

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21945Orig1s000

OFFICE DIRECTOR MEMO



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: February 3, 2011

SUBJECT: Approval Action for NDA 021945
Makena (hydroxyprogesterone caproate injection) for
intramuscular use
Applicant: Hologic Inc.

FROM: Julie Beitz, M.D.
Director, Office of Drug Evaluation III

Makena (hydroxyprogesterone caproate injection) is a synthetic progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth. Makena will be supplied as a sterile solution in a multidose vial; each 5 mL contains hydroxyprogesterone caproate (HPC) 250 mg/mL in a castor oil vehicle. One mL (250 mg) should be administered intramuscularly once weekly beginning between 16⁰ and 20⁶ weeks of gestation and continued until week 37 or delivery, whichever comes first.

This memorandum documents my concurrence with the recommendation from the Division of Reproductive and Urologic Products (DRUP)¹ for approval of Makena (hydroxyprogesterone caproate injection) to reduce the risk of preterm birth in women with a singleton pregnancy under Subpart H accelerated approval regulations. A large randomized controlled trial is ongoing to verify and confirm the clinical benefit of HPC. The design of this trial and its conduct to date have been carefully reviewed and found acceptable. No new efficacy or safety concerns have been identified in preliminary analyses of blinded events reported on the trial. A second study evaluating developmental milestones in infants born to women enrolled on the confirmatory trial is planned, and its design has also been carefully reviewed. Discussions regarding the product labeling, patient package insert, and postmarketing requirements and commitments have satisfactorily concluded, and there are no manufacturing or inspectional issues that would preclude product approval.

¹ Due to the length of time that HPC had been marketed without an NDA, and the complex issues that arose during the NDA process, regulatory authority was delegated to the Office of Drug Evaluation III on January 4, 2011.

Regulatory History, Review Findings and Actions Taken

Delalutin. In 1956, Delalutin (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, was originally approved based on a finding of safety (under NDAs 010347 and 016911 held by the Bristol-Myers Squibb Company [BMS]). The approved indications included treatment of several gynecologic and obstetrical conditions, including the treatment of habitual and threatened abortion. Several of the approved indications were subsequently reviewed for efficacy under the Drug Efficacy Implementation (DESI) program. In the **Federal Register** of September 9, 1971 (36 FR 18115), FDA announced that preparations containing hydroxyprogesterone caproate are probably effective for the treatment of habitual and threatened abortion.

In the **Federal Register** of October 10, 1973 (38 FR 27947), FDA announced that it was modifying its prior conclusions with respect to the indications for Delalutin and stated that the additional information submitted by BMS to support use of Delalutin in habitual and threatened abortion does not constitute substantial evidence of effectiveness. In addition, the notice stated that data had become available which suggested a possible association of prenatal hormonal treatment of mothers with congenital heart defects in the offspring. The notice stated that the potential risk of teratogenic effects is considered high enough to warrant removal of pregnancy-related indications from the labeling of progestins currently marketed for systemic use.

In the **Federal Register** of November 16, 1999 (64 FR 62110), FDA revoked its prior regulation requiring patient labeling for progestational drug products because it concluded, based on a review of the scientific data, that such labeling for all progestins was not warranted. In the notice, FDA stated that the diversity of drugs that can be described as progestational and the diversity of conditions these drugs may be used to treat make it inappropriate to consider these drugs a single class for labeling purposes. By letter dated September 13, 1999, BMS requested withdrawal of Delalutin (hydroxyprogesterone caproate) injection and stated that the drug product had not been marketed for several years. In the **Federal Register** of September 13, 2000 (65 FR 55264), FDA announced that it was withdrawing approval of NDAs 010347 and 016911, effective September 30, 2000.

CUSTOpharm, Inc., submitted a citizen petition dated March 27, 2006 (Docket No. FDA-2006-P-0089), under 21 CFR 10.30, requesting that the agency determine whether Delalutin was withdrawn from sale for reasons of safety or effectiveness and therefore is suitable for submission in an ANDA. After considering the citizen petition and reviewing agency records, FDA determined that Delalutin (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, was not withdrawn from sale for reasons of safety or effectiveness. The petitioner identified several publications discussing the potential teratogenic properties of Delalutin over the years but asserted that recent studies indicate that with proper administration (beginning in the second trimester) in high risk patients these risks are minimal or not evident. Based on its evaluation, FDA did not consider this information to indicate that Delalutin was withdrawn for reasons of safety or effectiveness. This determination was published in the **Federal Register** of June 25, 2010 (75 FR 36419).

