Subject: RE: Was there fraud - the guidance indicated there was?

All of these pathways of communication (involving FDA, company, Nationwide Children's, investigators, and parents) have become very messy; this "game of telephone" seems to have the potential to explode and cause significant injury.

There has been some sentiment today for 'setting the record straight' in terms of Serepta's morning press release, and we are seeing how much of this information is being overinterpreted and misinterpreted by the public – parents and investors.

So...I am wondering if we could orchestrate some type of joint press release with Serepta to set the record straight. Is that feasible? Other thoughts warmly welcomed...

From: Woodcock, Janet
Sent: Monday, October 27, 2014 6:44 PM
To: Jenkins, John K; Unger, Ellis; Dunn, Billy
Subject: FW: Was there fraud - the guidance indicated there was?

Fyi jw

From: Christine McSherry [mailto:christine@jettfoundation.org]
Sent: Monday, October 27, 2014 6:41 PM
To: Woodcock, Janet
Subject: Was there fraud - the guidance indicated there was?

Hi Janet,

Obviously, the guidance and delay of a submission of a NDA are more than concerning, but - what is truly deeply concerning is the accusation by the agency that something was "uncovered" at Nationwide Children's Hospital, signaling that there was fraudulent activity handling the biopsies and the methods around quantifying the dystrophin.

If this is true - the agency owes it to the sponsor and the public as to "what" was uncovered and nobody deserves that information more than the kids and families who donated their muscles and planning to donate again for a 4th biopsy...for if their biopsies were mishandled and the agency has an understanding of this, for the safety of our children, it needs to be made public.

Lastly, if there is a fraud being conducted at the institution - this affects the scientific integrity of hundreds of studies and thousands of published papers that have come out of Nationwide Childrens. As it stands today, this institution is the premiere site for many neurological trials in children.

This is a very serious position that either the agency has landed in or if all true, that the institution has found themselves in. Either way, we need clarity on this issue now...for the safety and well being of all the children who currently participating in

trials at this site.

Thank you for looking into this.

Speak soon.
Christine

--
Making...TODAY COUNT - TO CHANGE TOMORROW

Christine McSherry, RN

The Jett Foundation
68 Evergreen Street, Suite One
Kingston, MA 02364
(781) 585-5566
FAX: (781) 585-5233
CELL: (b) (6)
jettfoundation.org

From: Dunn, Billy
To: FSasinowski@hpm.com; Moscicki, Richard
Subject: Re: will try to reach dr. dunn to discuss this and propose possible path forward.
Date: Tuesday, October 28, 2014 3:47:28 PM

Frank - yes, I am out at two outside meetings.

Rich - thanks, and I can catch up when we have a moment.

Billy

From: Frank J. Sasinowski [mailto:FSasinowski@hpm.com]
Sent: Tuesday, October 28, 2014 01:24 PM
To: Moscicki, Richard; Dunn, Billy
Cc: Frank J. Sasinowski <FSasinowski@hpm.com>
Subject: RE: will try to reach dr. dunn to discuss this and propose possible path forward.

thank you VERY MUCH for our talk just now.
will share with folks at sarepta.
frank

> **From:** Moscicki, Richard [mailto:Richard.Moscicki@fda.hhs.gov]
> **Sent:** Tuesday, October 28, 2014 1:11 PM
> **To:** Frank J. Sasinowski; Dunn, Billy
> **Subject:** RE: will try to reach dr. dunn to discuss this and propose possible path forward.
>
> I believe Billy is out today at an outside meeting.
>
> **From:** Frank J. Sasinowski [mailto:FSasinowski@hpm.com]
> **Sent:** Tuesday, October 28, 2014 1:09 PM
> **To:** Moscicki, Richard; Dunn, Billy
> **Cc:** Frank J. Sasinowski
> **Subject:** will try to reach dr. dunn to discuss this and propose possible path forward.
>
> just spoke with chris garabedian..and am about to try to call dr. dunn.
> dr. dunn, if I miss you now, please call me anytime...I will be here in the office until 7pm.
> office number is 202 737 4287.
> many thanks.
> frank
>
> > **From:** Frank J. Sasinowski
> > **Sent:** Tuesday, October 28, 2014 11:01 AM
> > **To:** 'Moscicki, Richard'
> > **Cc:** Frank J. Sasinowski
> > **Subject:** RE: just got your voice message this morning re sarepta press release...plus pink sheet article on my orphan drug analysis
> >
> > I will get to company and discuss this.
> > thanks for heads up.
> > frank
> >
> > > **From:** Moscicki, Richard [mailto:Richard.Moscicki@fda.hhs.gov]
> > > **Sent:** Tuesday, October 28, 2014 10:54 AM
> > > **To:** Frank J. Sasinowski

Subject: RE: just got your voice message this morning re sarepta press release...plus pink sheet article on my orphan drug analysis

Frank, I was surprised how the press release framed or discussed our concerns on the dystrophin data, indeed, this has become problematic. Rich.

From: Frank J. Sasinowski [mailto:FSasinowski@hpm.com]
Sent: Monday, October 27, 2014 12:37 PM
To: Moscicki, Richard
Subject: RE: just got your voice message this morning re sarepta press release...plus pink sheet article on my orphan drug analysis

oh, perfect.
thanks for letting me know!

> **From:** Moscicki, Richard [mailto:Richard.Moscicki@fda.hhs.gov]
> **Sent:** Monday, October 27, 2014 12:36 PM
> **To:** Frank J. Sasinowski
> **Subject:** RE: just got your voice message this morning re sarepta press release...plus pink sheet article on my orphan drug analysis
>
> Thanks Frank, there was a decision not to comment on the press release.
> Rich.
>
> **From:** Frank J. Sasinowski [mailto:FSasinowski@hpm.com]
> **Sent:** Monday, October 27, 2014 12:33 PM
> **To:** Woodcock, Janet; Moscicki, Richard
> **Cc:** Frank J. Sasinowski
> **Subject:** FW: just got your voice message this morning re sarepta press release...plus pink sheet article on my orphan drug analysis
>
> > here is my note to dr. temple re my orphan drug analysis, together with today's pink sheet article
> > which reports the analysis in a way that shines a very favorable light on FDA.
>
> by the way, since both of you have been involved with the sarepta dmd therapy, I emailed to dr. dunn a press release on Friday afternoon, and asked him to let me know if he or drs. moscicki, unger or temple had any comments. when I was with dr. temple on Saturday, I asked whether he had any comments on press release and he knew nothing about it. my mistake: I had not checked to see if dr. dunn was in the office on Friday and he was not. so my fault!
> thought you both would want to see this pink sheet article on FDA flexibility reaffirmed by my new analysis.
> onward!
> frank
>
> > **From:** Frank J. Sasinowski
> > **Sent:** Monday, October 27, 2014 11:37 AM
> > **To:** Temple, Robert
> > **Cc:** Frank J. Sasinowski
> > **Subject:** just got your voice message this morning re sarepta press release...plus pink sheet article on my orphan drug analysis
> >
> > sorry, bob.

I kept my cell phone at my side all Saturday and Sunday.
this morning jackie listened to our messages on our home landline....and found your message.
my mistake.
by the way, here is an article from today's pink sheet on my talk last week at nord orphan drug summit.
it reports on my update analysis on my earlier paper/analysis.
I cited you in my talk..as the person responsible for having me conduct the analysis in 3 classifications.
I had only envisioned two: either the evidence was sufficient for a conventional approval or was evidence of FDA flexibility..and I explained that you counseled me to consider breaking the flexibility into two categories: those that stemmed from FDA's administrative flexibility...such as subpart h or the may 98 guidance (which I said that dr woodcock, who was next to me at nord summit, and you had been chiefly responsible for) or case-by-case flexibility.
so even though you were not at the summit, I made sure all there knew of your key role.
onward.
frank

Frank J. Sasinowski

Review my analysis: "Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs", Drug Information Journal, March 2012 http://www.hpm.com/pdf/SPDIJ_SASINOWSKI.PDF

Visit our blog: www.fdalawblog.net

From: Dunn, Billy
To: Moscicki, Richard
Subject: Re: sarepta press release.....announcing nda in 2nd quarter 2015
Date: Monday, October 27, 2014 10:21:44 AM

No doubt.

From: Moscicki, Richard
Sent: Monday, October 27, 2014 10:17 AM
To: Dunn, Billy
Subject: RE: sarepta press release.....announcing nda in 2nd quarter 2015

I am really surprised they mentioned our concerns regarding the dystrophin data. I am sure this infuriates their colleagues in Cincinatti. Rich.

From: Dunn, Billy
Sent: Sunday, October 26, 2014 9:39 PM
To: Unger, Ellis; Moscicki, Richard; Temple, Robert
Subject: Fw: sarepta press release.....announcing nda in 2nd quarter 2015

Gents,

See attached. I have not responded other than to acknowledge his email.

Billy

From: Frank J. Sasinowski [mailto:FSasinowski@hpm.com]
Sent: Friday, October 24, 2014 03:15 PM
To: Dunn, Billy
Cc: Frank J. Sasinowski <FSasinowski@hpm.com>
Subject: sarepta press release.....announcing nda in 2nd quarter 2015

chris garabedian and sarepta and I wanted you to see this press release that is intended for release on Monday at 8am.
I spoke with dr. moscicki at the nord orphan drug summit this week about this investigational therapy and the nda being developed.
I know that the ode 1 director and deputy director have been in all of our meetings as well.
if any of the 4 of you (I am not sharing with them) have comments, sarepta would be open to receiving them.
to allow time for sarepta to consider any comments, we would appreciate receiving them by 1pm on Sunday.
my cell phone number is (b) (6) and you have my email address.
many thanks for all your assistance along the developmental journey!
frank

Frank J. Sasinowski

Review my analysis: "Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs", Drug Information Journal, March 2012

http://www.hpm.com/pdf/SPDU_SASINOWSKI.PDF

Visit our blog: www.fdalawblog.net

From: Gross, Mary
To: Leptak, Christopher
Cc: Moscicki, Richard
Subject: RE: Dystrophin Workshop
Date: Friday, October 24, 2014 11:22:25 AM

My pleasure.

From: Leptak, Christopher
Sent: Friday, October 24, 2014 11:21 AM
To: Gross, Mary
Cc: Leptak, Christopher; Moscicki, Richard
Subject: RE: Dystrophin Workshop

Excellent! We can continue to shoot for Feb 2nd but can use Feb 27th if needed. Thanks Mary.

From: Gross, Mary
Sent: Friday, October 24, 2014 11:07 AM
To: Leptak, Christopher
Subject: RE: Dystrophin Workshop

There is only one date that appeared available and that was on Feb. 27. The meeting rooms are booked up for pretty much most of the rest of next year. I sent a note asking to reserve it.

Mary

From: Leptak, Christopher
Sent: Friday, October 24, 2014 9:25 AM
To: Gross, Mary
Cc: Moscicki, Richard
Subject: Dystrophin Workshop

Hi Mary,

As I look ahead at the workshop miles stones, I am thinking we should reserve the room for late Feb/1st week of March as a back-up. Now that we know that the co-sponsorship agreement is going to be more involved and we need a minimum of 3 months before the event to begin the FR Notice clearance, we are going to be in a bit of a time crunch to make the Feb 2 date. I know that Building and Facilities Management do not like groups to reserve multiple spots for the same event but maybe you could convince them to make an exception in this case. You can assure them that we will choose the final date no later than the end of Nov.

Sound like a plan?

Thanks

Chris

From: Leptak, Christopher
To: Moscicki, Richard
Subject: RE: Dystrophin Workshop
Date: Friday, October 03, 2014 2:33:21 PM

Hope it's a good one!

From: Moscicki, Richard
Sent: Friday, October 03, 2014 1:57 PM
To: Leptak, Christopher
Subject: RE: Dystrophin Workshop

OK then. Go for it. Btw that's my bday so it will be my present. Rich.

From: Leptak, Christopher
Sent: Friday, October 03, 2014 1:45 PM
To: Moscicki, Richard
Subject: RE: Dystrophin Workshop

FYI We just had our call with NIH. It looks to be a go on all fronts. Up to three of the NIH sub-sections (NCATS, NIAMS, and NINDS) are interested in co-sponsoring the event. We have tentative agreement to hold it here at White Oak on Feb 2. I will be setting up planning committee meetings (me, Ash, Ron, and reps from NIH) to review the agenda and to put together a speaker list.

From: Moscicki, Richard
Sent: Friday, October 03, 2014 11:23 AM
To: Leptak, Christopher
Subject: RE: Dystrophin Workshop

I too have but a slight preference for FDA but having said that, what do our NIH brethren say. If they feel strongly about it being on their campus then I think that would be fine but if not then lets go here. Rich.

From: Leptak, Christopher
Sent: Thursday, October 02, 2014 7:42 AM
To: Moscicki, Richard
Subject: Dystrophin Workshop

Rich,

RE workshop location (FDA vs NIH), here is what I have heard:

No preference: Ellis, Billy, Ron

Prefer FDA: Ash, Eric (restated potential concerns RE security based on past interactions)

Here is the breakdown as I see it:

1. For choosing White Oak: we have a room in Bldg 31 reserved, we have the infrastructure to easily webcast the event, and there is security available if needed. If held on our campus, we may psychologically have more leverage when it comes to choosing speakers (assuming NIH co-sponsorship becomes a reality) and having greater control over the agenda.

2. For choosing NIH: The focus is a scientific exchange of research methodologies, hence NIH is a more natural choice given its function.

I have a slight preference for FDA, but not worth going to bat if NIH feels strongly they should be the host. Your thoughts?

Chris

From:	Leptak, Christopher
To:	Gross, Mary; Unger, Ellis; Moscicki, Richard; Temple, Robert; Rao, Ashutosh; Farkas, Ronald; Dunn, Billy; Bastings, Eric; Kaiser, James; Pacanowski, Michael A; Rogers, Hobart
Subject:	RE: Dystrophin Workshop
Date:	Tuesday, September 30, 2014 6:00:35 PM

My understanding is that NIH has conference space available to its staff (much like our Bldg 31). If they co-sponsor the event, there should be no cost.

From: Gross, Mary
Sent: Tuesday, September 30, 2014 5:50 PM
To: Unger, Ellis; Leptak, Christopher; Moscicki, Richard; Temple, Robert; Rao, Ashutosh; Farkas, Ronald; Dunn, Billy; Bastings, Eric; Kaiser, James; Pacanowski, Michael A; Rogers, Hobart
Subject: RE: Dystrophin Workshop

Would we have to pay for NIH room?

From: Unger, Ellis
Sent: Tuesday, September 30, 2014 4:41 PM
To: Leptak, Christopher; Moscicki, Richard; Temple, Robert; Rao, Ashutosh; Farkas, Ronald; Dunn, Billy; Bastings, Eric; Kaiser, James; Pacanowski, Michael A; Rogers, Hobart
Cc: Gross, Mary
Subject: RE: Dystrophin Workshop

I don't have a preference on the venue, FDA vs. NIH, but others might.

From: Leptak, Christopher
Sent: Tuesday, September 30, 2014 3:20 PM
To: Moscicki, Richard; Temple, Robert; Rao, Ashutosh; Farkas, Ronald; Unger, Ellis; Dunn, Billy; Bastings, Eric; Kaiser, James; Pacanowski, Michael A; Rogers, Hobart
Cc: Gross, Mary; Leptak, Christopher
Subject: Dystrophin Workshop

Dystrophin Workshop Steering Committee members,

A couple of updates...

1. NIH (both NCATS and NINDS) have expressed interest in co-sponsoring the workshop. I have a Tcon with them on Friday to determine the possible terms (financial, administrative, planning, etc.).

2. Location. Mary was able to book part of the great room in Bldg 31 for Feb 2. NIH has also expressed interest in hosting the event. During our last meeting, we discussed the pros/cons of holding it at White Oak. Do folks have a strong preference for one over the other? It would be good to come to a consensus before Friday's discussion with NIH.

3. Speakers. Be thinking of possible speakers for each of our draft agenda topics. Once I know more to what extent NIH has interest in helping with the planning of the event, we can start to put forward names for the group's consideration.

All for now,

Chris

From: Bastings, Eric
To: Unger, Ellis; Leptak, Christopher; Moscicki, Richard; Temple, Robert; Rao, Ashutosh; Farkas, Ronald; Dunn, Billy; Kaiser, James; Pacanowski, Michael A; Rogers, Hobart
Cc: Gross, Mary
Subject: RE: Dystrophin Workshop
Date: Tuesday, September 30, 2014 4:53:09 PM

There was a lot of agitation in the DMD community around the time we had the last public DMD-related meeting, and we felt necessary to have security available for that meeting.

The situation is quieter now, but may get reignited by comments from one of the sponsors. If we need to have security available again, the White Oak location would be preferable.

Eric

From: Unger, Ellis
Sent: Tuesday, September 30, 2014 4:41 PM
To: Leptak, Christopher; Moscicki, Richard; Temple, Robert; Rao, Ashutosh; Farkas, Ronald; Dunn, Billy; Bastings, Eric; Kaiser, James; Pacanowski, Michael A; Rogers, Hobart
Cc: Gross, Mary
Subject: RE: Dystrophin Workshop

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Sent: Tuesday, September 30, 2014 3:20 PM
To: Moscicki, Richard; Temple, Robert; Rao, Ashutosh; Farkas, Ronald; Unger, Ellis; Dunn, Billy; Bastings, Eric; Kaiser, James; Pacanowski, Michael A; Rogers, Hobart
Cc: Gross, Mary; Leptak, Christopher
Subject: Dystrophin Workshop

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3. Speakers. Be thinking of possible speakers for each of our draft agenda topics. Once I know more to what extent NIH has interest in helping with the planning of the event, we can start to put forward names for the group's consideration.

All for now,

Chris

From: Leptak, Christopher
To: Unger, Ellis
Cc: Moscicki, Richard; Dunn, Billy
Subject: RE: Dystrophin meeting
Date: Monday, September 22, 2014 6:39:43 PM

Roger that... thanks for the clarification Ellis

From: Unger, Ellis
Sent: Monday, September 22, 2014 6:01 PM
To: Leptak, Christopher
Cc: Moscicki, Richard; Dunn, Billy
Subject: RE: Dystrophin meeting

Hi Chris,

Friday's meeting is with parents of boys with DMD – not scientists!

Ellis

From: Leptak, Christopher
Sent: Monday, September 22, 2014 5:56 PM
To: Unger, Ellis; Dunn, Billy
Subject: FW: Dystrophin meeting

Ellis and Billy,

Per Rich's response, touching base to see if you had any details RE Friday's DMD meeting.

Thanks
Chris

From: Moscicki, Richard
Sent: Monday, September 22, 2014 3:22 PM
To: Leptak, Christopher
Subject: Re: Dystrophin meeting

I don't know, I am out of town, ask Ellis or Billy

From: Leptak, Christopher
Sent: Monday, September 22, 2014 10:39 AM
To: Moscicki, Richard
Subject: Dystrophin meeting

Rich,

It was brought to my attention that Janet is meeting with John, Ellis, and Billy this Friday to discuss a DMD meeting. Is this the dystrophin meeting we are planning? Should we be included on the invite?

Best,

Chris

From: Gross, Mary
To: Moscicki, Richard
Subject: RE: Dystrophin Workshop
Date: Friday, September 12, 2014 10:38:56 AM

A closed meeting is by invitation only, there is no interest in hearing from stakeholder groups and nothing appears in the FR announcing the meeting.

From: Moscicki, Richard
Sent: Friday, September 12, 2014 9:17 AM
To: Gross, Mary
Subject: RE: Dystrophin Workshop

Maybe I am not synching on the term open vs closed.

From: Gross, Mary
Sent: Thursday, September 11, 2014 11:37 AM
To: Moscicki, Richard
Subject: RE: Dystrophin Workshop

At our last meeting (which was a while ago), you mentioned you wanted it closed. I hadn't heard anything different from that. - Mary

---

From: Moscicki, Richard
Sent: Thursday, September 11, 2014 11:34 AM
To: Gross, Mary
Subject: RE: Dystrophin Workshop

I thought we had decided on an open public meeting, had that changed? Rich.

From: Gross, Mary
Sent: Thursday, September 11, 2014 11:29 AM
To: Moscicki, Richard; Leptak, Christopher; Rao, Ashutosh; Kaiser, James
Cc: Gonzalez, Alina; Farkas, Ronald; Unger, Ellis; Bastings, Eric; Dunn, Billy; Temple, Robert; Pacanowski, Michael A; Clarke, Mary Beth; Gonzalez, Alina; Hunt, Michie
Subject: RE: Dystrophin Workshop

Are you still planning on going ahead with a closed meeting?

Mary

From: Moscicki, Richard
Sent: Thursday, September 11, 2014 11:25 AM
To: Leptak, Christopher; Rao, Ashutosh; Kaiser, James
Cc: Gonzalez, Alina; Farkas, Ronald; Gross, Mary; Unger, Ellis; Bastings, Eric; Dunn, Billy; Temple, Robert; Pacanowski, Michael A
Subject: RE: Dystrophin Workshop

I just spoke with Chris Austin at NCATS and he is interested in cosponsoring the Dystrophin

workshop with us. He suggested contacting John McCue, acting SV there with the financials and with the agenda. I will also send him the agenda. Rich.

From: Unger, Ellis
Sent: Wednesday, September 10, 2014 5:52 PM
To: Leptak, Christopher; Moscicki, Richard; Dunn, Billy; Bastings, Eric; Kaiser, James; Pacanowski, Michael A; Temple, Robert
Cc: Gonzalez, Alina; Farkas, Ronald; Rao, Ashutosh; Gross, Mary
Subject: RE: Dystrophin Workshop

Chris,

Thanks for clarifying. Somehow I got the mistaken impression that you were planning a discussion of 3 methods for immunohistochemistry. Because you said there would be 5 minutes for Q&A for each speaker, I figured that the 45 minutes was to be divided between 3 speakers, with each speaker given 10 min to talk and 5 min for Q&A. Now I see there will be 40 minutes for IHC and 5 for Q&A.

My mistake.

No problem.

Ellis

From: Leptak, Christopher
Sent: Wednesday, September 10, 2014 7:28 AM
To: Unger, Ellis; Moscicki, Richard; Dunn, Billy; Bastings, Eric; Kaiser, James; Pacanowski, Michael A; Temple, Robert
Cc: Gonzalez, Alina; Farkas, Ronald; Rao, Ashutosh; Gross, Mary
Subject: RE: Dystrophin Workshop

Ellis,

Thanks for the comments. RE time allotment for the methods discussion, to be clear, each method will have 30 min (not 10 min) except for immunohistochemistry which has 45 min. The times listed after a given method is the time committed for that method. And although there is 5 min Q&A for the methods discussion section, we will be introducing more discussion of methods in the afternoon panel session.

Is that adequate time?

Chris

From: Unger, Ellis
Sent: Tuesday, September 09, 2014 9:24 AM
To: Leptak, Christopher; Moscicki, Richard; Dunn, Billy; Bastings, Eric; Kaiser, James; Pacanowski, Michael A; Temple, Robert
Cc: Gonzalez, Alina; Farkas, Ronald; Rao, Ashutosh; Gross, Mary

Subject: RE: Dystrophin Workshop

This looks good, though I had a few comments and suggestions. I'm still a bit unfamiliar with Sharepoint, so I've attached my suggestions to the word document and I'm simply attaching it here.

Ellis

<< File: dystropen agenda.doc >>

From: Leptak, Christopher
Sent: Monday, September 08, 2014 11:46 AM
To: Moscicki, Richard; Unger, Ellis; Dunn, Billy; Bastings, Eric; Kaiser, James; Pacanowski, Michael A; Temple, Robert
Cc: Gonzalez, Alina; Farkas, Ronald; Rao, Ashutosh; Gross, Mary
Subject: Dystrophin Workshop

Hello everyone,

In preparation for next week's Dystrophin Workshop Steering Committee meeting, Ron, Ash, and I have created a Draft Agenda for your consideration and input. Please review and comment. The document can be found at:

http://sharepoint.fda.gov/orgs/CDER-Center-Wide/dystrophin/SitePages/Home.aspx

The file is under the tab "Workshop Agenda" and the document is titled Draft Agenda Dystrophin Workshop (modified Sept 8, 11:29 AM).

Best,

Chris, Ash, and Ron

From:	Leptak, Christopher
To:	Gross, Mary; Moscicki, Richard; Rao, Ashutosh; Kaiser, James
Cc:	Gonzalez, Alina; Farkas, Ronald; Unger, Ellis; Bastings, Eric; Dunn, Billy; Temple, Robert; Pacanowski, Michael A; Clarke, Mary Beth; Gonzalez, Alina; Hunt, Michie
Subject:	RE: Dystrophin Workshop
Date:	Thursday, September 11, 2014 2:41:10 PM

Mary,

It's one of the topics for discussion at our Steering Committee next Wed.

Thanks

Chris

From: Gross, Mary
Sent: Thursday, September 11, 2014 11:29 AM
To: Moscicki, Richard; Leptak, Christopher; Rao, Ashutosh; Kaiser, James
Cc: Gonzalez, Alina; Farkas, Ronald; Unger, Ellis; Bastings, Eric; Dunn, Billy; Temple, Robert; Pacanowski, Michael A; Clarke, Mary Beth; Gonzalez, Alina; Hunt, Michie
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Subject: Dystrophin Workshop

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http://sharepoint.fda.gov/orgs/CDER-Center-Wide/dystrophin/SitePages/Home.aspx

The file is under the tab "Workshop Agenda" and the document is titled Draft Agenda Dystrophin Workshop (modified Sept 8, 11:29 AM).

Best,

Chris, Ash, and Ron

From: Leptak, Christopher
To: Gonzalez, Alina; Moscicki, Richard
Cc: Gross, Mary
Subject: RE: Dystrophin Meeting
Date: Monday, August 18, 2014 2:30:07 PM

Thanks for the perspective Alina. Based on our last discussion, the goals of the dystrophin meeting, and the restrictions RE FDA meetings in general, I would agree that Brookings is likely the way to go.

We are currently working with Brookings on a PDUFA workshop; there have been some challenges. Once I hear back from NIH RE co-sponsorship (hopefully soon), we can revisit this topic.

Best,
Chris

From: Gonzalez, Alina
Sent: Monday, August 18, 2014 9:37 AM
To: Moscicki, Richard; Leptak, Christopher
Cc: Gross, Mary
Subject: Dystrophin Meeting

Hi Rich, and Chris,

We met with Mary Beth on Friday afternoon and for a number of reasons which we can explain in person, there was concern around having the Dystrophin meeting be anything other than a closed meeting facilitated by Brookings. Given the desired purpose and parameters of the meeting as discussed last Monday, we believe a closed meeting run by a third party (not FDA or NIH) is the best option.

We would like to discuss in person but I wanted to send this note out ASAP.

From: Gonzalez, Alina
To: Moscicki, Richard; Leptak, Christopher
Cc: Gross, Mary
Subject: Dystrophin Meeting
Date: Monday, August 18, 2014 9:37:07 AM

Hi Rich, and Chris,

We met with Mary Beth on Friday afternoon and for a number of reasons which we can explain in person, there was concern around having the Dystrophin meeting be anything other than a closed meeting facilitated by Brookings. Given the desired purpose and parameters of the meeting as discussed last Monday, we believe a closed meeting run by a third party (not FDA or NIH) is the best option.

We would like to discuss in person but I wanted to send this note out ASAP.

From: Buckman-Garner, ShaAvhrée
To: Leptak, Christopher; Moscicki, Richard; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh; Walton, Marc; Kaiser, James; Pacanowski, Michael A
Cc: Gonzalez, Alina; Gross, Mary; Jenkins, John K; Loewke, Sally A
Subject: RE: Dystrophin Workshop
Date: Wednesday, August 13, 2014 12:56:28 PM

Thanks for taking lead on this!

ShaAvhree

From: Leptak, Christopher
Sent: Wednesday, August 13, 2014 12:20 PM
To: Moscicki, Richard; Temple, Robert; Unger, Ellis; Dunn, Billy; Bastings, Eric; Farkas, Ronald; Rao, Ashutosh; Walton, Marc; Kaiser, James; Pacanowski, Michael A
Cc: Gonzalez, Alina; Gross, Mary; Jenkins, John K; Loewke, Sally A; Buckman-Garner, ShaAvhrée
Subject: Dystrophin Workshop

Hello everyone,

In follow-up to our post-CPIM discussion, we wanted to touch base to update you RE the Dystrophin Workshop planning.

1. Logistics:

   To respect everyone's busy schedules, we will have an Organizing Committee (Chris, Ash, and Rao) who will be responsible to for the workshop details (drafting the agenda, speaker list proposal, etc.). Alina and Mary have kindly offered their project management and knowledge of FDA operations support.

   You (the main recipients of this email) are a part of the Steering Committee for the workshop. At key junctures, we will reach out to you for your valuable insights and suggestions as the planning process moves forward. A Sharepoint site has been created and you should be receiving invites/links in the near future.

   If you wish to be more involved, please let us know and we can loop you in on the intermediate steps/planning.

2. Co-sponsorship

   NIH has tentatively expressed strong interest in co-sponsoring the meeting and a formal request has been submitted to them for their management review.

3. The Organizing Committee is working on a draft workshop agenda that will be circulated to the Steering Committee sometime next week for your review/input.

Best,

Chris, Ash, and Ron

From: Leptak, Christopher
To: Gonzalez, Alina; Gross, Mary
Cc: Moscicki, Richard; Farkas, Ronald; Rao, Ashutosh
Subject: RE: Materials for today"s discussion
Date: Wednesday, August 13, 2014 9:28:47 AM
Attachments: Dystrophin Workshop.doc

Thanks Alina!

1. For the Sharepoint site, please add the following folks with editing privileges:

Organizing Committee members:
Chris Leptak
Ash Rao
Ron Farkas

Steering Committee members:
Rich Moscicki
Ellis Unger
Billy Dunn
Eric Bastings
Marc Walton
Jim Kaiser
Mike Pacanowski

2. Attached is the most recent draft of the workshop agenda for uploading to the site:

3. Please set up a steering committee meeting for mid/late September. Agenda to follow…

Much appreciated!
Chris

From: Gonzalez, Alina
Sent: Tuesday, August 12, 2014 1:20 PM
To: Gross, Mary; Leptak, Christopher
Subject: RE: Materials for today's discussion

Hi Chris,

I have submitted a formal request for a Sharepoint site - please let me know the names of the people who should get permission to the site and I will invite them as soon as it has been established.

Let me know if you need assistance with setting up a steering committee meeting in September.

Also, I took notes while on the phone yesterday - I am cleaning them up and will send you the document for your review before sending it around to the group. I tried my best to capture action items and next steps and points of note, but a few times it was hard to hear on the phone (I know you were on the phone as well); but you can take a look and see if what I captured was accurate/in line with what you heard as well.

Thanks!

-Alina

From: Gross, Mary
Sent: Monday, August 11, 2014 3:52 PM
To: Leptak, Christopher
Cc: Gonzalez, Alina
Subject: RE: Materials for today's discussion

Thanks for sending this over for today's meeting.

Mary

From: Leptak, Christopher
Sent: Monday, August 11, 2014 11:12 AM
To: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald; Gonzalez, Alina; McLatchy, Johanna; Gross, Mary
Subject: Materials for today's discussion

Hello everyone,

For our meeting this afternoon, below are proposed topics for discussion:

1. Meeting planning logistics
a. Organizing Committee (us) + others including NIH?
b. Steering Committee (larger CPIM group participants)

2. Organization action items:
a. Create Sharepoint account and upload documents
b. Set up future meetings
c. Meeting minutes/summaries
d. FDA Budget: OCD SMO duties currently performed by Tanya Abbott

3. NIH Co-sponsorship Update
a. NIAMS/NINDS Glen Nuckolls - Interested and potential funding support
b. NAST Nora Yang - Not interested but potential funding assistance

4. Dystrophin Workshop
a. General: When, where, target audience, anticipated # participants, goals, desired outcomes
b. Discussion of Draft Agenda (attached below)

<< File: Dystrophin Workshop.doc >>

Best,
Chris

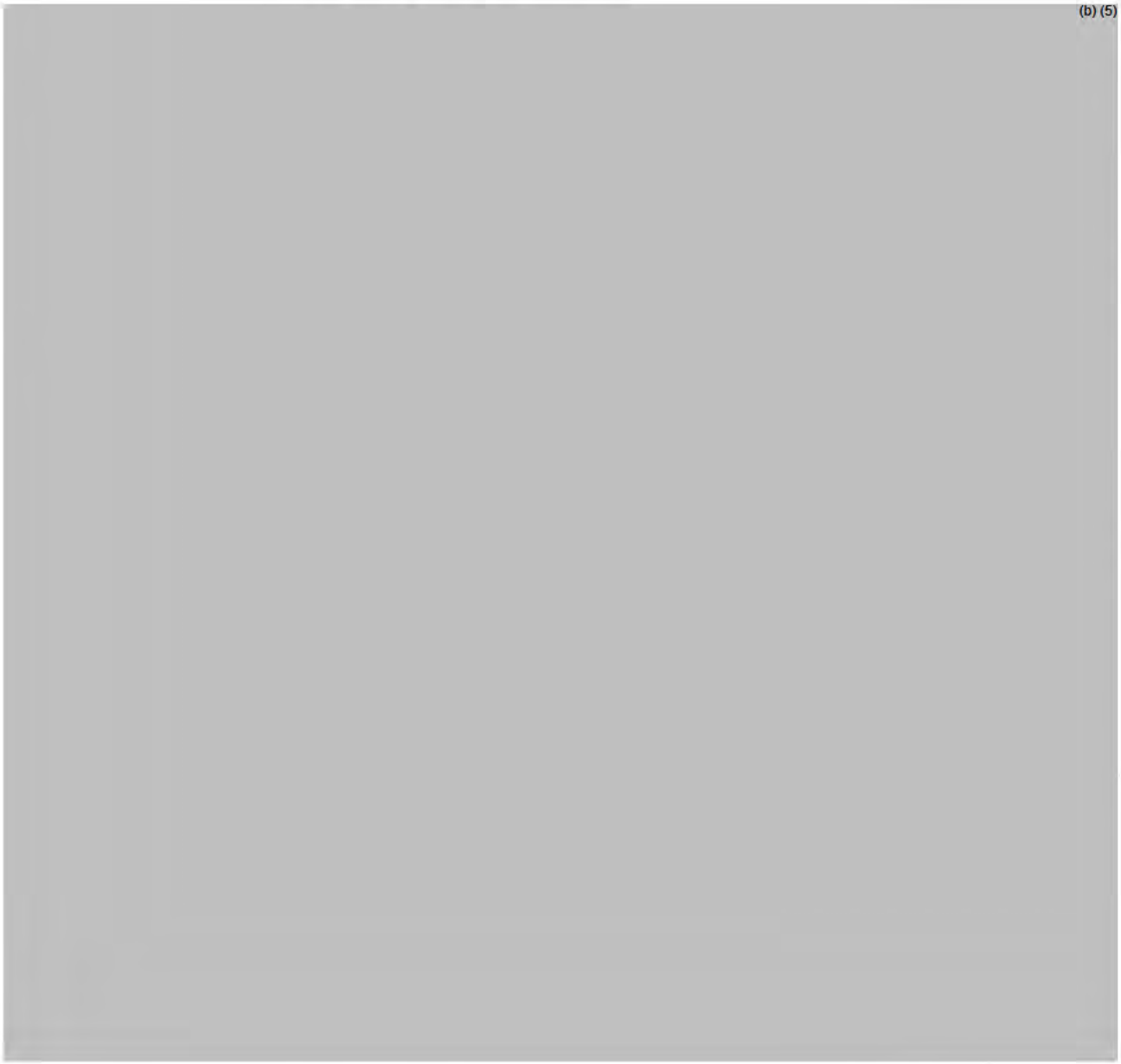
Dystrophin Workshop

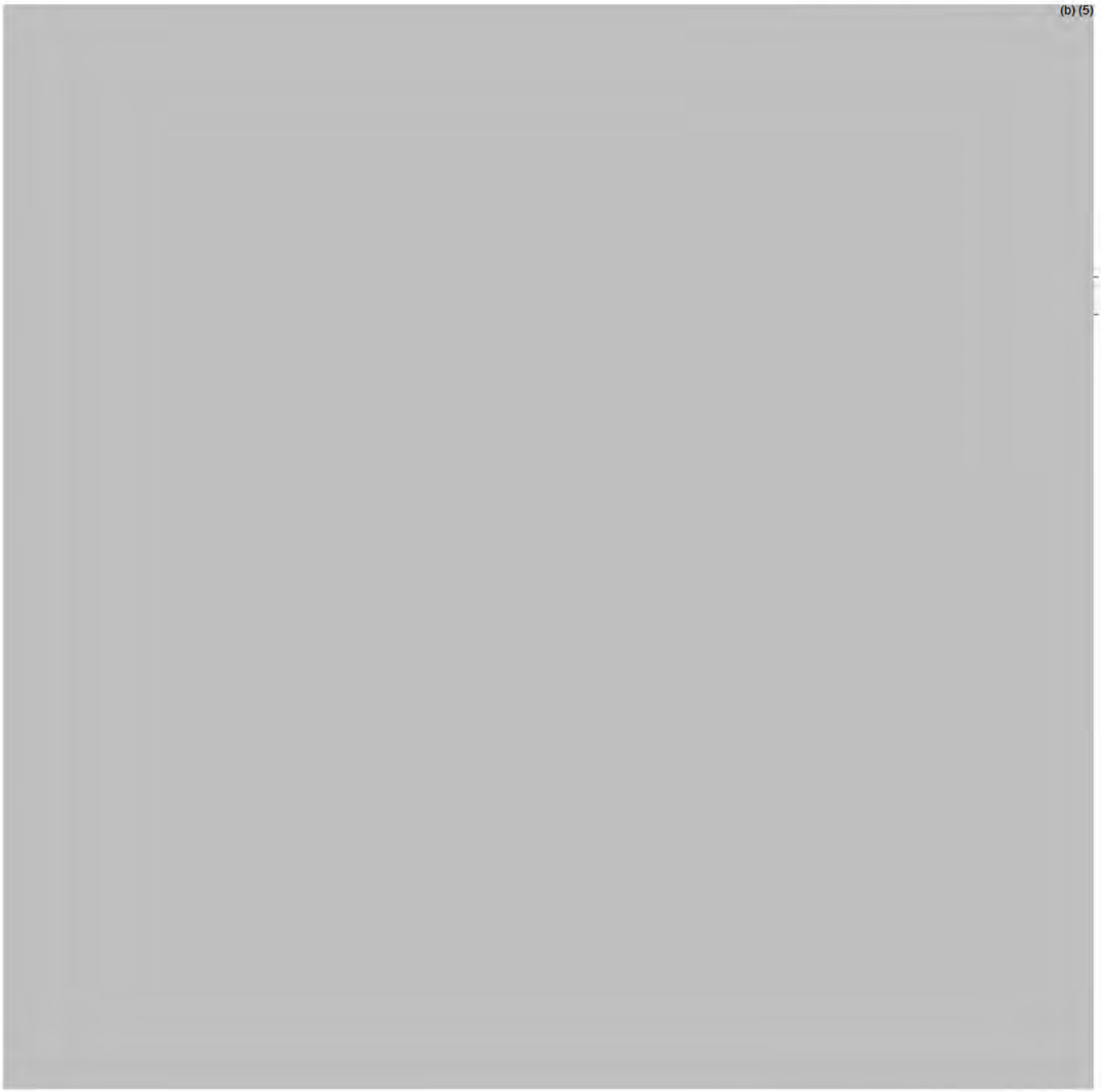
Location TBD

Date TBD

DRAFT-DO NOT DISTRIBUTE

(b) (5)

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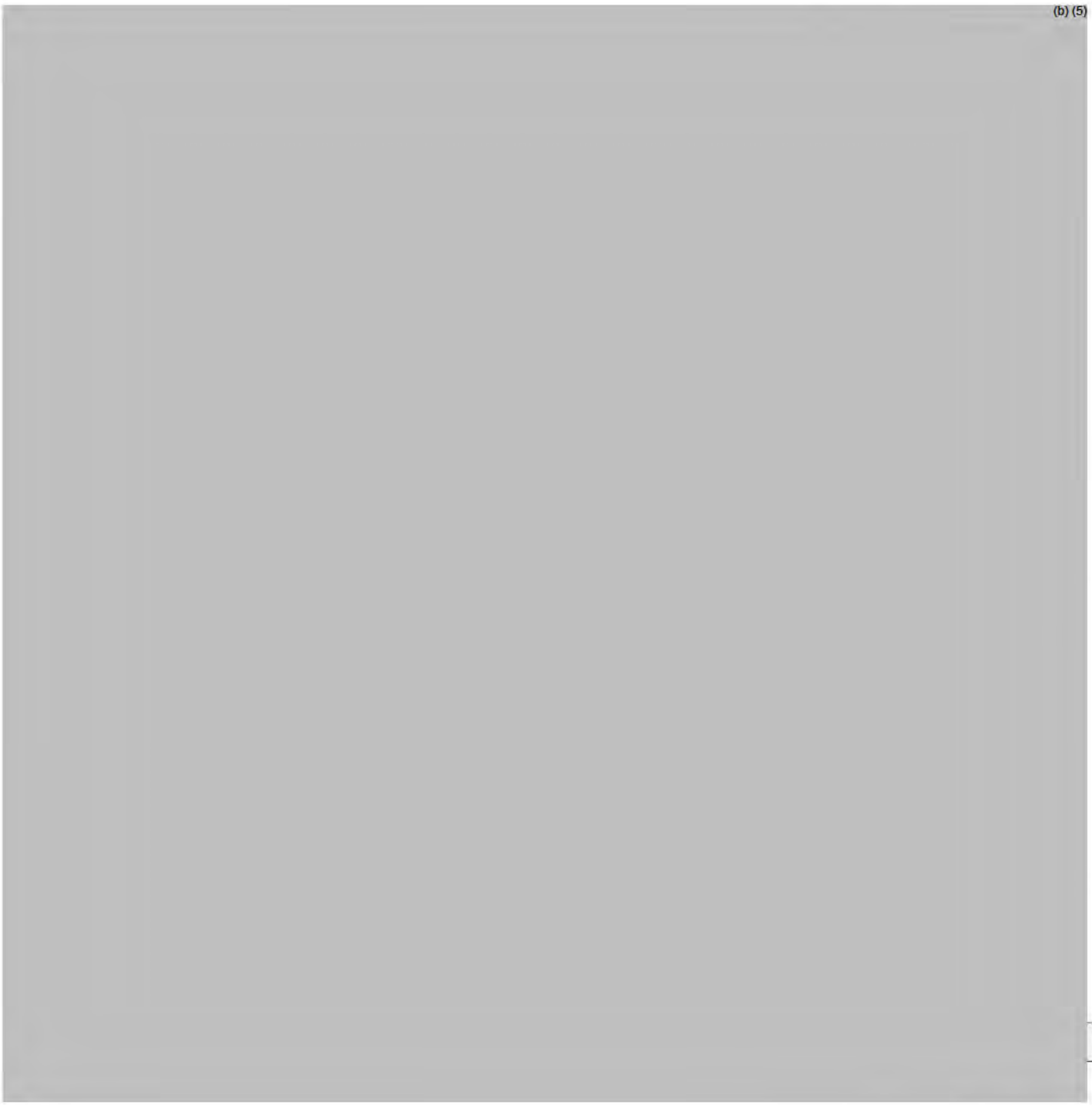
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(b) (5)

From: Clarke, Mary Beth
To: Moscicki, Richard
Cc: Gonzalez, Alina; Hunt, Michie
Subject: RE: Dystrophin meeting
Date: Thursday, August 07, 2014 10:46:08 AM

Rich,

My apologies that no one has gotten back to you. Alina Gonzalez will be the project manager, with back up help from Johanna McLatchy.

Mary Beth

From: Moscicki, Richard
Sent: Thursday, August 07, 2014 10:29 AM
To: Clarke, Mary Beth
Subject: FW: Dystrophin meeting

Hi Mary Beth, can I ask where we might be on project management help for this meeting on dystrophin early next year? Rich.

From: Leptak, Christopher
Sent: Thursday, August 07, 2014 8:35 AM
To: Moscicki, Richard
Subject: RE: Dystrophin meeting

Understood. FYI, I have a meeting with NIAMS and NCAST from NIH this afternoon to discuss potential co-sponsorship. Will keep you and the rest of the steering committee in the loop as progress continues.

Chris

From: Moscicki, Richard
Sent: Thursday, August 07, 2014 8:09 AM
To: Leptak, Christopher
Subject: Re: Dystrophin meeting

I have left it with Mary Beth, I will check in next week when back. Rich

---

From: Leptak, Christopher
Sent: Wednesday, August 06, 2014 09:39 AM
To: Moscicki, Richard
Subject: Dystrophin meeting

Hi Rich,

As I move forward with the planning for the Dystrophin meeting, touching base to see if you have had any luck identifying admin support for the effort.

Thanks

Chris

From: Clarke, Mary Beth
To: Moscicki, Richard; Hunt, Michie
Subject: RE: program management help
Date: Wednesday, July 30, 2014 9:13:22 AM

Rich,

Michie Hunt, OEP's Acting Deputy Director (while Heather is out), and I will take a look at the available resources and get back to you. Is there any flexibility on the timing of the meeting or does it need to occur in January?

Thanks,
Mary Beth

From: Moscicki, Richard
Sent: Tuesday, July 29, 2014 3:04 PM
To: Clarke, Mary Beth; Brown, Heather
Subject: program management help

Hi Mary Beth and Heather, I am looking for program management help to put together a public scientific workshop in January or so to examine dystrophin measurement methods, to select current best approaches for the field to use for regulatory purposes in developing drugs for Duchene's Muscular Dystrophy. Chris Leptek has offered to be the lead with technical and scientific help from Ash Rao, but they need a program manager to really get this done. ShaAvhrée seemed to think you might be able to help. Rich.

From: Choy, Fannie (Yuet)
To: Moscicki, Richard
Cc: Choy, Fannie (Yuet)
Subject: FW: (Pls Review) - Sarepta/eteplirsen dystrophin analysis request letter
Date: Monday, July 28, 2014 10:43:23 AM
Attachments: IND077429_eteplirsen_FINAL-Advice (dystrophin).doc

---

Good morning,

Attached please find the Sarepta letter for the request for independent dystrophin data analysis. This is the final version cleared by Ellis, Ron and Ash (7/25 1:15p).

We hope to send the letter today. Please review if you concur.

Thanks
Fannie
Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products

From: Dunn, Billy
Sent: Monday, July 28, 2014 12:05 AM
To: Choy, Fannie (Yuet)
Cc: Bastings, Eric; Farkas, Ronald
Subject: RE: (Pls Review) - Sarepta/eteplirsen dystrophin analysis request letter

If this has been written and cleared by Ash, Rich, and Ellis, and noting Ron's clearance below, then I will not make any edits and this can be signed.

Thanks,
Billy

From: Choy, Fannie (Yuet)
Sent: Friday, July 25, 2014 2:46 PM
To: Dunn, Billy
Cc: Bastings, Eric; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: (Pls Review) - Sarepta/eteplirsen dystrophin analysis request letter

Hi, Billy

Attached please see the letter for the dystrophin analysis request. Please review and let me know if you concur.

Thanks
Fannie

From: Farkas, Ronald

Sent: Friday, July 25, 2014 2:26 PM
To: Choy, Fannie (Yuet)
Cc: Rao, Ashutosh
Subject: RE: (Pls Review) RE: version 3

Fannie,
Looks good to go
Thanks
Ron

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	IND 077429
Communication Type:	Correspondence
Communication Group:	IND Information Request or Advice
Communication Name:	Advice/Information Request
Communication ID:	COR-INDAD-02
Drafted by:	FC
Clearance History:	Rao/Farkas/Unger 7/25/14; Moscicki
Finalized:	
Filename:	
Use Statement:	Use to send the IND sponsor either advice or a request for additional information for issues that would not potentially lead to a clinical hold and when the reviews are completed.
Notes:	NOTE-- IF THERE ARE SAFETY ISSUES THAT MAY LEAD TO A CLINICAL HOLD, USE "DEFICIENCY - POTENTIAL HOLD ISSUES (COR-INDAD-03)"

Version: DARRTS 03/27/2014

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077429

ADVICE/INFORMATION REQUEST

Sarepta Therapeutics, Inc.
Attention: Matthew Rael, MS
Manager, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. Rael:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eteplirsen (AVI-4658).

We also refer to your submission, dated May 21, 2014, providing an interim update on the new bioassay protocols under development for your validated dystrophin assessment methods.

We further refer to our May 29 and 30, 2014, site visit of the laboratories at Nationwide Children's Hospital Research Institute, where studies 201 and 202 were conducted.

Based on follow-up discussions with you and investigators at Nationwide Children's Hospital, we would like to request the following re-analysis of the stored raw images from previous phase 2 studies, to be completed at the earliest possible time. We have provided our requests, below, but please let us know if we can provide any additional information or clarification. Please submit a timetable for the estimated completion dates of each request.

1. **Percent Dystrophin Positive Fibers by Expert Assessment:** Please obtain blinded, independent assessment of the dystrophin scoring (positive/negative) from three pathologists or other experts.

   Please specifically address the following points:

   a. Include images obtained with MandyS106, Dys2, and Dys3 antibodies.

   b. Specify the computer equipment, software, and conditions under which the pathologists will analyze the images. We suggest use of a modern high-resolution LED monitor in a room where lighting is well controlled (i.e., dimly lighted).

   c. Ensure that the 20x image files are renamed and randomized with respect to patient number, block number, section number, and quadrant number, and that all reads are blinded. In other words, the 24 images for each stain/patient/and timepoint should be separated, intermixed with images from all other patients, and read blindly in random

order. The person(s) responsible for blinding the image files should not be involved in the image analyses.

d. Assess the inter-analyst and intra-analyst variability for your image analyses between the independent pathologists. We suggest that readers analyze several images on two occasions (mixed in with other images), and that the dual readings can be used to assess intra-reader variability.

2. **Histogram of Pixel intensity**: Please submit the tiff files for a subset of images composed of the first 3 images from each patient and time point (12 patients and 3 time points), and include similar images for your positive and negative controls. For each image, please also provide a histogram of the red intensity of the pixels in the image.

3. Please provide summarized data of the Bioquant fluorescence intensity analyses from study 201/202 using your 20x images.

4. Please provide the primary IHC and western blot data for the 12-week open-label phase 2 dose escalation study and conduct the same analyses as described above on the IHC images.

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}

Billy Dunn, M.D.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

From:	Kaiser, James
To:	Moscicki, Richard; Temple, Robert; Unger, Ellis; Rao, Ashutosh; Buckman-Garner, ShaAvhrée; Dunn, Billy; Bastings, Eric; Walton, Marc; Mansfield, Elizabeth; Farkas, Ronald; Rogers, Hobart; Yang, Xinning; Howard, Kristina; Ling, Xiang; Jin, Kun; Litwack, Ernest (David)
Cc:	Stuart, Alicia; Noone, Marianne
Subject:	Dystrophin July 14 CPIM: draft meeting summary for comment
Date:	Tuesday, July 22, 2014 4:06:57 PM
Attachments:	FDA CPIM summary dystrophin draft 22July2014.doc

Folks – Here is a first draft of the meeting summary from the meeting on July 14 concerning dystrophin, for comments and editing. Pardon me if I have sent you this if you did not participate! If there are participants whom I have left out of this email list, or on the document, please let me know so that I can forward this copy to them. In addition, I have done my best to get everyone's title and FDA working group right, so please forgive and correct any errors.

In the interest of being expeditious, I request that you return comments in a week's time or less: by COB July 29.

Please return editing and comments to Marianne Noone, who is covering for Alicia, and cc Alicia and me. Thanks.

