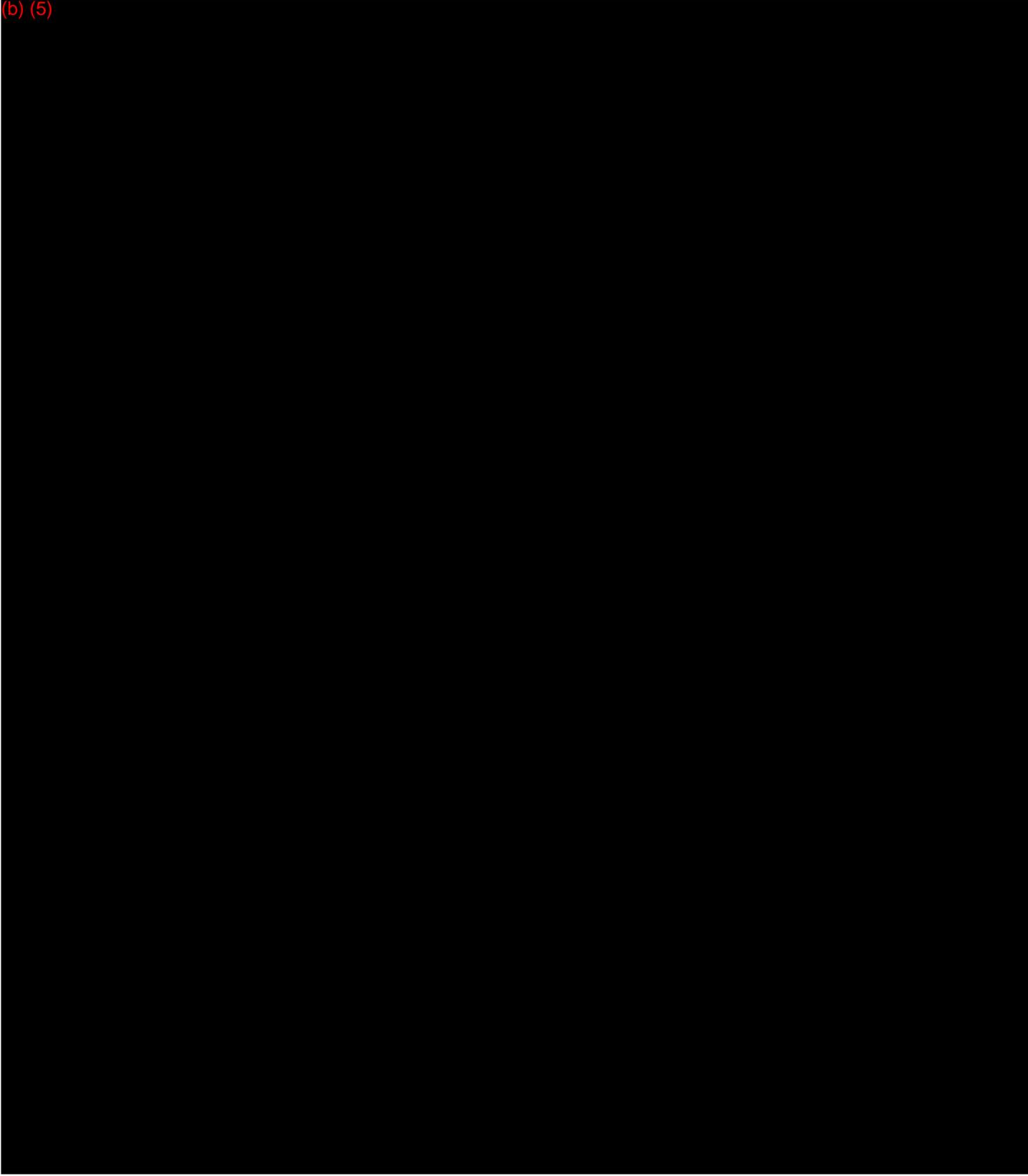
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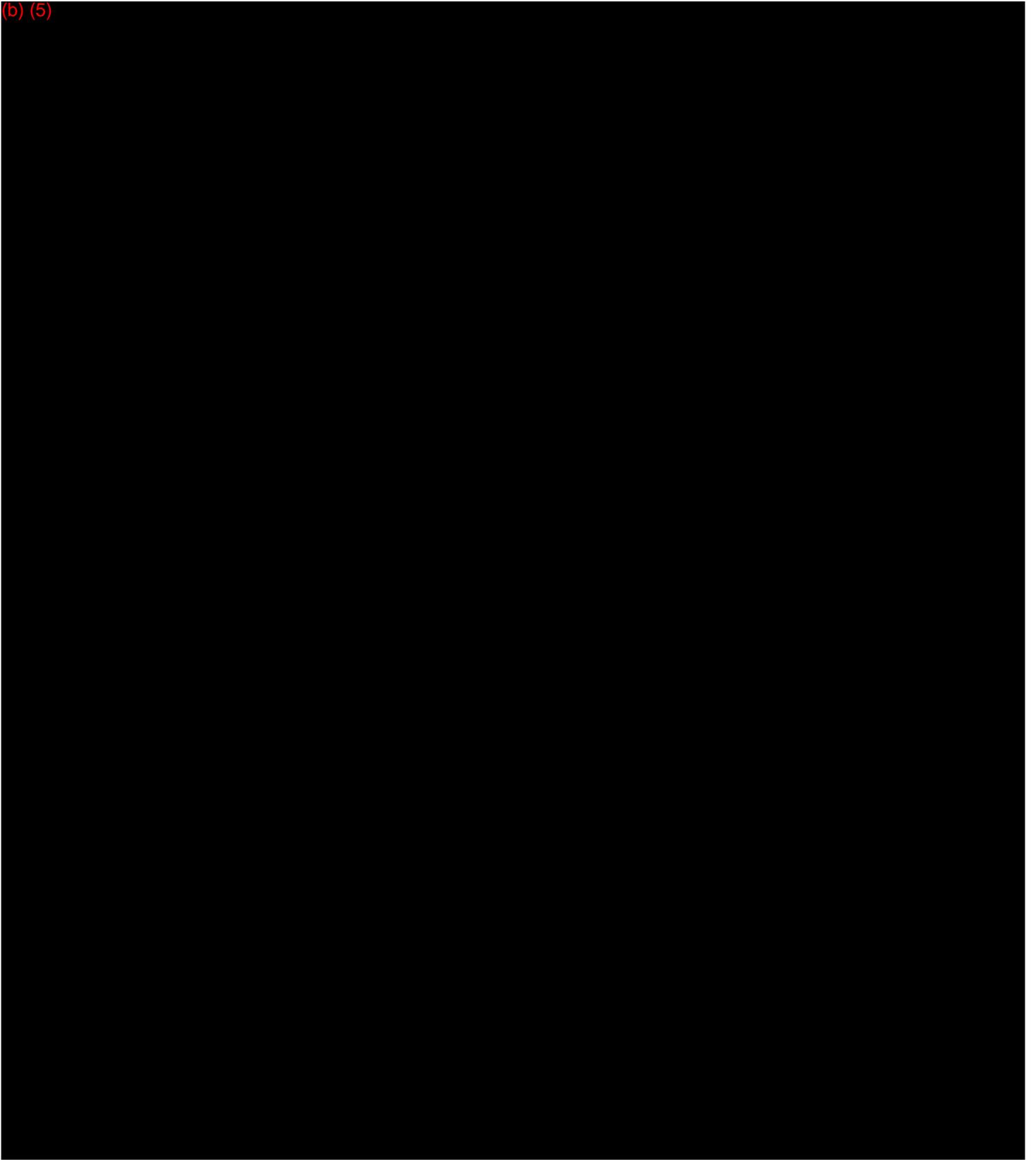
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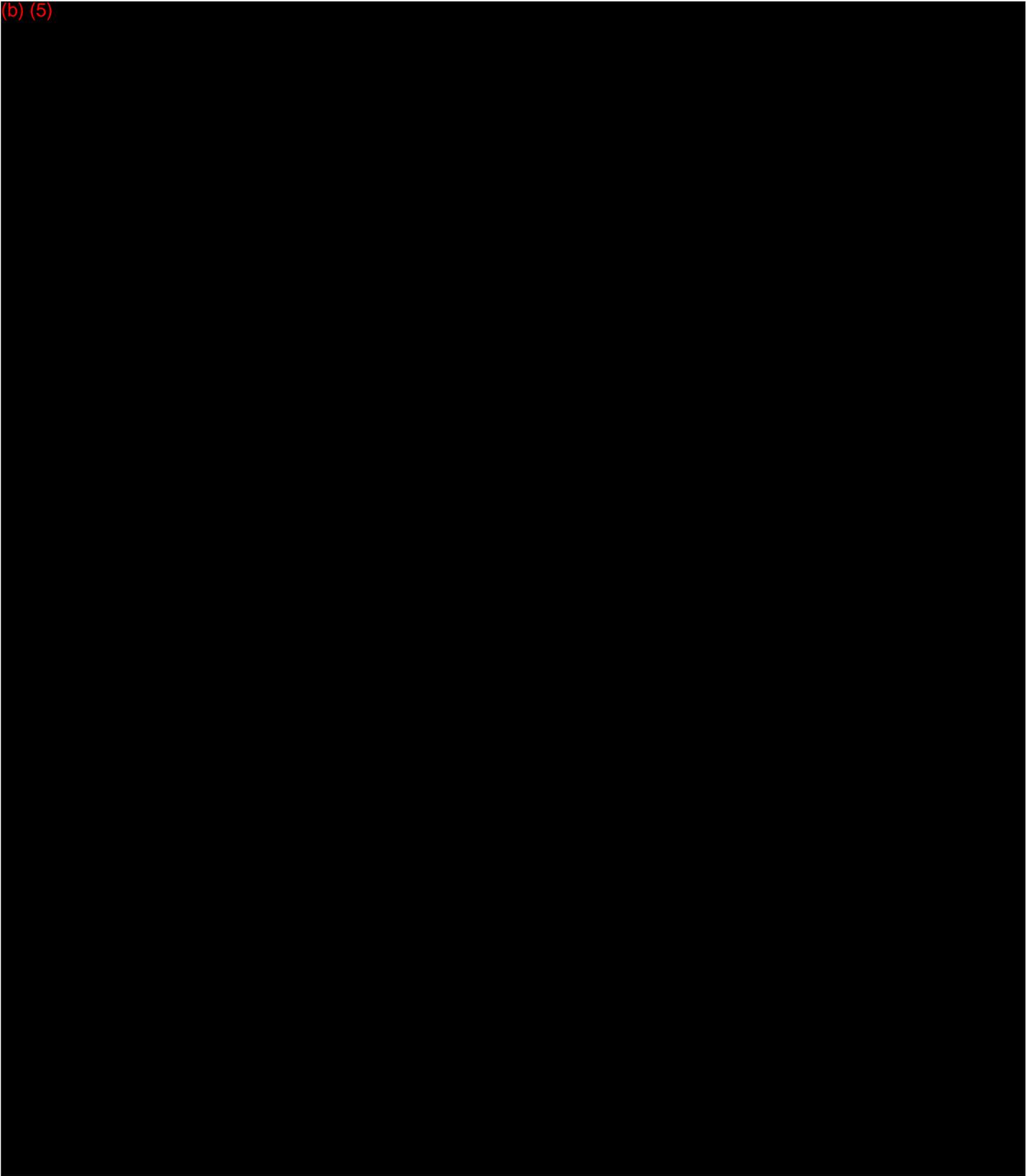
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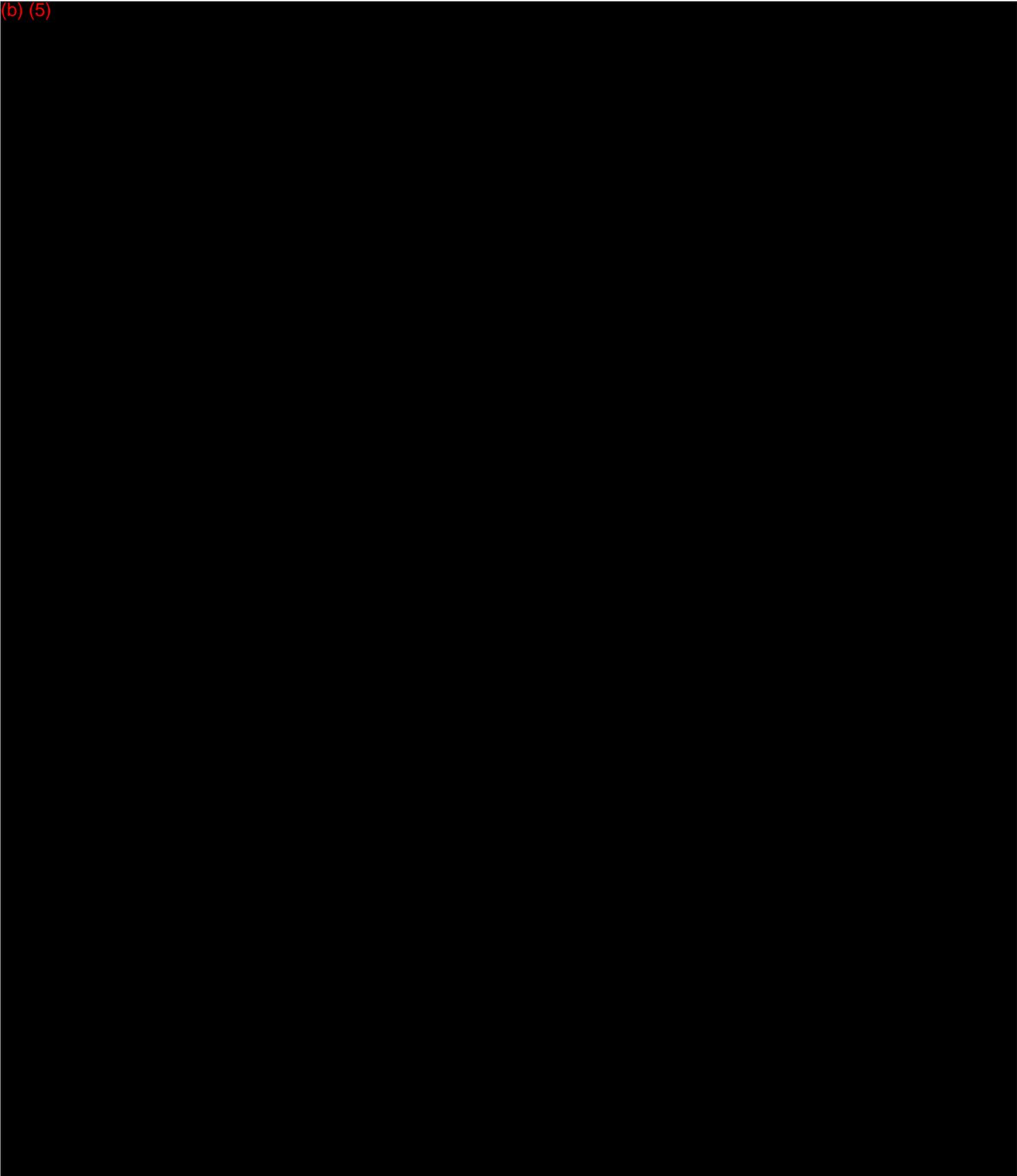
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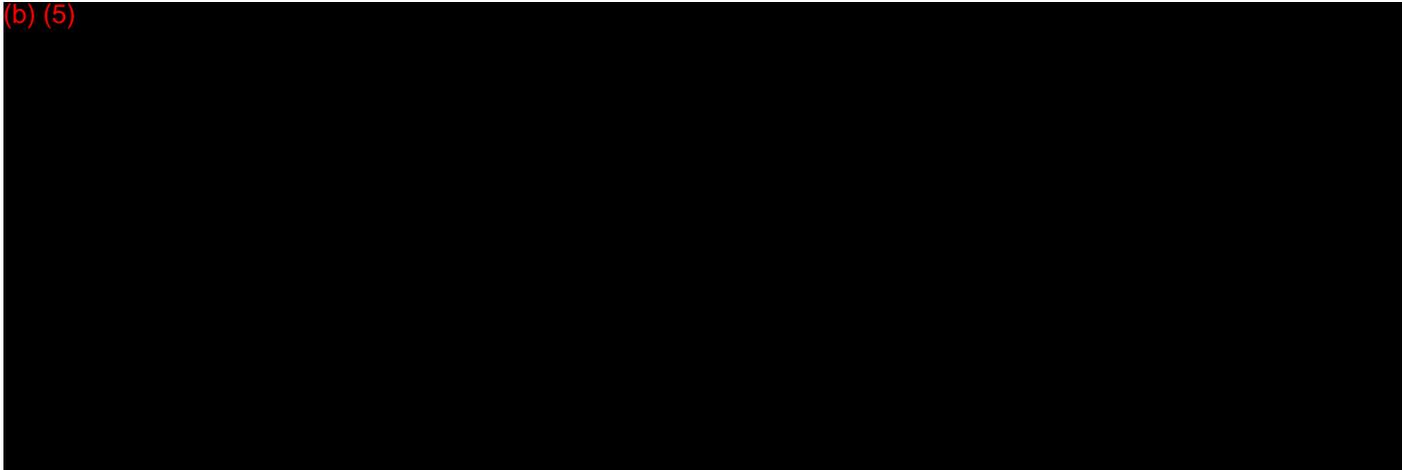
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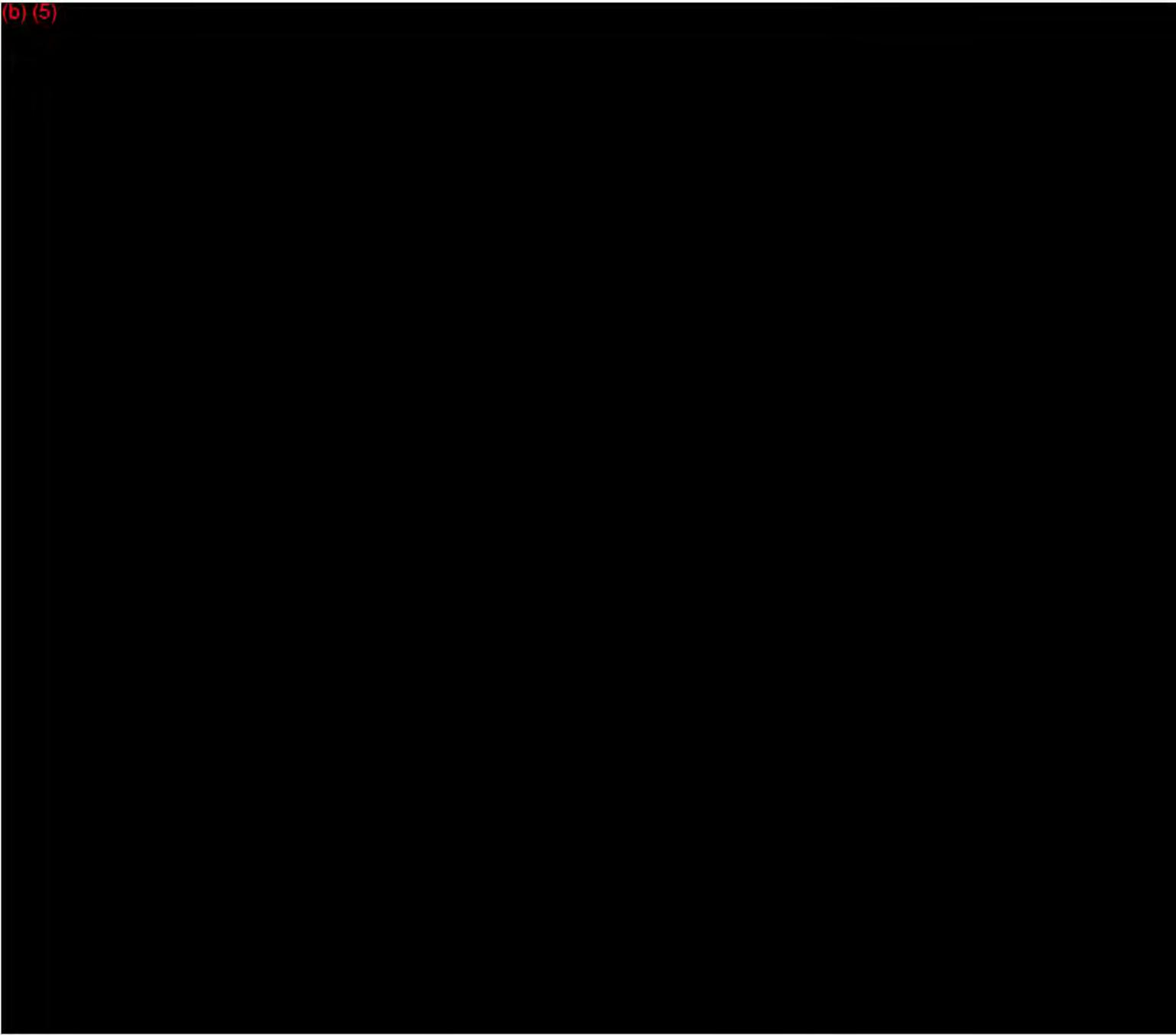
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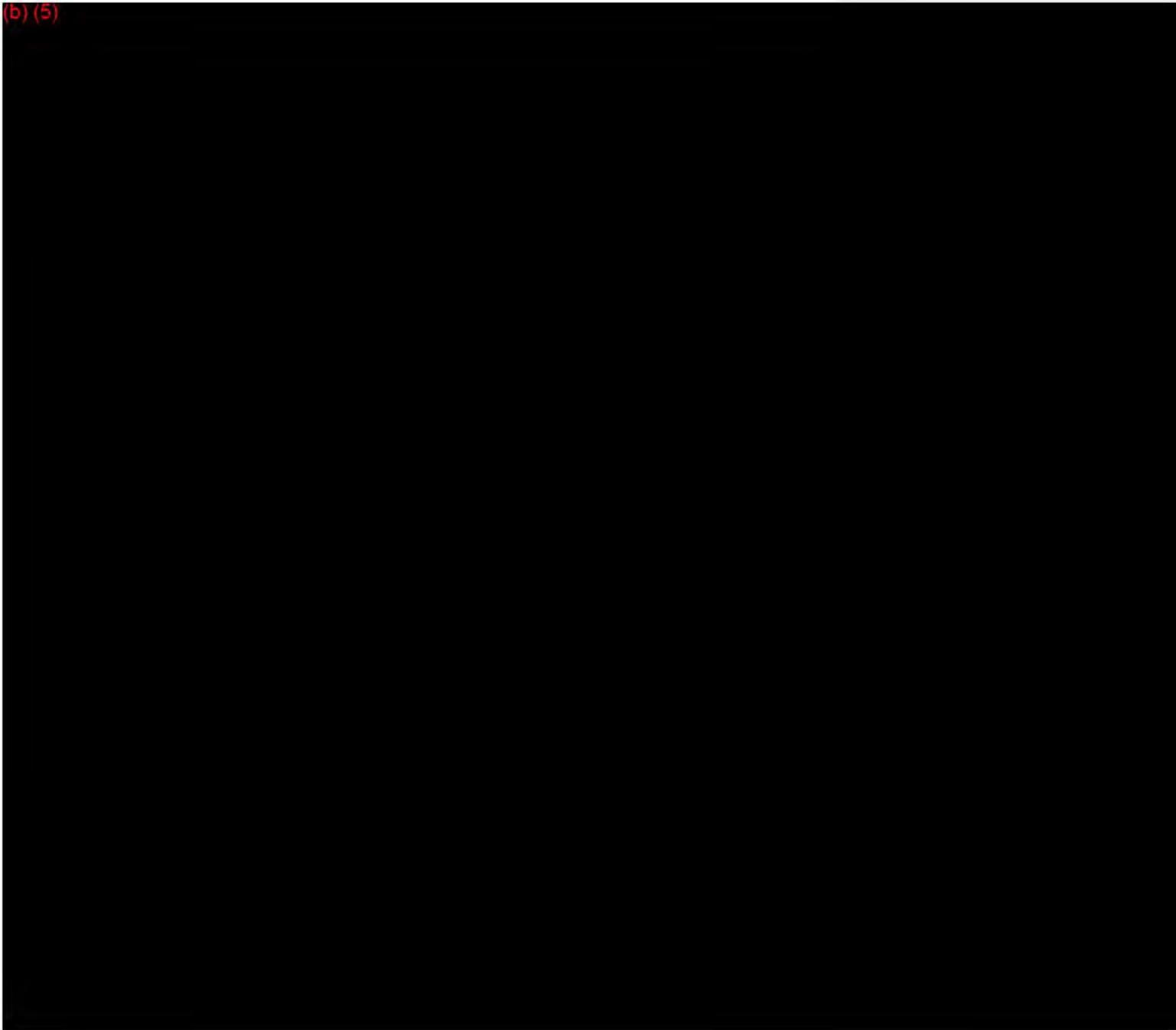
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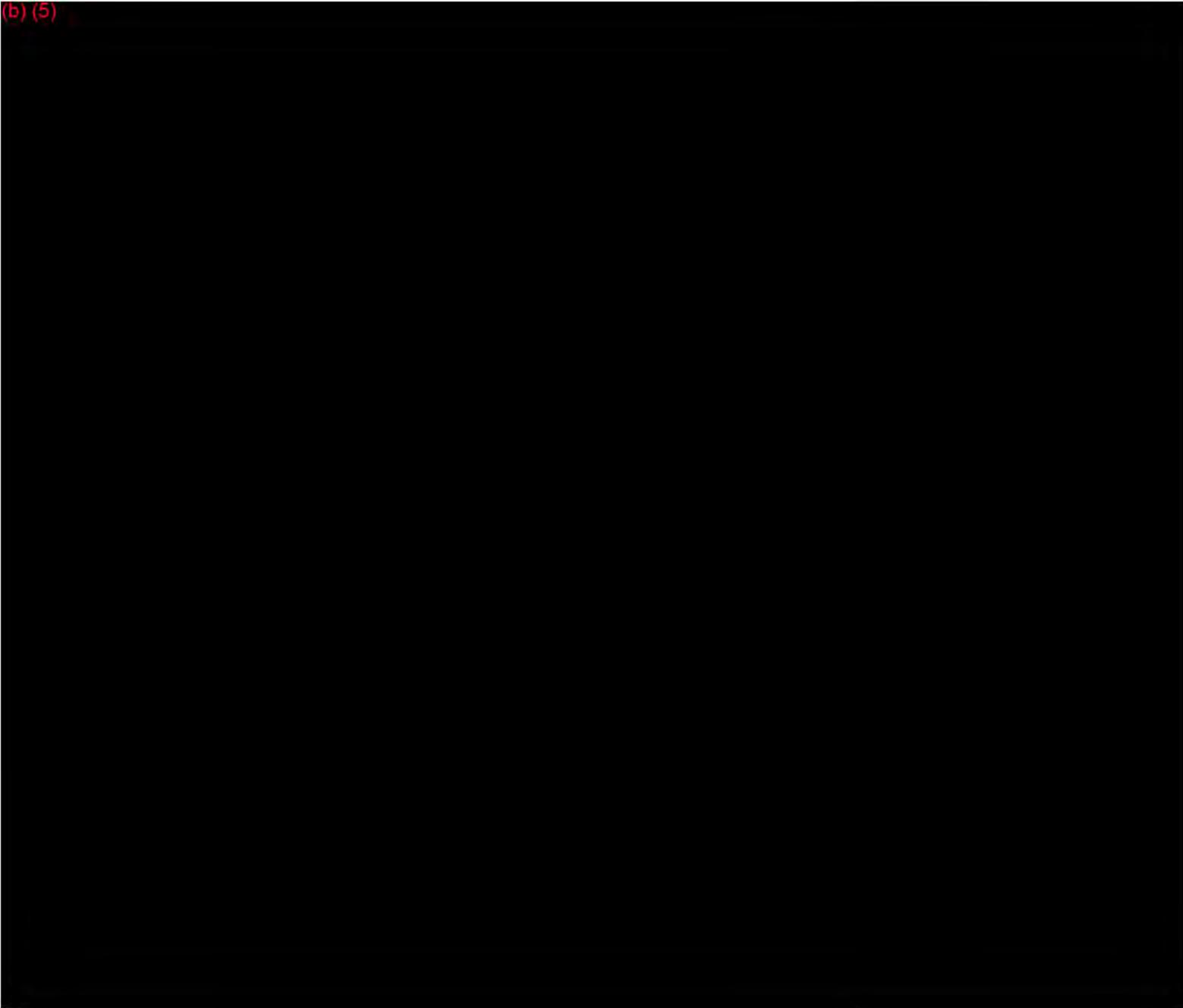
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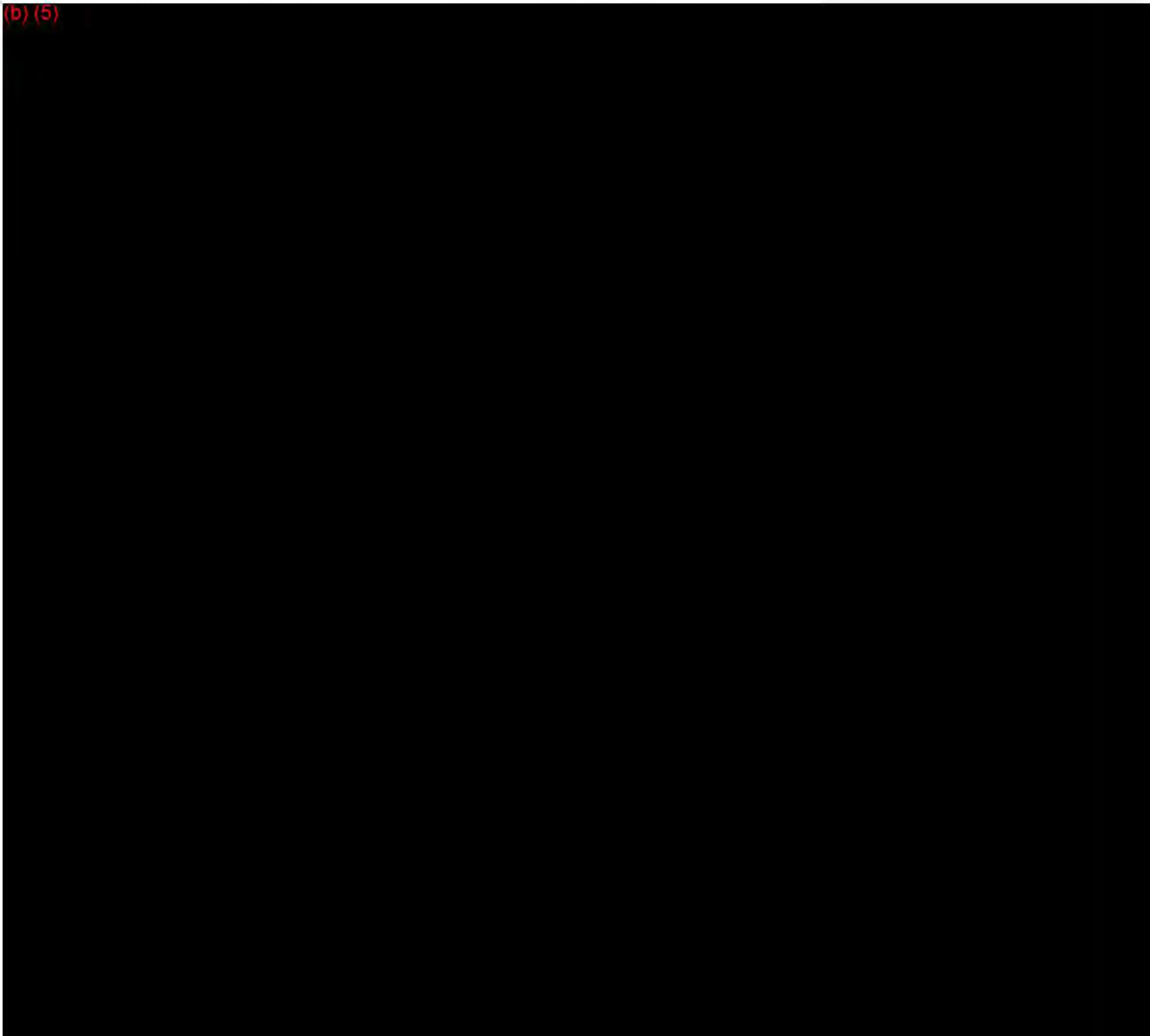
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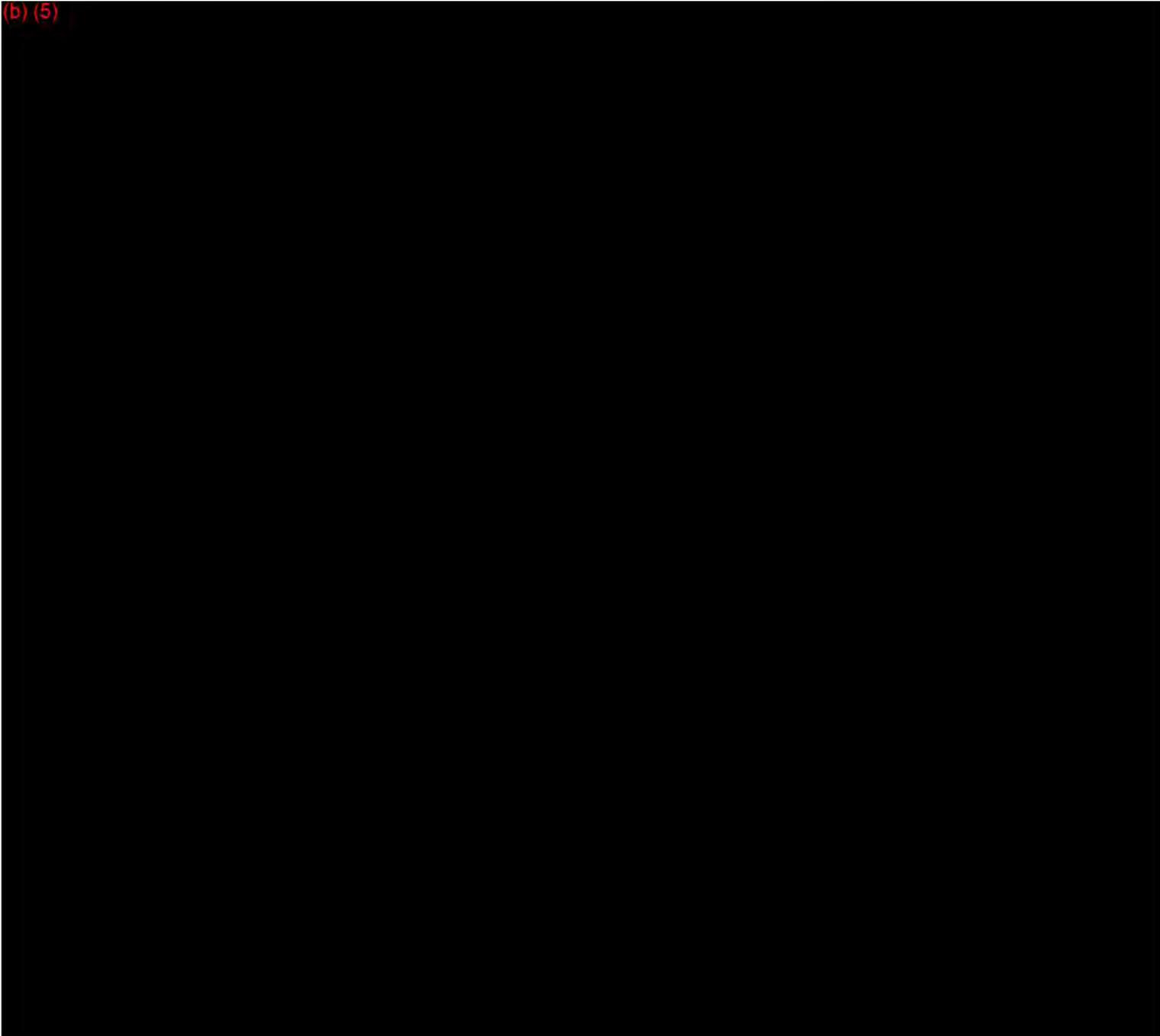
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From: [McCall, Jonathan *](#)
To: [Sherman, Rachel](#); [Califf, Robert](#)
Subject: RE: Slight change of plans
Date: Tuesday, August 23, 2016 12:00:35 PM
Attachments: [Eteplirsen_combined-comments_8-18-2016_reorganized_and_adopts_someRSOCCRCcomments_SEMI_CLEANrscm_rmcrs+OCCv2_Reformatted.doc](#)

Hello all –

I've reformatted, dropping the outline approach and opting for headers and subheaders. I've consolidated some concluding elements (have included notes where I did this) in the hopes of clearly demarcating thematic sections and conclusions specific to those sections.

I've eschewed using numbering for the headers, but we can certainly add those if people feel that they're useful. Headings are currently linked in the document for easier navigation.

Happy to refine further on this approach, or try something else entirely.

Thanks!

--
J

From: Sherman, Rachel
Sent: Monday, August 22, 2016 8:42 PM
To: Califf, Robert; Chasan-Sloan, Deborah (FDA)
Cc: McCall, Jonathan *
Subject: Slight change of plans

Hi,

Based on a conversation with Rob this evening, I inserted a few more comments – trying to emphasize the uncertainty and that Rob's fundamental decision is that he is not going to overrule Janet (at least that's how I understand his position).

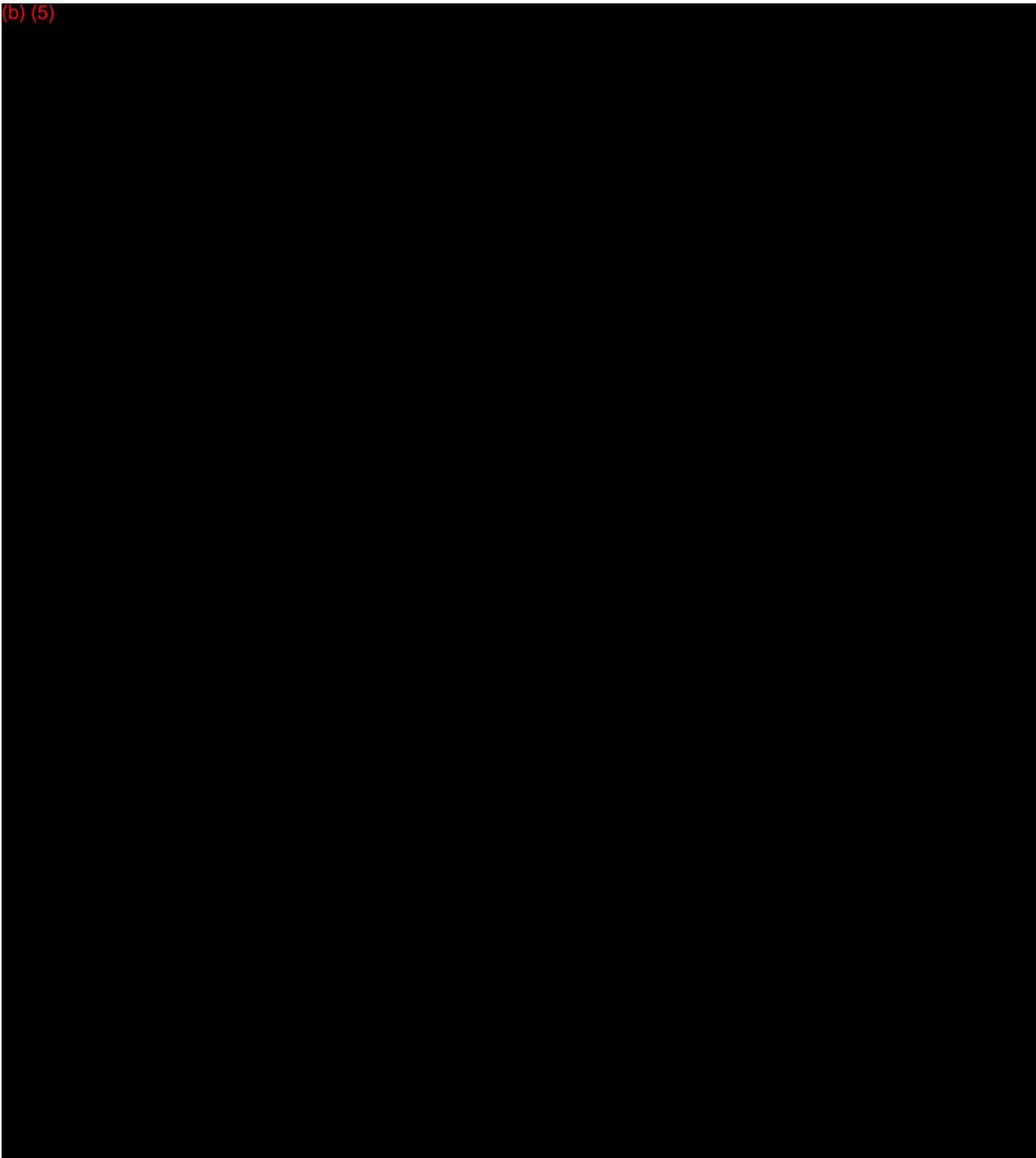
Rob – please let us know if you want Deborah to look or you want to look first.

I think Jonathan may be able to help by consolidating your conclusions in a more prominent space. I have highlighted the two places that seem buried. The last is right at the end so it is more obvious.