Currently, there are no drug products approved in the US to prevent or reduce the risk of preterm birth in women at risk for preterm birth, however HPC is available from pharmacies as a compounded product and is used widely for this purpose.

Makena. In 2003, the results from a randomized, double-blind, vehicle-controlled trial of HPC in women at risk for preterm birth were published.² The trial, conducted by the Maternal-Fetal Medicine Units Network for the National Institute for Child Health and Human Development (hereafter referred to as 17P-CT-002) enrolled 463 US women with a prior spontaneous preterm birth. Women at 16⁰-20⁶ weeks gestation were randomized in a 2:1 ratio to receive either weekly intramuscular injections of HPC 250 mg or inert oil vehicle until delivery or to 36⁶ weeks gestation. The mean duration of gestation at the time of the previous qualifying delivery was 31 weeks, and a third of the women enrolled had had more than one previous preterm delivery. Thus, the trial participants were considered to be at particularly high risk for another preterm delivery.

In 17P-CT-002, treatment with HPC resulted in a statistically significant reduction in preterm births < 37⁰ weeks gestation, the primary outcome of the trial. The proportion of HPC-treated women delivering at < 37⁰ weeks was 37.1% vs. 54.9% among vehicle-treated women, for a treatment difference of 17.8% (95% CI: -28.0%, -7.4%; p < 0.001). The reduction in preterm births < 37⁰ weeks was independent of maternal race, number of qualifying preterm births, and gestational age of the qualifying preterm birth. In addition, a 9.4% reduction (95% CI: -19.0, -0.4%) in preterm births was noted at < 35⁰ weeks, and a 7.7% reduction (95% CI: -16.1%, -0.3%) at < 32⁰ weeks with HPC treatment as compared to vehicle. The reductions observed in preterm births at < 37⁰ weeks and < 35⁰ weeks were consistent across trial centers; however, for preterm births at < 32⁰ weeks there was a greater reduction in HPC-treated women relative to vehicle at the largest accruing site (University of Alabama) compared to all other sites combined.

Neonatal deaths occurred in 2.6% of HPC-treated women and in 5.9% of vehicle-treated women. A composite neonatal morbidity/mortality index evaluated adverse outcomes in livebirths. The index counted any liveborn infant who experienced death, grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, or proven sepsis at any time during the birth hospitalization up through discharge from the neonatal ICU. Although the proportion of neonates who experienced 1 or more of these events was numerically lower in HPC-treated women (11.9% vs. 17.2%), the number of adverse outcomes was limited and the difference between treatment arms was not statistically significant.

Adeza Biomedical obtained access to the trial data in 2003 and initiated communications with FDA regarding submission of a 505(b)(2) new drug application. On January 25, 2007, Adeza Biomedical was granted orphan designation for the use of HPC (the active ingredient in *Makena*) for the prevention of preterm birth in singleton pregnancies. The original application, submitted on April 20, 2006, included data from this trial as well as follow-up information on infants born to mothers enrolled in that trial. FDA's review of the NDA encompassed three review cycles, highlights of which are summarized below.

² Meis PJ, Klebanoff M, and Thom E et al. Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate. *NEJM* 2003;348:2379-85.

Cycle 1: April 20, 2006 to October 20, 2006

NDA 021945 was granted a priority review. On August 29, 2006, FDA convened a meeting of the Advisory Committee for Reproductive Health Drugs (ACRHD) to discuss the application. At the conclusion of this review cycle, an approvable letter was issued describing deficiencies involving the following concerns:

Chemistry, Manufacturing and Controls. The drug product is photosensitive; the applicant needed to address the Agency's concerns regarding the detection of photo-degradation products and the adequacy of secondary packaging to protect the product from light. In addition, it was noted that the limited stability data supported an expiry of no more than 10 months (rather than the proposed 24 months).

Reproductive Toxicology. To address concerns about long-term effects in offspring *in utero*, the applicant was instructed to conduct a GLP-compliant, multi-generational reproductive toxicology study in rodents evaluating all stages of pregnancy during which dosing will be administered in humans.

Clinical Pharmacology. If HPC were approved, the applicant would need to characterize the pharmacokinetics of HPC and its metabolites in pregnant women, including assessment of the effects of body weight on pharmacokinetics, and an analysis of the effects of known strong inducers or inhibitors of the drug's metabolism.