Jim Kaiser
Medical Officer
Office of Translational Sciences

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE

Food and Drug Administration
Office of Translational Sciences
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Memorandum

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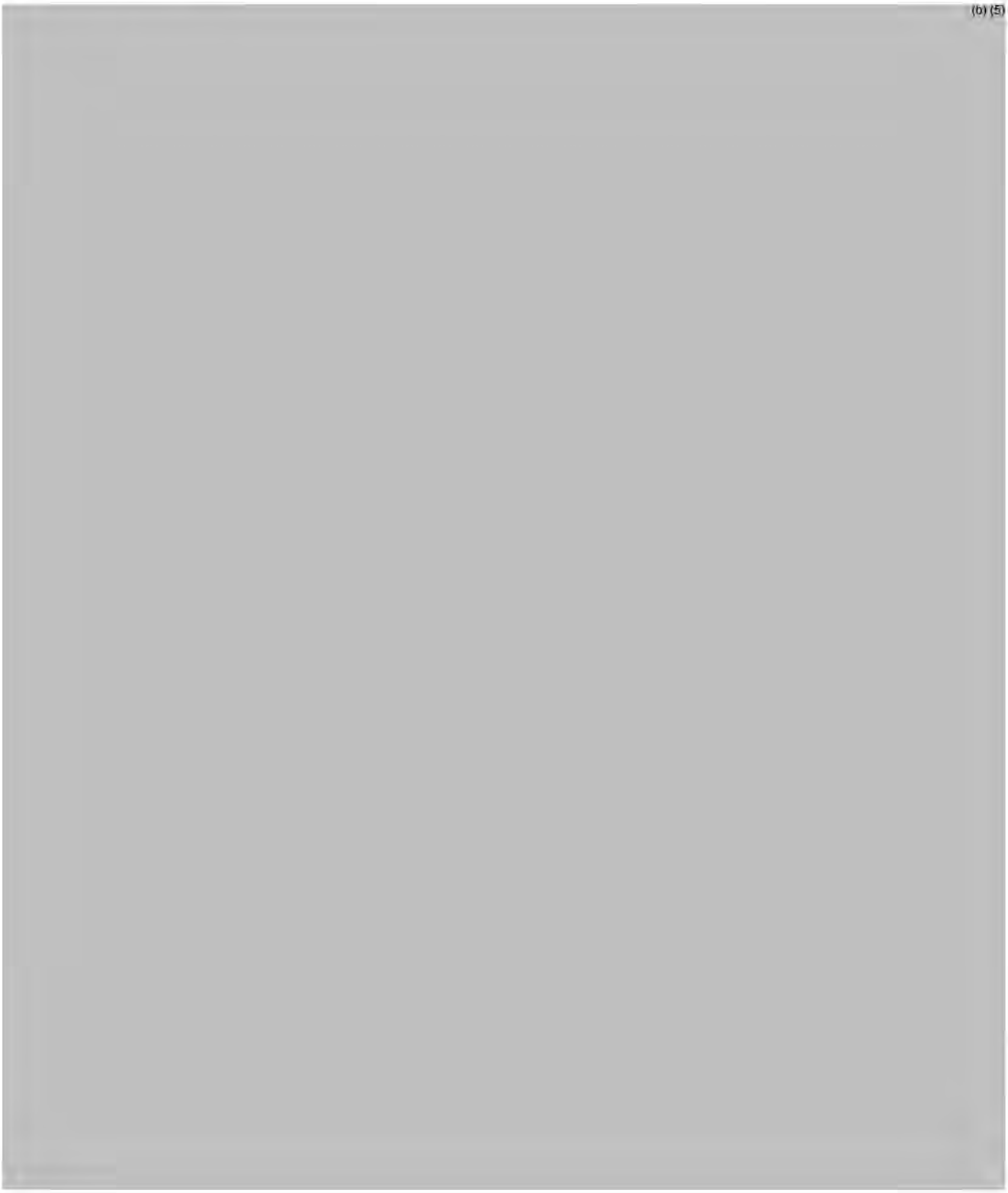

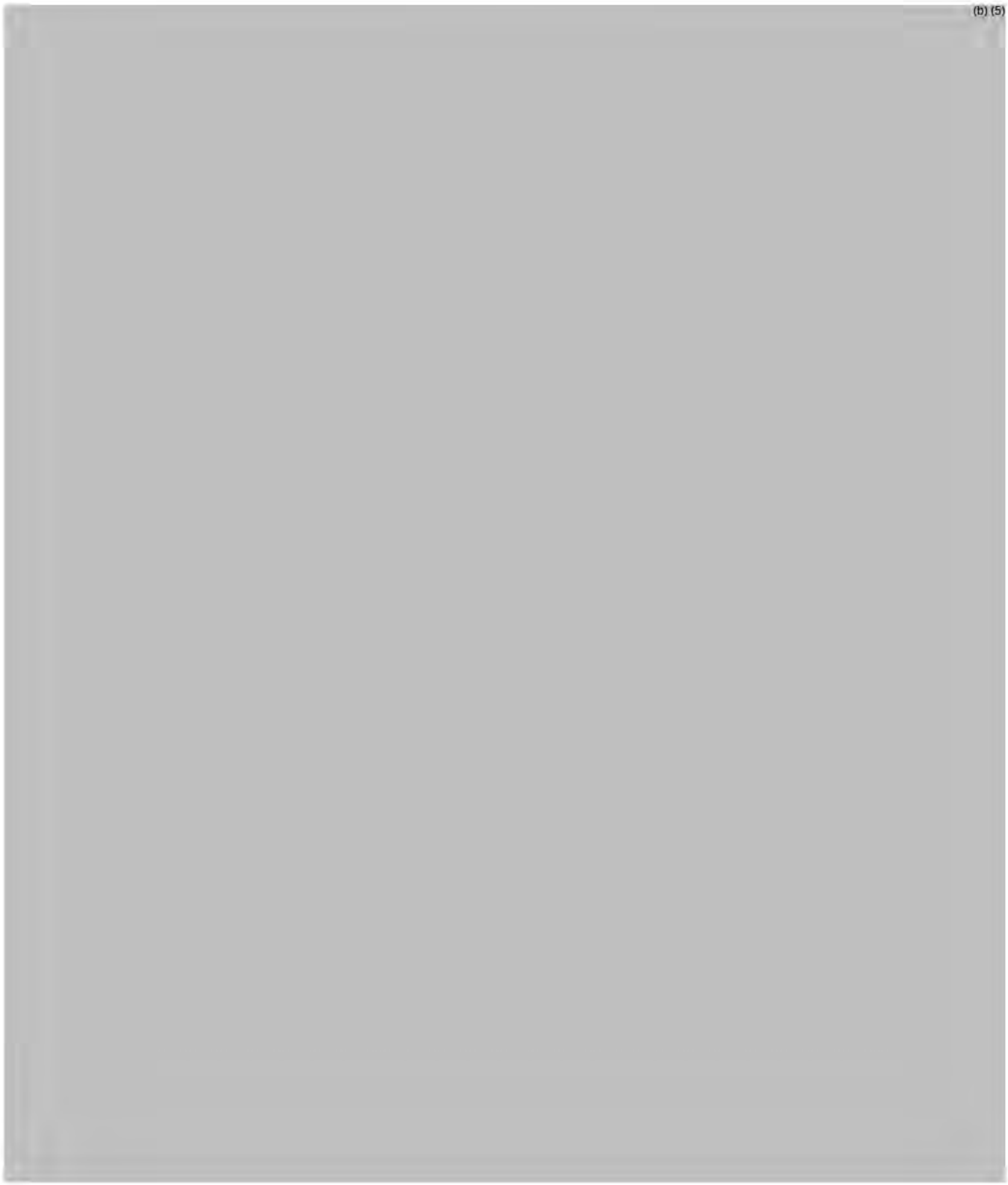
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(b) (5)

From: Farkas, Ronald
To: Moscicki, Richard; Unger, Ellis; Temple, Robert; Rao, Ashutosh; Rogers, Hobart
Subject: Dystrophin expression in model 51 BMD
Date: Monday, July 14, 2014 5:40:25 PM
Attachments: Anthony 2011 dystrophin quantification in becker.pdf

---

Regarding the amount of dystrophin expressed in BMD, this is from the Muntoni lab, showing that in the most severe BMD (patient 14), who was walking but unable to run at age 25, dystrophin expression was about 50% of normal. Patients with mild or asymptomatic disease had expression more like 75% of normal or higher. I'm not sure how to compare this data to Hoffman's groups slide today showing about 5% of normal dystrophin in BMD.
Thanks
Ron

Ronald Farkas, MD, PhD
ronald.farkas@fda.hhs.gov
Clinical Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 22, Room 4204
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

From: Stuart, Alicia
Cc: Stuart, Alicia
Subject: Agenda for dystrophin meeting and attendee list
Date: Monday, July 14, 2014 10:33:27 AM

Good morning:

Here is the agenda for today's meeting regarding dystrophin:

White Oak Campus Building 22, Room 1313

Teleconference: International participants use toll number 210.406.1493, passcode (b) (4)
US toll free number is 888.454.6812, passcode (b) (4)

Adobe Connect Information for Domestic and International Participants:
https://collaboration.fda.gov/abs2014/

1. Introduction and FDA opening remarks
2. Presentations
   a. Dr. Yetrib Hathout: Dystrophin Mass Spectrometry Based Assay – 15 minutes
      Q&A – 5 minutes
   b. BOM Working Group/Dr. Francesco Muntoni: International Benchmarking of Methods for Dystrophin Expression – 15 minutes
      Q&A – 5 minutes

3. Discussion, to include thoughts on a larger workshop to discuss the challenges and opportunities with the currently available methods for quantitative and objective measurement of dystrophin in patient samples.

FDA invitees to the meeting are:

Drs. Kristy Brown, Eric Hoffman and Yetrib Hathout, Children's National
Dr. Francesco Muntoni, UCL Institute of Child Health & Great Ormond Street Hospital for Children (GOSH)
Dr. Larry Bell, Prosensa
Drs. Matthew Rael, Pete Sazani and Art Krieg, Sarepta
Dr. Annemieke Aartsma-Rus, Leiden University Medical Center
Dr. Justin Fallon, Brown University
Dr. Louise Rodino-Klapac, Ohio State University

Thank you,

Alicia Barbieri Stuart (project manager, OTS)

Alicia Barbieri Stuart (AB)
CDER/Office of Translational Sciences

10903 New Hampshire Avenue
Silver Spring, MD 20903
Alicia.Stuart@FDA.HHS.GOV
301.796.3852
Remote Wednesday's & Friday's

doi:10.1093/brain/awr291 Brain 2011: 134; 3547–3559 | 3547

BRAIN
A JOURNAL OF NEUROLOGY

Dystrophin quantification and clinical correlations in Becker muscular dystrophy: implications for clinical trials

Karen Anthony,[1,*] Sebahattin Cirak,[1,*] Silvia Torelli,[1] Giorgio Tasca,[2] Lucy Feng,[1] Virginia Arechavala-Gomeza,[1] Annarita Armaroli,[3] Michela Guglieri,[4] Chiara S. Straathof,[5] Jan J. Verschuuren,[5] Annemieke Aartsma-Rus,[6] Paula Helderman-van den Enden,[6] Katherine Bushby,[4] Volker Straub,[4] Caroline Sewry,[1] Alessandra Ferlini,[3] Enzo Ricci,[7] Jennifer E. Morgan[1] and Francesco Muntoni[1]

Received May 31, 2011. Revised August 3, 2011. Accepted September 6, 2011. Advance Access publication November 18, 2011

From: Kaiser, James
To: Moscicki, Richard
Subject: FW: what to say at the meeting
Date: Friday, July 11, 2014 3:17:01 PM

From: Kaiser, James
Sent: Friday, July 11, 2014 2:10 PM
To: Rao, Ashutosh
Subject: what to say at the meeting

Ash – please take a look at the following.

It seems to me that we should solicit a head count of FDA folks who will be able to stay for an additional ½ hour. If principals have to leave, it will be hard to justify keeping the meeting going!

.....

Start of meeting:
OK, let's get started. It seems that we have everyone in attendance.

As a means of introduction...I'm Jim Kaiser, a medical officer in the Office of Translational Sciences. We have organized this meeting to provide an opportunity to have an exploratory discussion of dystrophin measurement in the development of drugs for Duchenne's Muscular Dystrophy. Another one of our goals is to start discussion of venues to continue, and possibly expand the discussions in the future, potentially in a public workshop.

I want to remind folks of the agenda: We will begin with two talks, one by Dr. Hathout and the other by [TBD]. Each will be up to 15 minutes, and we plan for about 5 minutes after each for questions. After the talks and Q&A, we invite participants to discuss the issues. I hope to enforce a strict time limit for the talks and Q&A to allow for the fullest discussion possible.

At the end of the meeting *[person]* will summarize the key points of the meeting and any action items that may have come up. **[Best done by someone at FDA with deep familiarity with the field]**

Now Dr. Moscicki has a few opening words.

.....

Starting the discussion
[Who will open the discussion, and what should be said? I would imagine that Dr. Moscicki could think of the appropriate way to get this started]

.....

At 50 minutes to the hour

I **[or other person as I commented above]** have to interrupt at this point to say that the hour is almost up. Would folks like to continue this for an additional ½ hour or so? **[It is not guaranteed that everyone will be comfortable with this....]** We have the room for that time.

.....

[If we cannot continue the meeting, or at 1 hr 20 minutes of the meeting]:

I **[or other person as I commented above]** would like to summarize some of the key points I have heard at this meeting. Please forgive me if I get something wrong.

- Point #1
- Point #2
- Action items??????? [Will there be any?]

Any comments?

[JK speaking] We will send a meeting summary to all the participants at this meeting. Thank you.

From: Kaiser, James
To: Unger, Ellis; Moscicki, Richard; Farkas, Ronald
Cc: Rao, Ashutosh
Subject: FYI: text of email with agenda and attendee list
Date: Friday, July 11, 2014 1:50:12 PM

Drs. Unger, Moscicki, and Farkas: For your information, here is a draft (with names and other details to be filled in) of an email OTS intends to send to participants at Monday's dystrophin meeting. At this point it looks unlikely that this will go out today. Comments invited, of course.

Jim

.....

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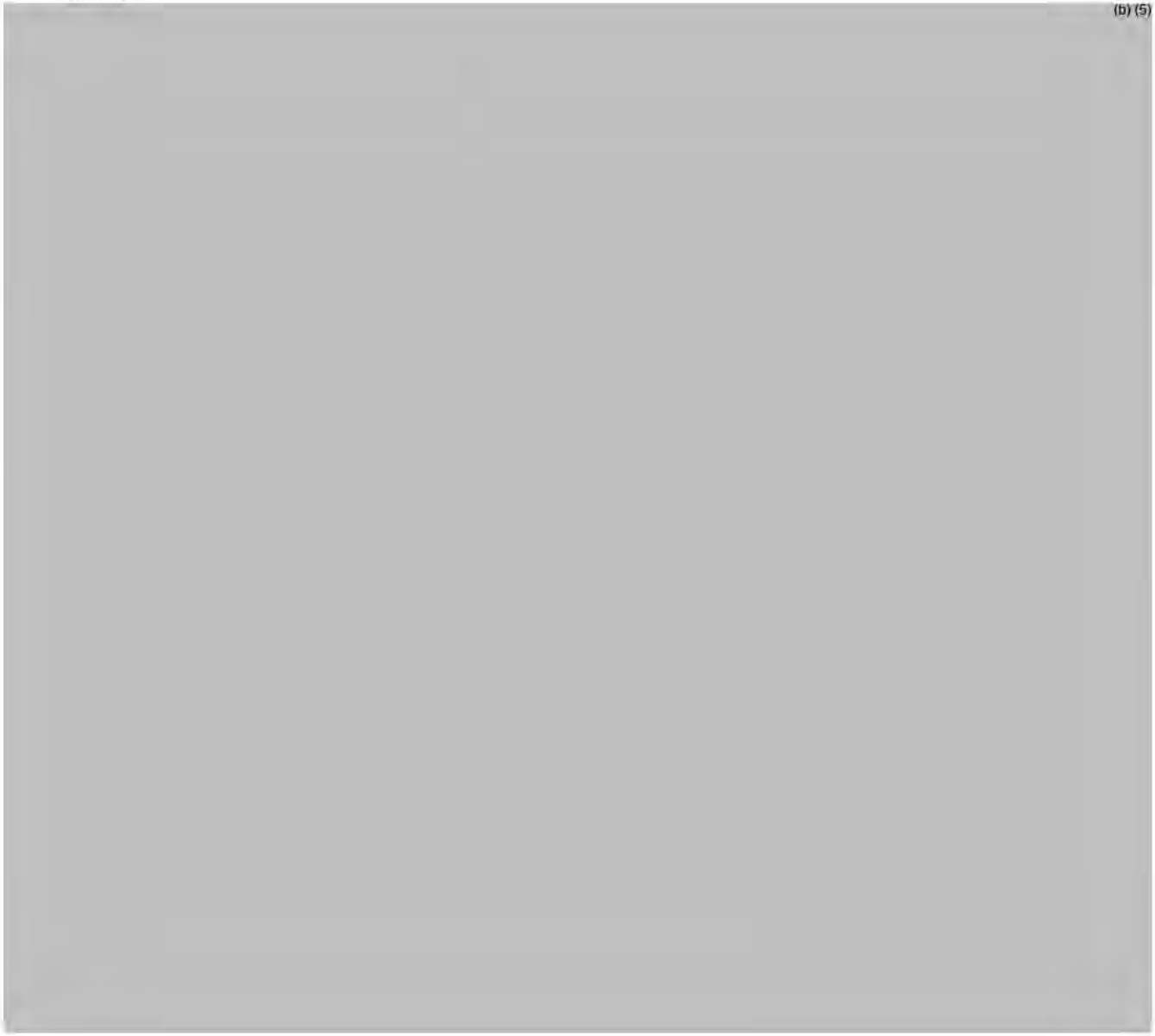

From: Kaiser, James
To: Moscicki, Richard; Rao, Ashutosh; Farkas, Ronald
Cc: Buckman-Garner, ShaAvhrée; Unger, Ellis; Dunn, Billy; Bastings, Eric; McCune, Susan; Walton, Marc
Subject: scheduling dystrophin meetings
Date: Wednesday, June 11, 2014 1:09:26 PM

Drs. Moscicki, Rao, and Farkas,

I would like to see if we are clear on the next steps from our meeting on May 15 regarding dystrophin discussions with outside groups. It is my understanding that we came to the conclusion that an invitation would be extended to Dr. Hoffman to have certain developers of dystrophin-targeted therapies for muscular dystrophy be invited to join his meeting scheduled for July 14 at 3 pm. If Dr. Hoffman is not favorable to that concept, the plan would be to have a separate meeting with these groups. We also discussed having a "small meeting" or a meeting involving consortium members closest to developing a treatment for muscular dystrophy with a view toward a larger workshop later in the year, but I am not sure whether there was a conclusion on this approach.

a. Is this correct or has the plan been modified?
b. If OTS makes the proposal for additional attendees to the meeting on July 14, do you have a list of names of the other invitees for consideration and discussion with Dr. Hoffman?

Thank you.

Jim

From: Dunn, Billy
To: Kaiser, James
Cc: Farkas, Ronald; Bastings, Eric; Rao, Ashutosh; Moscicki, Richard; Unger, Ellis
Subject: CPIM for dystrophin on 7/14
Date: Thursday, May 15, 2014 7:21:02 PM

Jim,

With regard to the scheduled meeting with the Children's National Medical Center folks (Brown, Hathout, Hoffman) on 7/14 to discuss methods for assessment of dystrophin expression, the previous arrangement with you and your colleagues providing administrative and scheduling support for the meeting and DNP providing the lead for content and structure will change somewhat. Going forward, Dr. Rao, Dr. Moscicki, and Dr. Unger will be leading the content and structure components of this meeting. They are the leads for a parallel dystrophin expression assessment project that is broader in scope and will take the lead on this meeting as part of that broader effort. It may be that the currently scheduled CPIM meeting may evolve to include other stakeholders, or it may be that the Children's National Medical Center folks will be invited to participate in a separate larger meeting while the currently scheduled meeting remains as is, or some other option. Dr. Rao, Dr. Moscicki, and Dr. Unger will provide guidance on that as the project evolves. DNP will continue to be engaged with this project and will participate in the meetings.

Thanks,
Billy

From: Kondas, Karen M
To: Rao, Ashutosh; Choi, Young M; Unger, Ellis; Moscicki, Richard
Cc: Choy, Fannie (Yuet)
Subject: RE: Background notes for NCH preinspection mtg
Date: Friday, May 23, 2014 10:50:35 AM

I have already contacted NCH and stated that we would arrive at 800AM on Thursday [5/29/14]. Mr. John Psurny is to meet us at the front door of the hospital. If you want to start earlier I can tell them.

The assignment stated that study should not be revealed ahead of time. If you want I can let them know what studies [201/202] we will be looking at.

I will issue the fda 482 at the beginning of the inspection. At this point I am not sure who the 482 will be issued to. I will cover the routine things that ORA usually does when working with the center. Usually we cover general facilities, training, sample handling/integrity.

Let me know

Karen

From: Rao, Ashutosh
Sent: Friday, May 23, 2014 10:26 AM
To: Choi, Young M; Unger, Ellis; Moscicki, Richard; Kondas, Karen M
Cc: Choy, Fannie (Yuet)
Subject: Background notes for NCH preinspection mtg

Hi all,

We only have a 30 minutes for our pre-inspection meeting on Tuesday so I am sending some background and preliminary thoughts by email. I can stay longer than 30 mins but most other calendars were booked.

1. **Background**: Nationwide Children's Hospital and its laboratories conducted the image acquisition and analyses of dystrophin from biopsies of pretreated and etiplersen-treated DMD patients. Data were collected from 12 patients and each patient sample had 24 raw data images that resulted in dystrophin-positive scoring and % fluorescence intensity quantitation. From my perspective, the methodology for tissue processing, immunohistochemistry staining, image acquisition (random/manual), image analyses (Bioquant/ImageJ software) would be important to review. There may be other aspects that others on the team would like to include and I may have missed something, please feel free to add. The clinical aspects of biopsy collection and DMD are outside my expertise.

2. We can use the first day for general questions on tissue processing, dystrophin measurement, and Bioquant analyses. Bioquant software analysis provides a % fluorescence intensity from the muscle fibers after image acquisition. The attached files (*Dystrophin data.doc* and 2 PDF files starting with *listing-mandys106*) provide the summarized and detailed raw data for % intensity and positive/negative scored fibers from the most recently

completed study. These should be good references as the investigators walk us through the raw data files and resulting image analyses. I suggest that we start the day early so we can get through as many data sets as possible. We can divide up some of the inspectional activities depending on other audits that ORA/OSI would like to conduct.

The second day could be spent on ImageJ analyses that provides a manual positive/negative scoring of the dystrophin-positive fibers. We can also discuss their immunohistochemistry procedures on day 2.

3. Dr. Choi, please confirm that Ms. Kondas or you will take the lead on opening the inspection with the facility administration and drafting the inspection report with input from myself, Dr. Unger, and Dr. Moscicki. From my perspective, any data outputs that are generated in our presence (*e.g.* the analyses of 24 images from patient #006 resulted in a mean fluorescence intensity of X%) would be an important part of our report so that DNP and other reviewers can look at this.

4. I suggest that we call NCH beforehand and provide a reminder on our 2 day plan so they can plan accordingly. It would be preferable if they don't have to scramble for arranging SOPs/data files/computers/projectors/microscopes/personnel while we wait. We may want to request that we can each have a copy of their SOPs as we go over their method and data. We should also request the availability of a room where the inspection team can meet with the investigators and discuss within ourselves as needed for the duration of the visit. Does that sound reasonable? **Fannie**, could you please help set up this call with NCH and I/others can join?

Please feel free to share your thoughts now or we can catch up on Tuesday at 10.30 am.

Thanks.
Ash

Ashutosh Rao, Ph.D.
Principal Investigator
Drug Quality Reviewer
Laboratory of Biochemistry
Division of Therapeutic Proteins
Office of Biotechnology Products
Office of Pharmaceutical Sciences
Center for Drug Evaluation and Research
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29 Lincoln Dr, HFD-122,
NIH Building 29A, Room 2A-11,
Bethesda, MD 20892

Tel: 301-827-4487
Fax: 301-480-3256
Email: Ashutosh.Rao@fda.hhs.gov

From: Buckman-Garner, ShaAvhrée
To: Moscicki, Richard
Cc: Ligon, Sharnell (CDER)
Subject: Can you join the Dystrophin call?
Date: Wednesday, May 21, 2014 3:06:40 PM
Attachments: image001.png

Thank you,

ShaAvhrée

ShaAvhrée Buckman-Garner, M.D., Ph.D., F.A.A.P.
Director
Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration
(301)796-2600
Fax: 301-796-9907

"Do, or do not. There is no try."

If you have feedback for OTS, click here:

From:	Buckman-Garner, ShaAvhrée
To:	Walton, Marc; Rao, Ashutosh; Kaiser, James; Dunn, Billy
Cc:	Farkas, Ronald; Bastings, Eric; Moscicki, Richard; Unger, Ellis; Stuart, Alicia; McCune, Susan
Subject:	RE: CPIM for dystrophin on 7/14
Date:	Friday, May 16, 2014 11:25:50 AM

We can also have them attend by phone and WebEx or video conference if needed. We can make this work.

S

From: Walton, Marc
Sent: Friday, May 16, 2014 11:15 AM
To: Rao, Ashutosh; Kaiser, James; Dunn, Billy
Cc: Farkas, Ronald; Bastings, Eric; Moscicki, Richard; Unger, Ellis; Buckman-Garner, ShaAvhrée; Stuart, Alicia; McCune, Susan
Subject: Re: CPIM for dystrophin on 7/14

Ok. We just need to have it decided right away what the format of the July meeting will be. And who you want from the outside to attend. We are only two months away and if you want people who will travel from any distance there is risk that their schedule might not accommodate the existing date if we don't get on their schedule soon (if not already conflicted).

Thanks
Marc

From: Rao, Ashutosh
Sent: Friday, May 16, 2014 10:05 AM Eastern Standard Time
To: Walton, Marc; Kaiser, James; Dunn, Billy
Cc: Farkas, Ronald; Bastings, Eric; Moscicki, Richard; Unger, Ellis; Buckman-Garner, ShaAvhrée; Stuart, Alicia; McCune, Susan
Subject: RE: CPIM for dystrophin on 7/14

Hi Marc,

From my perspective, it would be great if your office would remain the point of contact for Hoffman and others. I think the Critical Path program would be a good, neutral ground to allow a broad and open scientific discussion that may then allow more informed regulatory decisions.

Ash

From: Walton, Marc
Sent: Friday, May 16, 2014 9:25 AM
To: Rao, Ashutosh; Kaiser, James; Dunn, Billy
Cc: Farkas, Ronald; Bastings, Eric; Moscicki, Richard; Unger, Ellis; Buckman-Garner, ShaAvhrée; Stuart, Alicia; McCune, Susan
Subject: RE: CPIM for dystrophin on 7/14

Ash, Rich, Ellis,

Yes, we should have a talk to plan how to proceed.

A couple of questions - Do you want to shift the point of contact for the July meeting to one of your people, or do you want us to remain Hoffmann etal's point of contact. Happy to do whatever you prefer.

If it is to remain us, we do need to decide what the July meeting will be rather soon, and may need to keep Hoffmann etal informed also.

Thanks
Marc

From: Rao, Ashutosh
Sent: Friday, May 16, 2014 9:16 AM
To: Kaiser, James; Dunn, Billy
Cc: Farkas, Ronald; Bastings, Eric; Moscicki, Richard; Unger, Ellis; Buckman-Garner, ShaAvhrée; Walton, Marc; Stuart, Alicia; McCune, Susan
Subject: RE: CPIM for dystrophin on 7/14

Thanks, Billy.

Jim, it may be best if we set up a quick chat to discuss this. We will need to figure out a way to engage other DMD stakeholders. This may include other sponsors and investigators who are interested in outcome measures related to DMD.

Best,
Ash

From: Kaiser, James
Sent: Friday, May 16, 2014 8:43 AM
To: Dunn, Billy
Cc: Farkas, Ronald; Bastings, Eric; Rao, Ashutosh; Moscicki, Richard; Unger, Ellis; Buckman-Garner, ShaAvhrée; Walton, Marc; Stuart, Alicia; McCune, Susan
Subject: RE: CPIM for dystrophin on 7/14

Billy – Thanks for the update. I will stay tuned.

Jim

From: Dunn, Billy
Sent: Thursday, May 15, 2014 7:20 PM
To: Kaiser, James
Cc: Farkas, Ronald; Bastings, Eric; Rao, Ashutosh; Moscicki, Richard; Unger, Ellis
Subject: CPIM for dystrophin on 7/14

Jim,

With regard to the scheduled meeting with the Children's National Medical Center folks (Brown,

Hathout, Hoffman) on 7/14 to discuss methods for assessment of dystrophin expression, the previous arrangement with you and your colleagues providing administrative and scheduling support for the meeting and DNP providing the lead for content and structure will change somewhat. Going forward, Dr. Rao, Dr. Moscicki, and Dr. Unger will be leading the content and structure components of this meeting. They are the leads for a parallel dystrophin expression assessment project that is broader in scope and will take the lead on this meeting as part of that broader effort. It may be that the currently scheduled CPIM meeting may evolve to include other stakeholders, or it may be that the Children's National Medical Center folks will be invited to participate in a separate larger meeting while the currently scheduled meeting remains as is, or some other option. Dr. Rao, Dr. Moscicki, and Dr. Unger will provide guidance on that as the project evolves. DNP will continue to be engaged with this project and will participate in the meetings.

Thanks,
Billy

From: Dunn, Billy
To: Jenkins, John K; Unger, Ellis; Temple, Robert; Woodcock, Janet; Rao, Ashutosh; Moscicki, Richard; Bastings, Eric; Farkas, Ronald; Choy, Fannie (Yuet)
Subject: RE: Sarepta Proposal for Eteplirsen Program
Date: Friday, March 21, 2014 6:35:26 PM

John,

We began working with Janet's office yesterday on scheduling the internal meeting to discuss the sponsor's proposal and our post-brainstorming meeting comments to the sponsor. That will be on the calendar shortly following Fannie's confirmation of availability. The seminar/workshop idea should work well. We have an independent upcoming CPIM with one of the scientific groups interested in quantitative dystrophin measurements, and we should be able to join the seminar/workshop with the CPIM effort. We will discuss this at the internal meeting.

Billy

From: Jenkins, John K
Sent: Friday, March 21, 2014 2:44 PM
To: Unger, Ellis; Temple, Robert; Dunn, Billy; Woodcock, Janet; Rao, Ashutosh; Moscicki, Richard
Cc: Jenkins, John K
Subject: FW: Sarepta Proposal for Eteplirsen Program

Billy

We will need to schedule an internal meeting to review the sponsor's response to the brainstorming meeting. I discussed this with Janet on Wednesday and I think it is critical that we devote time and resources to understanding the differing conclusions regarding the immunohistochemistry data, since that is a pivotal part of any planned NDA, as well as working together to develop better methods for dystrophin quantification going forward. Janet suggested that we may want to ask Ash and Rich to help lead an effort for a scientific seminar/workshop (non-public) where we invite in sponsors and experts to better understand available methods and ways to enhance them. This could be an agenda topic at the next internal meeting. I am on leave starting today until Wednesday April 2. It is OK to hold the internal meeting without me to keep this project moving forward.

John

From: Chris Garabedian [mailto:cgarabedian@sarepta.com]
Sent: Friday, March 21, 2014 12:44 PM
To: Woodcock, Janet; Temple, Robert; Jenkins, John K; Unger, Ellis; Dunn, Billy
Cc: Shamim Ruff; Ty Howton; Frank J. Sasinowski
Subject: Sarepta Proposal for Eteplirsen Program

Dear Drs. Woodcock, Temple, Jenkins, Unger, and Dunn:

Thank you for the informal brainstorming meeting and the constructive dialogue that took place on Wednesday, March 19th. We have considered the various kinds of input that you provided at this brainstorming session and we propose the following course of actvities for you to consider. Once we receive formal guidance from the Agency, we will begin to move forward on finalizing these study protocols and begin the process of IRB approvals so we can begin screening and dosing new patients as soon as possible.

1. Clinical Studies

Sarepta proposes the following clinical trials for further discussion with you:

Proposed Eteplirsen Studies

Study Type	Population	N	Endpoints
Open label with control	Ambulatory exon-51-amenable DMD patients =7 years; Concurrent control arm of DMD patients with same inclusion/exclusion criteria that are non-exon-51 amenable	Approx. 60:60	6MWT, dystrophin, safety, exploratory functional endpoints
Open label	Exon-51-amenable DMD patients 4-6 years	Approx. 20	Safety, dystrophin, exploratory functional endpoints
Open label	Nonambulatory exon-51-amenable DMD patients =7 years	Approx. 20	Safety, dystrophin, exploratory functional endpoints
Non-interventional natural history	Non-exon-51 amenable DMD patients; all comers	TBD	Safety

2. Dystrophin Methodology

Thank you for your generous offer for us to engage with FDA experts, and also for your additional offer to allow us access to consult experts from the FDA laboratories as well as access to/use of FDA laboratories to work on standardization and refinement of our dystrophin assay methodology.

In order to clarify the quantification methodology of the dystrophin data from the existing Phase 2 clinical trial, we will ask the pathologistat Nationwide Children's Hospital who generated the dystrophin-positive fiber data to make herself available to you. This may allow you to better understand how these data were generated and interpreted. We look forward to scheduling these meetings as soon as possible.

Sarepta will work closely with the Agency to reach agreement on our dystrophin quantification methods for use in our upcoming studies. We have a protocol to conduct immunofluorescence, western blot, and RT-PCR assessments at a minimum. If the timing of muscle biopsies are expected to occur before agreement on these methodologies are reached with the Agency, Sarepta will explore freezing the blocks for future analysis. Sarepta will also investigate the potential assessment of nNOS as a confirmatory marker of functional dystrophin and use of new dystrophin detection and quantification methods, such as mass spectrometry, which may supplement but not initially replace our existing immunofluorescence-based assay.

3. NDA Submission

From the views we heard expressed by the Agency, it appears the FDA may be open to an NDA filing based on the clinical outcomes data from the existing Phase 2 study. Sarepta is prepared to submit the NDA this summer, with an understanding that the chances of a positive review would be bolstered by supplemental data, such as 144-week

clinical data (e.g., 6MWT, Pulmonary Function tests), early safety data from additional eteplirsen exposed patients in the upcoming studies, and/or a possible fourth muscle biopsy from the ongoing Phase 2 study.

4. **Follow-On Exon Skipping Drugs for DMD and Confirmatory Study**

   As discussed, we are in late preclinical development with two follow-on exon-skipping drugs targeting gene deletions amenable to exons 45 and 53 and we understand the Agency would like us to move these drugs into patients as soon as possible. To this end, we will work with the FDA on the design of this study that would include our drugs, SRPT-4045 and SRPT-4053 and will prepare a design that will include one or both of these drugs against a placebo control. Please note that we are currently at the pre-IND stage for these next 2 compounds and will need to prepare manufacturing scale-up for clinical trials with INDs submissions expected in the 2nd half of this year.

5. **Communication to the Public**

   Upon receipt of formal guidance from the Agency that reflects all of the meetings since November, 2013, as well as FDA's position on the course of activities proposed in this letter, we are prepared to share our planned draft press release with the appropriate contact at the FDA to ensure an alignment of communications between Sarepta and the Agency for this program.

We thank you for your active and broad engagement on this program across the Agency and the extensive time each of you have provided to assist us in evaluating eteplirsen for DMD boys. We look forward to your response to our proposal and we hope you that you find the approach we have outlined above acceptable, so that we, together with the DMD community, can move forward swiftly.

Sincerely,

Chris Garabedian
President & CEO
617.274.3993 direct
(b) (6) mobile
cgarabedian@sarepta.com

SAREPTA THERAPEUTICS

215 First Street, Cambridge MA 02142

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

February 11, 2014

ATTN: Kristy J. Brown, Ph.D.
George Washington University School of Medicine and Health Sciences
Department of Integrative Systems Biology
Children's National Medical Center
Center for Genetic Medicine
111 Michigan Avenue, NW, M5700
Washington, DC 20010
(202) 476-2472 phone
(202) 476-6014 fax

RE: Biomarker Qualification Letter of Intent submission

Dear Dr. Brown,

This letter is regarding your Biomarker Qualification Letter of Intent (LOI) submission to qualify dystrophin protein measurements in skeletal muscle biopsies as a surrogate endpoint in clinical trials aiming to restore full length or truncated dystrophin protein in patients with Duchene Muscular Dystrophy.

As we discussed by phone on Friday, January 31st, we would like to thank you for your patience as we reviewed the LOI. We have had many internal discussions regarding biomarkers for Duchene muscular dystrophy, including your LOI submission. The use of dystrophin measurement as a surrogate biomarker in Duchenne Muscular Dystrophy is a complex and difficult matter of substantial, active, and near-term interest to many people in the medical-scientific community. We believe that substantial effort is needed to develop the evidence to support qualification. Because of these complexities, we believe that working with an individual submitter (or working with several separate submitter groups) will not provide an efficient approach to determining the potential of dystrophin measurements to serve as a surrogate endpoint. We believe that a community-wide effort will be the most efficient approach to study the suitability of dystrophin measurements as a surrogate endpoint. As we discussed on our call, we suggest that you and others in the muscular dystrophy scientific community who are interested in this topic work collaboratively to accomplish this.

There are many paths to creating this organized effort. One approach that we believe can be effective is the creation of a broad-based consortium of interested parties. Consortia to undertake programs such as this have been formed under the guidance of, and with administrative support from, organizations such as the Critical Path Institute in Tucson, AZ (http://c-path.org/), and the Biomarkers Consortium in Bethesda, MD

(http://www.biomarkersconsortium.org/). We welcome any organizational structure that enables a broad-based effort to work on this issue, and CDER will be interested in offering our advice as liaisons to such an activity.

In addition, you may also wish to consider development of dystrophin measurements as a pharmacodynamic biomarker to serve important purposes earlier in drug development than when a surrogate endpoint would be used. For example, pharmacodynamic biomarkers may be used to aid in proof of concept studies, or aid in dose ranging studies for guiding selection of doses for phase 3 studies. Both uses can provide an important contribution towards a successful clinical development program of a drug. Both uses are separate contexts of use that might be qualified, and are distinct from the context of use as a surrogate endpoint. You may choose to pursue one or more of these earlier uses as well as the surrogate endpoint use. The strength of evidence to support these types of decisions in drug development is generally less than to support use as a surrogate endpoint.

As we discussed on January 31st, a next step for further discussion would be via our Critical Path Innovation Meeting (CPIM) format. These meetings are a pathway for investigators to meet and discuss with FDA innovative strategies to address challenges in drug development, and that may improve the efficiency and success of drug development programs. Experts from CDER, and other centers as appropriate, participate in these discussions. As we have advised you, Ms. Alicia Stuart will be the point of contact for this meeting, and she has already been in communication with you.

We look forward to further discussions with you.

Regards,

Shashi Amur, Ph.D.
Scientific Coordinator, Biomarker Qualification Program

Marc Walton, M.D., Ph.D.
Co-Director, Biomarker Qualification Program

The following are recommendations to the submitter of the Drug Development Tool Qualification Submission for dystrophin protein. The submitter intends to qualify quantitative levels of dystrophin protein as a surrogate endpoint in Duchenne muscular dystrophy (DMD). These recommendations should be considered in the submitter's preparation of a briefing document for further consideration by FDA of dystrophin as a surrogate in DMD.

The briefing document should clearly separate evidence addressing the following two distinct questions:

1. Do treatments that increase dystrophin protein in DMD result in clinical benefit? [addressed by DNP below]
2. What methods can be used to quantify the increased dystrophin? [to be addressed primarily by CDRH – DNP can comment on the CDRH text]

In the Letter of Intent, the submitter states that "restoration of dystrophin protein to accurately detectable levels (approximately 10% of normal) is indicative of an improved clinical outcome." However, it is not clear to DNP that this has been established. The submitter should present evidence that treatments that increase dystrophin in DMD result in clinical benefit. For example, what drugs have been shown to do this?

The submitters suggest that natural history data from Becker muscular dystrophy (BMD), which has a less severe phenotype than DMD, supports that restoration of dystrophin expression in DMD will result in clinical benefit. However, the submitter should address how differences between BMD and DMD might affect the relationship between protein levels and clinical course. For example, *restoration* of dystrophin in DMD would seemingly differ from life-long presence of dystrophin as occurs in BMD.

The submitter should also address the effect of *location* of the dystrophin on potential for clinical benefit. For example, is relatively high expression of dystrophin in some muscle cells, as seemingly occurs in revertant fibers in DMD, adequate for clinical benefit, and if not, what level of expression in what percentage of muscle cells is necessary?

The submitter should also address the *functionality* of the dystrophin produced. For example, are some truncated forms of dystrophin more likely to confer benefit in DMD than others, and if so, at what levels? Also, how might functionality of the protein be affected by existing damage in DMD muscle?

Data from animal models can sometimes provide support for effects in humans, but positive findings in animal models often have not been found to predict benefit for the human disease. The submitter cites animal studies, but should address the evidence that animal findings in DMD models predict human benefit.

From: Guidos, Robert
To: Woodcock, Janet; Throckmorton, Douglas C; Moscicki, Richard
Subject: Fw: Parents Hopeful FDA Grants Quick Approval for DMD Treatment
Date: Sunday, February 09, 2014 10:05:00 AM
Attachments: image001.png

See summary emails below.

From: Menon, Ramesh
Sent: Friday, February 07, 2014 09:05 PM
To: Guidos, Robert; Meister, Karen G; Vining, Elaine
Cc: Walinsky, Sarah; Whyte, John; Jenkins, John K
Subject: RE: Parents Hopeful FDA Grants Quick Approval for DMD Treatment

I accidentally left out a couple important details. Christine McSherry mentioned that they're doing more Hill outreach around rare disease day (Feb 28th), and they also showed a trailer for a documentary they're working on, which they plan on releasing around May. The trailer isn't available online, but my impression was that it seemed well put together. The theme of the trailer though was that FDA is standing in the way and delaying their kids' access to a life-saving drug.

From: Menon, Ramesh
Sent: Friday, February 07, 2014 7:12 PM
To: Guidos, Robert; Meister, Karen G; Vining, Elaine
Cc: Walinsky, Sarah; Whyte, John; Jenkins, John K
Subject: RE: Parents Hopeful FDA Grants Quick Approval for DMD Treatment

I can send more details on what the panelists said next week, but here are some key points that I heard some of the parents share today – (these are their opinions, not mine, and a lot of the detail was from essentially small conversations after the event, not their messages for staffers):

- It's clear that eteplirsen meets the criteria for accelerated approval under FDASIA– there are no side effects, and efficacy has been demonstrated.
- They think that eteplirsen has surpassed a bar that other drugs that have received accelerated approval have met.
- They were frustrated with the meeting with FDA yesterday and felt that FDA did not recognize the expertise of the scientists they brought in. They said that FDA has been saying "don't worry, we got this, we'll look at the data" and feel that nothing has happened even though they've had 6 meetings. They seemed to think the tone would change given the experts they brought in and evidently were disappointed.
- They say that eteplirsen is the first drug to make dystrophin. They said that for most boys drisapersen did not actually make protein
- At least some parents feel that FDA is comparing apples and oranges when looking at the drisapersen 48-week history and the 120 week trial for eteplirsen. They said that the boys in the eteplirsen trial had the three risk factors for steep decline, but they stabilized. They seemed to think that FDA felt that the stabilization in the 6 minute walk test was just due to "coincidences." I'm not sure, but they may have suggested the boys in the drisapersen trial didn't show the same risk factors in terms of how their disease may progress. I think they also said that 50% of the boys who stabilized actually worked farther at 120 weeks than they did at 96 weeks.

There were about 100 people in the room. The speakers were the scientists below, Christine McSherry, Mindy Lefler, and Jenn McNary. Michael Staley, Chief of Staff for Spencer Bachus (R-AL), introduced the event and mentioned that Rep. Keating is interested in it too. Michael was glad to see that FDA had someone attend (similarly, at the PPMD event in December he seemed really grateful we were there). He said he's thought about whether there needs to be a meeting with multiple members and FDA staff, but he didn't seem set on that idea and is really just looking for what he can do to be helpful. I reiterated that conversations between the community

and their experts and FDA are taking place, and offered to stay in touch if he has any questions. He said he'll give me a heads-up about future events like this.

Sen. Markey's office also called me and said they're going to be gathering signatures for a letter – some of which will thank FDA, but one of the items will be asking to ensure consistency on guidance for accelerated approval and expedited pathways. She mentioned that the DMD community is behind it, however it sounded like the letter wouldn't be worded quite in the way that DMD expresses their position.

From: Menon, Ramesh
Sent: Thursday, February 06, 2014 6:18 PM
To: Guidos, Robert; Meister, Karen G; Vining, Elaine
Cc: Walinsky, Sarah; Whyte, John; Jenkins, John K
Subject: RE: Parents Hopeful FDA Grants Quick Approval for DMD Treatment

As an fyi, the staffer just provided the following additional details about how this is being framed and who will be on the panel:

CONGRESSIONAL STAFF BRIEFING:

"Using FDASIA to Save Children with Duchenne Muscular Dystrophy"

An update on the current state of research into treatments for Duchenne Muscular Dystrophy and FDA initiatives to accelerate the approval process for promising new drugs

Friday, February 7, 10:00AM
334 Cannon HOB

Panelists:
Dr. Lou Kunkel –Director of the Program in Genomics at Children's Hospital Boston and Professor of Pediatrics and Genetics at Harvard Medical School

Dr. Steve Wilton – Director of the Australian Neuromuscular Research Institute

Dr. Jerry Mendell – The primary investigator for more trials on Duchenne muscular dystrophy than any doctor in the world, including the Eteplirsen study.

From: Guidos, Robert
Sent: Tuesday, February 04, 2014 12:30 PM
To: Menon, Ramesh; Meister, Karen G; Vining, Elaine

Cc: Walinsky, Sarah; Whyte, John; Jenkins, John K
Subject: RE: Parents Hopeful FDA Grants Quick Approval for DMD Treatment

Thx! Is someone from OL attending on Friday?

From: Menon, Ramesh
Sent: Tuesday, February 04, 2014 12:18 PM
To: Guidos, Robert; Meister, Karen G; Vining, Elaine
Cc: Walinsky, Sarah
Subject: RE: Parents Hopeful FDA Grants Quick Approval for DMD Treatment

I spoke with a staffer for a co-chair of the rare disease caucus. Looks like the Jett Foundation, Christine McSherry's group, is behind this event. She also pushed for the briefing CDER (I was on leave for this one, but I think it was Drs. Jenkins, Unger and Bastings) had with staff from Warren's and Markey's offices. I spoke to Christine briefly at the PPMD event in December, and she was very skeptical about FDA's commitment to work with the company (she thought we had already made up our mind even though we expressed that we're still working with Sarepta):

Here's the email the group has asked its members to send to Congress about the briefing:

> Dear :
>
> As your constituent, I am writing to ask that your health staff attend an important briefing this upcoming Friday, February 7, from 10:00am-11:00am in 334 Cannon House Office Building. The briefing will feature a preview of an upcoming documentary on the lives of boys who suffer from Duchenne Muscular Dystrophy (DMD). It will also include a brief presentation from a panel of renowned Duchenne researchers and scientists as well as DMD parents on opportunities to accelerate approval for the first-ever approved therapy for DMD using the tools Congress provided the FDA in the Food and Drug Administration Safety and Innovation Act (FDASIA), which was signed into law in 2012.
>
> I am the parent (friend/relative) of a boy with Duchenne Muscular Dystrophy, the leading genetic killer of children that affects about one out of every 3,500 boys born in the United States. Duchenne has a 100 percent fatality rate and there is no approved treatment. A boy diagnosed with DMD around the age of 5 is expected to experience a loss of muscle strength that leads to confinement to a wheelchair by adolescence and a short life assisted by ventilators. This progressive deterioration leads to death in the late teens or early twenties.
>
> Congress granted the FDA special authorities to accelerate approval of promising treatments for diseases just like DMD that are rare, orphan and fatal. We face a pivotal moment where a decision could determine whether our child is part of the last generation to die from DMD or among the first generation to live.
>
> I know there are many demands on your time and on your staff's time, but I am hoping you will be able to make time for this briefing to help my son (friend/relative) and so many more boys who have no hope unless our government acts to advance promising therapies.
>
> I ask that your staff please attend the briefing on Duchenne Muscular Dystrophy on February 7th from 10:00am-11:00am in 334 Cannon. Please let me know if you will be able to attend by responding toDMDaction@gmail.com.
>
> Sincerely,

Thanks,
Ramesh

-----Original Message-----
From: Guidos, Robert
Sent: Monday, February 03, 2014 11:37 AM
To: Menon, Ramesh; Meister, Karen G; Vining, Elaine
Subject: FW: Parents Hopeful FDA Grants Quick Approval for DMD Treatment

Hi, not sure who is working on this issue. I think it might be Ramesh. Any insight into this briefing. There isn't much information to go on.
Bob

-----Original Message-----
From: Zawisza, Julie
Sent: Monday, February 03, 2014 11:10 AM
To: Woodcock, Janet; Temple, Robert; Jenkins, John K; Unger, Ellis; Dunn, Billy; Whyte, John; Rawlings, Kimberly; Guidos, Robert
Subject: Parents Hopeful FDA Grants Quick Approval for DMD Treatment

Bob Guidos--Note Feb 7 Congressional briefing

http://www.babble.com/disney-dads/parents-hopeful-fda-gives-quick-approval-for-very-promising-dmd-treatment/

DISNEY DADS

Parents Hopeful FDA Will Give Quick Approval for Very Promising DMD Treatment
By JULIANE HIAM |
February 3rd, 2014 at 8:04 am
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Charley and dad Dr. Benjy Seckler. Charley is 13 and has Duchenne Muscular Dystophy.
(photo courtesy Tracy Seckler.)

This Friday, February 7th, at 10am, Congressional Staff will be briefed regarding a big decision the FDA is about to make that could greatly affect the futures of kids with Duchenne Muscular Dystrophy (DMD.)

According to Charley's Fund, a non-profit started by Benjamin and Tracy Seckler who are parents of a child with DMD, based on steps being taken this week, the FDA will decide whether to grant accelerated approval for a treatment drug that is the best bet ever for kids with DMD, and they are urging their followers to write their congressman and senators showing support so that the FDA will not hold the treatment back from kids who have no time to wait.

In case you're unfamiliar with the sobering facts about DMD, here are just a few that can help you understand what's at stake for these kids — and why time is of the essence. DMD is currently 100% fatal. Most kids with DMD are in wheelchairs by age 10 or 12 and die in their late teens or early 20s. It's the most common fatal genetic

disorder worldwide. Approximately 15-20 thousand children in the US alone are afflicted.

However, this amazing statement was just posted on the Charley's Fund website, "We have a drug that is safe and effective in a small clinical trial that has lasted more than two years. Some of the boys taking the medicine are even IMPROVING, a word that is never uttered in relation to Duchenne. Yet the drug is only available to the 12 kids in the trial, and it could be YEARS before other kids with Duchenne are allowed access."

Charley and a friend. (Photo courtesy Tracy Seckler.)

This is a big moment for the Secklers. As Tracy Seckler explains, "This drug cannot help Charley. But the company developing it has plans to develop 8 new drugs for Duchenne, and Charley can benefit from one of the next ones. The new drugs are all based on the same chemical backbone as this one [Eteplirsen, which alone can help combat the effects of Duchenne in 13% of kids while the 8 new drugs developed thereafter collectively would be able to treat 85% of kids with Duchenne.] So if it takes years to approve Eteplirsen, it will take a decade or more to do the rest. If Eterplirsen is granted accelerated approval, the others can get moving now."

If a drug is to help Charley, and all other boys like him, there is no time to spare. And that has been the driving force of Charley's Fund, which the Secklers started in 2004 when Charley was first diagnosed at the age of 3. Run with their tireless effort with the goal of saving their child's life, the Fund has already directed 25 million dollars into medical research for DMD. What they've done on behalf of their son — and all sons who have this destructive disease — is unprecedented.

Two years ago, I was in the audience of a TEDx talk given by Benjamin Seckler and was struck by the focus and relentless drive he had to race against time in pursuit of a cure for his son. What I walked out feeling was that prior to learning of his son's illness, he was just a parent, just someone looking to the bright future of his three kids before everything changed with one phone call from a doctor. I invited him to sit and tell me more about what it was like for him, as a parent — that horrific life altering moment when he learned of his son's diagnosis, and the journey he has found himself on ever since.

The following are his words:

"I remember the day that I found out. Tracy called me. I was at work in Hudson [New York.] Charley had gotten the official diagnosis for Duchenne. Of course, I left work immediately to go home, and I remember crying hysterically all the way home. And maybe this was kind of a weird thing to do — I'm sort of a weird person though — but I remember as I was crying uncontrollably, I looked at myself in the rear view mirror. I wanted to look at what a man who just found out his son had a fatal illness looked like. Like as if I were sitting in a restaurant and motioned to someone and said "See that guy over there? He just found out his son has a fatal illness." It was as if I had just become someone else. Everything had just changed. I wanted to see what this other person I had become looked like.

That was a bad day.

Right after they receive such news is when most parents are paralyzed by the emotions that go along with it. Many marriages don't survive. And since this disease affects mainly boys, sons, I think particularly of their fathers. I think it's safe to say that dads lean toward their sons in a certain way. In the same way that mothers think of their daughters, fathers think of their sons as a way of remaining immortal. Their sons are little versions of themselves.

In boys, the diagnosis for DMD generally comes between the ages of three and six. Charley was three. Sam is just 16 months older than Charley, and my wife, Tracy, was expecting Maizy when we found out about Charley's

diagnosis.

Both Tracy and I are the youngest in our families: Tracy is the youngest of four, and I'm the youngest of five. And my siblings are quite a bit older than me. So I always had that notion of looking toward the future, consciously planning out my life: Grow up, do all the right things that would get me into a good college, plan well, go to medical school, meet my wife, start a family.

Everything had always played itself out as I had expected, more or less. I did lose my father when I was 17, but the news about Charley was different. I suddenly knew, from that moment, my whole life was going to revolve around trying to save my child's life. I suddenly had a completely new horizon.

Charley hamming it up with cousins.

I really think the worst feeling is now, having things in my future I don't want to think about. The painful thought of having a funeral and burying my child. The thought that this is really going to happen. One of the most comforting things for a parent is the thought that your child will be here after you're gone. That is gone, too. It's like a double whammy.

One of the ways I explain what the pain feels like is this: It's like your child is in the middle of the road — tied to the middle of the road — and there's a car coming. The car is coming from a long way away. And although you're racing to get to the middle of the road, you can never get there. And you see that car in the distance getting closer and closer, and still you can't do anything to stop this accident that's going to happen.

So the work we do at Charley's Fund refocuses those obsessive thoughts. Instead of thinking about Doom's Day, I'm constantly thinking of the opposite. Tracy and I did manage to overcome the crucial crossroads of feeling paralyzed after the diagnosis. We formed Charley's Fund just four months later. Some of it has to do with our personalities, and some of it has to do with the silver lining of my being a young physician who understands the language of genetic medicine.

I was able, in those early stages, to mine though the research I found online. I would work all day as a radiologist, then I would be up all night studying the research. When the stakes are so high as in our situation, where you're fighting to save your child's life, you look at every angle; it forces you to examine the Rubik's cube in so many different ways. I think that's why we've been so successful. We had to be innovative. We had to think of possibility and hope. We have to keep our thoughts there.

I remember in those early days calling the clinicians and scientists in the labs directly until I formulated the early strategy of what we needed to do. The breakthrough was when we decided to hire a Ph.D-level scientist to work full time for us. All of a sudden we went from a small parent foundation to the next level. And eventually, over time, we even outgrew the brain power we had with that Ph.D. We decided to create an all-star team of drug development experts. Now we have formed our own virtual biotech company. By taking matters into our own hands, we are literally changing the way drug development happens in this country.