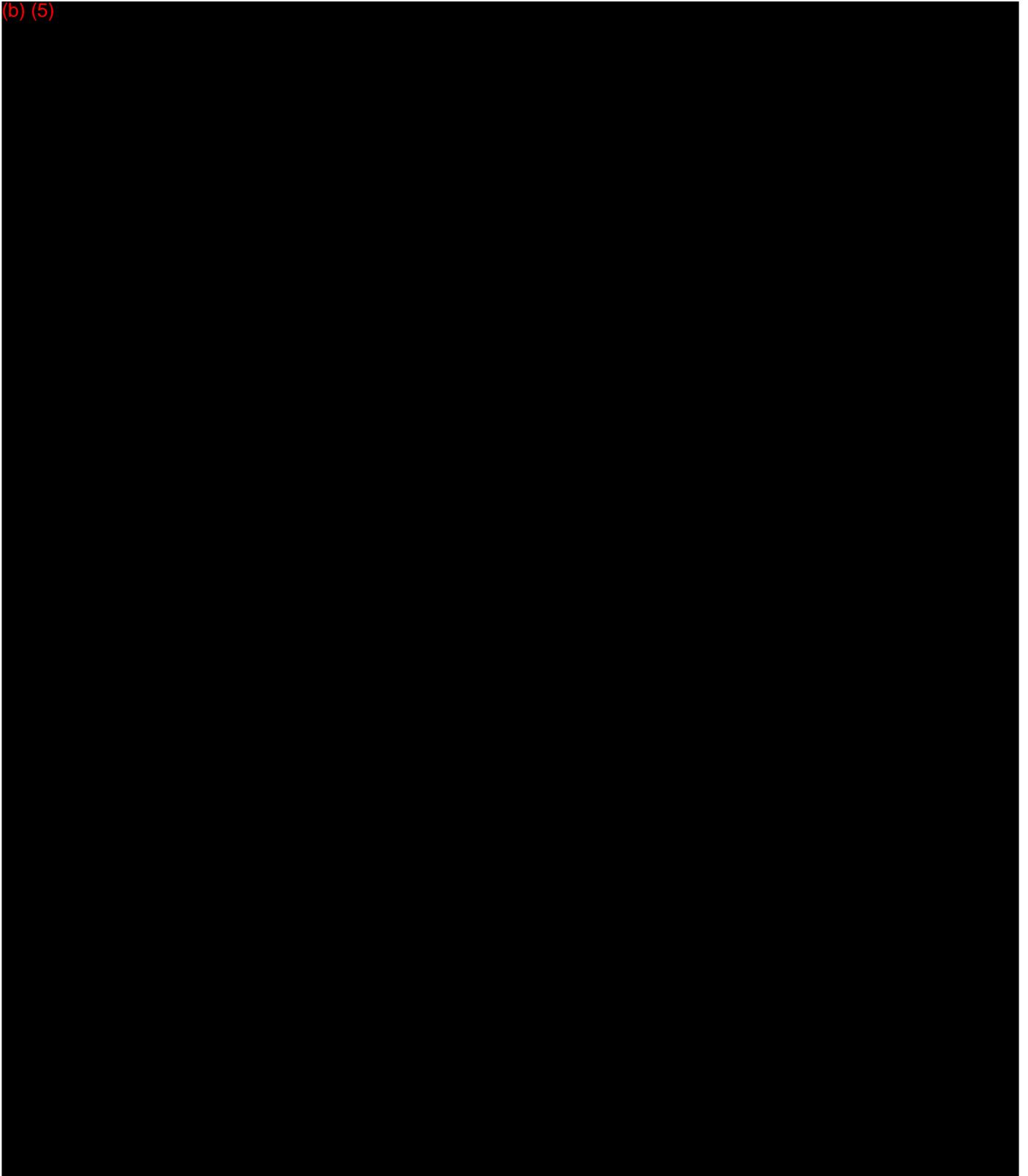
Rachel

Overview

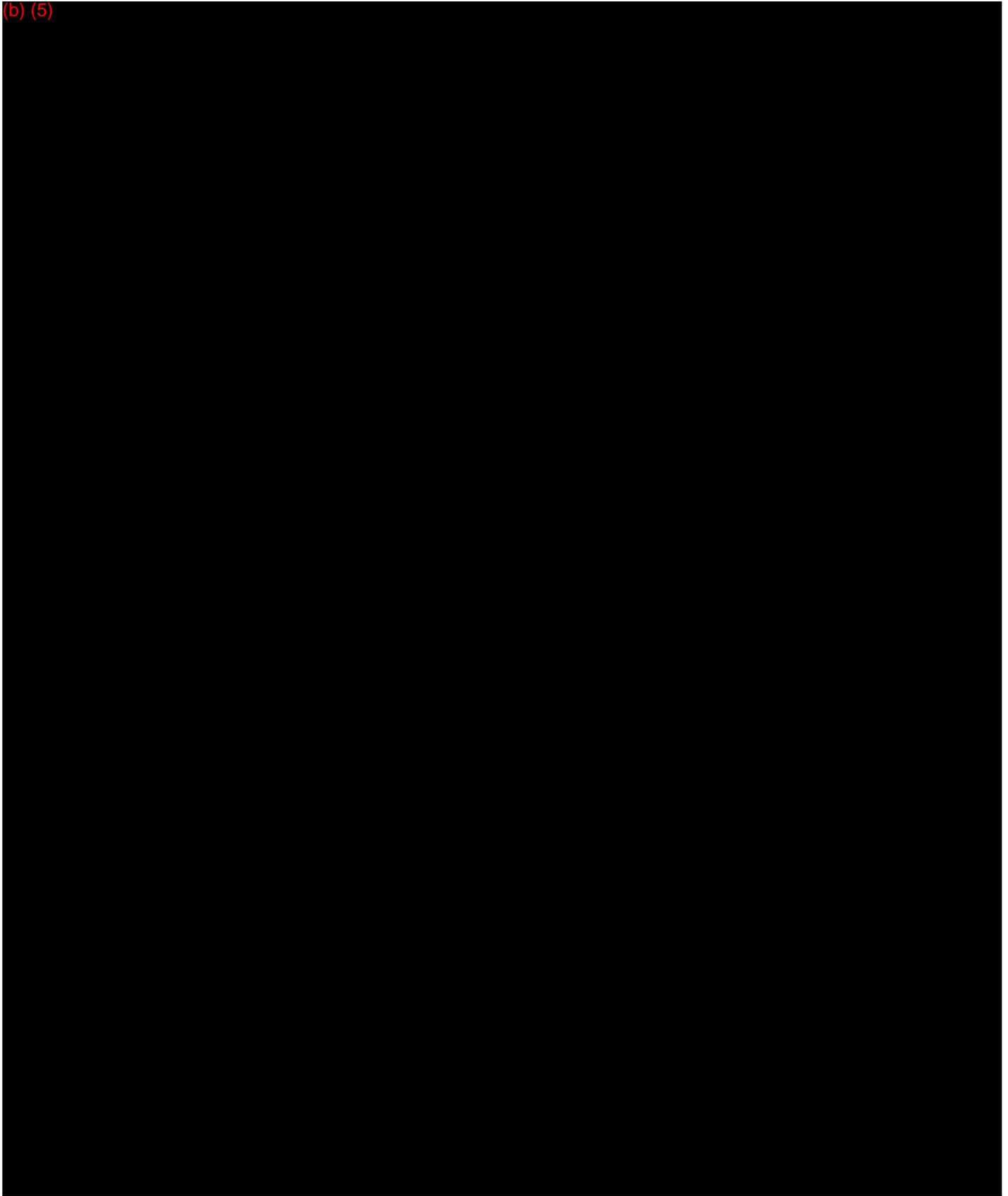
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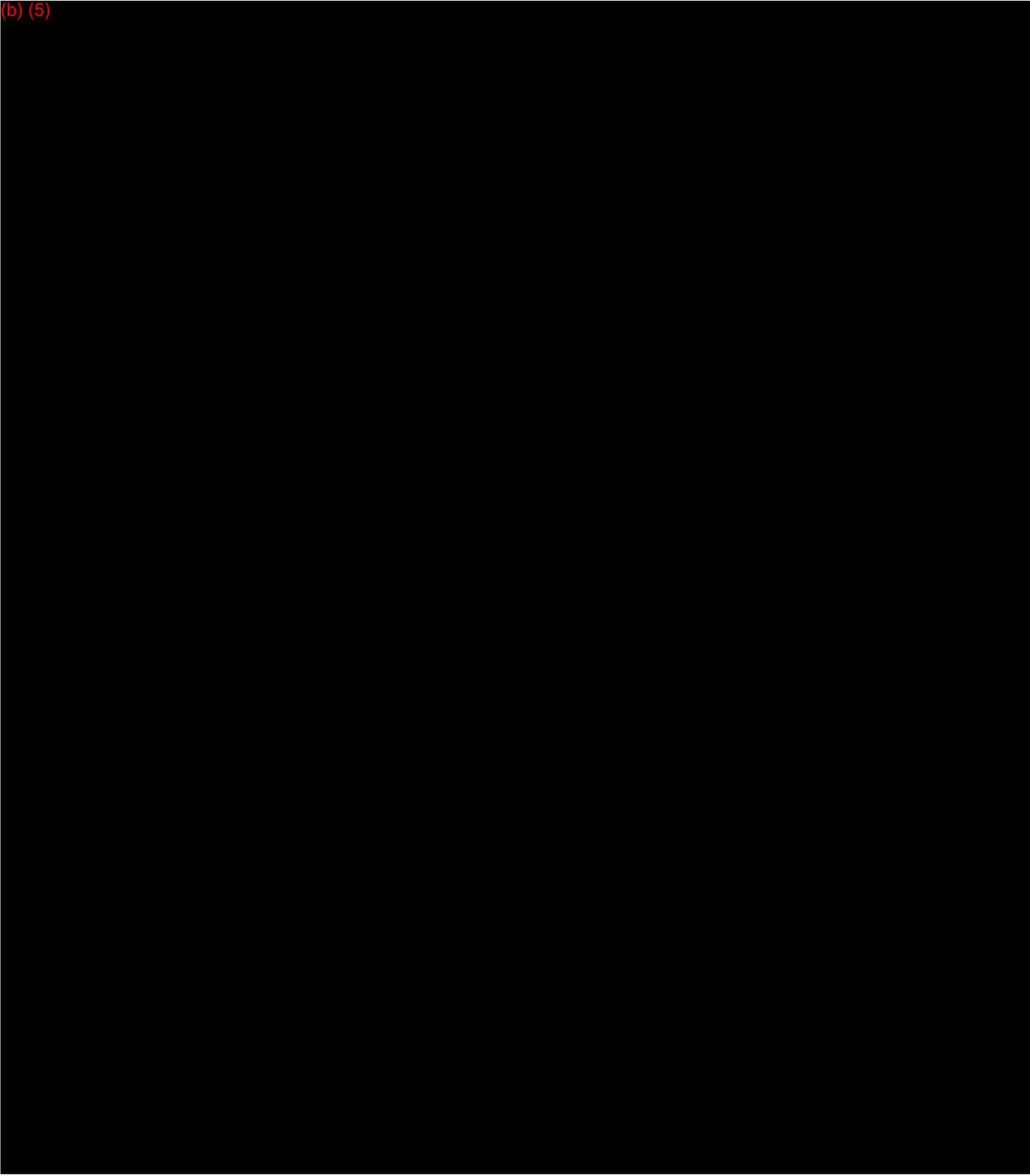
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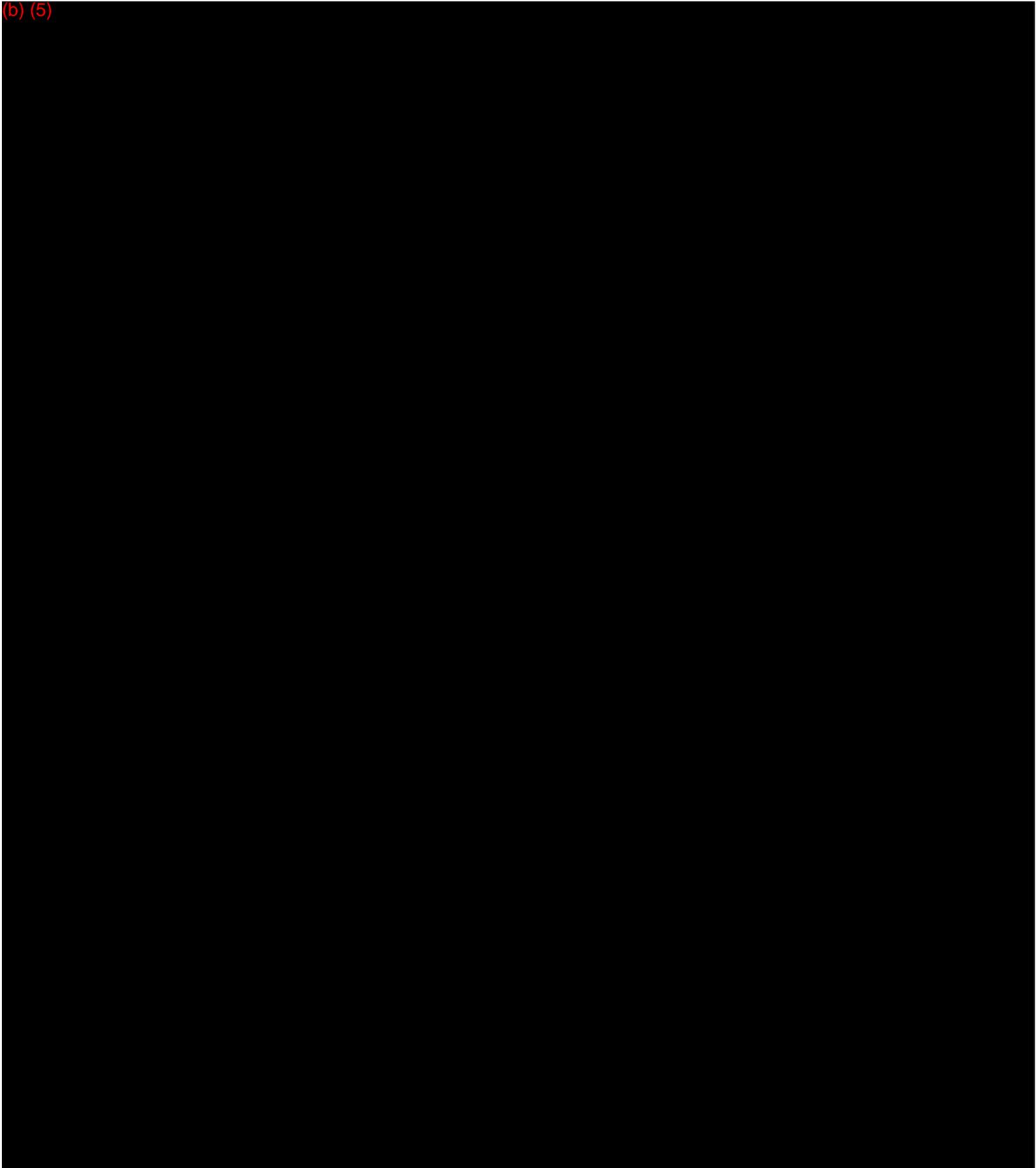
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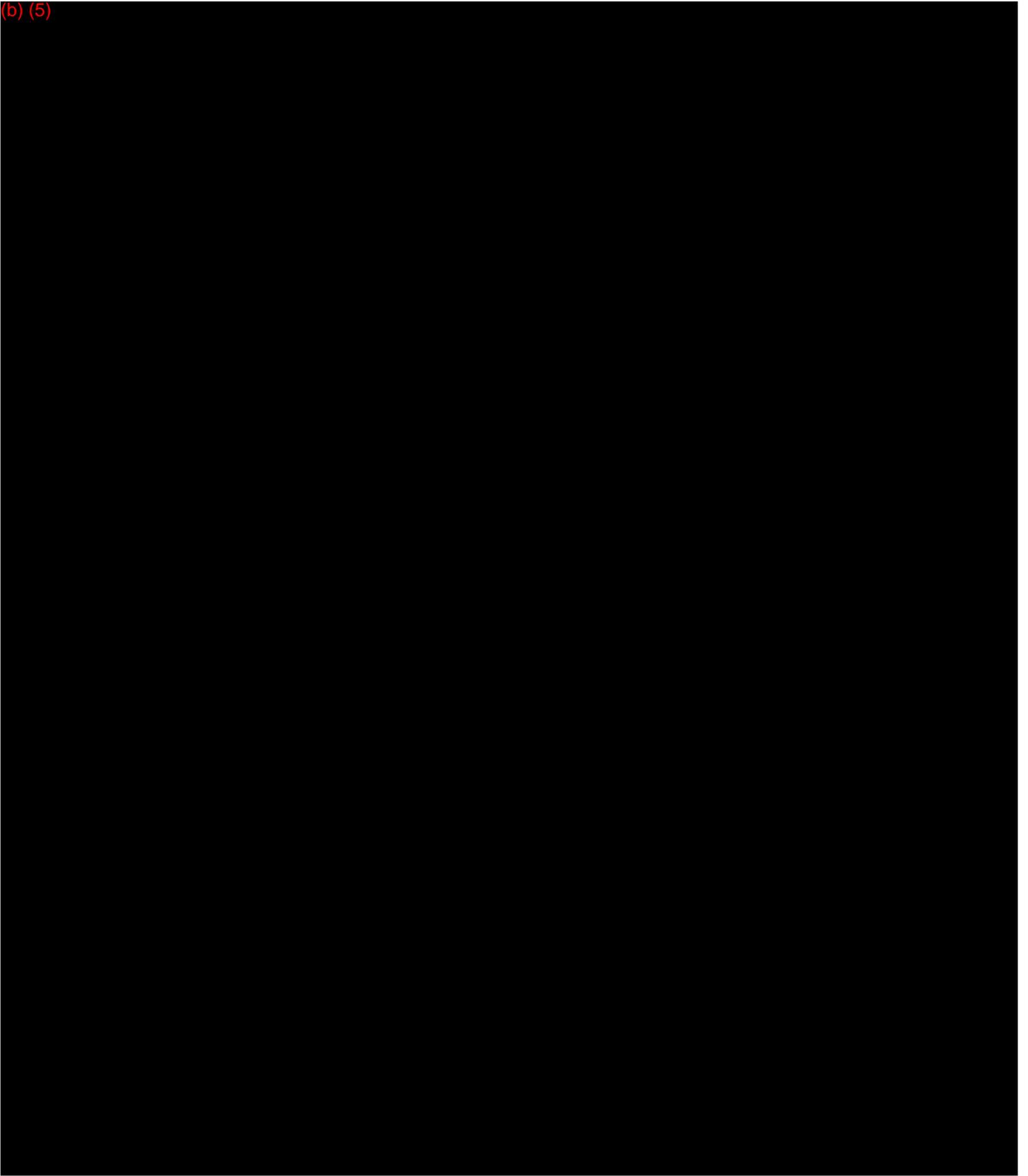
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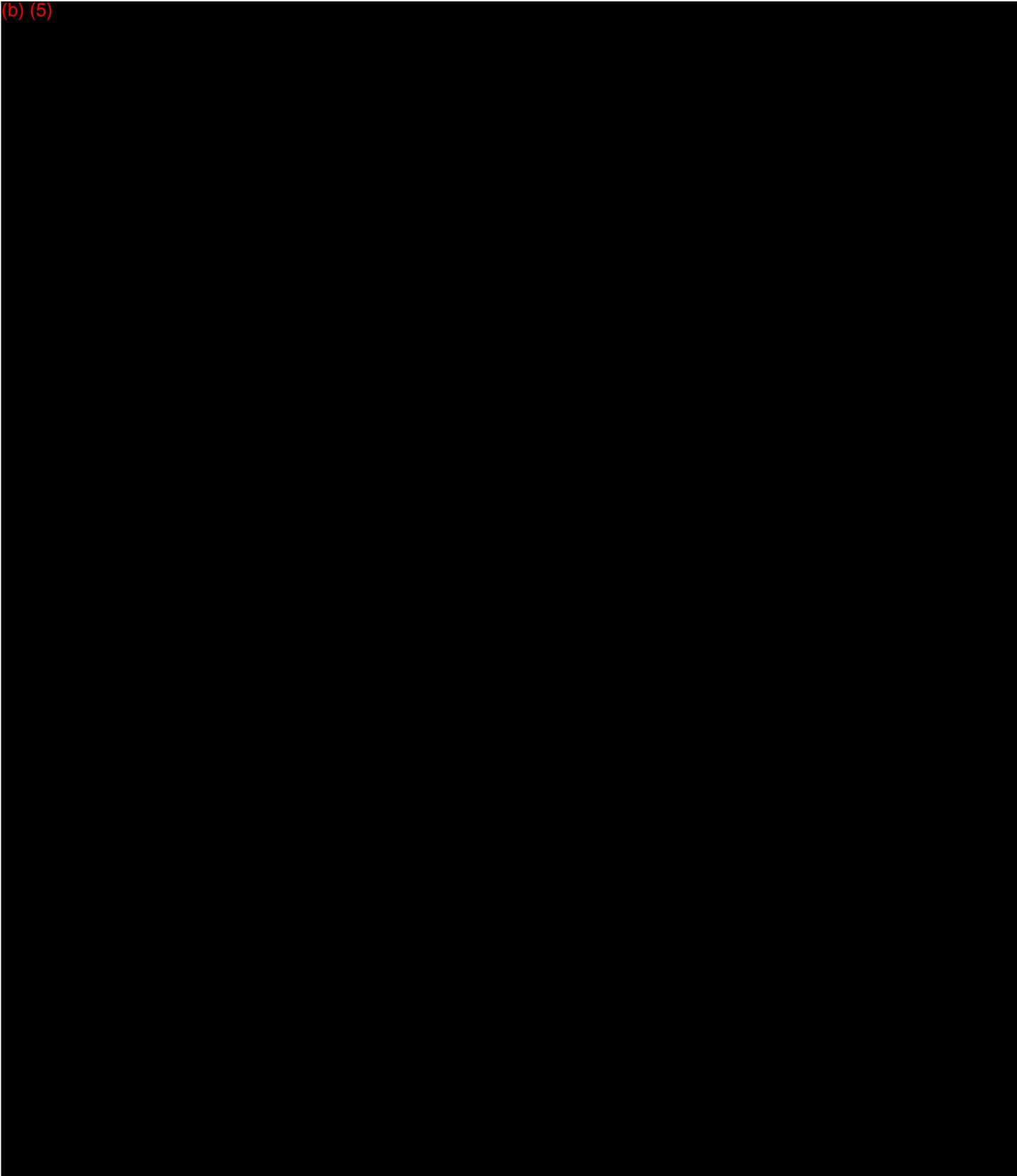
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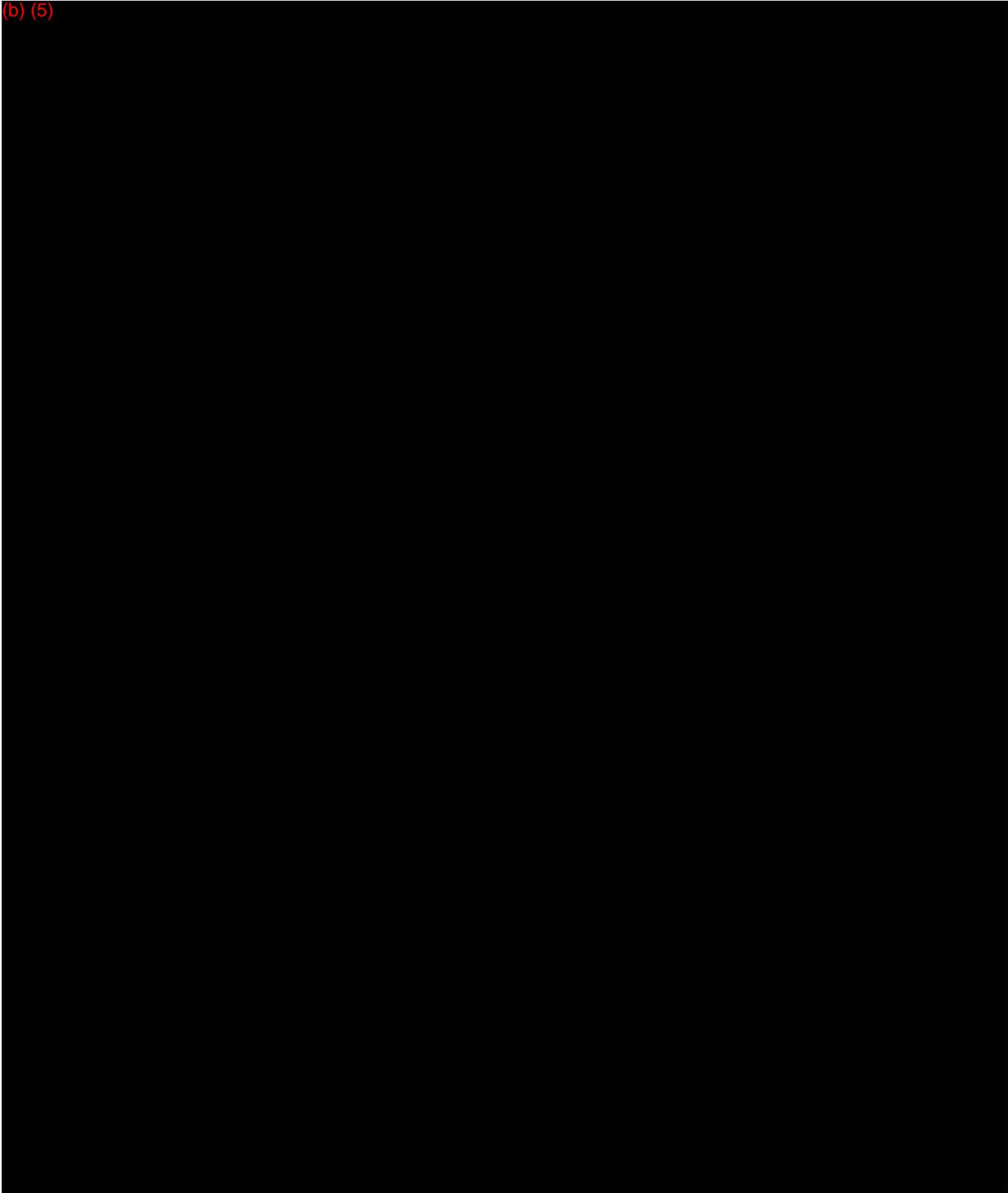
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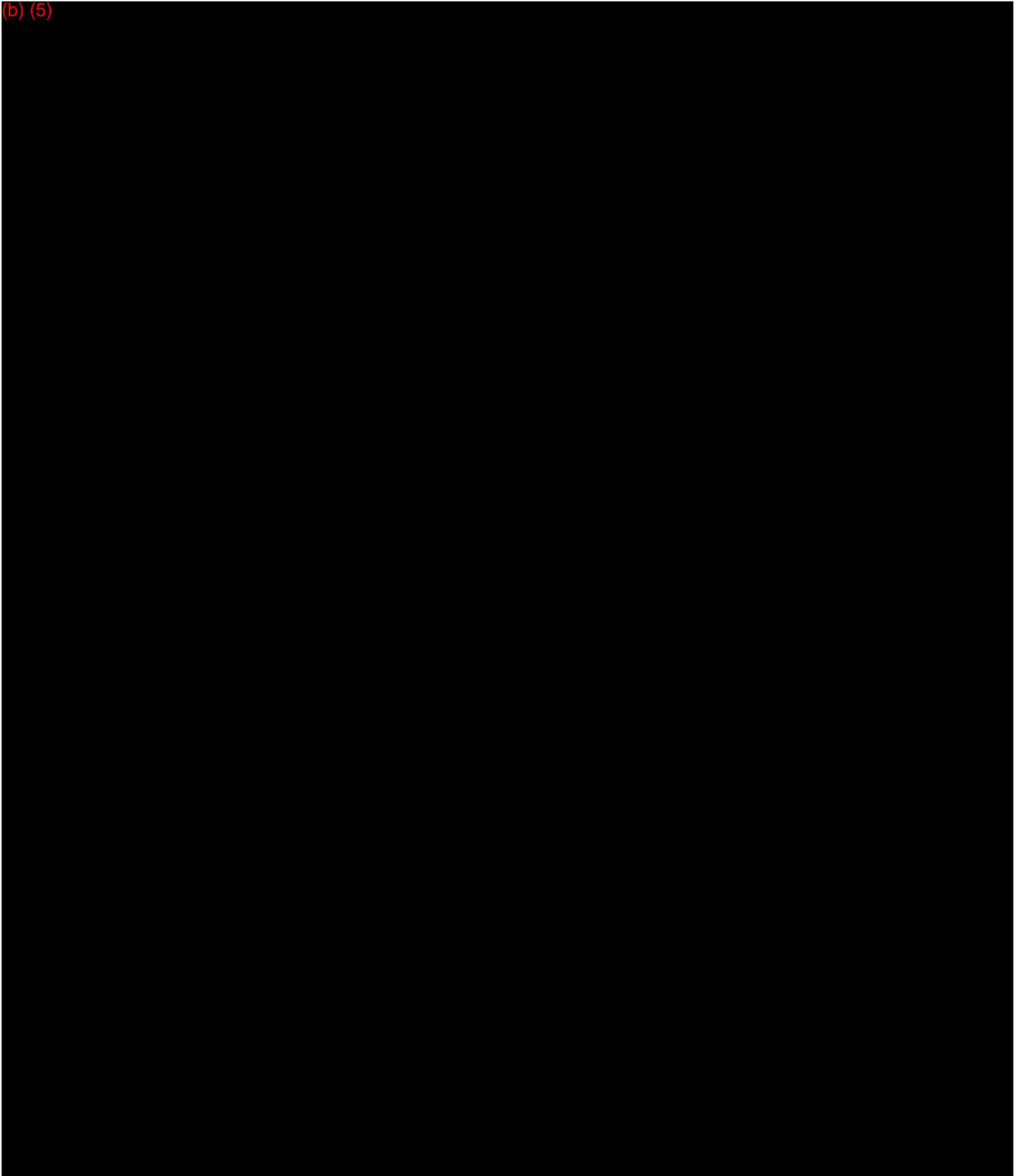
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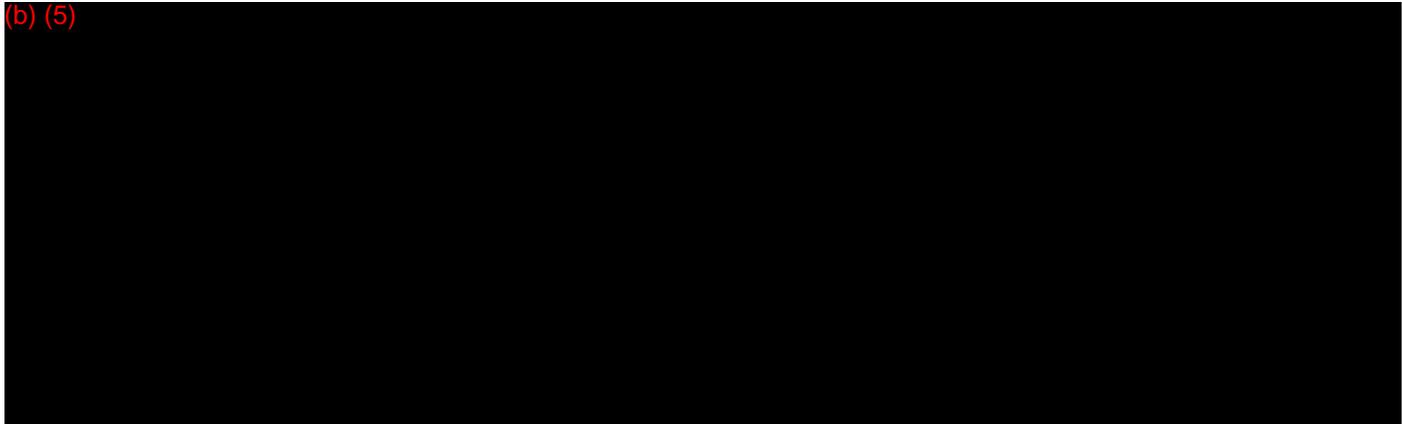
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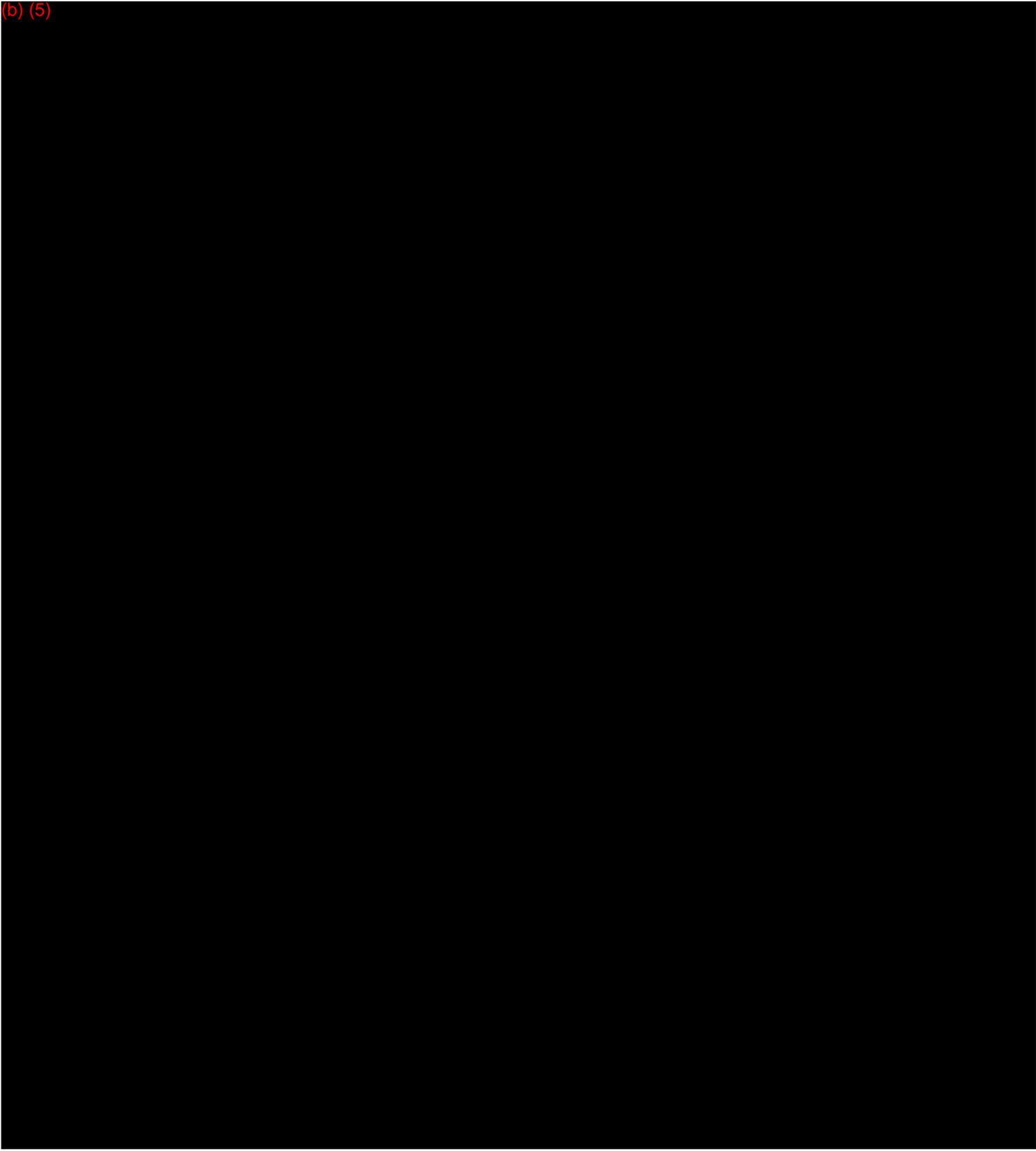
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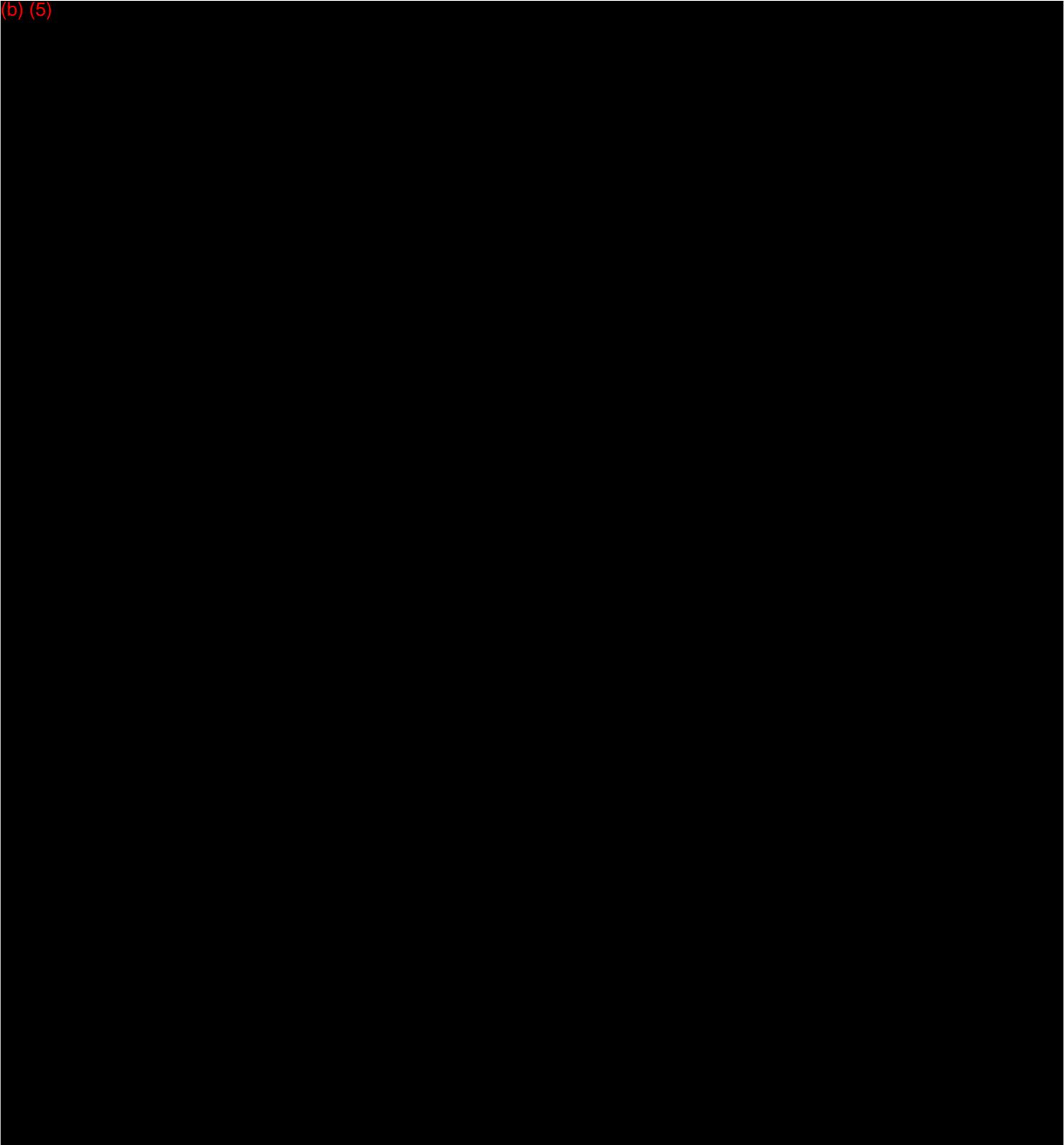
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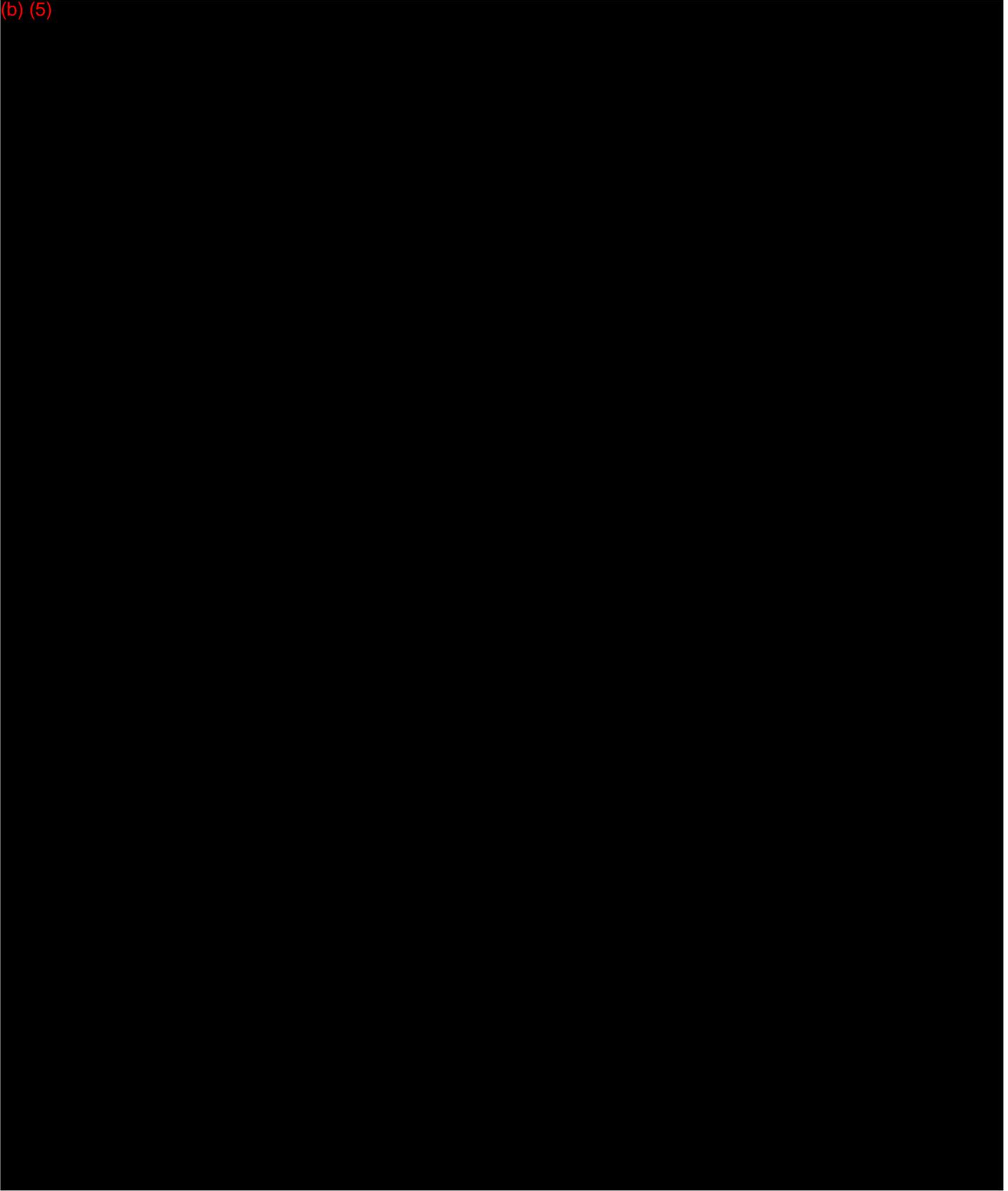
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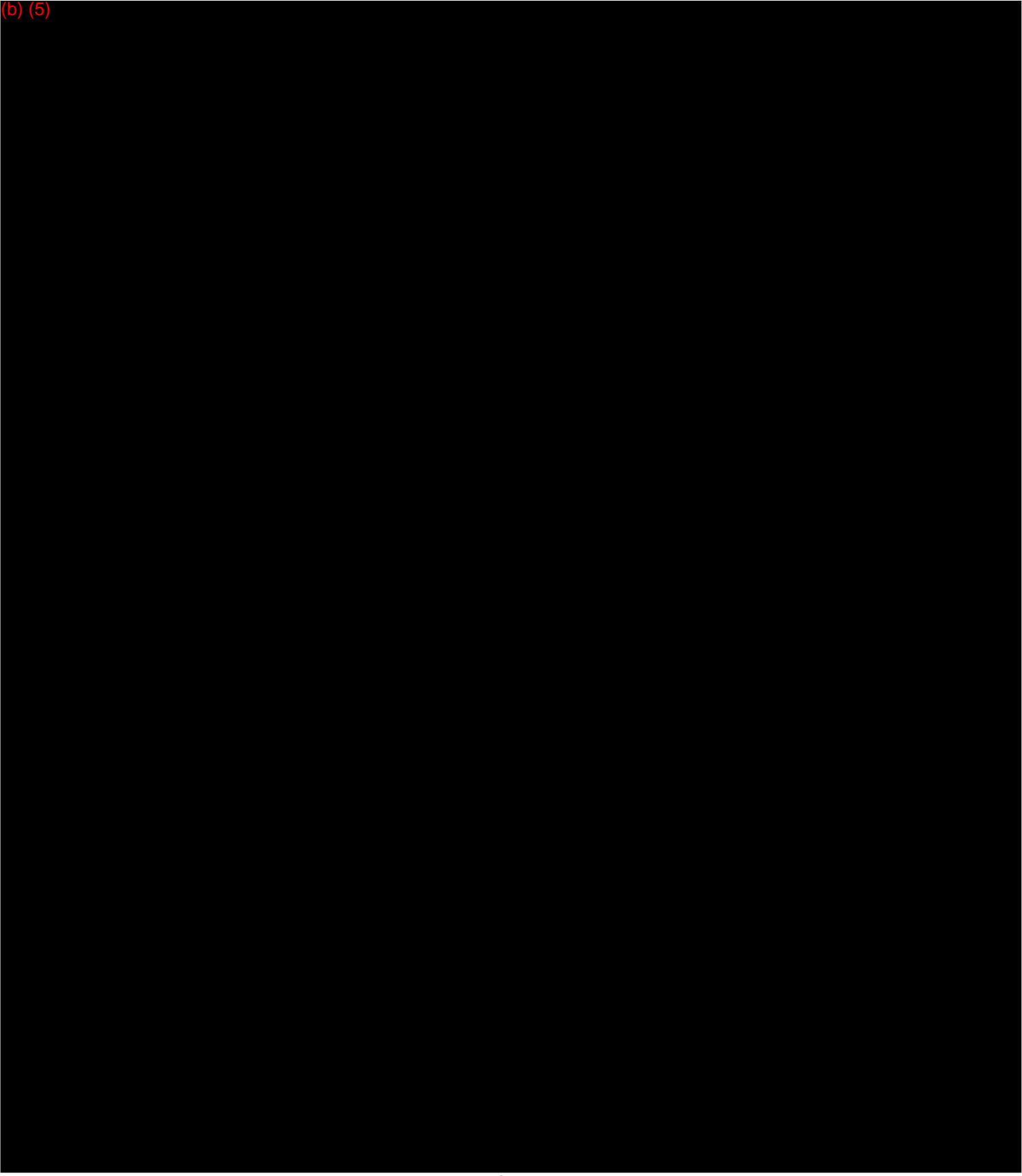
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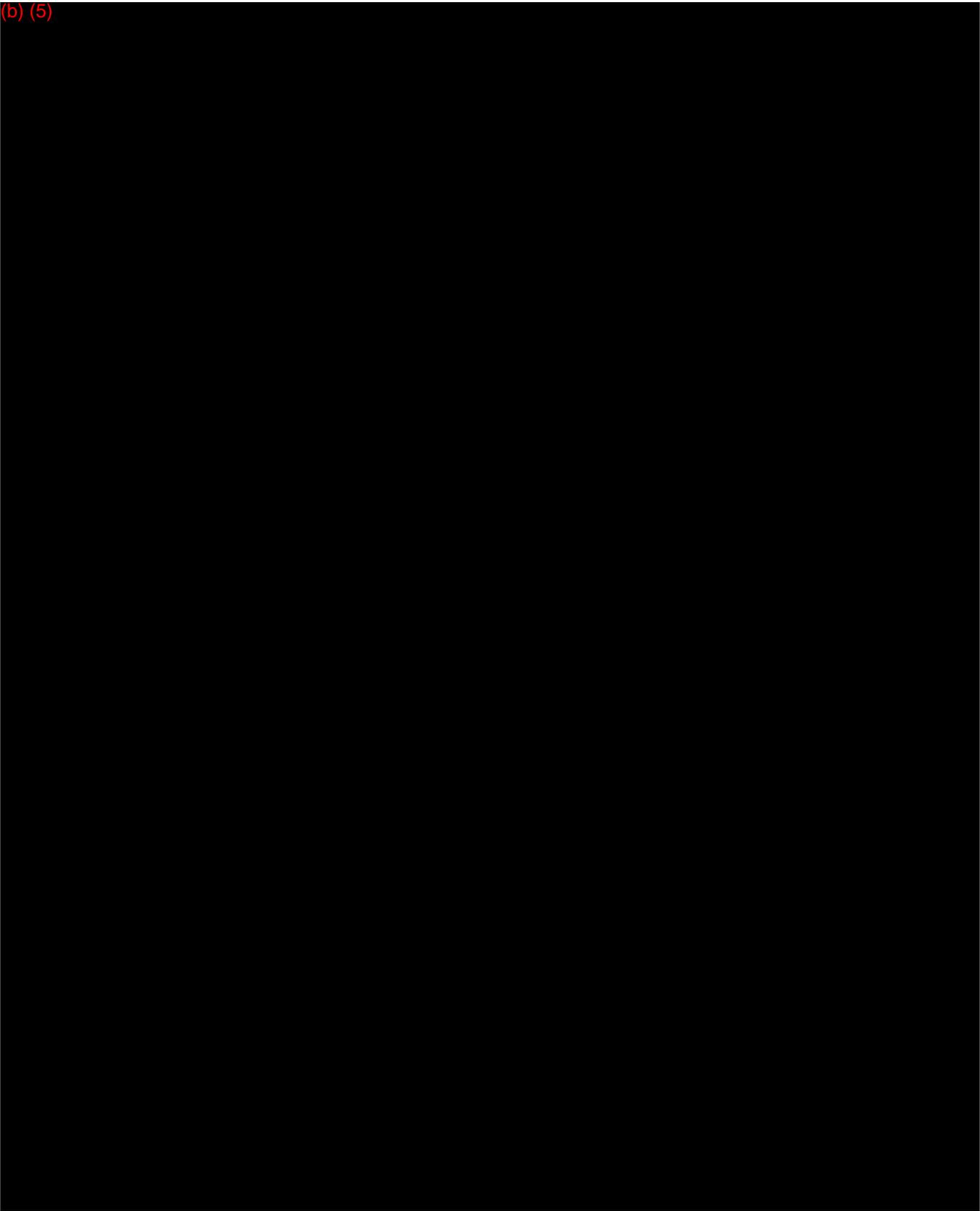
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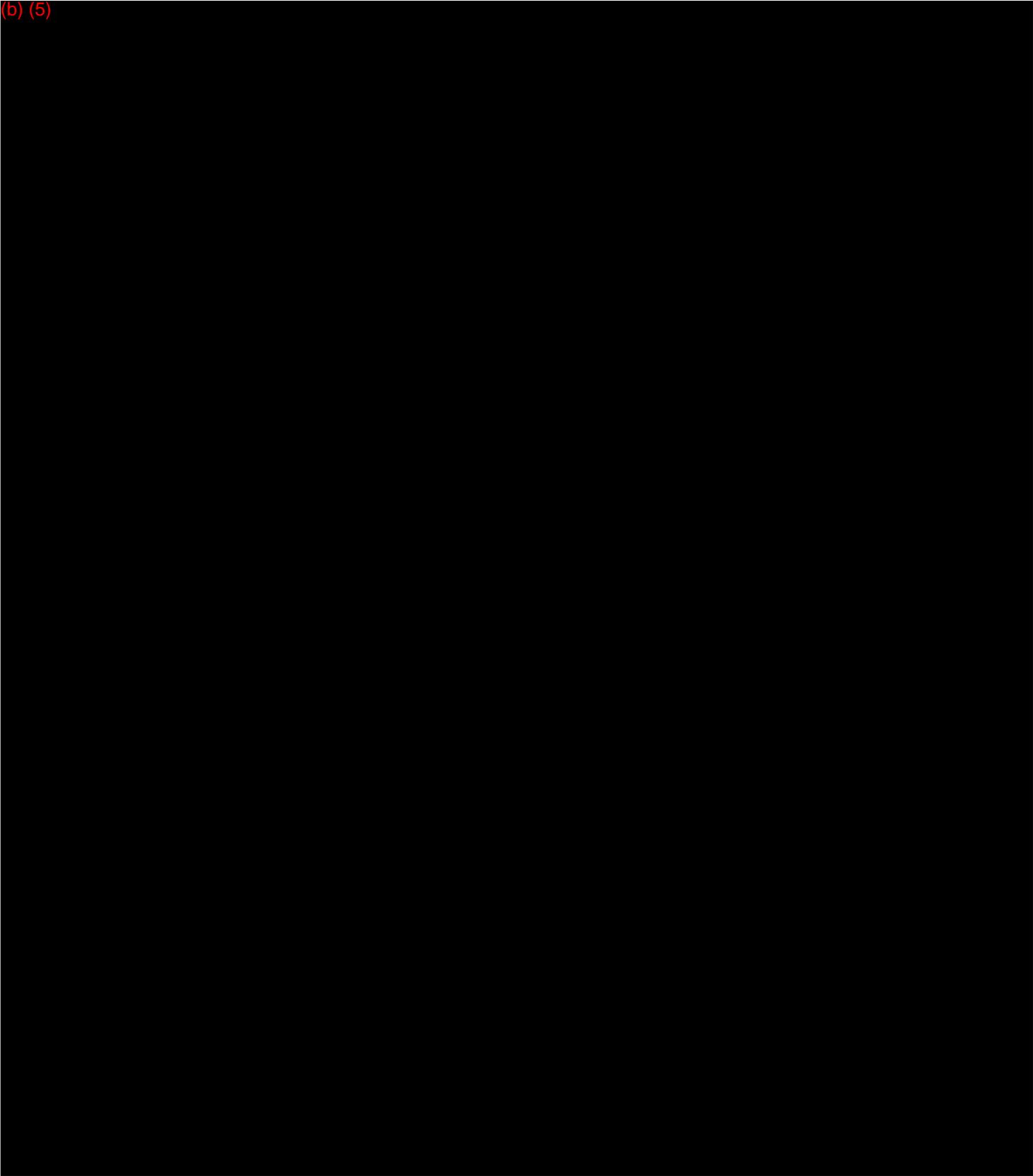
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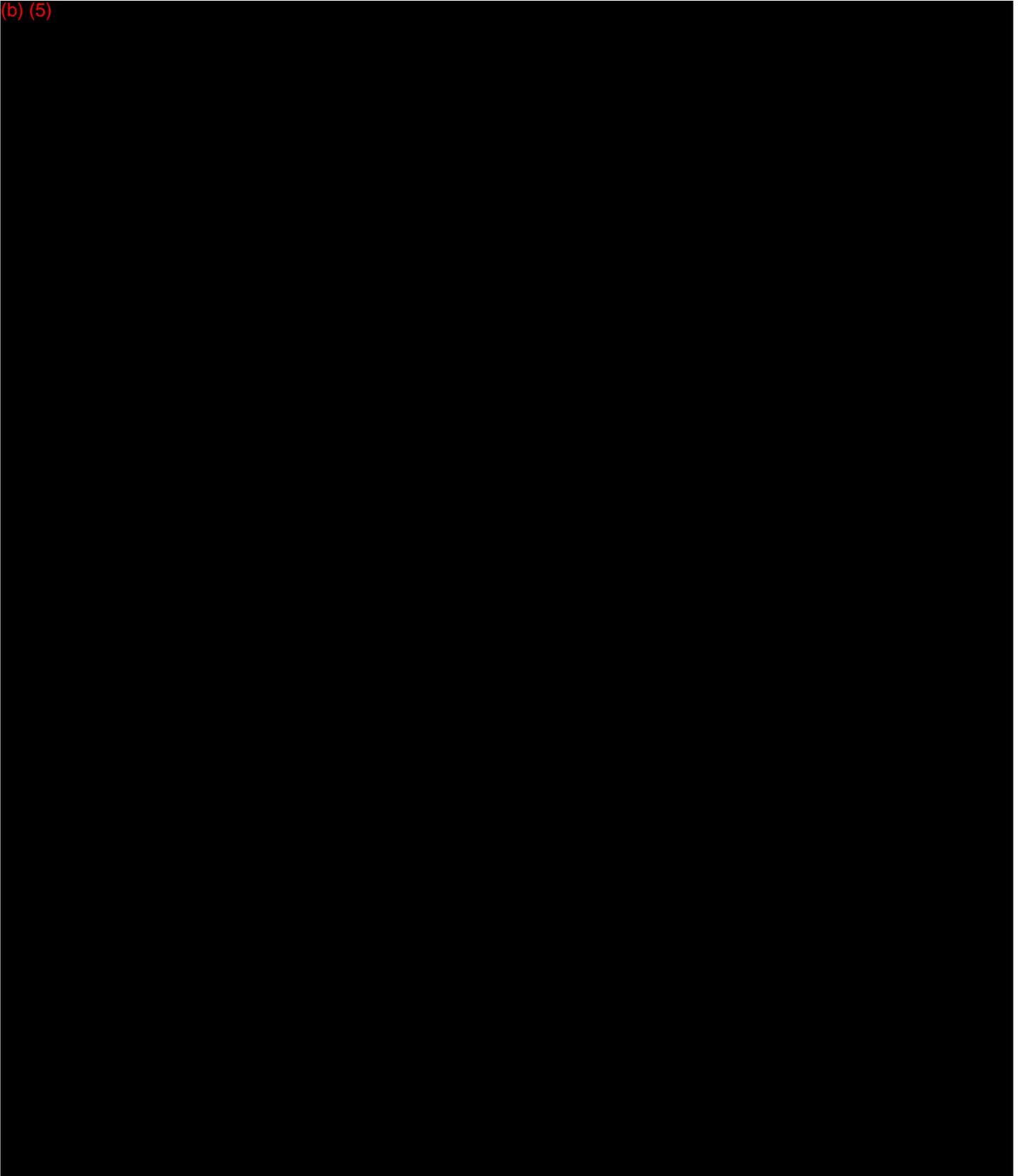
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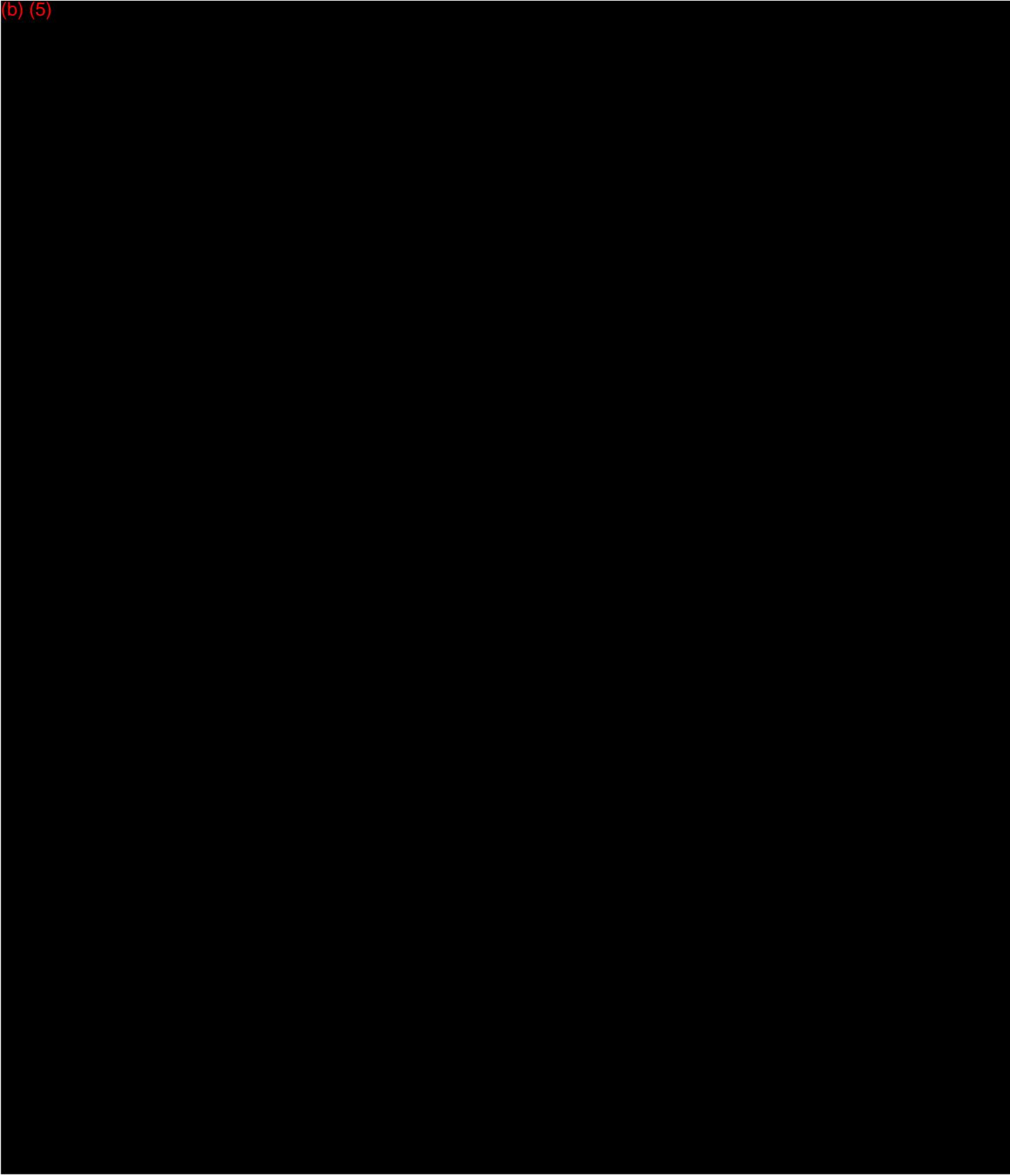
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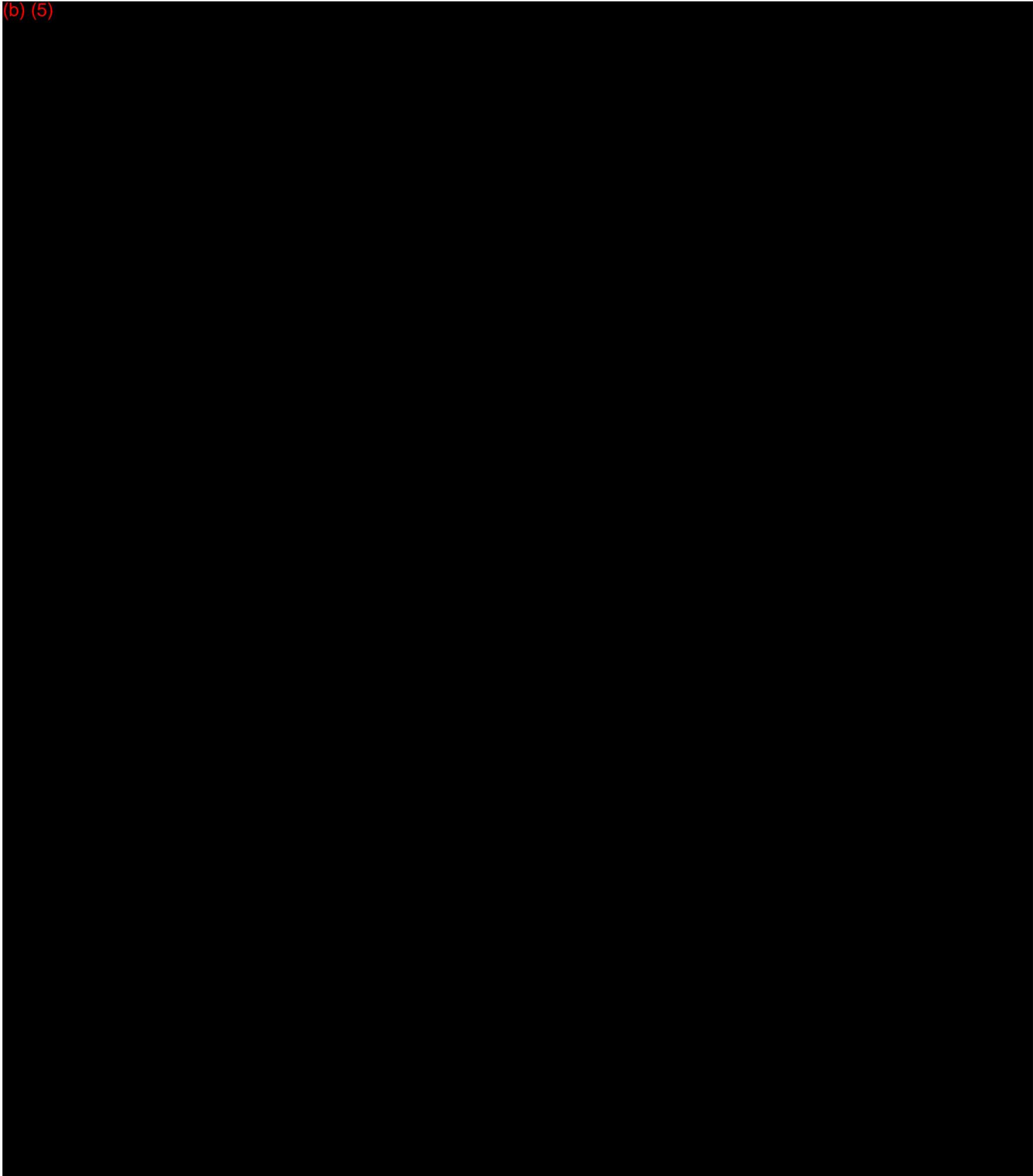
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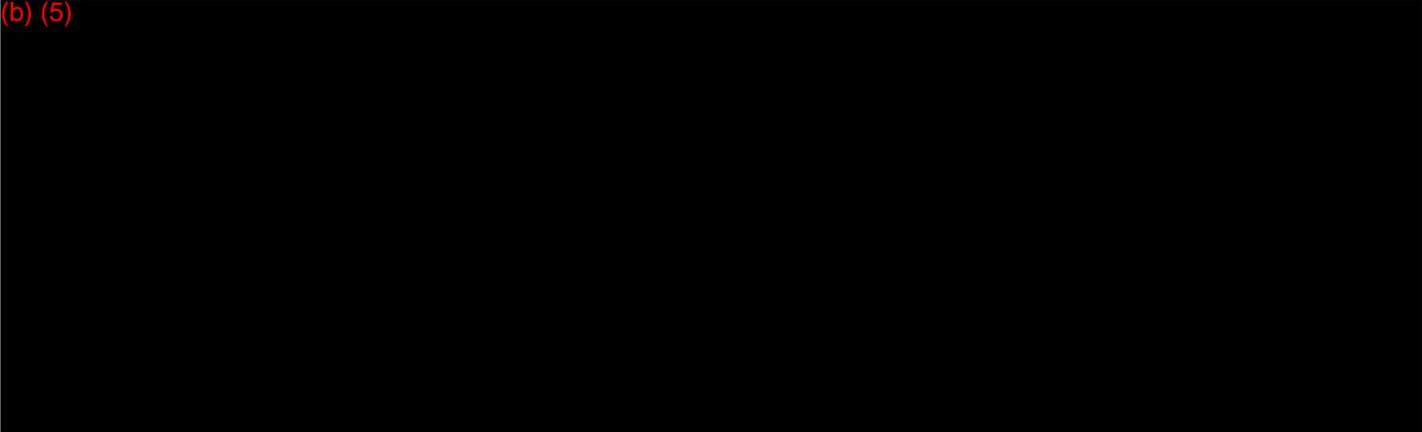
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From: [Menon, Ramesh](#)
To: [Califf, Robert](#)
Cc: [Cristinzio, Dayle](#); [Kraus, Tom](#); [Alexander, Uchenna](#)
Subject: Updated Warren backgrounder, UDI, and DMD info
Date: Wednesday, October 21, 2015 5:32:44 PM
Attachments: [Warren backgrounder.docx](#)
[Warren Final Signed UDI response from CMS.PDF](#)
[UDI TPs FINAL.DOC](#)
[Duchenne Muscular Dystrophy.docx](#)

Dr. Califf,

I've attached some updated information in advance of your meeting with Sen. Warren tomorrow. The first is an updated backgrounder (new content is highlighted in yellow) noting one additional area of interest, Duchenne Muscular Dystrophy, and a brief addition on what CMS has said to Warren on UDI. During this morning's prep it sounded like you wanted more detail on CMS's position on UDI, so in case it's helpful I've also attached the full response they sent to Sen. Warren's office, along with a set of messages that were cleared through the Department. Lastly, I have attached an issue paper on Duchenne Muscular Dystrophy. If you have any questions or comments, please let us know.

Thanks,
Ramesh

Duchenne Muscular Dystrophy (DMD)

Key Messages

Key Message #1: FDA recognizes the unmet medical need that exists in patients with DMD, the devastating nature of the disease for patients and their families, and the urgency to make new treatments available. We remain committed to working with all companies to expedite the development and approval of safe and effective drugs to treat the disease.

Key Message #2: The engagement by Parent Project Muscular Dystrophy (PPMD) in submitting their proposed guidance is an example of how early input from patients and caregivers can often contribute to drug development.

Questions and Answers

- 1. Why did FDA split up the advisory committee meetings for BioMarin's drisapersen and Sarepta's eteplirsen treatments for Duchenne Muscular Dystrophy?**
 - FDA cannot comment on the status of any applications nor can we provide agenda items for future meetings until they are announced in the Federal Register.
- 2. What impact will the draft guidance on developing drugs for treatment of DMD have for patients?**
 - Patients will benefit from open discussions about drug development with all stakeholders, including FDA, advocates and researchers. Drug development programs might be more successful if clinical trials are designed in such a way to gather the best information possible to support an application for FDA approval.
- 3. Why did FDA's draft guidance differ so greatly from the draft submitted by Parent Project Muscular Dystrophy?**
 - FDA values the effort and input provided by PPMD in their proposed guidance, submitted to FDA on June 25, 2014. The agency appreciates the thoughtfulness of the proposed guidance and comprehensive insight provided by the DMD community.

- As far as the Center for Drug Evaluation and Research knows, this is the first time an advocacy group has submitted draft guidance for drug development.
- PPMD's draft document provides helpful background about the disease and other information FDA does not typically include in guidance documents. Generally, FDA's guidances are limited to information sponsors should consider when developing drugs for a disease or disorder and are not meant to provide comprehensive information about the diagnosis, natural history and treatment of a disease.
- The purpose of this guidance is to assist drug companies and researchers in the clinical development of drugs to treat DMD. It covers important clinical considerations sponsors (such as drug manufacturers) should consider when conducting clinical trials, such as study populations, safety considerations and study design.

4. Are there currently drugs to treat DMD under development? When might one be approved?

- There are a number of companies that have publicly announced they've been developing DMD drugs. The public orphan drug designation database lists several investigational drugs. Information contained in any Investigational New Drug application or any New Drug Application is confidential and can only be released by the sponsor.
- FDA recognizes the unmet medical need in DMD and the devastating nature of the disease for patients and their families and the urgency to make new treatments available. We remain committed to working with all companies to expedite the development and approval of safe and effective drugs to treat the disease.

Background

- Senator Warren is the most likely member to raise this issue, however staff of a number of Senate HELP offices, including those from Alexander, Murray, Burr, Bennet, and Sanders have participated in briefings or sent us letters.
- In September, Senator Warren and others introduced the Advancing Targeted Therapies for Rare Diseases Act of 2015 – the bill would allow sponsors to leverage data from previous submissions for a therapeutic that treats the same disease but a different genetic mutation. It is similar to a provision Sarepta pushed for, part of which made it into the House cures bill. The bill could have impacts for DMD, and potentially other rare diseases.
- The stakeholder community has been very actively engaged on this issue, including holding briefing events on the Hill, creating a petition on the White House website that we responded to, and prompting numerous letters and briefing requests. One of the most

prominent stakeholders, a mother with a son who has DMD, is from MA and has actively engaged Senator Warren's office.

- We have not heard from the Hill on this issue yet, but there has been recent press regarding how the advisory committee meetings for BioMarin's drisapersen and Sarepta's eteplirsen are occurring two months apart. Articles have speculated on why that's the case and commented that news on the timing seemed to impact stock prices for both companies. The meeting on drisapersen is publicly scheduled for November 24. The topic of the January AC is technically still confidential - there's a tentative meeting date listed, and Sarepta has announced the tentative meeting date – but we're not able to discuss what the January meeting is about yet.

Unique Device Identifiers

Topline Points

- The Food and Drug Administration Amendments Act of 2007 (FDAAA) required the FDA to issue regulations establishing a unique device identification system for medical devices.
- In September 2012, the FDA issued a strategy for establishing a National Medical Device Postmarket Surveillance System (MDS) for gathering and analyzing real world data, or data collected as part of routine clinical practice and patient experience to improve post-market surveillance, expedite product recalls and enhance clinical research.
- The centerpiece – and most critical element -- of postmarket surveillance is the incorporation of UDIs into electronic health information; particularly electronic health records (EHRs) and device registries.
- UDIs incorporated into EHRs would allow the use of a device to be linked with a patient's experience with that device, thereby generating better information for patients and providers to make well-informed decisions, facilitate medical device innovation and safety surveillance, and further quality initiatives and value-based healthcare.
- The FDA, the Office of the National Coordinator for Health IT (ONC), and the Centers for Medicare & Medicaid Services (CMS) are working closely on the shared goal of incorporating UDIs into EHRs, starting with implantable devices. The recently released NPRM is an important step in this process.
- CMS and the FDA look forward to continuing to explore options that would improve surveillance in a timely and effective manner. CMS and FDA are committed to capturing appropriate data and sharing information transparently to improve the quality and safety of care delivered to people across the nation.
- FDA and CMS also support the recommendation by the National Committee on Vital and Health Statistics to consider conducting voluntary pilot tests of the benefits, costs, and feasibility of UDIs in claims reporting between providers and commercial payers.
 - Voluntary pilots should address key challenges to adding UDIs to claims including significant technological hurdles and costs (for providers, payers and others), as well as difficulties in validating UDIs reported on claims.
 - While inclusion in EHRs are critical, utilization on claims forms could allow assessment of longitudinal patient data for certain data points that could be helpful in surveillance efforts.

- We also support the recommendation by the National Committee on Vital and Health Statistics that FDA and stakeholders work together to improve existing mechanisms for post-market surveillance of devices.

Background: The UDI system, which is being phased in over several years, attempts to accomplish the goals of improving post-market surveillance, expediting product recalls, and enhancing clinical research with respect to medical devices. These uses will be particularly important with respect to high-risk implantable medical devices. In September 2012, the FDA issued a strategy for establishing a National Medical Device Postmarket Surveillance System (MDS) for gathering and analyzing real world data, or data collected as part of routine clinical practice and patient experience. The purpose of such a national system is to identify poorly performing devices in near real-time; characterize and disseminate information about the real-world performance of medical devices on the market; and facilitate the clearance and approval of new devices, or new uses of existing devices.

EHR

Currently, there are tens of thousands of medical devices used in healthcare but we generally cannot learn about their performance in clinical practice because there is no way to identify which device was used in which patient. Key challenges include a nationally standardized methodology for assigning the UDI, limited data and quality tools to assure accurate and consistent data capture as well as diverse EHR platforms with insufficient interoperability between platforms.

Registries

UDIs incorporated into device or procedure-related registries could have similar benefits as those noted for EHRs. Registries could promote post-surveillance monitoring and quality by serving as a single location where robust information would be collected. Key challenges include lack of standardized capture of the UDI on the label at point of care (POC), a challenge that also applies to claims reporting, and obstacles to electronic transmission of the UDI (e.g., from EHRs to registries). Professional societies, as they either modify or develop their registries, are increasingly enabling POC-capture of UDIs. Consistent with MDS, the FDA continues to promote registry development, both domestically and through international consortia. Additionally, standards development organizations are tackling how to standardize data transmission.

Claims

Some have proposed that incorporating UDIs into claims could also facilitate device safety surveillance, as well as initiatives to improve patient quality. As a first step, ASCX12, of which FDA and CMS are participants, is exploring business cases for including UDIs into health care transactions.

Senator Elizabeth Warren (D-MA)

Senior Senator

Residence: Cambridge

Born: June 22, 1949; Oklahoma City, Okla.

Religion: Methodist

Family: Husband, Bruce Mann; two children

Education: George Washington U., attended 1966-68; U. of Houston, B.S. 1970 (speech pathology & audiology); Rutgers U., J.D. 1976

Military Service: None

Career: Law professor; White House consumer protection adviser; financial markets oversight panel chairwoman; bankruptcy analyst; lawyer; homemaker; elementary school speech pathologist

First Elected: 2012 (1st term); Defeated Sen. Scott Brown, R

Latest Election: 2012 General (53.74%)

Political Highlights: No previous office



Committee Assignments:

- Banking, Housing & Urban Affairs (Economic Policy - ranking member; Financial Institutions & Consumer Protection; Securities, Insurance & Investment)
- Energy & Natural Resources (Energy; National Parks; Public Lands, Forests and Mining)
- Health, Education, Labor & Pensions (Primary Health and Retirement Security)
- Special Aging

Elizabeth Warren, a fearless consumer advocate who has made her life's work the fight for middle class families, was elected to the United States Senate on November 6, 2012, by the people of Massachusetts.

She is widely credited for the original thinking, political courage, and relentless persistence that led to the creation of the Consumer Financial Protection Bureau. President Obama asked her to set up the new agency to hold Wall Street banks and other financial institutions accountable, and to protect consumers from financial tricks and traps often hidden in mortgages, credit cards and other financial products.

In the aftermath of the 2008 financial crisis, Warren served as Chair of the Congressional Oversight Panel for the Troubled Asset Relief Program (TARP). Her independent and tireless efforts to protect taxpayers, to hold Wall Street accountable, and to ensure tough oversight of both the Bush and Obama Administrations won praise from both sides of the aisle. The *Boston Globe* named Elizabeth Warren Bostonian of the Year and *TIME Magazine* called her a "New Sheriff of Wall Street" for her oversight efforts.

Senator Warren was a law professor for more than 30 years, including nearly 20 years as the Leo Gottlieb Professor of Law at Harvard Law School. The graduating class at Harvard twice recognized her with the Sacks-Freund Award for excellence in teaching. She taught courses on commercial law, contracts, and bankruptcy and wrote more than a hundred articles and ten

books, including three national best-sellers, *A Fighting Chance*, *The Two-Income Trap*, and *All Your Worth*. *National Law Journal* named her one of the Most Influential Lawyers of the Decade, *TIME Magazine* has named her one of the 100 most influential people in the world three times, and she has been honored by the Massachusetts Women's Bar Association with the Lelia J. Robinson Award.

Elizabeth learned first-hand about the economic pressures facing working families, growing up in a family she says was "on the ragged edge of the middle class." She got married at 19, and after graduating from college, started teaching in elementary school. Her first baby, a daughter Amelia, was born when Elizabeth was 22. When Amelia was two, Elizabeth started law school. Shortly after she graduated, her son Alex was born. Elizabeth hung out a shingle and practiced law out of her living room, but she soon returned to teaching.

Elizabeth is a graduate of the University of Houston and Rutgers School of Law. Elizabeth and her husband Bruce Mann have been married for 35 years and live in Cambridge, Massachusetts. They have three grandchildren.

AREAS OF INTEREST

DRUGS

Duchenne Muscular Dystrophy (DMD): Sen. Warren's office has participated in multiple briefings on DMD. In September 2015, Sen. Warren the bill would allow sponsors to leverage data from previous submissions for a therapeutic that treats the same disease but a different genetic mutation. The sponsors of the bill have stated the goal is to help with development of treatments for DMD and other rare diseases.

Antibiotics: Senator Warren's staff have been very engaged on the antibiotics issue. They have been leading the effort in the Senate to draft legislation (part of the Senate Innovation initiative) to address the current concerns with the way FDA updates susceptibility test interpretive criteria (breakpoints). Sen. Warren is concerned about misuse of antimicrobials and is pushing for stronger stewardship legislation in this area.

Biomarkers: Sen. Warren's staff has been engaged on the biomarker qualification pathway legislation being drafted for the Senate Innovation initiative. Her staff has been strongly in FDA's corner in regards to keeping the pathway public, stopping unreasonable timelines, and allowing for prioritization of review.

Biologics Price Competition and Innovation Act (BPCIA) implementation: Senator Warren may bring up BPCIA, in the context that FDA is moving too slowly in issuing our guidances. During the recent Senate HELP hearing, she was very irate that FDA had not issued all the draft guidances.

Generic Labeling Proposed Rule (CBE-0): Senator Warren joined 40 Democratic House and Senate policymakers in supporting the proposed rule. The policymakers specifically argued that

the rule serves an important purpose in ensuring the public is informed of new safety information, and to make sure the labeling of generic drugs are up to date even when the branded product is either no longer being marketed, or has not undergone a labeling update to reflect newly discovered risks.

Patient Medical Information (PMI): Senator Warren’s office contacted us this summer requesting TA on their current draft of the Cody Miller Act, which was first introduced in 2012. (15-year-old Cody Miller committed suicide days after switching to a new allergy medication; the manufacturer subsequently added “suicidality” to the drug label) FDA is in the process of developing rulemaking for PMI, using input obtained from studies, meetings, and public comments. Senator Warren’s office is aware of the research that has been conducted in this area, and that we are working on our rulemaking process. They may be continuing to introduce legislation primarily to get the Agency to move more quickly on the issue. In our summer 2015 TA, we pushed back on their two-year timeframe and suggested that it might take four years to promulgate a final rule.