Clinical and Statistical. Demonstration of the safety and effectiveness of HPC relied on the findings of a single clinical trial, 17P-CT-002, and supportive information from the infant follow-up study, 17P-FU. Several issues were identified including:

- *Reduction in preterm births < 37⁰ weeks.* Although the reduction in preterm births < 37⁰ weeks observed in 17P-CT-002 was statistically persuasive ($p < 0.001$), DRUP expressed concern that this endpoint was not an adequate surrogate for clinical benefit, namely, a reduction in neonatal morbidity and mortality. This view was endorsed by 16 of 21 Advisory Committee members at the 2006 ACRHD meeting. In contrast, 13 of 21 Advisory Committee members indicated that reduction in preterm births < 35⁰ weeks would be an adequate surrogate for clinical benefit.
- *Reduction in preterm births < 35⁰ weeks.* Twelve Advisory Committee members voted that 17P-CT-002 had provided substantial evidence that HPC reduced preterm births < 35⁰ weeks. Although reassuring, this endorsement by expert panelists was not fully shared by the DRUP clinical reviewers or the statistical reviewer, Dr. Lisa Kammerman, who argued that since the evidence for the drug's effectiveness relied on the findings from a single trial, the effect of treatment on preterm births < 35⁰ weeks ($p=0.038$)³ would not meet the level of statistical significance generally expected to support approval based on the findings of a single trial.
- *Generalizability of 17P-CT-002 trial results.* Two concerns were raised regarding the generalizability of trial results to a larger population of women at risk for preterm delivery. First, in contrast to the US population, approximately 59% of trial participants were African American, a population known to have a higher rate of preterm birth than other racial or ethnic groups. In subgroup analyses, however, the

³ This p value represents adjustment for two interim analyses; further adjustment is needed to account for multiple endpoints. See Dr. Kammerman's review dated October 19, 2006 for additional details.

reduction in the risk of preterm births < 37 weeks in African American women treated with HPC was similar to that of non-African American women.⁴

Second, Dr. Kammerman noted that even if FDA were willing to accept a less robust result (e.g., for preterm births < 35⁰ weeks) as the basis for drug approval, she remained concerned that one clinical trial site, the University of Alabama, had enrolled 27% of the total sample size and a disproportionately higher number of subjects at 18 weeks gestation or earlier; both the benefits of HPC and the rate of fetal losses were most pronounced among women who started treatment at or before 18 weeks. DRUP clinical reviewers were reassured by the observation that rates of preterm birth < 37⁰ weeks and < 35⁰ weeks were similar for the Alabama site and the other sites combined. Divergent (actually better) results for this site were noted only for the rate of preterm birth < 32⁰ weeks. Additional analyses performed by the applicant that showed little likelihood that the overall treatment effect at < 32⁰ weeks was being driven by the Alabama site were found persuasive by some of the DRUP clinical reviewers.

- *Potential increase in selected maternal complications.* Among the maternal complications reported in the trial, rates of pre-eclampsia, gestational diabetes and oligohydramnios were numerically higher in women treated with HPC compared to control subjects.
- *Reduction in neonatal mortality.* Trial 17P-CT-002 was not powered to show a reduction in neonatal mortality. The rate of neonatal death was 2.6% among HPC-treated women, numerically lower than the rate of 5.9% among vehicle-treated women. This trend was also observed in analyses of racial subgroups.⁵
- *Potential increase in fetal loss.* Offsetting the small reduction in neonatal mortality among HPC-treated women was a trend toward an increase in early fetal loss in these women as compared to those receiving vehicle; the rates of late second trimester miscarriage were 2.4% vs. 0, and for stillbirth, the rates were 2.0% vs. 1.3%. This trend was also observed in analyses of racial subgroups.⁶

Additional information that was considered during this review cycle included:

- *Congenital anomalies.* Congenital anomalies in 17P-CT-002 were noted in 2% of infants born to mothers from both treatment groups, with a similar range of defects, including genitourinary and cardiovascular anomalies.

⁴ For African American women, the proportion of HPC-treated women delivering at < 37⁰ weeks was 36.1% vs. 52.2% of vehicle-treated women. For non-African American women, the proportion of HPC-treated women delivering at < 37⁰ weeks was 38.6% vs. 58.7% of vehicle-treated women.

⁵ For African American women, the rate of neonatal death among infants born to HPC-treated women was 3.3% vs. 7.8% among infants born to vehicle-treated women. For non-African American women, the rate of neonatal death among infants born to HPC-treated women was 1.6% vs. 3.2% among infants born to vehicle-treated women.