Because I was the youngest in my family, my siblings would always joke that everything was taken care of for me. I was 'the golden child.' The nickname my siblings gave me was 'Fog,' because I was oblivious to so much. It's interesting that after growing up with a nickname like 'Fog,' I am now involved in something that requires so much clarity. And I have that clarity."

Philips, Howard

From: Unger, Ellis
Sent: Tuesday, February 09, 2016 5:48 PM
To: Jenkins, John K
Cc: Dunn, Billy; Temple, Robert
Subject: RE: Briefing Document Issues Final.pptx
Attachments: Briefing Document Issues Final.pptx

John,

I have some concerns here. Rich has recused himself, and yet he seems to have some involvement.

And I am not comfortable talking with anyone about a pending application. Even if we were to guarantee that FDA was in 100% listening mode with Ms. Leffler, the optics don't seem appropriate to me.

Also, on a related subject, I continue to have concerns about a having patient voting on an AC whose (b) (6) owns stock in the company. That person cannot be unbiased, and if anyone/the press were to find out we let him sit on the committee with full knowledge of his (b) (6) Sarepta's stock holdings, we could not defend that position.

Ellis

From: Moscicki, Richard
Sent: Tuesday, February 09, 2016 4:27 PM
To: Dunn, Billy; Unger, Ellis
Subject: Briefing Document Issues Final.pptx

Janet asked me to join her for a discussion with Mindy Leffler, DMD patient advocate. Ms Leffler subsequently sent this slide deck to me with her concerns regarding the eteplirsen briefing document. I send it to you to review and consider. Rich.

Introduction: eteplirsen's impact is evident

In 2011, 12 boys aged 7-10 began a clinical trial to test eteplirsen, an experimental treatment for Duchenne muscular dystrophy. *Four years later, 10 out of the 12 boys are still walking: 83%.*

Still ambulatory

83%

In a group of untreated boys from a natural history database who matched the treated boys on key measures, after four years *only one out of 11 boys was still walking: 9%.*

Still ambulatory

9%

But the FDA's assessment of this drug's impact differs greatly from that of scientists, physicians, and DMD families

Physicians, scientists and families who live with, treat, and study the disease every day conclude that Eteplirsen slows disease progression.	The FDA concludes: "The clinical course of the 12 patients participating in study 201/202 appears to be within the expected natural history of DMD." *- FDA Briefing Documents, p 7*

Question: How could these conclusions be so different?

Answer: A fundamentally flawed FDA analysis

FDA's analysis is plagued by:

- Speculation unsubstantiated by data
- Lack of scientific rigor
- Key contradictions on crucial issues

A review of the FDA Briefing Information reveals significant errors in the analyses put forth.

Problem:
Speculation
unsubstantiated by data

FDA Speculation #1 Against LOA Data: Bias in historical control selection

Speculation	Fact
"There is no way to assure that criteria for selecting patients from a historical database are made by individuals who are blinded to individual results." *- FDA Briefing Information, p. 6*	No retrospective criteria were used, eliminating the possibility of bias.

Evidence: Sarepta's selection process for natural history control group

Sarepta's selection process for natural history control group:

1. Include ALL patients from any natural history study with four years of longitudinal data: Italian Telethon and Goemans
2. Select all patients from these two studies who fit the original inclusion criteria for Eteplirsen study 201/202

Eteplirsen inclusion criteria	Natural history matched cohort inclusion criteria
✓ 7 or older ✓ Steroid treated ✓ Amenable to skipping exon 51	✓ 7 or older ✓ Steroid treated ✓ Amenable to skipping exon 51

FDA Speculation #2 Against LOA Data: Treated group may have benefitted from better steroid treatment

Speculations	Facts
"Corticosteroid therapy appears to have been more intensive in Eteplirsen patients compared to the natural history patients selected by the applicant, and this, itself, may have been capable of affecting performance." *– FDA Briefing Information, p.30*	In the matched historical control of 11 patients, 91% maintained the recommended steroid dose throughout the four years, compared to 33% in the treated group.
"A higher proportion, 69% vs. 8%, of the natural history controls vs. Eteplirsen patients were on regimens other than daily dosing…that are thought to be associated with less efficacy" *– FDA Briefing Information, p.26*	In the matched historical control of 11 patients, 36% were on intermittent regimen compared to 8% of the treated group.

Evidence: Comparison of actual steroid dose and regimen in both groups

	Eteplirsen-treated Cohort	Natural History Matched Cohort
Dose	9 out of 12 on less than 2/3 of the recommended steroid dose at week 208. Only 3/12 increased dose with weight gain.	Only 1 out of 11 on a suboptimal steroid dose. 10/11 increased dose with weight gain.
Regimen	8% intermittent (1/12) 92% continuous (11/12)	36% intermittent (4/11) 64% continuous (7/11)

Evidence: Actual change in ambulation over time of boys on actual steroid regimens

Year of LOA	Eteplirsen-treated Cohort		Natural History Matched Cohort	
	Intermittent	Continuous	Intermittent	Continuous
Year 1		II		I
Year 2			I	I
Year 3			I	II
Year 4			II	II

Notably, difference between intermittent and continuous dosing did not affect LOA outcomes in either the eteplirsen or natural history cohorts. This is consistent with findings in the literature. For example, a 2011 paper noting "no significant difference between age at loss of ambulation and whether the patient was on a daily or nondaily regimen (p = 0.77). – *Bushby and Connor Clin Investig (Lond). 2011 Sep; 1(9): 1217–1235*

FDA Speculation #3 Against LOA Data: Treated group may have received better supportive care

Speculation	Fact
"Supportive care can prolong ambulation in DMD by several years, but its effectiveness is dependent on both type and intensity of care, which is likely to differ substantially between patients enrolled in observational studies or registries versus interventional treatment studies." *- FDA Briefing Information, p. 26*	There was no significant difference in physical therapy or supportive care between historical controls and Eteplirsen patients. In fact, controls received slightly more intensive physical therapy.

Evidence: Comparison of actual physical therapy received by each group

Table 8: Studies 201/202 Comparison of Physical Therapy and Use of Orthoses

		Italian Telethon N = 10	Study 201/202 Eteplirsen N = 12
Physical Therapy	**PT Regimen**	**# of Patients**	**# of Patients**
Home therapy	Stretching with parents/other	6	8
Swimming	1 day/week	5	1
	2-3 days week	0	1
Frequency of appointments with trained physical therapist	4-6 days/week	5	2
	2-3 days/week	5	3
	1 day/week	0	4
	1 day/year	0	1
Use of night splints to maintain ankle flexibility	Use orthoses	8	11
	Orthoses not needed (TA<10°)	2	0
	Orthoses not used	0	1

"In Italy we are quite lucky that the National Health System allows regular sessions of PT…generally varies from 3 to 5 times /week. We also train parents to perform daily stretches and encourage swimming. This is standard care in all the tertiary care centers such as those involved in our natural history data collection." -- Dr. Eugenio Mercuri, Professor of Pediatric Neurology, Universita Cattolica del Sacro Cuore. Areas of expertise: muscular dystrophy, outcome measurements and assessment tools in neuromuscular disorders. Over 130 publications on pediatric neurology and neuromuscular disorders.

FDA Speculation #4 Against LOA: Loss of ambulation (LOA) may be influenced by subjective factors

Speculation	Fact
"Near the time when patients lose ambulation, decisions are made by patients and caregivers about whether weakness has progressed to the point that it is in the patient's best interest to use a wheelchair to avoid the risk of falls and injuries and to decrease the effort and time required for mobility." *- FDA Briefing Information, p. 30*	LOA is a standardized, objective endpoint defined in both the eteplirsen trial protocol and the relevant natural history protocol as the inability to perform the 10 meter walk test as assessed by a clinician. It is not a patient or caregiver-reported endpoint. While there are studies that prove the influence of motivational factors on the 6MWT, there are no such studies proving, or even suggesting, that motivation affects the ability or inability to perform a 10 meter walk as assessed by a clinician – the basis for LOA.

Evidence: Established standards for evaluating established “LOA” endpoint

- The LOA data being compared in this context was captured in the clinic according to standardized study protocol under the supervision of a clinician.
- LOA under this definition reflects irreversible morbidity and is not effort-dependent when measured by a clinician
- LOA under this definition is considered a validated endpoint. In fact, FDA uses LOA to reference the treatment effect of steroids.

Problem:
Lack of scientific rigor

Rigor Failure #1: Proposing an alternate natural history control that fails to meet appropriate criteria

FDA Statement	Flaw
"In addition, the eteplirsen 6MWT open-label data were compared to publicly available data from patients treated with placebo in a recent large randomized controlled study in DMD patients with mutations amenable to exon 51 skipping (Figure 4). The declines in 6MWT over time in eteplirsen-treated patients (colored lines) appear to lie within the range of changes observed in the cohort of patients treated with placebo (grey lines)." *- FDA Briefing Information, p. 9*	The aggregate drisapersen placebo group that the FDA uses here as their natural history control to make this point does not match the eteplirsen group on key criteria.

Notably, the FDA fails to meet the standards they themselves set for science — and to which Sarepta is held accountable.

Evidence: Comparison of drisapersen placebo arm to the eteplirsen group fails the FDA's own stated standards

FDA briefing documents: "For externally controlled studies to be persuasive, detailed evidence should be presented that the study design and conduct adequately controlled for bias. For example, it would be critical to establish that the control group was well-matched across key baseline and prognostic variables, including age, baseline value of the primary efficacy measure and other measures of disease stage, type and intensity of supportive care, dose and duration of corticosteroid or other concomitant pharmacotherapy, and genotype, among others."

Eteplirsen 12	Drisapersen placebo arm
216 week duration	48 week duration
Ages 7-10	Ages 5-16
280-450 meters on 6MWT	>75 meters on 6MWT

Bringing the data points to life:

My son was deemed "too functional" for the Eteplirsen study by the principal investigator at screening. But, he was included in the drisapersen placebo (walked 510 meters at screening and 525 meters at 48 weeks).

He is a real-life example of a patient in the drisapersen placebo arm who is stronger than the eteplirsen patients – in his case, both by the numbers, and upon actual screen for the eteplirsen trial itself. How can the FDA consider him an appropriate datapoint for a comparative analysis?

Rigor Failure #2: Inconsistent position on "Loss of Ambulation" standard

FDA Statement	Flaw
"In fact, the clinical course of the 12 patients participating in Study 201/202 appears to be within the expected natural history of DMD. As discussed in the background materials, the natural history in patients amenable to exon 51 skipping indicates that the age range at loss of ambulation is wide, ranging from 8 to 16 years for most patients." - *FDA Briefing Information, p. 7*	The FDA would discredit the "persuasiveness of the historical control comparison" (p.7) by claiming the clinical course is "within the expected natural history" of DMD. But they have an inconsistent position on what the natural history 'Loss of Ambulation' standard includes, self-serving of this argument. Just 3 months earlier, in the Briefing Information for drisapersen's advisory committee, the FDA described the standard Loss of Ambulation window more narrowly as between ages 10 and 14.

Evidence: Documentation of inconsistent position on Loss of Ambulation window

	Eteplirsen briefing information	Drisapersen briefing information
FDA's referenced age range for Loss of Ambulation	Ages 8-16 (p. 7)	Ages 10 – 14 (p. xx)

Notably, 71% of boys in the eteplirsen group ages 14 and older can still walk

Rigor Failure #3: Using BioMarin experimental data as accepted fact to challenge Sarepta experimental data

FDA Statement	Flaw
"By Western blot, the most accurate quantitative method used by the applicant, mean dystrophin levels after 180 weeks of eteplirsen treatment were reported to be about 0.9% of normal (range <0.25% to 2.5%), with a relative increase of dystrophin of about 3-fold compared to the trace levels typically present in patients with DMD (about 0.3% of normal)." - *FDA Briefing Information, p. 4*	This assumption uses experimental data from another sponsor's application, which is acknowledged as a flawed estimate, as accepted fact to challenge other experimental data.

Evidence: Drisapersen Briefing Information highlights experimental, potentially flawed nature of .3% baseline

"The dystrophin band appears to diminish in some post-treatment samples (e.g. subject 277). Image below was provided by the Applicant upon request for raw data from this study. While the applicant has not compared their dystrophin values to the healthy control samples on the same gel, in most cases the dystrophin band appears to be at or lower than the lowest dilution of healthy control sample tested. The applicant was asked to clarify how the dystrophin values compared to the healthy controls on the same gels. They stated that while it is not possible to accurately calculate the relative dystrophin signal due to a lack of linearity at the low levels of signal from the DMD samples, they estimate that the dystrophin expression they observed is generally around 0.3% or below of the highest control dilution*." FDA Drisapersen Briefing Information p 73, FDA Drisapersen Briefing Documents*

Rigor Failure #4: Switching Patient Data

Figure 10: Rise Time, Study 201/202

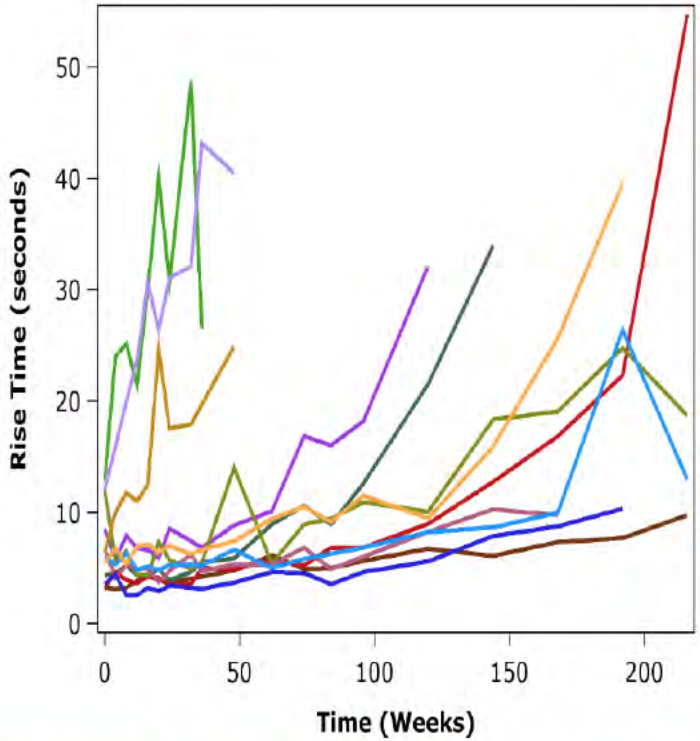
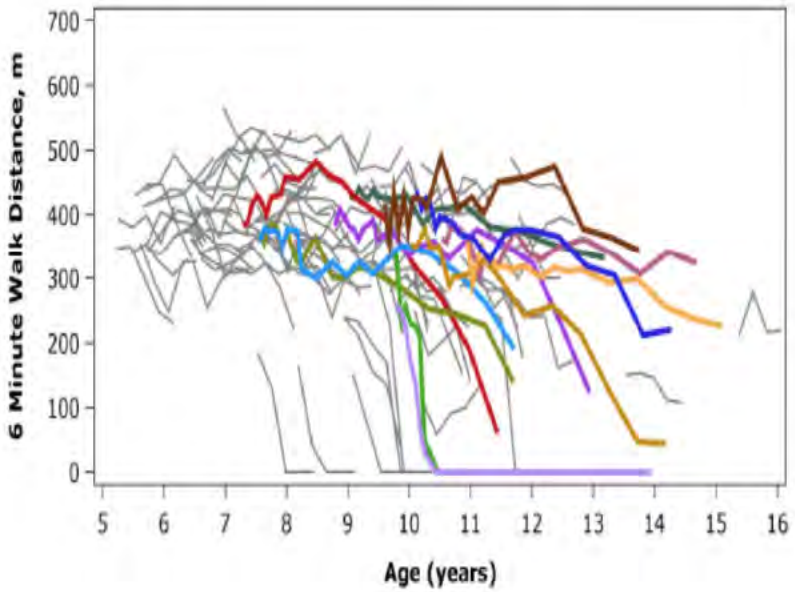


Figure 9: 6MWT, eteplirsen vs controls on placebo, all patients



According to FDA briefing documents, the lowest performing patient on the 6MWT – Patient 08 – has been unable to rise from the floor since Year 1.

Evidence: Patient 08 Can Still Rise from Floor

- In the correctly assigned data, Patient 08 can still rise from the floor at year 4 despite walking 55 meters on the 6MW for the last six months.
- FDA has switched patient 08's rise from floor data with a different eteplirsen patient in the briefing document's graph.

This switch obscures the fact that this patient is progressing atypically: FDA extrapolates the progression of the Eteplirsen patients out several years to conclude that they are progressing typically. The truth about this patient's progression is prohibitive to that claim. If he can still get off the floor, he is unlikely to lose ambulation in the next 48 weeks despite walking a short distance.

Problem:
Key contradictions on life or death issues

Key Contradictions

Finally, of great concern, key contradictions within the FDA documents reflect ongoing confusion at the Division regarding such critical issues as:

- Relationship of duration of treatment to dystrophin production
- Dystrophin measurement techniques
- Criteria for Accelerated Approval
- Use of natural history studies to determine efficacy of Eteplirsen

Key Contradiction #1: Conflicting view on relationship of treatment duration to dystrophin production

From FDA's Eteplirsen Briefing Information	From FDA's Drisapersen Briefing Documents
"the lack of even a positive trend at the earlier time point (with a higher dose) sheds doubt on the finding at a later time point." NEED PAGE #	"studies longer than 48 weeks may be desirable…to allow adequate time for the attainment of steady state levels of dystrophin" NEED PAGE #

Duration of therapy is important to enable consistent dystrophin production. How can the FDA establish that but then rely on an earlier time point as a basis for criticism?

Key Contradiction #2: Conflicting expectations for measurement methodologies

- FDA and NIH host a dystrophin workshop in March 2015 where experts conclude that multiple methodologies need to be employed in assessing dystrophin production, including both IHC and WB.
- Sarepta used a comprehensive approach to assessing dystrophin production including IHC and WB.
- From FDA's Briefing Documents: "Considerable confusion can be created by the fact that a number of different methods have been used to quantify dystrophin expression, some more quantitative than others, and some producing higher absolute numbers than others".
- FDA appears singularly focused on WB data, despite recognition that several assays are necessary and stating at the BioMarin drisapersen advisory committee meeting that orthogonal approaches are necessary.

Multiple methodologies are needed to assess dystrophin. How can FDA establish that but then highlight it as a vulnerability in a data package?

Key Contradiction #3: Conflicting positions on standards for Accelerated Approval

From FDA Letter to Duchenne Community, October 2014	From FDA's Briefing Documents
FDA also plans to present the NDA for eteplirsen to a public advisory committee meeting before making a decision on approval. This will afford FDA the ability to gain advice from outside experts and interested stakeholders on the adequacy of the data to support approval, including the possibility of "accelerated approval" – a mechanism to approve drugs in particular situations prior to the availability of definitive evidence of effectiveness.	It should be noted that accelerated approval is based on the endpoints selected (surrogates; intermediate), not on the adequacy of the studies supporting an effect on these endpoints. Thus, the evidence of an effect on an intermediate endpoint, if it is to serve as the basis for accelerated approval, must meet the evidentiary standard for an adequate and well-controlled study. In this case, the historically-controlled study would need to be considered adequate and well-controlled to support full or accelerated approval. – PAGE NUMBER??

Key Contradiction #4: Position regarding use of natural history controls

From FDA Letter to Duchenne Community, October 2014	From FDA's Briefing Documents
"FDA has also been consistent in its guidance to Sarepta that it would be necessary to submit data from the ongoing open-label trial of eteplirsen (Study 202) in an NDA, along with data from natural history studies that could show that patients treated with eteplirsen experienced slower decline in physical function. FDA has worked closely with Sarepta in efforts to obtain these natural history data from investigators."	FDA cites none of these natural history studies, but instead chooses an unmatched dataset from a competitor's placebo arm as the most appropriate natural history.

A strictly matched historical control was established with FDA guidance and assistance. How can the FDA now choose not to acknowledge this data but rather reference an unrelated, flawed new comparison?

But even the problems have a problem

Even in this flawed analysis, data would favor eteplirsen by loss of ambulation rate

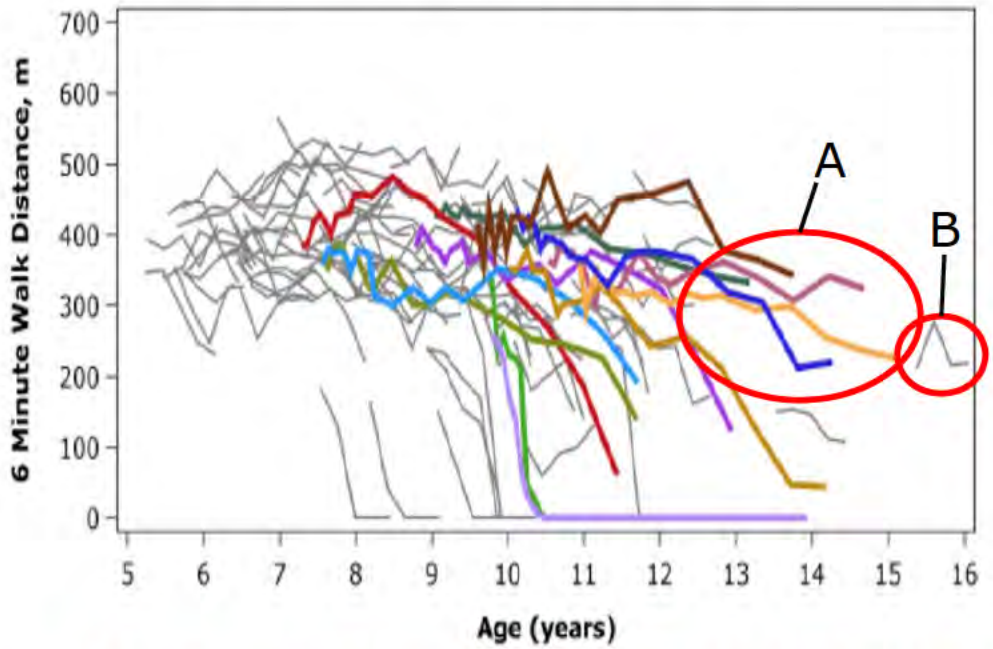
Even though the Drisapersen placebo arm is an inappropriate control group, the data still looks to favor Eteplirsen.

	Eteplirsen LOA rate	Drisapersen Placebo arm LOA rate
YEAR 1	**17%**	**12%**
YEAR 4	**17%**	**n/a**

For Drisapersen placebo arm rate to stay equal to or less than the Eteplirsen LOA rate, only 3 additional patients out of 60 can lose ambulation in the next three years. Likely?

Even in this flawed analysis, data would favor eteplirsen by % of boys walking 200+ meters at age 13+

Chart: eteplirsen group vs. drisapersen placebo 6MWT scores by age over time



Boys above the age of 13 and above 200 meters in the 6MWT	
A: eteplirsen	5 out of 12 (42%)
B: drisapersen placebo	1 out of 60 (2%)

The data directly conflicts with the FDA Briefing Information:

"The declines in 6MWT over time in the Eteplirsen-treated patients appear to lie within the range of changes observed in the cohort of patients treated with placebo."

A Missed Opportunity: eteplirsen data deviating from typical DMD milestone progression

Flaws in the analysis conducted perhaps explain on the absence of a helpful analysis: Milestone progression deviation

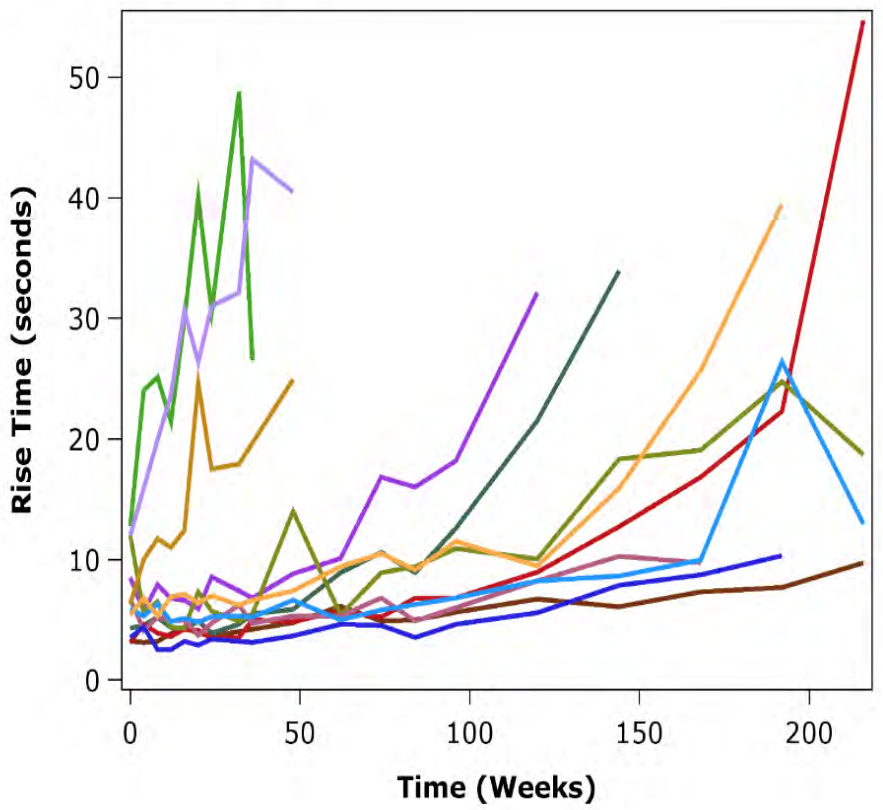
Milestone progression is a well-researched, well-documented way of determining disease progress – including in the FDA's own words:

- Boys with Duchenne lose function in a "stepwise fashion, with loss of ability to stand from the floor preceding loss of ability to walk independently, which itself precedes a decline in pulmonary function"
- "The loss of ambulatory ability in DMD almost always proceeds in sequence, with rise time steadily worsening (increasing), followed by loss of ability to rise from the floor but retained ability to walk, then loss of ability to walk, which often occurs with a sharp decline when 6MWT decreases below about 300 m."

Eteplirsen boys, however, are experiencing a delay in progressing to the next milestone

FDA asserts loss of ability to rise predicts loss of ambulation over the following 48 weeks

Figure 10: Rise Time, Study 201/202



"Loss of ability to rise has been described as a strong predictor of the loss of ambulation over the following 48 weeks."

Eteplirsen boys are experiencing a delayed loss to next milestone

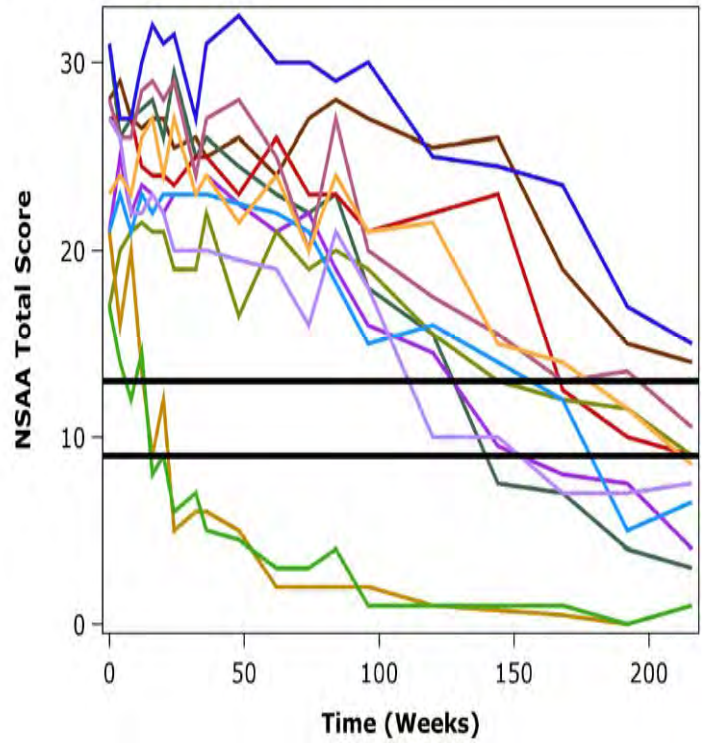
- One Eteplirsen patient lost the ability to get off the floor at one year and can still walk three years later
- One Eteplirsen patient lost the ability to get off the floor at two years and can still walk two years later
- One Eteplirsen patient lost the ability to get off the floor at 2 ½ years and can still walk 1 ½ years later
- One Eteplirsen patient lost the ability to get off the floor at 3 ½ years and can still walk 6 months later

This data proves that, like many Beckers patients, even when patients lose the quad strength to get off the floor, they retain the ability to walk for a longer period than one would expect. This SUGGESTS efficacy, not disproves it.

From FDA's Briefing Documents:

"The two horizontal lines in Figure 12 indicate NSAA scores of 9 and 13 that have been reported to be associated with being either 1 or 2 years, respectively, from loss of ambulation."

Figure 11: NSAA, Study 201/202



Eteplirsen Boys are Experiencing a Delay to loss of Next Milestone

- 3 Eteplirsen patients fell below 9 on the NSAA are are still walking over one year later
- 5 Eteplirsen patients have reached 13 on the NSAA around week 175, which when projected out based on FDA's reference on the previous slide, means that they are likely to still be walking at week 275, when the average age of Eteplirsen patients will be almost exactly 15 years old
- 2 Eteplirsen patients have not yet reached an NSAA score of 13, which means they are extremely likely to still be walking at week 275, when they will be 15 and 16 years old, respectively

*There is again a confusion in the NSAA chart by FDA between data from different patients.

Philips, Howard

From: Unger, Ellis
Sent: Tuesday, February 09, 2016 8:30 PM
To: Jenkins, John K
Cc: Dunn, Billy; Temple, Robert
Subject: RE: Briefing Document Issues Final.pptx

Categories: Red Category

Now that I've looked at the 37 slides – I would give her the standard allotment of time in the OPH, like everyone else.

Regarding point 3, I have to say that participation of a patient on the panel with an obvious bias – one who votes and only pretends to be objective – makes a travesty of the AC process.

I'll even speculate that with respect to the Drisa ACM, the presence of the patient who was consistently negative about the efficacy and safety of the drug may have 'enabled' the committee to be more critical of the data.

From: Jenkins, John K
Sent: Tuesday, February 09, 2016 6:58 PM
To: Unger, Ellis
Cc: Dunn, Billy; Temple, Robert
Subject: Re: Briefing Document Issues Final.pptx

Ellis

I understand your concerns. When Janet mentioned the Leffler call to me the other day she said she told her this was her (Mindy's) view of the data and could be presented if she wanted during the OPH. I had no idea how detailed her analyses were. I think this is an issue we can put to JW tomorrow; i.e. what are we to do with these "data". I suspect she will say we should consider them since we are supposed to approach our reviews with an open mind to the possibility that we made a mistake or missed something. Still an odd process that has been exacerbated by the AC delay.

On Rich, I agree this is awkward and I think we need to address this tomorrow as well.

On the AC member and his (b) (6) holdings, I don't know what to say other than the law does not impute parent's stock interests to (b) (6), though this does present an appearance of COI. If this were the major issue for this review life would be much better; i.e., I think there are bigger fish to fry.

John

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Unger, Ellis
Sent: Tuesday, February 9, 2016 5:48 PM
To: Jenkins, John K
Cc: Dunn, Billy; Temple, Robert
Subject: RE: Briefing Document Issues Final.pptx

John,

I have some concerns here. Rich has recused himself, and yet he seems to have some involvement.

And I am not comfortable talking with anyone about a pending application. Even if we were to guarantee that FDA was in 100% listening mode with Ms. Leffler, the optics don't seem appropriate to me.

Also, on a related subject, I continue to have concerns about a having patient voting on an AC whose (b) (6) owns stock in the company. That person cannot be unbiased, and if anyone/the press were to find out we let him sit on the committee with full knowledge of his (b) (6) Sarepta's stock holdings, we could not defend that position.

Ellis

From: Moscicki, Richard
Sent: Tuesday, February 09, 2016 4:27 PM
To: Dunn, Billy; Unger, Ellis
Subject: Briefing Document Issues Final.pptx

Janet asked me to join her for a discussion with Mindy Leffler, DMD patient advocate. Ms Leffler subsequently sent this slide deck to me with her concerns regarding the eteplirsen briefing document. I send it to you to review and consider. Rich.

Philips, Howard

From: Rodriguez, Jennifer
Sent: Thursday, April 06, 2017 4:43 PM
To: Moscicki, Richard
Subject: RE: Media question - Sarepta involvement

Understood, let me connect with ethics and see what they recommend.

From: Moscicki, Richard
Sent: Thursday, April 06, 2017 4:42 PM
To: Rodriguez, Jennifer
Subject: RE: Media question - Sarepta involvement

I am ok with it but you should understand that Ed Kaye worked for me at Genzyme and that we frequently sailed together, either I crewing on his boat or he on my boat outside of employment. Rich.

From: Rodriguez, Jennifer
Sent: Thursday, April 06, 2017 4:35 PM
To: Walsh, Sandy; Moscicki, Richard
Cc: Shreeve, Chris; Bolek, Michelle
Subject: RE: Media question - Sarepta involvement

Hi Rich,

Please see edits below based on your feedback. If you are OK with this language, we will run it by ethics to ensure it is worded properly.

Thanks!
Jen

The FDA is committed to ensuring agency employees avoid conflicts of interest. The agency has a thorough screening process for conflicts of interest and employees must comply with ethics laws and regulations. It is important to note that current ethics laws and regulations do not prohibit engagement with individuals simply because they have worked together at a common employer. However, in this case Dr. Moscicki had limited engagement with the company and its application, and recused himself from the decision making process.

From: Walsh, Sandy
Sent: Thursday, April 06, 2017 4:27 PM
To: Moscicki, Richard; Rodriguez, Jennifer
Cc: Shreeve, Chris; Bolek, Michelle
Subject: RE: Media question - Sarepta involvement

Thanks Rich,

We will get back to you with an edited draft based on your remarks.

Sandy Walsh
Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669
Sandy.Walsh@fda.hhs.gov

From: Moscicki, Richard
Sent: Thursday, April 06, 2017 4:22 PM
To: Walsh, Sandy
Subject: RE: Media question - Sarepta involvement

I was not required to be recused as the ethics laws do not require so for reasons of personal friendship but I did recuse myself as to any decisional role, rather my role was limited to communication and review of information when asked by the agency. That is the true case, not sure if that's what you wish to communicate.

From: Walsh, Sandy
Sent: Thursday, April 06, 2017 2:38 PM
To: Moscicki, Richard
Cc: Rodriguez, Jennifer; Bolek, Michelle; Shreeve, Chris
Subject: Media question - Sarepta involvement

Hi Rich,

A WSJ reporter, Susan Pulliam, has been working on a lengthy piece on Sarepta and eteplirsen. Her piece is focusing on what she says is how the company worked with the 12 patients and their families, using them as delegates to help get eteplirsen approved. She has talked to a number of people, including parents and advisory committee members and will note that interactions between the company and the families was ongoing and extensive and she is questioning why the FDA did not transparently disclose these interactions.

We have continued to refer her to the posted drug review documents that provide details on the decision and have decline her interview requests. We are providing a brief response from the FDA that notes the important role that patient insight provides and that our decisions are based on science.

Related to this story, she is asking why you were not recused from the discussions with Sarepta, noting your history/relationship with the CEO? She has asked us if there were internal discussion about having you be recused? She pointed out meeting minutes and emails that are in the public record that show you were involved in conversations with the CEO.

Here is a draft response, is there anything you'd like to add?

The FDA is committed to ensuring agency employees avoid conflicts of interest. The agency has a thorough screening process for conflicts of interest and employees must comply with ethics laws and regulations.

(I'll be out of the office starting tomorrow for a week. Please copy my colleague Jennifer Rodriguez on your response, as she will be covering for me.)

Sandy Walsh
Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669
Sandy.Walsh@fda.hhs.gov

From: Moscicki, Richard
Sent: Friday, April 07, 2017 12:15 PM
To: Rodriguez, Jennifer
Subject: RE: Media question - Sarepta/ethics on engagement

yes

From: Rodriguez, Jennifer
Sent: Friday, April 07, 2017 12:14 PM
To: Moscicki, Richard
Cc: Walsh, Sandy; Shreeve, Chris; Bolek, Michelle
Subject: RE: Media question - Sarepta/ethics on engagement

Thanks, I can explain to you offline (b) (5) .

But to confirm, the following is accurate: *In this case Dr. Moscicki had limited engagement with the company and its application, and recused himself from the decision making process.*

From: Moscicki, Richard
Sent: Friday, April 07, 2017 12:12 PM
To: Rodriguez, Jennifer
Cc: Walsh, Sandy; Shreeve, Chris; Bolek, Michelle
Subject: RE: Media question - Sarepta/ethics on engagement

That's why I initially thought it worthwhile to explain that no recusal was required but that I voluntarily recused myself from any decisional involvement and that I did participate in communications, review of data when requested, and to a lesser degree to internal discussions. Rich.

From: Rodriguez, Jennifer
Sent: Friday, April 07, 2017 11:39 AM
To: Moscicki, Richard
Cc: Walsh, Sandy; Shreeve, Chris; Bolek, Michelle
Subject: FW: Media question - Sarepta/ethics on engagement

Hi Rich,

(b) (5)

As Andy notes below, (b) (5)

RESPONSE: (b) (5)

.

Best,
Jen

From: Caplan, Andrew (HHS/OGC) [mailto:Andrew.Caplan@HHS.GOV]
Sent: Friday, April 07, 2017 11:30 AM
To: Rodriguez, Jennifer
Cc: Akbari, Asim; Walsh, Sandy
Subject: RE: Media question - Sarepta/ethics on engagement

(b) (5)

Andy

From: Rodriguez, Jennifer [mailto:Jennifer.Rodriguez@fda.hhs.gov]
Sent: Friday, April 07, 2017 11:09 AM
To: Caplan, Andrew (HHS/OGC)
Cc: Akbari, Asim (FDA/OC); Walsh, Sandy (FDA/OC)
Subject: RE: Media question - Sarepta/ethics on engagement

Hi Andy,

(b) (5)

From: Caplan, Andrew (HHS/OGC) [mailto:Andrew.Caplan@HHS.GOV]
Sent: Thursday, April 06, 2017 6:32 PM
To: Rodriguez, Jennifer
Cc: Akbari, Asim; Walsh, Sandy
Subject: RE: Media question - Sarepta/ethics on engagement

I should be available around 11:00.

Andy Caplan
Senior Ethics Counsel
Office of the General Counsel
U.S. Dept. of Health & Human Services
(202) 690-7256

From: Rodriguez, Jennifer [mailto:Jennifer.Rodriguez@fda.hhs.gov]
Sent: Thursday, April 06, 2017 5:54 PM
To: Caplan, Andrew (HHS/OGC)
Cc: Akbari, Asim (FDA/OC); Walsh, Sandy (FDA/OC)
Subject: RE: Media question - Sarepta/ethics on engagement

Thanks, Andy. This is helpful. (b) (5) Thanks!

Jen

From: Caplan, Andrew (HHS/OGC) <Andrew.Caplan@HHS.GOV>
Date: April 6, 2017 at 5:41:16 PM EDT
To: Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>
Cc: Walsh, Sandy <Sandy.Walsh@fda.hhs.gov>, Akbari, Asim <Asim.Akbari@fda.hhs.gov>
Subject: RE: Media question - Sarepta/ethics on engagement

The draft statement:

(b) (5)

(b) (5)

[redacted]

Andy Caplan
Senior Ethics Counsel
Office of the General Counsel
U.S. Dept. of Health & Human Services
(202) 690-7256

From: Rodriguez, Jennifer [mailto:Jennifer.Rodriguez@fda.hhs.gov]
Sent: Thursday, April 06, 2017 5:04 PM
To: Caplan, Andrew (HHS/OGC)
Cc: Akbari, Asim (FDA/OC); Walsh, Sandy (FDA/OC)
Subject: Media question - Sarepta/ethics on engagement

Hi Andy,

(b) (5)

[redacted]

Thanks,
Jen

From: Rodriguez, Jennifer <Jennifer.Rodriguez@fda.hhs.gov>
Date: April 6, 2017 at 4:44:22 PM EDT
To: Akbari, Asim <Asim.Akbari@fda.hhs.gov>
Cc: Walsh, Sandy <Sandy.Walsh@fda.hhs.gov>
Subject: ASIM PLEASE SEE: Media question - Sarepta involvement
Importance: High

Hi Asim,

Do you have a minute to speak today or early tomorrow about an ethics related question from the Wall Street Journal? It may be easiest for me to explain the issue as you consider the language below.

Thanks!
Jen

From: Moscicki, Richard
Sent: Thursday, April 06, 2017 4:42 PM
To: Rodriguez, Jennifer
Subject: RE: Media question - Sarepta involvement

I am ok with it but you should understand that Ed Kaye worked for me at Genzyme and that we frequently sailed together, either I crewing on his boat or he on my boat outside of employment. Rich.

From: Rodriguez, Jennifer
Sent: Thursday, April 06, 2017 4:35 PM
To: Walsh, Sandy; Moscicki, Richard
Cc: Shreeve, Chris; Bolek, Michelle
Subject: RE: Media question - Sarepta involvement

Hi Rich,

Please see edits below based on your feedback. If you are OK with this language, (b) (5) [redacted]

Thanks!
Jen

(b) (5) [redacted]

From: Walsh, Sandy
Sent: Thursday, April 06, 2017 4:27 PM
To: Moscicki, Richard; Rodriguez, Jennifer
Cc: Shreeve, Chris; Bolek, Michelle
Subject: RE: Media question - Sarepta involvement

Thanks Rich,

We will get back to you with an edited draft based on your remarks.

Sandy Walsh
Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669
Sandy.Walsh@fda.hhs.gov

From: Moscicki, Richard
Sent: Thursday, April 06, 2017 4:22 PM
To: Walsh, Sandy
Subject: RE: Media question - Sarepta involvement

I was not required to be recused as the ethics laws do not require so for reasons of personal friendship but I did recuse myself as to any decisional role, rather my role was limited to communication and review of information when asked by the agency. That is the true case, not sure if that's what you wish to communicate.

From: Walsh, Sandy
Sent: Thursday, April 06, 2017 2:38 PM
To: Moscicki, Richard
Cc: Rodriguez, Jennifer; Bolek, Michelle; Shreeve, Chris
Subject: Media question - Sarepta involvement

Hi Rich,

A WSJ reporter, Susan Pulliam, has been working on a lengthy piece on Sarepta and eteplirsen. Her piece is focusing on what she says is how the company worked with the 12 patients and their families, using them as delegates to help get eteplirsen approved. She has talked to a number of people, including parents and advisory committee members and will note that interactions between the company and the families was ongoing and extensive and she is questioning why the FDA did not transparently disclose these interactions.

We have continued to refer her to the posted drug review documents that provide details on the decision and have decline her interview requests. We are providing a brief response from the FDA that notes the important role that patient insight provides and that our decisions are based on science.

Related to this story, she is asking why you were not recused from the discussions with Sarepta, noting your history/relationship with the CEO? She has asked us if there were internal discussion about having you be recused? She pointed out meeting minutes and emails that are in the public record that show you were involved in conversations with the CEO.

Here is a draft response, is there anything you'd like to add?

(b) (5)

.

(I'll be out of the office starting tomorrow for a week. Please copy my colleague Jennifer Rodriguez on your response, as she will be covering for me.)

Sandy Walsh
Press Officer

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Tel: 301-796-4669
Sandy.Walsh@fda.hhs.gov

From: Henderson, Christopher M
To: Moscicki, Richard
Subject: Divest Letter ((b) (6), (b) (3) (A)
Date: Tuesday, May 24, 2016 8:51:00 AM
Attachments: Divest Letter (R. Moscicki).pdf
Divest Packet 2014.pdf

Mr. Moscicki,
Attached is a letter directing you to divest the (b) (6), (b) (3) (A) Also attached is a packet that provides information related to directed divestitures. Please let me know if you have any questions.

(b) (5), (b) (6), (b) (3) (A)

. Thus, please contact DEI upon the resolution of this claim.

Chris Henderson, J.D.
Division of Ethics and Integrity
Food and Drug Administration
240-402-8186

MEMORANDUM

Date: May 23, 2016

To: Richard Moscicki
CDER

From: Michael Gandolph
Supervisory Ethics Specialist
Ethics and Integrity Division

Michael A. Gandolph -S

Digitally signed by Michael A. Gandolph -S
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=0010112914, cn=Michael A. Gandolph -S
Date: 2016.05.23 11:51:41 -04'00'

Subject: Divestiture of Prohibited Holdings

PURPOSE The purpose of this memorandum is to inform you that we have reviewed the information you furnished on your OGE 450, financial disclosure report, which indicates you have a financial interest in (b) (6), (b) (3) (A) (b) (6) Since the ownership of this fund results in you having a financial interest in significantly regulated companies, you are prohibited from retaining this financial interest.

ISSUE

- (b) (6), (b) (3) (A) (b) (6), is a fund that, according to its 2015 Third Quarter Report, is invested in the following pharmaceutical companies: (b) (6), (b) (3) (A)
- These companies are regulated by FDA.
- This fund is not a mutual fund registered with the SEC under the 1940 Investment Company Act and thus does not qualify for a regulatory exemption despite not having a stated concentration of focusing its investments in any industry.
- Financial interest in significantly regulated firms is prohibited for confidential filers or the spouse or minor child of such employees, as explained in Section 5501.104 of the attached Supplemental Standards of Ethical Conduct for Employees of DHHS. (See Attachment 2)

ACTION Upon receipt of this document, you are required to disqualify yourself immediately from participating in matters pertaining to this prohibited interest, including matters which focus directly and exclusively on the closely competing products, processes, or services of other firms in order to prevent placing yourself in violation of the conflict of interest statute, 18 U.S.C. 208.

In making future investments, it is imperative that you consult the Listing of U.S. Industries, a copy of which is available on the Intranet at

http://inside.fda.gov:9003/EmployeeResources/Ethics/FDAEthicsProgram/ucm021366.htm or on the Internet at http://www.fda.gov/AboutFDA/WorkingatFDA/Ethics/ucm079482.htm (NOTE: This listing does not contain mutual funds.)

For more information about investing in mutual funds, please see the information available on our web page at the address below:

http://inside.fda.gov:9003/EmployeeResources/Ethics/FDAEthicsProgram/ucm008088.htm.

OPTIONS 1. If you feel our information is not current due to mergers, acquisitions, divestitures, or changes in a product's percent contribution to gross annual sales, we will evaluate any supporting documentation to confirm that the company cited is no longer significantly regulated. The Ethics and Integrity Staff must receive the documentation **as soon as possible, preferably within 30 days,** from the date of this memorandum. If you are unable to provide this information, please refer to Option 2, 3 or 4.

2. Provide written notification that you have divested of the prohibited interest (this could include transferring the prohibited holding to someone other than your spouse or minor child). Divestiture must take place within 90 days from the time the financial disclosure report or report of a prohibited interest is due (see DEADLINES for further explanation.) If that date has already passed, then divestiture must take place **as soon as possible** and no more than 30 days from the date you receive this memorandum. If you choose to apply for a CD Certificate of Divestiture see Option 3, or to apply for an Exception, see Option 4.

3. You may complete and submit a written request for a Certificate of Divestiture through the Ethics and Integrity Staff (Attachment 5). **IMPORTANT**: Also see Attachment 3 for additional information, procedures, and timeframes.

   A. You are permitted to apply for a Certificate of Divestiture pursuant to Section 1043 of the Internal Revenue Code (Title 26 U.S.C.) implemented at 5 CFR 2634.1001. (See Attachment 4) A Certificate of Divestiture would permit the **deferral** of capital gain for income tax purposes upon the disposition of property.

   B. **NOTE:** The issuance of a Certificate of Divestiture is governed by regulations administered by the IRS. The FDA is unable to amend the procedures or deadlines in any way.

C. You **are not** eligible to request a Certificate of Divestiture if your holding is within an IRA, 401(k), or your interest was purchased during FDA employment while you were designated as a confidential filer and its purchase was prohibited at the time of purchase.

D. You must commit to divest within 90 days from the date that the financial disclosure report or report of a prohibited interest was due (see DEADLINES for further explanation), unless an extension is granted on the basis of unusual hardship as determined by the Office of Government Ethics. Generally, FDA will not be able to secure an extension for you (see DEADLINES for further explanation of requirement.)

E. You must commit to divest within three months and 10 days after the interest first became prohibited, unless an extension is granted on the basis of undue hardship by the official designated by the Office of Government Ethics (OGE).

F. If you intend to request a Certificate of Divestiture, **DO NOT** sell your stock until you are notified whether your request has been approved or denied. Also, please submit your request as soon as possible in order to meet established timeframes.

4. You may submit a written application to the Ethics and Integrity Staff for an exception to hold the prohibited interest if you believe that you acquired this prohibited interest under exceptional circumstances. The format for requesting an exception is provided in Attachment 6. Please make note of the timeframes and deadlines as discussed below. You must also complete and submit the disqualification statement in Attachment 7. Please be aware that an exceptional circumstance does not include any of the following situations: purchasing a prohibited interest either personally or through the efforts of another person such as an investment broker, before or during FDA employment; receiving a prohibited interest as a gift, inheriting a prohibited interest, or obtaining a prohibited interest through marriage.

DEADLINES You must pay careful attention to all applicable deadlines. All divestiture actions must be completed within **90 days** from the date that the financial disclosure report or report of a prohibited interest was due.

NOTE: For new FDA public and confidential filers, the "date the financial disclosure report or report of a prohibited interest was due" is the date on which the new entrant public or confidential financial disclosure report (0GE 450/OGE 278) is due, i.e., 30 days after joining the agency in a filing position or assuming the filing position. For incumbent employees, the "date the financial disclosure report or report of a prohibited interest was due" is the date the report of a prohibited

interest (HHS-717-2) is due, i.e., 30 days after acquiring the prohibited financial interest. Acquiring the prohibited financial interest includes, but is not limited to, an employee's purchase of a prohibited financial interest, an employee's inheritance of a prohibited financial interest, and an employee's marriage to a spouse who holds a prohibited financial interest. It also includes the first day that a previously permissible holding was reclassified as being prohibited, or it could be the first date that an employee in a non-confidential filing position is reassigned to a filing position, or otherwise becomes a filer, for which the holding of the interest in a significantly regulated organization is prohibited.

Employees should check the "Listing of U.S. Industries" often for changes in an investments classification of "acceptable" or significantly regulated." The Listing of U.S. Industries is available on the ethics webpage.

All information should be sent to:

Division of Ethics and Integrity
8455 Colesville Road, (**COLE** – 8121)
Silver Spring, MD 20993-0002

CLOSING If you have questions on this matter, please contact Chris Henderson at 240 402 8186

ATTACHMENTS
1. Prohibited Interest Fact Sheet
2. Supplemental Standards of Ethical Conduct for Employees of DHHS
3. Certificate of Divestiture Fact Sheet
4. 5 CFR Part 2634
5. Sample "Request for Certificate of Divestiture"
6. Instructions for Employee Request for an Exception
7. Instructions for Notice of Disqualification

*** The Agency has provided you with access to the internet where you may view and/or print the complete Text of 5 CFR 2634 and 2635 which may be found at www.usoge.gov. If you are experiencing difficulty accessing this resource, please contact the Ethics and Integrity Staff. Contact information may be found at http://inside.fda.gov:9003/EmployeeResources/Ethics/FDAEthicsProgram/ucm020186.htm.

FACT SHEET
Prohibited Financial Interests

GENERAL PROHIBITION

The HHS Supplemental Regulations prohibit employees of the Food and Drug Administration who are designated as public or confidential filers, or the spouse or minor child of the employee, from holding a financial interest (e.g., a stock holding) in any FDA "significantly regulated organization."

"Significantly regulated organization" is defined as an organization for which the sales of products regulated by the FDA constitute ten percent or more of annual gross sales in the organization's previous fiscal year (where an organization does not have a record of sales of FDA-regulated products, it will be deemed to be significantly regulated if its operations are predominately in fields regulated by FDA, or if its research, development, or other business activities are reasonably expected to result in the development of products that are regulated by FDA).

EXCEPTIONS TO THE GENERAL PROHIBITION

1. An employee, or spouse or minor child of an employee, may hold a pension, or other employee benefit, arising from employment with a significantly regulated organization **if such holding does not conflict with the employee's official duties and thus require recusal from duties that are critical or central to their position.**

2. An employee who is not required to file a public or confidential financial disclosure report may hold a financial interest in a significantly regulated organization under certain conditions including that the value of the holding is less than $15,000.

3. An employee, or spouse or minor child of an employee, may have an interest in a significantly regulated organization if it is an underlying asset in a publicly traded, widely diversified, mutual fund. The rules are different for sector specific mutual funds invested in regulated areas. These sector type mutual funds are generally prohibited for FDA public and confidential filers.

4. The Commissioner or the Commissioner's designee may grant an employee a written exception to hold a financial interest in a significantly regulated organization based upon an exceptional circumstance as determined by the Commissioner or the designee.

OGE Form 450 – "Confidential Financial Disclosure Report"

Employees that are designated as confidential filers are required to complete and submit a report of their financial interests on Form OGE 450 "Confidential Financial Disclosure Report" within 30 days of entrance on duty, and then on an annual basis thereafter. (Note: applicants to higher level confidential filing positions in FDA may be asked to provide an OGE 450 form prior to entrance on duty as part of an internal pre-clearance process.)

The OGE 450 form undergoes an initial review by designated reviewers in the Centers and Offices, then an extensive review by the Division of Ethics and Integrity. Employees will be directed to divest of any financial holding that is prohibited by regulation or that will create a conflict of interest with the employee's official duties.

HHS Form 717-2 "Report of Prohibited Financial Interests"

All FDA employees are also required to report, within 30 days, the acquisition of a prohibited financial interest on Form HHS 717-2 "Report of Prohibited Interests for Employees of the Food and Drug Administration." Employees are responsible for monitoring their financial interests and if an employee learns that a financial holding has become "prohibited," the employee should immediately complete and submit Form HHS 717-2.