BIOLOGICS

MSM Blood Donation: Sen. Warren has been a consistent advocate for revising the blood donation policy for men who have sex with men (MSM), including leading a letter with 80+ members last December. Her staff participated in a briefing in September on the issue – they understand the rationale behind moving to a one-year deferral policy as a first step, but they urged FDA to provide a transparent implementation process to clarify what data would need to be considered to evaluate moving to a risk-based assessment. FDA intends to issue final guidance document before the end of 2015.

Vaccines and Medications in Pregnancy: Senator Warren actively supported additional funding from HHS for a Boston U study called the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS). CDER has agreed to provide funds for VAMPSS from their FY 2016 budget.

Bacterial Contamination of Platelets: Senator Warren has written to FDA in the past with her concerns about this leading infectious risk of blood transfusions and is seeking information from CBER about the draft guidance currently under review at FDA. In particular, a Massachusetts company that has developed a testing method, is interested in the outcome of the guidance.

DEVICES

Medical device safety: Senator Warren’s staff, along with Senators Whitehouse, Baldwin, and Murray, have served as a “left flank” during Senate negotiations, particularly with respect to the provisions on medical devices. Her staff has worked to add additional safety measures to many areas of the suite of device reforms under consideration in the Senate, and has serious concerns about codifying provisions on valid scientific evidence and third parties.

MEDTECH Act: Senator Warren’s staff is particularly concerned that the MEDTECH language may preclude FDA from reviewing software and health-IT related devices that may pose more risk to patients

than originally contemplated by the language. She is working with her Minority colleagues to provide maximum clarity to the MEDTECH language so sponsors of these have less legal ground to claim that they are exempt from FDA review, when they should be making premarket submissions to the Agency.

Laboratory developed tests: Senator Warren has supported FDA's issuance of its draft guidances proposing a regulatory framework for regulation of LDTs, and has concerns about proposals such as those from DTWG, CAP, and AMP that would (in many cases) reduce the level of evidence required to market LDTs and IVDs, and unduly place many authorities for oversight for LDTS under CMS' CLIA program.

Unique device identifier in health claims: The Senator is one of the Hill's champions for incorporating UDIs into health claims, as well as in electronic health records generally. She and Senator Grassley have written to CMS to express concern that CMS is not readily accommodating UDI into claims, and is fighting to include a provision in the Senate draft to make inclusion of UDI mandatory.

- In part, CMS said the following to Sen. Warren's office: "CMS believes that mechanisms other than claims reporting for collecting UDIs would avoid the significant challenges and risks of collecting UDIs on claims. CMS supports the FDA's engagement with the public to identify registries that could be utilized together with electronic health record information to better leverage real world clinical data to improve post market monitoring and surveillance."

Essure: Senator Warren expressed an interest in the Advisory Committee meeting held 9-24-15 concerning the adverse events attributed to the permanent contraceptive product, Essure. The AC recommended keeping the product on the market but FDA will continue to closely monitor future complaints.

FOODS

Nutrition Labeling – “Added Sugars”: In 2014, Senator Warren co-signed a letter to FDA regarding concerns from the cranberry industry about the proposed revision of the Nutrition Facts Label to require the inclusion of information about “added sugars.” FDA responded that we recognize that the proposed declaration of added sugars is of great concern to the cranberry industry, and that we intend to take all of the comments that we've received into careful consideration when drafting the final regulation.

Genetically Engineered (GE) Foods: In February 2015, Senator Warren co-sponsored the “Genetically Engineered Food Right-to-Know Act,” which would prohibit the sale of certain foods that have been genetically engineered or contain genetically engineered ingredients, unless that information is clearly disclosed. It would also prohibit the labeling or advertising of foods containing GE material as “natural.”

ANIMAL DRUGS

Antibiotic Resistance: In March 2015, Senator Warren co-sponsored the “Preventing Antibiotic Resistance Act,” which would require FDA re-review of certain antimicrobial drugs approved for use in food-producing animals and sets out new criteria for FDA review of new applications. The bill’s sponsors have expressed concern about a perceived “loophole” to GFI #213 which would allow low-dose and/or long or unspecified term administration of medically important antimicrobials, which they view as characteristic of production uses, continuing under the “guise” of prevention uses even after the judicious use strategy is fully implemented and, if they do not meet certain criteria as set forth in the bill, the drugs would have to be withdrawn from the market. In November 2014, Senator Warren co-signed a letter urging FDA to issue a proposed rule to increase data collection on the distribution of medically important antibiotics used in agriculture. In August 2014, Senator Warren co-signed a letter expressing concern about the public health threat posed by antibiotic resistant bacteria.

OTHER ISSUES

Clinical trial diversity: In 2014, Sen. Warren and several other senators wrote to FDA requesting that the Agency do more to include demographic subgroup analyses of clinical trial data in new drug applications, including data on females and members of ethnic groups. The letter was written in anticipation of the release of FDA’s Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data, which was issued in August 2014. The plan outlines the agency’s current policies and practices and also includes 27 separate action items, divided into the three over-arching priorities of Data Transparency, Data Quality, and Diverse Participation. FDA is currently implementing the plan.

Relevant Bill Introductions

- S. 2030, the “Advancing Targeted Therapies for Rare Diseases Act of 2015” with Senators Bennet, Burr, and Hatch. The bill would facilitate the development, review, and approval of genetically targeted drugs for a patient subgroup with a rare disease or conditions that is serious or life-threatening by allowing the sponsor of a genetically targeted drug to rely upon previously developed and submitted data and information for a drug that incorporates or utilizes the same or similar genetically targeted technology, or the same variant protein targeted technology.
- S. 511, the “Genetically Engineered Food Right-to-Know Act” with 14 other senators. The bill would prohibit the sale of food that has been genetically engineered or contains genetically engineered ingredients, unless that information is clearly disclosed, and would prohibit labeling or advertising foods containing genetically engineered material as “natural,” or using similar words.
- S. 621, the “Preventing Antibiotic Resistance Act,” with seven other senators. The bill would require FDA re-review of certain antimicrobial drugs approved for use in food-producing animals, and, if they do not meet certain criteria as set forth in the bill, the drugs

would have to be withdrawn from the market; it would also set out new criteria for FDA review of new applications for antimicrobial drugs for food-producing animals.

- S. 320, the “Medical Innovation Act of 2015,” with three cosponsors. The bill authorizes the collection of supplemental payments from other federal government programs to be used to increase congressional investment in medical research. The bill names FDA and NIH to be the recipients of these funds to further their efforts in regulatory science. Senator Warren featured this proposal in her talk at the 2014 MASS-BIO and MASS-MED convention.

Priority Letters

8/7/2015: To FDA, CDC, and BARDA, seeking financial support for the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) program and the Slone Birth Defects Study at Boston University (**open**)

7/9/2015: Inquiring about efforts to explore the benefits of medical marijuana (**open**)

4/24/2015: Concerns over continued delays in establishing updated final advice to pregnant women on seafood consumption.

03/27/2015: Writing regarding Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, Docket No. FDA-2013-N-0500 (CBE-0).

3/13/15: Writing regarding draft guidance entitled “Bacterial Detection Testing by Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion.”

Industry Presence in State

MASS-BIO and MASS-MEDIC - In 2014 and 2015 Senator Warren worked with sponsors of the annual convention of these two organizations in Boston. Continuing a tradition begun by Senators Kennedy and Kerry, in the past two years, Senator Warren invited FDA Commissioners to be the keynote speakers at these events and to lead roundtable discussions with CEOs and senior executives of many of the medical device and biotechnical companies in Massachusetts.

The biotech industries have a substantial presence in Massachusetts with more than 400 biotech companies located there. More than 800 drugs are being developed in Massachusetts-based companies, accounting for about 5.5 percent of the global drug pipeline. There are more than 45,000 biotech and pharmaceutical employees in Massachusetts. For every biotech manufacturing job, there are 5 additional supporting jobs created.



FEB 23 2015

Administrator
Washington, DC 20201

The Honorable Elizabeth Warren
United States Senate
Washington, DC 20510

Dear Senator Warren:

Thank you for your letter regarding Unique Device Identifiers (UDIs). The Centers for Medicare & Medicaid Services (CMS) supports the Food and Drug Administration's (FDA) goals to improve post-market monitoring and surveillance and product recall capability, and to enhance adverse event reporting and research with respect to high-risk implantable medical devices. We agree that UDIs would aid the FDA in these efforts. I appreciate your bringing your concerns to my attention.

In September 2012, the FDA issued a strategy for establishing a national medical device post-market surveillance system to quickly identify poorly performing devices, accurately characterize and disseminate information about real-world device performance, including the clinical benefits and risks of marketed devices, and efficiently generate data to support premarket clearance or approval of new devices and new uses of currently marketed devices. An important element of this system is the incorporation of unique device identifiers into electronic health information, in particular electronic health records and appropriate medical device and disease registries. CMS agrees with this approach. As we work closely with our colleagues in the Office of the National Coordinator for Health Information Technology in drafting new regulations for the Medicare and Medicaid EHR Incentive Program, we will seek opportunities to further the FDA's goals regarding electronic health records.

In addition to including UDIs in registries, electronic health records and other transactions, some have suggested that collecting UDIs on claims could provide additional, useful information. However, including UDIs on claims would entail significant technological challenges, costs, and risks to normal claims processing for Medicare and other payers. Many others share these concerns including the National Uniform Billing Committee (NUBC) and the National Uniform Claim Committee (NUCC).

On September 23, 2014, the National Committee on Vital and Health Statistics (NCVHS), the statutory advisory committee to the Secretary on health information policy and standards, recommended not mandating the capture, reporting and use of UDI in administrative transactions at the current time. Rather NCVHS recommended that "HHS should continue to work with the Industry to better understand and document the value, benefits and cost of reporting UDI in administrative transactions." This would include "the business reasons for, and costs and benefits of including UDIs in administrative transactions including the added burden for

providers and payers to capture, report and receive/use UDI and the system and workflow changes required” and “the potential post-market surveillance role of payers who receive UDI from providers via administrative transactions.” NCVHS also recommended consideration of implementing pilot tests and working to improve existing mechanisms for post-market surveillance of devices. At a January 2015 meeting of the claims/encounter workgroup of the American National Standards Institute's Accredited Standards Committee (ASC X12), concerns were expressed about the benefits of requiring UDIs to be reported on claims and the issue was referred to a special workgroup.

CMS believes that mechanisms other than claims reporting for collecting UDIs would avoid the significant challenges and risks of collecting UDIs on claims. CMS supports the FDA's engagement with the public to identify registries that could be utilized together with electronic health record information to better leverage real world clinical data to improve post market monitoring and surveillance.

The UDI comprises two pieces, the Device Identifier (DI) and the Production Identifier (PI). The DI is from 16 to 23 characters and is specific to a device version or model. The PI reflects information about the production of the device such as batch or lot number, expiration date or sometimes the serial number. When the DI is combined with the PI, the total UDI size can be 75 characters.

Efforts to collect UDIs on claims would engender many operational challenges. The Health Insurance Portability and Accountability Act (HIPAA) requires the Secretary to adopt standards for electronic health transactions, including health claims. All HIPAA covered entities (e.g., health plans, health care providers, and clearinghouses) use a standardized claim format adopted by the Secretary known as the 837, and can only require information to be reported on claims that is consistent with that form. The Secretary would need to adopt revisions to the 837 for covered entities to be able to report UDIs on claims.

Altering the 837 would involve a lengthy multi-party, multi-stepped process, summarized as follows: (1) ASC X12 would first adopt changes to the standard electronic claims formats and implementation guides to provide space for submission of multiple iterations of the UDI; (2) ASC X12 would then submit changes to the NCVHS; (3) NCVHS would consult with the NUBC, NUCC, Workgroup for Electronic Data Interchange, and the American Dental Association before any changes are adopted (NUBC and NUCC would likewise need to update paper forms); (4) the Secretary would consult with the NCVHS prior to making a decision; (5) the Secretary would issue proposed rulemaking to adopt the new standard, followed later, if the decision were made to finalize the proposed rule, by a final rule. This process typically takes several years.

Changing the claim format to include UDI would also require substantial, expensive, and time-consuming changes to claims processing systems and claims warehouses for all health plans, providers, clearinghouses, and vendors and business associates (e.g., billing services, and reprocessors). Retrofitting Medicare's legacy claims systems to accommodate UDI reporting would require extensive programming changes and claims edits that could negatively impact the

processing time and adjudication of the more than 1.2 billion claims that Medicare annually processes.

The time and expense to update CMS's systems when claims standards change varies depending upon the scope of the change. The recent claim form update from version 4010 to version 5010 took 5 years, at a total combined cost to CMS (for Medicare and Medicaid) of \$700 million, with other payers bearing additional costs. Without knowing the requirements for a UDI standard, it would not be possible to estimate implementation costs, but the systems changes required to accept the full UDI would likely make it a much more complicated change than that associated with the change from version 4010 to 5010.

Information reported on claims needs to be verified to ensure that it is valid. CMS is concerned that collecting UDIs on claims would be prone to errors because there are an estimated 300,000 UDIs just for high-risk implantable medical devices, multiple UDIs may need to be reported on a claim, UDIs vary in format depending on the UDI-assigning entities, the UDI is more than 10 times longer than an ICD-10 code, and the data are not essential to adjudicate claims. Without validity checks, simple errors could lead to improper identification of products and patients. Since a database that contains all full UDIs is not available, payers would not be able to validate that UDIs submitted on claims were actual assigned UDIs.

Some have suggested that, in lieu of reporting the full UDI, reporting just the DI portion of the UDI on claims would suffice. However, in addition to involving all the steps to change claims, claims edits would also be needed to: (a) verify that a valid DI was reported on a claim; (b) validate that the DI was appropriate for the claim billing unit (e.g., a DI for implantable infusion pump was not reported on a hospital claim for pacemaker insertion); and (c) identify claims for which a DI should have been reported but was not. Developing, applying, and continually updating claims edits would be expensive and challenging. For example, considering just high-risk implantable medical devices, 300,000 UDIs would need to be cross-walked to device dependent Medicare Severity Diagnosis Related Groups (MS-DRGs), Ambulatory Payment Classifications (APCs) and procedure codes for related physicians' services. While the FDA's Global Unique Device Identification Database (GUDID) could be used to verify DIs, claims edits would be needed to associate DIs with each different payment code used in every payment system by each payer. Claims edits would need to be continually updated to reflect new DIs. Moreover, there could be inconsistency in the quality of claims edits developed and applied among many different payers. The challenge of developing claims edits would increase when as many as 4 million UDIs covering all classes of medical devices (and involving an unknown lesser number of DIs) are phased-in over the next few years pursuant to the FDA's compliance dates for UDI requirements.

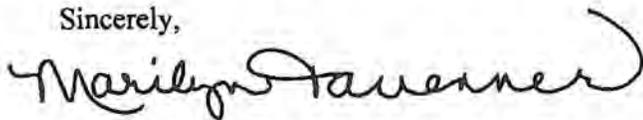
An additional technical issue is that the multiple entities that assign the UDIs currently do not use a standard format, with at least one assigning entity employing special characters in its UDIs. The use of special characters is a particularly difficult problem in a claims transaction, as special characters have specific and limited uses such as element delimiters (separators), segment terminators, and/or file terminators. While we understand that this issue is being addressed, until it is adequately dealt with, having a special character embedded in the UDI could cause major systems errors for payers expected to accept the UDI on claims transactions.

There is also an issue about whether payment systems are the best method to track devices. Patients change commercial insurance plans relatively frequently and there is no legal obligation for a plan to maintain contact with a formerly insured individual. This would hinder recalls. Moreover, some believe that many previously recalled devices had not yet reached patients, but, instead, remained in inventories along the supply chain, in which case reporting UDIs on claims would not yield a benefit.

We believe that collecting UDI information could be a valuable resource for many uses. These uses could include: improving the effectiveness of product recalls; assessment of long-term outcomes (by registries and others); assessment of patient safety as well as post-market monitoring and effectiveness research on devices; making public aggregate information on Medicare utilization and payments for medical devices; making available information to patients; and curbing fraud and abuse activities. Because of the extensive concerns about collecting UDI data via claims, however, we believe that collection mechanisms other than claims would best facilitate accurate reporting of valid UDIs. Such non-claims collection mechanisms would also allow collection of robust information (additional to UDI) that could not be collected on claims but could be helpful to these activities. For example, information on patient status, laboratory and imaging results, medication use, and surgical details are often used to evaluate post-market safety and in effectiveness research but cannot be captured on claims.

Thank you for sharing your perspective on the use of UDIs. I appreciate your interest in this important issue as we work toward our mutual goal of strengthening the Medicare program for all beneficiaries. Please do not hesitate to contact me if you have any further thoughts or concerns. I will also provide this response to Senator Charles E. Grassley.

Sincerely,

A handwritten signature in black ink that reads "Marilyn Tavenner". The signature is written in a cursive, flowing style with a large loop at the end.

Marilyn Tavenner

Smith, Celeste

From: Borio, Luciana
Sent: Friday, October 17, 2014 10:08 PM
To: Hamburg, Margaret
Subject: HHS position
Attachments: HHSpositiondraftEVDTherapies v2.docx

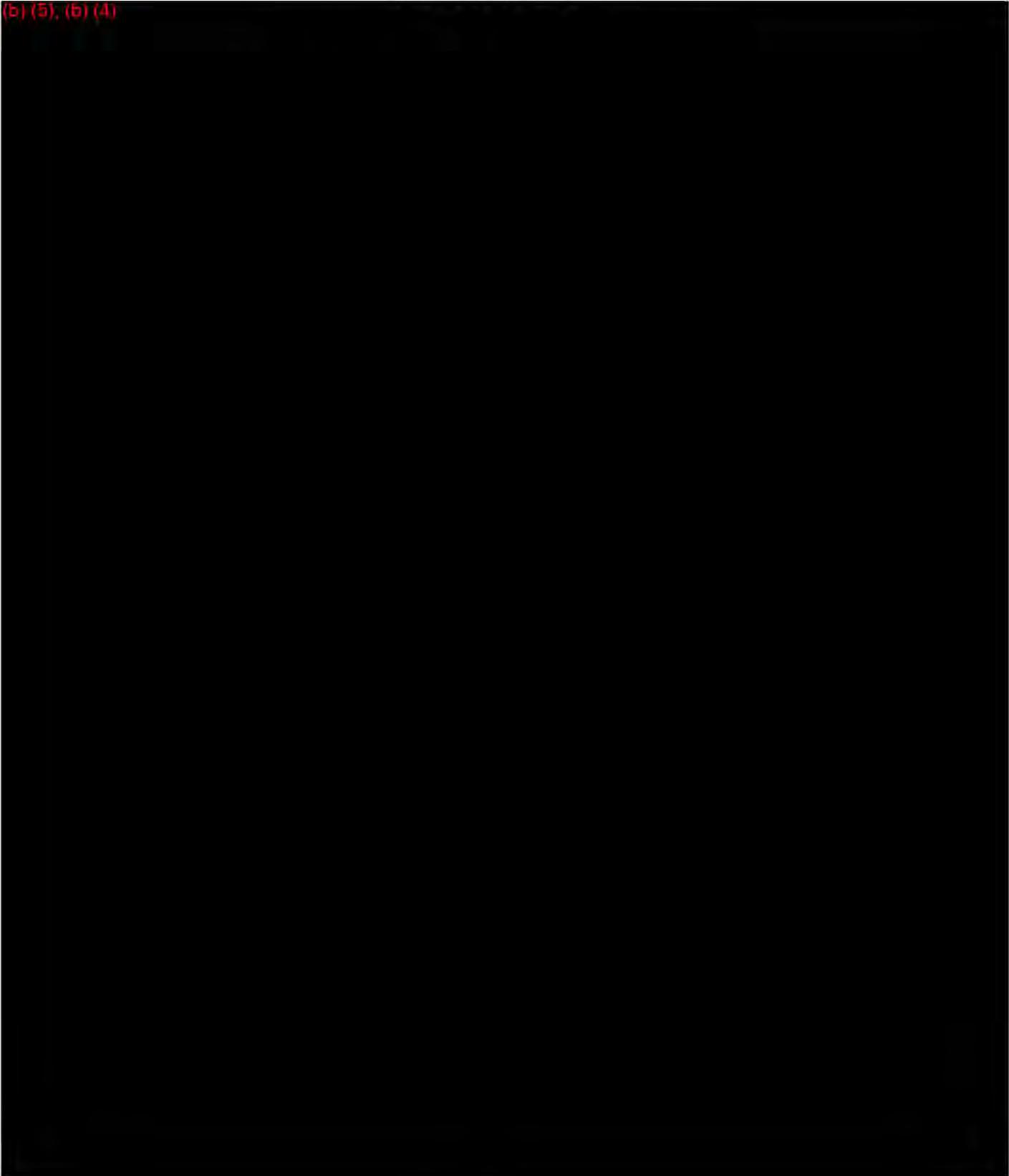
Hi Peggy – here is the position paper that Nicki asked me to pen. Ed Cox and NIH (Rick Davey and Cliff Lane) all drafted/edited.

Looks good.

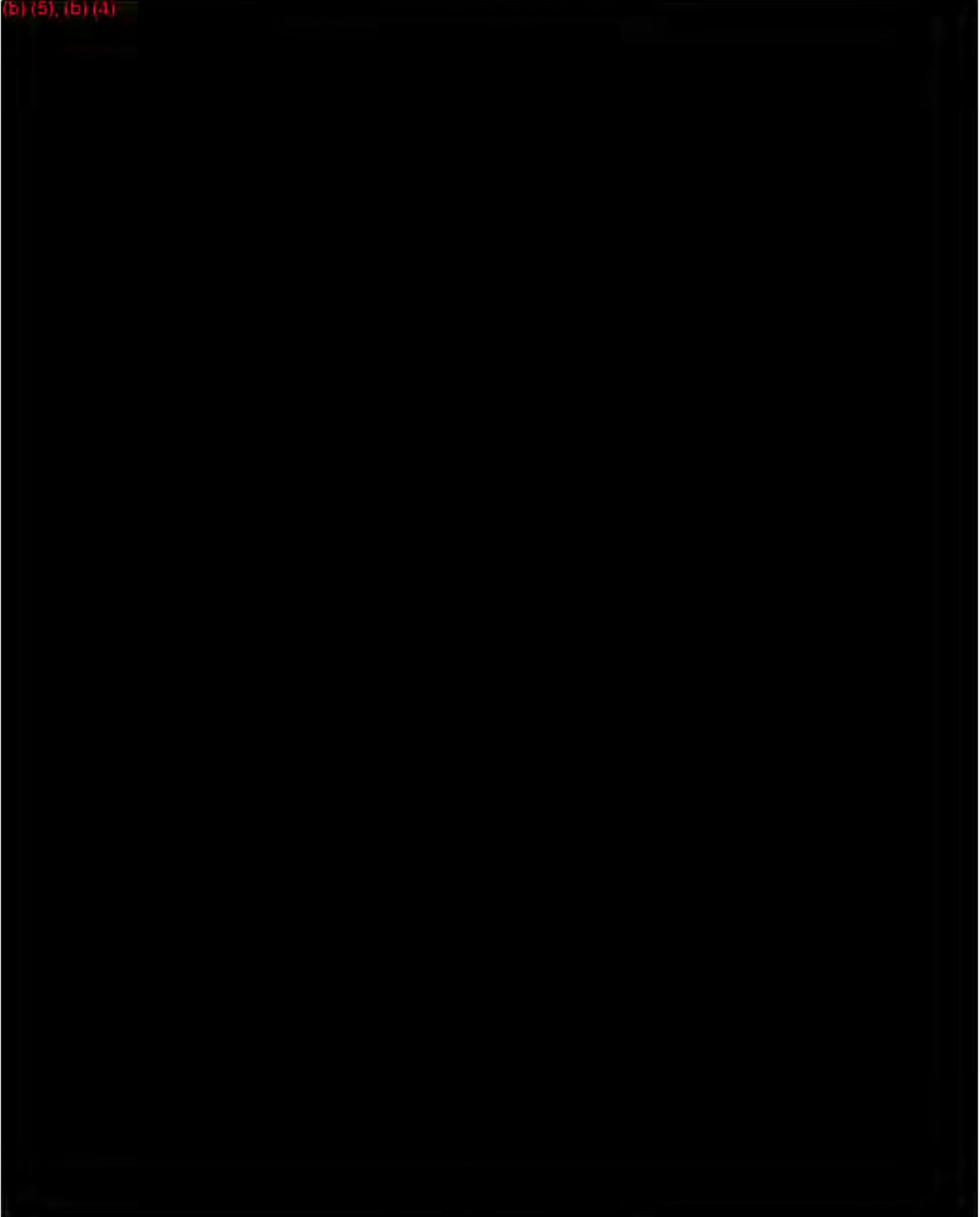
Hope you like it.

HHS Position Regarding Investigational Ebola Therapies
(DRAFT 10/15/14 8 PM)

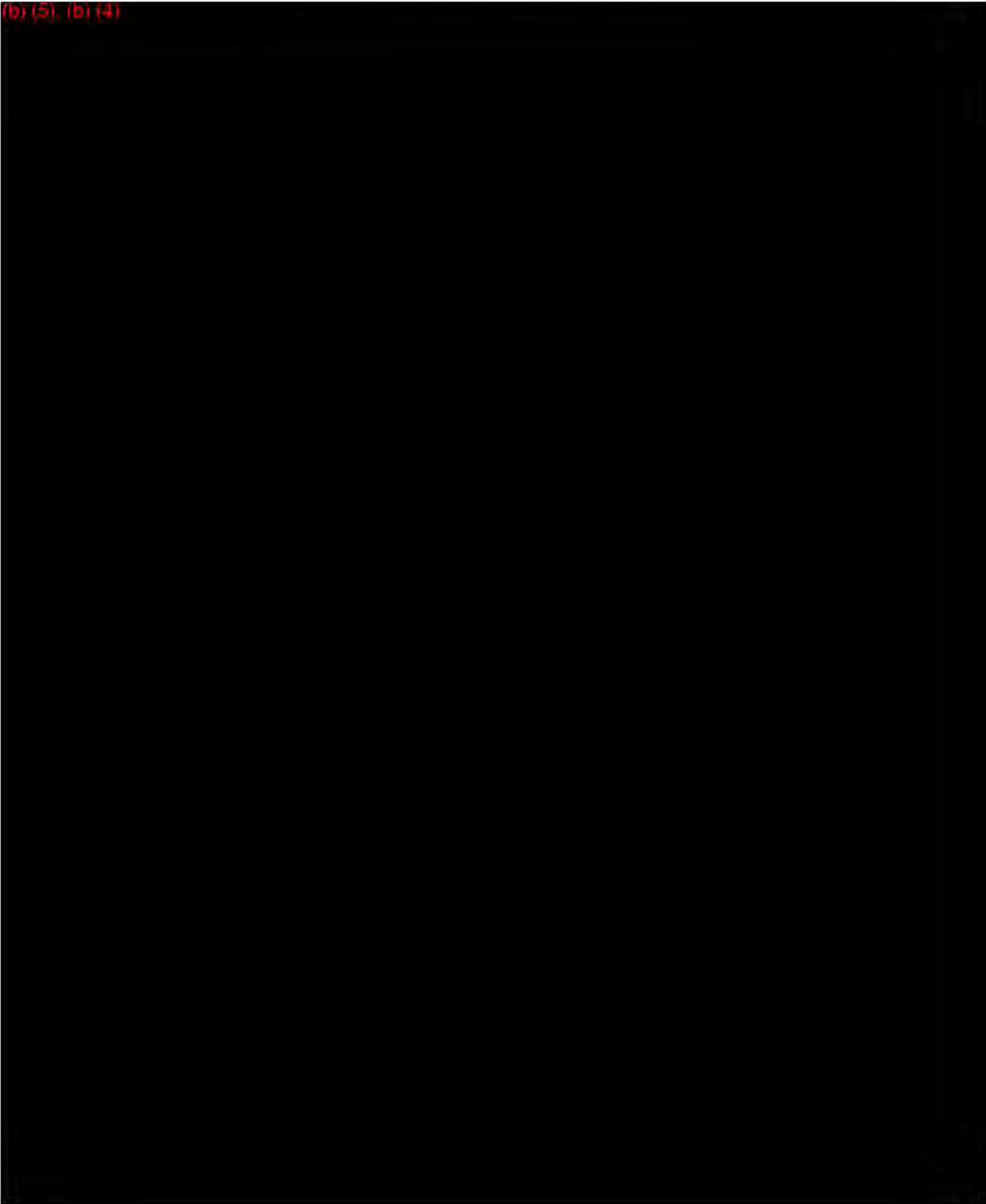
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(b) (5), (b) (4)



(b) (5), (b) (4)



Smith, Celeste

From: Hamburg, Margaret
Sent: Friday, October 17, 2014 10:33 PM
To: (b) (6) net'
Subject: Fw: HHS position
Attachments: HHSpositiondraftEVDTherapies v2.docx

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

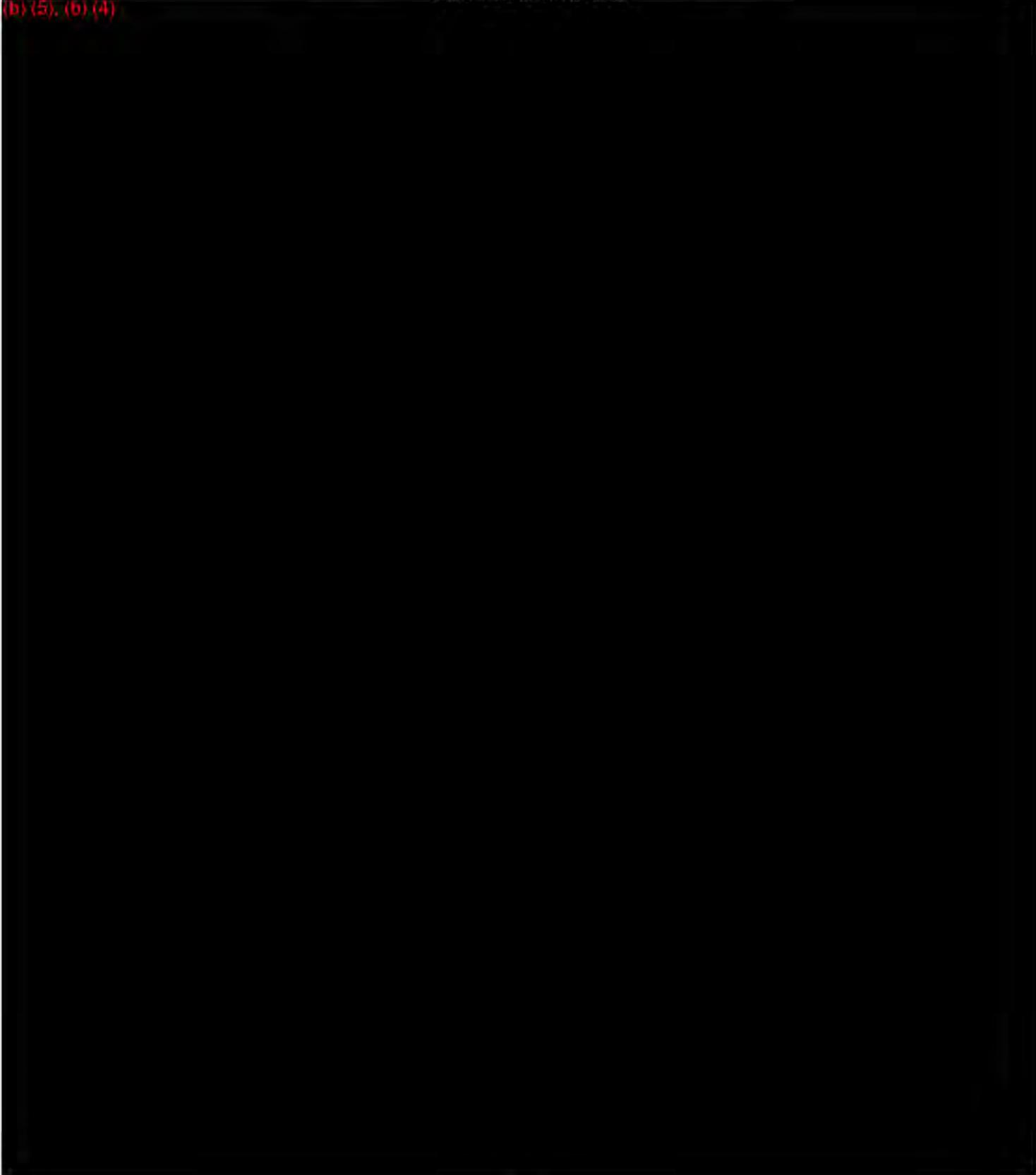
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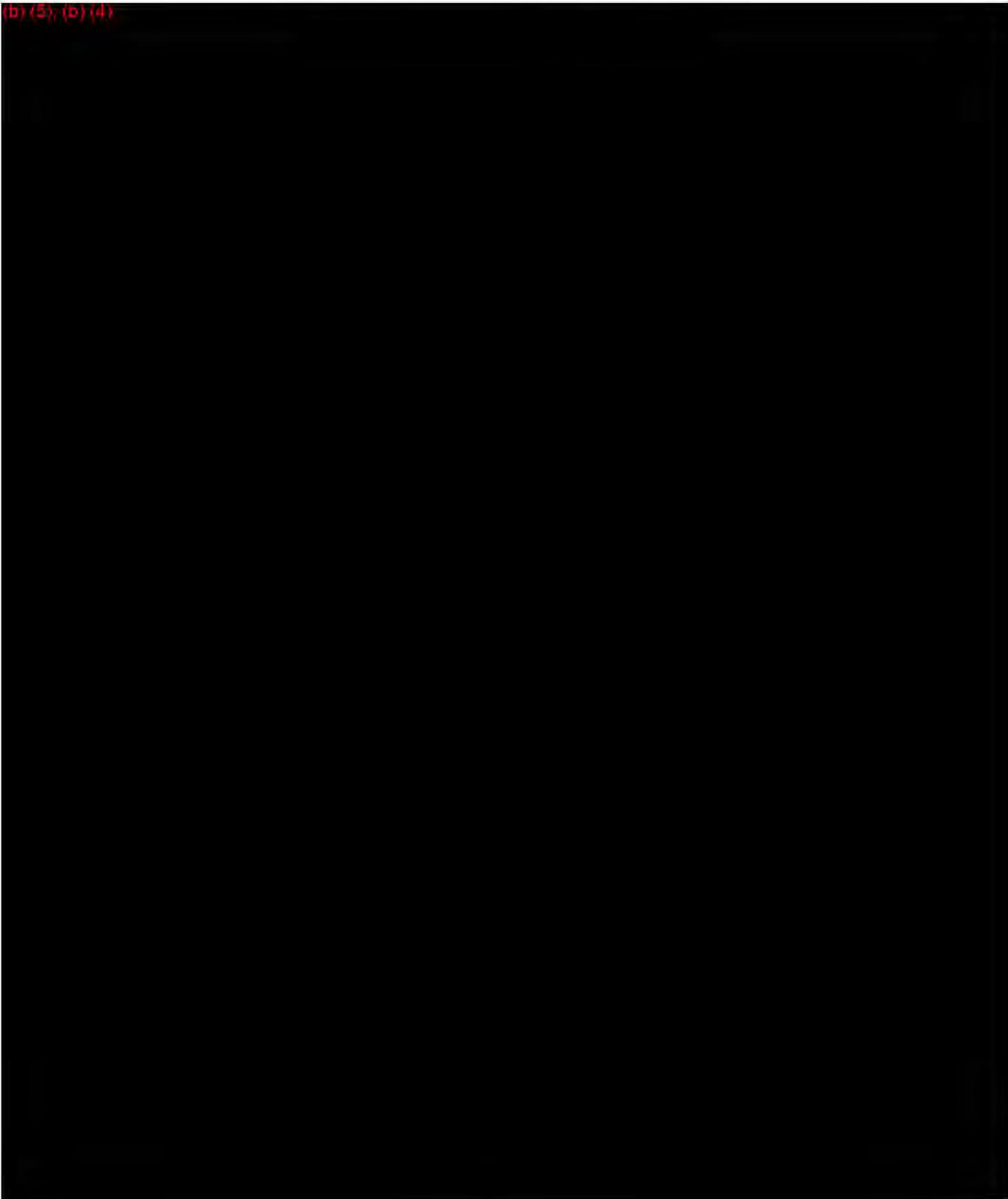
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HHS Position Regarding Investigational Ebola Therapies
(DRAFT 10/15/14 8 PM)

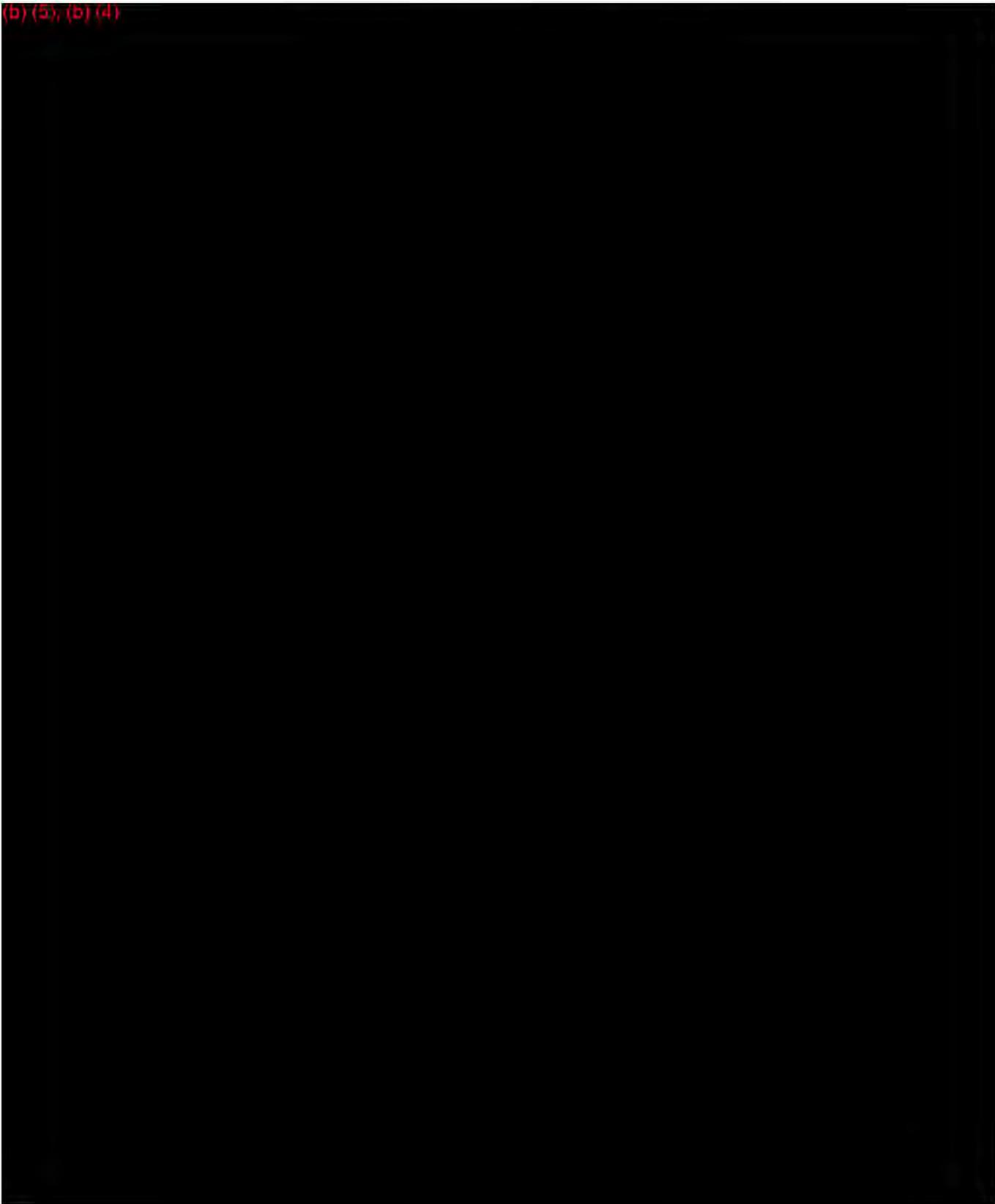
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(b) (5), (b) (4)



Smith, Celeste

From: The Pink Sheet DAILY <info@pharmamedtechbi.net>
Sent: Tuesday, October 28, 2014 6:12 AM
To: Hamburg, Margaret
Subject: "The Pink Sheet" DAILY | Today's News & Analysis



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Turning the Page on Zohydro? New Formulations, New Division Leadership Should Help FDA Move Forward in Opioids The long-time head of FDA's pain drug review group, Bob Rappaport, has retired after 20 years at FDA. The new acting Division Director is Sharon Hertz - suggesting continuity in the substance of reviews, but perhaps a symbolic change in moving beyond the controversy over Zohydro.

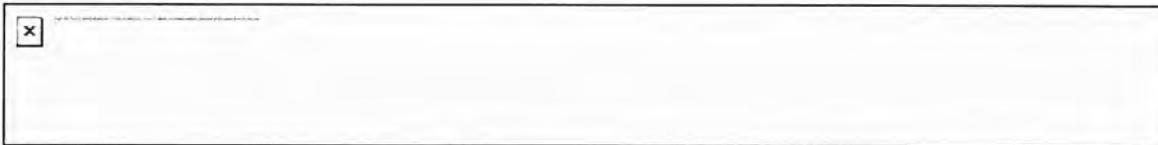
In Brief: Sarepta Filing Delay; Baxter Hemophilia Approval; Valeant To Increase Allergan Offer Sarepta says NDA submission for its muscular dystrophy treatment will be delayed until mid-2015 due to "new" and "updated" FDA requirements; agency approves Baxter's porcine-sourced Obizur for acquired hemophilia A.

As Merck's Keytruda Gains Momentum, Investors Look To The Future Keytruda, already the first anti-PD-1 drug to market for melanoma, received FDA breakthrough therapy

two-drug hepatitis C combo - helped to offset a decline in Merck's third quarter sales.

Legacy Devices The Weak Link In Cybersecurity Fence Device companies, hospitals and federal agencies are slowly moving towards adoption of a government framework to guide cybersecurity designs and safeguard newer products, but legacy devices are still vulnerable to hackers and may supply entry into secure systems, cybersecurity experts warn at a joint agency summit.

Remoxy Development Not 'Unmitigated Disaster,' CEO Reassures; Hunt Begins For New Partner Pfizer terminates agreement with Pain Therapeutics after reviewing top-line results of five studies done to address FDA complete response letter; Pain says data supports refiling of NDA for its abuse-deterrent long-acting oxycodone formulation by mid-2015.



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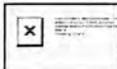
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Smith, Celeste

From: Hamburg, Margaret
Sent: Tuesday, October 28, 2014 3:04 PM
To: Pennington, Caitlin
Subject: Fw: "The Pink Sheet" DAILY | Today's News & Analysis

Print Zohydro story and Sarepta story
Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

From: The Pink Sheet DAILY [mailto:info@pharmamedtechbi.net]
Sent: Tuesday, October 28, 2014 06:11 AM
To: Hamburg, Margaret
Subject: "The Pink Sheet" DAILY | Today's News & Analysis

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Smith, Celeste

From: FDA Office of Media Affairs
Sent: Tuesday, October 28, 2014 4:08 PM
To: FDA Daily Report; HHS Press
Subject: FDA Daily Report for Oct. 28, 2014

FOLLOWING IS A COMPILATION OF NEWS MEDIA CALLS REPORTED BY THE FDA PRESS OFFICE AS OF 3:30 P.M. TODAY

Note to: See Distribution

From: FDA Office of Media Affairs (Press Office)

Date: Tuesday, October 28, 2014

PRESS RELEASE

N/A

MAJOR MEDIA CONTACTS

Lisa Gerion, LA Times, called asking about public meeting on abuse deterrent opioids. They are working on a story about the original approval of Oxycontin and plan to watch the abuse-deterrence meeting's webcast. I will know more about story direction after her and I speak again post-meeting. (JV)

Tod Marks, Consumer Reports, questions on labeling claims, gluten-free labeling. (JCD)

Korry Keeker, Consumer Digest magazine, fact checking a story on gum. In progress. (JCD)

Amy Smith, Newsweek Europe, questions about Sarepta's therapeutic drug candidate against Ebola (AVI-7537) and why, despite efficacy data, the government has not "resumed funding" for the drug. FDA cannot comment on development. Noted that FDA doesn't fund drug development and directed to BARDA. (JR)

Dilpreet Kainth, Today Show, seeking victims harmed by costume contact lenses. We do not provide personally identifiable information. (JR)

Dino Grandoni, Huffington Post, is covering a forthcoming Oceana report on shrimp labeling and is sending questions. Pending. (LS)

Mary Clare Jalonick, AP, and Carey Biron, Inter Press Service, have pending queries regarding a joint Center for Food Safety, Friends of the Earth, and Food & Water Watch announcement about AquaBounty being fined for environmental violations in Panama. (TE)

REGIONAL OUTLETS AND OTHER INTERVIEWS AND BACKGROUND

Sally Pollak, Burlington Free Press. Flagged an upcoming state-listening session on the Food Safety Modernization Act. (JCD)

Erik Richardson, BioWatch News LLC, provided general statement regarding FDA and Ebola. (JR)

Jim Hoffer, WABC, question about whether other agencies also need to approve Biofire's test before use is OK. (JR)

Elizabeth Orr, FDAnews, questions about everolimus adverse event reports and potential FDA action as a result. (TG)

Robin Erb, Detroit Free Press, inquired about FDA review of a citizens petition to have the labeling changed on Tamoxifen. (TG)

FOLLOWING IS A COMPILATION OF NEWS MEDIA INQUIRIES REPORTED BY THE FDA PRESS OFFICE AFTER 3:30 P.M. YESTERDAY, OCTOBER 27, 2014

PRESS RELEASE

N/A

MAJOR MEDIA CONTACTS

Mary Clare Jalonick, AP, inquired about data the FDA posted on fish species identification. No specific questions yet; she will get in touch when she's ready. (LS)

REGIONAL OUTLETS AND OTHER INTERVIEWS AND BACKGROUND

Brian Howard, National Geographic, inquired about data the FDA recently posted on fish species identification, as well as a forthcoming Oceana report on shrimp labeling. In progress. (LS)

Jennifer Corbett Dooren (JCD)

Theresa Eisenman (TE)

Andrea Fischer (AF)

Tara Goodin (TG)

Jennifer Haliski (JH)

Steven Immergut (SI)

Christopher Kelly (CK)

Susan Laine (SL)

Morgan Liscinsky (ML)

Juli Putnam (JP)

Heidi Rebello (HR)

Karen Riley (KJR)

Jennifer Rodriguez (JR)

Gloria Sanchez-Contreras (GS)

Fallon Smith (FS)

Lauren Sucher (LS)

Jeff Ventura (JV)

Sandy Walsh (SW)

Stephanie Yao (SY)

Smith, Celeste

From: Immergut, Steven
Sent: Thursday, October 30, 2014 3:09 PM
To: Hamburg, Margaret
Cc: Hoague, Angela
Subject: DMD- Sarepta
Attachments: Duchenne Muscular Dystrophy_ Moms Fight for FDA Approval of Sarepta Drug - Businessweek.pdf

Hi- yes at a few big stories on DMD/Sarepta this week. The announced earlier in week an update from their preNDA meeting. The one today from BusinessWeek sounds like the one you heard about - though strangely not in our clips this morning. Will need to check on that.

First link below and attached pdf in case you want to print and bring home

It's a really tough story on us. We didn't know was coming today but did work with reporter. This is a very difficult situation for us but need to think about how come off better than this.

<http://www.businessweek.com/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug>

The second and third one are more on the announcement - from Matt Herper at Forbes and Joe Walker at WSJ. Matt calls for CEO to resign.

<http://www.forbes.com/sites/matthewherper/2014/10/27/sarepta-needs-fda-expertise-stat/>

<http://online.wsj.com/articles/sarepta-therapeutics-sees-setback-in-eteplirsen-drug-application-1414414412>

here's the press release.

Sarepta Therapeutics Announces Regulatory Update on Eteplirsen

Updated and additional guidance received from FDA on specific data requirements for NDA;

FDA states further discussion needed to determine what constitutes a "complete" NDA submission;

NDA submission planned for mid-year 2015;

Company to hold teleconference today at 8:00 a.m. EDT

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 27, 2014-- Sarepta Therapeutics, Inc. (NASDAQ:SRPT), a developer of innovative RNA-based therapeutics, today provided an update on its discussions with the U.S. Food and Drug Administration (FDA) regarding its planned New Drug Application (NDA) submission for the approval of eteplirsen for the treatment of Duchenne muscular dystrophy (DMD).

In meeting minutes received last week from a Type B Pre-NDA meeting that took place in September 2014, the FDA provided updated guidance regarding the specific data to be included as part of, or at the time of, Sarepta's NDA submission. The guidance states that additional data are now required as part of the NDA submission, including the results from an independent assessment of dystrophin images and the

168-week clinical data from study 202. Additionally, the guidance requests more specific data including a minimum duration of safety in new patients exposed to eteplirsen, patient-level natural history data to be obtained by Sarepta from independent academic institutions, and MRI data from a recent study conducted by an independent academic group. The FDA indicated that further discussion with Sarepta "will be necessary to determine what would constitute a complete NDA." Based on these requests, Sarepta plans to submit an NDA by mid-year 2015, pending any additional requests from further discussions with the FDA.

"We are committed to satisfying the FDA's updated requests for these specific data to be included as part of an NDA submission and will continue to work with the Agency toward the goal of a complete and acceptable NDA filing," said Chris Garabedian, president and chief executive officer of Sarepta Therapeutics. "We believe all of the data requests and additional FDA discussions that have currently been outlined can be completed in time for an NDA submission by mid-year 2015. Obtaining an FDA approval of eteplirsen for the DMD patients who may benefit from the drug continues to be our highest priority."

Excerpts from the Pre-NDA Meeting Minutes related to information that the FDA is requesting as part of an NDA submission included:

"The sponsor should include 3-month data from at least 12 to 24 newly exposed patients at the time the NDA is submitted."

"Available data from the other patients enrolled in the new eteplirsen studies (studies 301, 203, 204) should also be included at the time the NDA is submitted, even if exposure is less than 3 months in duration."

"Additional data from later time points and from newly enrolled patients should be submitted in the 120-Day Safety Update."

"FDA strongly advises the sponsor to obtain and submit patient-level natural history data. FDA is prepared to appeal to the academic groups holding the data to allow the sponsor a means to acquire the data."

"The study 201/202 clinical site inspection conducted in May, 2014, after the issuance of the April 15, 2014, guidance letter, uncovered marked disparities in the immunohistochemistry methodology and concerns about the reproducibility of the data. The lack of confirmation of robust dystrophin measurement during the site visit necessitates including the independent assessment of dystrophin-positive fibers and 168-week efficacy data from study 201/202 in the NDA."

"FDA strongly urged the sponsor to submit the MRI data with appropriate natural history controls."

The FDA also stated that "[a]dditional discussion between the sponsor and the FDA will be necessary to determine what would constitute a complete NDA."

Conference Call Information

Sarepta will hold a conference call to discuss this update today at 8:00 a.m. EDT (5:00 a.m. PDT). The conference call may be accessed by dialing 800.708.4539 for domestic callers and 847.619.6396 for international callers. The passcode for the call is (b) (6). Please specify to the operator that you would like to join the "Sarepta Regulatory Update Call." The conference call will be webcast live under the investor relations section of Sarepta's website at www.sarepta.com and will be archived there following the call for 90 days. Please connect to Sarepta's website several minutes prior to the start of the broadcast

to ensure adequate time for any software download that may be necessary. An audio replay will be available through November 3, 2014 by calling 888.843.7419 or 630.652.3042 and entering access code

(b) (5)

About Duchenne Muscular Dystrophy

DMD is an X-linked rare degenerative neuromuscular disorder causing severe progressive muscle loss and premature death. DMD affects approximately one in every 3,500 boys born worldwide. A devastating and incurable muscle-wasting disease, DMD is associated with specific errors in the gene that codes for dystrophin, a protein that plays a key structural role in muscle fiber function. Progressive muscle weakness in the lower limbs spreads to the arms, neck and other areas. Eventually, increasing difficulty in breathing due to respiratory muscle dysfunction requires ventilation support, and cardiac dysfunction can lead to heart failure. The condition is universally fatal, and death usually occurs before the age of 30.

About Eteplirsen

Eteplirsen is Sarepta's lead drug candidate and is designed to address the underlying cause of DMD by enabling the production of a functional dystrophin protein. Data from clinical studies of eteplirsen in DMD patients have demonstrated a broadly favorable safety and tolerability profile and restoration of dystrophin protein expression.

Eteplirsen uses Sarepta's novel phosphorodiamidate morpholino oligomer (PMO)-based chemistry and proprietary exon-skipping technology to skip mutations affecting exon 51 of the dystrophin gene. Approximately 13 percent of the total DMD population is amenable to exon 51 skipping. By skipping exon 51, eteplirsen may restore the gene's ability to make a shorter, but still functional, form of dystrophin from messenger RNA, or mRNA. Promoting the synthesis of a truncated dystrophin protein is intended to stabilize or significantly slow the disease process and prolong and improve the quality of life for patients with DMD. Sarepta is also developing other PMO-based exon-skipping drug candidates intended to treat additional patients with DMD.

About Sarepta Therapeutics

Sarepta Therapeutics is focused on developing first-in-class RNA-based therapeutics to improve and save the lives of people affected by serious and life-threatening rare and infectious diseases. The Company's diverse pipeline includes its lead program eteplirsen, for DMD, as well as potential treatments for some of the world's most lethal infectious diseases. Sarepta aims to build a leading, independent biotech company dedicated to translating its RNA-based science into transformational therapeutics for patients who face significant unmet medical needs. For more information, please visit us at www.sarepta.com.

Forward-Looking Statements and Information

This press release contains forward-looking statements. These forward-looking statements generally can be identified by the use of words such as "believes or belief," "anticipates," "plans," "expects," "will," "intends," "potential," "possible," "advance" and similar expressions. These forward-looking statements include statements about Sarepta's planned timing for an NDA submission for eteplirsen in the treatment of DMD; Sarepta's plans to work with the FDA towards the goal of a complete and acceptable NDA filing; Sarepta's ability to satisfy the additional FDA requests; the timing and submission of additional data, analysis and other information to the FDA necessary for the FDA to make regulatory determinations; the timing of and ability to initiate additional studies for eteplirsen and other follow-on exons; and the potential

regulatory approval of eteplirsen.

Each forward-looking statement contained in this press release is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statement. Applicable risks and uncertainties include, among others: we

may not be able to comply with all FDA requests; the FDA may determine that substantial additional data is required for accelerated or other approval of eteplirsen or that our NDA submission for eteplirsen does not qualify for filing, even with additional information; the results of our ongoing and new clinical trials may not be positive; there may be delays in timelines relating to an NDA submission, initiating clinical trials, or making a product commercially available for regulatory or internal reasons; we may not be able to manufacture sufficient supply for clinical trials or commercialization; agency or court decisions with respect to our patents or those of third parties may negatively impact our business and those identified under the heading "Risk Factors" in Sarepta's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 filed with the Securities and Exchange Commission (SEC), and Sarepta's other filings with the SEC.

Any of the foregoing risks could materially and adversely affect Sarepta's business, results of operations and the trading price of Sarepta's common stock. For a detailed description of risks and uncertainties Sarepta faces, you are encouraged to review the Company's filings with the SEC. We caution investors not to place considerable reliance on the forward-looking statements contained in this press release. Sarepta does not undertake any obligation to publicly update its forward looking statements based on events or circumstances after the date hereof.

Source: Sarepta Therapeutics, Inc.

Sarepta Media Contact:

Tony Plohoros, 908-591-2839

tplohoros@6degreespr.com

or

Sarepta Investor Contact:

Stephanie Ascher, 212-362-1200

stephanie@sternir.com

Bloomberg Businessweek

Technology

<http://www.businessweek.com/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug>

Moms, Regulators, Biotech Startups, and the Battle Over a Potentially Life-Saving Drug

By Paul M. Barrett October 30, 2014



Photograph by Ryan PflugerLeffler's son (b) (6) was diagnosed with Duchenne in 2006

The 2014 World Cup elevated soccer to the top of (b) (6)'s roster of obsessions, rivaled only by endangered big cats—especially jaguars, “the coolest”—and *Star Wars* spaceships. In recognition of his new interest, he’s set up a miniature soccer field with 4-foot-wide goals in his backyard in suburban Bellevue, Wash. “Watch this!” he shouts, preparing to fire a penalty kick.

Small for his age, (b) (6), 11, moves awkwardly, shoulders high and hunched. He uses a lightweight plastic beach ball, not a regulation leather soccer ball. He begins his approach, pulls back his right foot, and ... collapses to the grass.

Mitch Leffler, the sole spectator, moves toward his son. “I’m OK,” (b) (6) says. “I can do it.” He struggles onto his hands and knees, raises his butt, places his hands one at a time on his thighs, and slowly pushes himself into an upright position. “My leg just wasn’t there,” he says matter-of-factly. His father nods, and the game resumes.

(b) (6) has Duchenne, the deadliest strain of muscular dystrophy. It’s inherited maternally on the X chromosome and mostly afflicts boys. Parents typically sense something is wrong when their sons at 3 or 4 don’t run around or they start falling for no obvious reason. Beginning in the legs, Duchenne destroys muscle, which is replaced by fat and scar tissue. Victims lose the ability to walk by adolescence. Eventually the disease causes cardiac and/or respiratory complications that lead to death by the mid-20s. One in 3,500 newborns has Duchenne, which translates to around 15,000 cases in the U.S. There’s no cure.

(b) (6) doesn’t really understand yet,” his mother, Mindy, says, “but it’s basically a slow-motion death sentence.”

There’s reason to hope—not for a miracle, but for a reprieve. Three small biotech companies are competing to develop drugs designed to address the cellular defects that cause some cases of Duchenne. If proven safe and effective, the drugs would turn Duchenne into a less devastating form of muscular dystrophy. Clinical trials, however, have yielded uneven results, and the U.S. Food and Drug Administration has made equivocal pronouncements about which of the drugs, if any, have a shot at approval. Even a marginally effective drug would likely command an astronomical price, making the winning company a billion-dollar sensation.

The hunt for a Duchenne treatment has generated a collision of commerce, cutting-edge science, and Wall Street speculation. The FDA, though, seems flummoxed over how to evaluate the experimental drugs, especially given a lack of large, clearly successful randomized studies. That’s left the Lefflers confused and increasingly desperate.



Photograph by Ryan PflugerMindy with her son (b) (6) who began college this fall

Mindy believes that one experimental treatment—eteplirsen, made by a company called Sarepta Therapeutics (SRPT)—has shown sufficient promise in a tiny trial to warrant wider availability. If approved, eteplirsen might help 13 percent of Duchenne boys who have certain genetic flaws. Mindy’s son is among the 13 percent. “I want (b) (6) on that drug,” she says, “and I want it to happen before he’s in a wheelchair or worse.”

She and a group of similarly minded moms are pressuring the FDA to give provisional approval to eteplirsen while Sarepta proceeds with confirmatory studies. Taking to Twitter, Facebook, YouTube, and Instagram, they’ve got the attention of top FDA officials. They’ve also encountered resistance from career FDA staff members and some rare-disease advocates alarmed by their assertiveness.

"What's hard to understand," says Mindy's friend Jennifer McNary, "is why the whole Duchenne community and the FDA aren't pulling together behind eteplirsen." McNary, who lives south of Boston, has two sons with the disease. Maternal genetic predisposition sometimes results in such sibling pairs. (b) (6) 12, gets eteplirsen in the small Sarepta trial; over the past two-and-a-half years, his symptoms have eased remarkably. Max's older brother, (b) (6) 15, didn't qualify for the study because he was already in a wheelchair when it started. He's declining physically, losing the use of his arms and having trouble feeding himself.

"Why doesn't the government let me have eteplirsen?" (b) (6) asks when we meet. He waits for an answer, which I don't have. His mother joins the conversation: "The FDA's inaction," she says, "is killing my son."

Mindy agrees with Jennifer and (b) (6) doesn't have time to wait for a perfect placebo-controlled trial with hundreds of subjects," she says. "The benefits outweigh any risks."

In 1986 researchers at Harvard isolated the gene responsible for making the protein dystrophin, a "shock absorber" that surrounds muscle cells. Boys with Duchenne have one of several genetic defects that inhibit production of dystrophin. Without it, ordinary physical exertion causes progressive muscle breakdown. The disease is named for Guillaume Duchenne, a French neurological pioneer who described the symptoms in the 1860s.

For generations, physicians reacted passively to Duchenne. Patricia Furlong's sons, Christopher and Patrick, were diagnosed in 1984. Her doctor told her to "take them home and love them," because there was nothing medicine could do. A former nurse with a stubborn streak, she began traveling the country from her home in central Ohio, pleading with researchers to look for a cure. "She was at NIH [National Institutes of Health]. She was on Capitol Hill. She was in my office," recalls Eric Hoffman, a genetic researcher at Children's National Medical Center in Washington. "Pat would not be denied." She couldn't save her sons, however, who died in the mid-1990s.

Angered by what she describes as the fatalism she encountered at the Muscular Dystrophy Association—sponsor of the long-running Labor Day telethon hosted by actor Jerry Lewis—Furlong formed a breakaway nonprofit: Parents Project Muscular Dystrophy, dedicated strictly to Duchenne. In 2001, largely because of her agitation, Congress passed the Muscular Dystrophy CARE Act, which over the following decade provided more than \$400 million in funding, much of it for Duchenne research. The federal backing, says Hoffman, "got the biotech companies thinking maybe there's money to be made with a Duchenne drug."