⁶ For African American women, the rate of miscarriage among HPC-treated women was 1.5% vs. 0 among vehicle-treated women. For non-African American women, the rate of miscarriage among HPC-treated women was 3.9% vs. 0% among vehicle-treated women. For African American women, the rate of stillbirth among HPC-treated women was 1.7% vs. 1.1% among vehicle-treated women. For non-African American women, the rate of stillbirth among HPC-treated women was 2.4% vs. 1.6% among vehicle-treated women.

- *Developmental outcomes in infants.* A follow-up study (17P-FU) evaluating developmental milestones in children aged 2.5-5 years of age was performed at DRUP's request. In total, 194 children born to women treated with HPC and 84 born to vehicle-treated women were evaluated using the Age and Stages Questionnaire (ASQ). The percentage of children whose ASQ scores suggested developmental problems was similar in the two groups.

Regulatory action. At the conclusion of the first review cycle, the clinical and statistical reviewers agreed that further study of HPC safety and effectiveness was needed and that regular approval (under 21 CFR 314.105) was not warranted at that time. However, the team members diverged in their recommendations regarding whether the additional safety and effectiveness data must be obtained pre-approval. From a statistical perspective, Dr. Kammerman concluded that the single clinical trial (17P-CT-002) did not meet the level of evidence needed to support efficacy, and that a second clinical trial would be needed prior to approval of the NDA.

On the other hand, the DRUP clinical reviewers acknowledged two key recommendations from the ACRHD, namely that reduction in preterm births < 35⁰ weeks was an adequate surrogate for clinical benefit in neonates (in terms of morbidity and mortality), and that further evaluation of the product's safety could be performed post-approval. In the end, DRUP concluded that the single clinical trial (17P-CT-002) had demonstrated efficacy with respect to the rate of preterm births < 35⁰ weeks and concluded that it would be possible to ultimately approve HPC under Subpart H accelerated approval regulations (21 CFR 314.510), with the requirement that the applicant conduct a second well-controlled trial to verify and confirm the clinical benefit of HPC post-approval. Data from this trial or another trial could further assess the product's safety.

On October 20, 2006, DRUP issued an approvable letter indicating that future approval under Subpart H would be possible but that the applicant would be required to conduct additional well-controlled trial(s), to 1) confirm the clinical benefit of HPC, and 2) evaluate the association of HPC treatment with a potential increased risk of second trimester miscarriage and stillbirth. The applicant was instructed to submit draft protocol(s) and evidence of feasibility of conducting these trial(s). Additional deficiencies regarding chemistry, manufacturing, and controls and reproductive toxicology were also described in the approvable letter.

Although not identified as approvability issues, the applicant was also requested to perform developmental assessments of children at ages 18-24 months who were born to women treated with HPC, if the drug were approved. In addition, the applicant would need to characterize the pharmacokinetics of HPC in pregnant women, as well as the effects of known strong inducers or inhibitors of the drug's metabolism.

Formal Dispute Resolution Request: March 16, 2007 to April 12, 2007

Adeza Biomedical submitted a formal request for dispute resolution regarding three study requirements stipulated in DRUP's approvable letter dated October 20, 2006. This request was handled by Dr. Daniel Shames, then Acting Deputy Director of the Office of Drug Evaluation III. The study requirements that were disputed involved: 1) the multi-generational reproductive toxicology study in rodents, 2) the confirmatory well-

controlled trial to verify and describe the clinical benefit of HPC, and 3) the requirement to evaluate the association of HPC treatment with a potential increased risk of second trimester miscarriage and stillbirth.

In his memo dated April 12, 2007, Dr. Shames also acknowledged the limited data available on the clinical effectiveness and safety of HPC. He upheld all three study requirements specified in the approvable letter that had been disputed and did not agree with the applicant that these requirements exceeded the recommendations of the ACRHD members.

Cycle 2: April 25, 2008 to January 23, 2009

On April 25, 2008, the applicant (now Cytoc Corporation)⁷ submitted a complete response that triggered a second review cycle; receipt of a major amendment extended the review clock by 90 days. Highlights of this review are summarized below.

Chemistry, Manufacturing and Controls. The applicant provided sufficient information to address the deficiencies previously identified in the approvable letter.