AGENCY FINANCIAL REVIEW PROCESS

The Agency conducts a review of the financial interests of public and confidential filers and an employee who is found to have a financial interest in a significantly regulated entity is notified in writing and directed to the proper course of action. Employees have four options to satisfy the divestiture requirements:

1) Include documentation to support that the company is not significantly regulated; or
2) Divest of the prohibited financial interest, which could include transferring the interest to someone other than a spouse or minor child; or
3) Apply for a Certificate of Divestiture from the Office of Government Ethics (OGE); or
4) Request an exception to hold the financial interest.

Certificate of Divestiture

This document allows for the deferral of capital gains for Federal Income Tax purposes if the monies derived from a directed divestiture action are rolled over into any obligation of the United States or any diversified investment fund. The OGE determines whether to issue a Certificate of Divestiture pursuant to certain conditions including the following:

1) Any employee who **purchases** a financial interest at a time when that interest is already prohibited for the employee will not be eligible for a Certificate of Divestiture. The "Listing of U.S. Industries" provides the names of U.S. public companies and indicates whether they are acceptable or prohibited holdings. The Listing can be accessed on the FDA Internet.

2) If divestiture will not occur within 90 days after the date divestiture is first directed by the agency, the employee will not be eligible for a Certificate of Divestiture unless OGE concurs with an extension of time because of unusual hardship.

Employee Request for an Exception to Retain a Prohibited Financial Interest

In cases involving "exceptional circumstances," the employee may be able to qualify for an exception to hold the prohibited interest. The Conflict of Interest Review Board will evaluate employee requests for an exception on an individual basis, and a determination will be made pursuant to applicable regulations. Please be aware that an exceptional circumstance does not include any of the following situations: purchasing a prohibited interest either personally or through the efforts of another person such as an investment broker, before or during FDA employment; receiving a prohibited interest as a gift, inheriting a prohibited interest, or obtaining a prohibited interest through marriage.

Reminder:

It is the responsibility of the ***employee***, not the Agency, to ensure that he/she remains in compliance with the financial interest regulations.

Division of Ethics and
Integrity
Office of Operations
Food and Drug Administration

FACT SHEET
The Certificate of Divestiture (CD) Program
(Key points FDA employees should know and understand)

- A Certificate of Divestiture (CD) is a personal tax benefit that allows the nonrecognition/deferral of capital gain in the case of sales of stocks, bonds, etc., that are made to comply with conflict of interest requirements.

- It is important to remember that a CD is a ***PERSONAL TAX BENEFIT.*** The employee is responsible for consulting with his or her own ***PERSONAL ADVISOR(S)*** concerning the legal, financial and tax aspects of the matter. Neither FDA nor the Office of the General Counsel acts as personal advisor or legal counsel to an employee in connection with a CD.

- Nonrecognition of capital gain occurs only in the year in which the asset is sold. In the typical case, recognition of the gain is deferred to the year in which the rollover property is sold.

  - Procedures and policies for issuance of Certificates of Divestitures are found at 5 C.F.R. 2634 1001 Subpart J. (http://www.usoge.gov/laws_regs/regulations/5cfr2634.aspx or Attachment 4).

- The Office of Government Ethics (OGE), a separate agency, administers the CD program. ***Neither FDA nor HHS issues or has authority to issue a CD.***

  - The OGE has a "90 day clock." This means:

1. OGE generally will not grant a CD if 90 days have elapsed since the date divestiture is first directed.

2. For new FDA public and confidential filers, the "date divestiture is first directed" is the date on which the new entrant public or confidential financial disclosure report (OGE 450/SF 278) is due, i.e., 30 days after joining the agency. For incumbent employees, the "date divestiture is first directed" is the date the report of a prohibited interest (HHS 717-2) is due, i.e., 30 days after acquiring the prohibited financial interest.

3. As early as possible within this timeframe, the Ethics and Integrity Staff in the Office of Management must be notified in writing that the employee holds a prohibited interest. The employee should report the interest on a Form OGE 450 Confidential Financial Disclosure Report, or on a Form HHS 717-2 Report of Prohibited Financial Interests for Employees of the Food and Drug Administration, as applicable, to initiate the CD request process. Form OGE 450 and HHS 717-2 are available at http://inside.fda.gov:9003/EmployeeResources/Ethics/FDAEthicsProgram/ucm008870.htm.

4. After the prohibited interest is reported to the Ethics and Integrity Staff, the employee will receive a letter directing the employee to divest. The letter will also provide the option for the employee to apply for a CD from the OGE. Employees must submit the request for a CD to the HHS Office of the General Counsel/Ethics Division, through the Ethics and Integrity Staff, by following the specified procedure. The written request must provide details on the exact number of shares held and how they were acquired. See Attachment 5 for a sample request. The request package is then forwarded by HHS to the OGE for CONSIDERATION, provided that it appears to comply with the OGE criteria.

5. If the request package arrives at the OGE after the employee has held the prohibited interest for 90 days, the request may be denied. Although the regulations permit exceptions in cases of "unusual hardship", they are granted only where the employee can demonstrate exceptional circumstances, typically beyond his or her control. Past OGE precedents indicate that an employee's lack of knowledge about the regulation or about the prohibited status of a stock that is listed in the "Listing of U.S. Industries" does not constitute unusual hardship.

6. Employees should consider how much time might elapse during this process (mailing time, review time, dealing with incomplete information, etc.). The 90 day time frame elapses quickly.

- A CD will not be issued if the holding is within an IRA or 401(k) plan.

- A CD will be denied if the interest was acquired during employment with FDA and was prohibited at the time it was purchased or given to the employee. If the interest was acquired during FDA employment through marriage, inheritance, or circumstances clearly beyond the employee's control, the employee may be eligible for a CD.

- Generally, employees must agree to divest ALL prohibited stocks held in order to receive a CD.

- Interests held within a trust often pose complicated questions and may require direct contact between the employee or the employee's legal representative and the Office of Government Ethics.

- A CD will not be issued **after** the interest has been sold.

- A CD is not needed if the interest will be sold at a loss, as there will be no capital gain in this situation.

- Once a CD is received, the stock must be sold within the 90-day window. Employees then have 60 days after the sale to reinvest in "permitted properties".

- "Permitted property" includes: diversified open mutual funds and/or U.S. Treasury securities. (NOTE: Employees may not use the proceeds for a vacation, stock investments, a new house or car or anything other than those two investment categories listed above if the tax benefit is to be preserved.)

THE CD PROGRAM IS VIEWED AS A BENEFIT PROGRAM FOR WHICH THE OGE VERY STRICTLY FOLLOWS AND ADMINISTERS THE REGULATIONS

All questions should be directed to the Ethics and Integrity Staff. Contact information may be found at the following website: http://inside fda.gov:9003/EmployeeResources/Ethics/FDAEthicsProgram/ucm020186 htm.

Ethics and Integrity Staff
Office of Management
Food and Drug Administration

October 2010

FACT SHEET
The Certificate of Divestiture (CD) Program
(Key points FDA employees should know and understand)

- A Certificate of Divestiture (CD) is a personal tax benefit that allows the nonrecognition/deferral of capital gain in the case of sales of stocks, bonds, etc., that are made to comply with conflict of interest requirements.

- It is important to remember that a CD is a ***PERSONAL TAX BENEFIT.*** The employee is responsible for consulting with his or her own ***PERSONAL ADVISOR(S)*** concerning the legal, financial and tax aspects of the matter. Neither FDA nor the Office of the General Counsel acts as personal advisor or legal counsel to an employee in connection with a CD.

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All questions should be directed to the Ethics and Integrity Staff. Contact information may be found at the following website: http://inside fda.gov:9003/EmployeeResources/Ethics/FDAEthicsProgram/ucm020186 htm.

Ethics and Integrity Staff
Office of Management
Food and Drug Administration

October 2010

Rules and Regulations

Federal Register
Vol. 69, No. 144
Wednesday, July 28, 2004

OFFICE OF GOVERNMENT ETHICS

5 CFR Part 2634

RIN 3209–AA00

Revisions to the Certificates of Divestiture Regulation

AGENCY: Office of Government Ethics (OGE).

ACTION: Final rule amendments.

SUMMARY: In this final rule, the Office of Government Ethics has rewritten its regulation concerning Certificates of Divestiture in plain language. This rule also revises certain procedures for issuing Certificates of Divestiture and the definition of permitted property into which proceeds of the sale of property are reinvested.

DATES: *Effective Date:* August 27, 2004.

FOR FURTHER INFORMATION CONTACT: Deborah J. Bortot, Office of Government Ethics; Telephone: 202–482–9300; TDD: 202–482–9293; FAX: 202–482–9237.

SUPPLEMENTARY INFORMATION:

I. Background

Section 1043 of the Internal Revenue Code of 1986, 26 U.S.C. 1043, was enacted as part of the Ethics Reform Act of 1989 (Pub. L. 101–194). Section 1043 authorizes the Director of OGE to issue a Certificate of Divestiture to an eligible person who is divesting property in order to comply with a Federal conflict of interest law, regulation, rule, or Executive order, or if requested by a congressional committee as a condition of confirmation. A person who receives a Certificate of Divestiture may defer payment of capital gains tax as long as he or she timely purchases certain permitted property with the proceeds of the sale. OGE published an interim rule on April 18, 1990 (at 55 FR 14407–14409) implementing section 1043. On June 25, 1996, the Office of Government Ethics published a final rule at 61 FR 32633–32636. The final rule was based on comments to the interim rule and on OGE's experience under the interim rule and the May 1990 Technical Corrections to the Ethics Reform Act of 1989 (Pub. L. 101–280), which amended section 1043 of the Internal Revenue Code of 1986. The OGE Certificates of Divestiture executive branchwide regulation is now codified at subpart J of 5 CFR part 2634.

On January 13, 2004, OGE published a set of proposed amendments to the regulation, proposing to make certain improvements. See 69 FR 1954–1957. The proposed rule provided a 60-day comment period. The Office of Government Ethics received one comment letter from an organization. After a careful review of the comment letter and making some additional plain language modifications, OGE is publishing this final rule.

II. Summary of Comments and Revisions

We have attempted to improve the current Certificates of Divestiture regulation by: Organizing the material more logically; using shorter sentences; eliminating unnecessary technical language; and stating the rule's requirements more clearly. The one comment letter suggested many changes to make the regulation even simpler. After careful review, OGE has adopted some of the suggestions. In particular, we have redrafted §§ 2634.1001 and 2634.1003 of the proposed rule to make them easier to understand. Consequently, § 2634.1001 of the proposed rule is now divided into §§ 2634.1001 and 2634.1002, and proposed sections 2634.1002–2634.1007 have been renumbered in this final rule accordingly.

The final rule retains the same revisions as set forth in the proposed rule. First, we changed the meaning of a ''diversified investment fund,'' in paragraph (2) of the definition of permitted property in new (renumbered) § 2634.1003, to track the definition of diversified mutual fund and diversified unit investment trust as those terms are used in 5 CFR 2640.102.[1] Second, several changes will streamline and simplify the procedure OGE uses to issue a Certificate of Divestiture. The final rule clarifies the information related to financial disclosure that needs to be submitted as part of the Certificate of Divestiture request and simplifies the procedure related to the timing of a submission of a request to OGE.

III. Matters of Regulatory Procedure

Executive Order 12866

In promulgating this final regulation, the Office of Government Ethics has adhered to the regulatory philosophy and the applicable principles of regulation set forth in section 1 of Executive Order 12866, Regulatory Planning and Review. This regulation has also been reviewed by the Office of Management and Budget under that Executive order. Moreover, in accordance with section 6(a)(3)(B) of E.O. 12866, the preambles to the proposed and final revisions, to be codified in a revised subpart J of 5 CFR part 2634, note the legal basis and benefits of as well as the need for the regulatory action. There should be no appreciable increase in costs to OGE or the executive branch of the Federal Government in administering this regulation, once it becomes effective, since the provisions only clarify and improve the Certificates of Divestiture regulatory procedures. Finally, this rulemaking is not economically significant under the Executive order and will not interfere with State, local or tribal governments.

Executive Order 12988

As Acting Director of the Office of Government Ethics, I have reviewed this final amendatory regulation in light of section 3 of Executive Order 12988, Civil Justice Reform, and certify that it meets the applicable standards provided therein.

Regulatory Flexibility Act

As Acting Director of the Office of Government Ethics, I certify under the Regulatory Flexibility Act (5 U.S.C.

[1] When the Certificate of Divestiture rule was first published in April 1990, the definition of ''diversified investment fund'' included common trust funds maintained by banks. At that time, common trust funds were required to be diversified under rules published by the Comptroller of the Currency. However, in December 1996, the Office of the Comptroller of the Currency eliminated the diversification requirement. *See* 61 FR 68543, 68551. Therefore, common trust funds are not a suitable alternative for permitted property and have been deleted from the definition of diversified investment fund. Eligible persons who invested in common trust funds as permitted property prior to the effective date of this final rule may continue to hold those funds.

chapter 6) that this amendatory rule will not have a significant economic impact on a substantial number of small entities because it primarily affects Federal executive branch employees and members of their immediate families.

Paperwork Reduction Act

The Paperwork Reduction Act (44 U.S.C. chapter 35) does not apply to this final amended regulation because it does not contain any information collection requirements that require the approval of the Office of Management and Budget.

Unfunded Mandates Reform Act

For purposes of the Unfunded Mandates Reform Act of 1995 (2 U.S.C. chapter 25, subchapter II), this final rule will not significantly or uniquely affect small governments and will not result in increased expenditures by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (as adjusted for inflation) in any one year.

Congressional Review Act

The Office of Government Ethics has determined that this rulemaking involves a nonmajor rule under the Congressional Review Act (5 U.S.C. chapter 8) and will submit a report thereon to the U.S. Senate, House of Representatives and General Accounting Office in accordance with that law at the same time this rulemaking document is sent to the Office of the Federal Register for publication in the **Federal Register**.

List of Subjects in 5 CFR Part 2634

Certificates of divestiture, Conflict of interests, Financial disclosure, Government employees, Penalties, Privacy, Reporting and recordkeeping requirements, Trusts and trustees.

Approved: July 21, 2004.

Marilyn L. Glynn,

Acting Director, Office of Government Ethics.

■ Accordingly, for the reasons set forth in the preamble, the Office of Government Ethics is amending 5 CFR part 2634 as follows:

PART 2634—EXECUTIVE BRANCH FINANCIAL DISCLOSURE, QUALIFIED TRUSTS, AND CERTIFICATES OF DIVESTITURE

■ 1. The authority citation for part 2634 continues to read as follows:

Authority: 5 U.S.C. App. (Ethics in Government Act of 1978); 26 U.S.C. 1043; Pub. L. 101–410, 104 Stat. 890, 28 U.S.C. 2461 note (Federal Civil Penalties Inflation Adjustment Act of 1990), as amended by Sec. 31001, Pub. L. 104–134, 110 Stat. 1321 (Debt Collection Improvement Act of 1996); E.O. 12674, 54 FR 15159, 3 CFR, 1989 Comp., p. 215, as modified by E.O. 12731, 55 FR 42547, 3 CFR, 1990 Comp., p. 306.

■ 2. Subpart J of part 2634 is revised to read as follows:

Subpart J—Certificates of Divestiture

Sec.

Subpart J—Certificates of Divestiture

§ 2634.1001 Overview.

(a) *Scope.* 26 U.S.C. 1043 and the rules of this subpart allow an eligible person to defer paying capital gains tax on property sold to comply with conflict of interest requirements. To defer the gains, an eligible person must obtain a Certificate of Divestiture from the Director of the Office of Government Ethics before selling the property. This subpart describes the circumstances when an eligible person may obtain a Certificate of Divestiture and establishes the procedure that the Office of Government Ethics uses to issue Certificates of Divestiture.

(b) *Purpose.* The purpose of section 1043 and this subpart is to minimize the burden that would result from paying capital gains tax on the sale of assets to comply with conflict of interest requirements. Minimizing this burden aids in attracting and retaining highly qualified personnel in the executive branch and ensures the confidence of the public in the integrity of Government officials and decision-making processes.

§ 2634.1002 Role of the Internal Revenue Service.

The Internal Revenue Service (IRS) has jurisdiction over the tax aspects of a divestiture made pursuant to a Certificate of Divestiture. Eligible persons seeking to defer capital gains:

(a) Must follow IRS requirements for reporting dispositions of property and electing under section 1043 not to recognize capital gains; and

(b) Should consult a personal tax advisor or the IRS for guidance on these matters.

§ 2634.1003 Definitions.

For purposes of this subpart:

Eligible person means:

(1) Any officer or employee of the executive branch of the Federal Government, except a person who is a special Government employee as defined in 18 U.S.C. 202;

(2) The spouse or any minor or dependent child of the individual referred to in paragraph (1) of this definition; and

(3) Any trustee holding property in a trust in which an individual referred to in paragraph (1) or (2) of this definition has a beneficial interest in principal or income.

Permitted property means:

(1) An obligation of the United States; or

(2) A diversified investment fund. A diversified investment fund is a diversified mutual fund or diversified unit investment trust, as defined in 5 CFR 2640.102(a), (k) and (u);

(3) Provided, however, a permitted property cannot be any holding prohibited by statute, regulation, rule, or Executive order. As a result, requirements applicable to specific agencies and positions may limit an eligible person's choices of permitted property. An employee seeking a Certificate of Divestiture should consult the appropriate designated agency ethics official to determine whether a statute, regulation, rule, or Executive order may limit choices of permitted property.

§ 2634.1004 General rule.

(a) The Director of the Office of Government Ethics may issue a Certificate of Divestiture for specific property in accordance with the procedures of § 2634.1005 of this subpart if:

(1) The Director determines that divestiture of the property by an eligible person is reasonably necessary to comply with 18 U.S.C. 208, or any other Federal conflict of interest statute, regulation, rule, or Executive order; or

(2) A congressional committee requires divestiture as a condition of confirmation.

(b) The Director of the Office of Government Ethics cannot issue a Certificate of Divestiture for property that already has been sold.

Example 1 to § 2634.1004: An employee is directed to divest shares of stock, a limited partnership interest, and foreign currencies. If the sale of these assets will result in capital gains under the Internal Revenue Code, the employee may request and receive a Certificate of Divestiture.

Example 2 to § 2634.1004: An employee of the Department of Commerce is directed to divest his shares of XYZ stock acquired through the exercise of options held in an employee benefit plan. His gain from the sale of the stock will be treated as ordinary

income. Because only capital gains realized under Federal tax law are eligible for deferral under section 1043, a Certificate of Divestiture cannot be issued for the sale of the XYZ stock.

Example 3 to § 2634.1004: During her Senate confirmation hearing, a nominee to a Department of Defense (DOD) position is directed to divest stock in a DOD contractor as a condition of her confirmation. Eager to comply with the order to divest, the nominee sells her stock immediately after the hearing and prior to being confirmed by the Senate. Once she is a DOD employee, she requests a Certificate of Divestiture for the stock. Because the Office of Government Ethics cannot issue a Certificate of Divestiture for property that has already been divested, the employee's request for a Certificate of Divestiture will be denied.

Example 4 to § 2634.1004: After receiving a Certificate of Divestiture, the spouse of a Food and Drug Administration employee sold stock in a regulated company. Between the time of the request for the Certificate of Divestiture and the sale of the stock, the stock price dropped and the spouse sold the stock at a loss. Because the sale of the stock did not result in capital gains, the spouse has no need for the Certificate of Divestiture and cannot submit it to the Internal Revenue Service for deferral of gains. No further action need be taken by the employee or the employee's spouse in connection with the Certificate of Divestiture.

§ 2634.1005 How to obtain a Certificate of Divestiture.

(a) *Employee's request to the designated agency ethics official.* An employee seeking a Certificate of Divestiture must submit a written request to the designated agency ethics official at his or her agency. The request must contain:

(1) A full and specific description of the property that will be divested. For example, if the property is corporate stock, the request must include the number of shares for which the eligible person seeks a Certificate of Divestiture;

(2) A brief description of how the eligible person acquired the property;

(3) A statement that the eligible person holding the property has agreed to divest the property; and

(4)(i) The date that the requirement to divest first applied; or

(ii) The date the employee first agreed that the eligible person would divest the property in order to comply with conflict of interest requirements.

(b) *Designated agency ethics official's submission to the Office of Government Ethics.* The designated agency ethics official must forward to the Director of the Office of Government Ethics the employee's written request described in paragraph (a) of this section. In addition, the designated agency ethics official must submit:

(1) A copy of the employee's latest financial disclosure report. If the employee is not required to file a financial disclosure report, the designated agency ethics official must obtain from the employee, and submit to the Office of Government Ethics, a listing of the employee's interests that would be required to be disclosed on a confidential financial disclosure report excluding gifts and travel reimbursements. For purposes of this listing, the reporting period is the preceding twelve months from the date the requirement to divest first applied or the date the employee first agreed that the eligible person would divest the property;

(2) An opinion that describes why divestiture of the property is reasonably necessary to comply with 18 U.S.C. 208, or any other Federal conflict of interest statute, regulation, rule, or Executive order; and

(3) A brief description of the employee's position or a citation to a statute that sets forth the duties of the position.

(c) *Divestitures required by a congressional committee.* In the case of a divestiture required by a congressional committee as a condition of confirmation, the designated agency ethics official must submit appropriate evidence that the committee requires the divestiture. A transcript of congressional testimony or a written statement from the designated agency ethics official concerning the committee's custom regarding divestiture are examples of evidence of the committee's requirements.

(d) *Divestitures for property held in a trust.* In the case of divestiture of property held in a trust, the employee must submit a copy of the trust instrument, as well as a list of the trust's current holdings, unless the holdings are listed on the employee's most recent financial disclosure report. In certain cases involving divestiture of property held in a trust, the Director may not issue a Certificate of Divestiture unless the parties take actions which, in the opinion of the Director, are appropriate to exclude, to the extent practicable, parties other than eligible persons from benefitting from the deferral of capital gains. Such actions may include, as permitted by applicable State law, division of the trust into separate portfolios, special distributions, dissolution of the trust, or anything else deemed feasible by the Director, in his or her sole discretion.

Example 1 to paragraph (d): An employee has a 90% beneficial interest in an irrevocable trust created by his grandfather. His four adult children have the remaining 10% beneficial interest in the trust. A number of the assets held in the trust must be sold to comply with conflicts of interest requirements. Due to State law, no action can be taken to separate the trust assets. Because the adult children have a small interest in the trust and the assets cannot be separated, the Director may consider issuing a Certificate of Divestiture to the trustee for the sale of all of the conflicting assets.

(e) *Time requirements.* A request for a Certificate of Divestiture does not extend the time in which an employee otherwise must divest property required to be divested pursuant to an ethics agreement, or prohibited by statute, regulation, rule, or Executive order. Therefore, an employee must submit his or her request for a Certificate of Divestiture as soon as possible once the requirement to divest becomes applicable. The Office of Government Ethics will consider requests submitted beyond the applicable time period for divestiture. If the designated agency ethics official submits a request to the Office of Government Ethics beyond the applicable time period for divestiture, he must explain the reason for the delay. (*See* 5 CFR 2634.802 and 2635.403 for rules relating to the time requirements for divestiture.)

(f) *Response by the Office of Government Ethics.* After reviewing the materials submitted by the employee and the designated agency ethics official, and making a determination that all requirements have been met, the Director will issue a Certificate of Divestiture. The certificate will be sent to the designated agency ethics official who will then forward it to the employee.

§ 2634.1006 Rollover into permitted property.

(a) *Reinvestment of proceeds.* In order to qualify for deferral of capital gains, an eligible person must reinvest the proceeds from the sale of the property divested pursuant to a Certificate of Divestiture into permitted property during the 60-day period beginning on the date of the sale. The proceeds may be reinvested into one or more types of permitted property.

Example 1 to paragraph (a): A recently hired employee of the Department of Transportation receives a Certificate of Divestiture for the sale of a large block of stock in an airline. He may split the proceeds of the sale and reinvest them in an S&P Index Fund, a diversified Growth Stock Fund, and U.S. Treasury bonds.

Example 2 to paragraph (a): The Secretary of Treasury sells certain stock after receiving a Certificate of Divestiture and is considering reinvesting the proceeds from the sale into U.S. Treasury securities. However, because the Secretary of the Treasury is prohibited by 31 U.S.C. 329 from being involved in buying obligations of the United States Government, the Secretary cannot reinvest the proceeds in

such securities. However, she may invest the proceeds in a diversified mutual fund. See the definition of *permitted property* at § 2634.1003.

(b) *Internal Revenue Service reporting requirements.* An eligible person who elects to defer the recognition of capital gains from the sale of property pursuant to a Certificate of Divestiture must follow Internal Revenue Service rules for reporting the sale of the property and the reinvestment transaction.

§ 2634.1007 Cases in which Certificates of Divestiture will not be issued.

The Director of the Office of Government Ethics, in his or her sole discretion, may deny a request for a Certificate of Divestiture in cases where an unfair or unintended benefit would result. Examples of such cases include:

(a) *Employee benefit plans.* The Director will not issue a Certificate of Divestiture if the property is held in a pension, profit-sharing, stock bonus, or other employee benefit plan and can otherwise be rolled over into an eligible tax-deferred retirement plan within the 60-day reinvestment period.

(b) *Complete divestiture.* The Director will not issue a Certificate of Divestiture unless the employee agrees to divest all of the property that presents a conflict of interest, as well as other similar or related property that presents a conflict of interest under a Federal conflict of interest statute, regulation, rule, or Executive order. However, any property that qualifies for a regulatory exemption at 5 CFR part 2640 need not be divested for a Certificate of Divestiture to be issued.

Example 1 to paragraph (b): A Department of Agriculture employee owns shares of stock in Better Workspace, Inc. valued at $25,000. As part of his official duties, the employee is assigned to evaluate bids for a contract to renovate office space at his agency. The Department's designated agency ethics official discovers that Better Workspace is one of the companies that has submitted a bid and directs the employee to sell his stock in the company. Because Better Workspace is a publicly traded security, the employee could retain up to $15,000 of the stock under the regulatory exemption for interests in securities at 5 CFR 2640.202(a). He would be able to request a Certificate of Divestiture for the $10,000 of Better Workspace stock that is not covered by the exemption. Alternatively, he could request a Certificate of Divestiture for the entire $25,000 worth of stock. If he chooses to sell his stock down to an amount permitted under the regulatory exemption, the Office of Government Ethics will not issue additional Certificates of Divestiture if the value of the stock goes above $15,000 again.

(c) *Property acquired under improper circumstances.* The Director will not issue a Certificate of Divestiture:

(1) If the eligible person acquired the property at a time when its acquisition was prohibited by statute, regulation, rule, or Executive order; or

(2) If circumstances would otherwise create the appearance of a conflict with the conscientious performance of Government responsibilities.

§ 2634.1008 Public access to a Certificate of Divestiture.

A Certificate of Divestiture issued pursuant to the provisions of this subpart is available to the public in accordance with the rules of § 2634.603 of this part.

[FR Doc. 04–17200 Filed 7–27–04; 8:45 am]

BILLING CODE 6345–02–P

DEPARTMENT OF AGRICULTURE

Rural Utilities Service

7 CFR Part 1739

RIN 0572–AB94

Broadband Grant Program

AGENCY: Rural Utilities Service, USDA.

ACTION: Final rule.

SUMMARY: The Rural Utilities Service (RUS) is publishing regulations to administer the Community Connect Grant Program for the provision of broadband transmission service in rural America. This final rule is intended to establish eligibility and application requirements, the review and approval process, and grant administration procedures for the Community Connect Grant Program.

EFFECTIVE DATE: July 28, 2004.

FOR FURTHER INFORMATION CONTACT: Roberta D. Purcell, Assistant Administrator, Telecommunications Program, Rural Utilities Service, STOP 1590, 1400 Independence Avenue SW., Washington, DC 20250–1590, Telephone (202) 720–9554, Facsimile (202) 720–0810. Email address: *Bobbie.Purcell@usda.gov*.

SUPPLEMENTARY INFORMATION:

Executive Order 12866

This final rule has been determined to be not significant for purposes of Executive Order 12866, and therefore has not been reviewed by the Office of Management and Budget (OMB).

Catalog of Federal Domestic Assistance

The Catalog of Federal Domestic Assistance (CFDA) Program number assigned to the Community Connect Grant Program is 10.863. The Catalog is available on a subscription basis from the Superintendent of Documents, the Unites States Government Printing Office, Washington, DC 20402–9325, telephone number (202) 512–1800.

Executive Order 12372

This program is not subject to the requirements of Executive Order 12372, ''Intergovernmental Review of Federal Programs,'' as implemented under USDA's regulations at 7 CFR part 3015.

Executive Order 12988

This final rule has been reviewed under Executive Order 12988, Civil Justice Reform. RUS has determined that this final rule meets the applicable standards provided in section 3 of the Executive Order. In addition, all state and local laws and regulations that are in conflict with this rule will be preempted, no retroactive effect will be given to this rule, and, in accordance with Section 212(e) of the Department of Agriculture Reorganization Act of 1994 (7 U.S.C. 6912(e)), administrative appeal procedures, if any, must be exhausted before an action against the Department or its agencies may be initiated.

Executive Order 13132, Federalism

The policies contained in this final rule do not have any substantial direct effect on states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Nor does this final rule impose substantial direct compliance costs on state and local governments. Therefore, consultation with states is not required.

Regulatory Flexibility Certification

Pursuant to 5 U.S.C. 553(a)(2), this final rule related to grants is exempt from the rulemaking requirements of the Administrative Procedure Act (5 U.S.C. 551 *et seq.*), including the requirement to provide prior notice and an opportunity for public comment. Because this final rule is not subject to a requirement to provide prior notice and an opportunity for public comment pursuant to 5 U.S.C. 553, or any other law, the analytical requirements of the Regulatory Flexibility Act (5 U.S.C. 601 *et seq.*) are inapplicable.

Unfunded Mandates

This final rule contains no Federal mandates (under the regulatory provision of Title II of the Unfunded Mandates Reform Act of 1995) for State, local, and tribal governments or the private sector. Therefore, this final rule is not subject to the requirements of sections 202 and 205 of the Unfunded Mandates Reform Act of 1995.

DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

Memorandum

Attachment 5 (SAMPLE)

Date:

From:

Subject: Request for Certificate of Divestiture

Through: Ethics and Integrity Staff
Office of Management

To: Edgar M. Swindell
Associate General Counsel for Ethics
Office of General Counsel/Ethics Division

In order to resolve a conflict of interest due to my financial interest in [list the firm(s) name(s)], I am requesting a Certificate of Divestiture under the Ethics Reform Act of 1989 and 5 CFR, Part 2634, Subpart J. This provision of the Act permits the nonrecognition of capital gain upon the disposition of property.

I understand the Certificate of Divestiture program is a matter of tax law, and implements section 1043 of the Internal Revenue Code. These rules operate not by eliminating the capital gains tax, but by merely deferring its imposition. These rules cannot be amended nor overlooked by FDA. For nonrecognition of gain in the case of sales to comply with conflict of interest requirements, rollover must be made into (1) any obligation of the United States; or (2) any diversified investment fund which is an open-end mutual fund. These are the only interests permitted for nonrecognition of gain. I will seek the advice of my personal tax advisor and/or the Internal Revenue Service for guidance as to the tax aspects of divestiture transactions and whether proposed acquisitions meet the requirements for permitted property.

In addition, I promise to divest the prohibited interest not later than 90 days after the date that divestiture was first directed by the Agency unless I am granted an extension of time. For new FDA public and confidential filers, the "date divestiture is first directed" is the date on which the new entrant public or confidential financial disclosure report (OGE 450/SF 278) is due, i.e., 30 days after joining the Agency. For incumbent employees, the "date divestiture is first directed" is the date the report of a prohibited interest (HHS 717-2) is due, i.e., 30 days after acquiring the prohibited financial interest.

The Director, Ethics and Integrity Staff, Office of Management of FDA has directed that I divest myself of this interest as set forth in the attached divestiture letter. (Describe the interest by providing the following: 1) exact number of shares in question; 2) date the interest was acquired; 3) detailed description of each stock; and 4) how the interest was acquired). I have also attached my current Confidential Financial Disclosure Report, OGE 450.

If you have additional questions concerning this submission, please contact the Ethics and Integrity Staff, Office of Management (301) 796-8438.

(Employee's signature)
(Spouse's signature if jointly owned)

Attachments

ATTACHMENT 6

EMPLOYEE REQUEST FOR AN EXCEPTION TO RETAIN A PROHIBITED FINANCIAL INTEREST

Please provide the information requested below in typed or printed form to the Ethics and Integrity Staff accompanied by the disqualification in Attachment 7.

Part I – Information Pertaining to Requestor

(a) Employee's name
(b) Title of position and grade
(c) Organization's Name (Center/Office/ORA and Region/District/Division [e.g., ORA/Pacific Region/Seattle District or CDER/OND/ODEI]
(d) Date entered on duty at FDA
(e) Date entered current position

Part II – Information Pertaining to Prohibited Financial Interest

(f) Identify prohibited financial interest (include type of interest [e.g., stock, bond, mutual fund] and company name)
(g) Number of shares held and current value of interest
(h) Date interest was acquired
(i) Owner(s) of the prohibited financial interest in question (e.g.,. self, spouse, minor child)
(j) Description of how the acquisition occurred (spouse's employment benefits, gifts to dependent child(ren), part of trust, etc) and why it involves "exceptional circumstances". Explain why these circumstances warrant FDA to make an exception to its prohibited holding regulations.

Part III – Information Supporting Exception

(k) Identify work unit (e.g., division/branch) and provide a brief description of official duties
(l) Identify prohibited financial interest and describe its regulated activities (e.g., Merck stock and new drug applications)
(m) Describe why holding the prohibited financial interest would not cause a question regarding the impartiality or objectivity with which FDA programs are administered. Provide any other pertinent information that would support the request.

Part IV – Notice of Disqualification

Insert here any products or firms, which the requesting employee has been disqualified from reviewing/inspecting.

Part V – Employee's Signature and Date

Ethics and Integrity Staff
Office of Management
Food and Drug Administration

October 2010

ATTACHMENT 7

INSTRUCTIONS FOR NOTICE OF DISQUALIFICATION FOR EMPLOYEES REQUESTING AN EXCEPTION TO RETAIN A PROHIBITED FINANCIAL INTEREST

The employee is required to give notice of disqualification to his/her supervisor and the supervisor is required to sign an acknowledgement of receipt and agrees not to give official assignments to the employee that may relate to his/her prohibited financial interest(s). This record shall be included with the employee's exception request.

Subject: Notice of Disqualification from Prohibited Financial Interest

To: _____
(*Supervisor's Name)*

I have a financial interest in _____ which is a prohibited financial
(Name of Company or Organization)

interest as defined by DHHS Supplemental Standards of Ethical Conduct (5 CFR 5501).

I am making an employee exception request to the Conflict of Interest Review Board (COIRB) in order to retain this prohibited financial interest.

I am required to inform you of this holding and request that until a determination is made by the Board, no official assignments be given to me related to this prohibited financial interest. This recusal obligation falls under a COI statute (Title 18 U.S.C. § 208). This means I should not be assigned, nor otherwise work on any particular matters, general or specific where _____ is a party. A specific party matter is one that affects the legal rights of a party like a grant, contract, inspection, audit, submission review, etc., as well as reviews of products from another company that closely competes with products. A general matter includes rulemaking, policy formulation, regulations, and legislation that could affect the entity as part of a class.

An exception to this disqualification may apply depending on the value of the financial interest. For example, if the value of the interest is below $15,000 (a regulatory exemption amount) then, during the time this case is before the Board, I may continue to work on matters as described above, unless the value exceeds this amount at any time. I understand that I must monitor my holding to assure that it stays below the $15,000 level. However, the financial interest is still prohibited and must still be divested unless the Conflict of Interest Review Board grants an exception and I am allowed to retain the financial holding. However, even if I am granted the exception, the recusal obligation under 208 still applies.

I will notify you of the final disposition of my request.

_____ _____
Employee's Signature *Date*

Subject: Acknowledgement of Receipt

To: _____
(*Employee's Name)*

I acknowledge receipt of this notice from _____
(Employee's Name)

advising me of the prohibited financial interest and the recusal obligation under Title 18 U.S.C. § 208. The named employee will be disqualified from participating in particular matters affecting this prohibited financial interest, either general or specific as identified above, until the disqualification is no longer necessary due to divestiture of the interest completely, or the value of the interest remaining below the regulatory exemption amount.

_____ _____
Supervisor's Name and Signature *Date*

Akbari, Asim

From: Akbari, Asim
Sent: Thursday, September 01, 2016 6:20 PM
To: Moscicki, Richard
Cc: Pupkar, Lynn
Subject: FW: (b) (6), (b) (3) Urgent

Hi Rich,

I wanted to forward to you the guidance that I received from OGC on your question. (b) (5), (b) (6), (b) (3) (A)

The issue of your filing an OGE 278 is something that we are taking a more broader look throughout the agency. We will notify you as soon as we come to a determination on this issue. If you or Hillary have any questions about the OGE 450 or any other matter, please do not hesitate to contact me.

Lynn,
When you get Dr. Moscicki's 450, please reassign it to me. I will review it myself. Thanks.

Asim

From: Sanft, Corbin (HHS/OGC) [mailto:Corbin.Sanft@hhs.gov]
Sent: Thursday, September 01, 2016 7:38 AM
To: Akbari, Asim
Subject: RE: (b) (6), (b) (3) Urgent

Hi Asim – Thanks for your patience.

(b) (5), (b) (6), (b) (3) (A)

(b) (5), (b) (6), (b) (3) (A)

[redacted]

Please let me know if I can assist further.

Corbin

Corbin G. Sanft
Attorney Advisor
Department of Health & Human Services
Office of the General Counsel
Ethics Division
Telephone: (240) 402-1096
Fax: (202) 205-9752

From: Akbari, Asim [mailto:Asim.Akbari@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 5:48 PM
To: Moscicki, Richard (FDA/CDER)
Cc: Sanft, Corbin (HHS/OGC)
Subject: RE: (b) (6), (b) (3) Urgent

Hi Rich,

Sorry that I was not clear in my earlier email. I partially misread your email and had been in meetings all day. I hope this email provide is more clear. You indicated (b) (5), (b) (6), (b) (3) (A)

[redacted]

(b) (5), (b) (6), (b) (3) (A)

I would be happy to discuss further if you would like.

Regards,
Asim

From: Moscicki, Richard
Sent: Wednesday, August 31, 2016 1:11 PM
To: Akbari, Asim
Subject: RE: (b) (6), (b) (3) Urgent

Thanks Asim but I don't quite understand the "ability and willingness recusal with the seller (me) for (b) (6), (b) (3) (A) "

From: Akbari, Asim
Sent: Wednesday, August 31, 2016 12:06 PM
To: Moscicki, Richard; Sanft, Corbin G (OS)
Cc: Pupkar, Lynn; Collins, Stephanie
Subject: RE: (b) (6), (b) (3) Urgent

(b) (5), (b) (6), (b) (3) (A)

?

Asim

From: Moscicki, Richard
Sent: Wednesday, August 31, 2016 12:02 PM
To: Akbari, Asim
Cc: Pupkar, Lynn; Collins, Stephanie
Subject: RE: (b) (6), (b) (3) Urgent

Asim, I have signed a LOI to sell my (b) (6), (b) (3) holding to (b) (6), (b) (3) (A) . We are completing the Purchase Sale Agreement. I can receive a better price if (b) (6), (b) (3) (A) . I would complete the sale for the agreed upon price with a signed agreement by Sept 30. (b) (6), (b) (3) would transfer ownership to (b) (6), (b) (3) (A) by the end of the quarter, possibly could take to end of next quarter, but I would then have no interest in the fund, no further possible benefit or harm from the fund. I just need your clearance that I can wait for my payment (essentially taking a promissory note from (b) (6), (b) (3) (A) Please call me or reply as soon as you can. I tried to call you and tried to leave a message but neither was possible for some reason. Rich.

From: Akbari, Asim
Sent: Tuesday, July 19, 2016 9:57 AM
To: Moscicki, Richard; Hill, Salisha
Subject: RE: (b) (6), (b) (3)

Hi Rich,

I got your voicemail. Sorry that I have not touched base with you sooner. Our office is being audited by the U.S. Office of Government Ethics. As a result, I have been busy trying to get a large volume of information together responding to their document request.

I spoke with our financial disclosure experts in the Office of the General Counsel. The informed me that (b) (6), (b) (3) (A) Can you provide me the latest (b) (6), (b) (3) statement so that I can review the underlying assets? I would like to go over this with you, but I need to meet the document request deadline this week. Can we touch base early next week?

Also, were we able to get that letter from the hedge fund manager at (b) (6), (b) (3) (A)

Regards,
Asim

Salisha,
Can you set up a tcon with Dr. Moscicki? Thanks.

From: Moscicki, Richard
Sent: Tuesday, July 19, 2016 9:33 AM
To: Akbari, Asim
Subject: (b) (6), (b) (3)

Asim, an update. I am still struggling to get rid of (b) (6), (b) (3) Do you have an answer on what constitutes divestment? If you remember, (b) (6), (b) (3) (A) I also left you a vm, the quarterly report just issued for (b) (6), (b) (3) and the only remaining pharmaceutical holding in the fund of relevance is (b) (6), (b) (3) (A) and they have reduced its value to zero and rate it as having 0% of the assets. Does that change the whole picture? I can share the report with you. Rich.

Akbari, Asim

From: Moscicki, Richard
Sent: Friday, April 07, 2017 2:31 PM
To: Akbari, Asim
Subject: my questions

Thank you Asim for our discussion yesterday, it was very helpful to get your input on my ongoing saga of my effort to sell my royalty stream. In the meantime I remain recused from any involvement with (b) (6), (b) (3) (A), or IBD at FDA. In the other matter, I will recuse myself from any involvement in FDA matters directly related to the nonprofit organization that wishes to meet with me regarding non FDA related issues. Rich.

Akbari, Asim

From: Akbari, Asim
Sent: Wednesday, June 22, 2016 3:29 PM
To: Moscicki, Richard
Subject: RE: Divest Letter (b) (6), (b) (3) (A)

Hi Rich,

Let me look into this and I will get back to you. Were you able to come to an arrangement with (b) (6), (b) (3) (A) ?
Asim

From: Moscicki, Richard
Sent: Wednesday, June 22, 2016 2:58 PM
To: Akbari, Asim
Subject: RE: Divest Letter ((b) (6), (b) (3) (A)

Asim, what would constitute divestment? I am told that even if I could execute a purchase and sales agreement with (b) (6), the change of ownership would not be registered (b) (3) until the end of 3d quarter!!! This is probably true for any transfer even in the secondary market. Is the signed P&S adequate in which I state that I am transferring ownership? Rich.

From: Akbari, Asim
Sent: Wednesday, June 22, 2016 12:38 PM
To: Moscicki, Richard
Subject: RE: Divest Letter ((b) (6), (b) (3) (A)

Thank you.

From: Moscicki, Richard
Sent: Wednesday, June 22, 2016 12:37 PM
To: Akbari, Asim
Cc: Woodcock, Janet; Uhl, Kathleen (CDER)
Subject: RE: Divest Letter ((b) (6), (b) (3) (A)

Asim, I am responding to acknowledge your email and to state that I will recuse myself from management or policy issues regarding generics until I resolve the conflict. RIch

---

From: Akbari, Asim
Sent: Monday, June 20, 2016 5:03 PM
To: Moscicki, Richard
Subject: RE: Divest Letter ((b) (6), (b) (3) (A)

Hi Dr. Moscicki,

As per our discussion, our office notified you of your need to divest of your financial interest in (b) (6), (b) (3) (A) a private equity investment, on May 23, 2016. You indicated below that you are unable to sell your financial interest in (b) (6), (b) (3) to (b) (6), (b) (3) (A) because (b) (6), is not a qualified investor. We then talked about your selling your investment interest in (b) (6), (b) (3) to (b) (6), (b) (3) (A) and entering into a financial arrangement with (b) (6), where you would provide (b) (6), a loan.

While you are exploring this arrangement with (b) (6), (b) (3) (A) I advised that you recuse from particular matters that would affect the following companies in which (b) (6), (b) (3) indicated that it held a position: (b) (6), (b) (3) (A) . We reviewed the information publicly-available on these companies websites and determined that an investment interest in (b) (6), (b) (3) (A) and (b) (6), (b) (3) (A) would not pose any conflict of interest concern since they do not sell any products in the United States. Also, (b) (6), (b) (3) (A) primarily sells animal health products and API. Finally, (b) (6), (b) (3) (A) sell generic drug products in the United States. You mentioned that you would speak to your supervisor, Janet Woodcock, about your need to recuse from particular matters that would have a direct and predictable effect on generic drug companies. This recusal obligation would cover specific party matters (e.g., applications, licenses, litigation that affect the legal rights of specific parties) as well as policies or legislation that would affect the entire class of generic drug companies.

Once you sell your financial interest in (b) (6), (b) (3) this recusal obligation would immediately expire.

Again, I sincerely appreciate your understanding regarding this matter. Please do not hesitate to give me a call if you would like to discuss this matter further.

Regards,
Asim

Asim A. Akbari
Director, Division of Ethics and Integrity
Food and Drug Administration
8455 Colesville Road, Rm 8112 (COLE-8121)
Silver Spring, MD 20993-0002
Ph:301-796-6959

From: Moscicki, Richard
Sent: Monday, June 20, 2016 3:08 PM
To: Akbari, Asim
Cc: DeMarco, Devota R
Subject: RE: Divest Letter ((b) (6), (b) (3) (A)

I am available this afternoon after 3 pm, please call me at (b) (6) . Otherwise, Wed mid day, Devota can find a time. Rich

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From: Akbari, Asim
Sent: Friday, June 17, 2016 6:00 PM
To: Henderson, Christopher M; Moscicki, Richard
Cc: Hill, Salisha
Subject: RE: Divest Letter ((b) (6), (b) (3) (A)

Hi Dr. Moscicki,

I understand that Chris had been working with you on your financial disclosure report and this issue in particular. He no longer works in the Division of Ethics and Integrity. I was hoping that you had some time next week so that we can discuss this matter further. Please let me know your availability.

Regards
Asim

Asim A. Akbari
Director, Division of Ethics and Integrity

Food and Drug Administration
8455 Colesville Road, Rm 8112 (COLE-8121)
Silver Spring, MD 20993-0002
Ph:301-796-6959

From: Moscicki, Richard
Sent: Tuesday, June 14, 2016 2:27 PM
To: Henderson, Christopher M
Cc: Pupkar, Lynn; Collins, Stephanie; Woodcock, Janet
Subject: RE: Divest Letter ((b) (6), (b) (3) (A)

Chris, I am working hard to divest my interest in (b) (6), (b) (3) (A) As you know, this fund is not liquid and cannot be sold by the broker, as I have committed to remain in the partnership for 10 years since my acquisition of the interest in 2007 and so it will not be liquidated until next year. I have attempted to transfer my ownership to one of my (b) (6), (b) (3) (A) but the fund and my broker have informed that it cannot be transferred except to a "qualified investor" ie someone with over 1 million in assets or who is earning more that 250,000 per year for the last two years. (b) (6), (b) (3) (A) don't qualify. I am now pursuing (b) (6), (b) (3) (A)

Rich Moscicki

From: Henderson, Christopher M
Sent: Tuesday, May 24, 2016 8:51 AM
To: Moscicki, Richard
Subject: Divest Letter ((b) (6), (b) (3) (A)

Mr. Moscicki,
Attached is a letter directing you to divest the (b) (6), (b) (3) (A) Also attached is a packet that provides information related to directed divestitures. Please let me know if you have any questions.
(b) (6), (b) (3) (A)
. Thus, please contact DEI upon the resolution of this claim.

Chris Henderson, J.D.
Division of Ethics and Integrity
Food and Drug Administration
240-402-8186

Akbari, Asim

From: Akbari, Asim
Sent: Wednesday, June 29, 2016 9:14 AM
To: Moscicki, Richard
Subject: RE: (b) (6), (b) (3) (A) nformation Attached

Sounds good. (b) (6), (b) (3) (A) I will let you know as soon as I hear back from him.
Regards,
Asim

From: Moscicki, Richard
Sent: Wednesday, June 29, 2016 9:12 AM
To: Akbari, Asim
Subject: FW: (b) (6), (b) (3) (A) Information Attached

FYI

From: (b) (6)
Sent: Tuesday, June 28, 2016 10:14 PM
To: Moscicki, (b) (6)
Cc: Akbari, Asim
Subject: RE: (b) (6), (b) (3) (A) Information Attached

Hi Rich, I'll reach out to our AI team in conjunction with (b) (6), (b) (3) (A) and they should be able to provide the requested information/document. Give me a few days and I'll come back to you, thanks for your patience!
Best,
(b) (6)

-----Original Message-----
From: Moscicki, Richard [Richard.Moscicki@fda.hhs.gov]
Sent: Tuesday, June 28, 2016 04:30 PM Eastern Standard Time
To: (b) (6)
Cc: Akbari, Asim
Subject: FW: (b) (6), (b) (3) (A) Information Attached

Dear (b) (6) please see below the request from our ethics group here at FDA as per our conversation. Rich.

From: Akbari, Asim
Sent: Tuesday, June 28, 2016 4:25 PM
To: Moscicki, Richard
Subject: RE: (b) (6), (b) (3) (A) Information Attached

Thanks

From: Moscicki, Richard
Sent: Tuesday, June 28, 2016 4:25 PM

To: Akbari, Asim; (b) (6)
Subject: RE: (b) (6), (b) (3) (A) Information Attached

Asim, I have reached out to (b) (6) office at (b) (6). They will handle the query for (b) (6), (b) (3) (A) Rich.

From: Akbari, Asim
Sent: Monday, June 27, 2016 4:52 PM
To: (b) (6) Moscicki, Richard
Subject: RE: (b) (6), (b) (3) (A) Information Attached

Hi (b) (6)

Chris Henderson no longer works in the ethics office at FDA. I will take over for him and have been working with Dr. Moscicki regarding the (b) (6), (b) (3) (A) Fund and (b) (6), (b) (3) investments interests. As I mentioned to him this morning, the information below allows to determine whether these investments is a excepted investment fund (EIF). Such a designation allows us to report only the name of the funds on his financial disclosure report and not the underlying assets in the funds.

The information provided by (b) (6), (b) (3) (A) does not provide us the underlying assets in the fund. To the extent (b) (6), (b) (3) (A) does not provide this information to any of its investors, Dr. Moscicki cannot possibly have knowledge of any investments held by the fund. Typically, hedge funds such as (b) (6), (b) (3) (A) do not disclose their proprietary trading methods. Nonetheless, we must ask (b) (6), (b) (3) (A) for such information. If they do not provide this information to any of its investors, we need a written communication from (b) (6), (b) (3) (A) simply stating the following:

"This letter serves to inform you that, as a matter of policy XXX fund does not provide individual investment position transparency to its investors. We cannot make an exception to this policy in this case."

I would appreciate if you could help us obtain this letter from (b) (6), (b) (3) (A) Please contact me if you would like to discuss further.

Regards,
Asim Akbari
Director, Division of Ethics and Integrity
(301) 796-6959

From: Henderson, Christopher M
Sent: Wednesday, June 22, 2016 12:54 PM
To: Akbari, Asim
Subject: FW: (b) (6), (b) (3) (A) Information Attached

FYI Rich Moscicki (b) (6), (b) (3) (A) (b) (6), (b) (3) (A) Fund.

From: (b) (6)
Sent: Wednesday, June 22, 2016 12:29 PM
To: (b) (6) r M
Cc:
Subject: Re: (b) (6), (b) (3) (A) Information Attached

Chris,

Attached is what we were able to obtain from (b) (6), (b) (3) (A). They have confirmed that there are over 100 participants, that the fund is not publicly traded and is independently managed.

Thanks,

(b) (6) Chief Operations & Compliance Officer

From: "Henderson, Christopher M" <Christopher.Henderson@fda.hhs.gov>
Dat
To: (b) (6)
Cc:
Sub **ned**

H (b) (6)
Can you answer whether the (b) (6), (b) (3) (A) (b) (6), (b) (3) (A) (b) (6), (b) (3) (A) meet the below highlighted criteria?
Thanks.

Chris Henderson, J.D.
Division of Ethics and Integrity
Food and Drug Administration
240-402-8186

From: Henderson, Christopher M
Sent: Thursday, May 19, 2016 4:55 PM
To: (b) (6)
Subject: RE: (b) (6), (b) (3) (A) Information Attached

Hello Ms. (b) (6),

I am in receipt of the documents you sent Dr. Moscicki. It may have been better if I had asked specific questions instead of obtaining the documents since I am not sure I can glean the answers I need from them. Such funds require the reporting of the underlying assets in which the fund is invested unless the fund qualifies as an excepted investment fund (IEF) as defined by the office of Government Ethics. An EIF is one that is

- ? widely held (>100 participants);
- · publicly traded (or available) or widely diversified; and
- · independently managed, that is, arranged so that the filer neither exercises control nor has the ability to exercise control over the financial interests held by the fund.

Funds which are or were at some time open to any investor are considered **publicly available**. Net worth or income requirements do not disqualify a fund from being publicly available. **Widely diversified** means that the fund:

• holds no more than 5% of the value of its portfolio in the securities of any issuer (other than the U.S. Government) and
• holds no more than 20% of the value of its portfolio in any particular economic or geographic sector.

Can you find out this information? If these factors are not met, we need the underlying assets of the fund, which I do not believe are provided in the documents sent.

I have been in contact with (b) (6) about a different asset but I ask you because you seemed to have provided the documents concerning this asset.

Thank you .

Chris Henderson, J.D.
Division of Ethics and Integrity
Food and Drug Administration
240-402-8186

From: Moscicki, Richard
Sent: Tuesday, February 23, 2016 9:31 AM
To: Henderson, Christopher M
Subject: FW: (b) (6), (b) (3) (A) Information Attached

This should answer your questions about (b) (6), (b) (3) (A) as you can see it is very diversified. Working on getting info on (b) (6), (b) (2) but it will be the same. Rich.