"What's hard to understand is why the whole Duchenne community and the FDA aren't pulling together behind eteplirsen"

A startup in New Jersey called PTC Therapeutics (PTCT) focuses on mutations that block dystrophin production. These "nonsense mutations" are akin to a period mistakenly placed in the middle of a sentence, which makes the genetic code incomprehensible. In 2008, Genzyme (SNY), a much larger biotech, gave credibility to PTC's research by paying the tiny company \$100 million upfront to secure future marketing rights to its drug outside North America.

Prosensa (RNA), a Dutch biotech, targets a different type of flaw in the exons, or segments, of the dystrophin gene. By "skipping" a defective exon, Prosensa's compound is supposed to allow the formation of a truncated version of dystrophin. In 2009 the pharmaceutical giant GlaxoSmithKline (GSK) added momentum to exon-skipping research by paying Prosensa \$25 million upfront for development and marketing rights and promising hundreds of millions more in future compensation.

In the U.S., Sarepta was also angling to get into the Duchenne chase. Choosing to work without a larger corporate partner, it began testing eteplirsen, an exon-skipping compound that relies on a different biochemical recipe from Prosensa's drug.

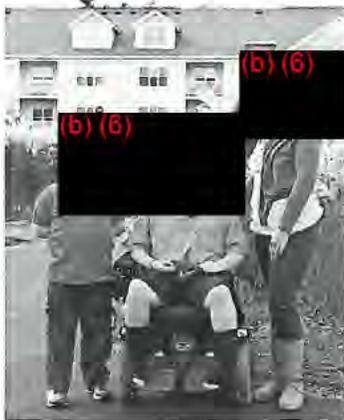
The proliferation of potential treatments gave the Lefflers reason for optimism after years of mounting apprehension. (b) (6) had first been diagnosed in 2006, at the age of almost 3, after breaking his leg while playing on a slide. As he lost strength, his parents installed an elevator at home so he could avoid stairs, but for the most part he remained ambulatory.

Mindy dug into the science of Duchenne, finding a place in genetics and chemistry, subjects she'd avoided as an English major in college. She works part-time developing software for a tech company and time-and-a-half seeking care for (b) (6) Mitch—she met her husband in the early 1990s when they were Seattle-area high school track stars—teaches gym and takes a lot of responsibility for (b) (6) two younger siblings. In 2010, the Lefflers felt inspired when the *New Yorker* published an article titled "Mother Courage" that described how the death of Furlong's sons propelled her campaign against Duchenne. "I thought, wow, Pat really got a lot done," says Mindy, "and now we're going to take the next step and actually find a treatment for (b) (6) he doesn't end up like Pat's boys."

In 2011, Mitch took (b) (6) to a hospital in Columbus, Ohio, where Sarepta was beginning a trial for eteplirsen. Then 7 (b) (6) was showing such ominous symptoms as knotty, seemingly overdeveloped calves—evidence of scar tissue swiftly replacing muscle. He performed well on a baseline walking test. Too well, it turned out: He was rejected for the study because he was much healthier than most other subjects whose disease was more advanced.

As a fallback, Mindy hustled to get (b) (6) enrolled in a 180-person Prosensa-GlaxoSmithKline trial at a test site in Vancouver. The trial proved to be an ordeal. Multiple muscle biopsies to check dystrophin levels required (b) (6) undergo surgery with general anesthesia. And almost immediately, Leffler suspected he was receiving a saline-solution placebo, rather than injections of Prosensa's drug. She figured this out when he didn't have the swelling and pain other moms said their sons experienced.

For 48 weeks, (b) (6) parents took him by plane or car to Vancouver every week for stays ranging from a few hours to several days, depending on the protocol, all the while suspecting he wasn't actually receiving medication. "This may be good for science," Leffler says she thought at the time, "but how's it good for my son?"



Photograph by Ryan Pfluger/McNary with her sons, (b) (6) who is receiving treatment, and (b) (6) who isn't

In late 2012, researchers switched all of the subjects on placebo over to treatment with Prosensa's compound, drisapersen. (b) (6) began to suffer the side effects from getting the drug, but Leffler couldn't tell whether his Duchenne symptoms were easing. "He fluctuated: sometimes better, sometimes worse," she says.

Over time, Leffler became jealous of moms with sons in the Sarepta study—the one from which (b) (6) had been rejected—because the company was reporting solid results. In October 2012, Sarepta announced that, after 48 weeks, boys receiving eteplirsen had stabilized, with statistically significant improvement in a standardized six-minute walking test. Moreover, unlike the Prosensa drug, which at higher doses creates risks that could lead to kidney damage, the Sarepta study didn't show any dangerous side effects.

The weakness of the Sarepta trial was that it had enrolled only 12 boys. Started in 1980 at the dawn of the biotech era, the company had gone public in 1997 but never put a drug on the market. After a series of management shake-ups, a newly hired chief executive officer, Chris Garabedian, decided in 2011 to bet Sarepta's few remaining chips on eteplirsen. The company simply couldn't

afford a larger trial. "We had a limited amount of drug and no capacity to make more," Garabedian says. "So we took what we had and did the best small trial we could design." Sarepta's shortage of eteplirsen also precluded providing the drug to individual applicants under the FDA's "compassionate use" program.

Despite the skimpy sample size, Sarepta's results ignited a stock market frenzy. The company's shares rose threefold on Oct. 3, 2012, to \$45. CNBC stockpicker Jim Cramer raved about Sarepta on his *Mad Money* show and interviewed Garabedian on camera. In June 2013, PTC announced an initial public offering that raised \$144 million. In their enthusiasm, investors were willing to overlook that PTC's drug, ataluren, had failed to show statistically significant improvement in subjects' walking ability in a clinical trial three years earlier. Prosensa soon followed with its own IPO, raising \$90 million, even though it hadn't yet reported results from its main ongoing clinical study. In July, Sarepta added to the bullishness by announcing that the FDA had provided guidance that it was open to considering eteplirsen for regulatory approval. (The agency routinely communicates with companies as they move toward a "new drug application.")

"It felt like a lot of good stuff was coming together," Leffler recalls.

Then the bubble burst. In September 2013, only three months after its IPO, the Prosensa-GSK trial in which Aidan was enrolled failed to show meaningful improvement on the six-minute walk test. The study was shut down, and Prosensa's stock plummeted 70 percent in a day. "No one called us," says Leffler. "We learned that the trial was over from a GSK investor conference call. There's no safety net. You just crash." London-based GSK and Prosensa later terminated their partnership.

More bad news followed in November: After encouraging Sarepta to apply for approval of eteplirsen, the FDA reversed itself and called such a move "premature." Explaining its turnaround, the agency cited Prosensa's and PTC's trial failures. The FDA expressed "considerable doubt" that dystrophin production—the goal set out by all three companies—could be linked to meaningful clinical benefits. Sarepta's stock fell 64 percent that day.

The Lefflers received word about the FDA about-face on Sarepta while at Walt Disney World on a vacation with (b) (6) and his younger brother and sister. After the Prosensa-GSK trial failure, "it was a double blow," Mindy says. "I felt like I couldn't breathe."

After collecting herself, Leffler decided to fight. She'd already been communicating with two other moms she'd met via Facebook and at Duchenne conferences: McNary, who had the exquisitely painful situation of one son doing well in the Sarepta trial while his older brother, denied the drug, declined, and Christine McSherry, whose son (b) (6) was a wheelchair-bound high school senior, struggled to sit up straight.

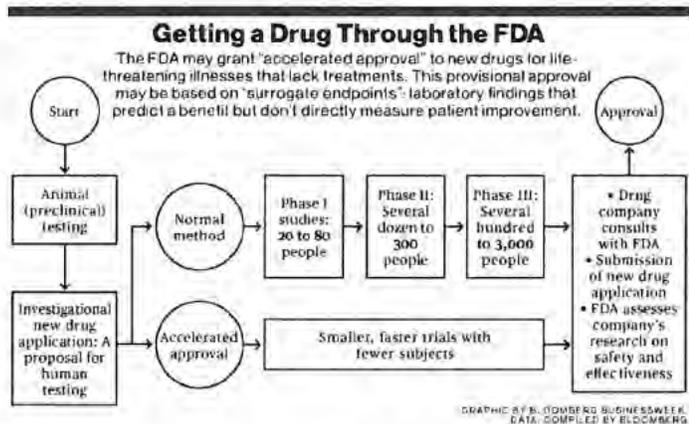
"The three of us, the 'Three Musketeers,' had a lot of the same questions," McSherry says. Why had Prosensa's and PTC's setbacks influenced the FDA to shun Sarepta? After all, the companies used different types of chemistry. The moms also didn't understand why the incipient scientific consensus on the importance of dystrophin production had suddenly become clouded. "We began to realize that the FDA was confused," says McSherry, a former nurse who is now 49. "Eteplirsen, a drug that appeared to work, was in danger of becoming a victim to the shortcomings of other drugs and other trials."

The moms had begun in 2012 demanding personal attention from FDA officials. Remarkably, they got a meeting—then another, and another. In a law enacted that year, Congress instructed the FDA to entertain more flexible paths to provisional approval of rare-disease drugs. Under the aegis of that statute, the trio became self-appointed consultants at FDA headquarters in Silver Spring, Md.

McNary organized an online petition demanding "accelerated approval" of eteplirsen. The 2012 FDA reform statute encouraged the agency to grant accelerated approval based on relatively small trials that achieve a "surrogate" goal—such as dystrophin production—with the burden left on the manufacturer to conduct broader research. The FDA can rescind accelerated approval if follow-up studies don't demonstrate efficacy. McNary swiftly gathered 180,000 signatures for her petition, and she and other moms bombarded the FDA with tweets, Instagrams, and YouTube videos showing boys in Sarepta's 12-person trial climbing rocks, dancing, and diving into swimming pools.

McNary's heart-rending tale became a centerpiece of the lobbying campaign. "I could possibly be the mother of the last child to die from Duchenne and first child to survive it," she said in a video that zinged around the Internet.

Following its standard policy, the FDA didn't respond publicly to the lobbying drive. But the agency's ambivalent reactions could be discerned from private communication with the three moms, who used blogs and websites to report on the back-and-forth. According to the moms, senior FDA leaders sought to reassure the Duchenne parents, while rank-and-file staff members tended to express more skepticism.



In July 2013, McSherry recounted on her blog a conference call with Janet Woodcock, the director of the FDA's Center for Drug Evaluation and Research. "As always, Dr. Woodcock was warm, compassionate, and extraordinarily supportive of our position," McSherry wrote. "We are one step closer to getting this drug [eteplirsen] to our boys."

Four months later, though, evaluators working under Woodcock's supervision told Sarepta not to bother applying for approval. Asked for comment, Sandy Walsh, an FDA spokeswoman, says: "Under the law, we are not able to discuss any investigational new drug or any drug application." She adds that the agency "has been working with Sarepta to provide guidance on various clinical and regulatory issues related to eteplirsen."

In February 2014, the three moms joined forces with a fourth, Tracy Seckler, to ratchet up the pressure on the FDA by organizing a two-day summit in Washington that included a visit to the agency by several leading Duchenne researchers. The next day, a bipartisan briefing on Capitol Hill sponsored by Representatives William Keating (D-Mass.) and Spencer Bachus (R-Ala.) drew an audience of dozens of congressional staff members.

Louis Kunkel, the Harvard Medical School professor who headed the team that isolated the dystrophin gene in 1986, told the gathering that boys receiving eteplirsen were making dystrophin and called this success "amazing." Steve Wilton, a leading neuromuscular researcher from Australia, was even more emphatic about eteplirsen's promise. "In Australia," he told attendees, "we'd say it's bleeding obvious."

Leffler added the moms' sense of impatience: "The FDA," she said, "is standing in the way." Not so, says the agency's Walsh: "The FDA is fully committed to make safe and effective drugs available for patients with Duchenne as soon as possible and is actively engaged with all drug companies developing new drugs for Duchenne."

Notably absent from the Washington event was Furlong. She'd held her own Washington round table two months earlier, one that was far more deferential to the FDA's authority

In an interview, Furlong, 68, says she was traveling on business in Europe at the time of the February summit and sent a representative from her organization. She decries what she describes as a splintering of "the Duchenne community" she has spent two decades building. Now a stateswoman rather than a firebrand, she criticizes younger mothers such as McNary, 34, who publicly describe their sons as dying: "What must those boys think?" she asks. More broadly, she adds, "It's just not smart strategy to chain yourself to the gates of the FDA in protest," an allusion to a tactic once used by AIDS activists.

While the more aggressive Duchenne moms haven't actually chained themselves to anything, their tone at times is abrasive. In March 2014, McNary appeared on John Stossel's government-bashing Fox Business News television show. A subscript running across the screen morphed from "Government Medicine Bullies" to "FDA Regulations Can Kill." Stossel asked McNary whether her son (b) (6) is "angry" because he couldn't get eteplirsen.

"Fifteen-year-olds in general are angry," McNary responded. "Fifteen-year-olds who are being betrayed by their government are even angrier." Stossel's other guest, Darcy Olsen of the libertarian Goldwater Institute, added: "What the FDA is doing here is an abomination."

In April, without public explanation, the FDA once again reversed its position on eteplirsen, saying Sarepta could move ahead toward regulatory approval. Given the absence of new data, the only plausible reason for the switch was escalating pressure from the three moms and their backers. Five months after rebuffing Sarepta, the FDA laid out a detailed "path forward" for eteplirsen to receive accelerated approval.

The agency's revised guidance—conveyed privately to Sarepta, then disclosed by the company—stressed government evaluators' continuing uneasiness regarding the data on eteplirsen. The company would have to conduct larger placebo-controlled studies before provisional approval would become permanent. Still, a closed door had cracked open.

Sarepta immediately said it would seek accelerated authorization by the end of 2014 and launch confirmatory studies. From April 17 to April 22, the company's stock rose 59 percent.

In June, the regulatory door opened further. Prosensa announced that the FDA would entertain an accelerated-approval application for drisapersen, even though the Dutch company's drug had failed its main clinical trial in 2013. Regulators' sudden receptivity struck some observers as peculiar, given the lack of fresh evidence of effectiveness. "It sure looks like the FDA wants to give itself cover and say, 'See, we're giving everyone a chance to apply, so parents, stop attacking us,'" says Steve Brozak, president of WBB Securities and a longtime analyst of the biotech industry.

Prosensa's CEO, Hans Schikan, disagrees with Brozak. The unsuccessful 2013 study was devised and run by GSK, he says. "Based on our reanalysis of our data, we strongly believe it was the trial that failed the drug, not the drug that failed the trial." Flaws in GSK's study design, he claims, muddied the results.

Adding yet another level of ambiguity to the situation, PTC, which had seemed out of the running for a Duchenne treatment, has reentered the race. "We shot ourselves in the foot" by conceding defeat after the failed 2010 ataluren trial, says Stuart Peltz, PTC's co-founder and chief executive. After reanalysis of its data, PTC concluded its drug actually works. "In biotech, you're building the airplane while you're trying to fly it at the same time," Peltz continues. "It took us a while to realize that when you focus on the boys with the most severe symptoms, ataluren does show a robust efficacy." In August the European Union's equivalent to the FDA granted conditional approval to ataluren, and PTC is beginning to sell the drug in Europe. After completing more clinical trials, Peltz says, his company will apply for full approval in Europe, the U.S., and elsewhere.

Furlong has faith the FDA will sort out which Duchenne drugs are effective. "Ideally," she says, "we'd like to see all of the drug candidates move forward in the regulatory process."

The three moms, in contrast, say the FDA's one-step-back, one-step-forward routine has them feeling unnerved, not reassured. "The boys on eteplirsen are walking when the natural history of the disease says that they should be in wheelchairs," says Leffler. Why, she wants to know, don't industry and government cooperate to get as many boys on eteplirsen as quickly as possible?

"That's not the way medical science works," says Hoffman, the Duchenne researcher at Children's National Medical Center. The FDA, Hoffman continues, "is doing the best it can, moving cautiously and looking skeptically at Sarepta's data, and all of the data from all of the companies." On Oct. 27, Sarepta announced that as a result of a new round of FDA data requests, the company would have to postpone its application for approval of eteplirsen until mid-2015. Hoffman, who for years has had a close working relationship with Furlong and her organization, expresses sympathy for moms like Leffler, McNary, and McSherry who are impatient for faster action. "They must mean well—their boys are sick," he says, "but their pressure tactics on the FDA seem like bullying more than anything else."

Leffler, 42, doesn't care anymore what anyone calls her tactics. Her determination to get (b) (6) eteplirsen became more urgent in August when he fell and fractured the femur in his left leg while kicking a ball in the backyard. Doctors told (b) (6) parents he had a 50-50 chance of ever getting back on his feet. He had surgery the next day to have a steel rod placed in his leg. Two weeks later, to his doctors' surprise, but not his parents', he started hobbling around with a walker. With some effort, he can even get in and out of the family minivan more or less on his own. "He's an amazing kid," Leffler says.

Soccer, even in modified form, is probably over forever. (b) (6) now in sixth grade, has redoubled his attention to big cats. He's writing fundraising letters and passing along the money to a conservation group called Panthera.

He's not oblivious to his medical predicament. If anything, he's growing more worried. The other day, Leffler found a piece of paper in her bathroom with a question written in (b) (6) neat block letters: "Does muscular dystrophy make you die sooner?"



Barrett is an assistant managing editor and senior writer at *Bloomberg Businessweek*. His new book, *Law of the Jungle*, tells the story of the Chevron oil pollution case in Ecuador.

SPONSOR CONTENT

Smith, Celeste

From: Hamburg, Margaret
Sent: Thursday, October 30, 2014 3:27 PM
To: Pennington, Caitlin
Subject: Fw: DMD- Sarepta
Attachments: Duchenne Muscular Dystrophy_ Moms Fight for FDA Approval of Sarepta Drug - Businessweek.pdf

Print. Folder: Sarepta/DMD
Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

From: Immergut, Steven
Sent: Thursday, October 30, 2014 03:08 PM
To: Hamburg, Margaret
Cc: Hoague, Angela
Subject: DMD- Sarepta

Hi- yes at a few big stories on DMD/Sarepta this week. The announced earlier in week an update from their preNDA meeting. The one today from BusinessWeek sounds like the one you heard about - though strangely not in our clips this morning. Will need to check on that.

First link below and attached pdf in case you want to print and bring home

It's a really tough story on us. We didn't know was coming today but did work with reporter. This is a very difficult situation for us but need to think about how come off better than this.

<http://www.businessweek.com/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug>

The second and third one are more on the announcement - from Matt Herper at Forbes and Joe Walker at WSJ. Matt calls for CEO to resign.

<http://www.forbes.com/sites/matthewherper/2014/10/27/sarepta-needs-fda-expertise-stat/>

<http://online.wsj.com/articles/sarepta-therapeutics-sees-setback-in-eteplirsen-drug-application-1414414412>

here's the press release.

Sarepta Therapeutics Announces Regulatory Update on Eteplirsen

Updated and additional guidance received from FDA on specific data requirements for NDA;

FDA states further discussion needed to determine what constitutes a "complete" NDA submission;

NDA submission planned for mid-year 2015;

Company to hold teleconference today at 8:00 a.m. EDT

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 27, 2014-- Sarepta Therapeutics, Inc.

(NASDAQ:SRPT), a developer of innovative RNA-based therapeutics, today provided an update on its discussions with the U.S. Food and Drug Administration (FDA) regarding its planned New Drug Application (NDA) submission for the approval of eteplirsen for the treatment of Duchenne muscular dystrophy (DMD).

In meeting minutes received last week from a Type B Pre-NDA meeting that took place in September 2014, the FDA provided updated guidance regarding the specific data to be included as part of, or at the time of, Sarepta's NDA submission. The guidance states that additional data are now required as part of the NDA submission, including the results from an independent assessment of dystrophin images and the 168-week clinical data from study 202. Additionally, the guidance requests more specific data including a minimum duration of safety in new patients exposed to eteplirsen, patient-level natural history data to be obtained by Sarepta from independent academic institutions, and MRI data from a recent study conducted by an independent academic group. The FDA indicated that further discussion with Sarepta "will be necessary to determine what would constitute a complete NDA." Based on these requests, Sarepta plans to submit an NDA by mid-year 2015, pending any additional requests from further discussions with the FDA.

"We are committed to satisfying the FDA's updated requests for these specific data to be included as part of an NDA submission and will continue to work with the Agency toward the goal of a complete and acceptable NDA filing," said Chris Garabedian, president and chief executive officer of Sarepta Therapeutics. "We believe all of the data requests and additional FDA discussions that have currently been outlined can be completed in time for an NDA submission by mid-year 2015. Obtaining an FDA approval of eteplirsen for the DMD patients who may benefit from the drug continues to be our highest priority."

Excerpts from the Pre-NDA Meeting Minutes related to information that the FDA is requesting as part of an NDA submission included:

"The sponsor should include 3-month data from at least 12 to 24 newly exposed patients at the time the NDA is submitted."

"Available data from the other patients enrolled in the new eteplirsen studies (studies 301, 203, 204) should also be included at the time the NDA is submitted, even if exposure is less than 3 months in duration."

"Additional data from later time points and from newly enrolled patients should be submitted in the 120-Day Safety Update."

"FDA strongly advises the sponsor to obtain and submit patient-level natural history data. FDA is prepared to appeal to the academic groups holding the data to allow the sponsor a means to acquire the data."

"The study 201/202 clinical site inspection conducted in May, 2014, after the issuance of the April 15, 2014, guidance letter, uncovered marked disparities in the immunohistochemistry methodology and concerns about the reproducibility of the data. The lack of confirmation of robust dystrophin measurement during the site visit necessitates including the independent assessment of dystrophin-positive fibers and 168-week efficacy data from study 201/202 in the NDA."

"FDA strongly urged the sponsor to submit the MRI data with appropriate natural history controls."

The FDA also stated that *"[a]dditional discussion between the sponsor and the FDA will be necessary to*

determine what would constitute a complete NDA.”

Conference Call Information

Sarepta will hold a conference call to discuss this update today at 8:00 a.m. EDT (5:00 a.m. PDT). The conference call may be accessed by dialing 800.708.4539 for domestic callers and 847.619.6396 for international callers. The passcode for the call is (b) (6). Please specify to the operator that you would like to join the "Sarepta Regulatory Update Call." The conference call will be webcast live under the investor relations section of Sarepta's website at www.sarepta.com and will be archived there following the call for 90 days. Please connect to Sarepta's website several minutes prior to the start of the broadcast to ensure adequate time for any software download that may be necessary. An audio replay will be available through November 3, 2014 by calling 888.843.7419 or 630.652.3042 and entering access code (b) (6).

About Duchenne Muscular Dystrophy

DMD is an X-linked rare degenerative neuromuscular disorder causing severe progressive muscle loss and premature death. DMD affects approximately one in every 3,500 boys born worldwide. A devastating and incurable muscle-wasting disease, DMD is associated with specific errors in the gene that codes for dystrophin, a protein that plays a key structural role in muscle fiber function. Progressive muscle weakness in the lower limbs spreads to the arms, neck and other areas. Eventually, increasing difficulty in breathing due to respiratory muscle dysfunction requires ventilation support, and cardiac dysfunction can lead to heart failure. The condition is universally fatal, and death usually occurs before the age of 30.

About Eteplirsen

Eteplirsen is Sarepta's lead drug candidate and is designed to address the underlying cause of DMD by enabling the production of a functional dystrophin protein. Data from clinical studies of eteplirsen in DMD patients have demonstrated a broadly favorable safety and tolerability profile and restoration of dystrophin protein expression.

Eteplirsen uses Sarepta's novel phosphorodiamidate morpholino oligomer (PMO)-based chemistry and proprietary exon-skipping technology to skip mutations affecting exon 51 of the dystrophin gene. Approximately 13 percent of the total DMD population is amenable to exon 51 skipping. By skipping exon 51, eteplirsen may restore the gene's ability to make a shorter, but still functional, form of dystrophin from messenger RNA, or mRNA. Promoting the synthesis of a truncated dystrophin protein is intended to stabilize or significantly slow the disease process and prolong and improve the quality of life for patients with DMD. Sarepta is also developing other PMO-based exon-skipping drug candidates intended to treat additional patients with DMD.

About Sarepta Therapeutics

Sarepta Therapeutics is focused on developing first-in-class RNA-based therapeutics to improve and save the lives of people affected by serious and life-threatening rare and infectious diseases. The Company's diverse pipeline includes its lead program eteplirsen, for DMD, as well as potential treatments for some of the world's most lethal infectious diseases. Sarepta aims to build a leading, independent biotech company dedicated to translating its RNA-based science into transformational therapeutics for patients who face significant unmet medical needs. For more information, please visit us at www.sarepta.com.

Forward-Looking Statements and Information

This press release contains forward-looking statements. These forward-looking statements generally can be identified by the use of words such as “believes or belief,” “anticipates,” “plans,” “expects,” “will,” “intends,” “potential,” “possible,” “advance” and similar expressions. These forward-looking statements include statements about Sarepta’s planned timing for an NDA submission for eteplirsen in the treatment of DMD; Sarepta’s plans to work with the FDA towards the goal of a complete and acceptable NDA filing; Sarepta’s ability to satisfy the additional FDA requests; the timing and submission of additional data, analysis and other information to the FDA necessary for the FDA to make regulatory determinations; the timing of and ability to initiate additional studies for eteplirsen and other follow-on exons; and the potential regulatory approval of eteplirsen.

Each forward-looking statement contained in this press release is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statement. Applicable risks and uncertainties include, among others: we

may not be able to comply with all FDA requests; the FDA may determine that substantial additional data is required for accelerated or other approval of eteplirsen or that our NDA submission for eteplirsen does not qualify for filing, even with additional information; the results of our ongoing and new clinical trials may not be positive; there may be delays in timelines relating to an NDA submission, initiating clinical trials, or making a product commercially available for regulatory or internal reasons; we may not be able to manufacture sufficient supply for clinical trials or commercialization; agency or court decisions with respect to our patents or those of third parties may negatively impact our business and those identified under the heading “Risk Factors” in Sarepta’s Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 filed with the Securities and Exchange Commission (SEC), and Sarepta’s other filings with the SEC.

Any of the foregoing risks could materially and adversely affect Sarepta’s business, results of operations and the trading price of Sarepta’s common stock. For a detailed description of risks and uncertainties Sarepta faces, you are encouraged to review the Company’s filings with the SEC. We caution investors not to place considerable reliance on the forward-looking statements contained in this press release. Sarepta does not undertake any obligation to publicly update its forward looking statements based on events or circumstances after the date hereof.

Source: Sarepta Therapeutics, Inc.

**Sarepta Media Contact:
Tony Plohoros, 908-591-2839
tplohoros@6degreespr.com**

or

**Sarepta Investor Contact:
Stephanie Ascher, 212-362-1200
stephanie@sternir.com**

Bloomberg Businessweek

Technology

<http://www.businessweek.com/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug>

Moms, Regulators, Biotech Startups, and the Battle Over a Potentially Life-Saving Drug

By Paul M. Barrett October 30, 2014



Photograph by Ryan PflugerLeffler's son, (b) (6), was diagnosed with Duchenne in 2006.

The 2014 World Cup elevated soccer to the top of (b) (6)'s roster of obsessions, rivaled only by endangered big cats—especially jaguars, “the coolest”—and *Star Wars* spaceships. In recognition of his new interest, he’s set up a miniature soccer field with 4-foot-wide goals in his backyard in suburban Bellevue, Wash. “Watch this!” he shouts, preparing to fire a penalty kick.

Small for his age, (b) (6), 11, moves awkwardly, shoulders high and hunched. He uses a lightweight plastic beach ball, not a regulation leather soccer ball. He begins his approach, pulls back his right foot, and ... collapses to the grass.

Mitch Leffler, the sole spectator, moves toward his son. “I’m OK,” (b) (6) says. “I can do it.” He struggles onto his hands and knees, raises his butt, places his hands one at a time on his thighs, and slowly pushes himself into an upright position. “My leg just wasn’t there,” he says matter-of-factly. His father nods, and the game resumes.

(b) (6) has Duchenne, the deadliest strain of muscular dystrophy. It’s inherited maternally on the X chromosome and mostly afflicts boys. Parents typically sense something is wrong when their sons at 3 or 4 don’t run around or they start falling for no obvious reason. Beginning in the legs, Duchenne destroys muscle, which is replaced by fat and scar tissue. Victims lose the ability to walk by adolescence. Eventually the disease causes cardiac and/or respiratory complications that lead to death by the mid-20s. One in 3,500 newborns has Duchenne, which translates to around 15,000 cases in the U.S. There’s no cure.

(b) (6) doesn’t really understand yet,” his mother, Mindy, says, “but it’s basically a slow-motion death sentence.”

There’s reason to hope—not for a miracle, but for a reprieve. Three small biotech companies are competing to develop drugs designed to address the cellular defects that cause some cases of Duchenne. If proven safe and effective, the drugs would turn Duchenne into a less devastating form of muscular dystrophy. Clinical trials, however, have yielded uneven results, and the U.S. Food and Drug Administration has made equivocal pronouncements about which of the drugs, if any, have a shot at approval. Even a marginally effective drug would likely command an astronomical price, making the winning company a billion-dollar sensation.

The hunt for a Duchenne treatment has generated a collision of commerce, cutting-edge science, and Wall Street speculation. The FDA, though, seems flummoxed over how to evaluate the experimental drugs, especially given a lack of large, clearly successful randomized studies. That’s left the Lefflers confused and increasingly desperate.



Photograph by Ryan PflugerMcSherry with her son, (b) (6), who began college this fall.

Mindy believes that one experimental treatment—eteplirsen, made by a company called Sarepta Therapeutics (SRPT)—has shown sufficient promise in a tiny trial to warrant wider availability. If approved, eteplirsen might help 13 percent of Duchenne boys who have certain genetic flaws. Mindy’s son is among the 13 percent. “I want (b) (6) on that drug,” she says, “and I want it to happen before he’s in a wheelchair or worse.”

She and a group of similarly minded moms are pressuring the FDA to give provisional approval to eteplirsen while Sarepta proceeds with confirmatory studies. Taking to Twitter, Facebook, YouTube, and Instagram, they’ve got the attention of top FDA officials. They’ve also encountered resistance from career FDA staff members and some rare-disease advocates alarmed by their assertiveness.

"What's hard to understand," says Mindy's friend Jennifer McNary, "is why the whole Duchenne community and the FDA aren't pulling together behind eteplirsen." McNary, who lives south of Boston, has two sons with the disease. Maternal genetic predisposition sometimes results in such sibling pairs. (b) (6) 12, gets eteplirsen in the small Sarepta trial; over the past two-and-a-half years, his symptoms have eased remarkably. Max's older brother, (b) (6) 5, didn't qualify for the study because he was already in a wheelchair when it started. He's declining physically, losing the use of his arms and having trouble feeding himself.

"Why doesn't the government let me have eteplirsen?" (b) (6) asks when we meet. He waits for an answer, which I don't have. His mother joins the conversation: "The FDA's inaction," she says, "is killing my son."

Mindy agrees with Jennifer and (b) (6) doesn't have time to wait for a perfect placebo-controlled trial with hundreds of subjects," she says. "The benefits outweigh any risks."

In 1986 researchers at Harvard isolated the gene responsible for making the protein dystrophin, a "shock absorber" that surrounds muscle cells. Boys with Duchenne have one of several genetic defects that inhibit production of dystrophin. Without it, ordinary physical exertion causes progressive muscle breakdown. The disease is named for Guillaume Duchenne, a French neurological pioneer who described the symptoms in the 1860s.

For generations, physicians reacted passively to Duchenne. Patricia Furlong's sons, Christopher and Patrick, were diagnosed in 1984. Her doctor told her to "take them home and love them, because there was nothing medicine could do." A former nurse with a stubborn streak, she began traveling the country from her home in central Ohio, pleading with researchers to look for a cure. "She was at NIH [National Institutes of Health]. She was on Capitol Hill. She was in my office," recalls Eric Hoffman, a genetic researcher at Children's National Medical Center in Washington. "Pat would not be denied." She couldn't save her sons, however, who died in the mid-1990s.

Angered by what she describes as the fatalism she encountered at the Muscular Dystrophy Association—sponsor of the long-running Labor Day telethon hosted by actor Jerry Lewis—Furlong formed a breakaway nonprofit: Parents Project Muscular Dystrophy, dedicated strictly to Duchenne. In 2001, largely because of her agitation, Congress passed the Muscular Dystrophy CARE Act, which over the following decade provided more than \$400 million in funding, much of it for Duchenne research. The federal backing, says Hoffman, "got the biotech companies thinking maybe there's money to be made with a Duchenne drug."

"What's hard to understand is why the whole Duchenne community and the FDA aren't pulling together behind eteplirsen"

A startup in New Jersey called PTC Therapeutics (PTCT) focuses on mutations that block dystrophin production. These "nonsense mutations" are akin to a period mistakenly placed in the middle of a sentence, which makes the genetic code incomprehensible. In 2008, Genzyme (SNY), a much larger biotech, gave credibility to PTC's research by paying the tiny company \$100 million upfront to secure future marketing rights to its drug outside North America.

Prosensa (RNA), a Dutch biotech, targets a different type of flaw in the exons, or segments, of the dystrophin gene. By "skipping" a defective exon, Prosensa's compound is supposed to allow the formation of a truncated version of dystrophin. In 2009 the pharmaceutical giant GlaxoSmithKline (GSK) added momentum to exon-skipping research by paying Prosensa \$25 million upfront for development and marketing rights and promising hundreds of millions more in future compensation.

In the U.S., Sarepta was also angling to get into the Duchenne chase. Choosing to work without a larger corporate partner, it began testing eteplirsen, an exon-skipping compound that relies on a different biochemical recipe from Prosensa's drug.

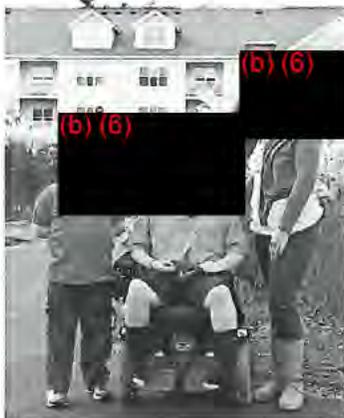
The proliferation of potential treatments gave the Lefflers reason for optimism after years of mounting apprehension. (b) (6) had first been diagnosed in 2006, at the age of almost 3, after breaking his leg while playing on a slide. As he lost strength, his parents installed an elevator at home so he could avoid stairs, but for the most part he remained ambulatory.

Mindy dug into the science of Duchenne, finding a place in genetics and chemistry, subjects she'd avoided as an English major in college. She works part-time developing software for a tech company and time-and-a-half seeking care for (b) (6) Mitch—she met her husband in the early 1990s when they were Seattle-area high school track stars—teaches gym and takes a lot of responsibility for (b) (6) two younger siblings. In 2010, the Lefflers felt inspired when the *New Yorker* published an article titled "Mother Courage" that described how the death of Furlong's sons propelled her campaign against Duchenne. "I thought, wow, Pat really got a lot done," says Mindy, "and now we're going to take the next step and actually find a treatment for (b) (6) he doesn't end up like Pat's boys."

In 2011, Mitch took (b) (6) to a hospital in Columbus, Ohio, where Sarepta was beginning a trial for eteplirsen. Then 7 (b) (6) was showing such ominous symptoms as knotty, seemingly overdeveloped calves—evidence of scar tissue swiftly replacing muscle. He performed well on a baseline walking test. Too well, it turned out: He was rejected for the study because he was much healthier than most other subjects whose disease was more advanced.

As a fallback, Mindy hustled to get (b) (6) enrolled in a 180-person Prosensa-GlaxoSmithKline trial at a test site in Vancouver. The trial proved to be an ordeal. Multiple muscle biopsies to check dystrophin levels required (b) (6) undergo surgery with general anesthesia. And almost immediately, Leffler suspected he was receiving a saline-solution placebo, rather than injections of Prosensa's drug. She figured this out when he didn't have the swelling and pain other moms said their sons experienced.

For 48 weeks, (b) (6) parents took him by plane or car to Vancouver every week for stays ranging from a few hours to several days, depending on the protocol, all the while suspecting he wasn't actually receiving medication. "This may be good for science," Leffler says she thought at the time, "but how's it good for my son?"



Photograph by Ryan Pfluger/McNary with her sons, (b) (6) who is receiving treatment, and (b) (6) who isn't

In late 2012, researchers switched all of the subjects on placebo over to treatment with Prosensa's compound, drisapersen. (b) (6) began to suffer the side effects from getting the drug, but Leffler couldn't tell whether his Duchenne symptoms were easing. "He fluctuated: sometimes better, sometimes worse," she says.

Over time, Leffler became jealous of moms with sons in the Sarepta study—the one from which (b) (6) had been rejected—because the company was reporting solid results. In October 2012, Sarepta announced that, after 48 weeks, boys receiving eteplirsen had stabilized, with statistically significant improvement in a standardized six-minute walking test. Moreover, unlike the Prosensa drug, which at higher doses creates risks that could lead to kidney damage, the Sarepta study didn't show any dangerous side effects.

The weakness of the Sarepta trial was that it had enrolled only 12 boys. Started in 1980 at the dawn of the biotech era, the company had gone public in 1997 but never put a drug on the market. After a series of management shake-ups, a newly hired chief executive officer, Chris Garabedian, decided in 2011 to bet Sarepta's few remaining chips on eteplirsen. The company simply couldn't

afford a larger trial. "We had a limited amount of drug and no capacity to make more," Garabedian says. "So we took what we had and did the best small trial we could design." Sarepta's shortage of eteplirsen also precluded providing the drug to individual applicants under the FDA's "compassionate use" program.

Despite the skimpy sample size, Sarepta's results ignited a stock market frenzy. The company's shares rose threefold on Oct. 3, 2012, to \$45. CNBC stockpicker Jim Cramer raved about Sarepta on his *Mad Money* show and interviewed Garabedian on camera. In June 2013, PTC announced an initial public offering that raised \$144 million. In their enthusiasm, investors were willing to overlook that PTC's drug, ataluren, had failed to show statistically significant improvement in subjects' walking ability in a clinical trial three years earlier. Prosensa soon followed with its own IPO, raising \$90 million, even though it hadn't yet reported results from its main ongoing clinical study. In July, Sarepta added to the bullishness by announcing that the FDA had provided guidance that it was open to considering eteplirsen for regulatory approval. (The agency routinely communicates with companies as they move toward a "new drug application.")

"It felt like a lot of good stuff was coming together," Leffler recalls.

Then the bubble burst. In September 2013, only three months after its IPO, the Prosensa-GSK trial in which Aidan was enrolled failed to show meaningful improvement on the six-minute walk test. The study was shut down, and Prosensa's stock plummeted 70 percent in a day. "No one called us," says Leffler. "We learned that the trial was over from a GSK investor conference call. There's no safety net. You just crash." London-based GSK and Prosensa later terminated their partnership.

More bad news followed in November: After encouraging Sarepta to apply for approval of eteplirsen, the FDA reversed itself and called such a move "premature." Explaining its turnaround, the agency cited Prosensa's and PTC's trial failures. The FDA expressed "considerable doubt" that dystrophin production—the goal set out by all three companies—could be linked to meaningful clinical benefits. Sarepta's stock fell 64 percent that day.

The Lefflers received word about the FDA about-face on Sarepta while at Walt Disney World on a vacation with (b) (3) and his younger brother and sister. After the Prosensa-GSK trial failure, "it was a double blow," Mindy says. "I felt like I couldn't breathe."

After collecting herself, Leffler decided to fight. She'd already been communicating with two other moms she'd met via Facebook and at Duchenne conferences: McNary, who had the exquisitely painful situation of one son doing well in the Sarepta trial while his older brother, denied the drug, declined, and Christine McSherry, whose son (b) (3) was a wheelchair-bound high school senior, struggled to sit up straight.

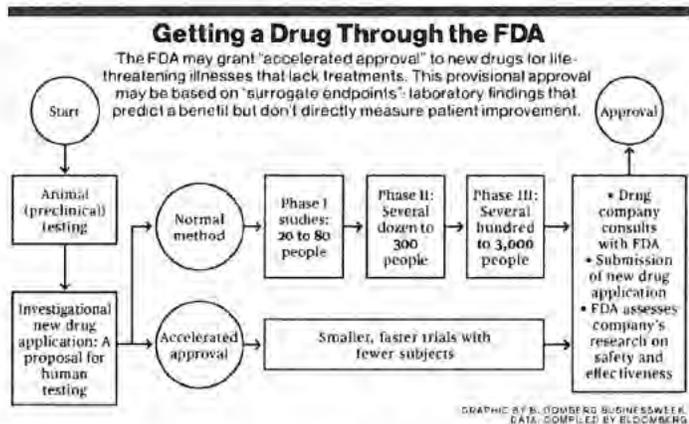
"The three of us, the 'Three Musketeers,' had a lot of the same questions," McSherry says. Why had Prosensa's and PTC's setbacks influenced the FDA to shun Sarepta? After all, the companies used different types of chemistry. The moms also didn't understand why the incipient scientific consensus on the importance of dystrophin production had suddenly become clouded. "We began to realize that the FDA was confused," says McSherry, a former nurse who is now 49. "Eteplirsen, a drug that appeared to work, was in danger of becoming a victim to the shortcomings of other drugs and other trials."

The moms had begun in 2012 demanding personal attention from FDA officials. Remarkably, they got a meeting—then another, and another. In a law enacted that year, Congress instructed the FDA to entertain more flexible paths to provisional approval of rare-disease drugs. Under the aegis of that statute, the trio became self-appointed consultants at FDA headquarters in Silver Spring, Md.

McNary organized an online petition demanding "accelerated approval" of eteplirsen. The 2012 FDA reform statute encouraged the agency to grant accelerated approval based on relatively small trials that achieve a "surrogate" goal—such as dystrophin production—with the burden left on the manufacturer to conduct broader research. The FDA can rescind accelerated approval if follow-up studies don't demonstrate efficacy. McNary swiftly gathered 180,000 signatures for her petition, and she and other moms bombarded the FDA with tweets, Instagrams, and YouTube videos showing boys in Sarepta's 12-person trial climbing rocks, dancing, and diving into swimming pools.

McNary's heart-rending tale became a centerpiece of the lobbying campaign. "I could possibly be the mother of the last child to die from Duchenne and first child to survive it," she said in a video that zinged around the Internet.

Following its standard policy, the FDA didn't respond publicly to the lobbying drive. But the agency's ambivalent reactions could be discerned from private communication with the three moms, who used blogs and websites to report on the back-and-forth. According to the moms, senior FDA leaders sought to reassure the Duchenne parents, while rank-and-file staff members tended to express more skepticism.



In July 2013, McSherry recounted on her blog a conference call with Janet Woodcock, the director of the FDA's Center for Drug Evaluation and Research. "As always, Dr. Woodcock was warm, compassionate, and extraordinarily supportive of our position," McSherry wrote. "We are one step closer to getting this drug [eteplirsen] to our boys."

Four months later, though, evaluators working under Woodcock's supervision told Sarepta not to bother applying for approval. Asked for comment, Sandy Walsh, an FDA spokeswoman, says: "Under the law, we are not able to discuss any investigational new drug or any drug application." She adds that the agency "has been working with Sarepta to provide guidance on various clinical and regulatory issues related to eteplirsen."

In February 2014, the three moms joined forces with a fourth, Tracy Seckler, to ratchet up the pressure on the FDA by organizing a two-day summit in Washington that included a visit to the agency by several leading Duchenne researchers. The next day, a bipartisan briefing on Capitol Hill sponsored by Representatives William Keating (D-Mass.) and Spencer Bachus (R-Ala.) drew an audience of dozens of congressional staff members.

Louis Kunkel, the Harvard Medical School professor who headed the team that isolated the dystrophin gene in 1986, told the gathering that boys receiving eteplirsen were making dystrophin and called this success "amazing." Steve Wilton, a leading neuromuscular researcher from Australia, was even more emphatic about eteplirsen's promise. "In Australia," he told attendees, "we'd say it's bleeding obvious."

Leffler added the moms' sense of impatience: "The FDA," she said, "is standing in the way." Not so, says the agency's Walsh: "The FDA is fully committed to make safe and effective drugs available for patients with Duchenne as soon as possible and is actively engaged with all drug companies developing new drugs for Duchenne."

Notably absent from the Washington event was Furlong. She'd held her own Washington round table two months earlier, one that was far more deferential to the FDA's authority

In an interview, Furlong, 68, says she was traveling on business in Europe at the time of the February summit and sent a representative from her organization. She decries what she describes as a splintering of "the Duchenne community" she has spent two decades building. Now a stateswoman rather than a firebrand, she criticizes younger mothers such as McNary, 34, who publicly describe their sons as dying: "What must those boys think?" she asks. More broadly, she adds, "It's just not smart strategy to chain yourself to the gates of the FDA in protest," an allusion to a tactic once used by AIDS activists.

While the more aggressive Duchenne moms haven't actually chained themselves to anything, their tone at times is abrasive. In March 2014, McNary appeared on John Stossel's government-bashing Fox Business News television show. A subscript running across the screen morphed from "Government Medicine Bullies" to "FDA Regulations Can Kill." Stossel asked McNary whether her son (b) (6) is "angry" because he couldn't get eteplirsen.

"Fifteen-year-olds in general are angry," McNary responded. "Fifteen-year-olds who are being betrayed by their government are even angrier." Stossel's other guest, Darcy Olsen of the libertarian Goldwater Institute, added: "What the FDA is doing here is an abomination."

In April, without public explanation, the FDA once again reversed its position on eteplirsen, saying Sarepta could move ahead toward regulatory approval. Given the absence of new data, the only plausible reason for the switch was escalating pressure from the three moms and their backers. Five months after rebuffing Sarepta, the FDA laid out a detailed "path forward" for eteplirsen to receive accelerated approval.

The agency's revised guidance—conveyed privately to Sarepta, then disclosed by the company—stressed government evaluators' continuing uneasiness regarding the data on eteplirsen. The company would have to conduct larger placebo-controlled studies before provisional approval would become permanent. Still, a closed door had cracked open.

Sarepta immediately said it would seek accelerated authorization by the end of 2014 and launch confirmatory studies. From April 17 to April 22, the company's stock rose 59 percent.

In June, the regulatory door opened further. Prosensa announced that the FDA would entertain an accelerated-approval application for drisapersen, even though the Dutch company's drug had failed its main clinical trial in 2013. Regulators' sudden receptivity struck some observers as peculiar, given the lack of fresh evidence of effectiveness. "It sure looks like the FDA wants to give itself cover and say, 'See, we're giving everyone a chance to apply, so parents, stop attacking us,'" says Steve Brozak, president of WBB Securities and a longtime analyst of the biotech industry.

Prosensa's CEO, Hans Schikan, disagrees with Brozak. The unsuccessful 2013 study was devised and run by GSK, he says. "Based on our reanalysis of our data, we strongly believe it was the trial that failed the drug, not the drug that failed the trial." Flaws in GSK's study design, he claims, muddied the results.

Adding yet another level of ambiguity to the situation, PTC, which had seemed out of the running for a Duchenne treatment, has reentered the race. "We shot ourselves in the foot" by conceding defeat after the failed 2010 ataluren trial, says Stuart Peltz, PTC's co-founder and chief executive. After reanalysis of its data, PTC concluded its drug actually works. "In biotech, you're building the airplane while you're trying to fly it at the same time," Peltz continues. "It took us a while to realize that when you focus on the boys with the most severe symptoms, ataluren does show a robust efficacy." In August the European Union's equivalent to the FDA granted conditional approval to ataluren, and PTC is beginning to sell the drug in Europe. After completing more clinical trials, Peltz says, his company will apply for full approval in Europe, the U.S., and elsewhere.

Furlong has faith the FDA will sort out which Duchenne drugs are effective. "Ideally," she says, "we'd like to see all of the drug candidates move forward in the regulatory process."

The three moms, in contrast, say the FDA's one-step-back, one-step-forward routine has them feeling unnerved, not reassured. "The boys on eteplirsen are walking when the natural history of the disease says that they should be in wheelchairs," says Leffler. Why, she wants to know, don't industry and government cooperate to get as many boys on eteplirsen as quickly as possible?

"That's not the way medical science works," says Hoffman, the Duchenne researcher at Children's National Medical Center. The FDA, Hoffman continues, "is doing the best it can, moving cautiously and looking skeptically at Sarepta's data, and all of the data from all of the companies." On Oct. 27, Sarepta announced that as a result of a new round of FDA data requests, the company would have to postpone its application for approval of eteplirsen until mid-2015. Hoffman, who for years has had a close working relationship with Furlong and her organization, expresses sympathy for moms like Leffler, McNary, and McSherry who are impatient for faster action. "They must mean well—their boys are sick," he says, "but their pressure tactics on the FDA seem like bullying more than anything else."

Leffler, 42, doesn't care anymore what anyone calls her tactics. Her determination to get (b) (6) eteplirsen became more urgent in August when he fell and fractured the femur in his left leg while kicking a ball in the backyard. Doctors told (b) (6) parents he had a 50-50 chance of ever getting back on his feet. He had surgery the next day to have a steel rod placed in his leg. Two weeks later, to his doctors' surprise, but not his parents', he started hobbling around with a walker. With some effort, he can even get in and out of the family minivan more or less on his own. "He's an amazing kid," Leffler says.

Soccer, even in modified form, is probably over forever. (b) (6) now in sixth grade, has redoubled his attention to big cats. He's writing fundraising letters and passing along the money to a conservation group called Panthera.

He's not oblivious to his medical predicament. If anything, he's growing more worried. The other day, Leffler found a piece of paper in her bathroom with a question written in (b) (6) neat block letters: "Does muscular dystrophy make you die sooner?"



Barrett is an assistant managing editor and senior writer at *Bloomberg Businessweek*. His new book, *Law of the Jungle*, tells the story of the Chevron oil pollution case in Ecuador.

SPONSOR CONTENT

Smith, Celeste

From: Immergut, Steven
Sent: Thursday, October 30, 2014 10:40 PM
To: Hamburg, Margaret; Dickinson, Elizabeth (FDA); Esposito, Denise; Barclay, Lisa; Lurie, Peter; Kraus, Tom; Howard, Sally
Subject: FW: DMD- Sarepta
Attachments: Duchenne Muscular Dystrophy_ Moms Fight for FDA Approval of Sarepta Drug - Businessweek.pdf

Following an announcement on Monday morning from Sarepta that their timeline for submitting the NDA on eteplirsen would be delayed until mid 2015, CDER got a lot of calls from the DMD community. There was also a very critical piece today in BloombergBusinessWeek. Late this afternoon CDER went ahead and posted a statement on the web (<http://www.fda.gov/Drugs/DrugSafety/ucm421270.htm>) in response to the calls they got and this coverage. (b) (5)

(b) (5)
(b) (5) poke to Kim Rawlings about that this evening. We sent the statement to a couple of reporters. WSJ has a short blurg up already.

FDA Comments on Talks With Sarepta on Muscular Dystrophy Drug

Agency Said Statement Was to Address Questions From Patients, Families

By
Joseph Walker

Updated Oct. 30, 2014 8:58 p.m. ET

The U.S. Food and Drug Administration took the unusual step of commenting on discussions it has had with Sarepta Therapeutics Inc., a Cambridge, Mass., biotechnology company that is developing a drug for a rare form of muscular dystrophy.

In a statement on its website Thursday, the FDA said it had asked Sarepta to collect additional data on its experimental drug, eteplirsen, in part to address the agency's concerns about the company's clinical trial data. But the agency also expressed its continued commitment to working with companies to bring new treatments to patients with Duchenne muscular dystrophy, a fatal disease that often kills patients by their 30s.

The statement essentially confirmed similar ones Sarepta made Monday, when it said the FDA's request for additional data would postpone the company's submission of a new drug application until 2015. The company had previously said it expected to file for FDA approval by the end of 2014. In response, shares of Sarepta plummeted 32% on Monday.

From: Immergut, Steven
Sent: Thursday, October 30, 2014 3:09 PM
To: Hamburg, Margaret

Cc: Hoague, Angela
Subject: DMD- Sarepta

Hi- yes at a few big stories on DMD/Sarepta this week. The announced earlier in week an update from their preNDA meeting. The one today from BusinessWeek sounds like the one you heard about - though strangely not in our clips this morning. Will need to check on that.

First link below and attached pdf in case you want to print and bring home

It's a really tough story on us. We didn't know was coming today but did work with reporter. This is a very difficult situation for us but need to think about how come off better than this.

<http://www.businessweek.com/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug>

The second and third one are more on the announcement - from Matt Herper at Forbes and Joe Walker at WSJ. Matt calls for CEO to resign.

<http://www.forbes.com/sites/matthewherper/2014/10/27/sarepta-needs-fda-expertise-stat/>

<http://online.wsj.com/articles/sarepta-therapeutics-sees-setback-in-eteplirsen-drug-application-1414414412>

here's the press release.

Sarepta Therapeutics Announces Regulatory Update on Eteplirsen

Updated and additional guidance received from FDA on specific data requirements for NDA;

FDA states further discussion needed to determine what constitutes a "complete" NDA submission;

NDA submission planned for mid-year 2015;

Company to hold teleconference today at 8:00 a.m. EDT

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 27, 2014-- Sarepta Therapeutics, Inc. (NASDAQ:SRPT), a developer of innovative RNA-based therapeutics, today provided an update on its discussions with the U.S. Food and Drug Administration (FDA) regarding its planned New Drug Application (NDA) submission for the approval of eteplirsen for the treatment of Duchenne muscular dystrophy (DMD).

In meeting minutes received last week from a Type B Pre-NDA meeting that took place in September 2014, the FDA provided updated guidance regarding the specific data to be included as part of, or at the time of, Sarepta's NDA submission. The guidance states that additional data are now required as part of the NDA submission, including the results from an independent assessment of dystrophin images and the 168-week clinical data from study 202. Additionally, the guidance requests more specific data including a minimum duration of safety in new patients exposed to eteplirsen, patient-level natural history data to be obtained by Sarepta from independent academic institutions, and MRI data from a recent study conducted by an independent academic group. The FDA indicated that further discussion with Sarepta "will be necessary to determine what would constitute a complete NDA." Based on these requests, Sarepta plans to submit an NDA by mid-year 2015, pending any additional requests from further discussions with the FDA.

"We are committed to satisfying the FDA's updated requests for these specific data to be included as part

of an NDA submission and will continue to work with the Agency toward the goal of a complete and acceptable NDA filing," said Chris Garabedian, president and chief executive officer of Sarepta Therapeutics. "We believe all of the data requests and additional FDA discussions that have currently been outlined can be completed in time for an NDA submission by mid-year 2015. Obtaining an FDA approval of eteplirsen for the DMD patients who may benefit from the drug continues to be our highest priority."

Excerpts from the Pre-NDA Meeting Minutes related to information that the FDA is requesting as part of an NDA submission included:

"The sponsor should include 3-month data from at least 12 to 24 newly exposed patients at the time the NDA is submitted."

"Available data from the other patients enrolled in the new eteplirsen studies (studies 301, 203, 204) should also be included at the time the NDA is submitted, even if exposure is less than 3 months in duration."

"Additional data from later time points and from newly enrolled patients should be submitted in the 120-Day Safety Update."

"FDA strongly advises the sponsor to obtain and submit patient-level natural history data. FDA is prepared to appeal to the academic groups holding the data to allow the sponsor a means to acquire the data."

"The study 201/202 clinical site inspection conducted in May, 2014, after the issuance of the April 15, 2014, guidance letter, uncovered marked disparities in the immunohistochemistry methodology and concerns about the reproducibility of the data. The lack of confirmation of robust dystrophin measurement during the site visit necessitates including the independent assessment of dystrophin-positive fibers and 168-week efficacy data from study 201/202 in the NDA."

"FDA strongly urged the sponsor to submit the MRI data with appropriate natural history controls."

The FDA also stated that "[a]dditional discussion between the sponsor and the FDA will be necessary to determine what would constitute a complete NDA."

Conference Call Information

Sarepta will hold a conference call to discuss this update today at 8:00 a.m. EDT (5:00 a.m. PDT). The conference call may be accessed by dialing 800.708.4539 for domestic callers and 847.619.6396 for international callers. The passcode for the call is (b) (6). Please specify to the operator that you would like to join the "Sarepta Regulatory Update Call." The conference call will be webcast live under the investor relations section of Sarepta's website at www.sarepta.com and will be archived there following the call for 90 days. Please connect to Sarepta's website several minutes prior to the start of the broadcast to ensure adequate time for any software download that may be necessary. An audio replay will be available through November 3, 2014 by calling 888.843.7419 or 630.652.3042 and entering access code (b) (6).

About Duchenne Muscular Dystrophy

DMD is an X-linked rare degenerative neuromuscular disorder causing severe progressive muscle loss and premature death. DMD affects approximately one in every 3,500 boys born worldwide. A devastating and incurable muscle-wasting disease, DMD is associated with specific errors in the gene that codes for

dystrophin, a protein that plays a key structural role in muscle fiber function. Progressive muscle weakness in the lower limbs spreads to the arms, neck and other areas. Eventually, increasing difficulty in breathing due to respiratory muscle dysfunction requires ventilation support, and cardiac dysfunction can lead to heart failure. The condition is universally fatal, and death usually occurs before the age of 30.

About Eteplirsen

Eteplirsen is Sarepta's lead drug candidate and is designed to address the underlying cause of DMD by enabling the production of a functional dystrophin protein. Data from clinical studies of eteplirsen in DMD patients have demonstrated a broadly favorable safety and tolerability profile and restoration of dystrophin protein expression.

Eteplirsen uses Sarepta's novel phosphorodiamidate morpholino oligomer (PMO)-based chemistry and proprietary exon-skipping technology to skip mutations affecting exon 51 of the dystrophin gene. Approximately 13 percent of the total DMD population is amenable to exon 51 skipping. By skipping exon 51, eteplirsen may restore the gene's ability to make a shorter, but still functional, form of dystrophin from messenger RNA, or mRNA. Promoting the synthesis of a truncated dystrophin protein is intended to stabilize or significantly slow the disease process and prolong and improve the quality of life for patients with DMD. Sarepta is also developing other PMO-based exon-skipping drug candidates intended to treat additional patients with DMD.

About Sarepta Therapeutics

Sarepta Therapeutics is focused on developing first-in-class RNA-based therapeutics to improve and save the lives of people affected by serious and life-threatening rare and infectious diseases. The Company's diverse pipeline includes its lead program eteplirsen, for DMD, as well as potential treatments for some of the world's most lethal infectious diseases. Sarepta aims to build a leading, independent biotech company dedicated to translating its RNA-based science into transformational therapeutics for patients who face significant unmet medical needs. For more information, please visit us at www.sarepta.com.

Forward-Looking Statements and Information

This press release contains forward-looking statements. These forward-looking statements generally can be identified by the use of words such as "believes or belief," "anticipates," "plans," "expects," "will," "intends," "potential," "possible," "advance" and similar expressions. These forward-looking statements include statements about Sarepta's planned timing for an NDA submission for eteplirsen in the treatment of DMD; Sarepta's plans to work with the FDA towards the goal of a complete and acceptable NDA filing; Sarepta's ability to satisfy the additional FDA requests; the timing and submission of additional data, analysis and other information to the FDA necessary for the FDA to make regulatory determinations; the timing of and ability to initiate additional studies for eteplirsen and other follow-on exons; and the potential regulatory approval of eteplirsen.

Each forward-looking statement contained in this press release is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statement. Applicable risks and uncertainties include, among others: we

may not be able to comply with all FDA requests; the FDA may determine that substantial additional data is required for accelerated or other approval of eteplirsen or that our NDA submission for eteplirsen does not qualify for filing, even with additional information; the results of our ongoing and new clinical trials may not be positive; there may be delays in timelines relating to an NDA submission, initiating clinical trials, or

making a product commercially available for regulatory or internal reasons; we may not be able to manufacture sufficient supply for clinical trials or commercialization; agency or court decisions with respect to our patents or those of third parties may negatively impact our business and those identified under the heading "Risk Factors" in Sarepta's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 filed with the Securities and Exchange Commission (SEC), and Sarepta's other filings with the SEC.

Any of the foregoing risks could materially and adversely affect Sarepta's business, results of operations and the trading price of Sarepta's common stock. For a detailed description of risks and uncertainties Sarepta faces, you are encouraged to review the Company's filings with the SEC. We caution investors not to place considerable reliance on the forward-looking statements contained in this press release. Sarepta does not undertake any obligation to publicly update its forward looking statements based on events or circumstances after the date hereof.

Source: Sarepta Therapeutics, Inc.

Sarepta Media Contact:

Tony Plohoros, 908-591-2839

tplohoros@6degreespr.com

or

Sarepta Investor Contact:

Stephanie Ascher, 212-362-1200

stephanie@sternir.com

Bloomberg Businessweek

Technology

<http://www.businessweek.com/articles/2014-10-30/duchenne-muscular-dystrophy-moms-fight-for-fda-approval-of-sarepta-drug>

Moms, Regulators, Biotech Startups, and the Battle Over a Potentially Life-Saving Drug

By Paul M. Barrett October 30, 2014



Photograph by Ryan PflugerLeffler's son (b) (6) was diagnosed with Duchenne in 2006

The 2014 World Cup elevated soccer to the top of (b) (6)'s roster of obsessions, rivaled only by endangered big cats—especially jaguars, “the coolest”—and *Star Wars* spaceships. In recognition of his new interest, he’s set up a miniature soccer field with 4-foot-wide goals in his backyard in suburban Bellevue, Wash. “Watch this!” he shouts, preparing to fire a penalty kick.