From: Richard Moscicki [mailto: (b) (6)
Sent: Monday, February 22, 2016 8:34 PM
To: Moscicki, Richard
Subject: FW: (b) (6), (b) (3) (A) Information Attached

From: (b) (6)
Sent: Saturday, February 20, 2016 1:30 PM
To: Richard Moscicki < (b) (6)
Subject: (b) (6), (b) (3) (A) Information Attached

Hi Rich,

This should answer their first question in regards to the (b) (6), (b) (3) (A) investments. (b) (6) is tracking down (b) (6), (b) (3) information.

(b) (6)

From: (b) (6)
Sent: Friday, February 19, 2016 4:52 PM
To: (b) (6)
Cc: (b) (6) >; Richard Moscicki
Subject: RE: Moscicki K-1's

Hi (b) (6),
Attached is the Client Material and Fund Commentary for (b) (6), (b) (3) (A) the only difference between the two mentioned below is the year in which the same fund was purchased. Let us know if anything else is needed.
Best,
(b) (6)

From: (b) (6)
Sent: Friday, February 19, 2016 2:35 PM
To: (b) (6)
Cc: (b) (6); Richard Moscicki
Subject: Moscicki K-1's

H (b) (6),

Rich is currently providing information on his investments to the Department of Ethics as required by his current position. One of their inquiries is a request for a prospectus or some other sort of support (nature of business, underlying assets) for the following investments:

1) (b) (6), (b) (2)
2) (b) (6), (b) (3) (A)

Is this something you would be able to track down for him?

Many thanks,

(b) (6)

(b) (6)

(b) (6)

(b) (6)

Akbari, Asim

From: Moscicki, Richard
Sent: Tuesday, October 18, 2016 2:47 PM
To: Akbari, Asim
Subject: Re: (b) (6), (b) (3) sale

Thank you Asim, the agreement on inventorship is on hold given changes in the royalty so back to square one. As such I asked my lawyer (b) (6), (b) (3) (A), I maintain my recusal in the meantime. Rich

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Akbari, Asim
Sent: Monday, October 17, 2016 10:56 AM
To: Moscicki, Richard; Pupkar, Lynn; Collins, Stephanie
Cc: Woodcock, Janet
Subject: RE: (b) (6), (b) (3) sale

Hi Dr. Moscicki,

Yes, you may now participate in FDA job duties involving generic drugs. Based on the information provided below, you indicated that you had completely divested your financial interest in (b) (6), (b) (3) a (b) (6), (b) (3) (A) s.

For your information, I have not heard back from (b) (6) regarding the trust for your royalty income. (b) (6), (b) (3) (A)

Please let me know if you would like to discuss these matters further.

Regards,
Asim

From: Moscicki, Richard
Sent: Friday, October 14, 2016 2:28 PM
To: Akbari, Asim; Pupkar, Lynn; Collins, Stephanie
Cc: Woodcock, Janet
Subject: Fw: (b) (6), (b) (3) sale

Please find attached the email confirming. My sale and transfer of (b) (6), (b) (3) interest. May I assume I can resume my work with OGD? Rich
Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: (b) (6)
Sent: Thursday, October 13, 2016 6:39 PM

To: Moscicki, R[illegible]rd
Subject: FW: (b) (6), (b) (3) sale

Sent from Mail for Windows 10

From (b)
Sent: Thursday, October 13, 2016 4:08 PM
To: Richard Moscicki
Subject: RE: (b) (6), (b) (3) sale

Rich,

There is a remaining balance in your account of $(b) (6), (b) (3) so we will mail you a check to your home address.

Please let me know if you have any additional questions.

Best

(b) (6)

From: (b) (6))
Sent: Thursday, October 13, 2016 4:07 PM
To: Richard Moscicki; (b) (6)
Cc: (b) (6)
Subject: RE: (b) (6), (b) (3) sale

Good afternoon Rich and (b) (6),

I just wanted to follow up to let you know the position successfully transferred out of Rich's account on October 5th. Thank you all for your cooperation and patience during the transfer process

Please let me know if you have any additional questions.

Best,

(b) (6)

(b) (6)

From: (b) (6)
Sent: Tuesday, October 04, 2016 12:53 PM
To: (b)
Cc: Richard Moscicki; (b) (6)
Subject: Re: (b) (6), (b) (3) sale

Great news - Thanks (b) (6)

Please let us know if you need anything.

(b) (6)

(b) (6)

On Tue, Oct 4, 2016 at 9:04 AM, (b) (6) > wrote:
Good morning (b) (6) and Rich,

The operations team is going to process the transfer manually with a 03/31/16 value date, which should be completed by the end of the week. The effective date of the transfer per (b) (6), (b) (3) will be 09/30/16.

Please let me know if you have any additional questions.

Best,

(b) (6)

From: (b)
Sent: Monday, October 03, 2016 1:04 PM
To: (b) (6)
Cc: 'Richard Moscicki'
Subject: RE: (b) (6), (b) (3) sale

Good afternoon (b) (6) and Rich,

The operations team of the Alternative Investments department is in receipt of the transfer paperwork and I am waiting for an update on the processing timeline.

I will continue to send updates as they are received.

Best,
(b) (6)

From: (b)
Sent: Thursday, September 29, 2016 2:20 PM
To: (b) (6)
Cc: Richard Moscicki
Subject: RE: (b) (6), (b) (3) sale

Good afternoon (b) (6),

I have not received an update today but I reached out to the AI department and will circle back with you when I receive a response.

Best,
(b) (6)

From: (b) (6)
Sent: Thursday, September 29, 2016 1:33 PM
To: (b)
Cc: Richard Moscicki
Subject: Re: (b) (6), (b) (3) sale

Hi (b) (6)

Any update here?

Thanks,
(b) (6)

(b) (6)

On Wed, Sep 28, 2016 at 2:19 PM, (b) (6) (b) (6) > wrote:
Rich,

I just heard back from the AI department and we are ready to process the transfer ticket. As we are going from/to accounts in different offices, the ticket has to be processed manually by the AI department and they will begin working on it this afternoon.

I will provide you additional updates as they come in.

Best,
(b) (6)

(b) (6)

-----Original Message-----
From: Richard Moscicki [mailto (b) (6)
Sent: Wednesday, September 28, 2016 1:25 PM

To: (b) (6)
Cc: (b) (6)
Subject: Re: (b) (6), (b) (3) sale

THanks again!

Sent from my iPad

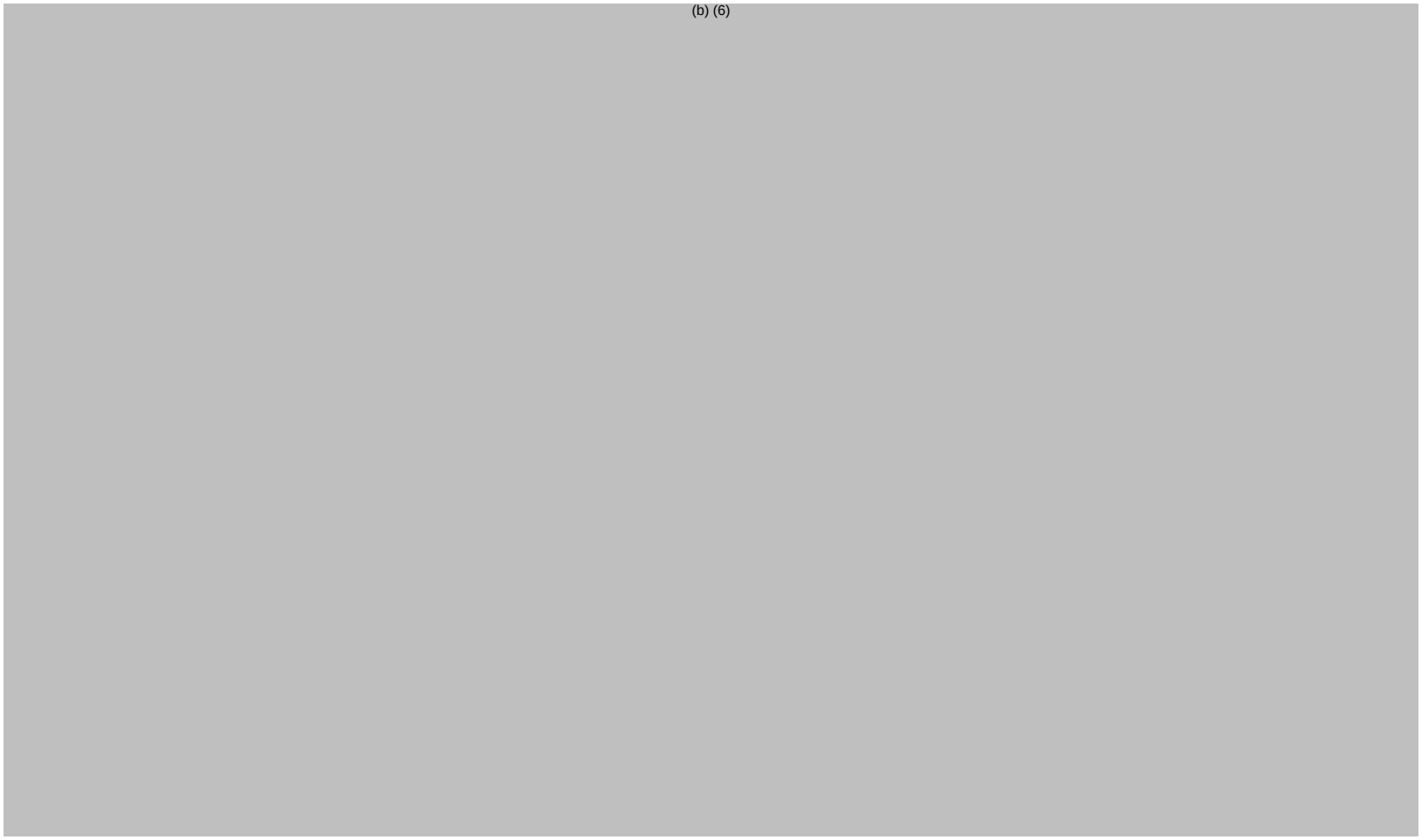
> On Sep 28, 2016, at 12:28 PM, "(b) (6)" > wrote:
>
> Good afternoon Rich,
>
> All of the signed documents were submitted on Friday to our Alternative Investments (AI) department, who is the liaison between you, (b) (6), (b) (3) (A) and (b) (6), (b) (3) The paperwork is currently with the AI operations team and they are working to get an approval from the fund and then we can process the transfer ticket.
>
> I will update you once the paperwork is approved and the transfer ticket submitted.
>
> Best,
> (b) (6)
>
>

(b) (6)

> -----Original Message-----
> From: Richard Moscicki [mailto (b) (6)
> Sent: Wednesday, September 28, 2016 12:04 PM
> To: (b) (6)
> Cc: (b) (6)
> Subject: (b) (6) sale
>
> Hi (b) (6) I just wanted to see where things stood on the transfer of my (b) (6), (b) (3) holdings to (b) (6), (b) (3) (A) You should have received my signed and witnessed transfer agreement. Have you and (b) (6) been in touch? Are they in touch with (b) (6), (b) (3) (A) Anything that I need to do? Thanks for all your help in this. Rich Sent from my iPhone
>
>
> ----------

(b) (6)

(b) (6)



Akbari, Asim

From: Moscicki, Richard
Sent: Monday, September 05, 2016 11:03 AM
To: Akbari, Asim
Subject: Re: (b) (6), (b) (3) Urgent

Yes, there would be NO tie to (b) (6), (b) (3) performance. Thank you for your help. Rich

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

From: Akbari, Asim
Sent: Thursday, September 1, 2016 6:19 PM
To: Moscicki, Richard
Cc: Pupkar, Lynn
Subject: FW: (b) (6), (b) (3) Urgent

Hi Rich,

I wanted to forward to you the guidance that I received from OGC on your question. (b) (5), (b) (6), (b) (3) (A) [redacted]. When you finish the OGE 450 report, I will personally review it and write a recusal statement memorializing the recusal obligations that we had discussed in these emails.

The issue of your filing an OGE 278 is something that we are taking a more broader look throughout the agency. We will notify you as soon as we come to a determination on this issue. If you or (b) (6) have any questions about the OGE 450 or any other matter, please do not hesitate to contact me.

Lynn,
When you get Dr. Moscicki's 450, please reassign it to me. I will review it myself. Thanks.

Asim

From: Sanft, Corbin (HHS/OGC) [mailto:Corbin.Sanft@hhs.gov]
Sent: Thursday, September 01, 2016 7:38 AM
To: Akbari, Asim
Subject: RE: (b) (6), (b) (3) Urgent

Hi Asim – Thanks for your patience.

(b) (5), (b) (6), (b) (3) (A) [redacted]

(b) (5), (b) (6), (b) (3) (A)

[redacted]

Please let me know if I can assist further.

Corbin

Corbin G. Sanft
Attorney Advisor
Department of Health & Human Services
Office of the General Counsel
Ethics Division
Telephone: (240) 402-1096
Fax: (202) 205-9752

From: Akbari, Asim [mailto:Asim.Akbari@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 5:48 PM
To: Moscicki, Richard (FDA/CDER)
Cc: Sanft, Corbin (HHS/OGC)
Subject: RE: (b) (6), (b) (3) Urgent

Hi Rich,

Sorry that I was not clear in my earlier email. I partially misread your email and had been in meetings all day. I hope this email provide is more clear. (b) (6), (b) (3) (A), (b) (5) [redacted]

(b) (6), (b) (3) (A), (b) (5)

I would be happy to discuss further if you would like.

Regards,
Asim

From: Moscicki, Richard
Sent: Wednesday, August 31, 2016 1:11 PM
To: Akbari, Asim
Subject: RE: (b) (6), (b) (3) Urgent

Thanks Asim but I don't quite understand the "ability and willingness recusal with the seller (me) for (b) (6), (b) (3) (A) "

From: Akbari, Asim
Sent: Wednesday, August 31, 2016 12:06 PM
To: Moscicki, Richard; Sanft, Corbin G (OS)
Cc: Pupkar, Lynn; Collins, Stephanie
Subject: RE: (b) (6), (b) (3) Urgent

(b) (6), (b) (3) (A), (b) (5)

Asim

From: Moscicki, Richard
Sent: Wednesday, August 31, 2016 12:02 PM
To: Akbari, Asim
Cc: Pupkar, Lynn; Collins, Stephanie
Subject: RE: (b) (6), (b) (3) Urgent

Asim, I have signed a LOI to sell my (b) (6), (b) (3) holding to (b) (6), (b) (3) (A). We are completing the Purchase Sale Agreement. I can receive a better price if (b) (6), (b) (3) (A). I would complete the sale for the agreed upon price with a signed agreement by Sept 30. (b) (6), (b) (3) would transfer ownership to (b) (6), (b) (3) (A) by the end of the quarter, possibly could take to end of next quarter, but I would then have no interest in the fund, no further possible benefit or harm from the fund. I just need your clearance that I can wait for my payment (essentially taking a promissory note from (b) (6), (b) (3) (A) Please call me or reply as soon as you can. I tried to call you and tried to leave a message but neither was possible for some reason. Rich.

From: Akbari, Asim
Sent: Tuesday, July 19, 2016 9:57 AM

To: Moscicki, Richard; Hill, Salisha
Subject: RE: (b) (6), (b) (3)

Hi Rich,

I got your voicemail. Sorry that I have not touched base with you sooner. Our office is being audited by the U.S. Office of Government Ethics. As a result, I have been busy trying to get a large volume of information together responding to their document request.

I spoke with our financial disclosure experts in the Office of the General Counsel. The informed me that your divestment will occur when the asset is actually sold and not when you obtain an agreement or arrangement for a sale. Can you provide me the latest (b) (6), (b) (3) statement so that I can review the underlying assets? I would like to go over this with you, but I need to meet the document request deadline this week. Can we touch base early next week?

Also, were we able to get that letter from the hedge fund manager at (b) (6), (b) (3) (A)

Regards,
Asim

Salisha,
Can you set up a tcon with Dr. Moscicki? Thanks.

From: Moscicki, Richard
Sent: Tuesday, July 19, 2016 9:33 AM
To: Akbari, Asim
Subject: (b) (6), (b) (3)

Asim, an update. I am still struggling to get rid of (b) (6), (b) (3) Do you have an answer on what constitutes divestment? If you remember, (b) (6), (b) (3) (A) I also left you a vm, the quarterly report just issued for (b) (6), (b) (3) and the only remaining pharmaceutical holding in the fund of relevance is (b) (6), (b) (3) (A) and they have reduced its value to zero and rate it as having 0% of the assets. Does that change the whole picture? I can share the report with you. Rich.

Akbari, Asim

From: Moscicki, Richard
Sent: Friday, February 03, 2017 12:34 PM
To: Simpson, Yvette; Akbari, Asim
Cc: Collins, Stephanie; Woodcock, Janet
Subject: Royalty

As agreement has been finally reached on my share of the royalty stream that (b) (6), (b) (3) (A) receives from (b) (6), (b) (3) (A) for the invention of (b) (6), (b) (3) (A), (b) (6), (b) (3) has issued me a check for royalties that accumulated during the time of negotiations. As I have stated before it is my intention to divest the future royalty stream. This divestment would be considered capital gains. I am requesting a letter of divestiture and a certificate of divestiture. Please let me know what additional procedures or forms I must complete in order to achieve this in a timely manner. I remind all that in the meantime I remain recused from involvement with (b) (6), (b) (3) (A), and inflammatory bowel disease. Rich.

Campbell, Shuvon

From: Campbell, Shuvon
Sent: Monday, January 19, 2015 9:50 AM
To: Moscicki, Richard
Subject: Farm interest memo

Good morning,

I am finalizing your Confidential Financial Disclosure Form (OGE 450) for the 2013 filing year. In Part I: Assets and Income you reported an interest in a farm: (b) (6), (b) (3) (A) (b) (6), (b) (3) (A) .

You have reported a financial interest in a farming operation. Farms that raise and sell agricultural products (crops and livestock) are, by definition, significantly regulated organizations and, therefore, are prohibited under the current prohibited financial interest regulations. The Agency recognizes the potential impact that the current rule may have on employees that have such interests and is taking steps to help mitigate the issue. FDA is currently seeking an amendment to the HHS Supplemental Standards of Ethical Conduct Regulations to allow for greater flexibility in certain farm ownership. Pending the outcome of that process, FDA has decided that all current as well as future issues involving financial interests by employees in farm ownership and operations will be held in abeyance except for ownership in publicly traded stock in farming corporations. Until a decision is made on an amendment, employees with current financial interests in farming operations, other than owning stock in a publicly traded farming organization, like ConAgra for example, will not be required to divest or otherwise alter their farm operations during the abeyance period. Therefore, you are not required at this time to take any action regarding this financial interest. However, as with all financial interests, you are required to disqualify yourself from taking official actions that will directly affect your farming operation. Once a final decision is made on the Supplemental amendment, this matter will be re-addressed. This process will most likely be lengthy as an amendment requires approval from senior agency management, including the Commissioner and the Secretary of HHS. It must also be approved by the Director of the Office of Government Ethics. In the meantime, you should continue to report your financial interest in farming operations on your OGE 450 form.

Thank you,

Shuvon Campbell
Ethics Specialist
Division of Ethics and Integrity
Food and Drug Administration
8455 Colesville Road (COLE-8121)
Silver Spring, MD 20993-0002
240-402-4591
Ethics Webpage: http://inside.fda.gov:9003/EmployeeResources/Ethics/FDAEthicsProgram/default.htm

Campbell, Shuvon

From: Tolino, Vincent R
Sent: Thursday, February 12, 2015 11:57 AM
To: Moscicki, Richard
Cc: Campbell, Shuvon
Subject: Restricted Stack Units - (b) (6), (b) (3) (A)

Dr. Moscicki - –

This is to re-cap the conversation between you, Shuvon Campbell of my staff, and myself on February 11, 2015, regarding restricted stock shares you have with (b) (6), (b) (3) (A). You informed me that you have had these shares since you entered into FDA but did not report them because you were of the understanding that wasn't necessary until the time the vesting period is up and the shares become available to you.

We discussed that restricted stock shares are reportable and are considered a personal financial interest for an employee subject to the full recusal obligation under title 18 USC – Section 208. (as an aside – the Office of Government Ethics defines a financial interest as anything that could result in a gain or a loss for an employee.)

I explained that due to the restricted stock shares in (b) (6), (b) (3) (A), you may not be involved in any particular FDA matter that can have a direct and predictable effect on your financial interests. Because the interest is with (b) (6), (b) (3) (A), you have a financial interest in that company which creates a recusal obligation requiring you to remove yourself from working on any particular matters, general or specific, affecting that company. This recusal obligation pertains to particular matters between specific parties, which would include (b) (6), (b) (3) (A) products as well as any competing products as well as other matters that could affect the legal rights of (b) (6), (b) (3) (A) like a contract, claim, investigation, audit, grant, warning letter, etc. In addition, it pertains to particular matters of general applicability, such as policies, or rule-making or legislation, affecting (b) (6), (b) (3) (A) as part of a discrete and identifiable class. If the recusal obligation will require recusal from matters central or critical to the performance of your official duties, then divestiture will be necessary.

In some cases there are regulatory exemptions that may allow you to work on matters affecting your financial interest under certain circumstances and depending on the overall value of the financial interest in question. However, the regulatory exemptions do not apply to stock options or restricted stock.

Accordingly, you indicated that you were going to discuss the matter with the CDER Center Director. I too am discussing the matter with my leadership in the Office of Operations. You also indicated that you would contact (b) (6), (b) (3) (A) to weigh your options on divesting of the shares.

Thank you –

Vince Tolino
Director, Division of Ethics and Integrity
8455 Colesville Road (COLE-8121)
Silver Spring, MD 20993-0002
301-796-8438
Ethics Webpage: http://inside.fda.gov:9003/EmployeeResources/Ethics/FDAEthicsProgram/default.htm

Smith, Reginald

From: Reid Knowlton <(b) (6)>
Sent: Friday, November 22, 2013 11:15 AM
To: Woodcock, Janet
Subject: Please help restore my faith in our goverment

Dear Drs. Woodcock, Jenkins, Temple, Unger, Bastings and Farkas,

I understand that the FDA has reversed its previous stance on whether to consider Sarepta's NDA for Eteplirsen. The Agency has cited the recent failure of other dystrophin-producing drugs as one reason to require that Sarepta conduct a large, placebo-controlled phase 3 study before applying for approval. I do not understand this reasoning, as we don't even know how much, if any, dystrophin was produced by the drugs that failed to meet their primary clinical trial endpoints. In contrast, we know that Eteplirsen produced dystrophin in all 12 treated patients at levels widely believed to lead to functional benefit. What's more, the treated patients have stabilized since the dystrophin took effect. One third of the children actually improved, a clinical outcome that is unheard of in Duchenne.

I do not have a rare fatal disease, but if I had one I would want the freedom to choose a drug in consultation with my physician that has a highly favorable safety profile and early indications of efficacy. I believe the FDA's #1 job is to protect people. While we understand there are certain risks with approving a medication studied in only 12 patients, the risk is a minimal and tolerable one compared to the certain pediatric deaths and losses of ambulation that will occur if you require several more years of study before approving this drug.
I implore you, work with Sarepta to accept the creative and aggressive confirmatory trial design they have planned. Understand that children will die and our kids will lose their ability to walk if this decision continues to be postponed.

Sincerely,

Reid Knowlton
(b) (6)

Smith, Reginald

From: Michelle Griffin < [redacted] (b) (6) >
Sent: Friday, November 22, 2013 10:52 AM
To: Woodcock, Janet; Temple, Robert; Jenkins, John K; Unger, Ellis; Bastings, Eric; Farkas, Ronald
Cc: Commissioner FDA MH
Subject: Please Save Lives

Dear Drs. Woodcock, Jenkins, Temple, Unger, Bastings and Farkas,

I understand that the FDA has reversed its previous stance on whether to consider Sarepta's NDA for Eterplisen. The Agency has cited the recent failure of other dystrophin-producing drugs as one reason to require that Sarepta conduct a large, placebo-controlled phase 3 study before applying for approval. I do not understand this reasoning, as we don't even know how much, if any, dystrophin was produced by the drugs that failed to meet their primary clinical trial endpoints. In contrast, we know that Eterplisen produced dystrophin in all 12 treated patients at levels widely believed to lead to functional benefit. What's more, the treated patients have stabilized since the dystrophin took effect. One third of the children actually improved, a clinical outcome that is unheard of in Duchenne.

I do not have a rare fatal disease, but if I had one I would want the freedom to choose a drug in consultation with my physician that has a highly favorable safety profile and early indications of efficacy. I believe the FDA's #1 job is to protect people. While we understand there are certain risks with approving a medication studied in only 12 patients, the risk is a minimal and tolerable one compared to the certain pediatric deaths and losses of ambulation that will occur if you require several more years of study before approving this drug.

I implore you, work with Sarepta to accept the creative and aggressive confirmatory trial design they have planned. Understand that children will die and our kids will lose their ability to walk if this decision continues to be postponed.

Sincerely,

Michelle Griffin

Smith, Reginald

From: heidi jaffe <(b) (6)>
Sent: Friday, November 22, 2013 12:44 PM
To: Woodcock, Janet; Temple, Robert; Jenkins, John K; Unger, Ellis; Bastings, Eric; Farkas, Ronald
Cc: Commissioner FDA MH
Subject: Muscular Dystrophy

Dear Drs. Woodcock, Jenkins, Temple, Unger, Bastings and Farkas,

I understand that the FDA has reversed its previous stance on whether to consider Sarepta's NDA for Eterplisen. The Agency has cited the recent failure of other dystrophin-producing drugs as one reason to require that Sarepta conduct a large, placebo-controlled phase 3 study before applying for approval. I do not understand this reasoning, as we don't even know how much, if any, dystrophin was produced by the drugs that failed to meet their primary clinical trial endpoints. In contrast, we know that Eterplisen produced dystrophin in all 12 treated patients at levels widely believed to lead to functional benefit. What's more, the treated patients have stabilized since the dystrophin took effect. One third of the children actually improved, a clinical outcome that is unheard of in Duchenne.

I do not have a rare fatal disease, but if I had one I would want the freedom to choose a drug in consultation with my physician that has a highly favorable safety profile and early indications of efficacy. I believe the FDA's #1 job is to protect people. While we understand there are certain risks with approving a medication studied in only 12 patients, the risk is a minimal and tolerable one compared to the certain pediatric deaths and losses of ambulation that will occur if you require several more years of study before approving this drug.

I implore you, work with Sarepta to accept the creative and aggressive confirmatory trial design they have planned. Understand that children will die and our kids will lose their ability to walk if this decision continues to be postponed.

Sincerely,

Heidi Jaffe

Philips, Howard

From: Jenn McNary (b) (6)
Sent: Monday, November 16, 2015 2:30 PM
To: Califf, Robert
Subject: Duchenne

Dear Dr. Califf
I know you are in the midst of preparing for your confirmation hearing tomorrow, but I wanted to send a note on a very relevant matter and hope that in the near future we can follow up in person. As a mother of two sons with a rare pediatric disease, Duchenne Muscular Dystrophy, and an advocate for all patients with Duchenne, I wanted to share insights that I hope will inform your priorities as you take the helm of the FDA. Patients and caregivers are counting on you to not only protect their health but actively promote it by using expedited programs and regulatory flexibility to speed development and approval of safe and effective drugs for patients with rare diseases

The journey of the Duchenne community in the past few years has been a roller coaster. Ever since FDASIA was passed in 2012 and it was made clear that the FDA was supposed to be extending the tools they've used successfully in the battle against cancer and HIV to rare disease we have had many meetings with the neurology division as well as upper level staff at the FDA. We are grateful for this level of engagement, and we have seen progress, for example in the issuance of draft guidance on Duchenne MD. We have also experienced times when FDA does not seem to share in the urgency of addressing the unmet medical need of this fatal disease. There have been delays resulting in those with Duchenne losing function that they will never get back, the FDA seems to revert to a pre-FDASIA mindset at times. We have done our research. We have seen other divisions at FDA fully embrace regulatory flexibility without sacrificing the high safety standards it upholds. We know this can be done, to patients enormous benefit.

Our children have already lost the genetic lottery. They should not be subject to another lottery where regulatory flexibility depends on which review division and which reviewers have experience and comfort using the tools and use them consistently. I hope your leadership leads to consistent adoption of FDASIA's flexibility across divisions, so that all patients may benefit, not just those who have won the FDA lottery.

Again, we are grateful for FDA's willingness to meet with us so often over the past years, and to the many obviously committed and dedicated individuals on staff. We hope under your tenure, our voice will finally have meaning, that the patient voice will be incorporated into the decision making process at the review division level. There is no one in a better position than parents and children living with Duchenne to inform the FDA's weighing of benefits and risk.

In Duchenne, the FDA has the opportunity to do what is right for the patients. FDA has the opportunity to show Congress and all stakeholders that they share our urgency to get drugs approved for rare disease faster, and that they are embracing the flexibility under FDASIA, down to the review divisions less experienced in applying such flexibility.

Thank you for taking the time to listen to read this email, I am fighting not only for my sons, Max and Austin, who were lucky enough to make it into a trial that seems to have halted the progression of their disease, but for all those living with Duchenne, and still waiting for their chance. I would welcome the opportunity to speak with you in person, at your convenience, to see how we may support you in your new role moving forward. I look forward to working together towards our common goal of treating those with rare disease, faster.
Best
Jenn

--
Jenn McNary

The Jett Foundation
68 Evergreen Street, Suite One
Cell (b) (6)
FAX (781) 585-5233
Jettfoundation.org

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Philips, Howard

From: Christine McSherry <christine@jettfoundation.org>
Sent: Tuesday, December 22, 2015 1:56 PM
To: Woodcock, Janet; Moscicki, Richard
Subject: Thank you and to reiterate our conversation

Dear Drs.Woodcock and Moscicki:

Thank you very much for taking the time to speak with (b) (6) and me on Friday evening. We truly appreciate your commitment to the Duchenne community and your interest in Sarepta's upcoming advisory panel.

Thank you for listening and considering our requests and concerns regarding Sarepta's January 22nd advisory panel. To review our call from Friday night I have included the main points of our discussion below.

Patient Reported Outcome Presentation: We greatly appreciate your counsel regarding Sarepta's potential donation of ten minutes of their sponsor presentation in the morning to allow the PRO report to be heard. After being specifically asked by FDA to develop this patient reported outcome presentation and following its positive reception by FDA, the sponsor and the Jett Foundation agree that it deserves to be heard by the Advisory Committee. It will be a groundbreaking moment for patient focused drug development.

PANEL Voting Questions: We believe that the questions on which the advisory panel is asked to vote should be clear, fair, and lead to a robust scientific discussion. Biomarin's advisory panel questions were as complicated and convoluted as their data, and the Duchenne community firmly believes that Sarepta's questions should be based on the three legs of approval; efficacy, safety, and benefit-risk.

Attendance: Dr. Woodcock, your presence at Sarepta's advisory committee would be an honor to the Duchenne community. You have been a friend to those suffering with Duchenne since the beginning of the Sarepta trials, and your relationship with the advocates for this specific drug is very unique. We would be forever grateful for your attendance at this historic event in rare disease.

Small n: We are concerned that the small number of patients -- the small n -- remains an FDA concern with Sarepta's trial. I would like to remind you that the n has always been this small, and that the NDA was accepted with the same small number of trial participants. Addressing the small number of trial participants was not an issue raised by the agency pre-NDA filing. Additionally, this number is representative of the ultra rare Duchenne population that is amenable to exon 51 skipping and the small population of boys with a 300-400 meter six minute test at the time of recruitment.

Once again, we thank you for your time and continued efforts in ensuring that our boys have the opportunity to outlive their diagnosis. If you have any questions, please do not hesitate to reach out.

Sincerely,

Christine

--

Making...TODAY COUNT - TO CHANGE TOMORROW

Christine McSherry, RN

The Jett Foundation
68 Evergreen Street, Suite One
Kingston, MA 02364
(781) 585-5566

Temple, Robert

eteplirsen

From: (b) (6)
Sent: Monday, January 18, 2016 1:53 PM
To: Dunn, Billy; Bastings, Eric; Unger, Ellis; Farkas, Ronald; Temple, Robert; Jenkins, John K; Woodcock, Janet
Cc: (b) (6)
Subject: Sarepta's Eteplirsen Briefing Documents & Addendum

January 18, 2016

Dr. Billy Dunn
Dr. Eric Bastings
Dr. Ellis Unger
Dr. Ronald Farkas
Dr. Robert Temple
Dr. John Jenkins
Dr. Janet Woodcock

My name is (b) (6) mother of (b) (6) age (b) (6) a trial participant in Sarepta's Eteplirsen Study 201/202 trials. I am writing on behalf & with permission of the other 201/202 trial parents whose emails are cc'd above. We collectively wish to address and express our deepest concerns about several misleading and erroneous remarks in the briefing documents released on Friday, January 15, 2016. These inaccuracies will be damaging to our chances of approval and directly affect our son's mortality. Know that we plan to do everything in our power to affect positive change for the best possible outcome of our adcomm for our children and all those waiting to receive this lifeline of a drug. I will address several points of dire concern below:

Point #1 Steroid Usage: Several times throughout the FDA briefing documents it is stated that, "Patients in Study 202 appeared to be getting optimal care, including intensive physical therapy and intensive steroid regimens". Elsewhere it is stated that "corticosteroid therapy appears to have been more intensive in the eteplirsen patients compared to the natural history patients"....."and this, itself, may have been capable of affecting performance."....."doses of corticosteroids appear to have been lower in the applicant's natural history patients"....."Adherence to treatment guidelines is difficult to measure, but adherence in the Eteplirsen study was reported to be exceptional, while there is evidence that care received in the regions of origin of many of the sponsor's historical control patients was likely of lower intensity."....."differences in individual care decisions, therefore, seemingly could produce large differences in 6MWT and time to loss of ambulation between eteplirsen patients and natural history controls."".....and finally FDA suggests that it is the "intensive physical therapy and intensive steroid regimen" most likely responsible for stability and not due to the Eteplirsen drug.

The study 201/202 parents want on record that we vehemently disagree to these damaging and misleading assertions. Our trial boys receive either minimal, standard, or NO physical therapy outside of the trial evals. Some comments from the parents regarding the FDA's false and misleading

assertions are, "no PT at all", "same PT and steroid regimen since age 3", "same low dose since age 3", "PT **NEVER** changed", "daily stretches/splints, which are all SOC from MDA clinic which is same recommendations for all DMD boys", "no extra PT", "same DMD regimen as those outside of the trial", "same low steroid dose for past 8 years and no private PT in 9 years, school PT released him from all PT a year ago because he has met, maintained, and exceeded all goals". So we take issue with the damaging assertions made in the briefing documents that eteplirsen boys received "optimal intensive physical therapy and intensive steroid regimens"....it simply isn't true! Furthermore, only 2 out of the 12 eteplirsen boys are on the appropriate recommended steroid dosage based on age/weight....all others are therefore **UNDERDOSED**. In contrast, the EC (external control) boys, 10 out of 13 boys were on the recommended dosage based on age/weight. In addition, **loss of ambulation at year 4** shows that **2/12** eteplirsen boys or **16.7%** lost ambulation in contrast to **10/13** EC boys or **89.7%** lost ambulation. Eteplirsen boys have not performed better due to 'optimal intensive physical therapy and intensive steroid regimens" as suggested in the documents because there was **NO** "intensive therapies" as stated above from the trial parents. Their performance is due to the eteplirsen drug.....all 0.9% of it which doesn't seem to be appreciated by the FDA and is considered negligible and not meaningful but to the eteplirsen parents and, more importantly our boys, this amount of dystrophin produced is a lifeline and has added meaningful QOL and continued stability with minor decline.

These inaccuracies are both misleading and erroneous whether accidental, intentional, or simply an oversight due to perhaps a hasty review but has now tainted the advisory committee members who are supposed to be unbiased but are now in receipt of inaccurate reports. This is unacceptable and we believe deceptive!

Point #2 Internal Inconsistencies: "By age 10-14, patients become wheel chair bound' (FDA drisaperson BD page 15)

"The age range at loss of ambulation is wide, ranging from 8-16 years for most patients (FDA eteplirsen BD page 7)

Our community was outraged at this lack of inconsistency! Why the change in age at loss of ambulation since November's adcom for a different DMD drug? Again, this is unacceptable and can potentially be damaging and sends an inaccurate message to the advisory committee members.

Point #3 Historical Control: If FDA was not going to support or accept post hoc selection of the control group, why did FDA make the suggestion to pursue this path in April 2014?

Point #4 Confirmatory Study Design: "With regard to future efficacy studies, any beneficial effects of eteplirsen are unlikely to be large enough to be detectable outside of a placebo controlled trial." (FDA BD page 51) Again, the FDA is challenging Sarepta on **their own provided guidance** (which is same guidance given to Prosensa on confirmatory trial design) Why provide the guidance to a company only to change your mind when reviewing an NDA package that was previously agreed upon? Our community sees this as setting a company up for failure! This is unacceptable!

Point #5 Cross trial comparison: This was not a matched comparison on crucial factors such as age and baseline 6MWT using the drisaperson placebo group and therefore unable to provide persuasive results. Again, this is a contradiction as to the FDA guidance provided to Sarepta on their path forward. This is unacceptable and a setup for failure!

Point #6 Lack of Independent Confirmation: (FDA Eteplirsen BD page 31) As agreed upon with the FDA, Sarepta did obtain findings from 3 independent pathologists who provided independent confirmation of statistically significant increase of dystrophin positive fibers. This independent

analysis is widely known throughout our Duchenne and scientific community. How could this be misrepresented to the advisory committee in the briefing documents? Our boys voluntarily underwent a painful 4th biopsy for this purpose in order to satisfy the FDA's concern of a single analysis; for the FDA to report that protocol wasn't followed and moreover violated guidance is deceptive. How could this happen and why?

In closing, study 201/202 trial parents & many in our community feel deceived and manipulated by provided guidance only to be led down a path of an uncertain outcome due to negligent reporting.

The FDA was created to help patients and not hurt them, but these briefing documents, much of it inaccurate, misleading, & deceptive is harming patients-not just any patients-but innocent children who are now considering and dreaming of driving, entering college, and choosing a career path. They are able to now dream of such things because they feel better and have a better quality of life and can now imagine a future because of their Eteplirsen treatment which will someday become part of a combination therapy. These misleading briefing documents can be their demise. Know that we will do everything in our power to make sure that this is not their demise. We are united, we are not a timid community, we are relentless, we will not let our boys die in vain. The law of FDASIA passed by Congress in 2012 allows for the patient voice to be heard and we will exercise that right.

We, too, look forward to a "fruitful" discussion on Friday.

Respectfully,

	PATIENT	DEL	AGE	VISIT	SIXMWT	FVCP	NSAA
	(b) (6)		(b) (6)				
1		50.0		baseline	380.0	73.0	31.0
2		50.0		1 year	352.0		26.0
3		50.0		2 years	326.0	81.0	20.0
4		50.0		3 years	195.0		14.0
5		50.0		4yrs , 6 m	0.0		
6		45-50		baseline	329.0	78.0	24.0
7		45-50		1 year	298.0	89.0	22.0
8		45-50		2 years	230.0	100.0	13.0
9		45-50		3 years	218.0	98.0	12.0
10		45-50		4 yrs	unable following tibial fracture		
11		52		baseline	458.0		25.0
12		52		1 year	495.0		26.0
13		52		2 years	435.0		25.0
14		52		3 years	362.0		22.0
15		52		4 yrs	300.0		
16		52		10 m later, fall with LOA	0.0		
17		52		baseline	373.0	70.0	24.0
18		52		1 year	259.0	70.0	13.0
19		52		2 years	305.0		11.0
20		52		3 years	273.0	74.0	8.0
21		52		3y 6m	154.0		4.0
22		52		3y 10 m	0.0		0.0
23		49-50		baseline	295.0	85.0	15.0
24		49-50		1 year	307.0	80.0	13.0
25		49-50		2 years	153.0	78.0	12.0
26		49-50		3 years	35.0	77.0	9.0
27		49-50		2 m after 3 yrs assessment	0.0		

	GOWERS	TENMETER	AGESTER	NOTE
1	2.9	4.0	(b)(6) years old	
2	3.7	5.5		
3	17.0	9.0		
4	unable	not performed		
5				
6	7.1	9.1	(b)(6) years old	
7	7.2	10.3		
8	ony with exernal support	11.5		
9		10.7		
10				
11	5.66	6.36	(b)(6) years old	
12	5.21	6.58		
13	4.31	7.60		
14	8.47	7.90		
15				
16				
17	4.09	6.48	(b)(6) years old	
18	5.04	9.06		
19	8.09	8.66		
20	not performed	9.73		
21				
22				
23	6.2	12.1	(b)(6) years old	LOST AMBULATION 1 MONTH AFTER LAST EVALUATION
24				
25	unable			
26	unable			
27				

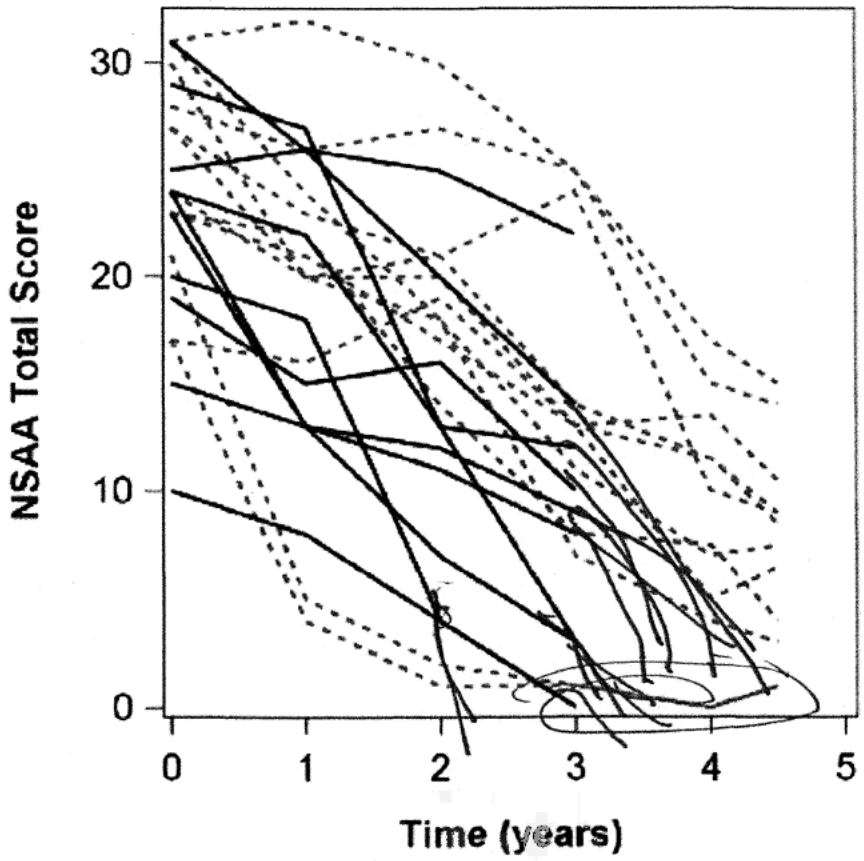
	NSAA
1	31.0
2	26.0
3	20.0
4	14.0
5	
6	24.0
7	22.0
8	13.0
9	12.0
10	
11	25.0
12	26.0
13	25.0
14	22.0
15	
16	
17	24.0
18	13.0
19	11.0
20	8.0
21	4.0
22	0.0
23	15.0
24	13.0
25	12.0
26	9.0
27	

NSAA

Eteplirsen vs. applicant's historical controls

- There was essentially no difference in NSAA, an endpoint that appears to be more resistant to bias in an open-label study than 6MWT or time to loss of ambulation

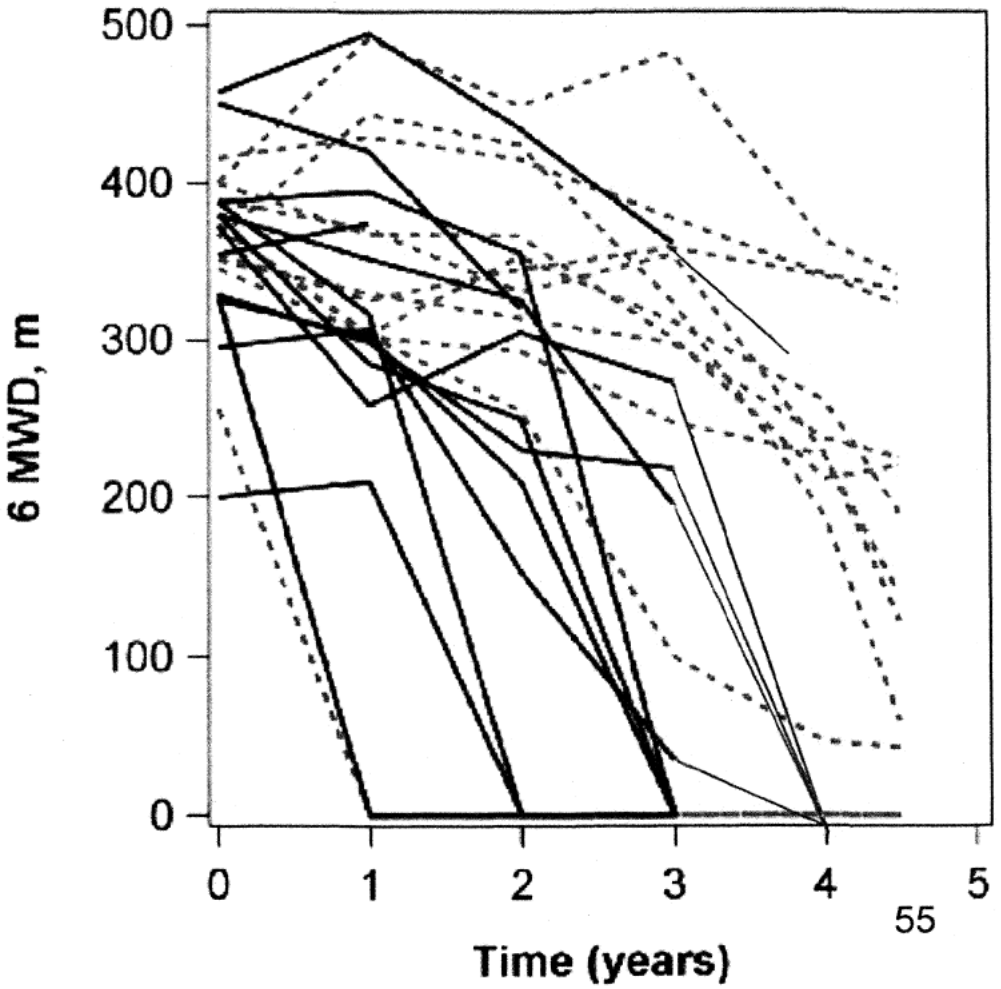
  (Note also false appearance of stabilization of 2 eteplirsen patients at scores near zero)



6MWT
Eteplirsen vs. applicant's historical controls

- The difference in 6MWT would be of clinical importance *if observed in a well-controlled trial*, but the finding is extremely difficult to interpret given all of the limitations just described

- The slides that follow show additional investigations FDA undertook to try to understand the data better



Temple, Robert

From:	Peter Ciszewski <(b) (6)>
Sent:	Tuesday, January 19, 2016 8:10 AM
To:	Woodcock, Janet; Temple, Robert; Jenkins, John K; Unger, Ellis; Bastings, Eric; Farkas, Ronald
Cc:	Commissioner FDA MH
Subject:	I have been watching the Duchenne muscular dystrophy story very closely . . .

Dear Drs. Farkas, Woodcock, Temple, Jenkins, Unger, and Bastings:

I seems extremely unfair how the agency is treating the Duchenne community and Sarepta Therapeutics.

I understand that the FDA has reversed its previous stance on whether to consider Sarepta's NDA for Eterplisen. The Agency has cited the recent failure of other dystrophin-producing drugs as one reason to require that Sarepta conduct a large, placebo-controlled phase 3 study before applying for approval. I do not understand this reasoning, as we don't even know how much, if any, dystrophin was produced by the drugs that failed to meet their primary clinical trial endpoints. In contrast, we know that Eterplisen produced dystrophin in all 12 treated patients at levels widely believed to lead to functional benefit. What's more, the treated patients have stabilized since the dystrophin took effect. One third of the children actually improved, a clinical outcome that is unheard of in Duchenne.

I do not have a rare fatal disease, but if I had one I would want the freedom to choose a drug in consultation with my physician that has a highly favorable safety profile and early indications of efficacy. I believe the FDA's #1 job is to protect people. While we understand there are certain risks with approving a medication studied in only 12 patients, the risk is a minimal and tolerable one compared to the certain pediatric deaths and losses of ambulation that will occur if you require several more years of study before approving this drug.

I implore you, work with Sarepta to accept the creative and aggressive confirmatory trial design they have planned. Understand that children will die and our kids will lose their ability to walk if this decision continues to be postponed.

Sincerely,

Peter Ciszewski
(b) (6)

--
Peter Ciszewski
(b) (6)

Philips, Howard

From: The Pink Sheet DAILY <info@pharmamedtechbi.net>
Sent: Tuesday, February 09, 2016 6:24 AM
To: Califf, Robert
Subject: "The Pink Sheet" DAILY | Today's News & Analysis

Daily, in-depth analysis of the key developments shaping the biopharma industry.

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Tuesday, February 09, 2016 | View in Browser | Forward to a Friend

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Purdue CEO: The Year For Transformative M&A Is Here The private specialty pharma is shopping for a transformative deal or a series of smaller deals that will diversify the company into a new area outside of pain and CNS disorders, CEO Mark Timney says during interview.

AstraZeneca's Durvalumab/Tremelimumab Combo Holds Its Own In NSCLC Phase Ib results for PD-L1/CTLA-4 combination look competitive, but editorial questions whether the company has moved too fast with development in response to intense market pressure.

Sarepta's Duchenne Treatment Likely Making Progress At FDA Data in advisory committee briefing addendum judged major amendment, requiring more review time.

Temple, Robert

From: Chris Liv <(b) (6)>
Sent: Tuesday, April 26, 2016 10:01 PM
To: Woodcock, Janet; Temple, Robert; Jenkins, John K; Unger, Ellis; Bastings, Eric; Farkas, Ronald
Cc: Commissioner FDA MH; Nicole.Cohen@mail.house.gov
Subject: Duchenne

Dear Drs. Woodcock, Jenkins, Temple, Unger, Bastings and Farkas,

I understand that the FDA has reversed its previous stance on whether to consider Sarepta's NDA for Eteplirsen. The Agency has cited the recent failure of other dystrophin-producing drugs as one reason to require that Sarepta conduct a large, placebo-controlled phase 3 study before applying for approval. I do not understand this reasoning, as we don't even know how much, if any, dystrophin was produced by the drugs that failed to meet their primary clinical trial endpoints. In contrast, we know that Eterplisen produced dystrophin in all 12 treated patients at levels widely believed to lead to functional benefit. What's more, the treated patients have stabilized since the dystrophin took effect. One third of the children actually improved, a clinical outcome that is unheard of in Duchenne.

I do not have a rare fatal disease, but if I had one I would want the freedom to choose a drug in consultation with my physician that has a highly favorable safety profile and early indications of efficacy. I believe the FDA's #1 job is to protect people. While we understand there are certain risks with approving a medication studied in only 12 patients, the risk is a minimal and tolerable one compared to the certain pediatric deaths and losses of ambulation that will occur if you require several more years of study before approving this drug.

I implore you, work with Sarepta to accept the creative and aggressive confirmatory trial design they have planned. Understand that boys will die and boys will lose their ability to walk if this decision continues to be postponed.

Sincerely,

Christine J. Livulpi

(b) (6)

Temple, Robert

From: Tara < (b) (6) >
Sent: Wednesday, April 27, 2016 7:55 PM
To: Unger, Ellis; Woodcock, Janet; Temple, Robert; Jenkins, John K; Bastings, Eric; Farkas, Ronald
Cc: Commissioner FDA MH; Nicole.Cohen@mail.house.gov
Subject: Eteplirsen

Dear Drs. Woodcock, Jenkins, Temple, Unger, Bastings and Farkas,

I understand that the FDA has reversed its previous stance on whether to consider Sarepta's NDA for Eteplirsen. The Agency has cited the recent failure of other dystrophin-producing drugs as one reason to require that Sarepta conduct a large, placebo-controlled phase 3 study before applying for approval. I do not understand this reasoning, as we don't even know how much, if any, dystrophin was produced by the drugs that failed to meet their primary clinical trial endpoints. In contrast, we know that Eterplisen produced dystrophin in all 12 treated patients at levels widely believed to lead to functional benefit. What's more, the treated patients have stabilized since the dystrophin took effect. One third of the children actually improved, a clinical outcome that is unheard of in Duchenne.

I do not have a rare fatal disease, but if I had one I would want the freedom to choose a drug in consultation with my physician that has a highly favorable safety profile and early indications of efficacy. I believe the FDA's #1 job is to protect people. While we understand there are certain risks with approving a medication studied in only 12 patients, the risk is a minimal and tolerable one compared to the certain pediatric deaths and losses of ambulation that will occur if you require several more years of study before approving this drug.

I implore you, work with Sarepta to accept the creative and aggressive confirmatory trial design they have planned. Understand that boys will die and boys will lose their ability to walk if this decision continues to be postponed.

Sincerely,

Tara Purr

THANK YOU!

Sent from my iPhone

From: (b) (6)
To: Woodcock, Janet
Subject: Thank you - Adcomm
Date: Wednesday, April 27, 2016 8:49:30 PM

Hi Dr. Woodcock –

I spoke at the Sarepta Adcomm on Monday, (b) (6). It was odd being on the other side of the podium, I (b) (6) and understand how it can be in your seat. I can't say that I have the responsibilities you have, but working with the public (especially on emotionally charged topics) is always an interesting part of the job and I can honestly say that each time I learn something new about people, both good and sometimes not so good.