Small for his age, (b) (6), 11, moves awkwardly, shoulders high and hunched. He uses a lightweight plastic beach ball, not a regulation leather soccer ball. He begins his approach, pulls back his right foot, and ... collapses to the grass.

Mitch Leffler, the sole spectator, moves toward his son. “I’m OK,” (b) (6) says. “I can do it.” He struggles onto his hands and knees, raises his butt, places his hands one at a time on his thighs, and slowly pushes himself into an upright position. “My leg just wasn’t there,” he says matter-of-factly. His father nods, and the game resumes.

(b) (6) has Duchenne, the deadliest strain of muscular dystrophy. It’s inherited maternally on the X chromosome and mostly afflicts boys. Parents typically sense something is wrong when their sons at 3 or 4 don’t run around or they start falling for no obvious reason. Beginning in the legs, Duchenne destroys muscle, which is replaced by fat and scar tissue. Victims lose the ability to walk by adolescence. Eventually the disease causes cardiac and/or respiratory complications that lead to death by the mid-20s. One in 3,500 newborns has Duchenne, which translates to around 15,000 cases in the U.S. There’s no cure.

(b) (6) doesn’t really understand yet,” his mother, Mindy, says, “but it’s basically a slow-motion death sentence.”

There’s reason to hope—not for a miracle, but for a reprieve. Three small biotech companies are competing to develop drugs designed to address the cellular defects that cause some cases of Duchenne. If proven safe and effective, the drugs would turn Duchenne into a less devastating form of muscular dystrophy. Clinical trials, however, have yielded uneven results, and the U.S. Food and Drug Administration has made equivocal pronouncements about which of the drugs, if any, have a shot at approval. Even a marginally effective drug would likely command an astronomical price, making the winning company a billion-dollar sensation.

The hunt for a Duchenne treatment has generated a collision of commerce, cutting-edge science, and Wall Street speculation. The FDA, though, seems flummoxed over how to evaluate the experimental drugs, especially given a lack of large, clearly successful randomized studies. That’s left the Lefflers confused and increasingly desperate.



Photograph by Ryan PflugerMindy with her son (b) (6) who began college this fall

Mindy believes that one experimental treatment—eteplirsen, made by a company called Sarepta Therapeutics (SRPT)—has shown sufficient promise in a tiny trial to warrant wider availability. If approved, eteplirsen might help 13 percent of Duchenne boys who have certain genetic flaws. Mindy’s son is among the 13 percent. “I want (b) (6) on that drug,” she says, “and I want it to happen before he’s in a wheelchair or worse.”

She and a group of similarly minded moms are pressuring the FDA to give provisional approval to eteplirsen while Sarepta proceeds with confirmatory studies. Taking to Twitter, Facebook, YouTube, and Instagram, they’ve got the attention of top FDA officials. They’ve also encountered resistance from career FDA staff members and some rare-disease advocates alarmed by their assertiveness.

"What's hard to understand," says Mindy's friend Jennifer McNary, "is why the whole Duchenne community and the FDA aren't pulling together behind eteplirsen." McNary, who lives south of Boston, has two sons with the disease. Maternal genetic predisposition sometimes results in such sibling pairs. (b) (6) 12, gets eteplirsen in the small Sarepta trial; over the past two-and-a-half years, his symptoms have eased remarkably. Max's older brother, (b) (6) 15, didn't qualify for the study because he was already in a wheelchair when it started. He's declining physically, losing the use of his arms and having trouble feeding himself.

"Why doesn't the government let me have eteplirsen?" (b) (6) asks when we meet. He waits for an answer, which I don't have. His mother joins the conversation: "The FDA's inaction," she says, "is killing my son."

Mindy agrees with Jennifer and (b) (6) doesn't have time to wait for a perfect placebo-controlled trial with hundreds of subjects," she says. "The benefits outweigh any risks."

In 1986 researchers at Harvard isolated the gene responsible for making the protein dystrophin, a "shock absorber" that surrounds muscle cells. Boys with Duchenne have one of several genetic defects that inhibit production of dystrophin. Without it, ordinary physical exertion causes progressive muscle breakdown. The disease is named for Guillaume Duchenne, a French neurological pioneer who described the symptoms in the 1860s.

For generations, physicians reacted passively to Duchenne. Patricia Furlong's sons, Christopher and Patrick, were diagnosed in 1984. Her doctor told her to "take them home and love them, because there was nothing medicine could do." A former nurse with a stubborn streak, she began traveling the country from her home in central Ohio, pleading with researchers to look for a cure. "She was at NIH [National Institutes of Health]. She was on Capitol Hill. She was in my office," recalls Eric Hoffman, a genetic researcher at Children's National Medical Center in Washington. "Pat would not be denied." She couldn't save her sons, however, who died in the mid-1990s.

Angered by what she describes as the fatalism she encountered at the Muscular Dystrophy Association—sponsor of the long-running Labor Day telethon hosted by actor Jerry Lewis—Furlong formed a breakaway nonprofit: Parents Project Muscular Dystrophy, dedicated strictly to Duchenne. In 2001, largely because of her agitation, Congress passed the Muscular Dystrophy CARE Act, which over the following decade provided more than \$400 million in funding, much of it for Duchenne research. The federal backing, says Hoffman, "got the biotech companies thinking maybe there's money to be made with a Duchenne drug."

"What's hard to understand is why the whole Duchenne community and the FDA aren't pulling together behind eteplirsen"

A startup in New Jersey called PTC Therapeutics (PTCT) focuses on mutations that block dystrophin production. These "nonsense mutations" are akin to a period mistakenly placed in the middle of a sentence, which makes the genetic code incomprehensible. In 2008, Genzyme (SNY), a much larger biotech, gave credibility to PTC's research by paying the tiny company \$100 million upfront to secure future marketing rights to its drug outside North America.

Prosensa (RNA), a Dutch biotech, targets a different type of flaw in the exons, or segments, of the dystrophin gene. By "skipping" a defective exon, Prosensa's compound is supposed to allow the formation of a truncated version of dystrophin. In 2009 the pharmaceutical giant GlaxoSmithKline (GSK) added momentum to exon-skipping research by paying Prosensa \$25 million upfront for development and marketing rights and promising hundreds of millions more in future compensation.

In the U.S., Sarepta was also angling to get into the Duchenne chase. Choosing to work without a larger corporate partner, it began testing eteplirsen, an exon-skipping compound that relies on a different biochemical recipe from Prosensa's drug.

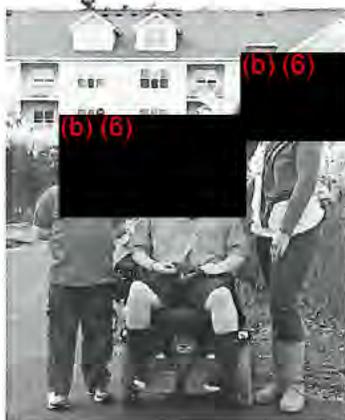
The proliferation of potential treatments gave the Lefflers reason for optimism after years of mounting apprehension. (b) (6) had first been diagnosed in 2006, at the age of almost 3, after breaking his leg while playing on a slide. As he lost strength, his parents installed an elevator at home so he could avoid stairs, but for the most part he remained ambulatory.

Mindy dug into the science of Duchenne, finding a place in genetics and chemistry, subjects she'd avoided as an English major in college. She works part-time developing software for a tech company and time-and-a-half seeking care for (b) (6) Mitch—she met her husband in the early 1990s when they were Seattle-area high school track stars—teaches gym and takes a lot of responsibility for (b) (6) two younger siblings. In 2010, the Lefflers felt inspired when the *New Yorker* published an article titled "Mother Courage" that described how the death of Furlong's sons propelled her campaign against Duchenne. "I thought, wow, Pat really got a lot done," says Mindy, "and now we're going to take the next step and actually find a treatment for (b) (6) he doesn't end up like Pat's boys."

In 2011, Mitch took (b) (6) to a hospital in Columbus, Ohio, where Sarepta was beginning a trial for eteplirsen. Then 7 (b) (6) was showing such ominous symptoms as knotty, seemingly overdeveloped calves—evidence of scar tissue swiftly replacing muscle. He performed well on a baseline walking test. Too well, it turned out: He was rejected for the study because he was much healthier than most other subjects whose disease was more advanced.

As a fallback, Mindy hustled to get (b) (6) enrolled in a 180-person Prosensa-GlaxoSmithKline trial at a test site in Vancouver. The trial proved to be an ordeal. Multiple muscle biopsies to check dystrophin levels required (b) (6) undergo surgery with general anesthesia. And almost immediately, Leffler suspected he was receiving a saline-solution placebo, rather than injections of Prosensa's drug. She figured this out when he didn't have the swelling and pain other moms said their sons experienced.

For 48 weeks, (b) (6) parents took him by plane or car to Vancouver every week for stays ranging from a few hours to several days, depending on the protocol, all the while suspecting he wasn't actually receiving medication. "This may be good for science," Leffler says she thought at the time, "but how's it good for my son?"



Photograph by Ryan Pfluger/McNary with her sons, (b) (6) who is receiving treatment, and (b) (6) who isn't

In late 2012, researchers switched all of the subjects on placebo over to treatment with Prosensa's compound, drisapersen. (b) (6) began to suffer the side effects from getting the drug, but Leffler couldn't tell whether his Duchenne symptoms were easing. "He fluctuated: sometimes better, sometimes worse," she says.

Over time, Leffler became jealous of moms with sons in the Sarepta study—the one from which (b) (6) had been rejected—because the company was reporting solid results. In October 2012, Sarepta announced that, after 48 weeks, boys receiving eteplirsen had stabilized, with statistically significant improvement in a standardized six-minute walking test. Moreover, unlike the Prosensa drug, which at higher doses creates risks that could lead to kidney damage, the Sarepta study didn't show any dangerous side effects.

The weakness of the Sarepta trial was that it had enrolled only 12 boys. Started in 1980 at the dawn of the biotech era, the company had gone public in 1997 but never put a drug on the market. After a series of management shake-ups, a newly hired chief executive officer, Chris Garabedian, decided in 2011 to bet Sarepta's few remaining chips on eteplirsen. The company simply couldn't

afford a larger trial. "We had a limited amount of drug and no capacity to make more," Garabedian says. "So we took what we had and did the best small trial we could design." Sarepta's shortage of eteplirsen also precluded providing the drug to individual applicants under the FDA's "compassionate use" program.

Despite the skimpy sample size, Sarepta's results ignited a stock market frenzy. The company's shares rose threefold on Oct. 3, 2012, to \$45. CNBC stockpicker Jim Cramer raved about Sarepta on his *Mad Money* show and interviewed Garabedian on camera. In June 2013, PTC announced an initial public offering that raised \$144 million. In their enthusiasm, investors were willing to overlook that PTC's drug, ataluren, had failed to show statistically significant improvement in subjects' walking ability in a clinical trial three years earlier. Prosensa soon followed with its own IPO, raising \$90 million, even though it hadn't yet reported results from its main ongoing clinical study. In July, Sarepta added to the bullishness by announcing that the FDA had provided guidance that it was open to considering eteplirsen for regulatory approval. (The agency routinely communicates with companies as they move toward a "new drug application.")

"It felt like a lot of good stuff was coming together," Leffler recalls.

Then the bubble burst. In September 2013, only three months after its IPO, the Prosensa-GSK trial in which Aidan was enrolled failed to show meaningful improvement on the six-minute walk test. The study was shut down, and Prosensa's stock plummeted 70 percent in a day. "No one called us," says Leffler. "We learned that the trial was over from a GSK investor conference call. There's no safety net. You just crash." London-based GSK and Prosensa later terminated their partnership.

More bad news followed in November: After encouraging Sarepta to apply for approval of eteplirsen, the FDA reversed itself and called such a move "premature." Explaining its turnaround, the agency cited Prosensa's and PTC's trial failures. The FDA expressed "considerable doubt" that dystrophin production—the goal set out by all three companies—could be linked to meaningful clinical benefits. Sarepta's stock fell 64 percent that day.

The Lefflers received word about the FDA about-face on Sarepta while at Walt Disney World on a vacation with (b) (6) and his younger brother and sister. After the Prosensa-GSK trial failure, "it was a double blow," Mindy says. "I felt like I couldn't breathe."

After collecting herself, Leffler decided to fight. She'd already been communicating with two other moms she'd met via Facebook and at Duchenne conferences: McNary, who had the exquisitely painful situation of one son doing well in the Sarepta trial while his older brother, denied the drug, declined, and Christine McSherry, whose son (b) (6) was a wheelchair-bound high school senior, struggled to sit up straight.

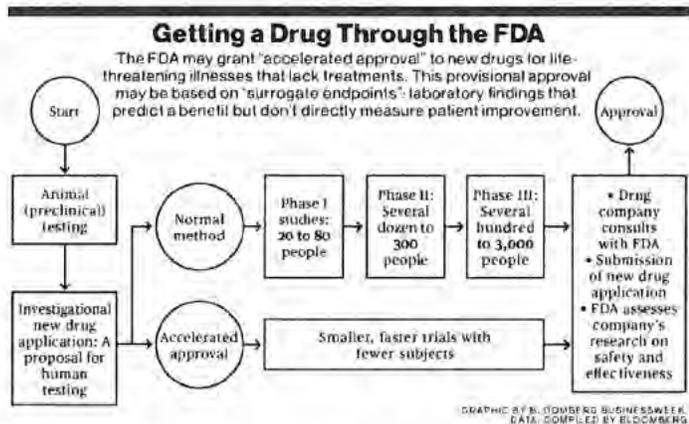
"The three of us, the 'Three Musketeers,' had a lot of the same questions," McSherry says. Why had Prosensa's and PTC's setbacks influenced the FDA to shun Sarepta? After all, the companies used different types of chemistry. The moms also didn't understand why the incipient scientific consensus on the importance of dystrophin production had suddenly become clouded. "We began to realize that the FDA was confused," says McSherry, a former nurse who is now 49. "Eteplirsen, a drug that appeared to work, was in danger of becoming a victim to the shortcomings of other drugs and other trials."

The moms had begun in 2012 demanding personal attention from FDA officials. Remarkably, they got a meeting—then another, and another. In a law enacted that year, Congress instructed the FDA to entertain more flexible paths to provisional approval of rare-disease drugs. Under the aegis of that statute, the trio became self-appointed consultants at FDA headquarters in Silver Spring, Md.

McNary organized an online petition demanding "accelerated approval" of eteplirsen. The 2012 FDA reform statute encouraged the agency to grant accelerated approval based on relatively small trials that achieve a "surrogate" goal—such as dystrophin production—with the burden left on the manufacturer to conduct broader research. The FDA can rescind accelerated approval if follow-up studies don't demonstrate efficacy. McNary swiftly gathered 180,000 signatures for her petition, and she and other moms bombarded the FDA with tweets, Instagrams, and YouTube videos showing boys in Sarepta's 12-person trial climbing rocks, dancing, and diving into swimming pools.

McNary's heart-rending tale became a centerpiece of the lobbying campaign. "I could possibly be the mother of the last child to die from Duchenne and first child to survive it," she said in a video that zinged around the Internet.

Following its standard policy, the FDA didn't respond publicly to the lobbying drive. But the agency's ambivalent reactions could be discerned from private communication with the three moms, who used blogs and websites to report on the back-and-forth. According to the moms, senior FDA leaders sought to reassure the Duchenne parents, while rank-and-file staff members tended to express more skepticism.



In July 2013, McSherry recounted on her blog a conference call with Janet Woodcock, the director of the FDA's Center for Drug Evaluation and Research. "As always, Dr. Woodcock was warm, compassionate, and extraordinarily supportive of our position," McSherry wrote. "We are one step closer to getting this drug [eteplirsen] to our boys."

Four months later, though, evaluators working under Woodcock's supervision told Sarepta not to bother applying for approval. Asked for comment, Sandy Walsh, an FDA spokeswoman, says: "Under the law, we are not able to discuss any investigational new drug or any drug application." She adds that the agency "has been working with Sarepta to provide guidance on various clinical and regulatory issues related to eteplirsen."

In February 2014, the three moms joined forces with a fourth, Tracy Seckler, to ratchet up the pressure on the FDA by organizing a two-day summit in Washington that included a visit to the agency by several leading Duchenne researchers. The next day, a bipartisan briefing on Capitol Hill sponsored by Representatives William Keating (D-Mass.) and Spencer Bachus (R-Ala.) drew an audience of dozens of congressional staff members.

Louis Kunkel, the Harvard Medical School professor who headed the team that isolated the dystrophin gene in 1986, told the gathering that boys receiving eteplirsen were making dystrophin and called this success "amazing." Steve Wilton, a leading neuromuscular researcher from Australia, was even more emphatic about eteplirsen's promise. "In Australia," he told attendees, "we'd say it's bleeding obvious."

Leffler added the moms' sense of impatience: "The FDA," she said, "is standing in the way." Not so, says the agency's Walsh: "The FDA is fully committed to make safe and effective drugs available for patients with Duchenne as soon as possible and is actively engaged with all drug companies developing new drugs for Duchenne."

Notably absent from the Washington event was Furlong. She'd held her own Washington round table two months earlier, one that was far more deferential to the FDA's authority.

In an interview, Furlong, 68, says she was traveling on business in Europe at the time of the February summit and sent a representative from her organization. She decries what she describes as a splintering of "the Duchenne community" she has spent two decades building. Now a stateswoman rather than a firebrand, she criticizes younger mothers such as McNary, 34, who publicly describe their sons as dying: "What must those boys think?" she asks. More broadly, she adds, "It's just not smart strategy to chain yourself to the gates of the FDA in protest," an allusion to a tactic once used by AIDS activists.

While the more aggressive Duchenne moms haven't actually chained themselves to anything, their tone at times is abrasive. In March 2014, McNary appeared on John Stossel's government-bashing Fox Business News television show. A subscript running across the screen morphed from "Government Medicine Bullies" to "FDA Regulations Can Kill." Stossel asked McNary whether her son (b) (6) is "angry" because he couldn't get eteplirsen.

"Fifteen-year-olds in general are angry," McNary responded. "Fifteen-year-olds who are being betrayed by their government are even angrier." Stossel's other guest, Darcy Olsen of the libertarian Goldwater Institute, added: "What the FDA is doing here is an abomination."

In April, without public explanation, the FDA once again reversed its position on eteplirsen, saying Sarepta could move ahead toward regulatory approval. Given the absence of new data, the only plausible reason for the switch was escalating pressure from the three moms and their backers. Five months after rebuffing Sarepta, the FDA laid out a detailed "path forward" for eteplirsen to receive accelerated approval.

The agency's revised guidance—conveyed privately to Sarepta, then disclosed by the company—stressed government evaluators' continuing uneasiness regarding the data on eteplirsen. The company would have to conduct larger placebo-controlled studies before provisional approval would become permanent. Still, a closed door had cracked open.

Sarepta immediately said it would seek accelerated authorization by the end of 2014 and launch confirmatory studies. From April 17 to April 22, the company's stock rose 59 percent.

In June, the regulatory door opened further. Prosensa announced that the FDA would entertain an accelerated-approval application for drisapersen, even though the Dutch company's drug had failed its main clinical trial in 2013. Regulators' sudden receptivity struck some observers as peculiar, given the lack of fresh evidence of effectiveness. "It sure looks like the FDA wants to give itself cover and say, 'See, we're giving everyone a chance to apply, so parents, stop attacking us,'" says Steve Brozak, president of WBB Securities and a longtime analyst of the biotech industry.

Prosensa's CEO, Hans Schikan, disagrees with Brozak. The unsuccessful 2013 study was devised and run by GSK, he says. "Based on our reanalysis of our data, we strongly believe it was the trial that failed the drug, not the drug that failed the trial." Flaws in GSK's study design, he claims, muddled the results.

Adding yet another level of ambiguity to the situation, PTC, which had seemed out of the running for a Duchenne treatment, has reentered the race. "We shot ourselves in the foot" by conceding defeat after the failed 2010 ataluren trial, says Stuart Peltz, PTC's co-founder and chief executive. After reanalysis of its data, PTC concluded its drug actually works. "In biotech, you're building the airplane while you're trying to fly it at the same time," Peltz continues. "It took us a while to realize that when you focus on the boys with the most severe symptoms, ataluren does show a robust efficacy." In August the European Union's equivalent to the FDA granted conditional approval to ataluren, and PTC is beginning to sell the drug in Europe. After completing more clinical trials, Peltz says, his company will apply for full approval in Europe, the U.S., and elsewhere.

Furlong has faith the FDA will sort out which Duchenne drugs are effective. "Ideally," she says, "we'd like to see all of the drug candidates move forward in the regulatory process."

The three moms, in contrast, say the FDA's one-step-back, one-step-forward routine has them feeling unnerved, not reassured. "The boys on eteplirsen are walking when the natural history of the disease says that they should be in wheelchairs," says Leffler. Why, she wants to know, don't industry and government cooperate to get as many boys on eteplirsen as quickly as possible?

"That's not the way medical science works," says Hoffman, the Duchenne researcher at Children's National Medical Center. The FDA, Hoffman continues, "is doing the best it can, moving cautiously and looking skeptically at Sarepta's data, and all of the data from all of the companies." On Oct. 27, Sarepta announced that as a result of a new round of FDA data requests, the company would have to postpone its application for approval of eteplirsen until mid-2015. Hoffman, who for years has had a close working relationship with Furlong and her organization, expresses sympathy for moms like Leffler, McNary, and McSherry who are impatient for faster action. "They must mean well—their boys are sick," he says, "but their pressure tactics on the FDA seem like bullying more than anything else."

Leffler, 42, doesn't care anymore what anyone calls her tactics. Her determination to get (b) (6) eteplirsen became more urgent in August when he fell and fractured the femur in his left leg while kicking a ball in the backyard. Doctors told (b) (6) parents he had a 50-50 chance of ever getting back on his feet. He had surgery the next day to have a steel rod placed in his leg. Two weeks later, to his doctors' surprise, but not his parents', he started hobbling around with a walker. With some effort, he can even get in and out of the family minivan more or less on his own. "He's an amazing kid," Leffler says.

Soccer, even in modified form, is probably over forever. (b) (6) now in sixth grade, has redoubled his attention to big cats. He's writing fundraising letters and passing along the money to a conservation group called Panthera.

He's not oblivious to his medical predicament. If anything, he's growing more worried. The other day, Leffler found a piece of paper in her bathroom with a question written in (b) (6) neat block letters: "Does muscular dystrophy make you die sooner?"

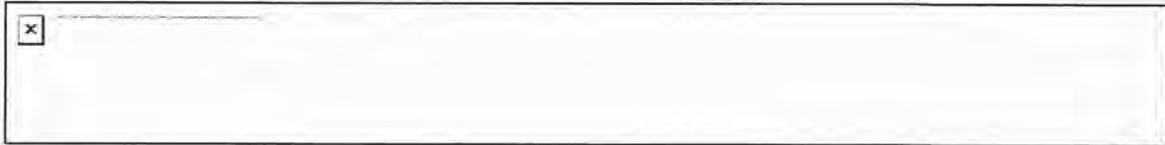


Barrett is an assistant managing editor and senior writer at *Bloomberg Businessweek*. His new book, *Law of the Jungle*, tells the story of the Chevron oil pollution case in Ecuador.

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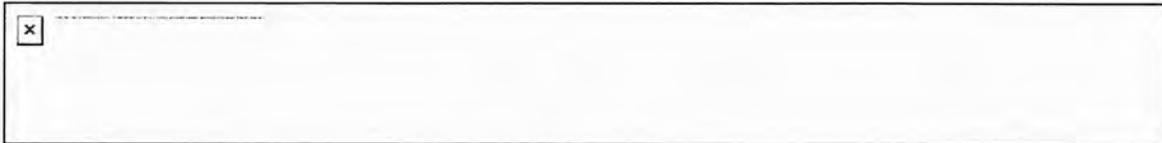
Abuse-Deterrent Opioids: FDA Regulatory Options Aired At Meeting Brand industry favors two- to three-year period for withdrawal or reformulation of products without abuse-deterrent features, while generic industry calls for expedited review pathway. Purdue and Zogenix agree to waive three-year market exclusivity for their respective hydrocodone products.

Sarepta Delay Due To Misinterpretation, Not Policy Change, FDA Says The regulatory agency made it clear to the Duchenne muscular dystrophy community that its message has remained consistent throughout the discussions regarding eteplirsen, despite Sarepta's comments to the contrary.

CheckMate-063: Bristol's Opdivo At Center Of Attention In Lung Immunotherapy In an interview with "The Pink Sheet" DAILY, Bristol's nivolumab lead exec Fouad Noumani comments on benefits and side effects - including pneumonitis - after Phase II third-line squamous lung cancer study

NICE Clears Pradaxa For DVT, Setting Up Another Clash With Xarelto NICE has given the thumbs up to Boehringer Ingelheim's Pradaxa in deep vein thrombosis and pulmonary embolism, which means the drug is now set to battle Bayer's Xarelto for market share in this indication.

Emerging Markets, New Products Help Takeda Takeda Chief Operating Officer Weber says the company's aim is to achieve a "more balanced geographic footprint over time," with emerging markets seen accounting for 25% of sales in fiscal 2017.



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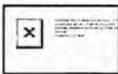
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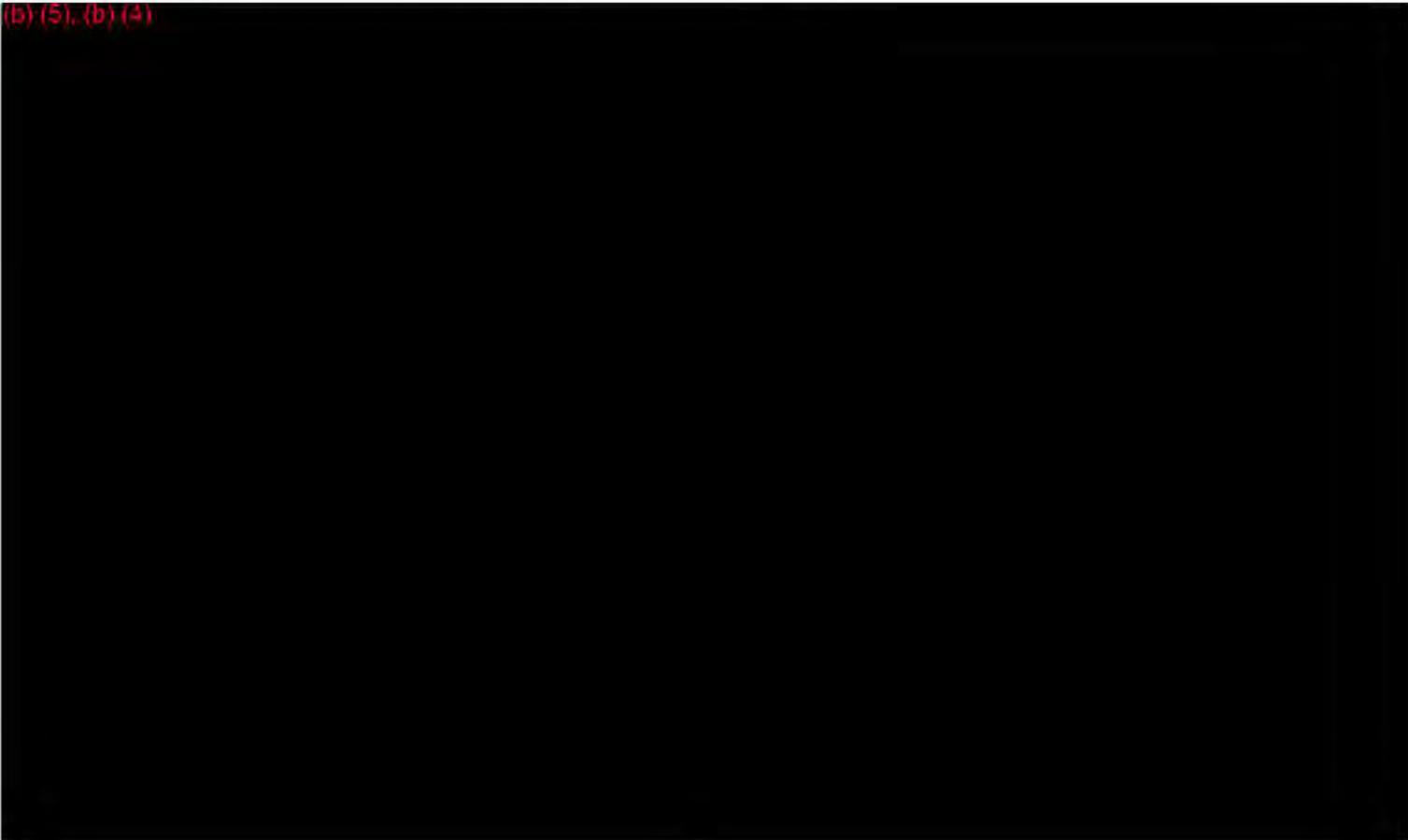
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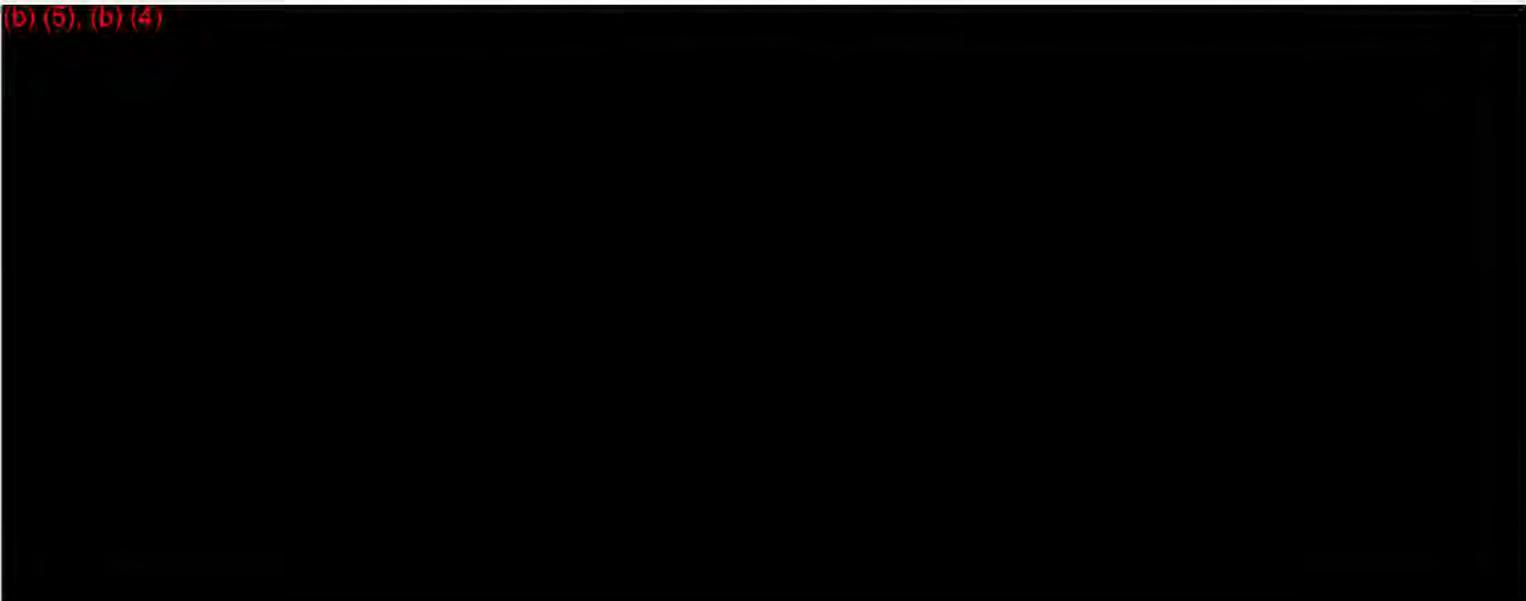
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From: Garza, Anthony
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To: Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
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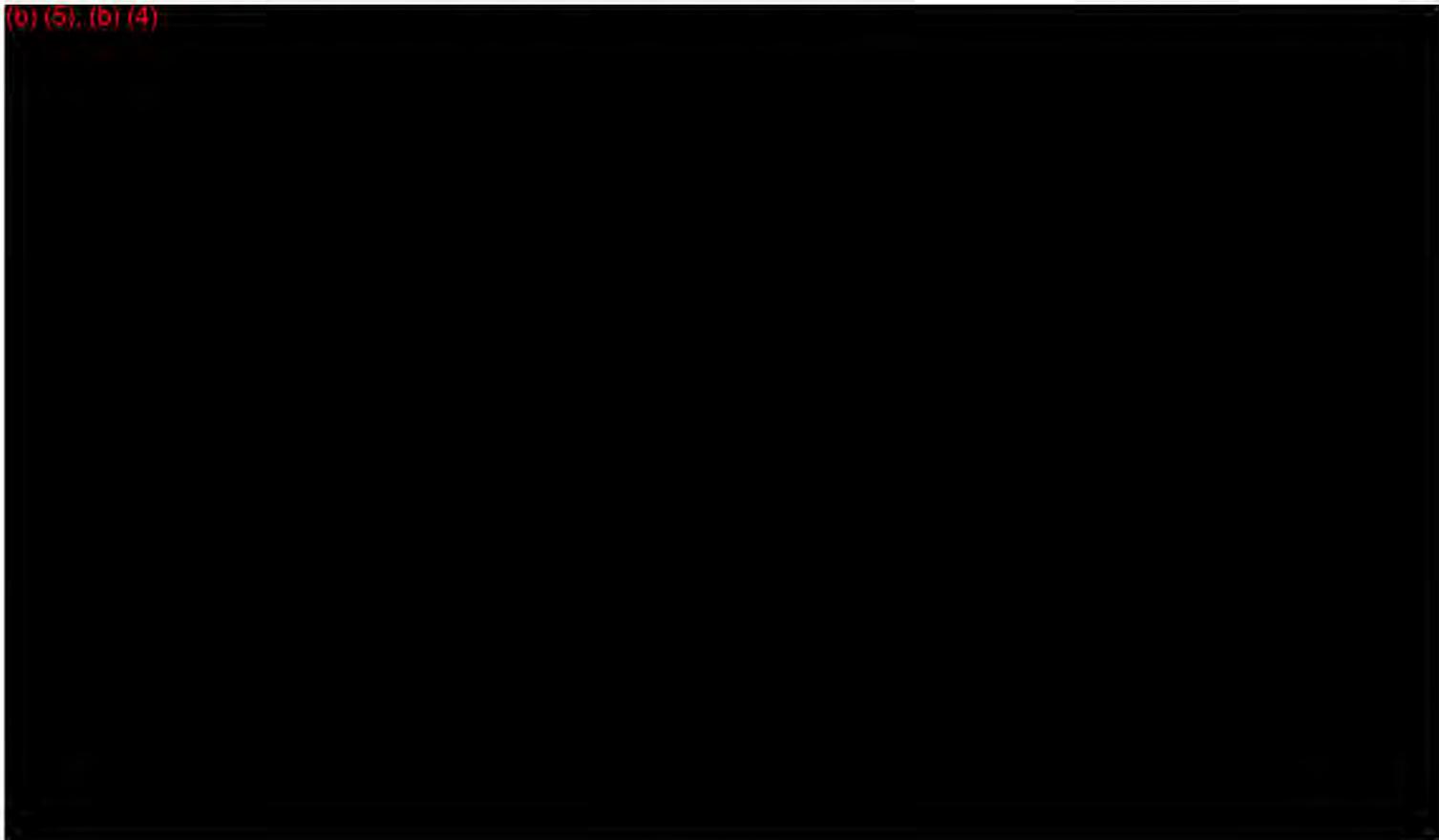
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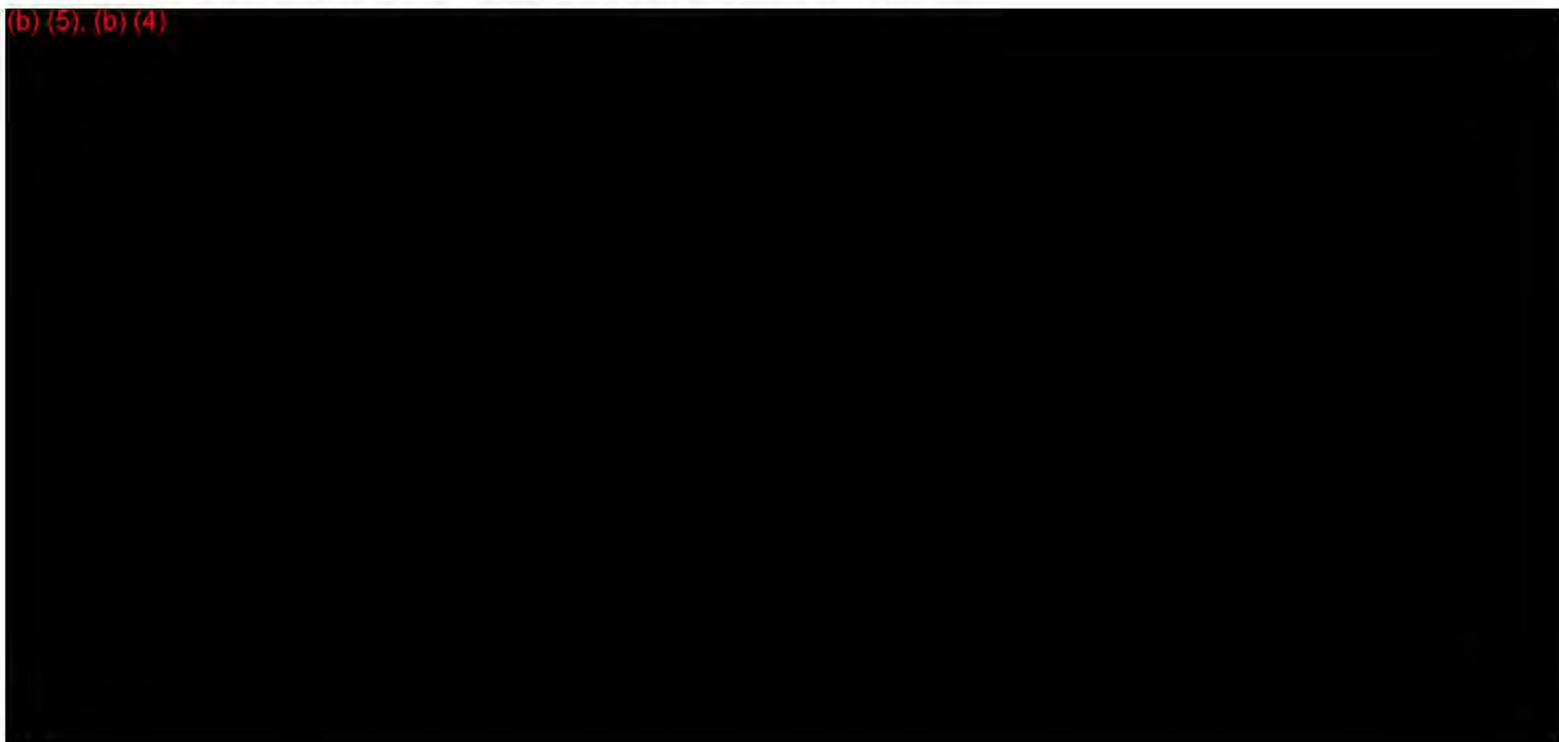
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From: Garza, Anthony
Sent: Friday, December 05, 2014 4:48 PM
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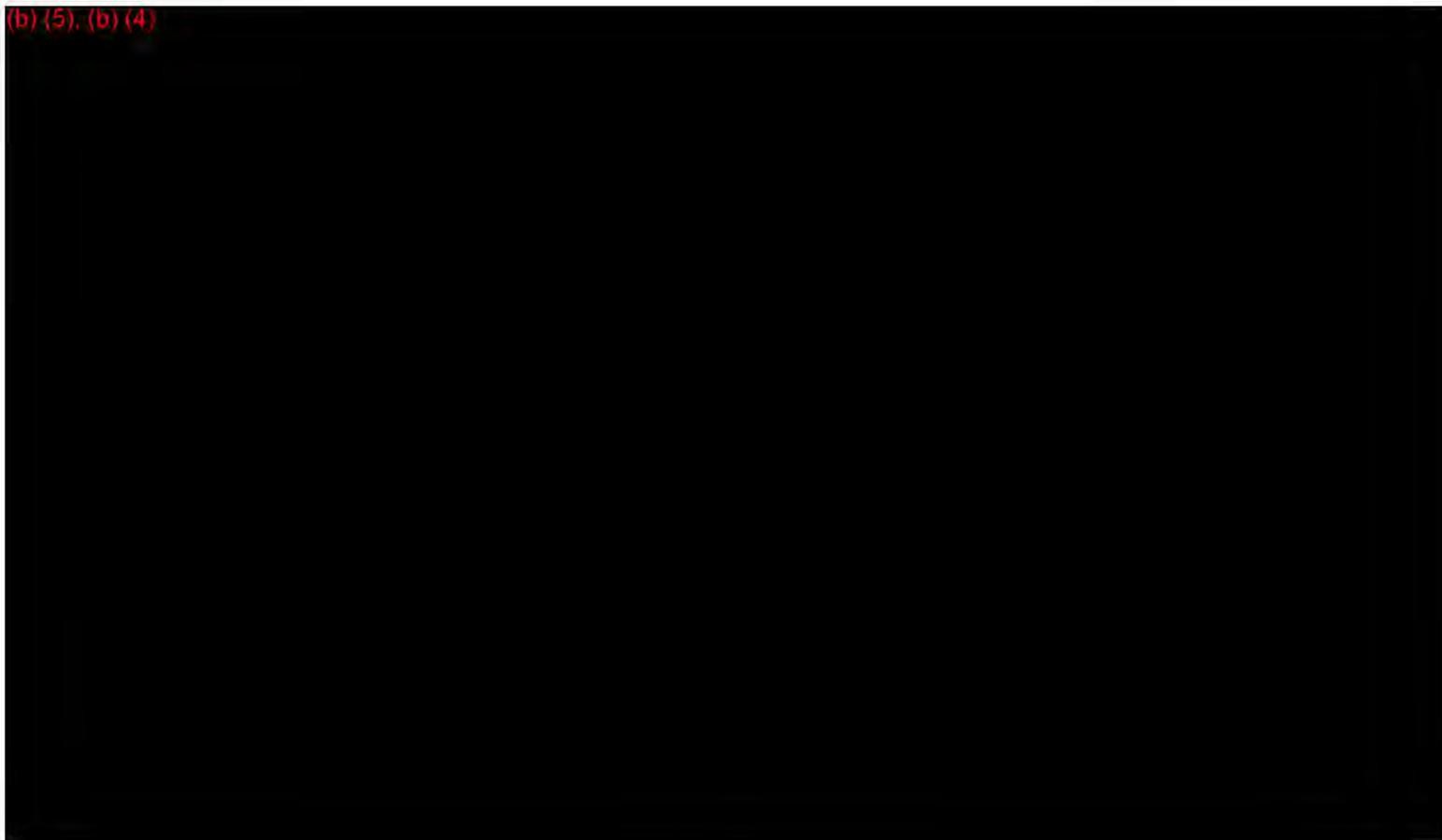
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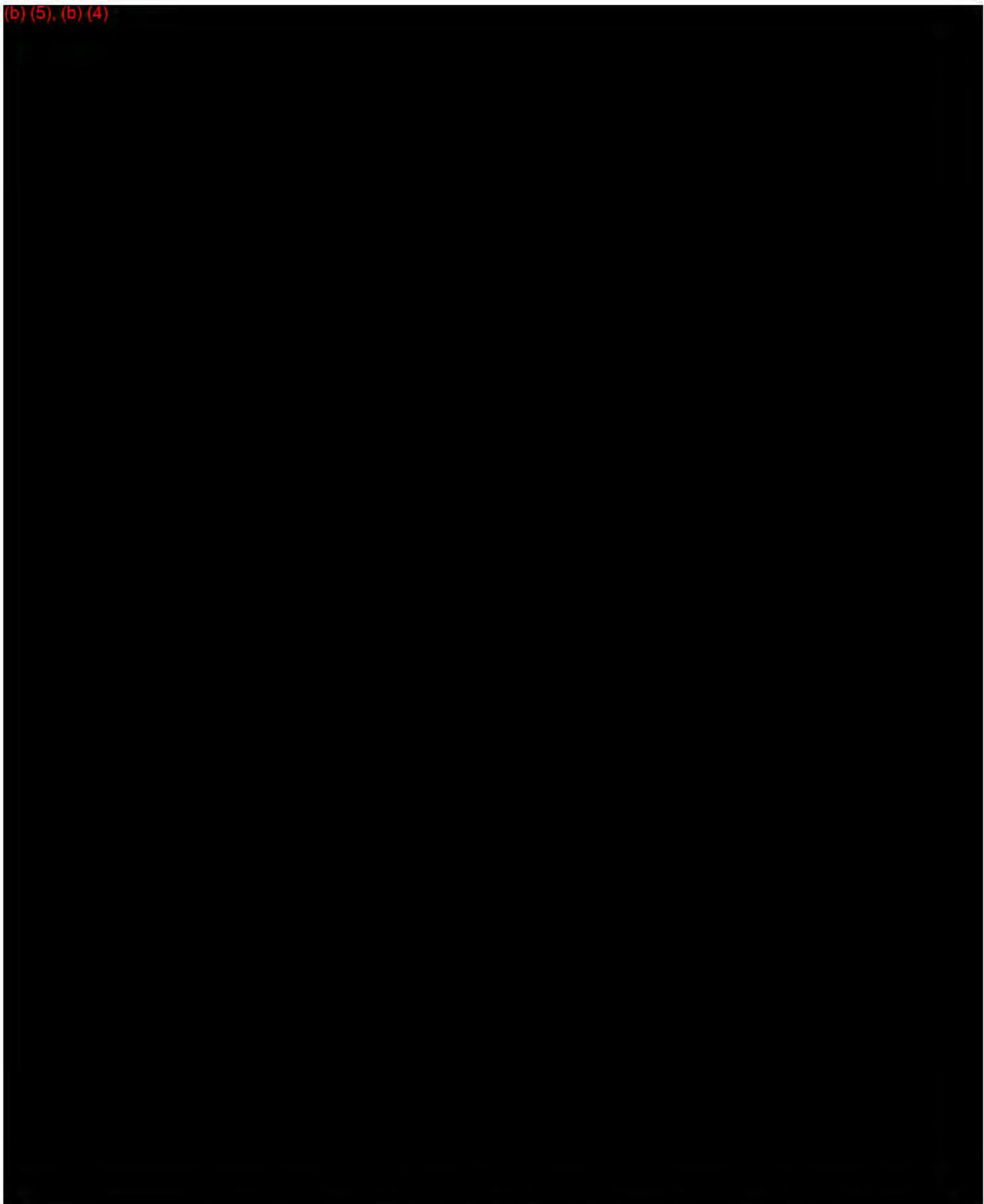
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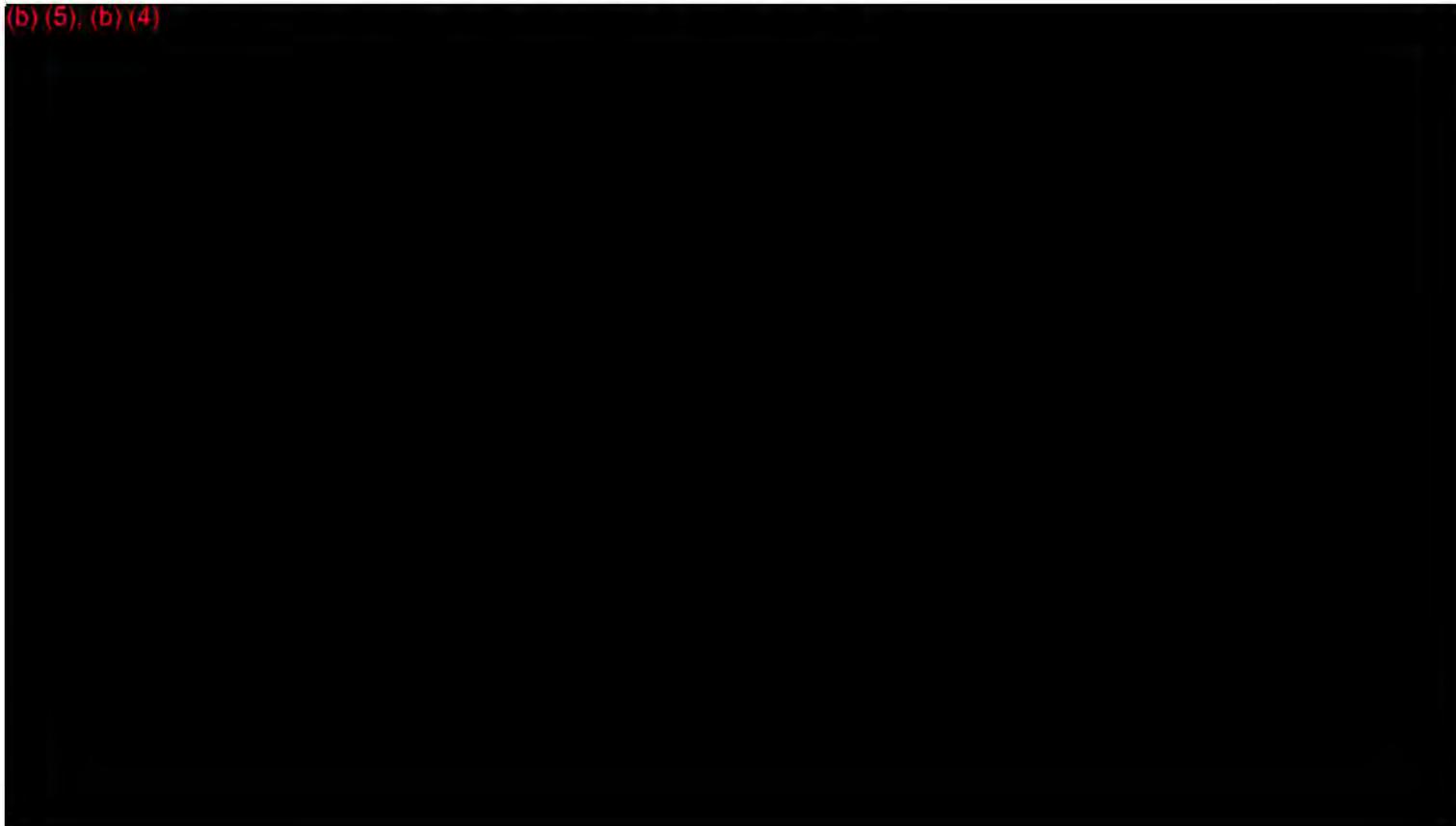
Smith, Celeste

From: Garza, Anthony
Sent: Friday, December 19, 2014 4:19 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #63
Attachments: 63 FDA 2014 Ebola Coordination Situation Report 2014-12-19.docx

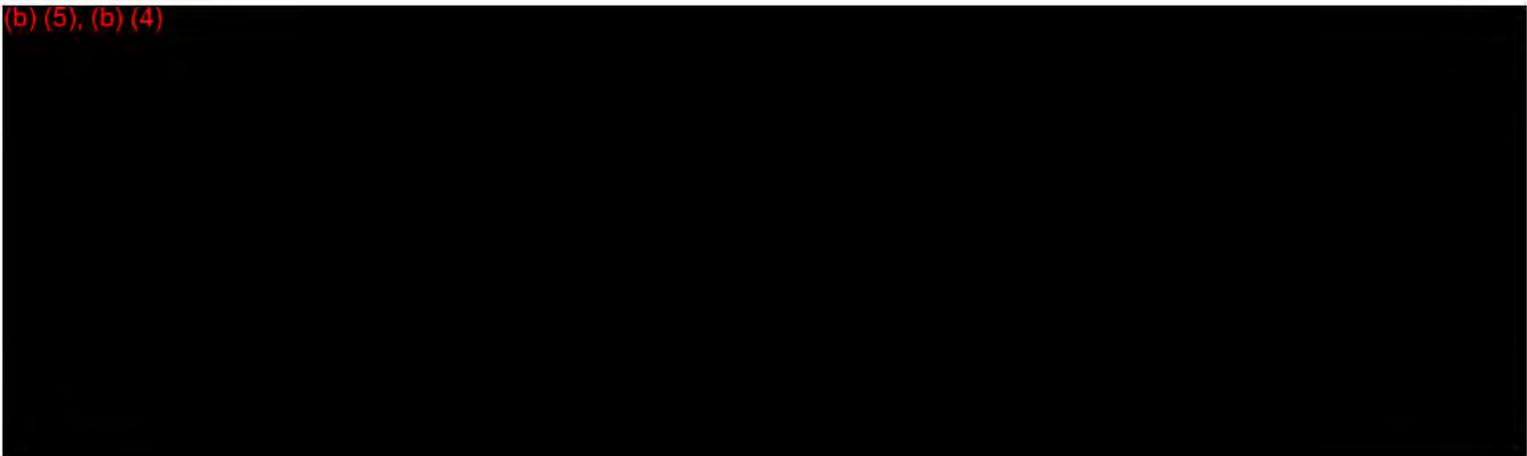
Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5); (b) (4)



(b) (5), (b) (4)



42 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Monday, December 22, 2014 5:04 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschel, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #64
Attachments: 64 FDA 2014 Ebola Coordination Situation Report 2014-12-22.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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Smith, Celeste

From: Garza, Anthony
Sent: Monday, December 29, 2014 4:01 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #66
Attachments: 66 FDA 2014 Ebola Coordination Situation Report 2014-12-29.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report which contains no new information. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

- 1) **There are no new updates for December 29, 2014.**
- 2) **Next SITREP will be produced on Wednesday December 31, 2014.**
- 3) **There will be no SITREP produced on Friday January 2, 2015.**

42 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, January 07, 2015 4:35 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #69
Attachments: 69 FDA 2014 Ebola Coordination Situation Report 2015-1-7.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



42 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, January 07, 2015 4:35 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #69
Attachments: 69 FDA 2014 Ebola Coordination Situation Report 2015-1-7.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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42 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

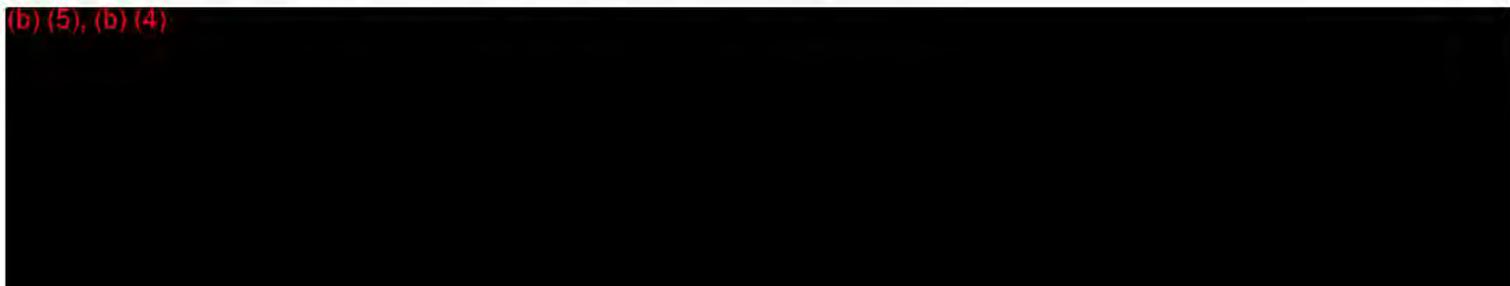
Smith, Celeste

From: Garza, Anthony
Sent: Friday, January 09, 2015 4:40 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #70
Attachments: 70 FDA 2014 Ebola Coordination Situation Report 2015-1-9.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



42 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Monday, January 12, 2015 4:29 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #71
Attachments: 71 FDA 2014 Ebola Coordination Situation Report 2015-1-12.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

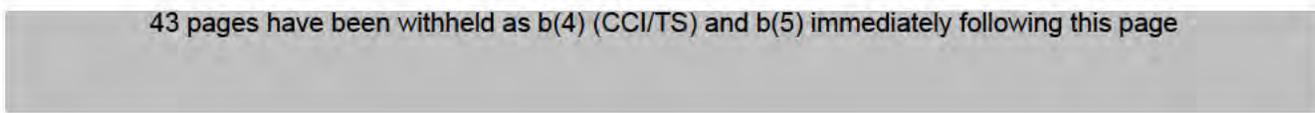
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(b) (5), (b) (4)



43 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page



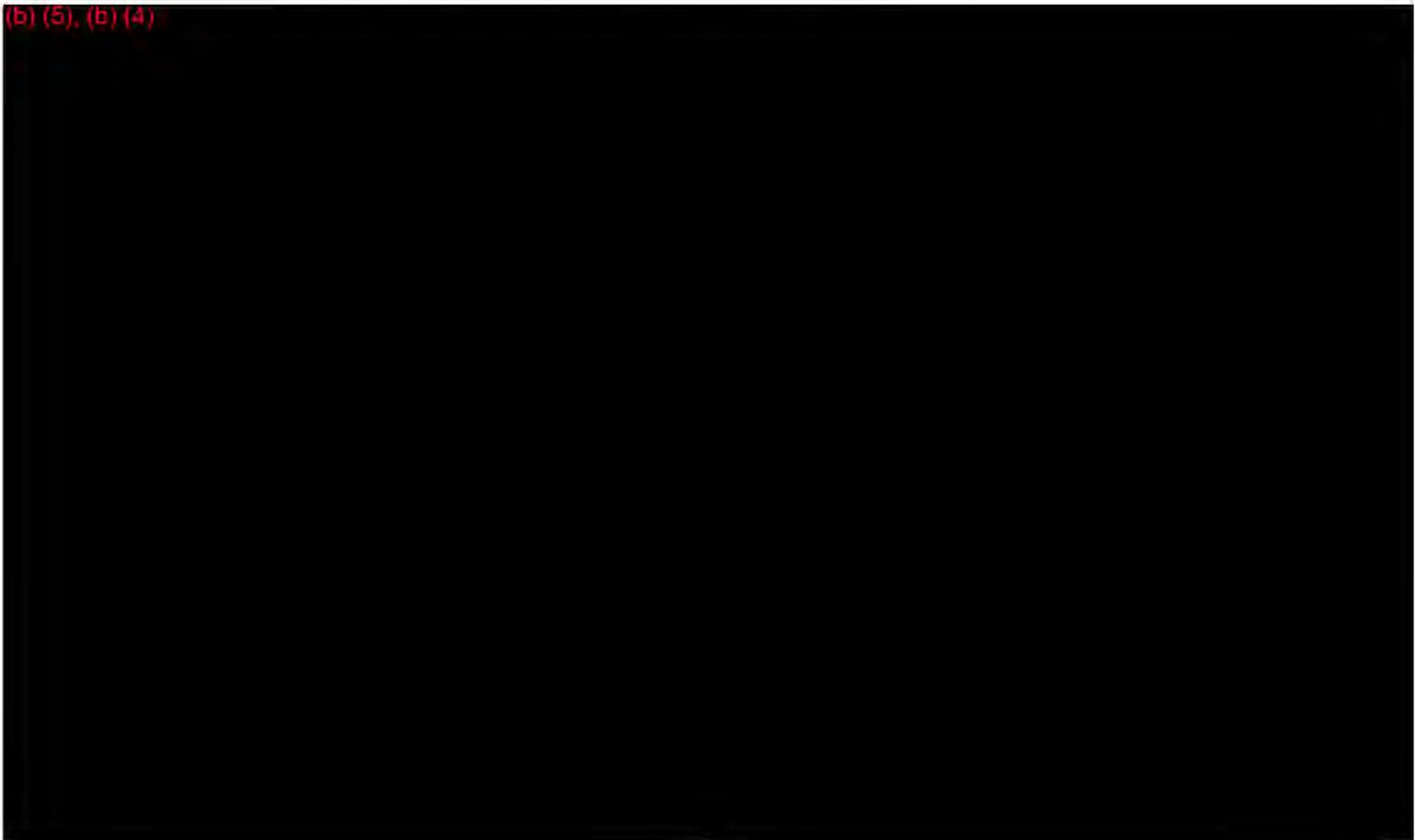
Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, January 14, 2015 4:47 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #72
Attachments: 72 FDA 2014 Ebola Coordination Situation Report 2015-1-14.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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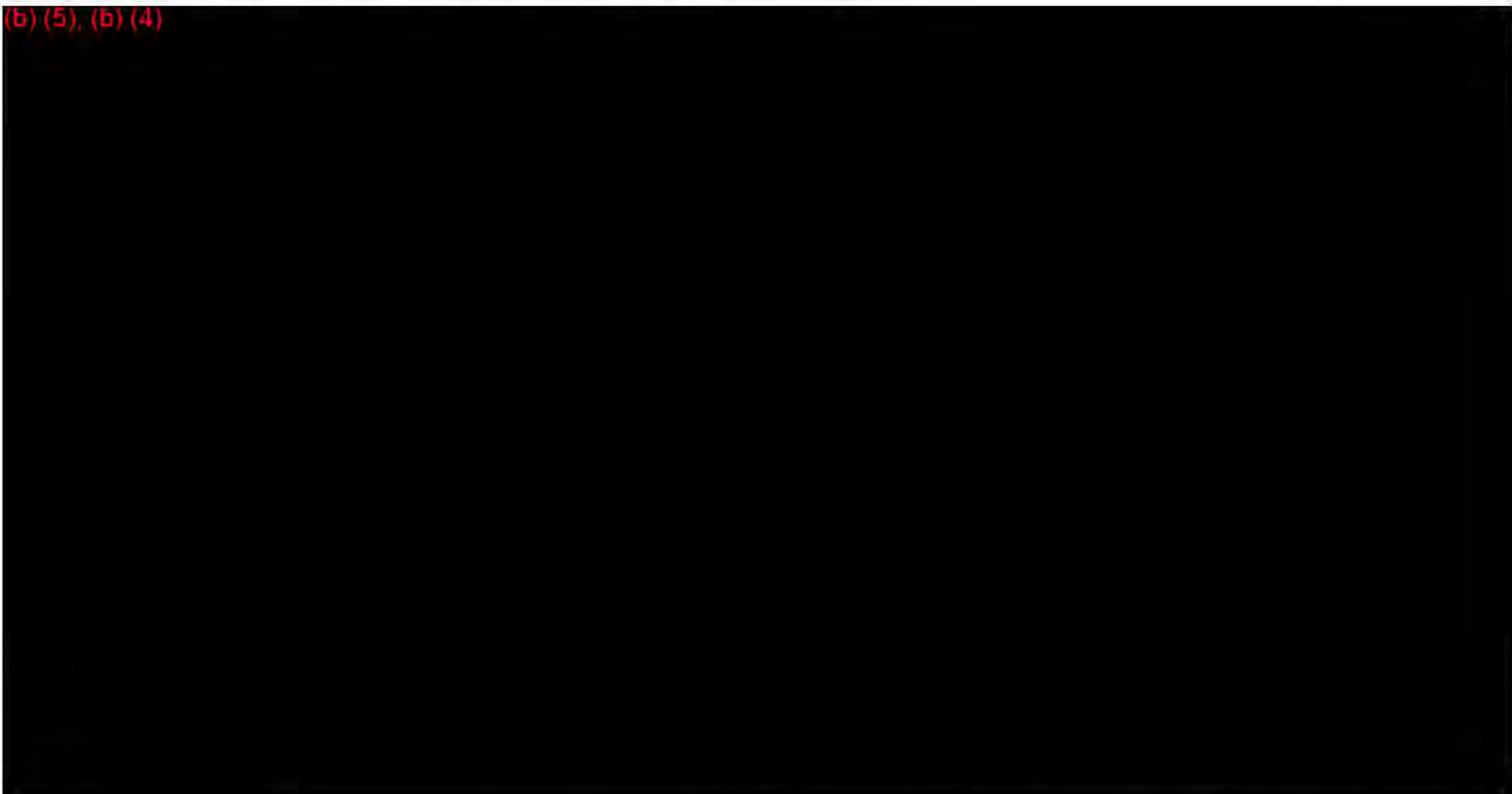
Smith, Celeste

From: Garza, Anthony
Sent: Friday, January 16, 2015 4:27 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #73
Attachments: 73 FDA 2014 Ebola Coordination Situation Report 2015-1-16.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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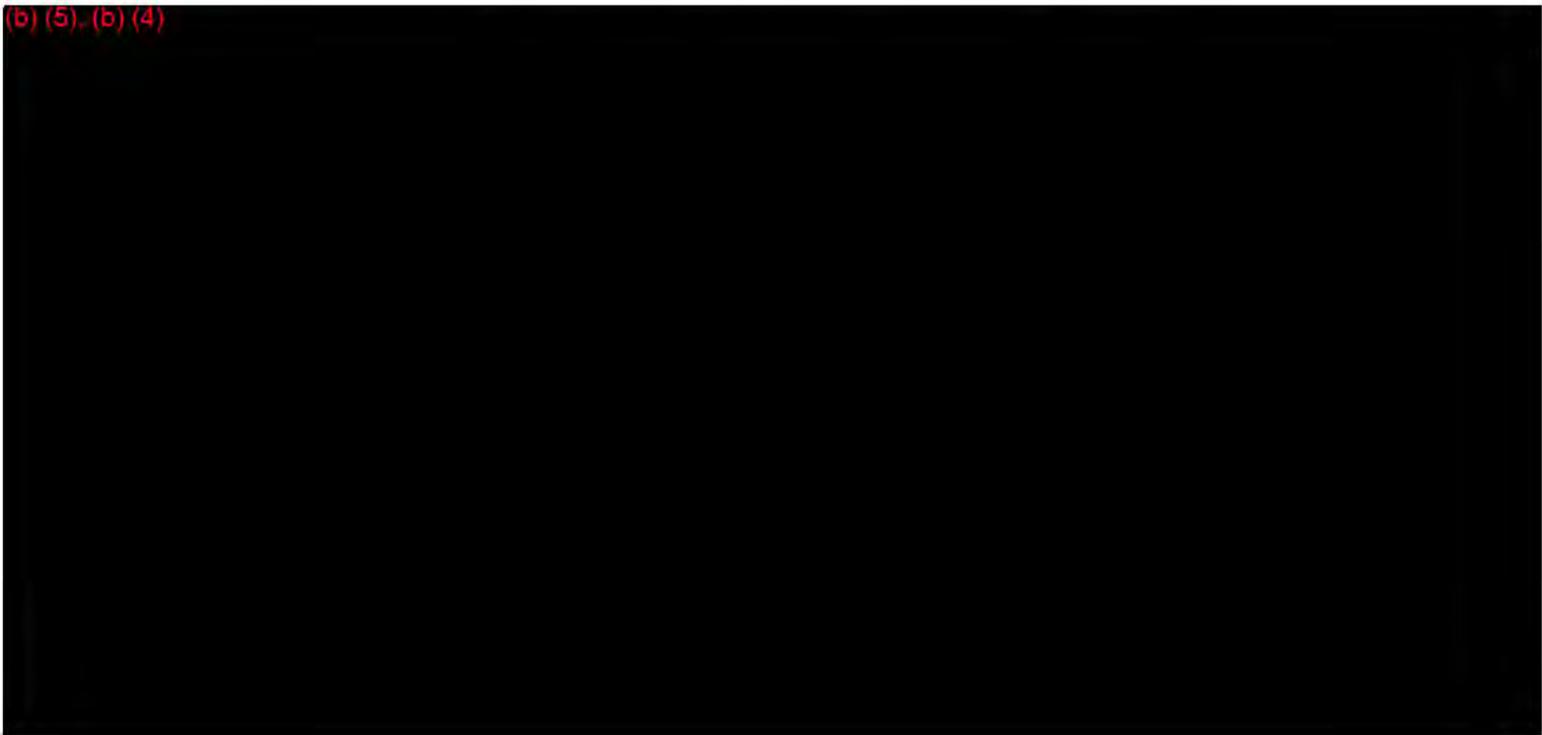


43 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, January 21, 2015 4:05 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #74
Attachments: 74 FDA 2014 Ebola Coordination Situation Report 2015-1-21.docx

(b) (5), (b) (4)



43 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

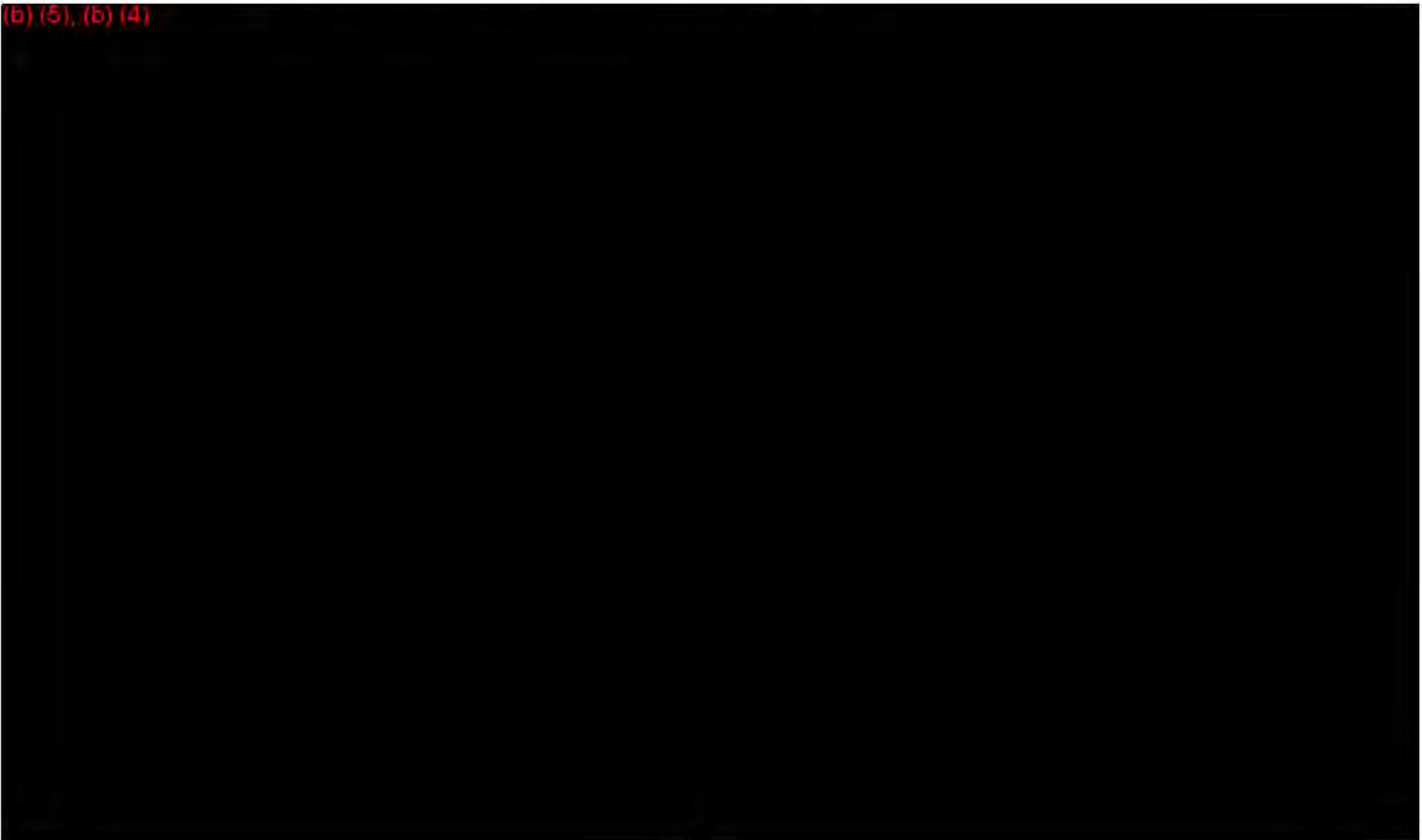
Smith, Celeste

From: Garza, Anthony
Sent: Friday, January 23, 2015 5:14 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #75
Attachments: 75 FDA 2014 Ebola Coordination Situation Report 2015-1-23.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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(b) (5), (b) (4)



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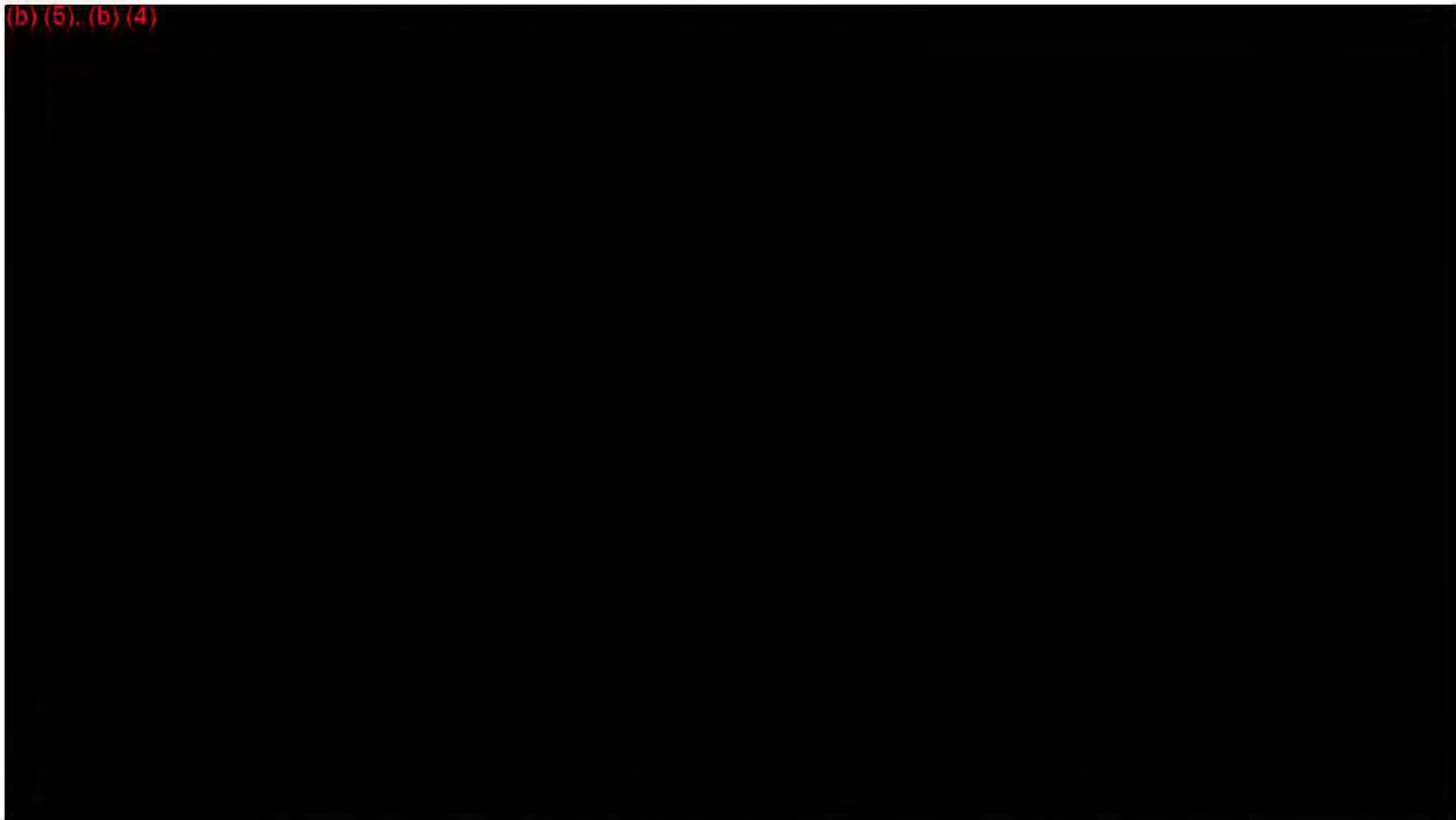
Smith, Celeste

From: Garza, Anthony
Sent: Monday, January 26, 2015 4:03 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #76
Attachments: 76 FDA 2014 Ebola Coordination Situation Report 2015-1-26.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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20 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

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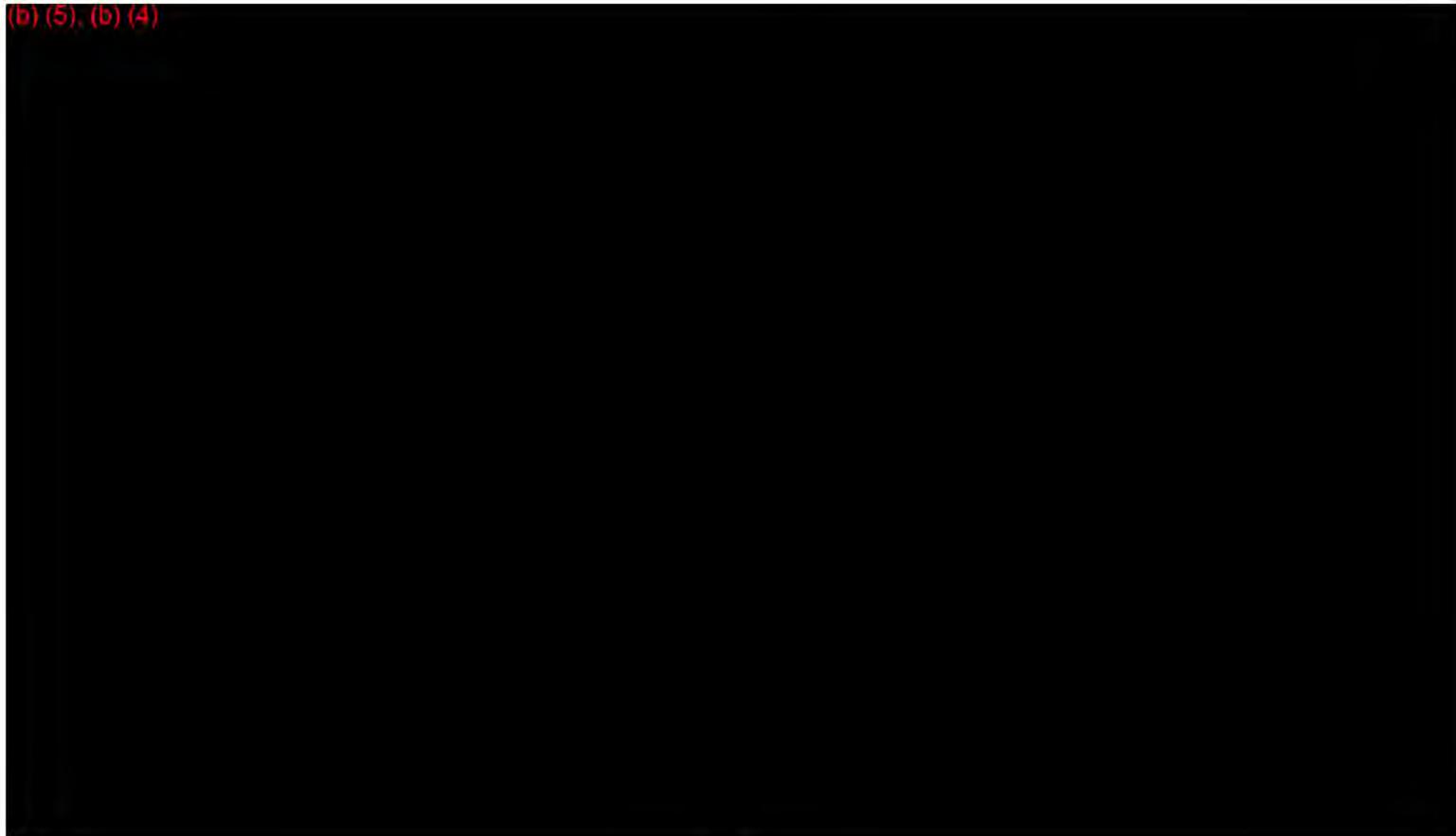
Smith, Celeste

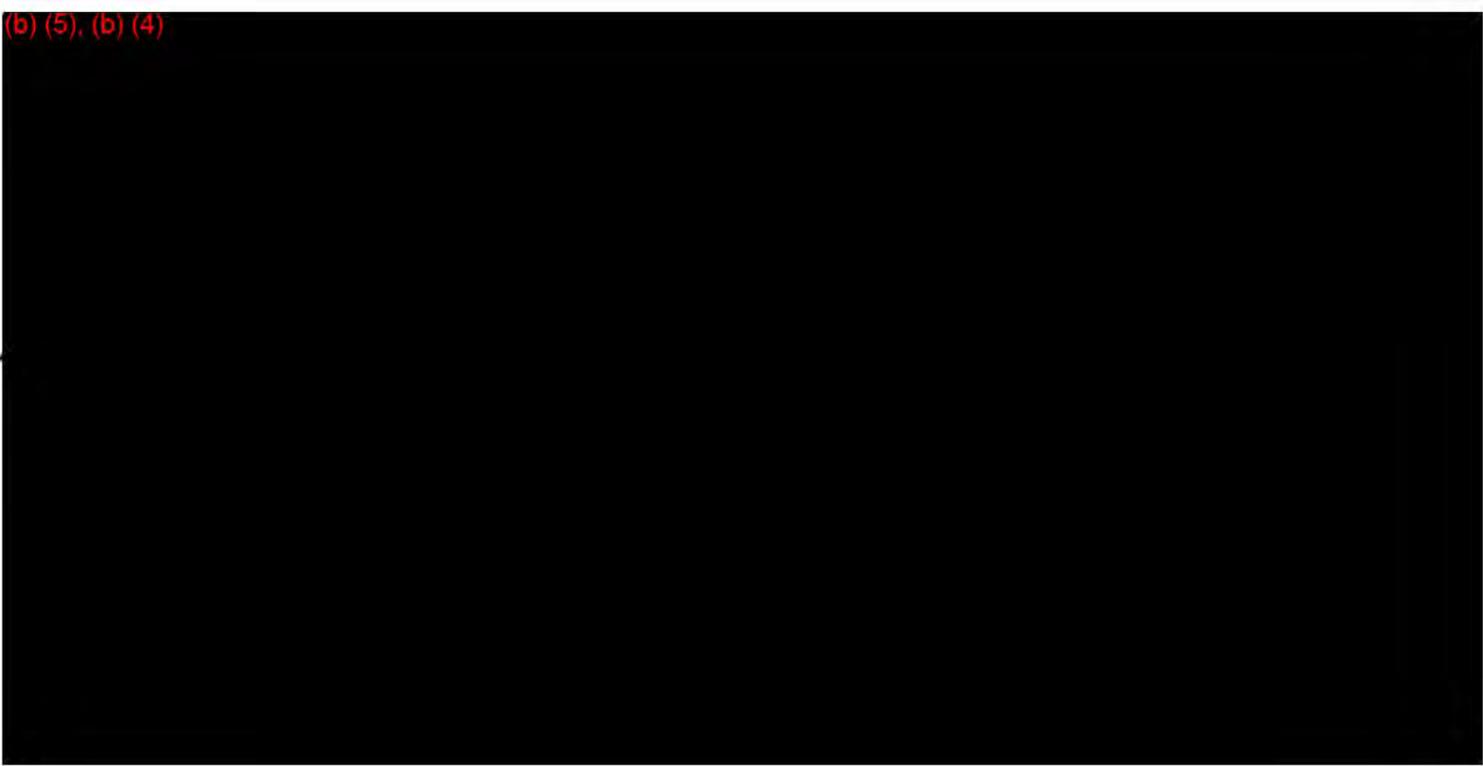
From: Garza, Anthony
Sent: Wednesday, January 28, 2015 4:28 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #77
Attachments: 77 FDA 2014 Ebola Coordination Situation Report 2015-1-28.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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Smith, Celeste

From: Garza, Anthony
Sent: Friday, January 30, 2015 4:16 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #78
Attachments: 78 FDA 2014 Ebola Coordination Situation Report 2015-1-30.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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(b) (5), (b) (4)



45 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

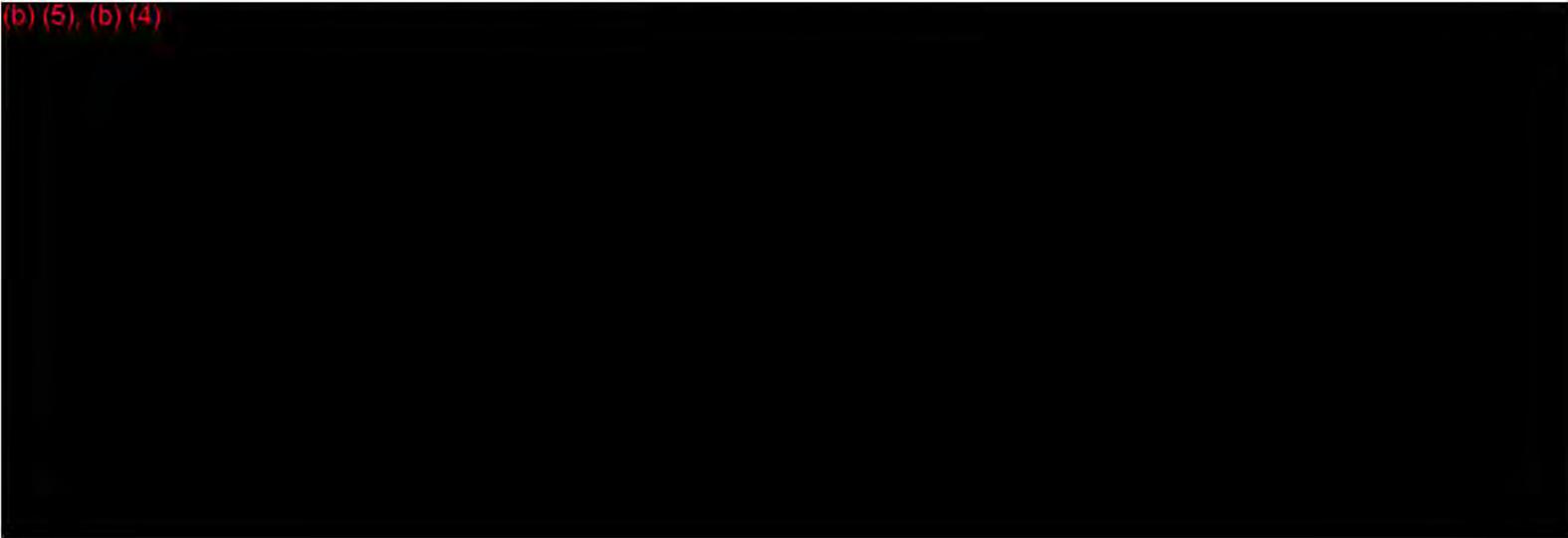
Smith, Celeste

From: Garza, Anthony
Sent: Monday, February 02, 2015 4:49 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #79
Attachments: 79 FDA 2014 Ebola Coordination Situation Report 2015-2-2.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



46 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

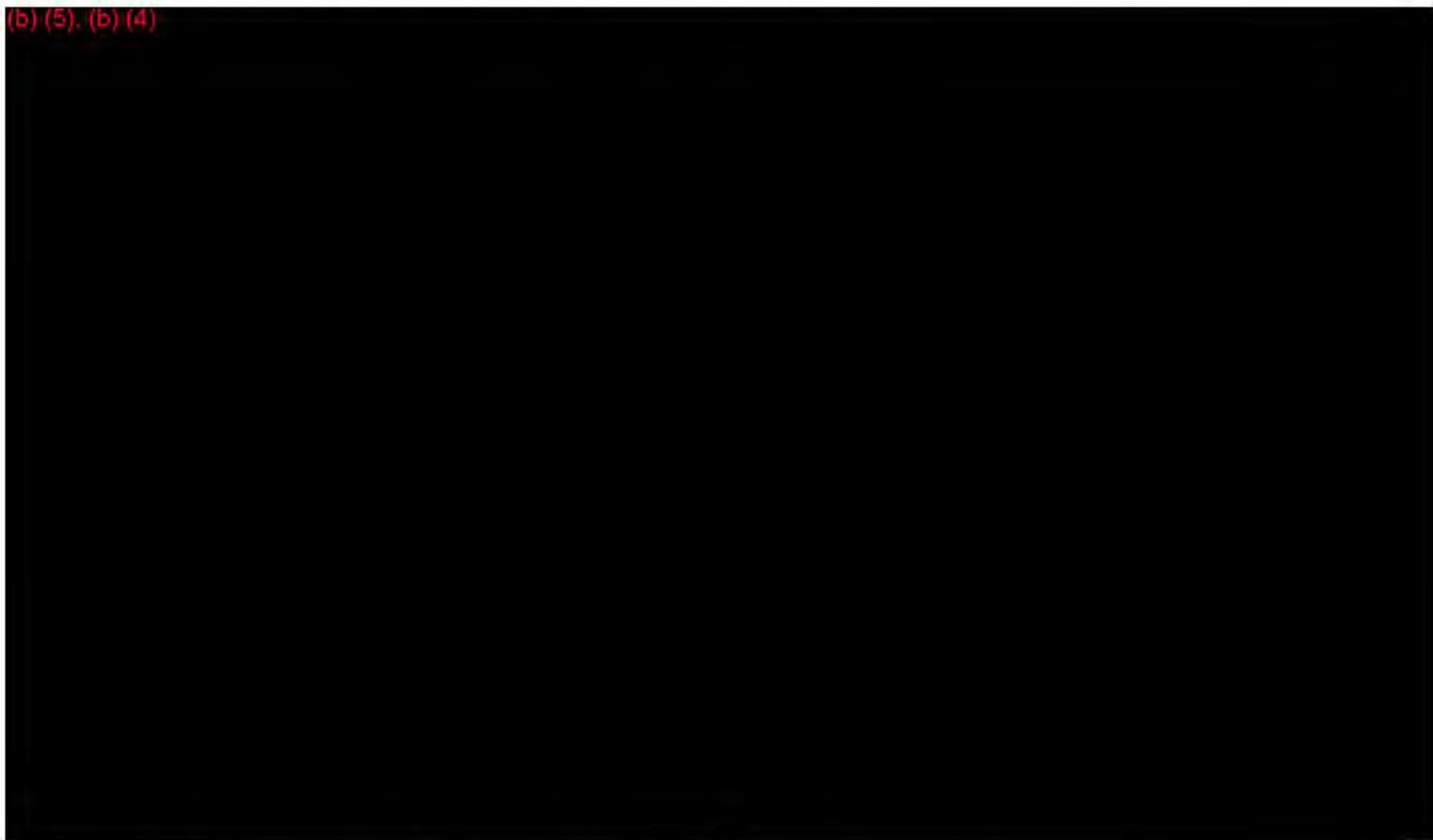
Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, February 04, 2015 4:06 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #80
Attachments: 80 FDA 2014 Ebola Coordination Situation Report 2015-2-4.docx

Good afternoon,

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(b) (5), (b) (4)



Smith, Celeste

From: Quinn, Kathleen
Sent: Thursday, February 05, 2015 1:43 PM
To: Fritsch, Beth F. (Beth.Fritsch@fda.hhs.gov); Marchand, Heidi (Heidi.Marchand@fda.hhs.gov)
Subject: for stakeholder search
Attachments: Commissioner Hamburg Resignation: Boston Business Journal, "FDA head Margaret Hamburg says she will step down after 6 years"; Commissioner Hamburg Resignation: CNN, "FDA chief to step down in March"; Commissioner Hamburg Resignation Coverage: Reuters, Fierce Pharma, Medcity News; Commissioner Hamburg Resignation Coverage: Bloomberg, Fierce Biotech, Pharmacy Times; Commissioner Hamburg Resignation Coverage: Medscape, The Hill, AP, Politico; Commissioner Hamburg Resignation Coverage: NPR, NYT, Washington Post

Smith, Celeste

From: Smith, Fallon
Sent: Thursday, February 05, 2015 1:23 PM
To: Hamburg, Margaret; Quinn, Kathleen; Kraus, Tom; Rebello, Heidi; Yao, Stephanie; Riley, Karen; Zawisza, Julie; Ostroff, Stephen; Hoague, Angela; Esposito, Denise; Pennington, Caitlin
Subject: Commissioner Hamburg Resignation: Boston Business Journal, "FDA head Margaret Hamburg says she will step down after 6 years"

FDA head Margaret Hamburg says she will step down after 6 years

By Don Seiffert

Margaret Hamburg, commissioner of the U.S. Food and Drug Administration for six years, said today she is stepping down as of March, according to the New York Times.

Hamburg, who came to Boston last April to speak at the MassBio annual meeting, has attracted both praise and criticism for her job overseeing the nation's top agency that oversees drug approvals. The past few years have seen more drug approvals in more than a decade as the biotech sector has enjoyed an explosion of innovation. She's overseen the implementation of new designations to help further speed up the approval process for certain kinds of drugs, particularly antibiotics and those which have promise to substantially improve treatment for life-threatening diseases.

At the same time, the agency has attracted significant criticism from patient advocates for not acting quickly enough on promising drugs to treat some diseases, such as Duchenne muscular dystrophy. Christine McSherry, a Pembroke mother of a 19-year-old with DMD and head of the Jett Foundation, a patient advocacy group, said that while Hamburg laid the foundation for the precision medicine initiative announce last week by President Barack Obama, she "hasn't done enough" to speed approval of rare diseases like DMD.

"We hope to have more focus going forward and implementation of faster processes across all the divisions... but would like to see all of these endeavors translated into action which would mean quicker access to drugs and faster approvals," said McSherry in an interview today.

While Hamburg has touted the agency's work to use accelerated approval in reviewing drugs for diseases which have not treatments, McSherry said that during Hamburg's tenure, the agency continues to burden small drug development companies with requirements that take months or years to fulfill. As a result, she said it still takes an average of seven years from when clinical trials start for a drug for a rare disease before that drug is approved. McSherry cited the example of Cambridge-based Sarepta Therapeutics (Nasdaq: SRPT), which has suffered numerous delays due to FDA's requirements in developing its DMD drug, despite the fact that no safety issues have surfaced in a trial of 12 boys that's lasted more than three years.

"The only thing that's happened in that time is more boys have died (from the disease)... and more safety data has accumulated," she said. McSherry said she's met with Hamburg three times in recent years and has found her empathetic, but says, "I don't believe she has full control over her agency."

Jim Greenwood, head of BIO, the world's largest trade association representing biotechnology companies, has also criticized the agency for not using post-marketing data in some cases to get life-saving drugs on the market sooner, while former FDA Commissioner Andrew von Eschenbach went so far last year as to say of the biotech industry, "the business model is basically falling apart" due to the FDA's increasing demands.

While there has reportedly not been a successor named, The Wall Street Journal reported that the FDA's chief scientist, Dr. Stephen Ostroff, will temporarily fill in. One likely successor could be Dr. Robert Califf of Duke University, who Hamburg recently recruited as the agency's deputy commissioner for medical products and tobacco.

Fallon Smith

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-8632
Fallon.Smith@fda.hhs.gov



Smith, Celeste

From: Smith, Fallon
Sent: Thursday, February 05, 2015 1:23 PM
To: Hamburg, Margaret; Quinn, Kathleen; Kraus, Tom; Rebello, Heidi; Yao, Stephanie; Riley, Karen; Zawisza, Julie; Ostroff, Stephen; Hoague, Angela; Esposito, Denise; Pennington, Caitlin
Subject: Commissioner Hamburg Resignation: Boston Business Journal, "FDA head Margaret Hamburg says she will step down after 6 years"

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At the same time, the agency has attracted significant criticism from patient advocates for not acting quickly enough on promising drugs to treat some diseases, such as Duchenne muscular dystrophy. Christine McSherry, a Pembroke mother of a 19-year-old with DMD and head of the Jett Foundation, a patient advocacy group, said that while Hamburg laid the foundation for the precision medicine initiative announce last week by President Barack Obama, she "hasn't done enough" to speed approval of rare diseases like DMD.

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Fallon Smith

Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-8632
Fallon.Smith@fda.hhs.gov



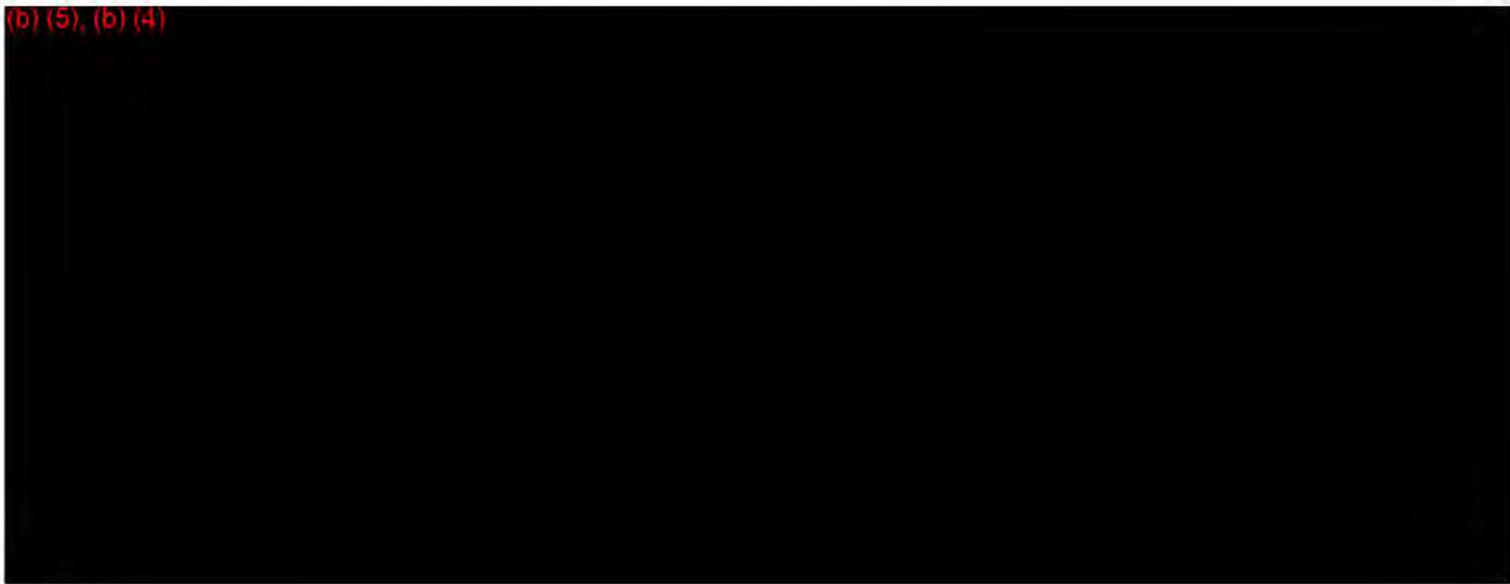
Smith, Celeste

From: Garza, Anthony
Sent: Friday, February 06, 2015 4:18 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #81
Attachments: 81 FDA 2014 Ebola Coordination Situation Report 2015-2-6.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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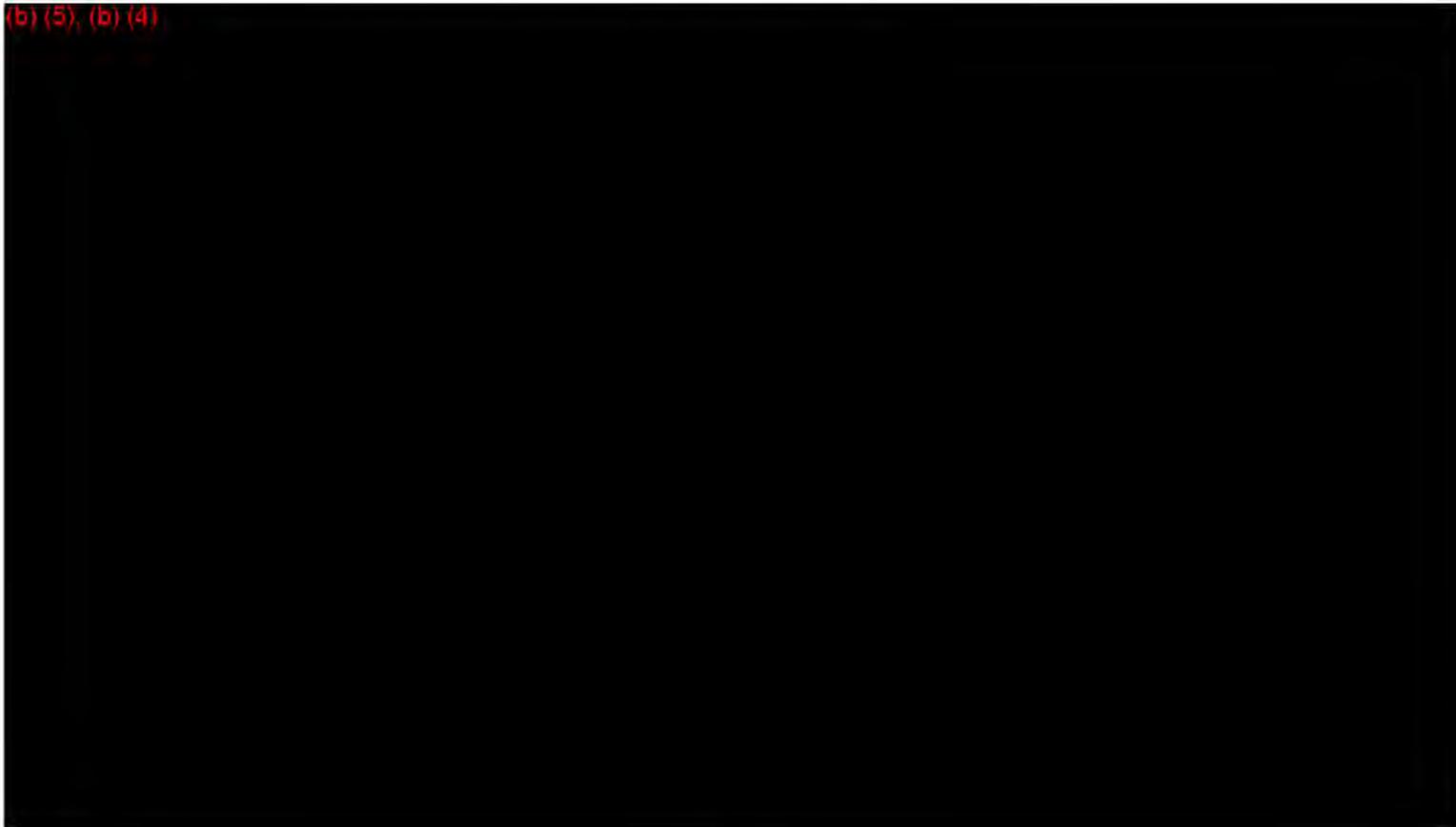
Smith, Celeste

From: Garza, Anthony
Sent: Friday, February 06, 2015 4:37 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: UPDATED: FDA 2014 Ebola Coordination Situation Report #81
Attachments: 81 FDA 2014 Ebola Coordination Situation Report 2015-2-6.docx

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Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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(b) (5), (b) (4)



47 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

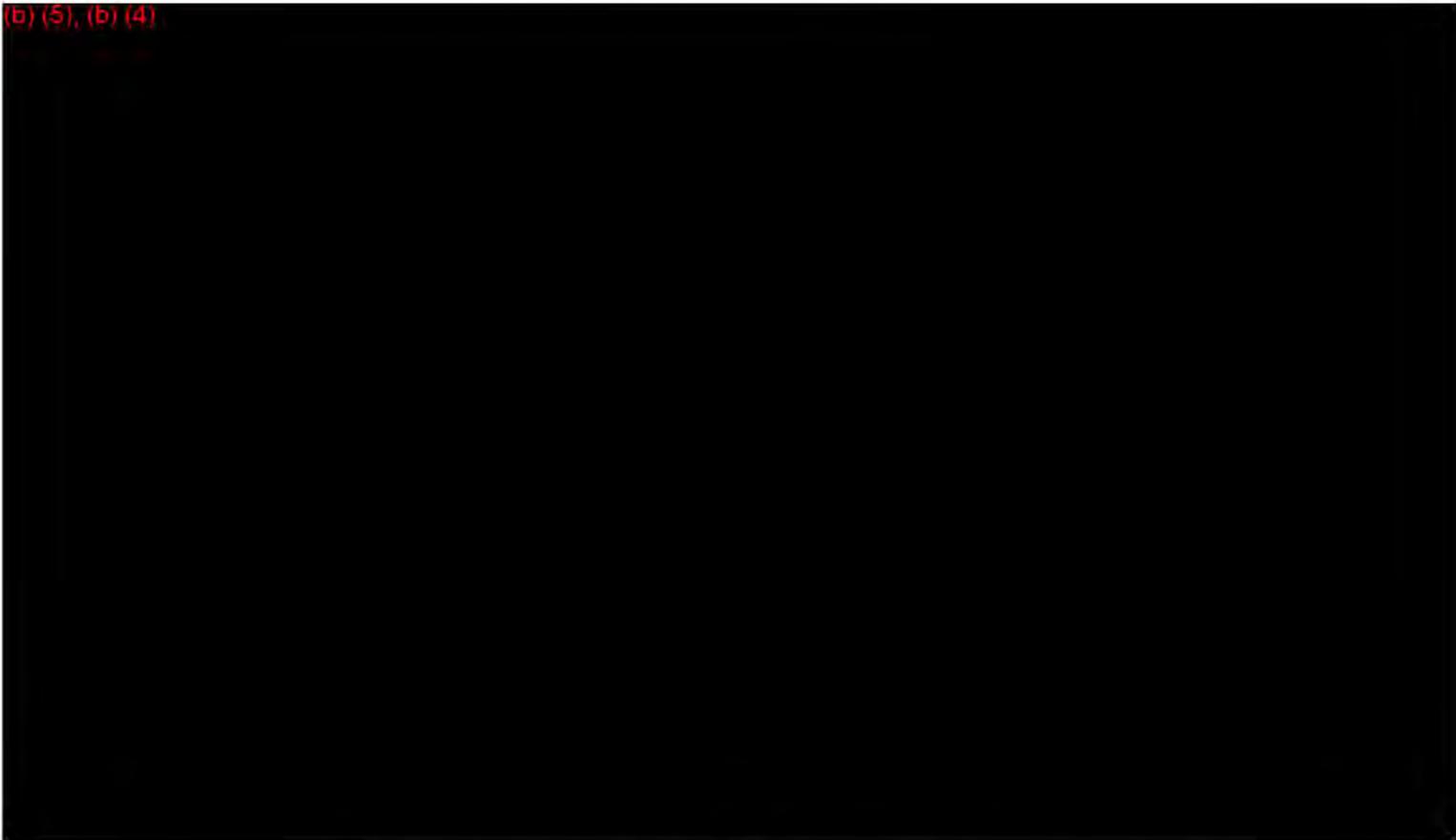
Smith, Celeste

From: Garza, Anthony
Sent: Monday, February 09, 2015 4:02 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #82
Attachments: 82 FDA 2014 Ebola Coordination Situation Report 2015-2-9.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



Smith, Celeste

From: Garza, Anthony
Sent: Friday, February 13, 2015 5:11 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #84
Attachments: 84 FDA 2014 Ebola Coordination Situation Report 2015-2-13.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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47 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, February 18, 2015 5:08 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #85
Attachments: 85 FDA 2014 Ebola Coordination Situation Report 2015-2-18.docx

Good afternoon,

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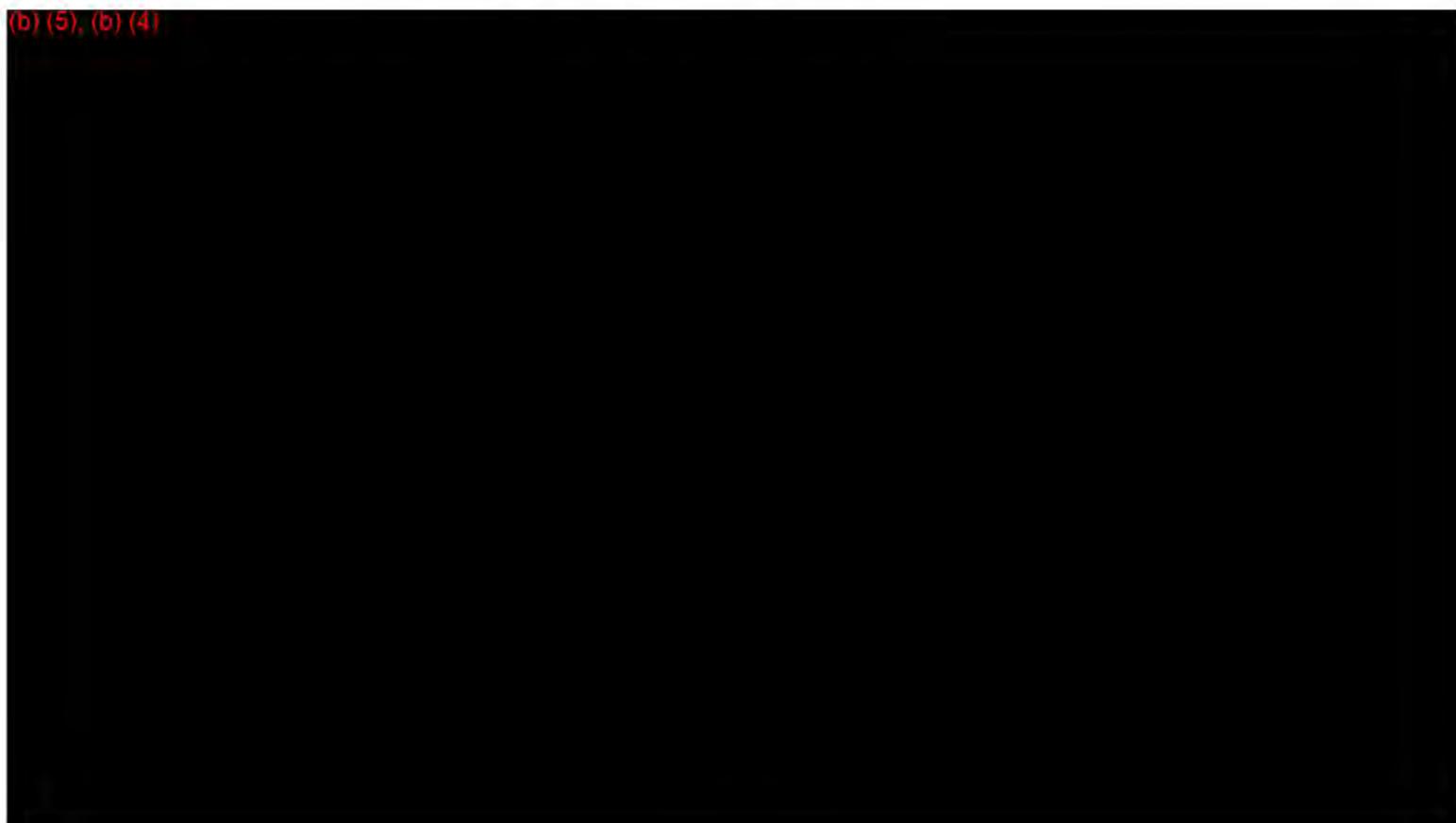
Smith, Celeste

From: Garza, Anthony
Sent: Friday, February 20, 2015 4:20 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #86
Attachments: 86 FDA 2014 Ebola Coordination Situation Report 2015-2-20.docx

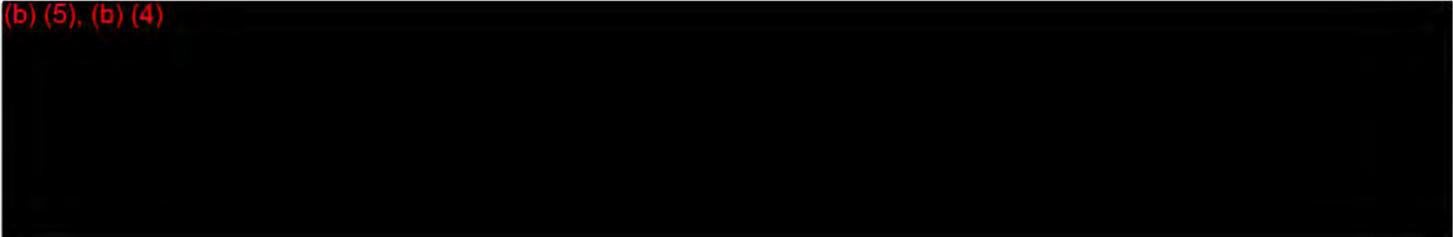
Good afternoon,

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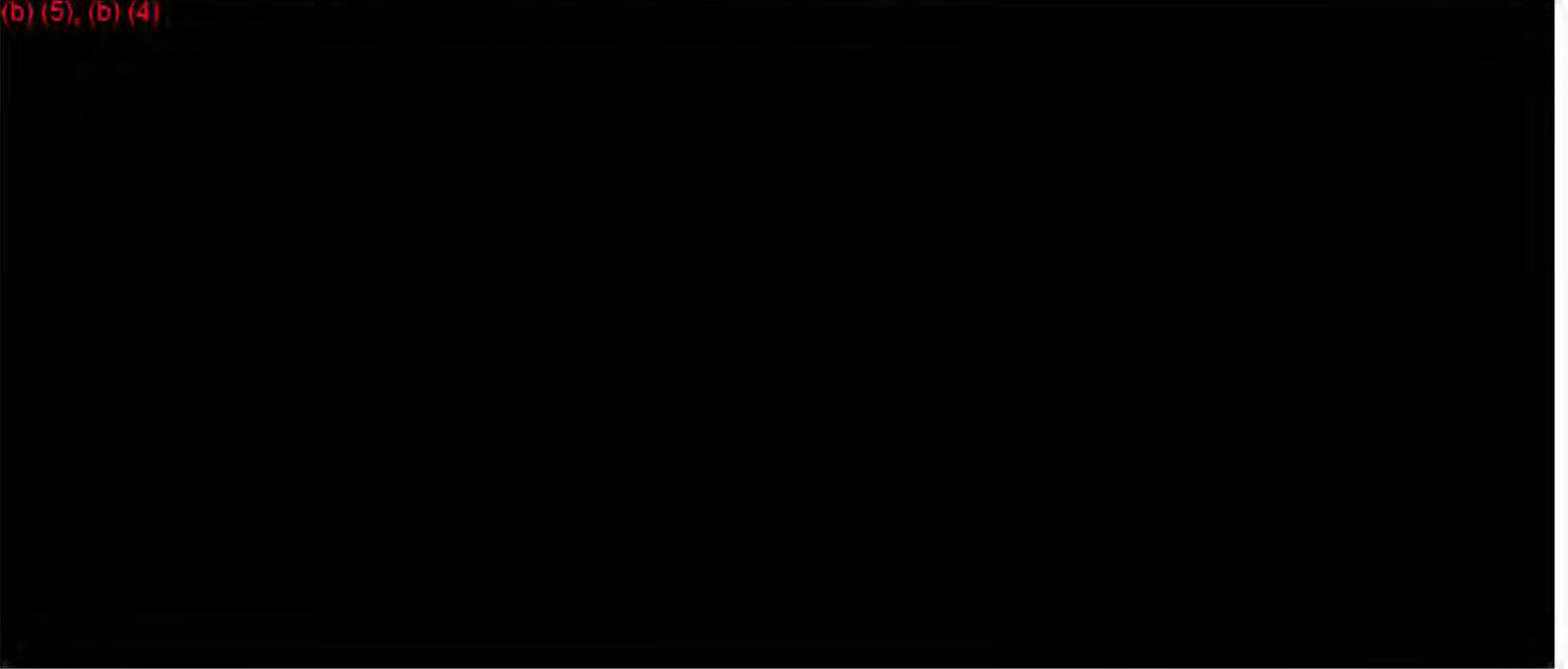
Smith, Celeste

From: Garza, Anthony
Sent: Monday, February 23, 2015 5:04 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony; Balboni, Armand
Subject: FDA 2014 Ebola Coordination Situation Report #87
Attachments: 87 FDA 2014 Ebola Coordination Situation Report 2015-2-23.docx

Good afternoon,

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48 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, February 25, 2015 5:03 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Balboni, Armand; Garza, Anthony; Fisher, Robert
Subject: FDA 2014 Ebola Coordination Situation Report #88
Attachments: 88 FDA 2014 Ebola Coordination Situation Report 2015-2-25.docx

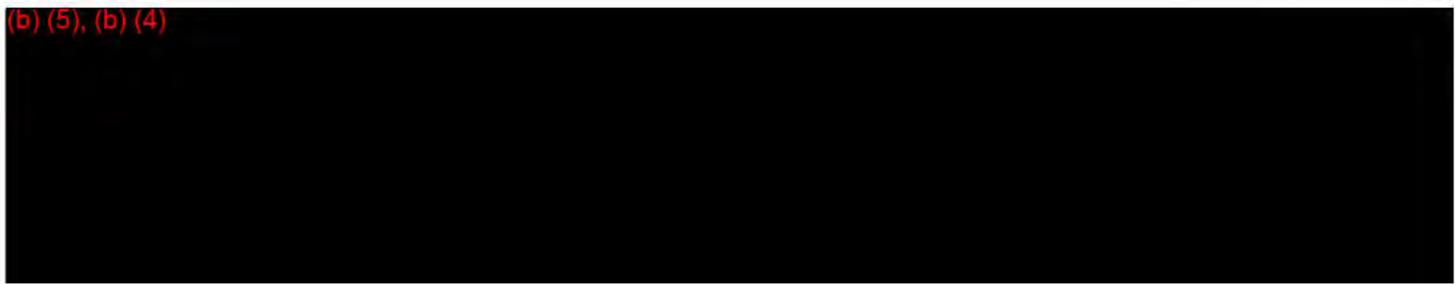
Good afternoon,

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(b) (5), (b) (4)



48 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Friday, February 27, 2015 5:00 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrej; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Balboni, Armand; Fisher, Robert; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #89
Attachments: 89 FDA 2014 Ebola Coordination Situation Report 2015-2-27.docx

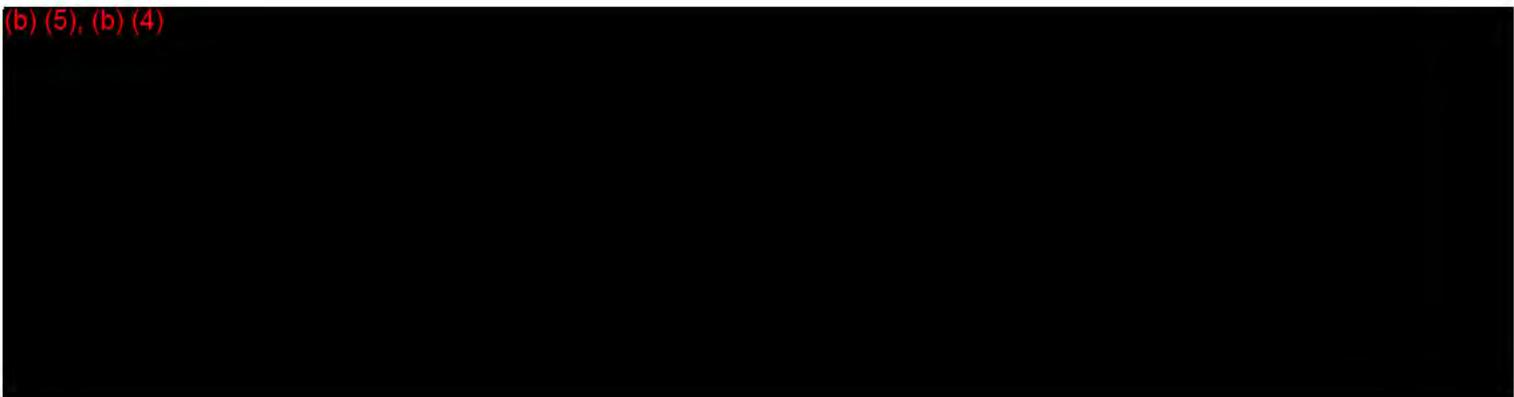
Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



(b) (5), (b) (4)



49 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

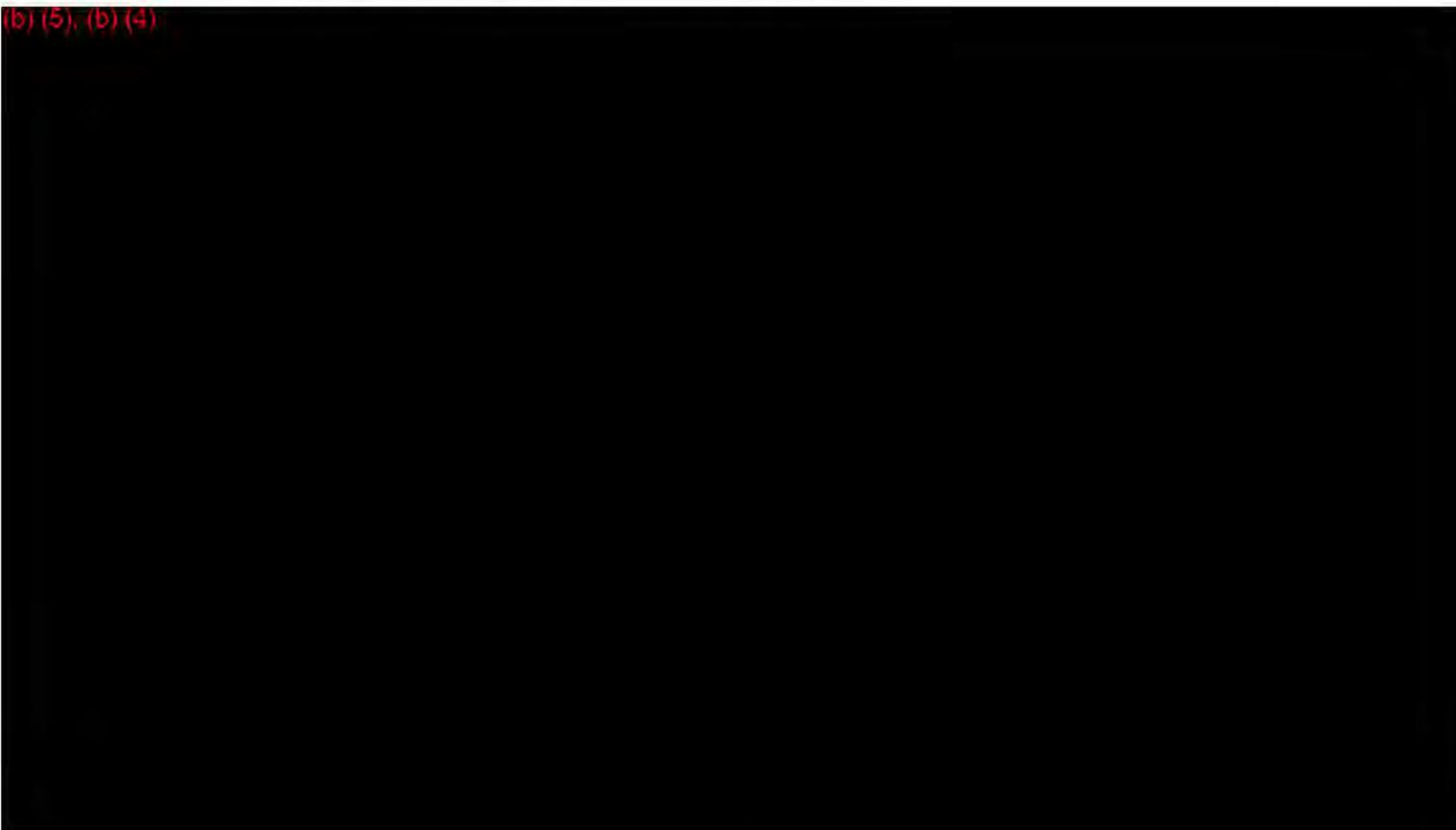
Smith, Celeste

From: Garza, Anthony
Sent: Friday, February 27, 2015 5:18 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Balboni, Armand; Fisher, Robert; Garza, Anthony
Subject: UPDATED: FDA 2014 Ebola Coordination Situation Report #89
Attachments: 89 FDA 2014 Ebola Coordination Situation Report 2015-2-27.docx