I wanted to thank you for your opening comments, I felt they were fairly stated and were very good to set the tone for the day. I also want to thank you for your attention to all the families that spoke. I was only able to see you up front from where I was sitting and you were attentive and it appeared you understood what was being said from the podiums. It can be hard for us as parents to pour our hearts into something that we live with every second of our lives and is scientifically measurable – sometimes these 2 items don't mesh well. I think in this case the physical changes and improvements are well fit for an emotional response to agree that something positive is happening with these kids in the trials.

My son cannot benefit from this version of Eteplirsen, but we can't get to the follow up exons if we can't get past this first one. This is why we came to support our Duchenne family. My son screened for the Exon 45 trial in (b) (6), he was able to pass all the requirements except for the pulmonary part. I can honestly say that we were a breath away from being able to help test a drug that might possibly help him.

I wished I could have stayed to meet you in person after the meeting but my son did not want to miss any more school and we had to drive back to (b) (6) I shared this video in my written submission, but if you have a few minutes, please watch (b) (6) In the long run we know what his progress will be, but we will make what time we have the best we possibly can – and with that said, I have to go help him with Geometry.

Good luck in your decision, I know it's a big one that you will need to make.

(b) (6)

From: Jody Wellensiek
To: Woodcock, Janet
Subject: Duchenne muscular dystropht
Date: Wednesday, April 27, 2016 8:59:36 PM

Please consider approval of the drug to help the young men with Duchenne's. Their battle doesn't have time for more studies, or a wait and see approach. You know the outcome without treatment....give them a new outcome.

Jody Wellensiek, RD, LMNT

Sent from Yahoo Mail for iPad

Temple, Robert

From: (b) (6)
Sent: Wednesday, April 27, 2016 9:45 PM
To: Woodcock, Janet; Temple, Robert; Jenkins, John K; Unger, Ellis; Bastings, Eric; Farkas, Ronald
Cc: Commissioner FDA MH; nicole.cohen@mail.house.gov
Subject: Cure Duchene

Hi All,

We are asking all of our friends and family on Facebook to take few minutes of their time and please read and send the email requested for (b) (6). Thank you in advance.

Duchenne is predictable. Duchenne is progressive. Children with the disease do not produce dystrophin, a protein necessary for muscle strength and function. Lack of dsytrophin leads to loss of ambulation, which leads to loss of upper body function, which leads to cardiac and/or pulmonary failure.

And they die....every single time.

As you can imagine, scientists have been working for decades to figure out how to get the body to produce dystrophin. Now we finally have a drug that does just that – produces the missing protein. What's more, the 12 boys who have been lucky enough to try this drug in a clinical trial have stabilized since the dystrophin was produced in their muscle cells. We know that in these 12 boys at least, we can produce dystrophin – dystrophin that works.

I will outline the crucial facts here, but if you want to help and you only have a minute, skip to the end of this blog entry right now, where it says "PLEASE HELP. " If you have 5-10 minutes, continue reading.

Some key facts about the 12 boys:

• Four boys have IMPROVED on the 6 minute walk test over the course of two years. Stabilization alone would be cause for champagne, but in 1/3 of the boys we are seeing actual improvement – they are STRONGER than they were two years ago, unheard of in Duchenne. Could this be a fluke? Could the 6 minute walk test be unreliable? Sure, but the test was done twice each time. And the results have held up for two years. And the boys are producing dystrophin. So to look for some other unlikely reason they might be doing better against all odds (Sheer will? Happen to have great days on testing days?) is akin to looking for a zebra when a horse is staring us in the face.

• Four boys in the trial were on placebo for the first 24 weeks, then crossed over to drug. While on placebo these four boys declined, as expected. When they first started treatment they continued to decline but once the dystrophin kicked in, they stabilized. We have followed hundreds of untreated boys in natural history studies and placebo arms of other clinical trials. I'll put my money down that there aren't many –if any — boys aged 9-11 who started to rapidly decline, then stabilized. If they are out there, I do not know them.

• Two of the 12 boys (twin brothers) lost their ability to walk near the start of the trial, before the dystrophin had a chance to start working. Those boys remain on drug and their upper body function and breathing ability remains stable.

Yesterday Sarepta, the company developing this drug, announced that the FDA does not encourage submission of a New Drug Application (NDA) at this time. This is a direct turnaround from the FDA's position just three months ago, when, according to Sarepta, they told the company they would accept an NDA. According to the press release Sarepta distributed on the morning of the 12th Novenber, the FDA raised many questions about the clinical trial data and about this therapeutic approach called exon skipping.

The FDA's change of position was most likely influenced by the recent failure of a different drug produced by Glaxo Smith Kline called Drisapersen. Like Eterplisen, Drisapersen is also designed to produce dystrophin via exon skipping, but a large clinical trial of Drispaersen did not result in stabilization or improvement in hundreds of boys. The FDA said those results call into question whether dystrophin production will lead to clinical benefit.

But here's the thing: No one knows if the kids in the failed Drisapersen trial were producing dystrophin, and if they were how much of it was found in the muscle fibers. We don't know because GSK hasn't released that data.

If we are to compare competitive products, the recent failure of Drispaersen should buttress Sarepta's case, not hurt it. Drispaersen was close to what our children need, but not quite right. Due to toxicity issues, the drug could not be dosed at high enough levels to have across-the-board efficacy. In contrast, Sarepta's drug has a stellar safety profile. In two years, not one drug-related adverse event has been reported.

This is a lot to take in, I know. But it can all be boiled down and stripped away to these essential points:

1. Eterplisen is safe. It is possible that unknown side effects may appear once children are on the medicine for longer than two years. But every single family I know is more than willing to take that risk. Most of us currently treat our boys with poisonous steroids that result in awful side effects, just to give our children two years' additional walking and breathing time.

2. Eteplirsen may not work. An N of 12 is certainly not a large-scale, fool-proof data set. Once hundreds of children are taking the drug, we may learn that the dystrophin production and functional benefit we saw in the 12 boys was a fluke. Again, every family I know is more than willing to take that risk. I am putting my money down that (b) (6) can now march in the Halloween parade and (b) (6) can now push his mom's shopping cart when they could not do those things before starting Eterplisen treatments because they are now producing dystrophin, not because all of a sudden they just happen to be feeling great.

3. We need to find out if this drug is the real deal. The FDA can move forward from here in two ways: approve it now on an accelerated basis because it produces dystrophin, and LACK OF DYSTROPHIN CAUSES DUCHENNE. Or, require longer, larger studies that will cost millions of dollars and – more important – many children's lives. As of yesterday, it looks like the FDA is choosing the latter. As a community, people impacted by Duchenne must come together to reinforce the reasons the FDA must consider moving forward with an accelerated approval. Our children's lives depend on it.

PLEASE HELP

All children with Duchenne need your help today in the form of two quick steps:
1) Cut and paste the following message into the body of an e-mail.
2) Send the e-mail to the addresses listed below.

Thank you!

Dear Drs. Woodcock, Jenkins, Temple, Unger, Bastings and Farkas,

I understand that the FDA has reversed its previous stance on whether to consider Sarepta's NDA for Eteplirsen. The Agency has cited the recent failure of other dystrophin-producing drugs as one reason to require that Sarepta conduct a large, placebo-controlled phase 3 study before applying for approval. I do not understand this reasoning, as we don't even know how much, if any, dystrophin was produced by the drugs that failed to meet their primary clinical trial endpoints. In contrast, we know that Eterplisen produced dystrophin in all 12 treated patients at levels widely believed to lead to functional benefit. What's more, the treated patients have stabilized since the dystrophin took effect. One third of the children actually improved, a clinical outcome that is unheard of in Duchenne.

I do not have a rare fatal disease, but if I had one I would want the freedom to choose a drug in consultation with my physician that has a highly favorable safety profile and early indications of efficacy. I believe the FDA's #1 job is to protect people. While we understand there are certain risks with approving a medication studied in only 12 patients, the risk is a minimal and tolerable one compared to the certain pediatric deaths and losses of ambulation that will occur if you require several more years of study before approving this drug.

I implore you, work with Sarepta to accept the creative and aggressive confirmatory trial design they have planned. Understand that boys will die and boys will lose their ability to walk if this decision continues to be postponed.

Sincerely,

(b) (6)

Send the e-mail to the following FDA officials:

janet.woodcock@fda.hhs.gov
robert.temple@fda.hhs.gov
John.Jenkins@fda.hhs.gov
Ellis.unger@fda.hhs.gov
Eric.bastings@fda.hhs.gov
Ronald.farkas@fda.hhs.gov

Be sure to cc these people:
margaret.hamburg@fda.hhs.gov
Nicole.Cohen@mail.house.gov

Margaret Hamburg is the FDA Chief
Nicole Cohen is the health care policy advisor to US Rep. Joe Crowley, co-chair of the Congressional Caucus on Rare Disease

THANK YOU!

From: Jody
To: Woodcock, Janet
Subject: FDA vote on
Date: Wednesday, April 27, 2016 8:14:06 PM

Dear Janet,
I am sure you are over whelmed with emails supporting the legalization of the drug eteplirsen. I was very disappointed to say the least in the opinion of the advisory board to reject eteplirsen. These young men that this drug will benefit suffer each and everyday from a multitude of health issues.
I have seen a young man first hand who I love dearly decline over the last (b)(6) years. I watched him run and play with my daughter one day and the. Fall and cry in pain the next. I watched him walk with a walker to most recently never leave a wheel chair. The mere thought of carrying his own glass of water is now just that a thought. I have tried to imagine what it would be like to never leave a chair and rely on someone else for all of you very need. But the most frustrating thing to me is, there is hope hope that he can get his own drink, hope that he can continue to feed himself for able longer by using this drug.
His mother is one of my very best friends and to watch the hope that she could have more time with her son be taken away because the "trial size was too small" is devastating. If a bigger trial size is needed, then allow each and every boy with DMD access to this drug. This is their last hope because this slow agonizing horrible disease sucks their hope from their body.

Please try and imagine what you would do if this was you son. Please give these young men hope as well as everyone who loves them.

Thank you,
Jody Wichmann
Writing in for hope for (b)(6)

Sent from my iPhone

From: (b) (6)
To: Woodcock, Janet
Subject: My boys with DMD
Date: Wednesday, April 27, 2016 10:15:53 PM

Sent from my iPhoneThese are my boys and love them more than anything! All I want is some treatment to help with their quality of life and eventually a cure for this horrible disease they are plagued with. This drug could possibly help them in the future if the FDA approves the use of it. I know it doesn't help every boy affected by Duchenne but it is also a gateway to other drugs that might become available for treatment or even a cure being available for the whole Duchenne community someday! This drug has shown to help the boys on it in strength and to take this away from them and let their muscles waste again because they can't have it is so unfair to them, their families and all of us living with this disease! Are our boys not worth living? This is so frustrating and so unfair! So please approve this drug and don't be unfair to all these boys that have gotten stronger from this drug and let the FDA know OUR BOYS are important to live like the rest of us, a long life with as much quality as they can have!!

Sent from my iPhone

From: Himanshu Gupta
To: Woodcock, Janet
Subject: Re: Eteplirsen review: ONE SCIENTIFIC POINT. [Slight correction to previous email]
Date: Thursday, April 28, 2016 9:20:06 AM
Attachments: points.pdf

Dear Dr. Woodcock,

Thanks for taking the time to read my previous email, and encouraging me to convey any additional points. I have enclosed a pdf attachment with my key thoughts/points.

I know that you are most supportive of the boys and the cause, and are trying your best to effect a favorable outcome. I hope my points are helpful to your efforts.

Thanks very much,
Himanshu

From: "Woodcock, Janet" <Janet.Woodcock@fda.hhs.gov>
Date: Wed, 27 Apr 2016 17:38:34 +0000
To: Himanshu Gupta <hgupta@cs.stonybrook.edu>
Subject: RE: Eteplirsen review: ONE SCIENTIFIC POINT. [Slight correction to previous email]

> Thank you, I have read this email and agree. No comparison is completely satisfactory. Happy to hear any of your points. Janet Woodcock
>
> **From:** Himanshu Gupta [mailto:hgupta@cs.stonybrook.edu]
> **Sent:** Wednesday, April 27, 2016 11:15 AM
> **To:** Woodcock, Janet; Temple, Robert
> **Subject:** Eteplirsen review: ONE SCIENTIFIC POINT. [Slight correction to previous email]
>
> Please ignore the previous email — this completes a partial sentence in the previous email.
>
> Dear Dr. Woodcock and Dr. Temple,
>
> I am sorry to bother you both with this email, but due to its paramount importance I am compelled to write. I just want to convey one issue regarding Eteplirsen's review — in particular, regarding FDA's comparison of patients based on age and baseline, at points other than "baseline".
>
> MY POINT: Consider two example patients X and Y who are both say 11 years old and have the same 6MWD of say 350. Patient X is untreated (control group), while Y has already been on Eteplirsen for 2 years (I.e., since he was 9 years old). If Eteplirsen is efficacious (important assumption), then Y's disease severity is likely to be worse than that of X, and thus X and Y are not comparable.
>
> REASON: Note Y's 6mwd is 350 only because of 2-year treatment with Eteplirsen, which presumably preserved his 6 MWD but perhaps didn't alter his inherent disease condition. Thus, Y's 6 MWD at 11 years may not be an accurate representation of his overall disease severity. In other words, their

baseline characteristics could be very different. My argument may be speculative — but I believe its rational enough to seriously question the comparison between X and Y. **This calls into question the analysis presented by FDA review team in Figures 3, 6, 7, 8, (of the memorandum by Dr. Dunn) and Figures 8, 9, 10, 11, 13, 16, 19, 20, 22 (of the memorandum by Dr. Farkas).**

The above point has been made by Sarepta too (e.g., in their addendum), but I thought I'll offer an independent and different perspective to you.

ABOUT ME: I'm an Associate Professor of Computer Science at Stony Brook University. I have a PhD in Computer Science from Stanford University. I am a long-term investor in (b) (6), but by now am very emotionally involved with the whole cause. I have intimate knowledge of almost everything public pertaining the drug.

I would greatly appreciate an acknowledgement that you have READ the email. I have a few more points to convey, and if you are receptive to them, I would be happy to email them to you (in brief).

Thanks very much.
Himanshu

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Himanshu Gupta, PhD (Stanford)
Associate Professor of Computer Science
Stony Brook University, Stony Brook NY
http://www.cs.stonybrook.edu/~hgupta

Temple, Robert

From: Christine <(b) (6)>
Sent: Thursday, April 28, 2016 10:14 AM
To: Woodcock, Janet; Temple, Robert
Subject: Eteplirsen

I am writing today regarding the upcoming FDA decision on accelerated approval for Eteplirsen. Under FDASIA, you have the legal and moral duty to grant approval by accepting patient testimony that clearly supports the benefit of this drug. As you have emphasized, we must avoid the type 2 error of rejecting a drug that has shown benefit. As you know, Eteplirsen is SAFE. There have been little to no side effects. Please give the DMD community a chance. In a rare disease like Duchenne, we must have a paradigm shift. Thank you for standing up for rare disease patients by urging your colleagues to use the tools Congress has granted under FDASIA!

Sincerely,

Christine Vernon Say
(b) (6)

From: Laura Speicher
To: Woodcock, Janet
Subject: Eteplirsen
Date: Thursday, April 28, 2016 10:45:27 AM

Good Morning-

Please consider approving the medication Eteplirsen. This medication is proven safe/effective and has the opportunity to open the door for more medications that will help others with various forms of MD. Children with MD don't have a lot of time, please do something.

Thank you for your consideration.

Laura Speicher

From: (b) (6)
To: Woodcock, Janet
Subject: FDA Approval of Eteplirsen Testing - Decision by May 26
Date: Thursday, April 28, 2016 10:51:25 AM

As a grandfather of a boy with Duchenne Muscular Dystrophy, writing regarding the upcoming FDA decision on accelerated approval for Eteplirsen. Under FDASIA, you have the legal and moral duty to grant approval by accepting patient testimony that clearly support the benefit of this drug. As you have emphasized, we must avoid the type 2 error of rejecting a drug that has shown benefit. As you know, Eteplirsen is safe. Please give the DMD community a chance. In a rare disease like Duchenne, we must have a paradigm shift. Thank you for standing up for rare disease patients by urging your colleagues to use the tools Congress has granted under FDASIA!

Thank you

(b) (6)

From: Susan Bolland
To: Woodcock, Janet
Subject: eteplirsen
Date: Thursday, April 28, 2016 10:58:34 AM

Dear Dr. Woodcock,

I am writing you on behalf of a very good friend who's grandchildren have Duchenne Muscular Dystrophy. They have suffered greatly and need some hope. I understand there will be a vote for the medicine Eteplirsen. I'm asking you to please vote for the use of the medicine to be FDA approved.

Thank you!

Sincerely,
Susie Bolland

From: Denny Walthers
To: Woodcock, Janet
Subject: Eteplirsen
Date: Thursday, April 28, 2016 11:58:39 AM

Dear Janet,

I am a 72 year old retired consultant to the pharmaceutical, med device industry. I have pent 30+ years assisting these companies with qualification of equipment, processes and printed materials. This is simply to provide some qualification that I have a relatively good knowledge of the agency.

In my *opinion* the drug in question provides substantial relief to these affected with DMD. I would like to offer my support of this drug to move forward. If the agency feels that some additional broader testing is needed then perhaps a 'conditional' approval for that purpose could be granted. This would allow those currently being helped to continue their regimen.

I have always and continue to support the agency in what you do. I realize that you rarely receive kudos. I wish to provide some kudos to you. Over the past 30+ years I have witnesses difficult decisions that the agency has made. Consent decrees for companies not meeting 21CFR and approvals for those that meet with standards and requirements for operation and approvals.

Thank you for your willingness to be in the position that you are and for your willingness to read my email

Should you ever desire to speak with me, my phone and email are listed below. I answer my phone 2x7.

Thank you again,

Denny Walthers
(b) (6)

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From: Gina Lonneville
To: Woodcock, Janet
Subject: Eteplirsen
Date: Thursday, April 28, 2016 3:57:48 PM

Please please let this medication become available to those with Muscular Dystropy! I have worked with many children and adults who have Duchenne Muscular Dystropy and it is heartbreaking that there is no hope for them. They are living a death sentence so taking this medication will give them some hope even if it is not the "cure". So many of these individuals and their families are lobbying for the approval of this drug and are willing to try it for the sake of many others to come. Listen to those who matter! Thank you.

Sincerely

Regina Lonneville

From: Amanda Kling
To: Woodcock, Janet
Subject: Duchenne Muscular Dystrophy -- Meet (b) (6) and (b)
Date: Thursday, April 28, 2016 4:23:34 PM

I would like you to meet (b) (6) and (b) (6) These little guys are an amazing part of our family. I had the pure pleasure of being (b) (6) preschool teacher back at time when he could walk and care for himself. He was an amazing child. Now he's a great teenager, but this disease is threatening his life. This disease will eventually take his life.

Put yourself in the place of (b) (6) and (b) (6) mother. This horrible disease took both of her brothers, and now she can do nothing but watch as it slowly takes away BOTH of her little boys. She would do anything to help them, if even only for days or months, but imagine how her heart yearns to have the opportunity to gain YEARS. The medication Eteplirsen is offering that hope. It's offering the hope of quality years with her children.

I understand that the FDA must consider all aspects of a medication, and I understand (like any medication) there could be side effects. However, in the four year study by Sarepta Theraeutics, this medication has shown helpful. In addition, while side effects were notes, those side effects are also things that occur will occur with these children regardless of the medication.

Please vote in favor or this medicine and in favor of all the boys like (b) (6) and (b) (6) They need this. They deserve this opportunity.

Sincerely,
Mandy Kling
(b) (6)

From: Melissa Dabbs
To: Woodcock, Janet
Subject: FDA approval
Date: Friday, April 29, 2016 4:44:01 PM

Please consider approving MD drug Eteplirsen. We have two little superheros in our town that deserve a chance. Not to mention the others around the U.S. As a parent I would do anything to help my children. Please help these parents help their babies. God bless and have a great day!

From: jared ribley
To: Woodcock, Janet; Temple, Robert
Subject: FDA decision for Eteplirsen
Date: Saturday, April 30, 2016 4:24:08 PM

Hello,

I am writing today regarding the upcoming FDA decision on accelerated approval for Eteplirsen.

Under FDASIA, you have the legal and moral duty to grant approval by accepting patient testimony that clearly supports the benefit of this drug. As you have emphasized, we must avoid the type 2 error of rejecting a drug that has shown benefit. As you know, Eteplirsen is SAFE. There have been little to no side effects.

Please give the DMD community a chance. In a rare disease like Duchenne, we must have a paradigm shift. Thank you for standing up for rare disease patients by urging your colleagues to use the tools Congress has granted under FDASIA!

Thank you,
Jared Ribley

Temple, Robert

From: kim danboise < (b) (6) >
Sent: Saturday, April 30, 2016 6:13 PM
To: Commissioner FDA; Temple, Robert; Woodcock, Janet
Subject: Dr. Connely

Dear Dr. Califf: Any one listening to this commentary realizes that DMD has a potent treatment. Data monkeys beware you are making a mistake thinking Etep doesn't work.
Sincerely,
Kim D
I'm a neurologist at (b) (6) in (b) (6) and I've worked with children and adults with neuromuscular disorders for 27 years. I have been a consultant for Sarepta, but stand to gain nothing financially from approval. Please consider what I have to say from the perspective of a clinical researcher in Duchenne dystrophy, a neuromuscular pathologist, and finally with their permission I speak for (b) (6) and (b) (6) who I've followed for three and a half years in the extension study.

I know well the difference between Duchenne and Becker muscular dystrophy as I have cared for more than a hundred and fifty boys and men with these disorders. If I have a question whether a boy has Duchenne or Becker I do in fact assess the number of dystrophin positive fibers. In the recent FDA briefing it was stated that the percent positive fibers is not a reliable way to quantify dystrophin. Not only do I disagree with you I ask you to review those biopsies carefully and note that the fibers with dystrophin are larger and more frequent than any biopsy I've ever seen with revertant fibers. I believe these dystrophin fibers are driving the clinical effect. Furthermore, because (b) (6) and (b) (6) are so much stronger than I would have expected, if I met them for the first time today I would have suggested they have muscle biopsies. When I consider the post Eteplirsen biopsies and their physical examinations I would have to classify them as having Becker muscular dystrophy. Thus, I do believe that dystrophin positive fibers are a clear biomarker for strength and rescue of muscle.
anboise

From: Gladys Van Nostrand
To: Woodcock, Janet
Subject: DMD
Date: Sunday, May 01, 2016 10:10:39 AM

I have a best friend that has a son that was diagnosed with DMD when he was 7 years old. (b)(6) is now (b)(6) and his disease has gotten progressively worse throughout the years. He can not do any normal routine tasks that normal young boy his age would be able to do. I speak with my friend every day, and I feel the pain she is going through every time we get on the phone. I have to count my blessings that my son was born healthy. No one knows how it feels everyday wondering weather or not he is going to survive the next until you have a son that has this terrible disease. She informed me of the drug that is now in clinical trials that they are trying to approve. I know it could help so many young boys with DMD. I am asking that this drug is approved and you will take into consideration that it could help many young boys with DMD. I thank you for your consideration in this matter.

Sincerely,

Gladys Van Nostrand

From:	MICHAEL SCANNELL
To:	Woodcock, Janet
Subject:	FDA Approval for Eteplirsen
Date:	Monday, May 02, 2016 6:57:32 PM

We are writing today regarding the upcoming FDA decision on accelerated approval for Eteplirsen. Under FDASIA, you have the legal and moral duty to grant approval by accepting patient testimony that clearly supports the benefit of this drug. As you have emphasized, we must avoid the type 2 error of rejecting a drug that has shown benefit. As you know, Eteplirsen is SAFE. There have been little to no side effects. Please give the DMD community a chance. In a rare disease like Duchenne, we must have a paradigm shift. Please help save the lives of these young boys. This is their last hope. Please don't allow the structure and wording of an Ad Comm question, keep thousands of young men from having a future beyond feeding tubes and breathing machines. Thank you for standing up for rare disease patients by urging your colleagues to use the tools Congress has granted under FDASIA.
Sincerely,
Michael & Rae Ann Scannell

From: (b) (6)
To: Woodcock, Janet
Subject: ETEPLIRSEN
Date: Wednesday, May 04, 2016 7:28:13 PM

Please approve eteplirsen to treat DMD. My nephew has this disease and this gives us hope. I urge you to do all you can for nephew (b) (6) and all the people that have this disease. Thank you so much for your time

(b) (6)

Sent from Yahoo Mail on Android

From:	Tobin Del Giudice
To:	Woodcock, Janet
Subject:	Eteplirsen
Date:	Friday, May 06, 2016 10:18:18 AM

Dr. Woodcock

I am writing to request that expanded testing and increased availability be allowed for a promising medication for DMD, Eteplirsen.

As I am sure you are aware the that life expectancy is about 25 years for individuals with DMD. For many young people and parents with DMD this is a desperate and tragic situation with only one outcome, at this point. This medication offers the rare possibility of to some extent altering that course. Despite the need for further research, given the inevitable outcome of the disorder and the promise Eteplirsen as suggested by current research, please allow expanded testing and availability of this medication to other individual with this disorder.

Thank you,

Tobin Del Giudice, Ph.D.,LP

From: (b) (6) on behalf of Todd Rodzen
To: Dunn, Billy
Cc: Woodcock, Janet
Subject: Eteplirsen Adcom
Date: Sunday, May 08, 2016 5:30:32 PM

Dear Billy Dunn and Janet Woodcock,

I am writing you today to call your attention to our report we submitted in writing under the written submissions guidelines for Sarepta Eteplirsen NDA.

Our report completed the statistical analysis that the FDA reviewers refused to do. It's the job of statistical analist to complete a thorough analysis of the data as presented. We did that and find the FDA's Xiang Ling"s refusal based on preconcieved expectations as unacceptable.

We continue to stand behind our report and data analysis as submitted. Our report has been viewed over 7000 times. It has been reviewed by experts in statistical analysis, DMD doctors, and vetted by Sarepta experts internally and externally. We have no changes or corrections.

In contrast, we find Ronald Farkas' corrections and clarifying statements in his updated BD to be an attempt to justify an extremely unscientific and inadequate original briefing document.

Along with many arguments already provided by Sarepta and prominent members of the DMD community we also find the following to be in error in the updated BD.

1. Dystrophin quantification based on normalization as defined in the FDA dystrophin workshop panel of June 2015. In the final conclusion of that panel it was unanimous that quantification should be based on normalization using values from both WB and IMF. Not just one being more important. Greg Wierenga submitted this error to you by email on May 4 regarding your incorrect figure 9. I stand with Greg's conclusion that Dystrophin quantification based on normalization is correct and the quantification methods presented by the FDA at the Adcom is extremely biased and incorrect.

2. Different definition of LOA. The different definitions of LOA between a 6MWT, the CINRG study and the Baggar Study all go to prove the Etep group exceed's natural history and further explained below.

2a. The three EC that each had once completed a 10m walk/run but did not complete the 6 minute walk test and then had multiple following 6mwt & 10mWalkRun zeros goes to prove the EC is MORE correct and correlates to natural history (not less correct.) To explain, if you use the CINRG study definition of LOA; those 3 EC with 10m walk/run data points would find 3 of 12 ambulatory, that in fact matches the CINRG percentage at that age group. So that tidbit of data reconfirms the EC matches natural history. Since all EC then have multiple following zeros and it has been confirmed all in fact are non ambulatory, then it's completely logical that those 3 were on the verge of going non ambulatory and although they were able to reach a endpoint goal of walking 10 meters they were not able or willing to risk a "Duchenne Fall" and probable fracture by trying to walk further for a 6mwt. This does not mean the data is incorrect. The 10m walk/run is just a different data set.

2b. Since the EC matches natural history as defined by CINRG and Baggar studies, then when the EC group is compared to Etep group there is extremely statistically significant difference.

Because of the LOA difference of definition, the % ambulatory at different ages presented by Ron Farkas at the Adcom is extremely biased and incorrect.

3. One scientific point by Ron Farkas was that the Etep patients received steroids on average almost a year before the EC group. What he failed to point out is the groups are matched extremely well on average age with less than .3 year age difference. But most important, if you use the 6mwt values of the lower year of the EC and compare to one year older test values from the most recent Etep group 6mwt tests, the Etep group still defies natural history with an extremely significant statistical difference and that would be a comparison giving the EC group an extreme favorable bias of almost one full year younger average age.

Furthermore there is no study that clearly demonstrates that being on steroids earlier for longer periods equates to walking at later ages. In contrary, it is widely known that longer steroid use results in lessening value or diminished returns. Therefore the steroid argument presented by Ron Farkas at the Adcom is extremely biased and incorrect.

4. From a statistical analysis point of view, I find Ron Farkas' reliance on a spaghetti line chart to be quite disturbing. No statistical analysis would stop at a spaghetti line chart without looking at the overall data distribution. As you can see in our scatter charts of the same yearly data points, the mean difference is continually improving. In addition looking at a box plot graph to show the distribution of data or as we presented a 3D graph showing the distribution by number of years on Eteplirsen and by patient age, are the best interpretation of the data. Those interpretations show clearly the extreme significant statistical difference. Therefore the narrow minded presentation of only showing the spaghetti line chart as presented at the Adcom is extremely biased and incorrect.

Therefore the only valid conclusion based on the addional data provided by the updated BD, is the EC group is well matched and well controlled.

Finally I would like to comment on the Adcom process which is in theory is suppose to be a fair and balanced trial of sorts with a fair and balanced judge and jury. This did not happen. It was an unequivocal filibuster controlled by the judge (the FDA controlling the microphone.) This is clear when the entire room "Boo's" the FDA in their refusal to allow Sarepta to respond during the open discussion phase. Multiple times FDA refused to allow Sarepta to respond. and on multiple times cut off Sarepta advocates yet allowed Ron Farkas to filibuster well beyond his alloted time. In the words of Senator Marco Rubio on the Senate floor the following day, this was very "jarring". It was not a fair and balanced process.

I have completed this review independently and have not received compensation for this review nor do I have any conflicts of interest.

Reference: 4yr Data Analysis Report
http://gtk.link/etep

Sincerely,
Todd Rodzen
(b) (6)

From: [redacted] (b) (6)
Date: May 21, 2016 at 3:47:47 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: FDA's Upcoming Decision on Eteplirsen

Dr. Woodcock,

I know that you are an extremely busy person, and that you likely get hundreds or even thousands of letters from people like me who want to weigh in an issues pending before the FDA. However, I assure you that the attached letter it is worth your time and consideration prior to issuing the FDA's ruling on Thursday.

Thank you for your sincere consideration. If you would like to discuss this matter further, please do not hesitate to call me.

[redacted] (b) (6)

(b) (6)

May 21, 2016

VIA E-MAIL TRANSMISSION
janet.woodcock@fda.hhs.gov

Janet Woodcock, M.D., Director
Center for Drug Evaluation and Research
United States Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Re: Plea for Accelerated FDA Approval of Eteplirsen

Dr. Woodcock,

You are about to make the most important decision of my (b) (6)-year-old son (b) (6) life. I am writing to you today on behalf (b) (6) to plea that you make the right decision. I know that you have heard from many parents of children with Duchenne Muscular Dystrophy, and that each one has a heart-wrenching story. I was at the AdComm on April 25, and I believed you when you stated that the FDA wants to grant approval for a drug to treat Duchenne. I also realize that you may feel constrained by the law to rule against approval. However, I am writing to tell you that not only will the law *allow* you to approve Eteplirsen – it *mandates* approval.

(b) (6) story begins on (b) (6). Early that morning, my wife (b) (6) went into labor with our first and only child. It was a stressful drive to the hospital delivery, as we had to deviate from our planned route to avoid an oncoming tornado. Labor progressed normally for a few hours, but then there was a complication that necessitated an emergency cesarean section. Things got really scary in the delivery room for a while, as (b) (6) pulse rate dropped, and (b) (6) raced. We were both so relieved to hear the first tiny scream from his beet-red head, as the rest of his body was as blue as a Smurf. It was a close call, but both (b) (6) and (b) (6) survived the delivery and

seemed to be perfectly healthy. However, when we brought (b) (6) home from the hospital, it was quickly evident that something just wasn't quite right. As an infant, (b) (6) was often reluctant to feed, and he would often cry incessantly for no apparent reason. It was rare for him to sleep for more than a few hours at a time, and his limbs always seemed very stiff. When several of our friends' one-year-olds were starting to walk and talk, we were worried that (b) (6) had not even started to crawl yet. It wasn't until he was almost (b) (6) old that he finally took his first Frankenstein-like steps, and even then, he would always fall after only a few unsteady toddles.

(b) (6) and I consulted numerous doctors, specialists, and other medical professionals, only to be told time and time again, "All kids develop at different rates. Don't worry. (b) (6) is fine." One doctor told us that (b) (6) might have a condition on the autism spectrum, but subsequent testing all but ruled that out. A parent's intuition doesn't lie though, and we always knew that something was amiss. In the back of our minds, we always thought that maybe it had something to do with the scary delivery. Maybe he didn't get enough oxygen. Or maybe we didn't know what we were doing as parents. Maybe this is somehow *our* fault.

In September 2013, we thought we had found a solution. We had (b) (6) evaluated by the county (b) (6), and they identified several motor, cognitive, language, and social developmental delays. They recommended speech, occupational, and physical therapy services, which were provided several times per month for over a year. We saw marked improvement in (b) (6) function, but there came a point where his progress "hit a wall". We enlisted the services of private therapists, and after about a year of intensive physical therapy and speech therapy, it seemed that (b) (6) was starting to "catch up" to what would be considered on the lower end of "normal" for his age. As a (b) (6)-year old, (b) (6) was toddling around like a typical (b) (6)-old. He would still fall several times a day, but he was learning to catch himself with his arms. He could crawl up short flights of stairs, and had learned to scoot down them on his bottom. Potty-training wasn't even a possibility yet, as the muscles that control those functions were not strong enough to allow (b) (6) to make it to the bathroom. Nevertheless, we were very proud of the progress he had made, and were hopeful that his function would continue to improve.

Then in July 2015, (b) (6) physical therapist noted that (b) (6) was starting to lose some of the gains he had worked so hard to achieve. All of the sudden, (b) (6) wasn't as strong or as flexible as he had been a few short weeks earlier. Measurements revealed that the muscles in his lower extremities had atrophied, despite the fact that his activity level hadn't changed. Although he had finally gotten to the point where he could climb and descend stairs by holding onto a railing, he was now back to crawling up and down. He was falling more frequently. He couldn't get up off the floor by himself. He would cry in the middle of the night every night because he had leg cramps and stomach cramps. His calf muscles would get knots in them the size of golf balls, and he would scream in agony as we tried to massage them out. He regressed to the point where he was often walking on his tip-toes, and at times refusing to walk at all. His therapist encouraged us to see an orthopedist and a neurologist to investigate the cause further. In August, blood tests revealed that (b) (6) creatine kinase (CK) level was over 30,000. Genetic tests were ordered, and in November

2015, we learned that (b) (6) has Duchenne.

As you can imagine, the news was devastating. However, we immediately started out in search of any resources that might be out there to help him – and help us – cope with the frightening prospect that (b) (6) has a disease that will almost certainly take our precious baby from us before he ever attains adulthood. As you can imagine, we were even more devastated when we learned that there *are no approved treatments available*. When we heard about the Eteplirsen trial, we immediately contacted the research coordinator, and signed (b) (6) up to participate in the trial at (b) (6).

(b) (6) had his (b) (6) birthday on (b) (6) of this year, a mere three days before he started the Eteplirsen trial. He had a birthday party at the local YMCA, which has a small indoor playground made for toddlers. A few dozen of his preschool classmates attended, and they had a blast climbing, sliding, and rough-housing like four-year-olds do. It was a happy day for (b) (6) but it was bittersweet. It was great to see (b) (6) enjoy the company of his little friends, and have one more day to act like a "normal" kid before he embarked on the journey he is now on. However, there were times that day when we would look at (b) (6) and know he had to be thinking "Why can't I climb up that slide like they can? Why do I get tired so quickly when they are not? Why can't I do all the things they can do?"

(b) (6) started receiving weekly Eteplirsen infusions on (b) (6), and since that time his life has continued to improve dramatically. He actually looks forward to his weekly infusions where the doctors "put medicine in his super-hero button" (his port through which the infusions are administered), because he knows that it is helping him get stronger. In thirteen (13) short weeks, we have already seen drastic improvements in (b) (6) function. He is noticeably stronger. He can get up off the floor a lot quicker than before. He no longer has a positive Gowers' sign. He can walk up stairs – upright – without using the railing to assist him. His toddler gait is a thing of the past, and he can run really fast now (he couldn't even run in January). He can hop and jump now, and he can even balance on one leg for long enough to put his pants on. He hasn't spontaneously fallen down in almost two months, whereas that used to occur several times every day. He sleeps through the night now because he doesn't have leg and stomach cramps any more. He can play for hours on end without getting tired. He is dressing and undressing himself with little to no assistance, even buttoning buttons and zipping zippers. And perhaps the biggest thing – he is now going to the bathroom by himself, and he hasn't worn a diaper in over two months. Every day, (b) (6) and I are amazed at the new things (b) (6) is able to do now that he has never been able to do before. (b) (6) preschool teachers, friends, and physical therapists have all noted the drastic changes as well. Most importantly, (b) (6) is so much happier now that he can do a lot of the things other kids his age can do. And all of this has come with no negative side-effects whatsoever.

We all know that Eteplirsen is not a cure for Duchenne. The harsh reality is that there is no cure, and there may not ever be one. However, Eteplirsen is not only the best option for kids with DMD – right now it's the *only* option. Eteplirsen, in our experience, is an option that shows tremendous potential, and tremendous hope. This drug can pave the way for other, more effective

treatments in the future.

(b) (6) is one of the few lucky ones to be getting treatment right now. In fact, (b) (6) is going to keep getting his weekly dose of Eteplirsen for the next two years, regardless of whether the FDA approves the drug for use outside of his clinical trial. For that, we are eternally grateful. However, we strongly believe that every single child suffering from a form of Duchenne that is amenable to exon-51 skipping deserves a chance at the life-altering treatment that (b) (6) is getting now. Additionally, we want to ensure that (b) (6) continues to receive treatment after the trial is over.

At the April 25 AdComm, Sarepta was tasked with providing "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." I submit to you that this is the incorrect standard to apply in this case. Furthermore, I submit to you that evaluating Eteplirsen, or any drug for that matter, on such a standard is blatantly unconstitutional. To fully understand why this efficacy requirement is unconstitutional, one has to first understand that the federal government and its agencies only have powers which have been bestowed upon it by the people. The United States Constitution is the only source of such power. If the Constitution does not give the government the power to do something, then the government has no such power. That applies even when dually elected members of Congress have passed a law purporting to bestow such power. In other words, it is unconstitutional for any governmental agency to exercise any power that is neither explicitly nor implicitly provided in the constitution.

Over the years, the United States Supreme Court has issued rulings in specific cases that interpret the Constitution as providing "implied powers" to the government. One such set of powers are what are known as the "police powers". Generally speaking, the police powers are the authority of the government to regulate and enforce order for the betterment of health, safety, and general welfare of the people. The government can regulate a wide spectrum of activities under the guise of the police powers. However, there are limitations on the government's police powers: (i) Laws must apply equally to all under like circumstances; (ii) Government interferences with individual rights must be reasonable; and (iii) Regulations must have a clear relation to some legitimate legislative purpose. Most significantly, laws passed under the guise of the federal government's police powers are subject to a heightened standard of review, which demands that the least restrictive limitation to constitutional rights be used to further a compelling government interest.

The FDA is a federal agency that was created pursuant to the federal government's police powers. The Food And Drug Administration was established by Congress by the passage of the Food, Drug and Cosmetic Act of 1938 (FFDCA). The stated purpose of the FDA was to ensure the safety of food, drugs and cosmetics harvested, manufactured, distributed, and consumed in the United States. Conspicuously missing from the 1938 version of the FFDCA was any authority for the FDA to ensure that food, drugs or cosmetics actually worked. It was not until 1962 when Congress passed the Kefauver-Harris Amendment that the FDA was tasked with ensuring that drugs were effective as well as safe. Once enacted, those laws required that in order to obtain marketing

approval, manufacturers must demonstrate the effectiveness of their products "through the conduct of adequate and well-controlled studies". See, 21 C.F.R. 314.

Tasking the FDA with certifying any particular drug's efficacy does not have the required "clear relation to the health, safety, or welfare of the people". Additionally, requiring that a drug sponsor demonstrate a likely clinical benefit is not the least restrictive means by which to regulate efficacy. Since the FDA was created under the implied authority of the police powers, I submit to you that the FDA does not even have the constitutional authority to regulate drugs based on efficacy – only safety. However, if the FDA is going to regulate drugs based on efficacy, it must do so by the least restrictive means necessary.

The "least restrictive means" to regulate drugs in this case would be a simple risk-benefit analysis. If the potential benefits of a drug substantially outweigh its risks, then the FDA must approve the drug. Although the Advisory Committee was split as to whether there are benefits to taking Eteplirsen, they all agreed that there are no risks associated with the drug. That evidence is on the record. The drug is safe, and has no substantial risk. Therefore, any possible clinical benefit, however small or remote it may be, far outweighs no risk whatsoever.

Regardless of whether you agree with my position on the FDA's constitutional authority tio regulate efficacy, I believe that we can agree that the FDA's primary purpose is to protect the people. Denying approval of Eteplirsen is not protecting anyone. There is no risk associated with the drug to protect the people from. Approving Eteplirsen may protect thousands of young boys from the threat of not being able to walk, to breathe, or to survive into adulthood. The FDA has a duty to protect these young boys from that risk. The FDA has a duty to approve Eteplirsen. For these reasons, I plea for your approval.

From:	(b) (6)
To:	Woodcock, Janet; Temple, Robert
Cc:	Dunn, Billy; Bastings, Eric
Subject:	Eteplirsen
Date:	Monday, May 23, 2016 9:27:34 PM

Dear Drs. Woodcock & Temple,

I urge you to grant Eteplirsen accelerated approval. In the dark landscape of Duchenne, Eteplirsen cracks the surface and offers hope to families. This hope is based on the very real benefits that the 12 boys experience -- whether dystrophin production is quantified at 0.9% or otherwise. Putting off accelerated approval will cost lives, my son's included.

I cannot begin to fathom the pressure you are under. I pray that you will err on the side of our sons. Use the flexibility that Congress has granted FDA.

In hope,

(b) (6)
(b) (6) Mom

Ring the bells that still can ring
Forget your perfect offering
There is a crack in everything
That's how the light gets in.
Leonard Cohen (1992)

From: Alexander, Scott
To: Woodcock, Janet
Subject: Well Wishes For You
Date: Tuesday, May 24, 2016 11:39:25 AM

Good Morning Dr. Woodcock,

I just wanted to express my well wishes and prayers for you as you face the tremendous pressures surrounding the approval decision on Eteplirsen. I'm praying for a positive outcome of this drug for these boys' sake (my eyes still well up thinking of their testimonies at AdCom and how their lives have been positively changed by this drug) but I'm also lifting prayers for you given the intense stresses I'm sure you're facing.

Best Regards,
Scott M. Alexander

Scott M. Alexander

Facility Quality Manager

Solar Energy Research Facility (SERF), Science & Technology Facility (S&TF), and Outdoor Test Facility (OTF)

National Renewable Energy Laboratory (NREL)

15013 Denver West Parkway | Golden, CO 80401

O: 303-384-7225 | M: (b) (6)

scott.alexander@nrel.gov | www.nrel.gov

From:	Carrie Miceli
To:	Woodcock, Janet
Cc:	Nelson, Stanley F.
Subject:	eteplirsen adcom video
Date:	Tuesday, May 24, 2016 3:25:27 PM

Dear Dr .Woodcock,

The CDMD at UCLA has put together an educational video highlighting the expert voice at the open public hearing. Our students and the Duchenne community have been following this adcom closely, given that it demonstrates the challenges and flexibility that can be afforded to drugs for rare disease with dire circumstances and unmet need and the role the public expert and patient voice can have on approval. We remain convinced that eteplirsen shows substantial evidence of efficacy and that dystrophin is induced to the extent that it is reasonable likely to predict clinical efficacy. We hope that you might find the video useful. Thanks for you continued attention to this matter.

https://www.youtube.com/watch?v=OsPoPq65ZCQ

Best Regards,

Carrie and Stan

M. Carrie Miceli, Ph.D.
Professor of Microbiology, Immunology and Molecular Genetics
Co-Director, Center for Duchenne Muscular Dystrophy
David Geffen School of Medicine and College of Letters and Sciences at UCLA
277B Biomedical Sciences Research Building, 615 Charles E. Young Dr. S.
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Stanley Nelson, MD
Professor of Human Genetics
Professor of Pathology and Laboratory Medicine
Co-Director, Center for Duchenne Muscular Dystrophy
Co-Director, Clinical Genomics Center
David Geffen School of Medicine at UCLA
Los Angeles
CEL: 310-991-2635
FAX: 310-794-5446

From: (b) (6)
To: Woodcock, Janet
Cc: (b) (6)
Subject: My Son with Duchenne
Date: Tuesday, May 24, 2016 4:22:09 PM

Ms. Woodcock,

I have been meaning to e-mail for weeks....since the board's rejection of the drug Eteplirsen for Duchenne Muscular Dystrophy sufferers.

My awesome (b) (6)-year old son has this progressive disease that just won't quit. (b) (6) is a vibrant, smart, stubborn, young man, who should have a bright future ahead of him. Instead we are facing death, even though we try to fight it off every single minute of every single day. When he was diagnosed at (b) years old, I assumed we had lots of time for a drug to be available to help him, to prolong his life, to give us a hope for the future. Now my (b) (6) student has to have help using restroom, taking a shower, lifting his arms. Although he is still able to take his daily medicine, feed himself and use a keyboard, there is not much else he can do on his own. I'm not sure if you have any experience with a (b) (6)-year old boy, but those limited abilities are only a tiny fraction of what they want to do.

I've always told (b) (6) that it isn't just him that is afflicted with this disease, it is our whole family. Our whole family suffers. We pray. We hope.

Please, I beg you, give Accelerated Approval of Eteplirsen. For our boys. For our families. For hope. For love. For a future.

Thank you for reading this and for your consideration.

(b) (6)
A Mom
(b) (6)

From: (b) (6)
To: Woodcock, Janet
Subject: Eteplirsen Adcom
Date: Tuesday, May 24, 2016 4:45:29 PM

Dear Ms. Woodcock, I was one of the 52 speakers in the OPH at the Adcom on April 25th. My son (b) (6) has been getting infusions for one year of eteplirsen as part of the 204 Safety trial. He has seen AMAZING results!!
While we were in DC, his classmates and students in 4th grade at (b) (6) in (b) (6) made this amazing video! I feel it speaks for itself.

(b) (6)

Thank you for taking the time to view this brief video!

Sincerely,
(b) (6)

Sent from my iPhone

From:	Steve Hayes
To:	Woodcock, Janet
Cc:	Temple, Robert; Moscicki, Richard
Subject:	Eteplirsen
Date:	Wednesday, May 25, 2016 11:27:06 AM

My name is Steve Hayes and I appreciate you taking the time to read this. I believe I have a unique perspective regarding your important decision concerning Eteplirsen because I bring both the views as a former "scientist" and then clergyman. In college and then after graduation, I had the incredible opportunity to work in the lab of Dr. Francis Collins both in gene discovery and then the human genome project. I was there around the time when, in collaboration with many others, our lab discovered the genes responsible for Cystic Fibrosis, Neurofibromatosis, and Huntington's disease. It was an amazing place to work and the excitement was palpable every day. I remember firmly believing that our work would lead to the treatment, if not cure, of these diseases within a decade. Unfortunately, as you know, the more we discovered, the more we learned what we didn't know. I distinctly remember one lab meeting, when Francis hypothesized that the delta F508 mutation in CF could be modified to produce a partially functional truncated protein. Sadly, and amazingly, here we are 25 years later and not one drug has been approved to treat one of those diseases based on genomic science. When Francis left to move to Bethesda, I made the difficult decision to leave science and pursue a career as a pastor which I have continued to this day.

I want to urge you to grant accelerated approval for the following reasons.
First, dystrophin production is clearly an acceptable surrogate biomarker. The FDA acknowledged at Adcom, that it is being produced. We know it is the missing protein causing DMD. While I am disappointed by the amount being measured, I want to urge you not to miss the ground-breaking science before our eyes. This is what we dreamed of 25 years ago when we worked night and day to discover these genes and then sequence the genome. There now appears to be a drug that actually produces a protein that is not produced in the diseased state! Please, realize that we sit at a historic moment and this decision can move us forward into a whole new world of disease-modifying drugs or set us back many years. Dr. Chamberlin testified that even small amounts of dystrophin benefit the cell. The "reasonably likely" language of FDASIA seems clearly met scientifically.

When faced with a difficult decision, I have learned to to try to simplify it to the most basic facts. From a genetic standpoint, the decision seems clear. Is dystrophin an acceptable surrogate endpoint? Does Eteplirsen induce the production of dystrophin? Is this production reasonably likely to produce clinical benefit? If the scientific community who are experts in DMD would answer yes to those three questions, I urge you to grant accelerated approval.

Secondly, from my moral and ethical perspective as a pastor, I urge you to grant accelerated approval. The drug appears safe. The parents, patients, and medical community caring for the patients testified to it's safety and efficacy. I wept during the parent and patient testimony. How can we call ourselves a compassionate society if we deny a safe drug to terminal children with no hope when the consensus of the DMD parent, patient, and scientific community supports approval? Are there DMD doctors or scientists asking you to protect DMD children from this drug? If the answer is no, I urge you to approve.

Finally, as a pastor, I am a student of human nature. It was clear to me that there may be a damaged relationship between some in the agency and the company. I plead with you to exercise your leadership and not allow damaged egos to affect this decision. I was quite

disappointed with the quality and tone of the FDA presentation. I was very disappointed with the wording of the questions which seemed to lead to a particular result. In spite of that, the vote was close 7-6. I urge you to override that vote and approve Eteplirsen. As you so wisely pointed out, a type 2 mistake in this instance would exact a devastating affect on the ones who are most vulnerable and have very little voice.

Thank you for serving the public. I was moved by the compassion you showed by staying with the families after such a long, emotional, and draining day. I urge you to wed your compassion with action. Countless lives will benefit from your leadership in the DMD community and many other communities as you pave the way for a new generation of life-changing medicines.

Sincerely,

Reverend Steven Hayes

From: (b) (6)
To: Woodcock, Janet
Subject: Drug for Duchenne
Date: Wednesday, May 25, 2016 11:53:02 AM

Janet,
I know you all must be going through hell with the decision on Sarepta and the Duchenne drugs. If I were in your position, I wouldn't want to say no to 3 drugs. I feel really bad for the kids who have gone through so much to be in this trial. We fly half way across the country to (b) (6) every other month for Halo and we have struggled, so going every week is another level of commitment. This is why I don't say too much on facebook while they are telling their side of the story. However, I think it's more humane to say no to Eteplirsen because it really is giving the kids and families false hope. Not being on either drug, I believe that I can look at this more objectively than some. After (b) (6) years on drug, I think we know what it will or will not do.

As a mom wanting a drug that will work, I first went looking for people on Drisapersen and saw their videos of boys jumping in cars,riding bikes, running up hills and playing soccer. For the older boys I see stable muscle integrity, driving cars, getting on buses up stairs, doing laundry, walking to school and jumping in pools. When I met (b) (6) from the original Belgium trial, I was blown away by him being almost (b) (6) and walking to school. This is not normal at his age. I heard that they got results in 6 months because they were on a loading dose.

Then I look at (b) (6) and (b) (6) who are on Eteplirsen and (b) (6) walks way up on his toes and doesn't look good to me. There really weren't too many videos or people speaking for Eteplirsen that were in the original 12 trial. I knew that the youngest boy was declining and had heard through the grapevine that half of them no longer walk and they are all declining. Then, I look at the data where they are all declining 50-60 meters on the 6mwt a year. This follows the well known natural history of the disease. Then I see the data where their rise from floor time going up and the NSAA going down. Even with the historical control they used being bad (and I think that it is dishonest for them to zero out the walk times for everyone when they were walking 300 meters just 6 months earlier), the data shouldn't be going down period. Then I hear the massive amount of dystrophin they claim to have is really less than 1 percent. That isn't good enough. I want a drug that works just as much as everyone else don't get me wrong. But I don't want the community to hold their hat on a drug that doesn't work and not do other trials. False hope can also be a dangerous conclusion. I believe that this will hurt the community in the long run.

If I were the FDA, I would reconvene with Biomarin and look at their long term data that does support efficacy. In my eyes, both drugs have the same amount of protein in the urine, both have things that we don't like like a painful shot or port that can get infected and rashes have happened. They say the other drug is toxic. Boys with Duchenne have protein in the urine anyway so that is not the case. The facts are no boys on Eteplirsen can ride a bike, run up a hill, run up stairs and play on a regular ball team even after 4 years on drug. However, on Drisapersen, many can do these things. There is a big difference between the two drugs efficacy.

Thank you for your time and concern for the community. I am confident that we will have approved drugs in the future for Duchenne. I look forward to meeting with you about better clinical trial designs for Duchenne. Despite the delays, I am confident that we will have approved drugs in the future for Duchenne. I'm never giving up hope.

Best Regards,
(b) (6)

From: Dianne Tornay
To: Woodcock, Janet
Subject: Eteplirsen
Date: Wednesday, May 25, 2016 12:50:46 PM

Dear Ms Woodcock,
I am writing because I encourage you to approve the use of
Eteplirsen.
It can be very helpful in the treatment of patients with DuChenne.
I understand that part of the reason its use is being blocked is that it is not profitable.
Let's put patients first!
Please approve Eteplirsen.
Thank you for your consideration.