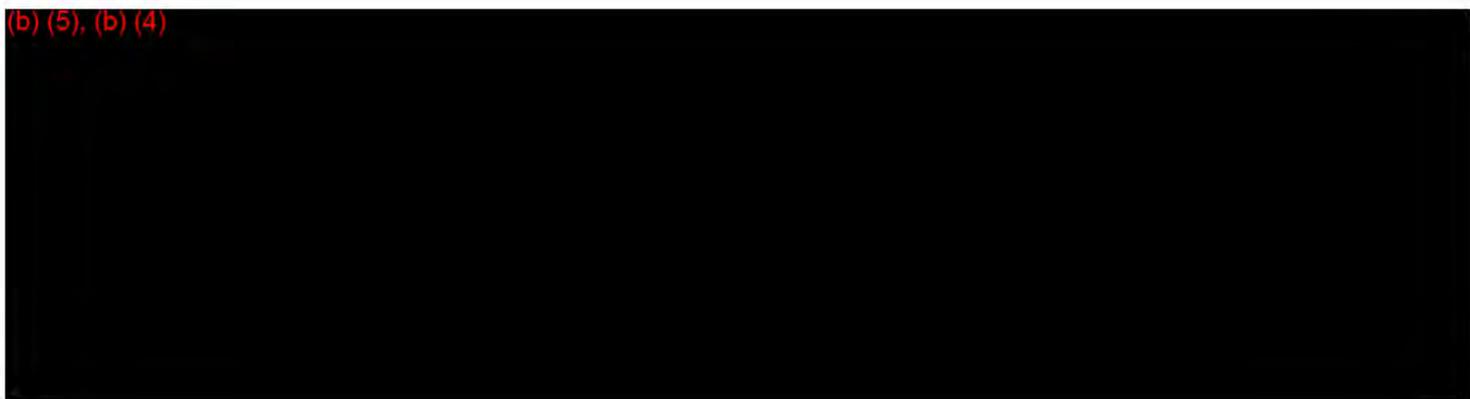
Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



(b) (5), (b) (4)



81 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

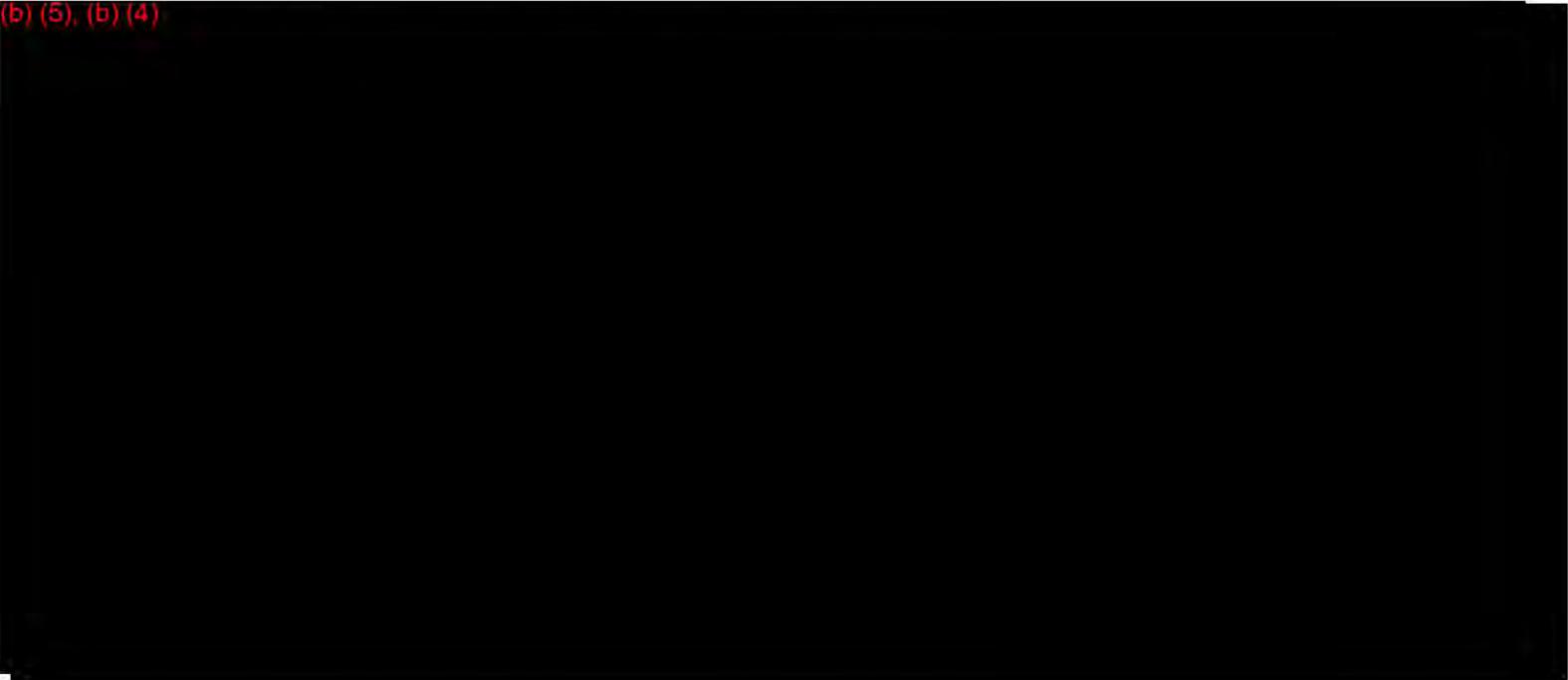
Smith, Celeste

From: Garza, Anthony
Sent: Monday, March 02, 2015 4:51 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschel, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Balboni, Armand; Fisher, Robert; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #90
Attachments: 90 FDA 2014 Ebola Coordination Situation Report 2015-3-2.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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70 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

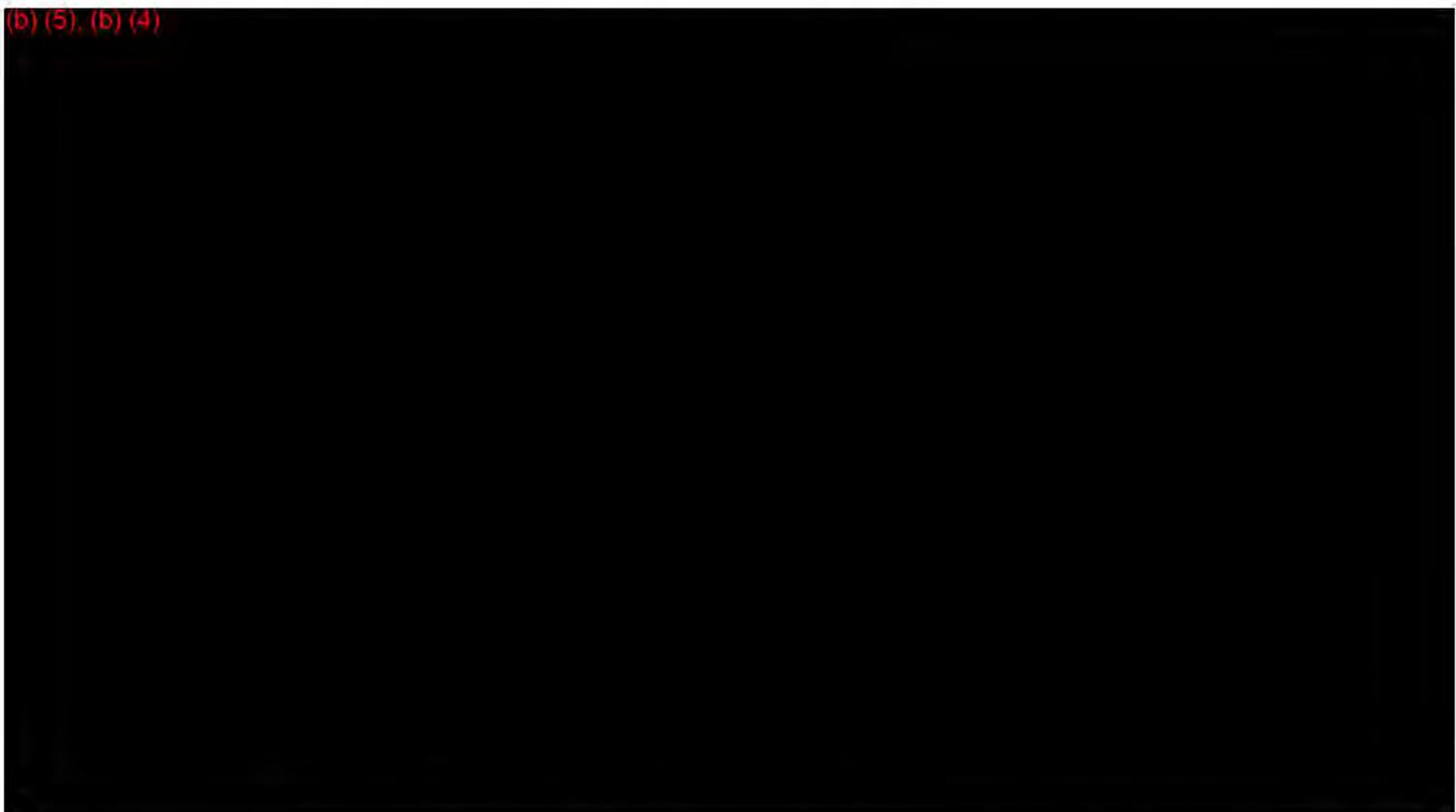
Smith, Celeste

From: Garza, Anthony
Sent: Friday, April 03, 2015 3:51 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Balboni, Armand; Fisher, Robert; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #97
Attachments: 97 FDA 2014 Ebola Coordination Situation Report 2015-4-03.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



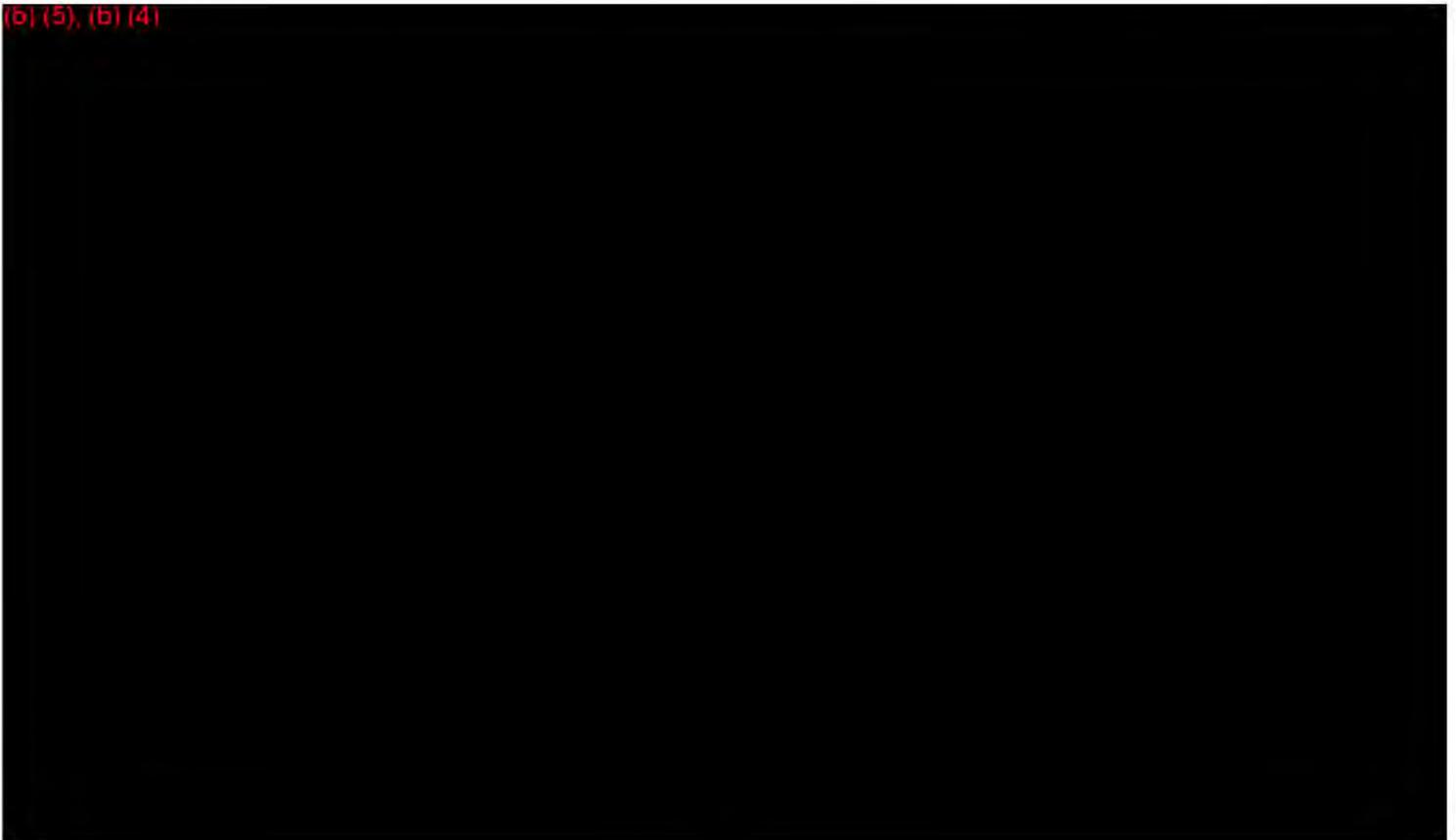
Smith, Celeste

From: Garza, Anthony
Sent: Friday, March 20, 2015 4:11 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Balboni, Armand; Fisher, Robert; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #95
Attachments: 95 FDA 2014 Ebola Coordination Situation Report 2015-3-20.docx

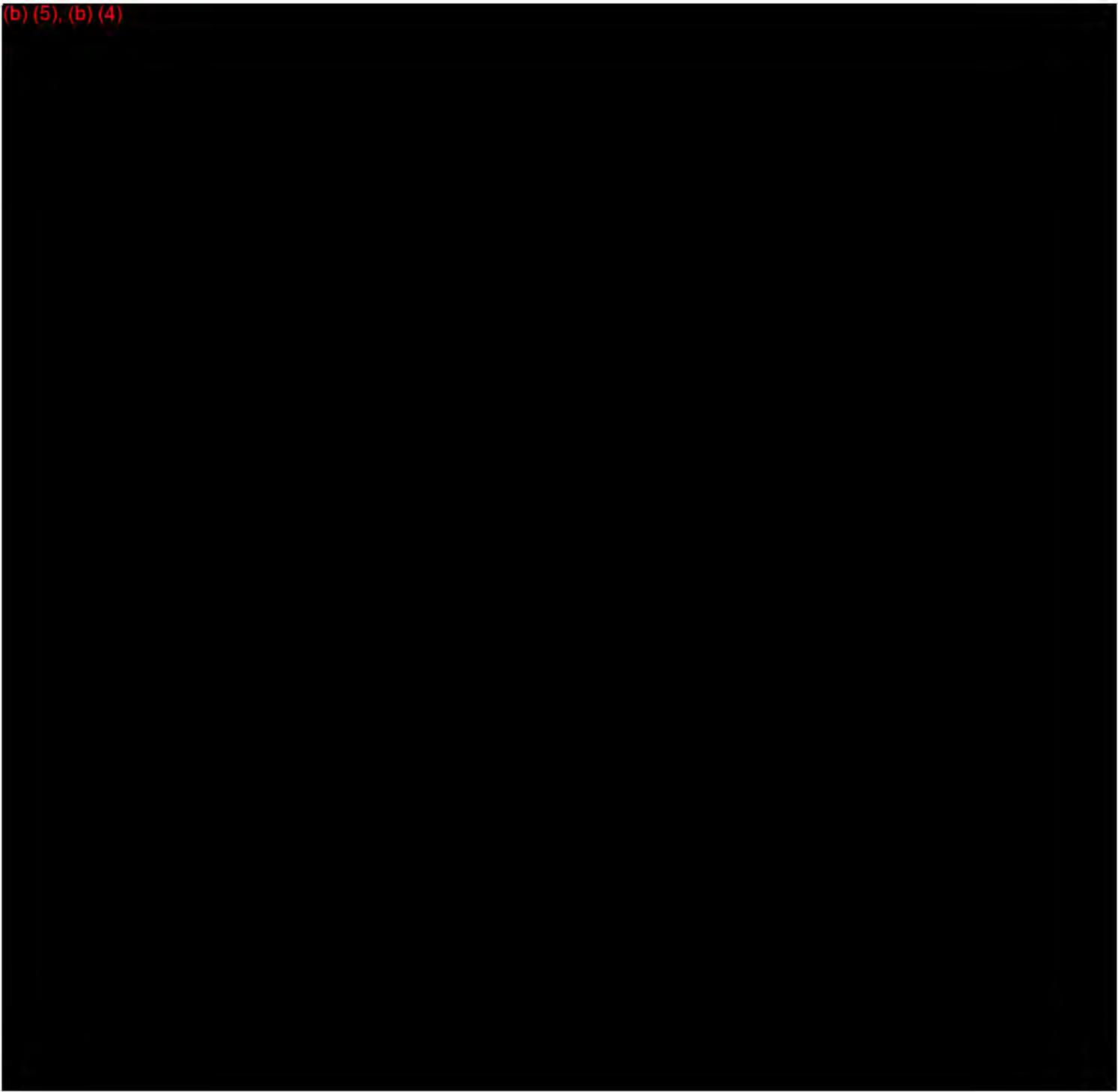
Good afternoon,

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(b) (5), (b) (4)



(b) (5), (b) (4)



51 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

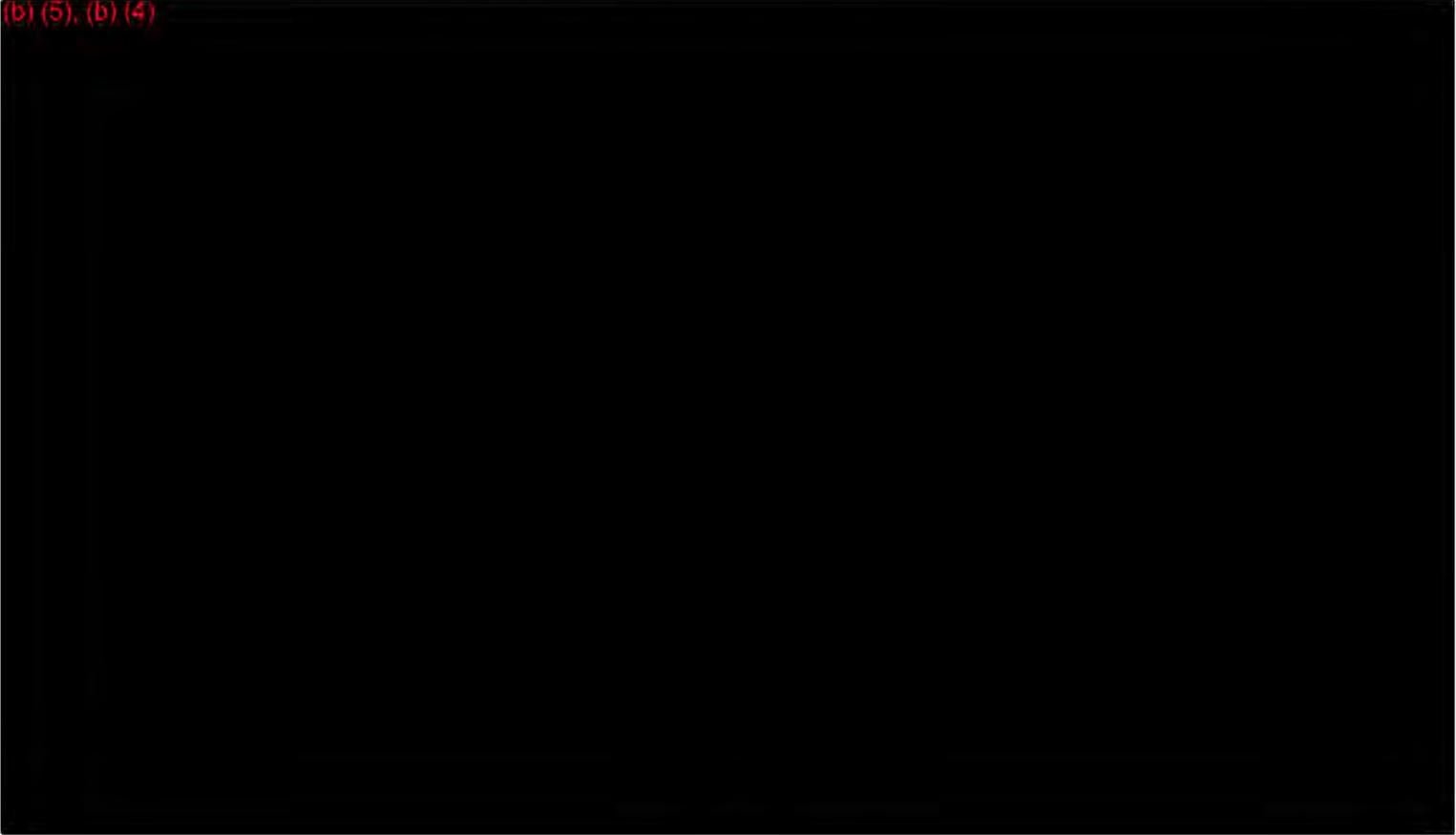
Smith, Celeste

From: Garza, Anthony
Sent: Friday, March 27, 2015 4:28 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Balboni, Armand; Fisher, Robert; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #96
Attachments: 96 FDA 2014 Ebola Coordination Situation Report 2015-3-27.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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(b) (5), (b) (4)



72 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

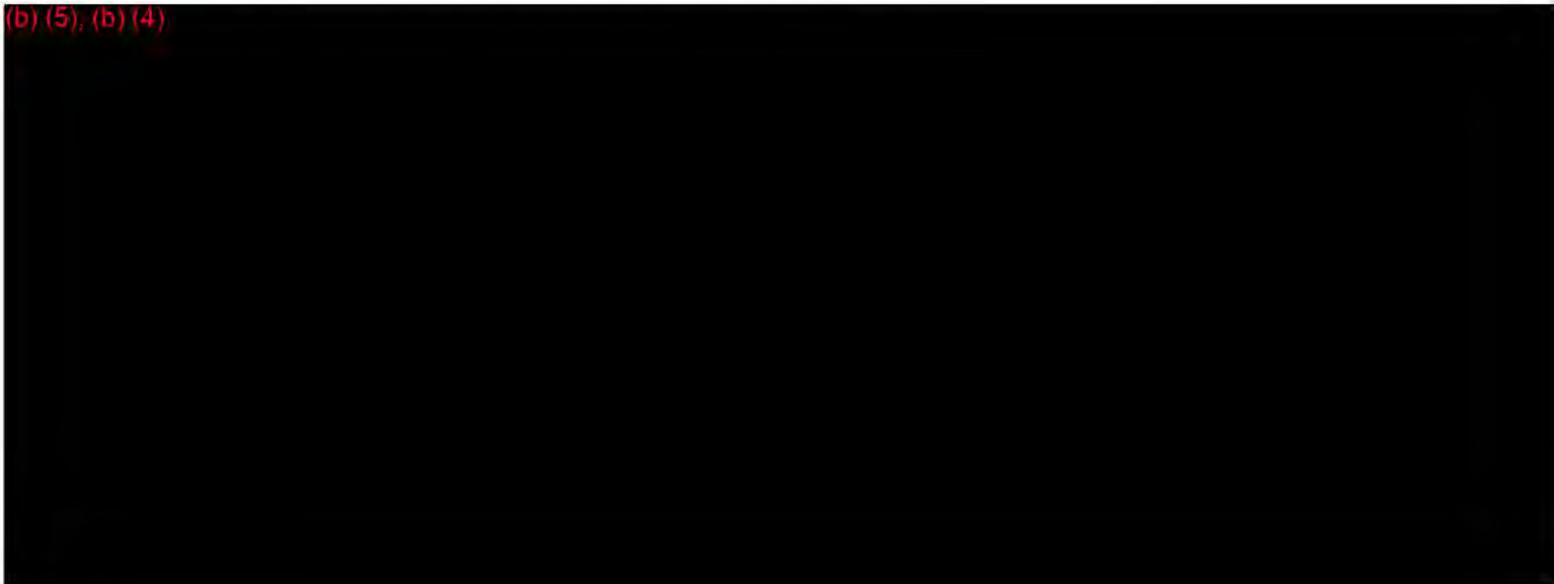
Smith, Celeste

From: Garza, Anthony
Sent: Monday, March 09, 2015 5:05 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Balboni, Armand; Fisher, Robert; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #93
Attachments: 93 FDA 2014 Ebola Coordination Situation Report 2015-3-9.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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49 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

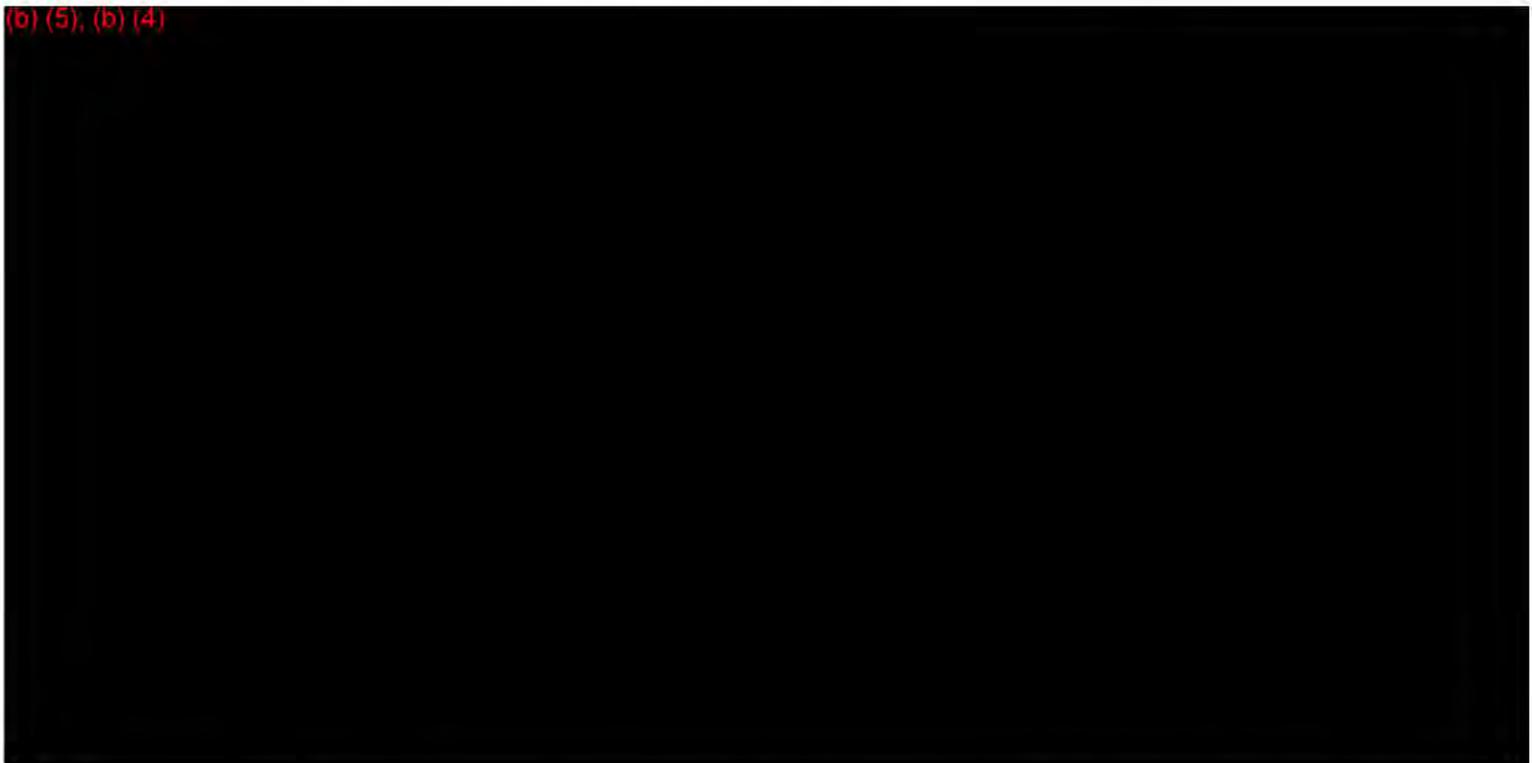
Smith, Celeste

From: Garza, Anthony
Sent: Friday, March 06, 2015 4:51 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony; Balboni, Armand; Fisher, Robert
Subject: FDA 2014 Ebola Coordination Situation Report #92
Attachments: 92 FDA 2014 Ebola Coordination Situation Report 2015-3-6.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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18 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, March 04, 2015 4:40 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Balboni, Armand; Fisher, Robert; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #91
Attachments: 91 FDA 2014 Ebola Coordination Situation Report 2015-3-4.docx

Good afternoon,

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49 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Friday, March 06, 2015 4:51 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony; Balboni, Armand; Fisher, Robert
Subject: FDA 2014 Ebola Coordination Situation Report #92
Attachments: 92 FDA 2014 Ebola Coordination Situation Report 2015-3-6.docx

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(b) (5), (b) (4)



Smith, Celeste

From: Hamburg, Margaret
Sent: Thursday, February 19, 2015 10:44 AM
To: Pennington, Caitlin
Subject: Fw: CONFIDENTIAL: Information Advisory (IA) - FDA to Announce a Public Scientific Workshop to Discuss Dystrophin Protein Quantification Methodologies for Human Tissue
Attachments: Workshop Dystrophin Protein in D Muscular Dystrophy patients FINAL.doc

Print
Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

From: Moran, Kristy
Sent: Thursday, February 19, 2015 09:58 AM
To: FDA Senior Executives; OC-Executive Secretariat
Cc: FDA Senior Executive Assistants; FDA - Information Advisories; OC OEA OMA-Press; Lu, Wei; CDER EXSEC; Sullivan, Diane; Mfum-Gyau, Akua
Subject: FW: CONFIDENTIAL: Information Advisory (IA) - FDA to Announce a Public Scientific Workshop to Discuss Dystrophin Protein Quantification Methodologies for Human Tissue

Good morning,

The attached IA was sent to the Department.

From: Moran, Kristy
Sent: Thursday, February 19, 2015 9:57 AM
To: Potts, Oliver (OS); Weeden, C'Reda (OS); Hall, Bill (OS); Horowitz, David J (OS); Pakulis, Averi (OS); Daniels, Carla L (OS)
Subject: CONFIDENTIAL: Information Advisory (IA) - FDA to Announce a Public Scientific Workshop to Discuss Dystrophin Protein Quantification Methodologies for Human Tissue

Good morning,

Please see the attached Information Advisory, FDA to Announce a Public Scientific Workshop to Discuss Dystrophin Protein Quantification Methodologies for Human Tissue

Best regards,
Kristy Moran
Policy Analyst
FDA/OES
301-796-4678

Date: February 19, 2015

**INFORMATION ADVISORY
(CONFIDENTIAL)**

SUBJECT/LEAD COMPONENT: FDA to Announce a Public Scientific Workshop to Discuss Dystrophin Protein Quantification Methodologies for Human Tissue

WHY THIS INFORMATION IS IMPORTANT FOR THE SECRETARY: On or about February 23, FDA will issue a notice in the *Federal Register* announcing a public scientific workshop entitled “Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data,” to be held on March 20. This workshop is being co-sponsored by the National Institutes of Health. The purpose of the workshop is to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development. The intended audiences for this workshop are scientists and clinicians involved in acquiring, measuring, and analyzing proteins associated with Duchenne muscular dystrophy (DMD). Muscular dystrophy is a group of diseases that cause progressive weakness and loss of muscle mass. DMD is a rapidly progressive form of muscular dystrophy that occurs primarily in boys. This announcement is expected to be of interest to industry, scientists, and clinicians diagnosing and treating patients with DMD. FDA will not issue a press release.

SUMMARY OF ISSUE, BACKGROUND, AND DEPARTMENT RESPONSE/ACTIONS:

- Dystrophin is a structural protein that is found in small amounts in normal muscle, but is absent or present in abnormally small amounts in individuals with DMD. Dystrophinopathies (types of muscular dystrophy) result from genetic mutations in the dystrophin gene that decrease dystrophin protein levels and result in altered dystrophin function. These changes can lead to muscle degeneration and, in many patients, downstream pathologies, including inflammation and fibrosis that interfere with muscle regeneration, loss of movement, orthopedic complications, and ultimately respiratory and cardiac failure.
- The workshop will focus on:
 - current methodologies being used in drug development and scientific research for DMD; and
 - recent scientific advances that present opportunities for developing and validating robust methods for the objective, reliable, and quantitative measurement of DMD-associated proteins.
- The workshop will include overviews of current technologies used to detect dystrophin (including limitations, detection sensitivities, and reproducibility). A panel discussion will identify challenges of developing new detection methods. Muscle biopsy collection, sample handling, reference materials, and image analysis will also be discussed.

CONTACTS: Wei Lu, CDER/DEO, (301) 796-3448; Kristy Moran, FDA/OES, (301) 796-4678; Oliver Potts, OS/ES, (202) 401-4273

Date: February 19, 2015

**INFORMATION ADVISORY
(CONFIDENTIAL)**

SUBJECT/LEAD COMPONENT: FDA to Announce a Public Scientific Workshop to Discuss Dystrophin Protein Quantification Methodologies for Human Tissue

WHY THIS INFORMATION IS IMPORTANT FOR THE SECRETARY: On or about February 23, FDA will issue a notice in the *Federal Register* announcing a public scientific workshop entitled “Measuring Dystrophin in Dystrophinopathy Patients and Interpreting the Data,” to be held on March 20. This workshop is being co-sponsored by the National Institutes of Health. The purpose of the workshop is to discuss currently available methodologies and to identify scientific knowledge gaps and opportunities for improving dystrophin protein detection in the context of drug development. The intended audiences for this workshop are scientists and clinicians involved in acquiring, measuring, and analyzing proteins associated with Duchenne muscular dystrophy (DMD). Muscular dystrophy is a group of diseases that cause progressive weakness and loss of muscle mass. DMD is a rapidly progressive form of muscular dystrophy that occurs primarily in boys. This announcement is expected to be of interest to industry, scientists, and clinicians diagnosing and treating patients with DMD. FDA will not issue a press release.

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 - recent scientific advances that present opportunities for developing and validating robust methods for the objective, reliable, and quantitative measurement of DMD-associated proteins.
- The workshop will include overviews of current technologies used to detect dystrophin (including limitations, detection sensitivities, and reproducibility). A panel discussion will identify challenges of developing new detection methods. Muscle biopsy collection, sample handling, reference materials, and image analysis will also be discussed.

CONTACTS: Wei Lu, CDER/DEO, (301) 796-3448; Kristy Moran, FDA/OES, (301) 796-4678; Oliver Potts, OS/ES, (202) 401-4273

Smith, Celeste

From: Garza, Anthony
Sent: Friday, March 13, 2015 4:52 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Balboni, Armand; Fisher, Robert; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #94
Attachments: 94 FDA 2014 Ebola Coordination Situation Report 2015-3-13.docx

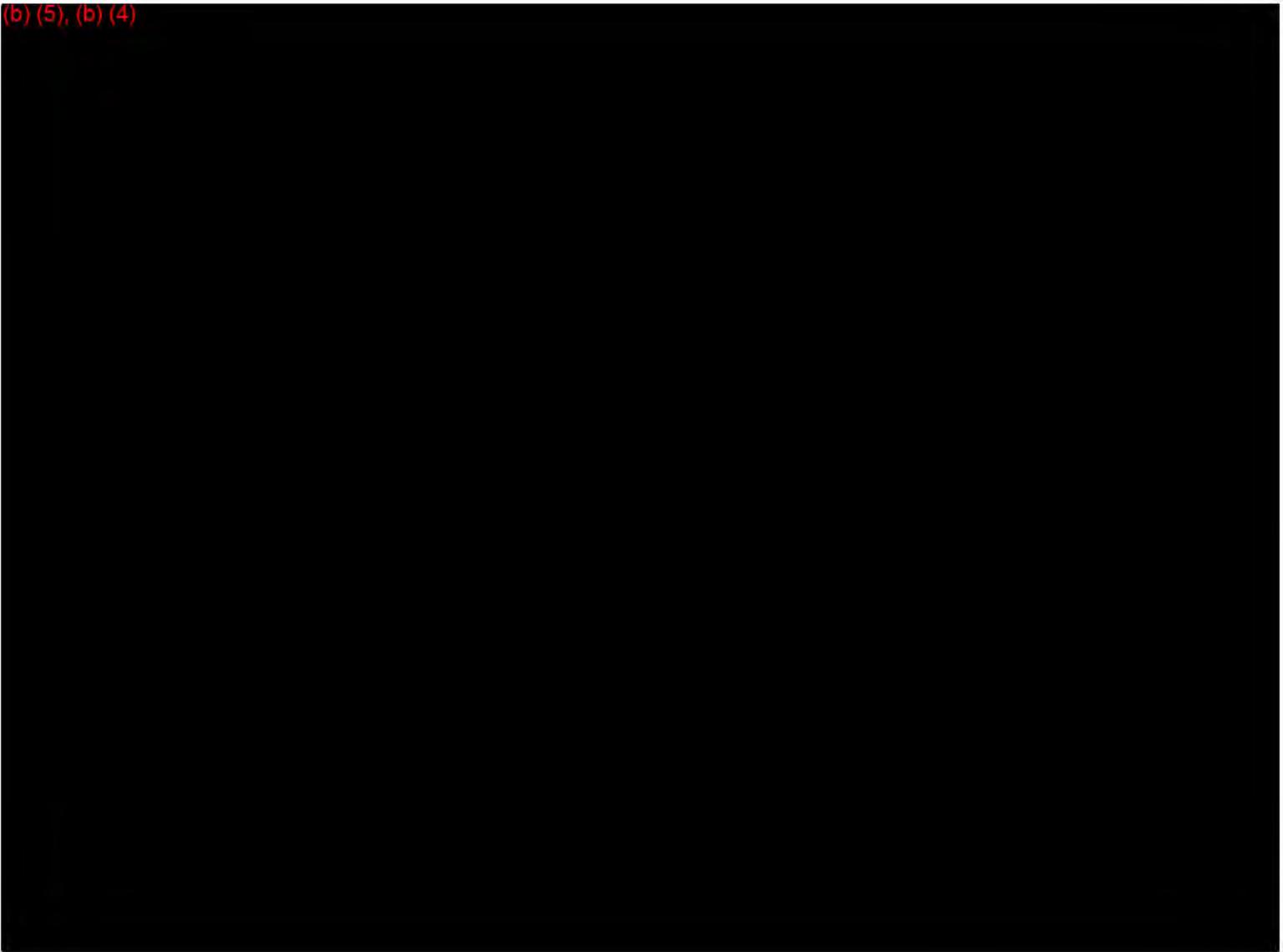
Good afternoon,

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(b) (5), (b) (4)



(b) (5), (b) (4)



50 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

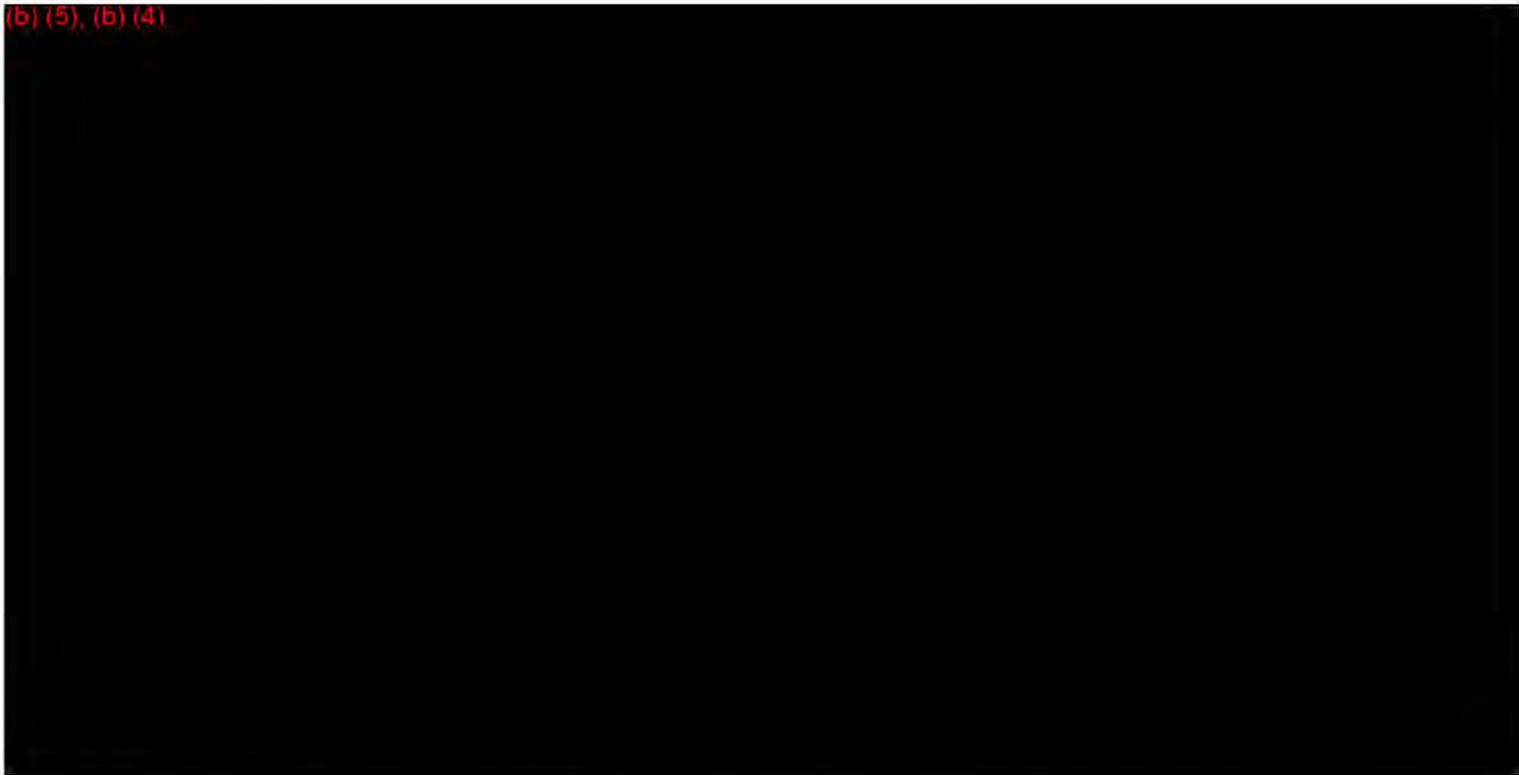
Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, February 11, 2015 4:55 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Marks, Peter; Kraus, Tom; Esposito, Denise; Quinn, Kathleen
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschel, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal, Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #83
Attachments: 83 FDA 2014 Ebola Coordination Situation Report 2015-2-11.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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47 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Garza, Anthony
Sent: Monday, January 05, 2015 3:56 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Drew, Carol E; Garza, Anthony
Subject: FDA 2014/2015 Ebola Coordination Situation Report #68
Attachments: 68 FDA 2014 Ebola Coordination Situation Report 2015-1-5.docx

Good afternoon,

Please find attached today's FDA 2014/2015 Ebola Coordination Situation Report which contains no new information. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

1) There are no new updates for January 5, 2015.

42 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

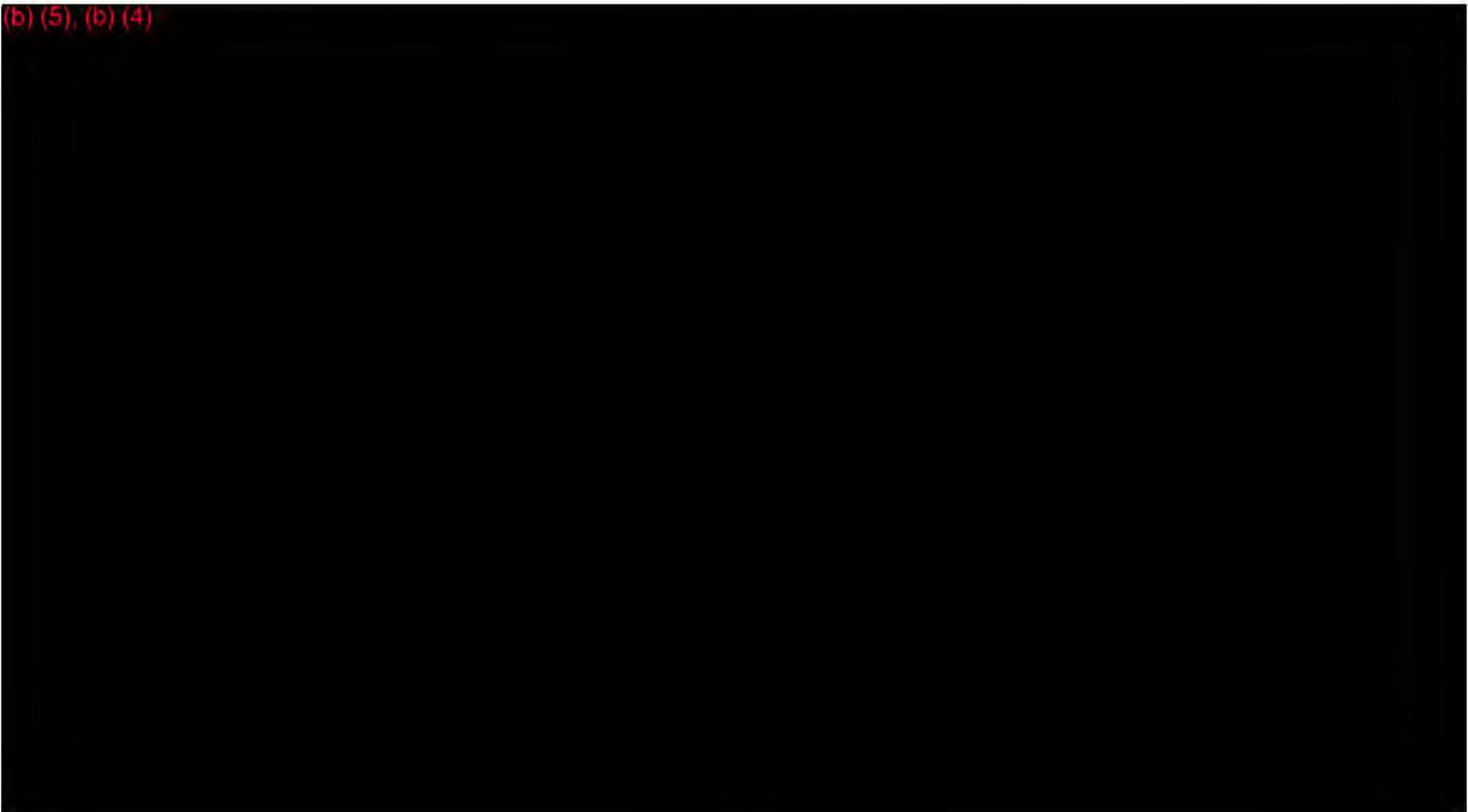
Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, December 24, 2014 1:46 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Garza, Anthony; Drew, Carol E
Subject: FDA 2014 Ebola Coordination Situation Report #65
Attachments: 65 FDA 2014 Ebola Coordination Situation Report 2014-12-24.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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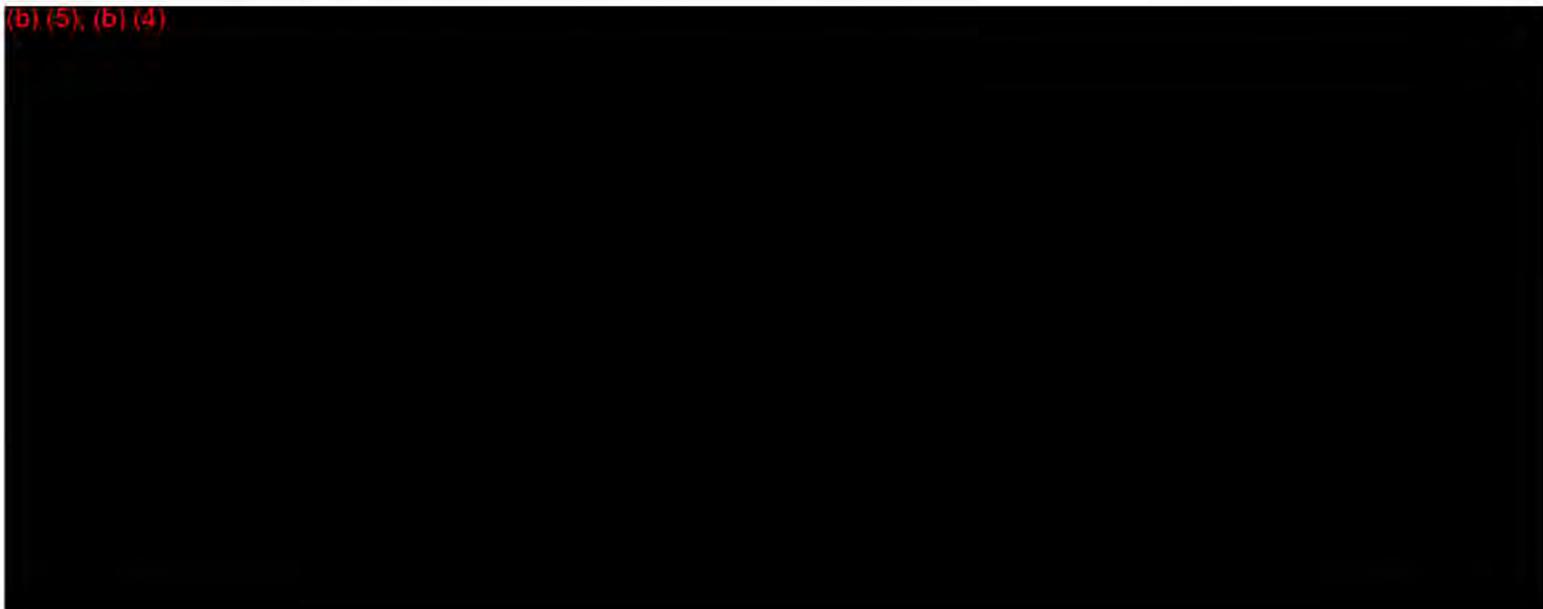
Smith, Celeste

From: Garza, Anthony
Sent: Monday, December 08, 2014 4:23 PM
To: Hamburg, Margaret; Borio, Luciana; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Jefferson, Erica; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Garza, Anthony
Subject: RE: FDA 2014 Ebola Coordination Situation Report #58
Attachments: 58 FDA 2014 Ebola Coordination Situation Report 2014-12-08.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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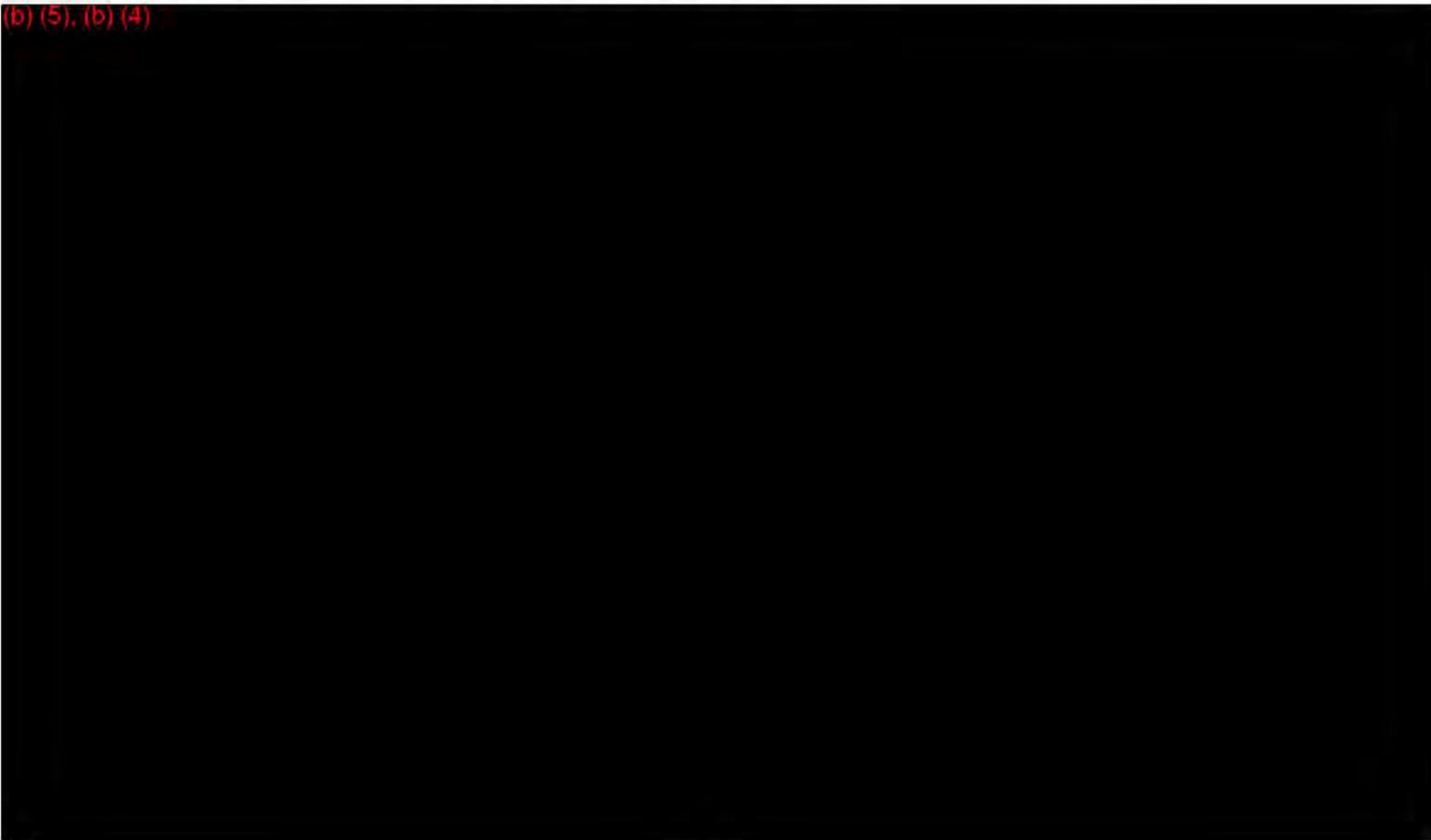
Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, November 26, 2014 3:36 PM
To: Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom; Esposito, Denise
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Jefferson, Erica; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Fisher, Robert; Finnen, April; Segal (Reisman), Melissa; Zink, Donald; Mair, Michael; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #54
Attachments: 54 FDA 2014 Ebola Coordination Situation Report 2014-11-26.docx

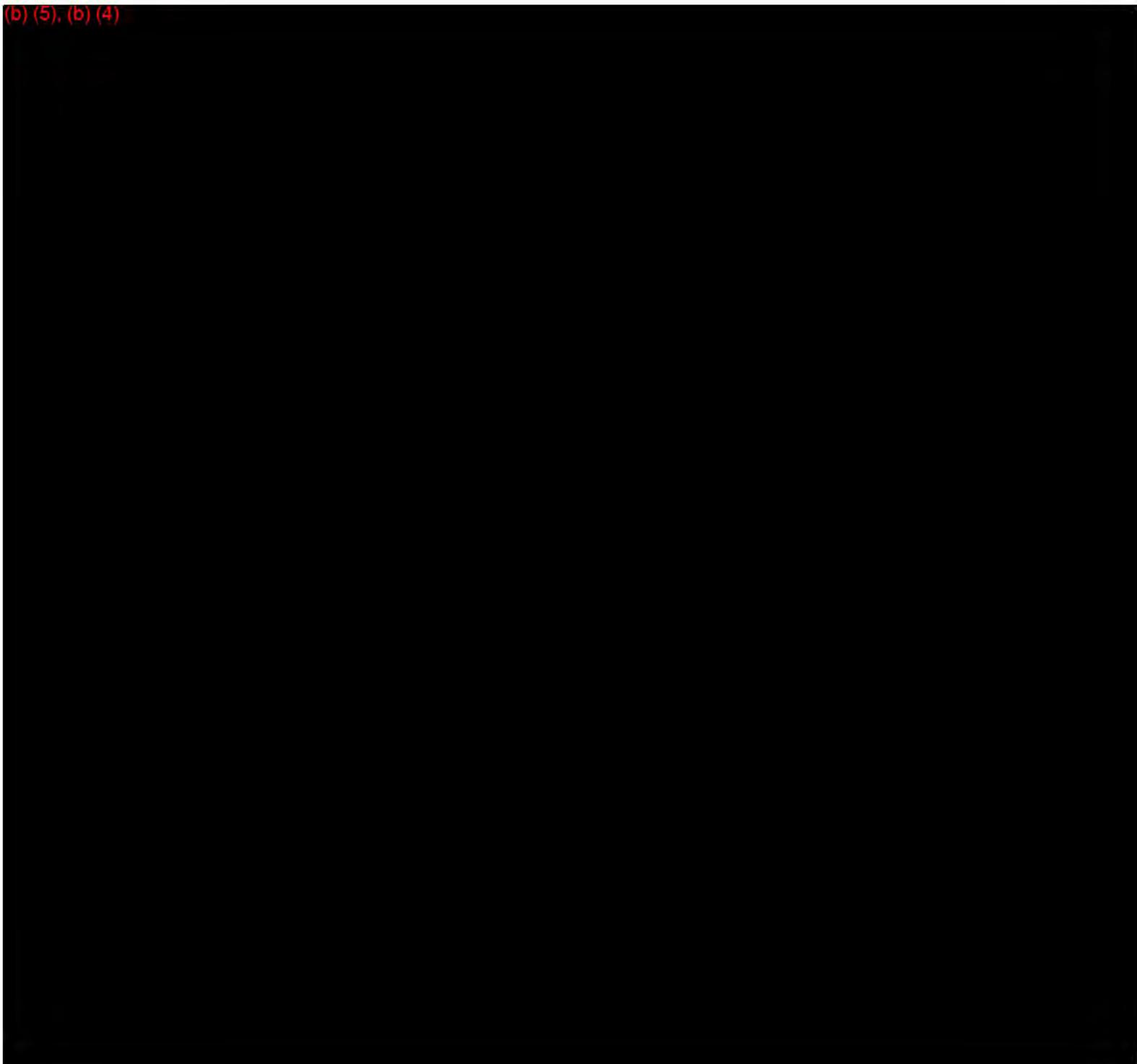
Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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Smith, Celeste