Sincerely,
Dianne Tornay
(b) (6)

From: Cornelius, Robin ([redacted] Local Schools)
To: Woodcock, Janet
Subject: Eteplirsen Approval
Date: Wednesday, May 25, 2016 1:02:05 PM

Dear Ms. Woodcock,
Please approve Eteplirsen. As a second grade teacher it is devastating to watch a student with DMD deteriorate physically over a school year while other students are becoming taller and stronger.

Sincerely,
Robin Cornelius

From: Ray Ward
To: Woodcock, Janet
Subject: Need Your Help ---- Sarepta
Date: Wednesday, May 25, 2016 3:49:35 PM

Dr. Woodcock ,

I have tried almost all my connections to reach you before Thursday 5 / 26 / 2016 . As you and I know this drug is very important to a lot of young children now and possible children in the future that have or may incur Deschene M D . My little (b) (6) year old friend was diagnosed about (b) years ago, and along with his parents we have always done everything we could , for his future. From what I am hearing now this new drug could be the last chance . Not just for him but many other children. I am hoping that you can help advise the council members to re think their votes on this matter and look into the future for the children affected and the ones that may be affected in the future. As you can tell I am not very good at typing better at talking face to face with people. I hope you have a chance to read this and be able to help out with Thursdays talks.

Thanks for your time with this , look forward to hearing back from you

Ray Ward

(b) (6)

From: Robert Escott
To: Woodcock, Janet
Subject: Eteplirsen
Date: Thursday, May 26, 2016 2:10:39 PM

Dear Dr. Woodcock,

I have been following the Eteplirsen saga for the past three years. I urge you to expedite the approval of Eteplirsen with the option of it being withdrawn if evidence ultimately emerges that it is not a good drug. With zero adverse effects showing up after all this time and with evidence considered convincing by what seem to be all Duchenne experts, approval will likely help patients with no other options. At worst, we will know shortly if this optimistic assessment is misguided, without putting the boys under any known risk.

Disclosure: I own no shares of any company having anything to do with Duchenne Muscular Dystrophy.

Sincerely,
Robert Escott
(b) (6)

From: Schwartz, Jeffrey
To: Woodcock, Janet; FDA Commissioner
Subject: DMD at 38 years old
Date: Friday, May 27, 2016 11:45:13 AM

Hello Dr. Woodcock,

I am a pharmacist in (b) (6) and I work with a patient who is a (b) (6) year old DMD patient. He says all doctors have to say when they talk to him, is "how are you still alive?", I'm sure in a nicer manner but it's all the same to him. I took it upon myself to research potential treatment so I had something other to talk to him about than his grim fate.
Starting a few months ago, I have been following the FDA's process play out for Eteplirsen. It is now all he talks about and like (b) (6) (the (b) (6) year old DMD patient), he is more concerned about the younger, more recently diagnosed DMD patients. He is driving me nuts with his questions about when a decision will be made. I have told him that I read anywhere between 3 weeks to 3 months. Can you please give me a better idea of when the decision may be rendered? My initial thought is that it would be a few extra days. I really hope you can narrow it down for me so that I may at least set his mind at ease. He is eager to hear news, and I would like to be the one to give him at least something for which to look forward, since that is all he has at this point. I thank you for your support and compassion that you have shown to the DMD community.

Sincerely,

Jeff Schwartz, Pharm.D.
Arizona State Board of Pharmacy license # S012861
(b) (6)

From: (b)(6)
To: Woodcock, Janet
Subject: Important point of view regarding the Eteplirsen decision
Date: Friday, May 27, 2016 8:56:39 PM

Dr. Woodcock,

While I could write ten pages of reasons, opinions, and facts that I believe would compell you to approve Eteplirsen, I am sure you have heard most of them, so I will concentrate on a few I believe have been overlooked. I have followed this story from the beginning, over five years plus ago. I watched the ADCOM and was distressed at the inherent bias against the sponsor in what seemed to be an almost personal way. I have seen this in other situations between FDA and other companies(I know of one ongoing even now for 8 years or more) and this is not the time for egos, personal feelings based on percieved slights or whatever causes adults to behave like children, especially when children are the ones who are at risk. I believe that the scientific evidence has proven that this drug produces some level of dystrophin, as admitted by even the FDA's own, in my opinion, flawed analysis of the data. So my first observation is that a reasearch doctor who was there to present evidence that even the smallest amount of dystrophin produced has a meaningful benefit as it positively affects surrounding tissue per his research had his slide presentation bungled by FDA staff. Then when a panel member tried to revisit this compelling testimony, he was rebuffed by the chairman, without receiving an answer from said presenter. As it was asserted that there is no known quantity of dystrophin that would produce a benefit, this doctor's testimony was speaking directly to that question as his research has shown any increase provides more benefit than would be expected on an empirical assay. While the results of the 6MWT of the treated vs. the historical control has been a point of dissent between the DMD experts and FDA, I think a more important, in truth the most important, endpoint has been clearly demonstrated by the patient testimony. That is quality of life. While we know, and no one has suggested that Eteplirsen is a cure, it surely is an effective treatment. Take the example of the patient whose family testified that prior to treatment he was constipated and only able to have a bowel movement every 3-5 days with the help of laxitives. Post treatment, while adhearing to the same diet this child became regular with regard to bowel movements without laxitives. If you don't think that is not a quality of life improvement, then you have never been constipated. What a small thing overlooked by the hype of this vs that yet a happier more comfortable life for this child. Placebo will not, nor cannot, have this type of effect. Neither can a placebo last almost 5 years contrary to your staff member suggesting the DMD kids can just try harder and their results will be better. Despicable, that someone could be so ignorant, callous, and be in charge of such an important drug review. That a Donald Trump is where he is speaks to the disconnect that the public feels toward a broken government beauracracy. Kids are still walking when they shouldn't be, sleeping better at night than they had before, feeding themselves, hugging their family members, throwing footballs, pulling themselves out of the swimming pool, using the bathroom without discomfort and trying to maintain a bit of hope. Quality of life is worth everything to these children and their families. Give them this bridge to the future where they can be around when a true cure can and will be discovered. Anything other than conditional approval would be a travesty and the one mistake the agency has to avoid at any cost, denying a treatment that might(I believe it does) work and has no safety issues. Give the approval until more effective methods of testing can be determined. The kids have no more time to wait. While everyday that passes puts us all one day closer to death, the fact remains that they have far fewer days than the rest of us. Thank you for your time and consideration.

Respectfuly,
Patrick H Smith

From: joe
To: Woodcock, Janet
Subject: Duchenne"s Muscular dystrophy
Date: Saturday, May 28, 2016 5:37:27 PM

Dear Dr. Woodcock,

I am an internist with a primary care practice in [redacted] (b) (6). I realize that you must be enormously busy, so if this email has reached you successfully, many thanks for taking a minute to look at it.

I am glad that you decided to delay the decision about the possible new drug for DMD. After the rejection last month by the Adcom advisory panel, this delay action has revived some much needed hope for the DMD community.

I watched and listened carefully to the testimonials of the doctors and scientists who spoke at the Adcom meeting. The patients & families' emotional words offer a glimpse into the toll & suffering this disease inflicts of the young boys and their parents, for certain. I also know that similar "impact statements" can be said for any number of devastating diseases without good treatments out there. I also realize that there has got exist large amounts of pressures mounting on all sides from politics and big pharma and insurance coverage issues as well as sometimes big egos of drug company execs and even Adcom panel members maybe.

Personally, I don't care much for politics and I don't care much for folks with big egos either.

I liked a lot what you said about a type 2 error...(paraphrasing) that it would be bad to approve a drug that didn't work but worse not to approve a drug that, in fact, does work. That notion has been ringing in my head for a month now.

I also listened to the DMD researchers who spoke. They seemed smart, dedicated to their work, and very sincere in their words. Most seemed apolitical, too, which I really liked. I got the sense that they would have preferred to be back at home in their labs or with their patients than on the center stage. In other words, I didn't smell any hidden agendas or arrogance. I liked when someone said that ANY amount of dystrophin production is meaningful. So, one can debate the biopsy results and quantification techniques for measuring dystrophin until the cows come home, but the treated boys & their parents say the drug works. The researchers who have spent years in the field and the clinical neurologists who treat the boys believe it works, too. Since the drug appears safe, my feeling is to approve it, and then the quantification of dystrophin levels will come later. After all, even aspirin was known to be effective for a long time before the why and how were satisfactorily elucidated.

I am not an expert in DMD, nor am I a researcher. I am a clinician who treats my patients with evidence-based medicine whenever possible, and there ALWAYS exists the visceral element of clinical instinct that physicians develop over time.

I recall a DMD patient of mine who passed away several years ago. His disease followed the typical course for DMD. Each time he presented for an office visit, I regretted having nothing to offer him. Yet, he maintained the strength of his inner spirit and attended schools and even graduated from a local college. He held a part-time job until he could no longer. One day, he no-showed his appointment. I found out he had been admitted to an outside hospital and died from pneumonia. I never got to tell him how courageous I thought he was. He probably wouldn't have wanted my praise anyway.

Dr. Woodcock, please use your power to give this new drug an undiluted green light. It appears safe, and the experts in the field and the patients all say it works. Clarifiying data will come later for certain.

Thanks again for taking time to read this.

Sincerely,

Joseph Shalhoub M.D.

From:	kim danboise
To:	Commissioner FDA; Temple, Robert; Farkas, Ronald; Woodcock, Janet
Subject:	EC/Eteplirsen
Date:	Sunday, May 29, 2016 6:50:24 PM

Dear Dr. Califf: Please tell me which EC is more appropriate? Christ what a joke DNP is.

External Controls...

Thus, 2 external control groups were identified for comparative analysis to eteplirsen-treated patients:

External control group amenable to exon 51 skipping (N = 13) Primary Analysis This is the most relevant comparator for the 4-year 6MWT data from Study 201/202 eteplirsen-treated patients. A subset of 10 external control patients from the Italian Telethon registry had 3-year NSAA data; NSAA data were not provided for patients in the Leuven NMRC.

External control group amenable to any exon skipping (N = 50) Secondary Analysis This secondary group provided a larger sized group for comparison of the 6MWT data for 3 years, albeit in a population of DMD with a mutation amenable to any kind of exon skipping. The secondary group also included 8 patients with DMD mutations amenable to skipping exon 44, which typically have a milder disease course. Less

From: (b) (6)
To: Woodcock, Janet
Subject: Eteplirsen treatment of DMD
Date: Monday, May 30, 2016 7:21:48 PM

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30 May 2016
Dear Dr. Woodcock,
I am writing to humbly, but strongly encourage you to approve the use of eteplirsen to treat Duchennes Muscular Dystrophy (DMD). I have a nephew, (b) (6), who has been courageously fighting this terribly debilitating disease nearly his whole life. For more than (b) (6) years my family has watched his mother, my sister, (b) (6), do everything in a parent's power to find every potentially positive option for her son in living with and fighting his battle with DMD, including research programs, various treatments, and finding the best benefits and facilities possible to make his life as "normal," happy, fulfilling, and constructive as possible. Though he is an incredible fighter and tries to remain positive, time is running out for him, and for his family. And I have met many other young people, involved in the same fight. Clearly, this drug, eteplirsen, has shown true promise for many individuals in stabilizing their condition, and in some cases, improving it. I am a research scientist, and I understand that additional testing may be required to generate the rigorous data necessary to one day hopefully be able to conclude with significant confidence that this drug has broad, consistent positive effects in fighting this horrible disease. But as Senator Marco Rubio explains, and as you clearly well understand, due to how rare this disease is, many of the young people fighting it today, including my nephew, (b) (6) don't have time to wait for what are considered scientifically rigorous sample sizes. Right now, at the individual level, for many individuals, this chemical treatment has had a significant degree of success and has made a huge difference in the lives of many. So I implore you, please approve the use of this eteplirsen treatment for the many, like (b) (6) that do not have the time to wait, and may now derive significant benefit and additional time.
Thank you very much for your consideration.
Sincerely,
(b) (6)

From: (b) (6)
To: Woodcock, Janet
Subject: RE: Meet Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research
Date: Monday, May 30, 2016 10:10:46 PM

Indeed. I had a fantastic time at the park that day, but at the end of the video, you can see that I was afraid because I couldn't balance myself properly. I cried for Uncle (b) (6) to get me down.

And you're right, because Duchenne muscular dystrophy has stolen pretty much every part of my physicality. All that remains of me is one finger to communicate with you via a computer mouse. It takes me quite a while to simply type with my on-screen keyboard by clicking each letter. I'm grateful for the word prediction feature, which makes everything a little faster. However, I'm proud to say that I'm on my third book, a romance novel, if you will!

The funny thing is that I seem to regret the things I have no control over. I mean if I knew what the future was like, I wouldn't have played so many video games as a child. It's so much more than a muscle waster, this disease. I call it a time waster because although I'm (b) (6) years old, most of the time, it feels like I'm still in the (b) (6) grade. I feel like my life still hasn't begun.

I remember in October of (b) (6), I saw the painting I did in my favourite class and what a mess I had created. Including the fact that the high school no longer funded full-time assistants and I lost the ability to pee myself, quitting became the only option. I never looked back after that van ride home. I lost my dream of a cartoonist career.

One good thing is that through the loss of drawing, I found writing instead, which was inspired by a girl in the mall elevator. She said my parking was perfect, and you guessed it, all I could mutter was, "Yup!" I realized I had so much more to say, and thus started my journey in the literary arts. I've kind of already given up on walking again, but my biggest dream is romantic love. I've never had a girlfriend before; either they never give me a chance, or they change their minds, but I choose not to be resentful towards women because I understand the sacredness of choice.

With DMD, I was never given an option, and it gave me the opportunity to learn

respect for women. I write on the subject of romance to partially fulfill the void in my heart. It's a lonely road.

Yes, of course I'm trying to convince you to say yes to the Accelerated Approval of Eteplirsen with these ramblings of mine. I want to share my experiences with you as well. Janet, here is a blog I wrote that might interest you, about what I would do if I could walk again:

(b) (6)

Happy Memorial Day from Canada!

(b) (6)

From: Woodcock, Janet [mailto:Janet.Woodcock@fda.hhs.gov]
Sent: May-26-16 10:31 AM
To: (b) (6)
Subject: RE: Meet Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research

This disease has taken a lot from you. You had a great time at the park that day. Janet W

From: (b) (6)
Sent: Wednesday, May 25, 2016 10:29 PM
To: Woodcock, Janet
Subject: RE: Meet Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research

You don't need to respond, but you saw me in the present. This video below is of me before Duchenne muscular dystrophy stole my body:

(b) (6)

Please watch.

(b) (6)

From: Woodcock, Janet [mailto:Janet.Woodcock@fda.hhs.gov]
Sent: May-24-16 7:56 AM
To: (b) (6)
Subject: RE: Meet Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research

Thank you so much for sending me this video message. I salute your courage in taking action on behalf of the community, despite the severe pain you are suffering. I assure you I will take your message to heart. Janet Woodcock

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From: (b) (6)

Sent: Monday, May 23, 2016 9:44 PM
To: Woodcock, Janet; FDA Commissioner
Subject: Meet Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research

http://www.fda.gov/AboutFDA/CentersOffices/ucm193984.htm

Dear Janet,

My name (b) (6) is and I'm (b) (6) years old. I have Duchenne muscular dystrophy. Please watch the following video message that I made for you regarding the Accelerated Approval of Eteplirsen:

(b) (6)

I've included subtitles if you have a hard time understanding me.

Thank you,
(b) (6)

From:	Charles Thurman
To:	President Obama; Senator Shelby; Senator Nelson; (b) (6); Adams-King, Janice; (b) (6); Baker, Emily; Berkhousen, Katherine; Buhse, Lucinda; Woodcock, Janet; Unger, Ellis; Temple, Robert
Cc:	CNBC2; CNBC1 CNBC1; CNBC9 CNBC9; CNBC4; CNBC3; ABC NEWS; WAFF WAFF1; NY Times2; Foxnews (b) (6); H Times1; orlando journal; (b) (6); Letters MSNBC; NY Times; Washington Post; H Times4; NY Times1; PBS PBS
Subject:	FDASIA - US Senate needs to investigate the FDA - cut ALL funding to FDA
Date:	Wednesday, June 01, 2016 2:14:31 PM

FDA fails to decide on non-toxic eteplirsen (Sarepta) by their imposed deadline of 05/26.
FDA is preparing a CRL, to be released on a Friday at 5pm, to avoid all press coverage.
The FDA refuses to follow the FDASIA rules, as passed by into LAW in 2012. DE-FUND THE FDA.
FDASIA is a law that applies to non-toxic eteplirsen. FDA must be defunded and closed forever.

Temple, Robert

From: (b) (6)
Sent: Thursday, June 02, 2016 11:31 AM
To: Temple, Robert
Subject: (b) (6) needs a port

Hello Dr. Temple,
For the past four weeks, (b) (6) veins have blown every time we have tried to access them. The consensus is that after 84 infusions of Eteplirsen following two years of bi-weekly blood draws for Drisapersen, his veins are worn out.

Because we are the family whose kid fractured his femur two weeks before screening opened for the eteplirsen confirmatory, of course we are now the family whose kid needs a port just when his access to Eteplirsen is at risk.

I don't exactly know what I'm asking for in writing you. I'm just a mom who needs to make the best medical decision possible for her kid, and after everything I've put him through, I don't quite think I could forgive myself if I put him through surgery only to find out that the port is useless in a month.

Human being to human being, what do I do?

(b) (6)

From:	Charles Thurman
To:	President Obama; Senator Shelby; Senator Nelson (b) (6); Adams-King, Janice; (b) (6) Baker, Emily; Berkhousen, Katherine; Buhse, Lucinda; Woodcock, Janet; Unger, Ellis; Temple, Robert
Cc:	CNBC2; CNBC1 CNBC1; CNBC9 CNBC9; CNBC4; CNBC3; ABC NEWS; WAFF WAFF1; NY Times2; Foxnews (b) (6) H Times1; orlando journal (b) (6); Letters MSNBC; NY Times; Washington Post; H Times4; NY Times1; PBS PBS
Subject:	FDASIA - US Senate needs to investigate the FDA - cut ALL funding to FDA
Date:	Thursday, June 02, 2016 11:49:15 AM

The FDA tells Sarepta that they must give away eteplirsen for FREE. Sarepta will be bankrupt.
DMD patients must die. BMRN and SRPT are out of business - bankrupt.
FDA fails to decide on non-toxic eteplirsen (Sarepta) by their imposed deadline of 05/26.
FDA is preparing a CRL, to be released on a Friday at 5pm, to avoid all press coverage.
The FDA refuses to follow the FDASIA rules, as passed by into LAW in 2012. DE-FUND THE FDA.
FDASIA is a law that applies to non-toxic eteplirsen. FDA must be defunded and closed forever.

From:	Charles Thurman
To:	President Obama; Senator Shelby; Senator Nelson (b) (6); Adams-King, Janice; (b) (6) Baker, Emily; Berkhousen, Katherine; Buhse, Lucinda; Woodcock, Janet; Unger, Ellis; Temple, Robert
Cc:	CNBC2; CNBC1 CNBC1; CNBC9 CNBC9; CNBC4; CNBC3; ABC NEWS; WAFF WAFF1; NY Times2; Foxnews (b) (6) H Times1; orlando journal; (b) (6); Letters MSNBC; NY Times; Washington Post; H Times4; NY Times1; PBS PBS
Subject:	FDASIA Law 2012 = Sarepta and Eteplirsen = Breakthrough Therapy
Date:	Friday, June 03, 2016 9:29:58 AM

FDASIA gives FDA a new and powerful expedited drug development tool, known as the breakthrough therapy designation. This new designation helps FDA assist drug developers to expedite the development and review of new drugs with preliminary clinical evidence that indicates the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases. (quoted from FDA website)

From: (b) (6)
To: Woodcock, Janet
Subject: Devastating news from Biomarin
Date: Friday, June 03, 2016 9:55:07 AM

Janet,
Sorry to keep bugging you. I am devastated at the news that Biomarin is now scrapping Drisapersen. Mary called me at Biomarin and explained in the US it's because they cannot do another blinded placebo control trial since there are no more patients available for exon 51 in the US with two drug companies. That is a legitimate problem for both companies to do that at this point. However, I still believe that when more American's get to 96 weeks on Drisa, there will be more (b) (6) out there. It's a miracle that he now presents as Becker. I beggec (b) (6) to at least keep the boys on drug through the summer to see if the trend repeats which I strongly believe that it will. Then she told me that in EMA they are concerned about the 2% that have SAE's. I think any and all drugs will have a small percentage chance of something bad happening. However, we are willing to take the risk. That is a poor reason to deny a drug if you ask me. Also, I told her that there is a genetic test for low blood platelets that can be performed ahead to see if you are predisposed to getting that and then those boys just get denied access. To me that seems like a simple answer. I heard that there is 10 years supply of drug left so I hope that the boys will get to keep the drug. It would be so cruel for the ones who got better on the drug to lose it. If there is anything you can do to help us work something out to save Drisapersen's future, that would be most appreciated. It's a big blow to the community.

Meanwhile, my son is declining rapidly off HT-100 for 5 months now and it's heartbreaking to watch him lose function each day. We are desperate to get our drug back. I've heard that the results were inconclusive so I hope the next FDA and Akashi meeting will be fruitful so that we can work something out to get us back on drug soon. I had always thought that Halo and Drisapersen together would make an great treatment for Duchenne. One repairs muscle and the other stops it from breaking down again. I sure hope that we can find a way to get both these drugs back on track.

Best Regards,
(b) (6)

From:	kim danboise
To:	Commissioner FDA; Temple, Robert; Woodcock, Janet; Farkas, Ronald; christine@jettfoundation.org
Subject:	Farkas/dystrophin/eteplirsen
Date:	Tuesday, June 07, 2016 8:56:41 PM

Dear Dr. Califf: This is what most scientist believe, FDA needs to clean house at DNP.

% Percent of Normal....

I've read the debate of quantified dystrophin as % of normal and it is stupid. Comparing DMD exon 51 WB measurements to normal boys is preposterous especially considering no one knows at what level increase results in a clinical benefit. The only human data that supports a measurement with clinical benefit is Sarepta's WB of 0.9% of normal. The only way to conclude anything is to compare dystrophin measurements to baseline and try and correlate increases in physical clinical functions like 6MWT etc. Anyone that places any weight in Farkas's analysis and/or knowledge of DMD pathophysiology is delusional. Sorry for being so harsh but I can't take it.

From: (b) (6)
To: Woodcock, Janet
Cc: Unger, Ellis; Temple, Robert
Subject: Video
Date: Wednesday, June 29, 2016 10:56:50 AM
Attachments: IMG_0783.MOV-1.mov

Hi Janet,

As I mentioned, I was able to spend a few minutes talking with Dr. Unger at DIA yesterday. During our conversation, we explored ways to capture meaningful PRO data. Dr. Unger was extremely helpful in reminding us that PRO's can be helpful when they capture what is "meaningful" to the patient.

I took the liberty of showing him a recent video of (b) (6) As I reported to Dr. Unger, I ask (b) (6) to raise his arms to the ceiling EVERY morning. It is part of our stretch/exercise routine. Two weeks ago, (b) (6) did something with his right arm (only) that he has NOT been able to do since he was ~ 15 years old.

I was shocked. This is 18 months after starting treatment, this tells me that it may take longer to see the clinical benefit, but as Dr. Temple would say - it appears "reasonably likely".

Attached is the video.

(b) (6) asked me to order a trapeze for his bed - he is hopeful it will help him reposition himself in bed.

--

(b) (6)

From:	kim danboise
To:	Commissioner FDA; Temple, Robert; Woodcock, Janet; christine@jettfoundation.org
Subject:	Eteplirsen
Date:	Thursday, June 30, 2016 6:59:07 PM

Dear Dr. Califf: Has FDA become so arrogant, callused, self centered, its just become another branch of the police. The" us against them" mentality was obvious at the adcom and sets a dangerous precedent for a organization that is supposedly science based. Everyone involved in the "science" and treatment of the disease has seen the same data DNP has seen and came to a very different conclusion.

Its time for someone at the FDA to get a handle on the situation, this ridiculous joke of a review has turned into a sick fight over who's the boss.

Sincerely,
Kim Danboise

From: (b) (6)
To: Woodcock, Janet
Subject: (b) (6) veins
Date: Friday, July 01, 2016 7:27:03 PM

Hello Dr Woodcock,
I had a conversation with Dr Jeff Chamberlain yesterday, the man who spoke at adcom about how dystrophin positive fibers have a protective effect on the surrounding negative fibers. He spent quite some time on the phone with me explaining how the processing of muscle tissue for western blotting makes it likely that existing dystrophin is damaged and unquantifiable. He was extremely concerned about the possibility of underestimation with a total reliance on western blot.

On another note, we've just returned from infusion, where it took seven tries to find a vein. Needless to say, we are both pretty traumatized. I'm well aware that you can't tell me anything on timing, but please hurry. Neither (b) (6) not myself can tolerate this kind of limbo much longer.

Thank you,
(b) (6)

Sent from my iPhone

From: (b) (6)
To: Woodcock, Janet
Date: Sunday, July 03, 2016 1:49:54 PM

Dear Ms. Woodcock,

I am writing you on behalf of my son, (b) (6) He is (b) (6) years old and one of the original 12 participants. As I am sure you know, we are anxious for the FDA's determination on the approval for Eteplirsen. We pleaded to the advisory committee along with the others on the benefits we have witnessed. At the age of (b) (6) he is still able to walk independently, which I am sure wouldn't be the case if he wasn't on Eteplirsen. More importantly, his heart and lung functions are normal. There has not been any negative effects from this, only benefits. Each day that passes for this decision, we are losing more boys to this dreaded disease. This decision is a matter of life and death. Those are (b) (6) words, not mine. Those are tough words to hear from your child, thoughts no child should even have to think about. We need approval so our son's heart and lung function can continue to be stable and want others to be able to experience the positive effects of this medication.

Kindest regards,
(b) (6)

Sent from the all new AOL Mobile Mail
Get Outlook for iOS and Android: mail.mobile.aol.com

From: Gloria Orozco
To: Woodcock, Janet
Subject: Decision on Eteplirsen
Date: Sunday, July 03, 2016 2:02:38 PM

Dear Dr. Woodcock:

We anxiously await the FDA's decision on eteplirsen and appreciate the fact that you requested and are reviewing additional biopsies from the confirmatory study in order to reach a final decision.

If these additional biopsies show an increase in dystrophin, that finding -- in concert with all of the other data that has been presented -supports an accelerated approval for eteplirsen. The growing body of evidence on dystrophin indicates that even small amounts of the protein are associated with milder disease progression. Hence, even a small increase over baseline is reasonably likely to lead to clinical benefit.

We urge the FDA to assess the data in consideration of the complementary set of analytical methods needed to inform a complete picture of the change over baseline.The FDA's own dystrophin workshop on March 20, 2015 focused on three different ways to measure dystrophin, and the consensus from the experts was that all three methods are important indicators of dystrophin levels. Each measure plays an important role in dystrophin detection, and it is through all of the data that a true view to changes is understood.

For example, an exclusive focus on Western blot, which is the least sensitive measure, may not give an accurate depiction of the presence of increased dystrophin.

The question FDA needs to answer is whether there was more dystrophin after treatment. If so, then the drug is reasonably likely to lead to clinical benefit and should be approved.

Respectfully,

The Race to Yes
Parent Project Muscular Dystrophy
The Jett Foundation

Sent from my iPhone

From: (b) (6)
To: Woodcock, Janet
Subject: Letter from (b) (6), Mother of #2 (b) 204
Date: Monday, July 04, 2016 8:45:41 AM

Dear Ms. Woodcock

I hope you had a wonderful Independence Day. Coming back to work on the heels of what our forefathers gave to us, to work especially in your esteemed job in the FDA, must bring joy to your heart, knowing that like all the men and women that have fought to preserve our freedoms, you also are fighting for freedoms.

Your position with the FDA is critical to sustain quality and quantity of life for those needing new drugs. Plan and simply, you like our forefathers, preserve the future for generations to come.

I applaud that. I appreciate that. Thank you for the job you do in serving our Nation.

I am a Duchenne mom. You may or may not remember me. (b) (6) is our son, he is (b) (6) and is on Eteplirsen. You have heard from hundreds in our community over the last four years regarding the original Serepta trial for Eteplirsen. More recently, you heard my testimony at the FDA Adcom on 4.25.16 regarding my son in the 204 study.

I fully expected after the years of service our Duchenne boys have served for the FDA proving that Eteplirsen was safe, that May 26 our Nation would be celebrating the first approval of a Duchenne drug therapy. Yet as of today, there is nothing but silence with regard to the yes or no for the Serepta NDA for Eteplirsen.

This tears my core not just as a mother, or just as an advocate for Duchenne, but as a Citizen of the United States. Simply, my Government is failing not just my son, but thousands of boys that need this drug immediately.

I do liken having Duchenne with being at war. And in war there are many battles and hopefully some victories. There are Sargent's, Generals, leaders and followers. Typically you know your enemy. But in our case, I can't help but wonder if Duchenne is not our only Enemy. I think too, you and your staff have fallen into the silent darkness of the shadows, just on the sideline of the enemy (ref: Farkas). Your silence and inaction to approve this safe and effective drug makes it clear you're not on the side of life. Add to the fact your demand for a 96 week placebo for 45 and 53..... absolutely tortuous to give a Duchenne boy saline for 96 weeks just to satisfy your checklist.... Certainly you are hiding in the shadows and certainly you by all fronts are appearing as the enemy.

Circle back to Independence Day. Can you imagine if all of the red tape, bureaucracy and government shadows existed as we fought as a Nation for our Freedoms? We'd certainly not be the nation we are today. I'd have to imagine, back in 1776 people did what they said they would do and then they did it. That is how things got done.

I am disheartened, angered, confused and beyond lost in the faith that I once had in you.
Yes, Janet.
You.
You have the ability to rise above the nonsense and stop delaying dystrophin in our boys every single day. And yes, that is what you and your staff are doing, you are destroying our boys by enabling Duchenne to win the war.

Your staff member, Mr. Farkas, made it very clear at Adcom that he would be ignoring science. His statement of opinion (Not Scientific fact) that if Duchenne Boys Tried Harder they could Walk Longer and if Duchenne Boys Just Put Their Mind To It they could walk longer to hundreds of Duchenne families, who live with this killer every day, was not only irrational and irresponsible but deplorable. Then turning on a question parents answered at their son's age of 4 that a Yes or No question could never be validated because of course there is no science behind a child walking at 4 years of age and of course, us Duchenne parents are not smart enough to truly know if he was walking. I am enraged that you allow your staff to act like this in public, let alone in deciding the fate, or rather the life, of thousands of boys. Based on what? Opinion.

Certainly, Mr. Farkas is leading this war against our boys. And even worse, my tax dollars are paying him to do so. We've lost so much of what our Forefathers wanted for our Country. And still, silence.

Eteplirsen produces Dystrophin and even more it produces enough Dystrophin for (b) (6).

It is Safe, (b) (6) has been on this for 65 weeks and has had ZERO negative side effects.
(b) (6) is doing things he STOPPED DOING prior to being on Eteplirsen. Fact not Farkas Opinion and Fact not because he tried harder or put his mind to it. If you know anything about Duchenne, you know it is a muscle killer despite how many mind tricks you play on it.

I get that (b) (6) is 1 person, and does not fit nicely into your mold of trial participants in the 1,000s.

I do no not understand why you and your staff want to slip deeper into the shadows and become the clear enemy.... Isn't it 'We the People"?

I just do not understand. I will be praying that the shameful disregard of life you and your staff continue to display will somehow, someway be removed and that you will stop this war on our kids and do what is right.

Say yes to Science. Say Yes to Eteplirsen.

(b) (6)

Mother of (b) (6)
#(b) (6)Serepta 204 (b) (6)
7.4.16

www.joainc.org
Don't let Duchenne derail another boy's life
Stop Duchenne, in it's tracks

Join Us in our Many Events to Derail Duchenne http://www.joainc.org/events.html

Make your life one that is meant to shine

From: (b) (6)
To: Woodcock, Janet
Subject: Eteplirsen Approval
Date: Monday, July 11, 2016 11:33:51 AM

Dear Janet,

My name is (b) (6) I live in (b) (6) and I am the Mother of 2 boys with Duchenne Muscular Dystrophy, (b) (6) and (b) (6). I first reached out to you in November of 2014 in regard to Eteplirsen.

My sons are among the 13% of those with Duchenne, that are amenable to Exon 51 skipping and therefore would benefit from Eteplirsen. My older son (b) (6) and I (along with my husband and several other family members) were in attendance for the Adcomm on April 25, 2016. My husband I stood up and spoke before the Committee. As you could imagine, we were devastated to find out that the Committee's overall vote was not in favor of accelerated approval. We felt a second devastating blow, when we discovered that we would not get our answer by May 26th, as we were originally told. It is now July 11th and we are still waiting!

I have recently noticed a major decline in both of my sons' ability to lift their arms. (b) (6) has really been struggling lately. As you know, there are older boys on Eteplirsen, (b) (6) and (b) (6) whom you are aware of, who's arm strength has not just been stabilized but actually improved! Knowing that there is a drug out there that can not only stabilize function but improve it, yet I cannot gain access to it for my children is beyond heartbreaking. If my sons don't get this drug soon, they will loose arm function. Can you imagine your child not being able to hug you?

We know this drug is SAFE and EFFECTIVE. We know it has the potential to save lives! Though I sincerely appreciate the FDA's careful consideration for the approval of Eteplirsen, I respectfully ask you....Where is the drug? What are you waiting for?

I know this, my sons will DIE if they don't get Eteplirsen. (b) (6) is (b) (6) and (b) (6) is (b) (6) WE ARE RUNNING OUT OF TIME!!! Please do the right thing and approve Eteplirsen. The time is NOW!

Sincerely,

(b) (6)

I have attached a picture of (b) (6) and (b) (6)

From: (b) (6)
To: Woodcock, Janet
Cc: Elnabarawy, Tamir (Tamir.Elnabarawy@mail.house.gov); (b) (6)
Subject: RE: Could the refuse to file Ataluren be a type two error? Our son (b) (6) 8 year experience on this drug
Date: Monday, July 25, 2016 10:35:04 AM

Dear Dr. Woodcock,

Thank you for your response. I am very happy to share that the UK has approved Ataluren/Translaurna and this drug is currently available to DMD patients in over 25 countries outside of the US.

Thank you for your commitment to take these issues very seriously. The public and the DMD community is very concerned with yet another refuse to file by the FDA of a drug that is safe and is effective. http://santhera.com/docs/default-source/2016/2016-07-14_pr-regulatory-update_e_final.pdf?sfvrsn=4

I would very much appreciate if you could clarify this issue. It seems to me that the DNP has turned the standard of safety and efficacy on its head. Most people believe the standard for drug approval as stated by Dr. Mitchel Mathis, the Director of the Division of Psychiatry Products, who wrote in the case of pimavanserin that if a "… drug is completely without safety signals, then we need not spend too much time defining clinical meaningfulness because benefit, however small, outweighs zero risk, and even a small benefit in a disabling disease is valuable."

Compare that statement to what Dr. Farkas says is the standard for approval at the Division of Neurological Products: "Although approvability of a drug reflects a benefit-risk assessment, the decision about approvability is necessarily stepwise, requiring first that the drug be found effective, prior to consideration of benefit-risk."

For Dr. Mathis, the evidentiary standard of proof increases with the safety risks of the drug. In other words, efficacy does not have to be proven beyond a reasonable doubt in the case of a drug that is safe because a benefit however small outweighs zero risk. In contrast, Dr. Farkas requires all drugs to be proven effective beyond a reasonable doubt regardless of their safety profile.

This is of great concern to the DMD community that the evaluation of new drugs especially for a rare lethal diagnosis is not consistent at the FDA and is not following PDUFA and FDASIA. That the standard of proof required to approve a new drug varies so much between these two Divisions. If this process is to have integrity, the FDA must apply the rules for drug approval consistently. Therefore, Dr. Farkas and Dr. Mathis cannot both be right. The

FDA needs to clearly say whether it is Dr. Mathis or Dr. Farkas who has stated the correct evidentiary standard for drug approvals.

In the case of Ataluren, the FDA refused to allow the company to file for approval. The drug has a clean safety profile, had it been reviewed by the DPP, it would have been accepted because Dr. Mathis' standard of proof would have been used. However, since the drug is before the DNP, then Dr. Farkas' standard of proof is what was used to justify the refusal to file.

My understanding is the one of the reasons for the refuse to file is potential abuse this drug. We know this drug has a very narrow therapeutic window so why would anyone give their child a larger dose? In addition this drug will be very expensive and no one could afford to abuse it. So frankly this doesn't make any sense.
We know the drug works in a prespecified FDA approved trial of a 47 meter difference over the placebo group. In the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA). There is one paragraph I would like to bring to your attention:

"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."

The statute clearly says that accelerated approvals do not have to rest solely on evidence from adequate and well-controlled trials.

Lastly, you may want to see these recently published articles on boys on this drug.

http://www.parentherald.com/articles/55996/20160720/family-affected-by-rare-form-of-childhood-muscular-dystrophy-hoping-for-a-treatment.htm
http://themighty.com/2016/07/advocating-for-treatment-for-duchenne-muscular-dystrophy/

Thank you for your commitment for a fair review of this drug for our sons!
Respectfully yours,
(b) (6)

From: Woodcock, Janet [mailto:Janet.Woodcock@fda.hhs.gov]
Sent: Tuesday, July 19, 2016 1:57 PM
To: (b) (6)
Subject: RE: Could the refuse to file Ataluren be a type two error? Our son (b) (6) 8 year experience on this drug

Thank you for writing and sending the picture of (b) (6) I enjoyed your comments at the Advisory Committee meeting.

I will definitely take your points into account. I have spoken to Rep. Peterson recently, and also given him my commitment to take these issues very seriously.

I hope (b) (6) continues to do well. Janet Woodcock

From: (b) (6)
Sent: Tuesday, June 21, 2016 4:14 PM
To: Woodcock, Janet
Cc: (b) (6)
Subject: Could the refuse to file Ataluren be a type two error? Our son (b) (6) 8 year experience on this drug

Dear Dr. Woodcock,
I had the privilege to visit with you as a member of the recent Eteplirsen advisory committee. Thank you for attending the meeting and for your concern for boys with Duchenne. I truly appreciated your comments on the flexibility of the FDA and the explanation of a type-two error (b) (6) at the FDA may make. I am writing you with my grave concern a Type 2 error will be made by the FDA in regard to the drug Ataluren and we will lose this generation of Duchenne boys with a premature stop codon. If you see the attached poster, you will see that there will be unnecessarily deaths as this drug is safe and it works. I will share our firsthand experience with this drug.

I've attached a photo of our son (b) (6) who has been on Ataluren for over (b) (6) years with no side effects. When the trial was stopped and he was taken off the drug a few years ago, he had a very fast decline. When he started back on the drug he appeared to stabilize and it has definitely slowed down his deterioration. (b) (6) will be (b) (6) years old in October. His PFTs are still in the low normal range and his ejection fraction is 50. He recently graduated from college with a degree in social work and will be doing an internship in the (b) (6) Governor's office to hopefully work on health care policy. All of the boys he went to MDA camp with are now dead. Other friends with Duchenne who are his age are on a ventilator. The only reason (b) (6) is doing this well is due to Ataluren. This drug is safe; (b) (6) had no side

effects.

Given the FDA's recent ruling to refuse to file Ataluren, I am very concerned the drug will be pulled. As you know, this ruling is currently in the appeals process. There are no other drugs in the pipeline that will get here in time for (b) (6) and this generation of boys. This Type 2 error will mean these boys will see an early death. I am convinced that the drug is helping (b) (6) and all the other boys on this drug. I have seen firsthand the rapid decline in boys who have gone off the drug. I believe it is totally unfair to the boys on Ataluren, and to the boys that are waiting for the chance to try Ataluren, not to give a more thorough hearing to the data in hand. The FDA decision to not allow PTC Therapeutics to file their data package for review and possible hearings is enormously frustrating given that PTC Therapeutics has by far the most compelling data to consider.

More than ten years after the Ataluren trial was started we have learned so much more about trial design, however, I believe this was not taken into consideration when the FDA reviewed this drug. I also saw this problem when I participated on in the Drisperson advisory committee. When there is a problem with trial design then there also is a problem with the guidance the FDA provided the company for the past decade. I fully believe the drug companies and the FDA have done the best they can with the data available at the time these trials were developed. If we now know a better trial design it should not have an adverse effect on these boys who have sacrificed so much and have no other hope to live. I do not feel the FDA reviewers have fully considered what it takes for the boys to participate in these trials and the toll on a family who most often has other children and are trying to live normal lives in spite of this deadly diagnosis.

The underlying problem we now know that has hampered the development of both exon skipping and nonsense suppression is the outcome measure that is being used as the primary endpoint. The 6-minute walk test (6MWT) is being evaluated in patients that have too little muscle in their thighs to have major benefit from any type of therapy. This was not apparent at the time that drug development in DMD began, but has become clear during the last 3 years because of the MRI natural history study that is currently being done at University of Florida. In general, boys who walk less than 300 meters in the 6MWT have lost the majority of their muscles in the thigh that serve such functions as running, climbing stairs, and getting up off the floor. What was not known 10 years ago is how little muscle is needed to allow the boys to continue to walk. It is now clear that therapies that use walking as the primary endpoint need to enroll patients with >300 meter walking ability at baseline. Boys walking less than this have a high probability in losing ambulation in under a year because they have lost more than half of the muscles involved in ambulation in the thigh. In essence they are fragile walkers with too little muscle to rescue to prevent further decline. It is likely that they become relatively inactive and that ambulation is an occasional activity, which will drive a rapid decline by coupling disuse with dystrophy. It is not that these boys cannot benefit from Ataluren. It does preserve arm and respiratory function, but it is too late to save ambulation in these boys.

Because of this, the trials should have been focused on boys walking greater than 300 meters. The problem is that the companies do not want to conduct multi-year trials, so they don't want to enroll boys walking more than 400 meters, since natural history suggests that they will likely be stable or even improve their walking over the next year. The MR studies reveal that they are losing muscle during this time, even though their 6MWT times are either improving or stable, further underscoring the difficulty of using the 6MWT as a primary endpoint for DMD. What you are left with is a narrow recruitment window (300-400 meters baseline) if

the goal is to show an effect on the 6MWT in a one-year treatment period. The boys who ultimately will benefit the most are the ones who have the most muscle, but their decline in 6MWT times will be years away in the absence of drug.
The data that PTC does have with Ataluren in the 300-400 meter baseline 6MWT is compelling and was shown in two separate trials. Importantly, PTC pre-specified that this group would be one that would likely show benefit. One can make the case that this is the population that truly reveals the potential of the drug that will take years to show if given to younger patients with walking used as the primary outcome measure. This effect of Ataluren in this subpopulation clearly deserves more discussion by the FDA and the DMD community as the possible basis for drug approval.

Recently I visited with U.S. Rep. Collin Peterson, who authored the MD-Care Act after he met (b) (6) many years ago. He and his colleagues who worked on this legislation have serious concerns that the FDA is not following legislative intent in using the flexibility that was given in FDSIA. I strongly believe the FDA needs to take in consideration the challenges with conducting trials in a rare disease where we do not completely understand the natural history and therefore how to design trials.

Not only is there a need to be flexible in interpreting the trial results in this patient population but also a need to incorporate all available scientific information on the disease as it becomes available. What attempts to be flexible in this case have been made? I urge you to reconsider and allow PTC Therapeutics to file and have a public hearing of their data. In fairness to the patients, there needs to be a public discussion involving the scientific and patient community of the data and its interpretation. Even if a public hearing does not alter your eventual decision, I think that a public discussion of the limitations of the 6MWT and how it is applied to DMD is critical to prevent more companies from failing because of trial design and not because of lack of drug effect. For this reason alone, I think you should rethink granting PTC a public hearing. Otherwise my fear is that companies will stop entering the DMD space since they will feel that we do not know how to design an effective trial and there will be an outcry from the community. I know you want to do what is best for our sons. The depth of my appreciation for your help is the depth of my love for our son.

Respectfully yours,
(b) (6)

From: [redacted] (b) (6)
To: Woodcock, Janet
Subject: FDA decision for Sarepta Therapeutics Eteplirsen
Date: Thursday, July 28, 2016 11:39:08 AM

Dear Ms. Woodcock,

I thank you in advance for your time in reading this short note.

I appreciate and respect the many decisions the FDA is tasked with on a daily bases, however, I wanted to know if you have any insight you can share as to why it is taking so long to facilitate a "prompt decision" from the FDA, as mentioned in a press release from Sarepta Therapeutics dated June 6, 2016, in regards to the FDA request for additional dystrophin data from the thirteen patient biopsy samples at baseline and week 48.

It has been nearly 8 weeks since this June 6, 2016 press release and there is still no decision from the FDA on this NDA.

Thank you again for your time and I look forward to your reply.

Best Regards,

Djahanguir Irannejad
Investor

From: Wolman, Alan
To: Woodcock, Janet
Subject: Sarepta
Date: Tuesday, August 02, 2016 4:41:20 PM

Dear Dr. Woodcock,

Would it be possible to provide even a small hint as to the seemingly endless delay on a decision on Eteplirsin?

Sincerely,

Alan Wolman

Alan C Wolman
Senior Vice President/Investments
Stifel Nicolaus & Company Inc.
(b) (6)

From: Don Seiffert
To: Woodcock, Janet
Subject: Anything to say to the Duchenne community?
Date: Wednesday, August 03, 2016 12:29:00 PM

Hello Janet Woodcock —

I am writing another update (for the Boston Business Journal) on the wait for a decision on approval of eteplirsen, now a couple months past the latest PDUFA date and half a year since the original PDUFA date in February.

As you well know, the community is waiting for this drug, parents are waiting (in some cases) on starting trials of other drugs for Duchenne until a decision comes down for this one. Is there anything you can say on the record as to the cause for the ongoing delay? Please let me know. I can talk directly at (b) (6) .

Don Seiffert
Life Sciences Editor
Boston Business Journal
617-316-3271
dseiffert@bizjournals.com

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From: "Woodcock, Janet" <Janet.Woodcock@fda.hhs.gov>
Date: Friday, June 3, 2016 at 3:12 PM
To: Don Seiffert <dseiffert@bizjournals.com>
Subject: RE: Question regarding Compassionate Use policy and Sarepta

Sure. No link between review of NDAs and the access (as we call it) policy. And actually this is just a new form. jw

From: Don Seiffert [mailto:dseiffert@bizjournals.com]
Sent: Friday, June 03, 2016 3:12 PM
To: Woodcock, Janet
Subject: Re: Question regarding Compassionate Use policy and Sarepta

Thank you so much Janet. I will likely post a short story on this citing you soon.

Don Seiffert
Life Sciences Editor
Boston Business Journal
617-316-3271
dseiffert@bizjournals.com

From: James Gelb
To: Woodcock, Janet
Date: Thursday, August 04, 2016 12:59:10 PM

Hi Dr. Woodcock,
After reading Boston Captain's article today in Seeking Alpha, it brings me back to my comment to you the other day that Farkas is an evil egomaniac. It keeps me up at night thinking about the rumor that Farkas said, "Eteplirsen will get AA over my dead body" to Garabedian. Is there any way to confirm this? Once again, Farkas and others like him are cancers that need to be eradicated from your agency with extreme prejudice. Thanks for listening.
-Jim

Sent from my iPhone

From: "Woodcock, Janet" <Janet.Woodcock@fda.hhs.gov>
Date: Friday, June 3, 2016 at 12:57 PM
To: Don Seiffert <dseiffert@bizjournals.com>
Subject: RE: Question regarding Compassionate Use policy and Sarepta

There is no connection between the "Compassionate Use" Policy form and any review activity. These access programs have been in place for decades, all the agency was doing was announcing a streamlined form to use—which is great, but doesn't change any underlying policy. So these regulations on expanded access have been on the books for a very long time. jw

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From: Don Seiffert [mailto:dseiffert@bizjournals.com]
Sent: Friday, June 03, 2016 12:45 PM
To: Woodcock, Janet
Subject: Question regarding Compassionate Use policy and Sarepta

Hello Janet Woodcock —

I'm the life sciences editor fro the Boston Business Journal, and I'm writing regarding the timing of the Compassionate Use policy this week and the resulting speculation about how it affects Sarepta Therapeutics' chances of drug approval in coming days/weeks.

I assume you are familiar with the speculation that the policy was timed to come out so that if the FDA gives eteplirsen a CRL, this would provide a way for patients to possibly receive the drug regardless. Could you clarify either in an email or in person by phone today whether there is any connection between the timing of the events? I think a short story would make sense given the speculation and resulting stock decline at Sarepta.

Please let me know if that's possible & I appreciate your consideration.

Don Seiffert
Life Sciences Editor
Boston Business Journal
617-316-3271
dseiffert@bizjournals.com

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Temple, Robert

From: Pat Furlong <Pat@parentprojectmd.org>
Sent: Thursday, August 11, 2016 11:27 AM
To: Woodcock, Janet; Dunn, Billy; Unger, Ellis; Temple, Robert; Bastings, Eric
Subject: requesting your help
Attachments: JW.paf.8.11.16.pdf

August 11, 2016

Janet Woodcock, MD Director,
CDER U.S. Food & Drug Administration
10903 New Hampshire Avenue
Room 6133 Silver Spring, MD 20993

Dear Dr. Woodcock:

On behalf of Parent Project Muscular Dystrophy (PPMD), I am writing to request that the FDA take any steps possible to provide an update and clearly communicate the status of various regulatory actions of tremendous importance to the Duchenne community.

As you know, our families are experiencing an unprecedented series of challenges related to potentially conflicting information about the Duchenne therapy development pipeline. We appreciate everything that you and your colleagues have done to engage our community in this process. Nevertheless, several critical issues are unresolved at this time, with potentially dire consequences for our community.
Specifically, we need your assistance to bring greater clarity and consistency to a process that at times appears confusing to many. We recognize that each candidate therapy is reviewed on its own merits and respect that there is a commitment to confidentiality. At the same time, families living with Duchenne face desperate unmet medical needs. We cannot sit back and assume that these regulatory decisions have fully taken parent and patient considerations into account without better information and more detailed explanations.

Our concerns revolve around a cascade of unfavorable and seemingly contradictory decisions over the last several months. First, we experienced the failure of Biomarin's drisapersen to gain market authorization without the opportunity to have a formal benefit/risk analysis within the review documents by the agency. This was followed closely by the protracted and still ongoing technical scrutiny of Sarepta's eteplirsen in the wake of an unprecedented Advisory Committee experience for our community. We have also witnessed the refusal to file decision against PTC's ataluren (Translarna) which would deny that potential therapy its opportunity for a completed review, and finally the denial of an accelerated approval pathway for Santhera's idebenone, which met its primary endpoint in their clinical trial. In aggregate, these actions have left the Duchenne community greatly concerned about the consistency and transparency of the FDA approval process.

Again, we appreciate the fact that the FDA is making unprecedented efforts to consider the patient perspective in conducting these life-changing decisions. Our request to you now is to move even more completely in this direction by fully explaining these reviews with the insight and authority that only the FDA can bring to our families.

Thank you for considering this request. We are anxiously awaiting your reply and stand ready to provide any assistance that would be useful.

Sincerely,

Pat

cc:
Eric Bastings, MD
Billy Dunn, MD
Robert Temple, MD
Ellis Unger, MD

Pat Furlong
President & CEO

EndDuchenne.org Parent Project Muscular Dystrophy

401 Hackensack Avenue, 9th Floor
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t. 201-250-8440 f. 201-250-8435
ParentProjectMD.org :: DuchenneConnect.org :: RunForOurSons.org :: CoachToCureMD.org

Connect with the Duchenne Community!
Community.ParentProjectMD.org :: Facebook.com/ParentProjectMD :: Twitter.com/ParentProjectMD

From: Christine McSherry
To: Ed Kaye
Cc: Woodcock, Janet; Stuntz, Grace (HELP Committee)
Subject: Request for DATES and DATA
Date: Monday, August 15, 2016 12:57:35 PM

Dear Dr. Kaye:

We are writing today to seek confirmation that Sarepta has submitted all of the data requested by the Food and Drug Administration (FDA) to complete its review of eteplirsen.

We understand the FDA requested that Sarepta provide dystrophin data, as measured by western blot, from biopsies already obtained from the ongoing PROMOVI confirmatory study of eteplirsen. According to the company's June 6 press release, the company indicated plans to submit the data to the FDA "over the coming weeks to facilitate a prompt decision...by the Agency."

Today marks nearly 3 months since eteplirsen's revised PDUFA date of May 26 th , and more than 10 weeks since the company's announcement about providing additional data. Unfortunately, our community is still anxiously awaiting a decision on FDA approval for eteplirsen.

We respectfully request confirmation that Sarepta has submitted the data requested by the FDA, and the date by which it was submitted.

In addition, we encourage Sarepta to release the formal communications the company has had with the FDA, including meeting minutes, letters, and other similar documents, as well as any other documents, data, presentations, or other materials that support the eteplirsen's NDA.

Thank you for your ongoing efforts to gain FDA approval for eteplirsen.

Sincerely,
Christine McSherry

--

Making...TODAY COUNT - TO CHANGE TOMORROW

Christine McSherry, RN

The Jett Foundation
68 Evergreen Street, Suite One
Kingston, MA 02364
(781) 585-5566
FAX: (781) 585-5233
CELL (b)(6)
jettfoundation.org

From: alan wolman
To: Woodcock, Janet
Subject: Sarepta
Date: Thursday, August 18, 2016 10:32:29 PM

Dear Dr. Woodcock,

Don't you think this nonsense has gone on long enough?

Stop the torture already.

Sincerely

Alan Wolman

http://www.bizjournals.com/boston/blog/bioflash/2016/08/sarepta-trial-patients-respond-to-placebo-effect.html?ana=twt

From: (b) (6)
To: Woodcock, Janet; Commissioner FDA
Subject: (b) (6) still walking after 5 complete years on Sarepta"s Eteplirsen
Date: Friday, August 19, 2016 2:38:56 PM

Drs. Woodcock & Califf,

On Wednesday, (b) (6) officially started his 6th year in Sarepta's Eteplirsen trial. (b) (6) will turn 16 on (b) (6)

It's truly amazing to watch his steady gait and pace after his completion of infusion on Wednesday. Many noticed that his heels are still close to the ground after 5 years on the drug. Dozens of parents are commenting that he walks as well as their 6 and 7 year olds while most are commenting that their sons never walked past 11 and 12.

I wanted you both to see and observe and please understand that even with less than 1% dystrophin produced, this is the effect that even a small amount of dystrophin adds to our boys' quality of life. The boy and neighbor friend walking with (b) (6) is one year younger than (b) (6)

Eteplirsen works and preserves ambulation and so much more--here is more proof in this video without any motivation or encouragement from mom. (b) (6) continues to walk in and out of (b) (6) every Wednesday.

More patients deserve the help that this drug can provide without any serious safety issues. This should be the quintessential example of risk vs benefit in a drug.

This laughter should continue and not questions such as "will I become paralyzed without my Eteplirsen drug", that he asked me Wednesday evening.

Respectfully,

(b) (6)
(b) (6) mom

Sent from my iPhone

From:	kim danboise
To:	Commissioner FDA; Temple, Robert; Farkas, Ronald; Unger, Ellis; Bastings, Eric; Woodcock, Janet; Jenkins, John K
Subject:	Eteplirsen
Date:	Sunday, August 21, 2016 6:55:31 AM

Dear DR. Califf: No effect? Really! 5 years later still walking. Morons each and every one of you.

Sincerely,
Kim Danboise

(b) (6) health had been declining rapidly in the months before the trial started, said (b) (6) in an interview last week. "We had noticed things were getting harder for him and he was making compensations for things," she said.

No one knew at the time whether (b) (6) was being infused with the actual drug or with a placebo. But within a couple of months, (b) (6) started to have suspicions. She remembers watching her son come home from the fourth grade and jump into the pool rather than sit and rest.

"It was not right away. But in a couple months, I would see a real boost in energy for him," she said. "I would be like, 'There's something going on.'... in the back of my head, I said, 'I think he's on the medication.'"

(b) (6) learned in the spring of 2012 that (b) (6) had indeed been in the arm of patients who received eteplirsen. He has continued to receive the drug once a week, as the company that developed the drug extended what was initially a six-month, placebo-controlled trial into an open-label one that has lasted five years as of today.

From: James Gelb
To: Woodcock, Janet
Date: Thursday, August 25, 2016 11:30:33 AM

One more question Dr. Woodcock:
What is the latest date that Farkas and /or Bastings could have filed their DPO? Thanks.
-Jim

Sent from my iPad

From:	kim danboise
To:	Commissioner FDA; Temple, Robert; Woodcock, Janet; Jenkins, John K; Farkas, Ronald; Bastings, Eric; Unger, Ellis
Subject:	eteplirsen
Date:	Friday, August 26, 2016 6:42:50 AM

Dear DR. Califf: Nothing DNP says has any validity after the fiasco that was eteplirsen's adcom. DNP lied, falsified data presentations and turned the adcom into a dog and pony show. They should all be fired.
Sincerely,
Kim Danboise

docs.google.com/document/d/141...

From: (b) (6)
To: Woodcock, Janet
Subject: (b) piece
Date: Sunday, August 28, 2016 6:39:52 PM

Hi Janet
I wanted to touch base and share with you this sweet piece that (b) (6) aired today on rare disease. The boys are featured quite prominently and I think (b) (6) did a nice job.
(b) (6) is in NYC this weekend with friends, traveling in a manual wheelchair, because at almost (b) (6) years old he has recovered some trunk strength and stamina enough to be able to hold himself up, and enjoy a road trip from (b) (6) to the city, while other (b) (6) yrs olds are in the end stages of Duchenne, after almost 2 years on eteplirsen, (b) (6) is thriving and applying to colleges.

(b) (6) is starting (b) (6) th grade this week, on his feet, with only occasional use of a scooter when distance is involved. Today he ran and jumped into our pool.
I want to continue to encourage you to do the right thing, and soon. It matters, kids are waiting and we need to move on to the next treatment in this Duchenne cocktail to keep my boys living normal, happy, productive lives.

Thanks so much, and enjoy this clip.

(b) (6)

Best
(b) (6)

Sent from my iPhone

From: Wolman, Alan
To: Woodcock, Janet
Subject: Eteplirsin status
Date: Tuesday, August 30, 2016 11:08:39 AM

Dear Dr. Woodcock,

The endless delays on approval of eteplirsin is truly unfortunate and bewildering. This is especially true since it is so clear to dozens of DMD experts, parents, and patients that the drug is safe and effective, and so clear how distorted and biased the FDA process has been to this point.

But what is even worse is the limbo - simply not knowing the status of what's going on. What is happening, how long will it take, when will we get an answer, etc. This is emotional waterboarding; the parents and kids deserve better.

There is simply no justifiable reason why the FDA cannot give an "update" regarding the current status of this submission. For that matter, there is simply no justifiable reason why this drug is not now approved and available.

Thank you.

Alan Wolman

Alan C Wolman
Senior Vice President/Investments
Stifel Nicolaus & Company Inc.
(b) (6)
[redacted]

From: (b) (6)
To: Woodcock, Janet; Commissioner FDA
Subject: (b) Sarepta 202 patient, briskly walking into 1st day of 10th grade
Date: Tuesday, August 30, 2016 8:47:05 PM

Drs. Woodcock and Califf,

I wanted to share this video of (b) (6) easily exiting my car, closing the car door, and briskly walking into (b) (6) school on his first day of the new school year yesterday. He is officially a (b) (6) As you will see, he still has a great steady pace and stable gait. He was an extreme toewalker prior to and at beginning of the trial but that has been reversed with his heels still remaining fairly close to the ground 5 years later. I never imagined that I'd witness him walking into his (b) (6) year of (b) (6) school. Of course, I attribute his continued stability and lack of major decline to his Eteplirsen drug.

As we are nearing 100 days since our delayed PDUFA date, parents' anger has escalated, and many are now grieving and distraught as their sons' have significantly declined and are now ineligible to qualify for future trials. Some may have written you. They are justified in asking to whom they should hold accountable for these many and lengthy delays that have caused irreparable damage to their children. The boys also continue to suffer and now must adapt to a new way of life without ambulation. This in addition to psychological fallout of not having access to a drug that they see having benefit and helping other boys. (b) (6) and the other trial boys continue to worry about their lives without this drug. I hope you can appreciate and understand the damage that would materialize if this drug is taken from our boys. In addition to the grief that our community must endure as they bury their sons, our community is in disbelief that a Duchenne drug has yet to be approved. (b) (6) drug, Eteplirsen, poses zero safety risks and our Duchenne experts in the scientific community can attest to without a doubt that Eteplirsen can reasonably predict clinical benefit. (b) (6) recent videos continue to clearly demonstrate this clinical benefit 5 years later. Furthermore, he's not the only trial boy walking through the front doors of (b) (6) school this new school year.

I sincerely hope that the agency does not commit a "Type 2 error". Eteplirsen works! Look at what .9% dystrophin production is doing for (b) (6) and the other boys. It is giving them a quality of life that we never expected to see at this age. More boys deserve this treatment. More boys deserve a better quality of life.

With Eteplirsen, I feel reassured and confident that I will witness (b) (6) walking (b) (6) . Please allow us to witness this miracle and please join us in (b) (6) as (b) (6) walks (b) (6) (b) (6) .

Respectfully,

(b) (6)
(b) (6) mom
(b) (6)

Sent from my iPhone

From:	kim danboise
To:	Commissioner FDA; Temple, Robert; Farkas, Ronald; Bastings, Eric; Woodcock, Janet
Subject:	Eteplirsen
Date:	Sunday, September 04, 2016 1:01:03 PM

Dear Dr. Califf: The boys at DMD are scientific morons or biased against a small trial approval which is it? Moeone each and every one of them.One such example is that Dr. Farkas asserted that findings of 25-50% dystrophin positive fibers originally reported by the sponsor in support of dystrophin induction are inconsistent with finding of .93 % of wildtype dystrophin protein expression and uses this argument to disqualify the strong scientific evidence provided in support of dystrophin induction. *"So this is the fourth biopsy results, and it's one of the most important slides that we're going to be looking at today. So instead of the expected 25 to 50 percent normal dystrophin, as was mentioned before, there was only 0.93 plus or minus 0.84 percent of normal dystrophin in the treated patients. This was measured by Western blot, the most accurate method of quantification used by the applicant. It seems concerning that the fourth biopsy result was so inconsistent with earlier results, and this appears to raise additional important questions and to highlight the need for independent confirmation of findings."* This makes little sense and demonstrates a lack of understanding of the core metrics used for quantifying dystrophin in muscle and relevance to the disease process. There is no expectation that the number of dystrophin positive fibers correlate with the overall percentage of dystrophin expressed relative to normal. Immunofluorescence is used to assess distribution of dystrophin across muscle fibers, and western blot to quantitate the overall level of dystrophin distributed within the whole muscle sample. It is entirely plausibly and somewhat expected that relatively low levels of dystrophin would be distributed across a limited subset of the fibers. Indeed, on average .93% of wild type dystrophin was distributed across on average of 15% of the muscle fibers. Similarly, Dr. Farkas argued that the data from the fourth biopsy could not be interpreted due to the lack of matched pre-treatment control samples for all but 2 patients. Pre-treatment biopsies from Promovi were run alongside three pretreatment biopsies from the 202 study. Given that the same three pre- treatment 202 patient samples were present in analysis of biopsies 1-3 and biopsy 4, these samples serve as an internal reference that should enable validation of the PROMOVI study pretreatment biopsies as typical of the original pre-biopsy cohort. The findings are interpretable and provide strong support for dystrophin induction in response to eteplirsen treatment.

In a second example, Dr. Farkas refers to a single recent CINRG publication authored by Dr. Craig McDonald erroneously indicating that it represents the best and most robust data available reflecting typical age at of loss of ambulation; and concluding that loss of ambulation in DMD often occurs at 16- 18 years. He persisted in that view despite clarification from Dr. McDonald and others that: the quoted 16-18 yr estimate was based strictly on 3 data points, that multiple available natural histories assessing much larger cohorts were available and are comparable to the clinical course of untreated external control group, with a mean age at loss of ambulation of about 12.5 years with steroid treatment. We note that the additional comparison based on LOA comparison with steroid treated/comparable mutation groups from DuchenneConnect further support that the 12 201/202 study participants are deviating from the expected disease course (independent analysis submitted to Dr. Woodcock in our email dated May 13. Dr. McDonald's data was also used to highlight apparent discrepancies between functional abilities measured by rise from floor data and 6MWT. When the sponsor asked that Dr. McDonald himself be able to explain his view that the FDA interpretation of the his study was not correct, the request that he clarify aspects of his own data set was denied by Dr. Alexander,

leaving stand an erroneous criticism that made the data seem less credible than it actually is.

In response to quantitative comparisons of clinical data, Dr Farkas stated "But as to your question of numerical comparisons, I mean, I think that's an important point that that's not the way we can analyze studies like this. This is just the truth about historically controlled trials. There's not really going to be an answer in the numbers because we have to account for these other sources of differences between the groups." This was a shocking comment. Perhaps this attitude, dismissive of a data-driven approach, is why data presented to contradict the efficacy of eteplirsen were not subjected to standard statistical analysis and rather presented as subjective data that for the reader/viewer to "eyeball". Similarly, these analyses made no attempt to match subjects for potential skewing imposed by the inclusion criterion.

From: (b) (6)
To: Woodcock, Janet
Subject: three Duchenne items
Date: Tuesday, September 06, 2016 2:05:22 PM
Attachments: (b) (6) tedx talk.png (b) (6)

Hi Dr. Woodcock,

I'm writing to you for three reasons. I'll briefly outline them here, but I welcome the opportunity to meet with you next Wednesday, Sept 14th to discuss them in more detail.

I'm sure you can guess at reason #1. It's 102 days past the PDUFA date for eteplirsen and our community is left in the dark. We are close to a boiling point. Families whose children can benefit from eteplirsen are in limbo, facing tough decisions about ports. In my case, this latest delay has meant three more months of shelf-time for the exon skipping drug that could help my son. (b) (6) turns (b) in November, a birthday I am not looking forward to in the absence of some progress toward helping him produce even a modicum of dystrophin to help prolong the muscle function he still has. He can't run or climb stairs, but a hug means the world to us. When 36 renowned experts agree that eteplirsen induces enough dystrophin to be reasonably likely to lead to clinical benefit, our community deserves to know why it is taking so long for the FDA to render a decision.

Reason #2: As you know, much more is at stake here than one drug or even one therapeutic approach. Multiple therapies for DMD are in clinical development. Our community is committed to making sure the actions of the Division of Neurology Products are based on sound science and thoughtful review that incorporate both real expert input as well as the patient perspective. Unfortunately, we do not have confidence that thoughtful review, sound science and meaningful expert input are key elements of the DNP's decision making process. For that reason, I would like to draw your attention to the attached document, the (b) (4) submitted to the DNP last week by Akashi Therapeutics (of which I am a (b) (6)). (b) (4) . I would greatly appreciate your review of this (b) (4) so you are aware of the situation while the DNP is considering the filing. On a personal note, my son (b) (6) was on the lowest dose of this drug for two years. He did not experience one negative side effect, and -- notably-- he remained stable from ages (b) (6) while on this experimental medication. Since the clinical hold was imposed in January of this year, he has experienced significant decline in speed and strength. Similar experiences are echoed by families who have written letters to Akashi pleading to restart dosing (included as an appendix in the filing).

Finally #3: I will be on Capitol Hill next Wednesday, Sept 14th for a speaking engagement before members of Congress and staff regarding innovation, drug pricing, and other issues critical to the rare disease community. I just wanted to give you a heads up that I will be speaking about our efforts. The DMD community is anxious to build a productive working relationship with the FDA, as we are committed to seeing multiple complementary therapies through to approval and commercialization. The time is now to transform Duchenne from an aggressive killer with zero treatment options to a manageable, chronic condition. We just need a little help from you to get that done. Please let me know if you are available at 9 am or after 2:30 pm next Wednesday.

My best regards,

(b) (6)

From: Tom Orsini
To: Woodcock, Janet
Subject: Re: Sarepta
Date: Thursday, September 08, 2016 5:25:52 PM

Hi Janet,

Thank you for your prompt reply.

Would you be able to nudge the FDA to come out with some sort of response regarding where things are at? I think many in the community are growing impatience with the lack of communication from both the manufacture and government.

> On Aug 22, 2016, at 1:35 PM, Woodcock, Janet <Janet.Woodcock@fda.hhs.gov> wrote:
>
> Unfortunately, we are not able to say anything about actions pending before the Agency (by law). Sorry I cn't be more informative. Janet Woodcock
>
> -----Original Message-----
> From: Tom Orsini [mailto (b) (6)]
> Sent: Monday, August 22, 2016 2:07 PM
> To: Woodcock, Janet
> Subject: Sarepta
>
> Hi Janet,
>
> When will the FDA come out a say if Sarepta's DMD product will be approved or denied? It's been quite some time since I have heard an update from your agency.
>
> Thank you for your help.
> Tom
>

From: (b) (6)
To: Woodcock, Janet
Subject: DMD
Date: Wednesday, September 14, 2016 7:42:29 PM

Please approve Duchenne drugs. My nephew, (b) (6), and all the other boys deserve all the help they can get.

God bless!

Sincerely,
(b) (6)

From: kim danboise
To: Commissioner FDA; Temple, Robert; Woodcock, Janet; Dunn, Billy; Bastings, Eric; (b) (6)
Subject: Damage/farkas
Date: Wednesday, September 14, 2016 8:48:15 PM

Dear Dr. Califf: It is nearly impossible to measure the amount of damage Ron Farkas did to the DMD community as a whole, Sarepta, and the FDA s reputation. Along with Erick Bastings and Billy Dunn this could not have been a bigger fiasco. He stunk and the rest of FDA stunk along side him for allowing the adcom and the Etep review to have ever happened as it did.

When government agencies act as DNP/FDA has the whole country suffers.

Sincerely,
Kim Danboise

From: (b) (6)
To: Woodcock, Janet
Subject: Re: three Duchenne items
Date: Thursday, September 15, 2016 9:23:05 AM

Hi Dr. Woodcock,

Thanks for your timely reply. Sorry mine is not so timely! I hope yesterday's ad comm meeting went well. While I was in DC yesterday I had a chance to catch up with Christine McSherry, and I wanted to let you know that we are working on constructive solutions to help DMD drug reviews go as smoothly as possible. As a community, we are lucky to have multiple drugs in clinical development, and I am personally dedicated to making sure we all do our absolute best to determine which ones are safe and effective as quickly and efficiently as possible. More on that soon.

As the co-founder of a nonprofit research organization and board member of a biotech company, the work I do can sometimes feel abstract. Will this or that effort actually help a real, live child? But as a mom, the effects could not be more tangible. There is an actual chance that within a few months (b) (6) could be preventing and even reducing his fibrosis (if he gets back on ht-100). Soon thereafter he could be producing small amounts of truncated dystrophin (if Sarepta moves forward with their other exon skipping drugs). That's a lot of "ifs," but it's also a 1-2 punch that could buy him valuable strength and time.

Thank you again for your thoughtful consideration of everything we've thrown at you, and for your dedication to this enterprise.

My best,
(b) (6)

On Tue, Sep 6, 2016 at 3:47 PM, Woodcock, Janet <Janet.Woodcock@fda.hhs.gov> wrote:

> Thank you for writing. I am at an Advisory Committee Meeting at White Oak on that date and therefore cannot meet down on the hill.
>
> I am well aware of the Community's concerns about the timing of the eteplirsin decision.
>
> Thank you for sending the review of the serious adverse event. As you probably know, I am not able to comment on this.
>
> Hope your work on the Hill goes well.

Janet Woodcock

From: (b) (6)
Sent: Tuesday, September 06, 2016 2:05 PM
To: Woodcock, Janet
Subject: three Duchenne items

Hi Dr. Woodcock,

I'm writing to you for three reasons. I'll briefly outline them here, but I welcome the opportunity to meet with you next Wednesday, Sept 14th to discuss them in more detail.

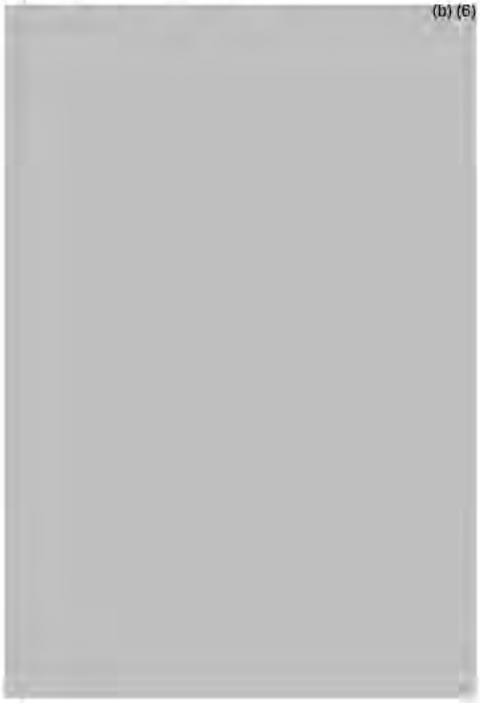
I'm sure you can guess at reason #1. It's 102 days past the PDUFA date for eteplirsen and our community is left in the dark. We are close to a boiling point. Families whose children can benefit from eteplirsen are in limbo, facing tough decisions about ports. In my case, this latest delay has meant three more months of shelf-time for the exon skipping drug that could help my son. (b) (6) turns (b) (6) in November, a birthday I am not looking forward to in the absence of some progress toward helping him produce even a modicum of dystrophin to help prolong the muscle function he still has. He can't run or climb stairs, but a hug means the world to us. When 36 renowned experts agree that eteplirsen induces enough dystrophin to be reasonably likely to lead to clinical benefit, our community deserves to know why it is taking so long for the FDA to render a decision.

Reason #2: As you know, much more is at stake here than one drug or even one therapeutic approach. Multiple therapies for DMD are in clinical development. Our community is committed to making sure the actions of the Division of Neurology Products are based on sound science and thoughtful review that incorporate both real expert input as well as the patient perspective. Unfortunately, we do not have confidence that thoughtful review, sound science and meaningful expert input are key elements of the DNP's decision making process. For that reason, I would like to draw your attention to the attached document, the (b) (4) submitted to the DNP last week by Akashi Therapeutics (of which I am a (b) (6)). (b) (4) . I would greatly appreciate your review of this (b) (4) so you are aware of the situation while the DNP is considering the filing. On a personal note, my son (b) (6) was on the lowest dose of this drug for two years. He did not experience one negative side effect, and -- notably-- he remained stable from ages (b) (6) while on this experimental medication. Since the clinical hold was imposed in January of this year, he has experienced significant decline in speed and strength. Similar experiences are echoed by families who have written letters to Akashi pleading to restart dosing (included as an appendix in the filing).

Finally #3: I will be on Capitol Hill next Wednesday, Sept 14th for a speaking engagement before members of Congress and staff regarding innovation, drug pricing, and other issues critical to the

rare disease community. I just wanted to give you a heads up that I will be speaking about our efforts. The DMD community is anxious to build a productive working relationship with the FDA, as we are committed to seeing multiple complementary therapies through to approval and commercialization. The time is now to transform Duchenne from an aggressive killer with zero treatment options to a manageable, chronic condition. We just need a little help from you to get that done. Please let me know if you are available at 9 am or after 2:30 pm next Wednesday.

My best regards,



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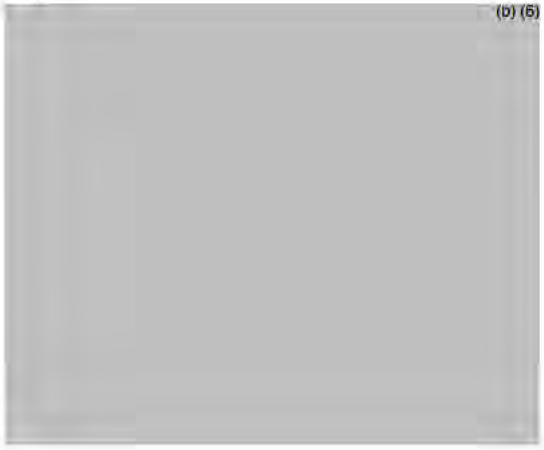

From: Shana Fonnesbeck
To: Woodcock, Janet
Subject: Approve the Sarepta Drug
Date: Thursday, September 15, 2016 1:41:15 PM

Ms. Woodcock,

I am writing to voice my support for the approval of Eteplirsen, which is safe and effective. Congress has given the FDA tools and flexibility to accelerate approval for drugs that meet unmet needs, and this is certainly an unmet need for the Duchenne community.

Best regards,

Shana Fonnesbeck

From: joe
To: Woodcock, Janet
Subject: Re: Duchenne"s Muscular dystrophy
Date: Thursday, September 15, 2016 8:29:56 PM

Hi Dr. Woodcock,

Thank you for taking a moment to read this.

I know the FDA has not yet made a final decision on the new drug for DMD using exon-skipping. I am aware that more muscle biopsy samples were requested which are under review. I hope you will decide in favor of the drug's approval.

No one seems to argue about safety issues. Rather, the issue seems to be efficacy. Please use your authoritative powers to make this drug available to these DMD patients.

In essence, the boys are really just asking to live, to grow up, and not to die. I certainly do not know all the behind-the-scenes FDA scientific discussions, but I believe strongly this drug should be allowed. It offers the possibility to alter DMD's clinical course with the more benign form of the disease. I do believe this treatment offers the boys a chance. Post-approval analysis will be ongoing I'm sure.

Might help, won't hurt, nothing really to lose. Most importantly, approval would bring much-needed hope for many, including the boys, the parents, the families & friends, and even the doctors & nurses who treat these patients.

I have watched Youtube and Facebook videos of the "treated" DMD boys, some of whom spoke at the ADCOM advisory panel meeting in the Spring. Although anecdotal, some of these videos are impressive with strength and function. The video testamonials certainly play on one's heartstrings.

Sincerely,

Joseph Shalhoub M.D.
(b) (6)

(b) (6)

Woodcock@fda.hhs.gov>

To: joe < (b) (6) >
Sent: Sunday, May 29, 2016 1:15 PM
Subject: Re: Duchenne's Muscular dystrophy

Thank you very much for writing. You sound like the kind of doctor most people hope to have take care of them.Janet Woodcock

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From: joe <(b) (6)>
Date: May 28, 2016 at 5:37:26 PM EDT
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: Duchenne's Muscular dystrophy

Dear Dr. Woodcock,

I am an internist with a primary care practice in (b) (6). I realize that you must be enormously busy, so if this email has reached you successfully, many thanks for taking a minute to look at it.

I am glad that you decided to delay the decision about the possible new drug for DMD. After the rejection last month by the Adcom advisory panel, this delay action has revived some much needed hope for the DMD community.

I watched and listened carefully to the testimonials of the doctors and scientists who spoke at the Adcom meeting. The patients & families' emotional words offer a glimpse into the toll & suffering this disease inflicts of the young boys and their parents, for certain. I also know that similar "impact statements" can be said for any number of devastating diseases without good treatments out there. I also realize that there has got exist large amounts of pressures mounting on all sides from politics and big pharma and insurance coverage issues as well as sometimes big egos of drug company execs and even Adcom panel members maybe.

Personally, I don't care much for politics and I don't care much for folks with big egos either.

I liked a lot what you said about a type 2 error...(paraphrasing) that it would be bad to approve a drug that didn't work but worse not to approve a drug that, in fact, does work. That notion has been ringing in my head for a month now.

I also listened to the DMD researchers who spoke. They seemed smart, dedicated to their work, and very sincere in their words. Most seemed apolitical, too, which I really liked. I got the sense that they would have preferred to be back at home in their labs or with their patients than on the center stage. In other words, I didn't smell any hidden agendas or arrogance. I liked when someone said that ANY amount of dystrophin production is meaningful. So, one can debate the biopsy results and quantification techniques for measuring dystrophin until the cows come home, but the treated boys & their parents say the drug works. The researchers who have spent years in the field and the clinical neurologists who treat the boys believe it works, too.

Since the drug appears safe, my feeling is to approve it, and then the quantification of dystrophin levels will come later. After all, even aspirin was known to be effective for a long time before the why and how were satisfactorily elucidated.

I am not an expert in DMD, nor am I a researcher. I am a clinician who treats my patients with evidence-based medicine whenever possible, and there ALWAYS exists the visceral element of clinical instinct that physicians develop over time.

I recall a DMD patient of mine who passed away several years ago. His disease followed the typical course for DMD. Each time he presented for an office visit, I regretted having nothing to offer him. Yet, he maintained the strength of his inner spirit and attended schools and even graduated from a local college. He held a part-time job until he could no longer. One day, he no-showed his appointment. I found out he had been admitted to an outside hospital and died from pneumonia. I never got to tell him how courageous I thought he was. He probably wouldn't have wanted my praise anyway.

Dr. Woodcock, please use your power to give this new drug an undiluted green light. It appears safe, and the experts in the field and the patients all say it works. Clarifiying data will come later for certain.

Thanks again for taking time to read this.

Sincerely,

Joseph Shalhoub M.D.

From: (b) (6)
To: Woodcock, Janet
Subject: Thank you
Date: Monday, September 19, 2016 10:15:43 AM

Janet
I'm sure I will never really know what went on, but what I do know, is that you at least played a part in this approval. For that, I will be eternally grateful. This is just the start, we have so much work to do, but we are lucky to have a woman like you fighting for the lives of our boys. I hope some day soon we can share a drink and celebrate, longer, stronger, healthier lives for the boys and young men with Duchenne.

best
(b) (6)

From: (b) (6)
To: Woodcock, Janet
Cc: Dunn, Billy
Subject: Why?/ Conflict of Interest
Date: Monday, September 19, 2016 7:57:16 PM

Dear Dr. Woodcock, Dunn and Bastings,
Today I'm writing you in complete disbelief and devastation. The FDA who is supposed to protect us the citizen's of the United States has completely failed me, my family, my son and thousands of others. I want change, I want those who testify to be sworn in, I want conflicts of interests looked at. Because why do I hear that some of the FDA officials making decisions are in fact "friends" with Saretpa attorney's and plays tennis and sails, is this correct? How could this happen????? Really, why is anyone associated able to assess a medication.

My son participated in the Drisapersen clinical Drug trial from November 2011 until his last injection August 4th 2016. The FDA failed my son and I will not sleep until I get justice for my son and the other boys.

We've been drug through the mud. I listened to you Dr. Dunne during the Eteplirsen Adcomm, I heard you say that Sarepta Therapeutics mis-lead this community and the FDA. That not only that but all panel members received mysterious packages for them to review.

My family and I and my son and many others didn't deserve the treatment we received from investors of Sarepta. Many found me and told me what a horrible Mother I am for giving my son a toxic medication. We'll that toxic medication rescued my son and I will prove this beyond a shadow of a doubt. I offered my son's medical records and I have many more videos that what I showed everyone at the Drisapersen adcomm. The denial of Drisapersen is a type 2 error. My son was in the so called "failed" trial yet he's far more functional than any of the Eteplirsen kids and I will prove it. I watched my cousin die from this disease.

Why, did the FDA call me, Phillip Bautista and his Supervisor to tell me I could not have my husband (b) (6) signed up as a speaker?? I was told you and your husband share the same perspective as so either take myself off the list or (b) (6) Also, I can name at least 2 people, (b) (6) and (b) (6) signed up to testify, but they didn't sign up to testify, they wanted to force a lottery and in fact there were what 8 people signed up that never intended to speak. Then I watch the Eteplirsen adcomm and it's stated that our whole community was there is support. I wasn't there. Then I see family member after family member speaking on behaf of Eteplirsen. What is this??? why was this whole process different for us??

I have an email that I was sent from Christine McSherry's Jett Foundation that if you or anyone you know even knows of someone with Duchenne, there is travel assistance available? What??? My family and I used the airline miles my son and I accumulated over time to travel to testify.

Drisapersen also produces dystrophin, it's even stated in the Briefing Docs, that one could argue that Drisapersen is better than placebo. Well, my son walks 670 meters folks, he went from a 24/34 to a 34/34 NSAA score. I will prove this, my son walked in the low 400's when he started in the Drisapersen trial and now can walk 670meters. I challenge any of you to check my son over. When these panel memebers start asking whether or not a disease is like a sinus issue or if it's MS, damn it they shouldn't be making life and death situations for children's lives. Why doesn't the FDA require being sworn in???? why??? you've destroyed my son's life. You now tell me that a so called "therapy" for my son could be walking under 200 meters at 11 and my son walks 670m at 10 1/2. Come on this isn't a miracle my son improved it's Drisapersen.

This is not okay. My son is put on a drug, taken off, put on a drug, taken off. What are you doing to my son????????? The FDA gives a "Breakthrough Designation in 2013" to Drisapersen come on and then says well the phase III data is confusing? What??? why did you accept and NDA based off of the same data you had for years. Why?? why have my son doing all this testing just to not even look at it. Do you have any concept of clinical trials. I have other children. I live in (b) (6) I cannot be across the country advocating, why did you do this to us?? why??

I will go to the ends of the earth to prove this is more than just a type 2 error. This is not okay. My beautiful son deserved more. There is no comparison the boys on Drisapersen compared to Eteplirsen. No comparison and my son's neurologists agree, the decisions you've made are killing my son and others.

I've cried all day long, this isn't okay to do to human beings. I would have never set out to stop any child from a medication that works beyond a shadow of a doubt. We didn't have any members of the FDA stay and speak with us. We had Carrie Miceli and Stan Nelson behind us praying for Drisapersen to be dismissed. They wanted to make their millions because of their patent on the exon skipping enhancer. Yep, this Mama did her homework and I want justice for my precious son.

I request a meeting with you. It's not okay that this is happening and I will be heard one way or another and my precious son's life matters. My son rides a bike, rises no gower and declined last time he was taken off medication. My son's last injection was August 4th thanks to the FDA. Oh, and my son doesn't qualify for Sarepta's trial, HE'S FAR TOO FUNCTIONAL. Why did you do this to us???? why??? it's not right.

I want an investigation, I want you to over turn your decision on Drisapersen, it produced dystrophin. My son was in the so called "failed" trial, My son has improved on every single measure, so have many others. The side effect of Duchenne is death and I will not rest until my son has justice. If you approve Eteplirsen then you need to approve Drisapersen.

(b) (6), Mom of (b) (6) who deserved you to fight for him.

My phone number is (b) (6), if you need attorneys or congress members to speak with me so be it.

From: Steven Walker
To: Woodcock, Janet
Subject: Thank you Janet
Date: Monday, September 19, 2016 10:21:15 PM

Doing the right thing is often not easy, but you have earned the support and respect of a lot of people for doing the right thing with eteplirsen. Those who decide to leave the FDA because they didn't get their way are, in my opinion, making room for people who will do a better job, something that is much needed in DNP.

Change is hard, and it requires leaders willing to drive it. You just did that.

Thanks

Steven T. Walker M.S., P.G.
Co-Founder
Abigail Alliance for Better Access to Developmental Drugs
www.abigail-alliance.org

Mobile: (b) (6)
e-mail: (b) (6)

From: (b) (6)
To: Woodcock, Janet
Subject: Thank you
Date: Tuesday, September 20, 2016 9:05:11 AM
Attachments: ATT00001.txt

After reading through the summary review of the Eteplirsen NDA, it is apparent you looked at the whole picture of the impact of Duchenne on our boys. I will admit, after months of hearing nothing on a decision, I started to lose faith; that our pleas for flexibility fell on deaf ears and our boys would never get a fighting chance.

I want to thank you for making the right decision, even though it wasn't the popular decision among your staff. For our opinions to be continually dismissed as emotionally-driven and characterized as those borne of desperation cut deep. When my son was diagnosed 4 years ago, I left a very good paying job (as the breadwinner of my family) to launch a DMD foundation to fund research. I spent countless hours researching potential therapies, educating myself on Duchenne, and meeting with anyone and everyone who knew more than me. I made myself physically sick with my obsession to find that one glimmer of hope to save my son. I've questioned my own sanity. Unfortunately, I am now an expert on DMD. I knew as soon as I laid eyes on the boys in the Eteplirsen trial that the drug was doing SOMETHING to ameliorate the symptoms of DMD, even if the data wasn't a slam dunk.

Despite the fact that Eteplirsen will not currently help my son, yesterday was the first time I've felt real, tangible hope for his future and the future of all our boys. You've helped us kick down a door and gain momentum, and shown amazing courage in doing so.

Thank you,

(b) (6)

From: David M. Rodman, M.D.
To: Woodcock, Janet
Subject: Rare disease drug development
Date: Tuesday, September 20, 2016 12:44:39 PM

Dear Dr. Woodcock,

I am writing to express my personal appreciation for the decision you made on Eteplirsen. During my time leading Cystic Fibrosis Drug Development at Vertex Pharmaceuticals I had the occasion to participate with you in a discussion of some of the challenges we faced in bringing novel, potentially transformative therapies to children and adults with genetic diseases. Confronting the hard, practical consequences of your decision on Eteplirsen in the face of the limited clinical information available was a "Trumanesque" demonstration of leadership. Sarepta made some compromises in their development program that put all stakeholders in a bad spot, and as a rare disease developer I hope that one lesson we all take away is how unfair it is to patients to provide an inadequate dataset and force such a difficult decision. Due to your decision, Serepta now has both the mandate for and access to sufficient time and resources to perform a proper trial with more frequent dosing and accurate quantification of dystrophin expression. Even a well powered comparison between the approved regimen, a daily regimen and inclusion of a properly designed, prospective case-control standard-of-care comparator arm (if placebo is not practical) should answer the question of whether the drug does indeed provide meaningful clinical benefit to these boys. The human cost of not having an effective therapy for DMD is overwhelming, and I hope that the final chapter of the story is that by enabling this proper next step in development, the drug does indeed make a meaningful difference. However, it is important for all of us in the field that this trial is properly designed, efficiently executed and that should the trial fail to demonstrate dose-dependent pharmacodynamic and clinical efficacy, Exondys 51 is expeditiously removed from the market. Your courage is greatly appreciated.

Best

David M Rodman MD

David M. Rodman, M.D.
Chief Medical Officer & EVP of Discovery
p 720-945-7721 | m (b) (6) | f 303-440-8399

Nivalis Therapeutics, Inc. - www.nivalis.com
3122 Sterling Circle Boulder, CO 80301

From: Marlene Fumia
To: Woodcock, Janet
Subject: Thank you!
Date: Tuesday, September 20, 2016 1:58:36 PM

Before I do another thing, I have to send a thank you! Thank you for all you did and continue to do on behalf of those with DMD. I won't pretend to know just how contentious things got, but I do know that you were compassionate and listened to us all through the process.

I just wanted to say thank you! I pray that Alex Johnson said it best,

I want to add a special thank you to Dr Janet Woodcock for listening to our community, our researchers and our clinicians. She has provided us with a pathway forward that allows us to gather additional data, develop more drugs and understand the disease better. A lot can be learnt from her leadership. She has understood FDASIA and the lessons that we have learnt for the AIDS community. HIV was once a death sentence it is still a severe disease but a manageable one. We will like them build on these first generation drugs and develop more effective therapies.

The development of Exondys 51, has, at times has been so painful – and no one can deny this. We must learn so many lessons from this and make sure other companies developing drugs for DMD learn from the lessons and don't make the same mistakes. We can't afford to go through this again. We need therapies fast and processes that reflect that. Our community deserves only the best.

Thank you!

Marlene Fumia
(b) (6)

From: susan j ward
To: Woodcock, Janet
Subject: RE: leadership
Date: Wednesday, September 28, 2016 7:37:17 PM

You are very gracious, thank you.
Well said - when someone's comfort zone is defined by science sufficiently comprehensive and black and white that the distinction between 'informing' and 'deciding' blurs, it must be a very scary thing to step up to the much harder task of making an 'informed' decision in the absence of certainty.
I wish you well
S

Susan J. Ward, Ph.D.
(b) (6)

From: Woodcock, Janet [mailto:Janet.Woodcock@fda.hhs.gov]
Sent: Wednesday, September 28, 2016 3:54 PM
To: 'susan j ward'
Subject: RE: leadership

Thank you. Your words capture and expand upon my position! It is true that more formal consideration of the consequences of failing to approve a beneficial therapy would help balance the discussion. Science can't MAKE decisions, it can inform them, and both sides of the dilemma can be informed by science. Janet W

From: susan j ward [(b) (6)]
Sent: Tuesday, September 27, 2016 10:43 PM
To: Woodcock, Janet
Subject: leadership

Hi Janet,

I hope by now your DMD in-box is calming down a shade after last week's galvanizing news.

In your opening remarks to the eteplirsen AdComm on April 25th, you accomplished a rare feat. That "the regulatory process should take into account the patients' view/voice" is a truly nice idea, yet however much merit that idea has, it is another thing entirely to articulate a practical and actionable "how" that regulators, as well as academic experts, drug sponsors, and patient advocates, can both understand and get behind. You articulated that "how" with clarity and commitment.

I enclose a short article championing your stance, written on my way home from that AdComm meeting, to document, as is my habit, those rare moments in life one is witness to something portentous. Clearly, my professional role prohibits publication of personal opinion – but since I haven't seen a similar view espoused in any of those publications that make it to my news feed, I'm awarding myself (as an individual, not as a representative of my organization), the freedom to

speak (however clumsily) in strident support of the change you are driving.

More than 50 years ago, FDA rescued this country from snake oil with solutions that brought much-needed rigor and objectivity to drug evaluation. Today, we desperately need the 21st century equivalent –which is, as your vision makes clear, a more sophisticated application of those principles, most notably in precision medicine and rare disease. I hope fervently that your message does not get lost in the inevitable swirl and controversy over FDA decision-making in Duchenne.

You are one of the few who can truly translate. Please, do stick with it.

My very best wishes,
Susan

Susan J. Ward, Ph.D.
The TAP Collaboration
(b) (6)

From: (b) (6)
To: Woodcock, Janet
Subject: My enduring respect and admiration
Date: Tuesday, September 20, 2016 5:47:55 PM

Janet
I am so honored to think of you as my colleague and friend. I continue to be in awe of your courage and fortitude to always do what you believe is in the best interests of patients. You are consistently above all your titles and responsibilities a physician who sees suffering and undauntingly serves to alleviate it. You have always been strong enough to rise above criticism and carping but maybe it helps a little bit to know that I am cheering for you and your decision to approve eteplirsen.
Hope all is well with family
Andy

Sent from my BlackBerry 10 smartphone.

From:	kim danboise
To:	Commissioner FDA; Temple, Robert; Woodcock, Janet; Dunn, Billy
Subject:	eteplirsen
Date:	Tuesday, September 13, 2016 11:28:03 PM

Dear Dr. Dunn: Think you fucking genius s might have missed something here?

Dawn Rezkalla (b) (6)

109 days. How many other DMD patients could rock climb by now if they had access? #enddmd #eteplirsenworks $srpt

From:	kim danboise
To:	Commissioner FDA; Temple, Robert; Woodcock, Janet; christine@jettfoundation.org
Subject:	Eteplirsen/adcom farkas/shills
Date:	Wednesday, September 14, 2016 6:14:34 AM

Dear Dr. Califf: Farkas is gone-now-what you going to do about those 3 fucking shills he had at the adcom? If FDA doesn't pull those goddamn grants there is no justice!
Sincerely,
Kim danboise

From:	kim danboise
To:	Commissioner FDA; Temple, Robert; Woodcock, Janet; Dunn, Billy; Bastings, Eric
Subject:	Sarepta adcom
Date:	Saturday, September 17, 2016 9:50:00 PM

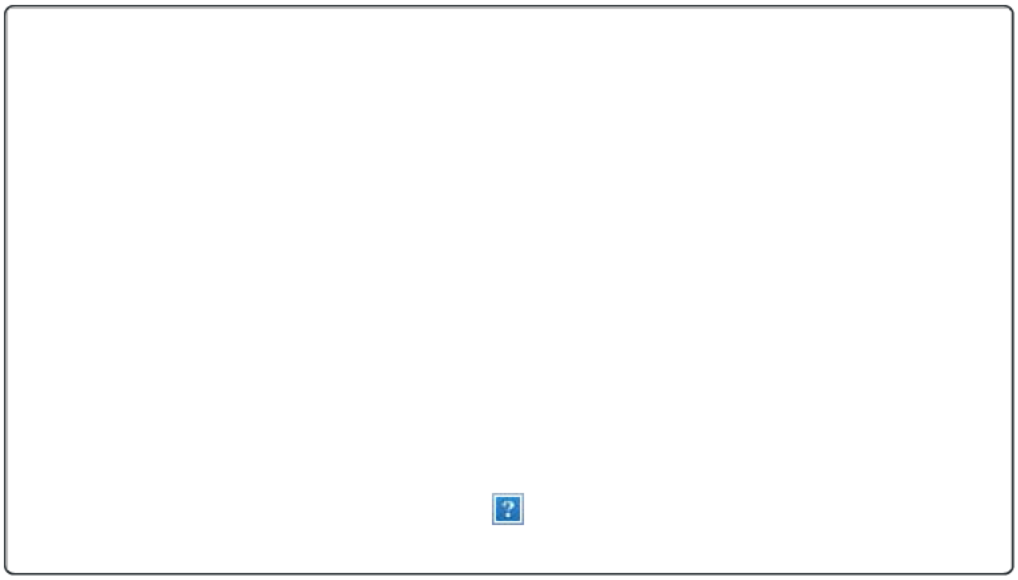
Dear Dr. Califf: Ron Farkas was an idiot and a dirty rotten prick. Bastings and Dunn backed the fucker all the way. What does that make them?They helped rig the adcom and tried to make bull shit look like a scientific endeavor. FDA has a lot to answer for and 14,000 DMD kids are waiting for the answers.

Sincerely,
Kim Danboise

From: kim danboise
To: Commissioner FDA; Temple, Robert; Woodcock, Janet
Subject: Eteplirsen review
Date: Sunday, September 18, 2016 7:51:51 PM

Dear Dr. Califf: This is the kind of shit all those "experts" and their "through" "exhaustive" review missed time and again. Science based organization my ass.
Sincerely,
Kim Danboise

$SRPT it is hard to see how someone making the types of conceptual errors would keep job. just 1 example of many



From:	kim danboise
To:	Commissioner FDA; Jenkins, John K; Unger, Ellis; Bastings, Eric; Woodcock, Janet
Subject:	Dysrtophin
Date:	Friday, October 28, 2016 9:49:27 PM

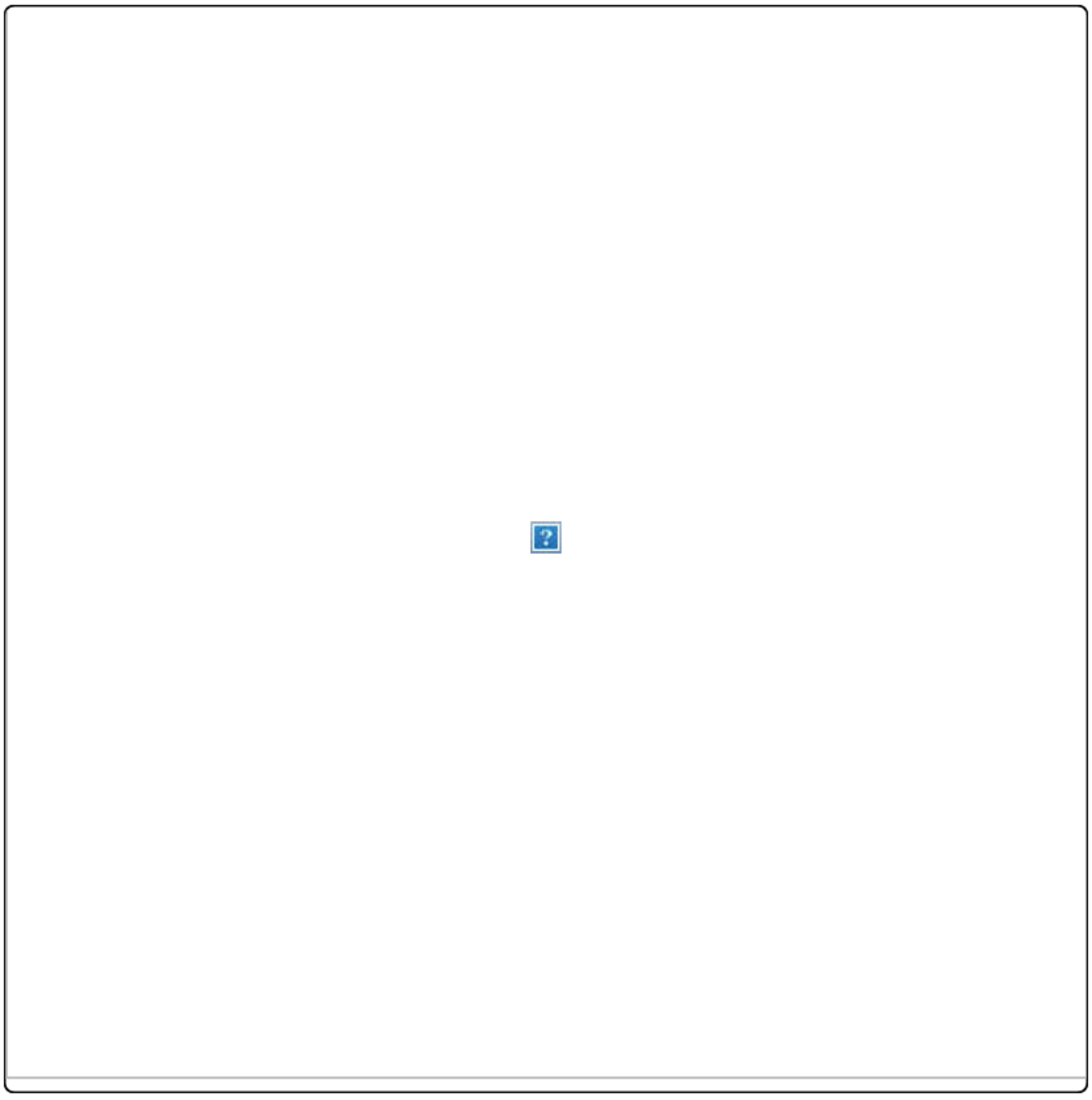
Dear Dr. Califf: DNP tried to make an idiotic decision based on a poor measurement technique and the whole scientific world knew it. Its time for the FDA to get with the program and hire people that understand new science, and get rid of the dinosaurs.
Sincerely,
Kim danboise

Kaye confirms my position that inflammatory proteases limit WBlot quant. IHC with new quant. algorithm is the near term quant paradigm

From: kim danboise
To: Commissioner FDA; Bastings, Eric; Unger, Ellis; Temple, Robert; Woodcock, Janet
Subject: Stable on eteplirsen
Date: Friday, December 23, 2016 5:17:31 AM

Dear Dr. Califf FDA still thinks this drug hasn't proven efficacy, you morons need to get the other exons approved.

$SRPT I don't believe I've ever seen a doctor report say #StableDuchenne #exondys51



From:	kim danboise
To:	Commissioner FDA; Unger, Ellis; Bastings, Eric; Temple, Robert; Woodcock, Janet
Subject:	WSJ
Date:	Friday, December 30, 2016 11:00:33 PM

Dear Dr. Califf: Everyone involved as an community member, or investor saw the whole thing. FDA stunk it up on this one and sick kids were the ones who suffered the most, some of you should rot in hell.

Among the Republican priorities in 2017 should be dismantling a culture of bureaucratic control at the Food and Drug Administration that poisons innovation and costs lives. Here's an idea: Update part of the approval process that was patient zero for distorting data on a drug for Duchenne muscular dystrophy.

We've reported on the drama over eteplirsen, which FDA approved in September and is now marketed as Exondys 51 by Sarepta Therapeutics. Midlevel bureaucrats have since disparaged the therapy in public, and some insurers are denying coverage. Much of the confusion results from an April show trial known as an advisory committee meeting. A process that is supposed to provide independent advice to the FDA instead became a venue to mislead a panel of nonexperts—and the public—about the drug's efficacy.

Advisory committees exist so FDA can solicit expert counsel, but the agency stacks panels with allies whose career currency is prestige and government funding. Such committees usually vote the way FDA wants—and then the agency tends to follow the recommendation. On eteplirsen, the panel voted 6-7 against accelerated approval after a critical FDA review, which was later overruled by agency management in a rare exception amid unusual public scrutiny.

The 13-member committee that checked out eteplirsen included: a psychiatrist, a stroke doctor and several others with no experience in Duchenne. The agency seldom invites true experts because anyone who has ever talked to a drug company is deemed financially conflicted. In rare diseases like Duchenne, that problem is more pronounced because the pool of experts can be so limited.

Yet meet Caleb Alexander, chairman of the committee. Dr. Alexander invited speakers at the meeting to state organizations they represent. He read this statement at least a dozen times but neglected to mention his own conflict of interest: Dr. Alexander has received a large FDA grant, information that is available online. The conceit is that fo ks l ke Dr. Alexander are less motivated by pecuniary interests than someone who has consulted for a company. Dr. Alexander voted against approval.

Sarepta was barely allowed to defend itself at the meeting, which allowed agency distortions to appear as fact. One example: FDA's documents for Sarepta claim that patients "commonly maintain ambulation to older ages than is often realized, to 18 years or perhaps even older." Yet the same materials for a Duchenne drug reviewed fewer than six months earlier say that "by age 10-14, patients become wheel chair bound." This looks like an attempt to make Sarepta's clinical results look less significant.

FDA's review also relied on a chart to convince the panel that boys on the drug over time walked no better than patients who were not treated. But we've reviewed compelling evidence that someone manipulated the x-axis in later years to make the results look more damning for Exondys. This contentious visual was treated as gospel.

Supportive experts were relegated to the public hearing portion of the meeting for brief comments. Pediatric neurologists, the geneticist who discovered the gene for Duchenne, clinical researchers and others had to move fast through slides and data. The FDA's lead reviewer, an eye doctor, talked for about an hour.

The nonprofit Jett Foundation collected data on falls, fatigue and other outcomes that the panel more or less ignored. These patient measures will be invaluable as rare diseases become better understood. FDA has the legal authority to incorporate patient data in decisions, but the bureaucracy never does.

At the end of the day, panelists vote on approval questions, and even here FDA tilts the outcome. The agency's guidance says questions should have "minimal qualifiers" so as not to confuse the committee. So let's look at one of the questions FDA asked the panel to ponder: "Do the clinical results of the single historically-controlled study (Study 201/202) provide substantial evidence (i.e., evidence from adequate and well-controlled studies or evidence from a single highly persuasive adequate and well-controlled study that is accompanied by independent findings that substantiate efficacy) that eteplirsen is effective for the treatment of DMD?"

Are you still reading? The obfuscation led one committee member who voted no, Bruce Ovbiagele, to deliver this insight: "Based on all that I heard, the drug definitely works, but the question was framed differently." Imagine hearing this if you are the parent of a Duchenne boy.

If FDA is going to run these committees merely to achieve a predetermined outcome, then let's skip the exercise. Drug sponsors should at least be allowed to object to candidates for the panel and be granted time to refute the agency's contentions, as Joseph Gulfo, executive director of the Lewis Center for Healthcare Innovation and Technology, has suggested. The panels should also include several members who have treated the disease.

These changes would return advisory committee meetings to their original purpose as an outside check on FDA bias or groupthink. If Donald Trump is serious about making government accountable to the people who pay for it, FDA is a prime candidate for reform.