From: Garza, Anthony
Sent: Monday, September 29, 2014 5:04 PM
To: Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Jefferson, Erica; Vining, Elaine; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Hu-Primmer, Jean; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA); Mair, Michael; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #30
Attachments: 30 FDA 2014 Ebola Coordination Situation Report 2014-09-29.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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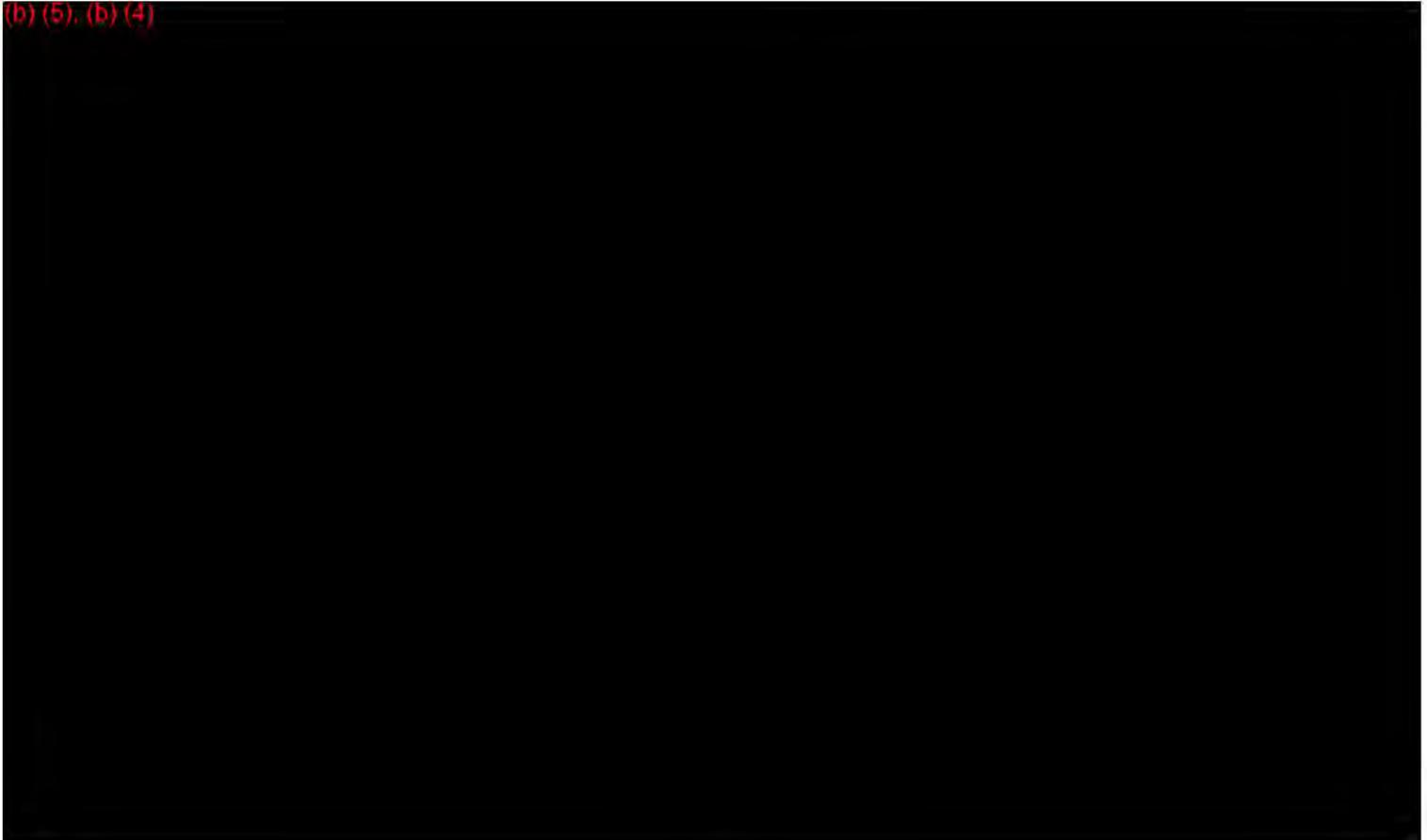
Smith, Celeste

From: Mair, Michael
Sent: Monday, September 15, 2014 4:51 PM
To: Garza, Anthony; Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Jefferson, Erica; Vining, Elaine; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Hu-Primmer, Jean; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA)
Subject: FDA 2014 Ebola Coordination Situation Report #24
Attachments: 24 FDA 2014 Ebola Coordination Situation Report 2014-09-15.docx

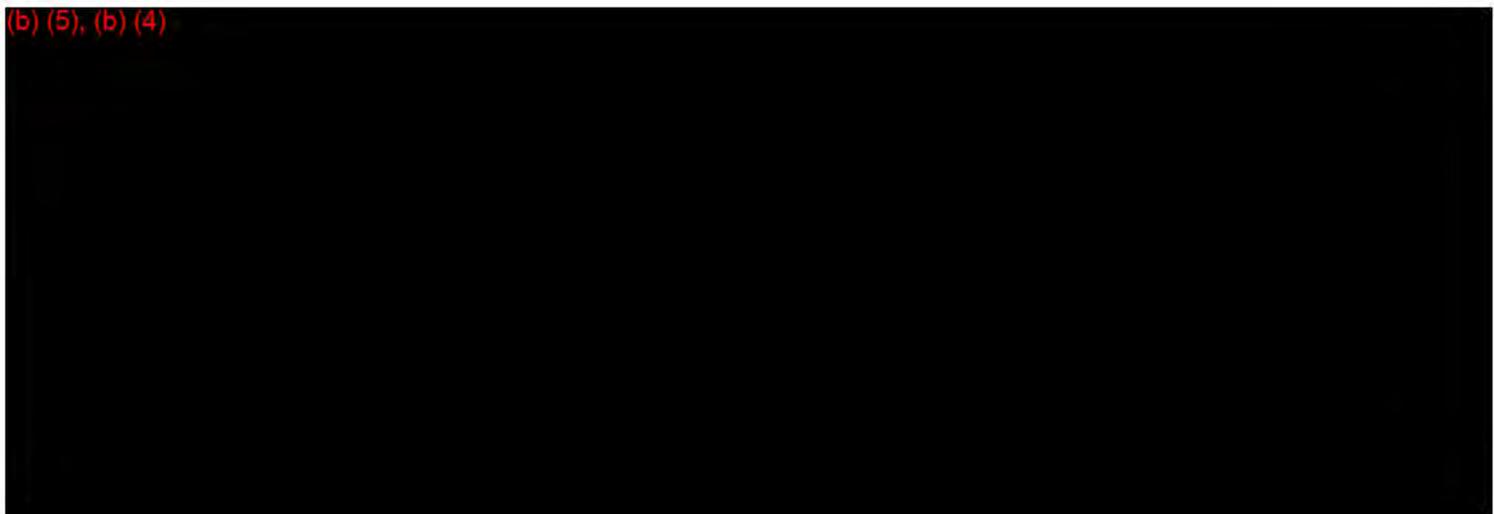
Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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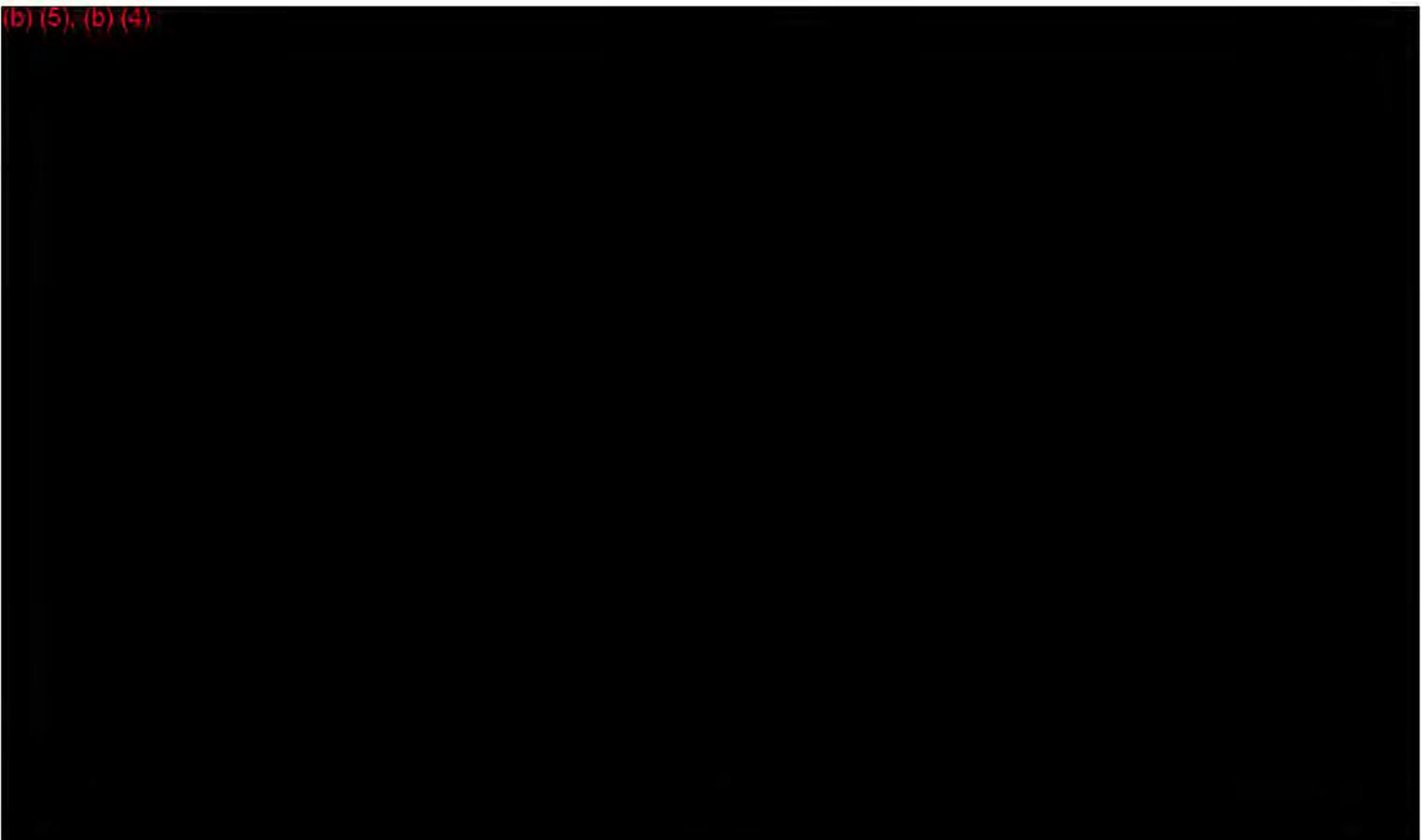
Smith, Celeste

From: Mair, Michael
Sent: Friday, September 12, 2014 5:50 PM
To: Garza, Anthony; Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midhun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Jefferson, Erica; Vining, Elaine; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Hu-Primmer, Jean; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Bull, Jonca; Johnson, Elise (FDA)
Subject: FDA 2014 Ebola Coordination Situation Report #23
Attachments: 23 FDA 2014 Ebola Coordination Situation Report 2014-09-12.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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13 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

From: Hamburg, Margaret
Sent: Tuesday, September 02, 2014 7:37 AM
To: Pennington, Caitlin
Subject: Fw: Useful information: WHO Consultation on potential Ebola therapies and vaccines, 4-5 September, Starling Hotel Geneva
Attachments: Agenda_Consultation_potential_Ebola_therapies_4-5 September_WHO_web.docx;
LOP_Consultation_potential_Ebola_therapies_4-5 September_WHO_web.docx

Print

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

From: Borio, Luciana
Sent: Monday, September 01, 2014 08:44 PM
To: Hamburg, Margaret
Cc: Barclay, Lisa
Subject: FW: Useful information: WHO Consultation on potential Ebola therapies and vaccines, 4-5 September, Starling Hotel Geneva

FYI. Lot's of people...

From: SPARROW, Erin Grace [<mailto:sparrowe@who.int>]
Sent: Monday, September 01, 2014 4:11 PM
Cc: ebola2014archive
Subject: Useful information: WHO Consultation on potential Ebola therapies and vaccines, 4-5 September, Starling Hotel Geneva

Dear All,

Please find attached the latest agenda and list of participants for the upcoming meeting on 4-5 September 2014.

Please be reminded that the meeting will take place at the Starling Hotel in Geneva, Route François-Peyrot 34, 1218 le Grand-Saconnex, Geneva (<http://www.shgeneva.com/>). When traveling to and from the airport, the hotel offers a free complimentary limousine service every 15 minutes. For those of you coming from abroad, the hotel will offer you a free transport card for the duration of your stay which can be used on all public transport in the Geneva area.

Soon, we will be sharing some background documents with you in advance of the meeting (also available in hardcopy during registration). In addition, we will be sending you a short questionnaire to be completed and handed in at the meeting.

The meeting room at the Starling Hotel is called "Montana" and registration will start outside this room from 08:00 on Thursday morning, the meeting will begin promptly at 09:00.

Please do not hesitate to contact me should you require further information.

Many thanks,
Erin
Ms Erin Sparrow
Technical Officer

Technology Transfer Initiative (TTi)
Public Health Innovation and Intellectual Property (PHI)
Department of Essential Medicines and Health Products (EMP)
World Health Organization
Office 3032, Avenue Appia 20, 1211 Geneva, Switzerland
Email: sparrowe@who.int | Tel: +41 22 791 12 38 | Fax: +41 22 791 49 09
www.who.int/phi/programme_technology_transfer

**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel**

Background:

In response to the outbreak of Ebola in West Africa, on 11 August 2014, WHO convened a panel of medical ethicists, scientific experts, and lay people from the affected countries to consider and assess the ethical implications for clinical decision-making of the potential use of unapproved interventions. In the particular circumstances of this outbreak, and provided certain conditions are met, the panel reached consensus that it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention.

Purpose:

This meeting is being organized to discuss lead experimental treatments and vaccines for Ebola (including potential risks and benefits, availability in the short and long term, potential use and barriers for use) and key considerations for deployment in West Africa, clinical testing, use, ethics, regulation and data collection.

Objectives:

- To discuss needs in West Africa and other countries
- To discuss information on lead experimental products including:
 - Potential risks and benefits
 - Overview of product development (preclinical studies, clinical studies conducted or planned)
 - Product availability in the short and longer term
 - Considerations for use in different individuals/groups
- To discuss key issues to be taken into considerations for decision making:
 - Deployment issues
 - Regulatory issues
 - Ethical issues
 - Product availability issues
 - Liability issues
 - Financing issues (donation, procurement)
 - Data collection, product evaluation issues and clinical trials where appropriate
 - Communication issues
- To review strategies for deployment

Expected outcomes:

- Accurate information on experimental products disseminated
- Consensus on key issues to take into consideration for decision making
- Data gathering issues and sharing mechanisms identified
- NRAs informed of regulatory status of products and contacts made between countries and manufacturers

**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

Draft Agenda

Rapporteur: David Fitzsimons

Thursday 4 September

08:00-09:00 ***Registration***

Session Chair: Anarfi Asamoah-Baah

09:00-09:15 Welcome, objectives of meeting, expected outcomes, Marie-Paule Kieny

09:15-09:45 General introduction/background to Ebola epidemic etc., Sylvie Briand

09:45-10:15 Presentation by Ebola expert, Amadou Sall

10:15-10:45 ***Coffee***

10:45-12:30 Country perspectives

- Sierra Leone, (TBD)
- Nigeria, Abdulsalami Nasidi
- Canada, Theresa Tam
- Switzerland, Daniel Koch
- Other (TBD)

12:30-14:00 ***Lunch***

14:00-15:30 Presentation on overview of lead experimental products and product specific considerations, Michael Kurilla

- Immunoglobulins
- Immune modulators
- Small molecule drugs
- Vaccines

15:30-16:00 ***Coffee***

Session Chair: Marie-Paule Kieny

16:00-16:30 Presentations of key considerations for decision makers, Fred Hayden

16:30-17:30 Overview of ethical issues for consideration and presentation of ethical frameworks, Oyewale Tomori

17:30-18:00 Discussion

18:00-18:15 Wrap up of day 1

18:30 ***Cocktail reception***



**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

Friday 5 September

Session Chair: Oyewale Tomori

09:00-09:30 Overview of regulatory issues for consideration, Helen Byomire Ndagije

09:30-10:00 Discussion

10:00-10:30 Overview of practical issues for consideration, Armand Sprecher

10:30-11:00 Discussion

11:00-11:30 *Coffee*

11:30-12:00 Overview of issues for risk mitigation and management, Ambrose Isah

12:00-12:30 Discussion

12:30-14:00 *Lunch*

Session Chair: Jeremy Farrar

14:00-15:30 Structured discussion

1. *What should be the overall OBJECTIVES of a plan for the evaluation and use of potential interventions (therapies and vaccines)?*
2. *What are the most important ACTIONS to ensure successful evaluation and use (if appropriate) of any of potential interventions (therapies and vaccines)?*
3. *What kind of SUPPORT is required to ensure proposed plans for the evaluation and use of potential interventions (therapies and vaccines) are successfully implemented?*

15:30-16:00 *Coffee*

16:00-16:30 Preparedness for prophylaxis and therapeutics for future epidemics

16:30-17:00 Wrap up, next steps, meeting closure

**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel**

List of participants:

1. Dr Marylyn Addo, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
2. Dr Clement Adebamowo, Chairman, National Health Research Ethics Committee of Nigeria, Federal Ministry of Health of Nigeria, Abuja, Nigeria
3. Dr Selidji Agnandji, Gabon
4. Dr Umberto d'Alessandro Director, MRC Laboratories, The Gambia
5. Dr Enrica Alteri, Head of Safety and Efficacy of Medicines, Human Medicines Development and Evaluation Unit, European Medicines Agency, United Kingdom
6. Dr Sylvain Baize, Biology of viral Emerging Infections, Institute Pasteur, France
7. Dr Younoussa Ballo, Secrétaire général du Ministère de la Santé, Guinea
8. Dr Ripley Ballou, GlaxoSmithKline Biologicals SA, Rixensart, Belgium
9. Ms. Helia Baradarani, Tekmira's Manager of Medical Countermeasure Business Development
10. Dr Jarbas Barbosa, Vice Minister, Ministry of Health Brazil
11. Dr Daniel Bausch, Associate Professor, Department of Tropical Medicine, Tulane University School of Public Health and Tropical Medicine, New Orleans, USA
12. Dr Sina Bavari, CIV USARMY MEDCOM USAMRIID, USA
13. Dr Stephan Becker, Direktor, Institut für Virologie, Marburg, Germany
14. Dr Fred Binka, Vice Chancellor of the University of Health and Allied Sciences, Ho, Ghana
15. Dr Fatorma Bolay, Director of the Liberia Institute for Biomedical Research, Liberia
16. Dr Luciana Borio, Director of the Office of Counterterrorism and Emerging Threats (OCET) in the Office of the Chief Scientist, U.S. Food and Drug Administration (FDA), USA
17. Dr Abdullah Brooks, Centre for Health and Population Research, Dhaka, Bangladesh
18. Dr Philippe Calain, Unité de Recherche sur les Enjeux et Pratiques Humanitaires (UREPH), Médecins Sans Frontières, Geneva, Switzerland



**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

19. Dr Michael Callahan, Command Physician, Rescue Medicine/Réseau Médical Patient Filovirus, Kinsasha, Harvard Medical School, Massachusetts General Hospital, Boston,, USA
20. Dr Benoit Callendret, Crucell, The Netherlands
21. Dr Iris Chang, Hong Kong Academy of Pharmacy, Hong Kong
22. Dr George Christopher, Chief Medical Officer, Joint Project Manager – Medical Countermeasure Systems, Department of Defense
23. Dr Supamit Chunsuttiwat, Ministry of Health, Thailand
24. Dr Jacob Cohn, Bavarian-Nordic, Denmark
25. Dr Christoph Conrad, Paul-Ehrlich-Institut, Germany
26. Mr Stephan Cook, Vice President, Vaccine Global Regulatory Affairs, Vaccine Value & Health Science, GlaxoSmithKline Biologicals SA, Rixensart, Belgium
27. Dr Marion Danis, Head, Sect. on Ethics & Health Policy (NIH), USA
28. Prof Jean-François Delfraissy,, Director of Agence nationale de recherche (ANRS), France
29. Dr Antal Tal Dia, NITAG Senegal chairman, Senegal
30. Dr Alpha Amadou Diallo, rapporteur du Comité national d’Ethique et de recherche en Santé, Guinea
31. Dr Mireille Dosso, Directrice de l'IP de Cote d'Ivoire
32. Pr Ousmane Doumbia, Secrétaire Général du Ministère de la Santé et del'Hygiène Publique, Mali
33. Dr Karifa Douno, Chef de la Division Etablissements Biopharmaceutiques, Ministère de la Santé, Guinea
34. Dr Mattias Egger, Professor of Epidemiology and Public Health, University of Bern, Switzerland
35. Dr Lindsay Elmgren, Director, Centre for Biologics Evaluation, Biologics and Genetic Therapies Directorate, Health Canada, Canada
36. Dr Carol Epstein, MediVector, Inc. Fujifilm Pharmaceuticals USA, Inc., Boston, USA
37. Dr Jeremy Farrar, Director, Wellcome Trust, UK
38. Dr Patricia Fast, International AIDS Vaccine Initiative, New York, USA



**World Health
Organization**

Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana

39. Dr Eleanor Fish, University of Toronto, Canada
40. Mr David Fitzsimmons, Meeting Rapporteur
41. Prof. Fu Gao, Deputy Director General for sciences, China CDC, China
42. Jennifer Gibson, Director, Joint Centre for Bioethics, Director, World Health Organization Collaborating Centre for Bioethics, Associate Professor, Institute of Health Policy, Management & Evaluation, University of Toronto, Canada
43. Dr Jesse Goodman, George Town University, USA
44. Dr Dennis Giesing, MediVector, Inc. Fujifilm Pharmaceuticals USA, Inc., Boston, USA
45. Dr Barney Graham, Vaccine Research Centre, NIAID, NIH, USA
46. Dr Nyankoye Haba, National Blood Service, Guinea
47. Dr Fred Hayden, University of Virginia/WHO consultant, USA
48. Dr Lisa Hensley, NIH NIAID, USA
49. Dr Elizabeth Higgs, Global Health Science Advisor, Office of the Director, Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, USA
50. Dr David Hone, Chief, Vaccine Branch, Research and Development Directorate (J9), Defense Threat Reduction Agency DTRA, DoD, USA
51. Dr Johan van Hoof, Crucell, The Netherlands
52. Dr Peter Horby, University of Oxford, UK
53. Dr Ryuichi Ida, Member of the Expert Panel on Bioethics (National Bioethics Committee), Japan
54. Dr Giuseppe Ippolito, Scientific Director, National Institute for, Infectious Diseases Lazzaro Spallanzani, Rome, Italy
55. Dr Ambrose Isah, GACVS representative, Nigeria
56. Dr Aikichi Iwamoto, The Institute of Medical Sciences, Research Center for Asian Infectious Diseases, Japan
57. Dr Amandua Jacinto, Commissioner Clinical Services, Ministry of Health, Uganda
58. Mr Wiltshire Johnson, Registrar, Pharmacy Board, Sierra Leone



**World Health
Organization**

**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

59. Dr Franca Jones, Medical Director, Chemical and Biological Defense Program Office of the Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs OASD(NCB/CB) Washington, DC, USA
60. Dr Markieu Jenneh-Kaira, Chief Pharmacist/ Registrar, National Pharmaceutical Services, Department of State for Health and Social Welfare, Ministry of Health and Social Welfare, Banjul, Gambia
61. Dr Robinah Kaitiritimba, Uganda National Health Consumers' Organisation (UNHCO), Kampala Uganda
62. Dr Francis N. Kateh, Medical Director / CEO, Jackson F. Doe Memorial Regional Referral Hospital, Tappita City, Lower Nimba County, Liberia
63. Dr Samuel Kargbo, Director, Reproductive and Child Health, Ministry of Health Sierra Leone
64. Dr Christopher Karp, Deputy Director, Discovery & Translational Sciences, Bill & Melinda Gates Foundation, Seattle, USA
65. Dr Steve Kern, Deputy Director, Integrated Development, Bill & Melinda Gates Foundation, Seattle, USA
66. Dr Nadia Khelef, Institut Pasteur, France
67. Dr Gary Kobinger, Public Health Agency of Canada
68. Dr Daniel Koch, Federal Office of Public Health, Bern, Switzerland
69. Dr Kader Kondé, Prèsident de la Commission Recherche Ébola, Guinée
70. Dr Bocar Kouyate, Office of the Minister of Health, Ministry of Health, Ouagadougou, Burkina Faso
71. Dr Sanjeev Krishna, London, UK
72. Dr Michael Kurilla, Director, Office of BioDefense, Research Resources, and Translational Research, Associate Director for BioDefense Product Development, DMID, NIAID, NIH, DHHS, Rockville, USA
73. Dr Randall Lanier, Executive Director of Biology, Chimerix Inc. Durham, USA
74. Dr James Lawler, Director, ACESO / clinical research partner in Uganda
75. Dr Robert Lenk, MediVector, Inc. Fujifilm Pharmaceuticals USA, Inc., Boston, USA



**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

76. Dr Bertand Lepine, FabEntech, Lyon, France
77. Dr Mike Levine, Director, Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, USA
78. Dr Nicole Lurie, Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS), USA
79. Dr Ian MacLachlan, Executive Vice President & Chief Technical Officer, Tekmira Pharmaceuticals Corp., Canada
80. Dr Alan Magill, Director, Malaria, Bill & Melinda Gates Foundation, Seattle, USA
81. Prof. Denis Malvy, Proffesor in Infectious Diseases, France
82. Dr Brian K. Martin, Director, Infectious Disease Division, BioProtection Systems, a wholly-owned subsidiary of NewLink Genetics, Ames, USA
83. Dr Jacques-François Martin, Fab Entech, Lyon, France
84. Dr Eric Mast, CDC Deputy Director Science and Research, USA
85. Dr Gisele Mbuyi, Department of Disease Control, Ministry of Health, DRC
86. Dr Jeffrey N. Meshulam, President, Profectus BioSciences, Inc., USA
87. Dr Philip Minor, NIBSC, UK
88. Ms Viviana Munoz, Manager of the Innovation and Access to Knowledge Programme at the South Centre, Geneva, Switzerland
89. Prof. Jean-Jacques Muyembe, National Institute for Biological Research, DRC
90. Dr Abdulsalami Nasidi, CDC Nigeria
91. Dr Helen Byomire Ndagije, Head of the Drug Information Department in the Ugandan National Drug Authority (NDA), Uganda
92. Dr Mariane Ngoulla, Special Adviser on Health to ECOWAS President, Nigeria
93. Dr Sérgio Nishioka, clinical expert, Brazil
94. Prof. Cheikh Niang, Anthropologist, Cheikh Anta Diop University, Senegal

**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

95. Dr Dieudonné Nkoghe, Ministère de la Santé Publique, Centre International de Recherches Médicales de Franceville, Gabon
96. Dr Jeanne Novak, Principal, CBR International, Mapp Biopharmaceutical, Inc., USA
97. Dr Jean-Marc Olive, Scientific Researcher, French National Centre for Scientific Research, France
98. Dr Paul Orhii, Director General, NAFDAC, Nigeria
99. Dr Olga Popova, Crucell, The Netherlands
100. Prof. Peyramond , de l'hôpital de la Croix Rouse, Lyon, France
101. Dr W. Jay Ramsey, Clinical & Regulatory Compliance Officer, NewLink Genetics, Ames, USA
102. Dr Robin Robinson, Director of BARDA, US Department of Health and Human Services, USA
103. Dr Francois Roman, GSK
104. Dr Robin Ruepp, EMA
105. Dr Leonard Ruiz, International Medical Foundation
106. Dr Amadou Sall, Institut Pasteur, Dakar, Senegal
107. Dr Mohamed Samai, Deputy Director for Research, MOH, Sierra Leone
108. Dr Sangeeta Sashikant, Third World Network, Geneva, WHO
109. Dr Manuel Schilber, HUG, Geneva, Switzerland
110. Dr Michael Schmoyer, Director, Office of Pandemics and Emerging Threats, Office of Global Affairs–International Health Action for a Healthier US, U.S. Department of Health & Human Services, USA
111. Dr Jürg Seiler, toxicologist/assessor, Switzerland
112. Dr Michael Selgelid, Director of the Centre for Human Bioethics, Monash University, Australia
113. Ms Caroline Semaille, directeur des médicaments anti-infectieux, hépato-gastroentérologie, dermatologie, et maladies métaboliques rares from agence nationale de sécurité des médicaments, France
114. Dr Moussa Seydi, Professor and chief of SMIT, Senegal



**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

115. Dr William P. Sheridan, Senior Vice President and Chief Medical Officer, BioCryst Pharmaceuticals Inc. USA
116. Peter Smith, Professor of Tropical Epidemiology, London School of Tropical Medicine and Hygiene, UK
117. Dr Martin De Smet, Médecins sans Frontières, Brussels, Belgium
118. Dr Malamin Sonko, Chairman The Gambian ERC, The Gambia
119. Dr Kabiné Souaré, Directeur national de la pharmacie et des Laboratoires, Ministère de la Santé, Guinea
120. Dr Samba Sow, Director General, Center for Vaccine Development-Mali (CVD-Mali), CNAM, Bamako, Mali
121. Dr Christina Spiropolou, CDC, USA
122. Dr Armand Sprecher, Médecins sans Frontières, Brussels, Belgium
123. Dr Vernon Stringer, Health Canada, Canada
124. Dr Theresa Tam, Branch Head, Health Security Infrastructure Branch, Public Health Agency of Canada Public Health Agency of Canada
125. Dr Oyewale Tomori, Professor of Virology, Redemer's University, Nigeria
126. Dr Aissatou Toure, Head of Immunology Department, Pasteur Institute, Dakar, Senegal
127. Prof. Mamadou Souncalo Traore, Directeur Général de l'Institut national de recherche en santé publique, Mali
128. Dr Ross Upshur, Director, Joint Centre for Bioethics, University of Toronto, Canada
129. Ms Laurent Vacher, Responsable R&D et Business Development, Fab Entech, Lyon, France
130. Francisca Valdivieso, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Santiago, Chile
131. Dr Johan van Griensven, Clinical Sciences Department, Institute of Tropical Medicine, Antwerp, Belgium
132. Dr Ariane Volkman, Ebola vaccine program, Bavarian Nordic, Denmark
133. Dr Jay Wang, Program Manager, Emerging Infectious Diseases Therapeutics, Joint Project Manager – Medical Countermeasure Systems, Department of Defense, USA

**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

134. Dr Linghang Wang, Beijing Ditan Hospital, China
135. Dr John Whitehead, Lancaster, UK
136. Dr Christopher Whitty, Director Research & Evidence and Chief Scientific Adviser, DFID, UK
137. Dr Michael Wong, Sarepta, USA
138. Dr Tom Wong, Director, Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada, Ottawa, Canada
139. Kacey Wulff, Special Assistant to the Assistant Secretary of Preparedness and Response, US Department of Health and Human Services, USA
140. Dr Larry Zeitlin, President, Mapp Biopharmaceutical, Inc, USA

WHO Secretariat

141. Dr Dicky Akanmori, Technical Officer, AF/RIN - Routine Immunization and New Vaccines, WHO AFRO, Brazzaville, The Republic of Congo
142. Dr Bruce Aylward, Assistant Director General, Polio, Emergencies and Country Collaboration (PEC), Geneva, Switzerland
143. Dr Anarfi Asamoah-Baah, Deputy Director, Geneva, Switzerland
144. Mr Christopher Bailey, Coordinator, Online Communications, DCO, Geneva, Switzerland
145. Dr Marie Charlotte Bouesseau, Service Delivery and Safety, Geneva, Switzerland
146. Dr David Brett-Major, Global Preparedness, Surveillance and Response, Geneva, Switzerland
147. Dr Sylvie Briand, Director, Pandemic and Epidemic Diseases, Geneva, Switzerland
148. Dr Margaret Chan, Director General, Geneva, Switzerland
149. Mr Alejandro Costa, Scientist, Control of Epidemic Diseases, Geneva, Switzerland
150. Dr Caroline Marie Cross, Director, Staff Health & Wellbeing Services, Geneva, Switzerland
151. Dr Philippe Duclos, Immunization, Vaccines and Biologicals, Geneva, Switzerland
152. Dr Thomas Fletcher, Infection Control and Publications, Geneva, Switzerland

**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

153. Dr Pierre Formenty, Scientist, Control of Epidemic Diseases, HSE, Geneva, Switzerland
154. Dr Martin Friede, Scientist, Essential Medicines and Health Products, HIS, Geneva, Switzerland
155. Dr Keji Fukuda, Assistant Director General, Health Security and Environment (HSE), Geneva Switzerland
156. Dr Gaya Gamhewage, Coordinator, Communication Capacity Building, DCO, Geneva Switzerland
157. Mr Theo Grace, Technical Officer, Essential Medicines and Health Products, HIS, Geneva, Switzerland
158. Ms Marisol Guraiib, Technical Officer, Global Health Ethics, Geneva, Switzerland
159. Ms Celine Gurry, Global Preparedness, Surveillance and Response, Geneva, Switzerland
160. Dr Margaret Harris, DCO, Geneva, Switzerland
161. Dr Ana Maria Henao Restrepo, Technical Officer, Immunization, Vaccines and Biologicals, Geneva, Switzerland
162. Dr Marie-Paule Kieny, Assistant Director General, Health Systems and Innovation (HIS), Geneva Switzerland
163. Dr Rüdiger Krech, Director, Office of the Assistant Director-General, Health Systems and Innovation, Geneva, Switzerland
164. Mr Olivier Christian Lapujade, WHO Prequalification, Essential Medicines and Health Products, HIS, Geneva, Switzerland
165. Dr André Loua, Regional Adviser, Blood Safety, Laboratories and Health Technology, WHO AFRO, Brazzaville, Republic of the Congo
166. Dr Nicola Magrini, Scientist, Essential Medicines and Health Products, HIS, Geneva, Switzerland
167. Dr Dermot Maher, Coordinator, TDR, Geneva, Switzerland
168. Mr Issa Matta, Commercial and Contractual Matters, Geneva, Switzerland
169. Ms Anne Mazur, Principal Legal Officer, Commercial and Contractual Matters, Geneva, Switzerland
170. Dr Andrew Meek, WHO Prequalification, Essential Medicines and Health Products, HIS, Geneva, Switzerland
171. Ms Lisa Menning, Technical Officer, Immunization, Vaccines and Biologicals, Geneva, Switzerland



**Consultation on potential Ebola therapies and vaccines
4-5 September 2014
Geneva, Starling Hotel, Room Montana**

172. Dr Vasee Moorthy, Technical Officer, Immunization, Vaccines and Biologicals, Geneva, Switzerland
173. Dr Jean-Marie Okwo-Bele, Direction, Immunization, Vaccines and Biologicals, Geneva, Switzerland
174. Dr Ana Maria Padilla, Essential Medicines and Health Products, HSE, Geneva, Switzerland
175. Dr Shanthi Pal, Group Lead, Medicines Safety, Safety & Vigilance, Geneva, Switzerland
176. Mr James Pfitzer, Technical Officer, Essential Medicines and Health Products, HSE, Geneva, Switzerland
177. Dr Analia Porras, Medicine Unit, PAHO/AMRO, Washington DC, USA
178. Dr Andreas Reis, Technical Officer, Global Health Ethics, Geneva, Switzerland
179. Dr Carmen Rodriguez-Hernandez, WHO Prequalification, Essential Medicines and Health Products, HIS, Geneva, Switzerland
180. Dr Cathy Roth, Advisor, HSE, Geneva, Switzerland
181. Dr Carla Saenz, Bioethics advisor, PAHO/AMRO, Washington DC, USA
182. Dr Abha Saxena, Coordinator, Global Health Ethics, HIS, Geneva, Switzerland
183. Dr Nahoko Shindo, Medical Officer, Health Security and Environment (HSE), Geneva Switzerland
184. Ms Erin Sparrow, Technical Officer, Essential Medicines and Health Products, HIS, Geneva, Switzerland
185. Mr Ludy Suryantoro, External Relations Officer, HSE, Geneva, Switzerland
186. Dr Kirsten Vannice, Technical Officer, Immunization, Vaccines and Biologicals, Geneva, Switzerland
187. Dr David Wood, Coordination, Technologies Standards and Norms, HIS, Geneva, Switzerland
188. Dr Wondiyfraw Worku, WHO Prequalification, Essential Medicines and Health Products, HIS, Geneva, Switzerland
189. Dr Patrick Zuber, Medical Officer, Safety and Vigilance, HIS, Geneva, Switzerland

Smith, Celeste

From: Mair, Michael
Sent: Friday, August 29, 2014 3:19 PM
To: Garza, Anthony; Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Jefferson, Erica; Vining, Elaine; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Hu-Primmer, Jean; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert
Subject: FDA 2014 Ebola Coordination Situation Report #18
Attachments: 18 FDA 2014 Ebola Coordination Situation Report 2014-08-29.docx

Good afternoon,

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

Have a great and safe holiday weekend.

(b) (5), (b) (4)



(b) (5), (b) (4)



10 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

Smith, Celeste

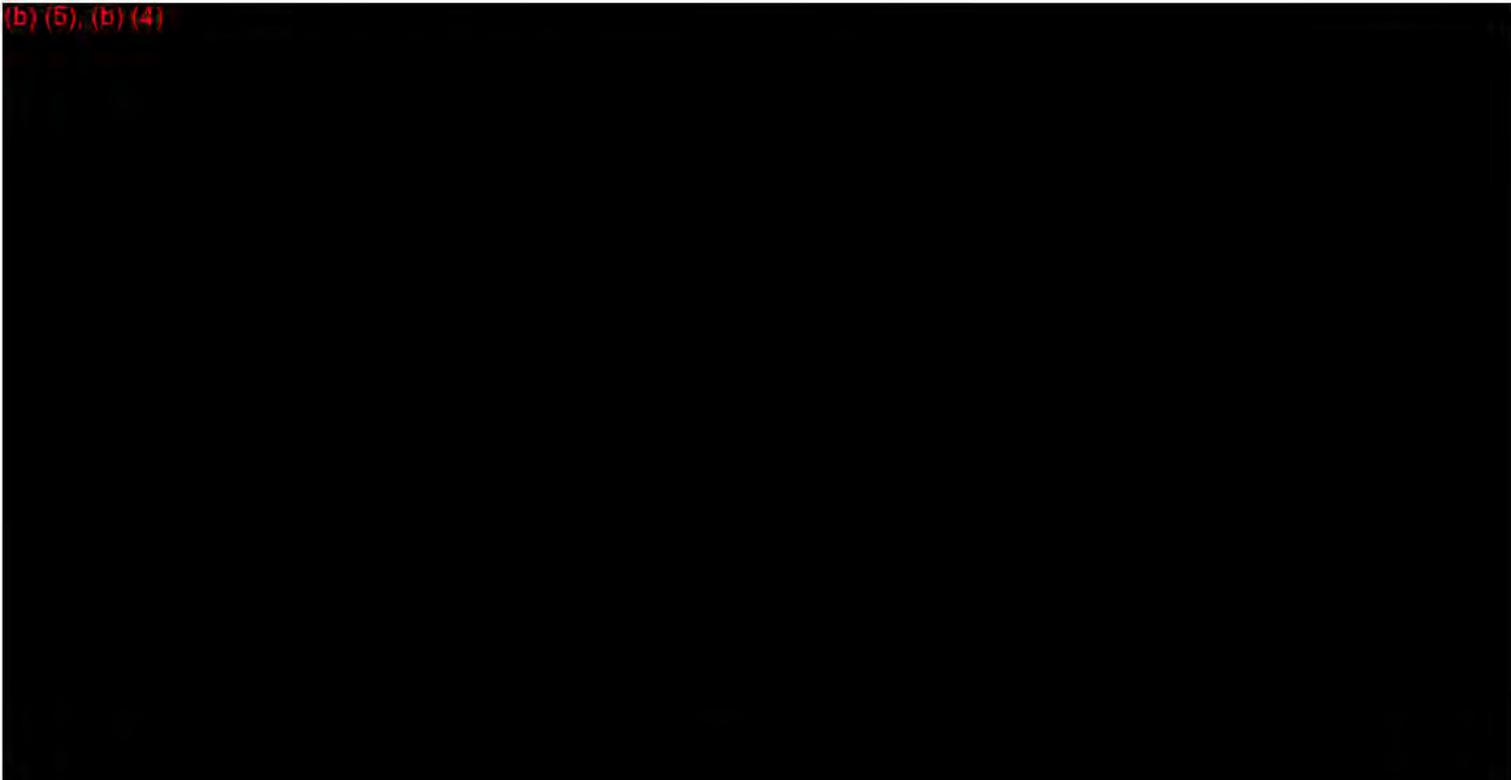
From: Garza, Anthony
Sent: Wednesday, August 27, 2014 5:24 PM
To: Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter; Kraus, Tom
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Jefferson, Erica; Vining, Elaine; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette; Hu-Primmer, Jean; Courtney, Brooke; Sadove, Elizabeth; Raza, Mark; Barth, Abram; Jenkins, John K; Durkin, Robert; Mair, Michael; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #17
Attachments: 17 FDA 2014 Ebola Coordination Situation Report 2014-08-27.docx

Good afternoon,

Starting today, FDA will be moving from a daily Ebola Coordination Situation Report to three times a week (Monday, Wednesday and Friday) reporting.

Please find attached today's FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

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(b) (5), (b) (4)



LCDR Anthony (Tony) Garza, USPHS
SR. Program Manager
Office of Counterterrorism & Emerging Threats (OCET)
Office of the Chief Scientist
Food and Drug Administration (FDA)
Department of Health and Human Services (HHS)
10903 New Hampshire Ave.
WO 1, 4328
Silver Spring, MD 20993
Office: 301-796-8247
BB: 240-620-9293

9 pages have been withheld as b(4) (CCI/TS) and b(5) immediately following this page

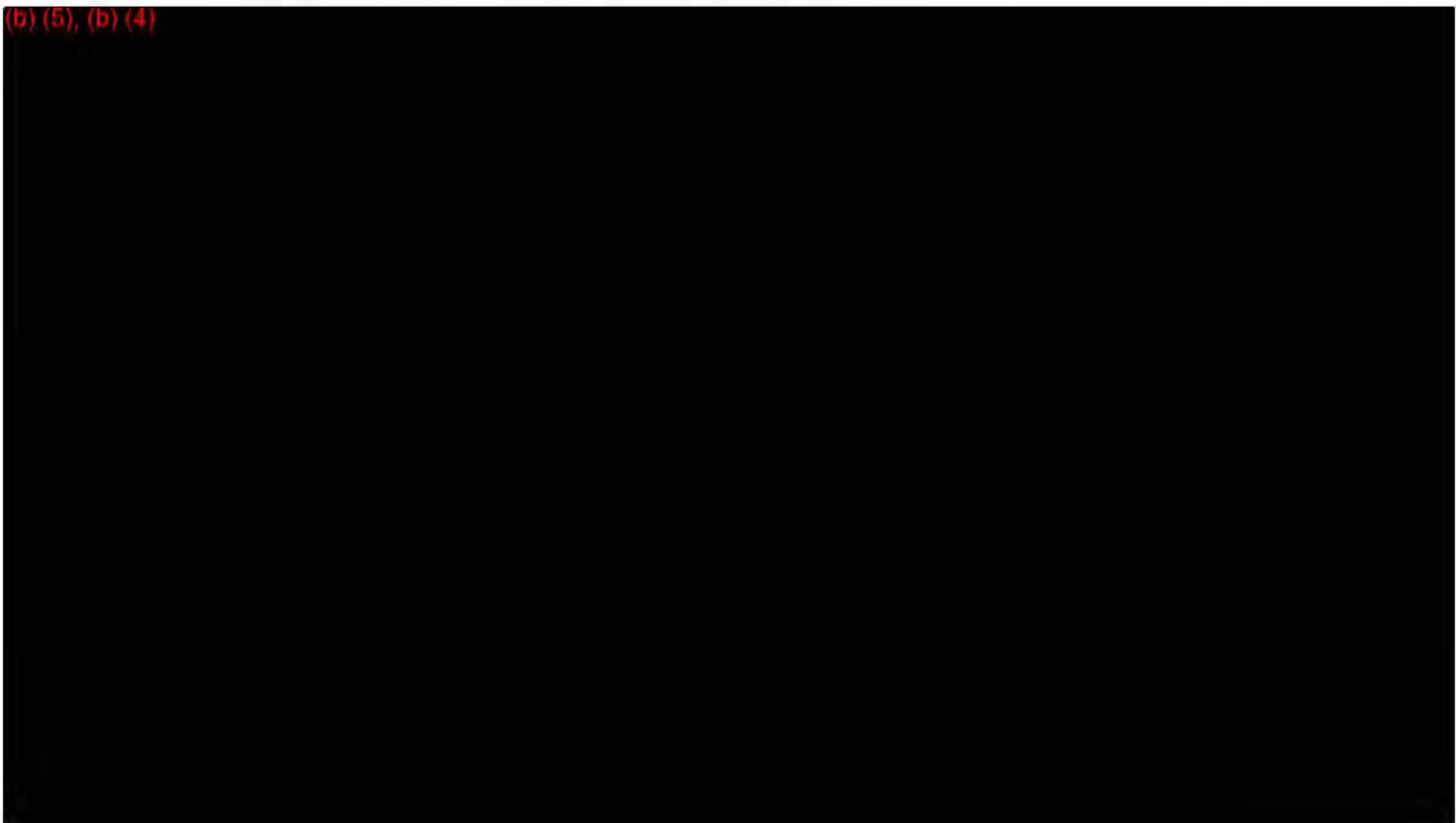
Smith, Celeste

From: Hu-Primmer, Jean
Sent: Tuesday, August 12, 2014 4:30 PM
To: Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Janet.Woodcock; Shuren, Jeff; Russo, Mark; Immergut, Steven; Marks, Peter
Cc: Garza, Anthony; Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Mair, Michael; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henschal, Erik; Jefferson, Erica; Vining, Elaine; Walinsky, Sarah; Stevens, Joy S; Meister, Karen G; Rouse, David; Devore, Nicolette
Subject: FDA 2014 Ebola Coordination Situation Report #07
Attachments: 07 FDA 2014 Ebola Coordination Situation Report 2014-08-12.docx

Good afternoon,

Please find attached the daily FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



Thanks,
Jean

Jean Hu-Primmer

Director, MCMi Regulatory Science
Office of Counterterrorism and Emerging Threats
OCS/OC/FDA
10903 New Hampshire Ave
Silver Spring, MD 20993
voice (direct): 301-796-8511
Blackberry: 240-507-7448
fax: 301-847-8615
jean.hu-primmer@fda.hhs.gov

Website: www.fda.gov/medicalcountermeasures
Twitter: @FDA_MCMi

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for
LCDR Anthony (Tony) Garza, USPHS
SR. Program Manager
Office of Counterterrorism & Emerging Threats (OCET)
Office of the Chief Scientist
Food and Drug Administration (FDA)
Department of Health and Human Services (HHS)
10903 New Hampshire Ave.
WO 1, 4328
Silver Spring, MD 20993
Office: 301-796-8247
BB: 240-620-9293

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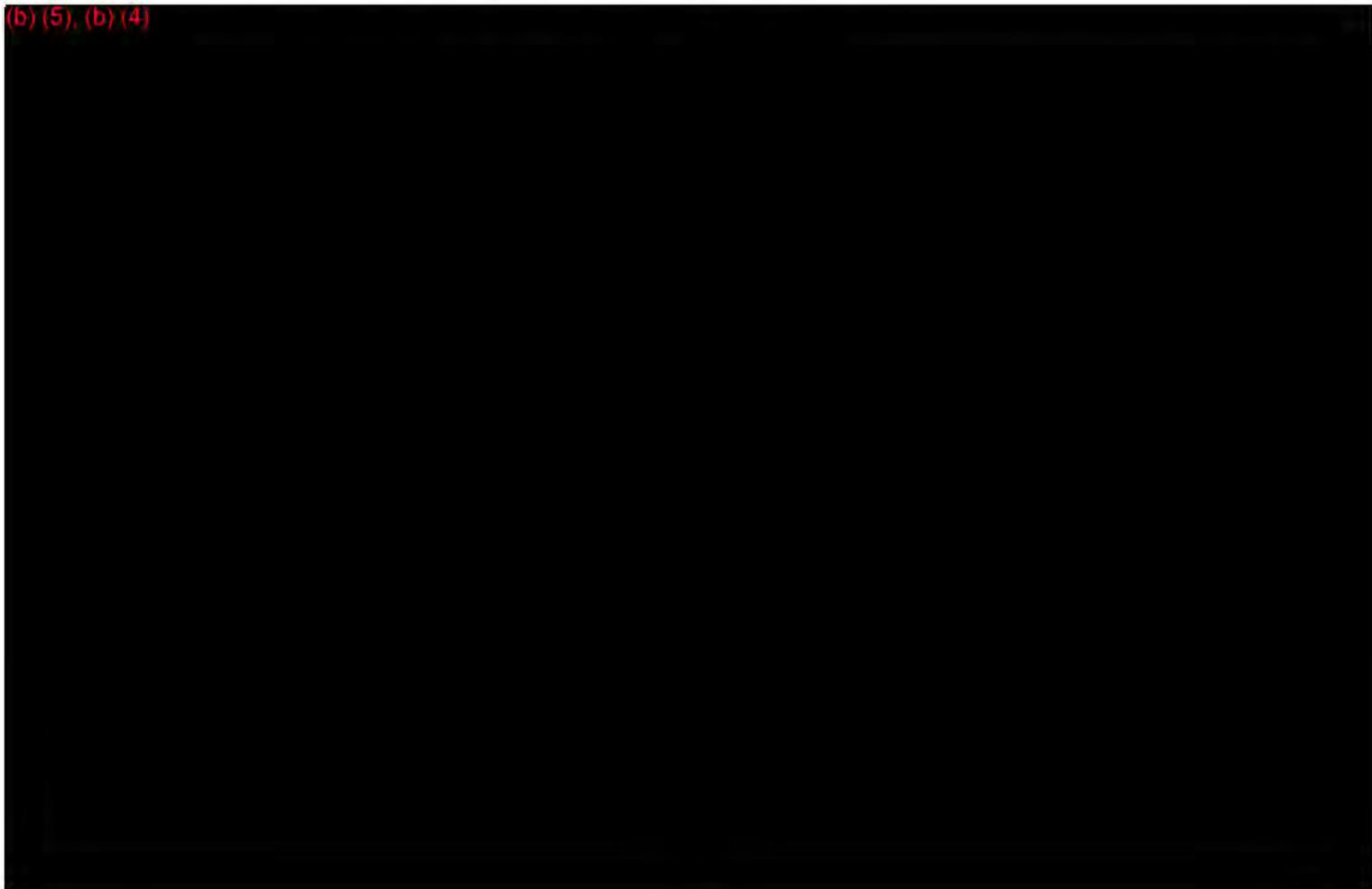
Smith, Celeste

From: Garza, Anthony
Sent: Wednesday, August 06, 2014 4:38 PM
To: Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Hu-Primmer, Jean; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Mair, Michael; Coody, Gary; Perlloni, Andrei; Beers, Donald; Rebello, Heidi; Henchal, Erik; Jefferson, Erica; Garza, Anthony
Subject: FDA 2014 Ebola Coordination Situation Report #03
Attachments: 03 FDA 2014 Ebola Coordination Situation Report 2014-08-06.docx

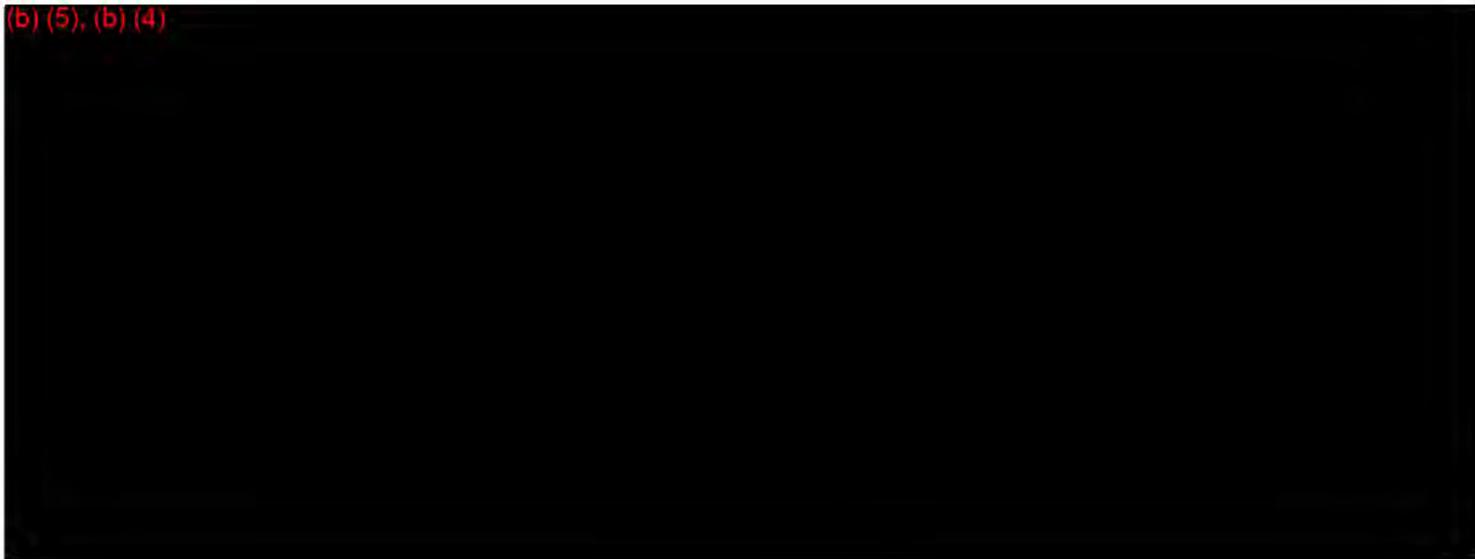
Good afternoon,

Please find attached the daily FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



(b) (5), (b) (4)



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SR. Program Manager
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Office of the Chief Scientist
Food and Drug Administration (FDA)
Department of Health and Human Services (HHS)
10903 New Hampshire Ave.
WO 1, 4328
Silver Spring, MD 20993
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BB: 240-620-9293

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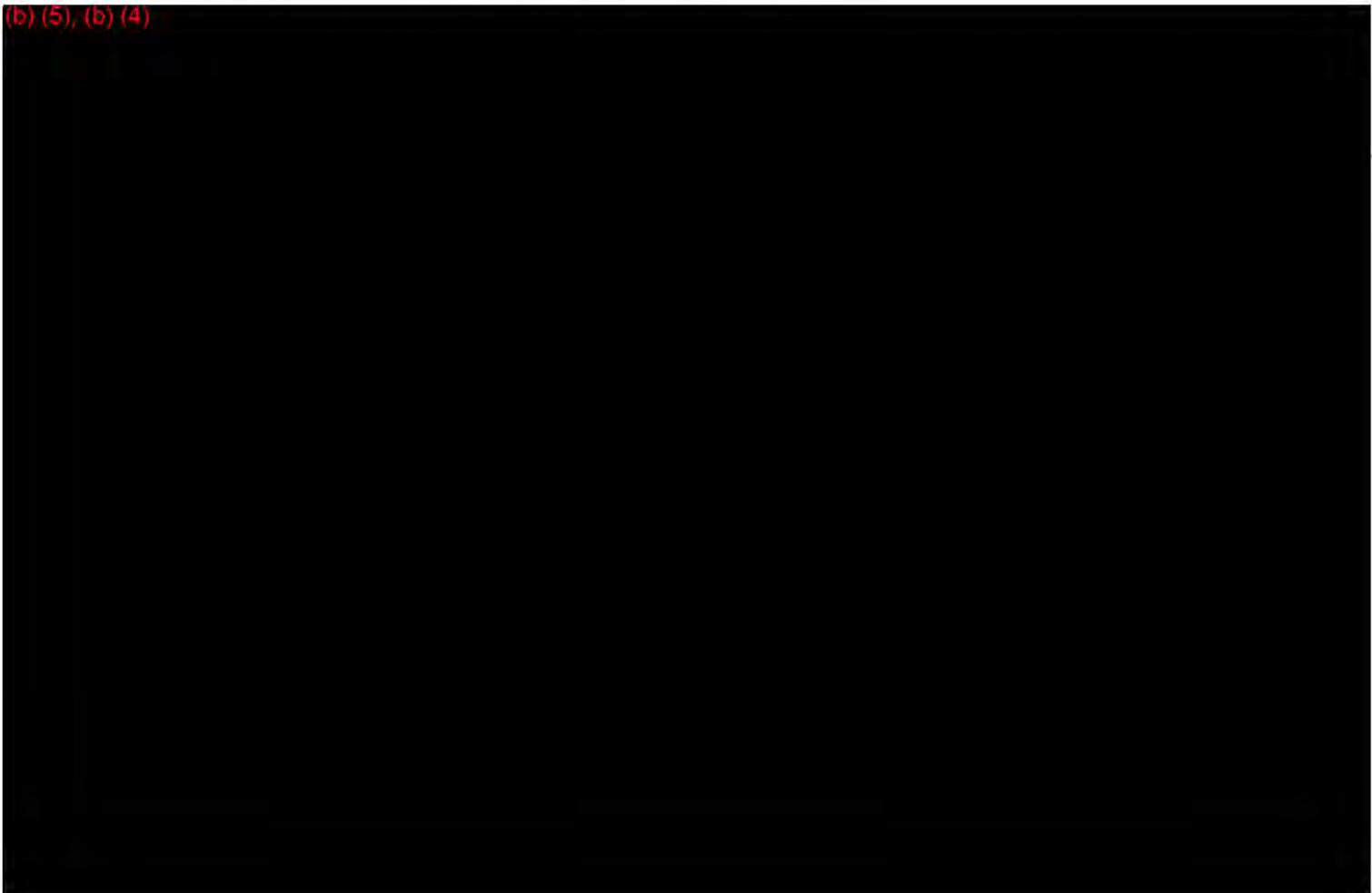
Smith, Celeste

From: Garza, Anthony
Sent: Tuesday, August 05, 2014 5:30 PM
To: Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark; Immergut, Steven
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Hu-Primmer, Jean; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Mair, Michael; Perlloni, Andrei; Beers, Donald; Rebello, Heidi
Subject: FDA 2014 Ebola Coordination Situation Report #02
Attachments: 02 FDA 2014 Ebola Coordination Situation Report 2014-08-05.docx

Good afternoon,

Please find attached the daily FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains previous information and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



(b) (5), (b) (4)



LCDR Anthony (Tony) Garza, USPHS
SR. Program Manager
Office of Counterterrorism & Emerging Threats (OCET)
Office of the Chief Scientist
Food and Drug Administration (FDA)
Department of Health and Human Services (HHS)
10903 New Hampshire Ave.
WO 1, 4328
Silver Spring, MD 20993
Office: 301-796-8247
BB: 240-620-9293

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Smith, Celeste

From: Garza, Anthony
Sent: Monday, August 04, 2014 5:46 PM
To: Hamburg, Margaret; Borio, Luciana; Barclay, Lisa; Harris, Walter; Howard, Sally; Ostroff, Stephen; Maher, Carmen; Sklamberg, Howard; Midthun, Karen; Woodcock, Janet; Shuren, Jeff; Russo, Mark
Cc: Roeder, David L; Valdez, Mary Lou; Rovin, Lisa; Hu-Primmer, Jean; Garza, Anthony; Birnkrant, Debra B; Cox, Edward M; Roberts, Rosemary; Leissa, Brad G; Kelley, Cynthia; Schwartz, Suzanne; Gutierrez, Alberto; Hojvat, Sally A; Epstein, Jay; Gruber, Marion; Krause, Philip; Mair, Michael; Perlloni, Andrei; Beers, Donald
Subject: FDA 2014 Ebola Coordination Situation Report #01
Attachments: 01 FDA 2014 Ebola Coordination Situation Report 2014-08-04.docx

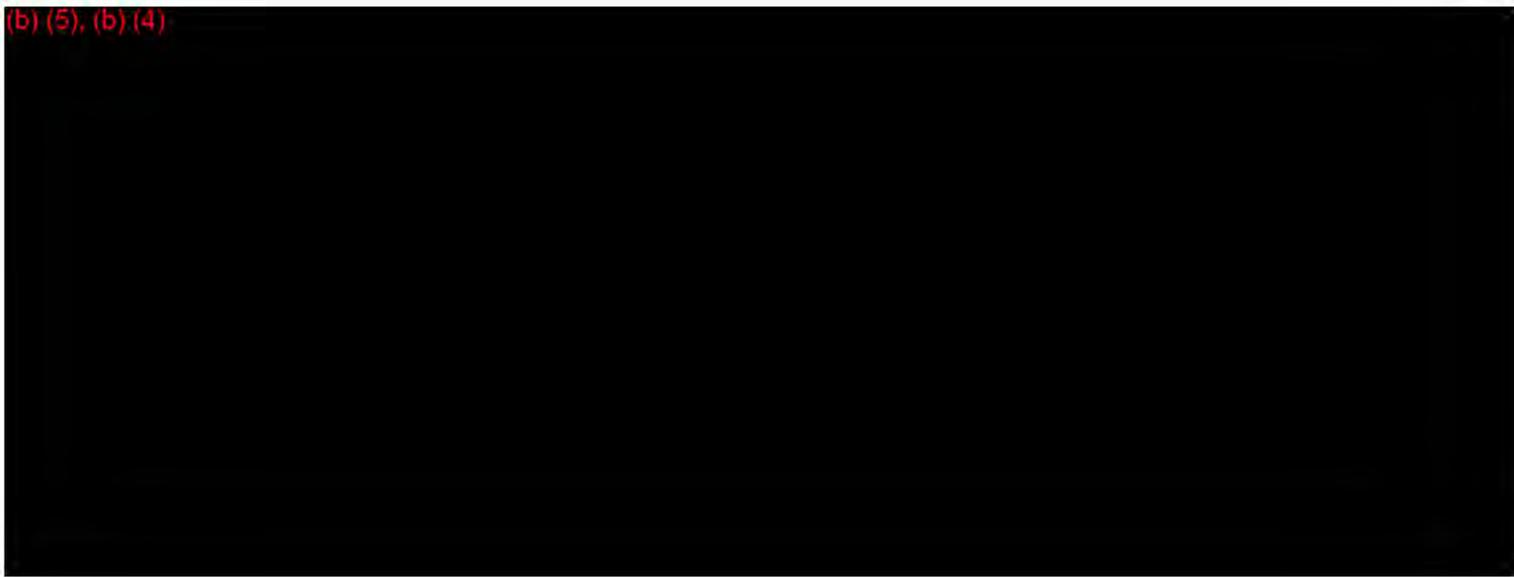
Good afternoon,

Please find attached the first daily FDA 2014 Ebola Coordination Situation Report. Contained within the document you will find black colored text that contains information that was circulated over the weekend and blue colored text which contains new information as of today. This new information is also provided below for easy viewing. Please do not distribute these situation reports outside of FDA given that the reports may contain commercial confidential information (CCI), also please consider restricting further internal distribution to those involved in the response.

(b) (5), (b) (4)



(b) (5), (b) (4)



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