Reproductive Toxicology. The applicant submitted results from a multi-generational reproductive toxicology study in rats that found no evidence for reproductive or developmental toxicity or impaired fertility. When HPC was administered intramuscularly at gestational exposures up to 5 times the recommended human dose, no adverse effects were seen on the parental dams, their developing offspring (F₁), or the latter offspring's ability to produce a viable, normal second generation (F₂). Therefore, the previously identified toxicology deficiency was adequately addressed.

Clinical Pharmacology. The applicant agreed to submit results from an ongoing NIH-sponsored trial at the University of Pittsburgh evaluating the pharmacokinetics of HPC and its metabolites in pregnant women throughout different gestational stages. Publication of the trial findings is targeted for December 2011. If this trial does not sufficiently address FDA's concerns, the applicant agreed to conduct an additional pharmacokinetic trial in pregnant women.

In response to the Agency's request that the effects of known strong inducers or inhibitors of the drug's metabolism be evaluated, the applicant also committed to conduct an *in vitro* study in human hepatocytes to determine whether HPC induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.

Clinical and Statistical. The applicant submitted draft protocols for two post-approval studies, a confirmatory clinical trial evaluating the safety and effectiveness of HPC to reduce preterm births and neonatal morbidity and mortality, and a follow-up study in infants born to women who had participated in the confirmatory trial.

Confirmatory trial (17P-ES-003). In accordance with Subpart H accelerated approval regulations, the applicant proposed a randomized, vehicle-controlled trial to confirm the clinical benefit of HPC treatment in 1230 women (randomized 2:1) with a singleton

⁷ Cytoc Corporation acquired Adeza Biomedical on April 2, 2007.

pregnancy who have had a previous spontaneous preterm birth. The primary objective was to determine the effect of treatment on preterm births < 35⁰ weeks of gestation. Secondary objectives were to assess whether treatment with HPC compared to vehicle reduced the rates of neonatal morbidity/mortality, as measured by a composite index, as well as rates of preterm births < 32⁰ weeks and fetal loss.

In a teleconference held on November 19, 2008, DRUP clinical reviewers and Dr. Kammerman requested that the composite neonatal morbidity/mortality index be evaluated in a hierarchical manner if the primary endpoint of preterm delivery < 35⁰ weeks attained statistical significance. This would provide the needed link between the surrogate endpoint of gestational age at delivery and clinical benefit as measured by the neonatal morbidity/mortality index. In response to these requests, the applicant made several protocol revisions, including increasing the proposed sample size to 1707. The proposed trial would have 98% power to detect a 30% reduction (30% to 21%) in the rate of preterm birth at < 35⁰ weeks, and 90% power to detect a 35% reduction (17% to 11%) in the composite neonatal morbidity/mortality index, allowing for fetal loss occurring in 2.5% of the pregnancies. The power to rule out a doubling of risk of fetal loss, assuming a rate of 4%, would be 83% (that is, the upper bound of the confidence interval for the relative risk of HPC compared to vehicle would be ≤ 2.0).

Although Dr. Kammerman agreed with the above-mentioned protocol revisions, in her review dated January 23, 2009, she reiterated her concern that the level of evidence from the applicant's single trial (17P-CT-002) was not sufficient to support the effectiveness of HPC. Further, she proposed that interim results regarding the reduction in preterm birth in a sufficient number of women from this second controlled trial (17P-ES-003) be submitted for review. If efficacy was established, then in her view, the NDA could be approved under Subpart H regulations. Results for clinical outcomes (such as fetal loss, neonatal morbidity and mortality) could be reviewed post-approval; if efficacy for these endpoints was established, then standard approval could be granted. DRUP did not pursue this proposal with the applicant, intending instead to approve HPC based on its effect on a surrogate endpoint (reduction in preterm births < 35⁰ weeks in 17P-CT-002), and accept the proposed second clinical trial as confirmation of the drug's clinical benefit in neonates.

In late 2008, the American College of Obstetricians and Gynecologists (ACOG) issued a revised opinion regarding the use of progesterone supplementation to reduce the risk of preterm birth. In that opinion, the ACOG recommended progesterone supplementation be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to preterm labor or premature rupture of membranes.⁸ Despite letters of intent from several US investigators to participate in the applicant's proposed confirmatory trial (17P-ES-003), DRUP remained concerned about the feasibility of enrolling US subjects on the placebo-controlled confirmatory trial.

Infant follow-up study (17P-FU-004). The applicant also proposed to enroll 375 children ages 23-25 months in a follow-up study to assess developmental milestones using the Ages and Stages Questionnaire, including 250 infants exposed *in utero* to HPC and 125

⁸ Use of Progesterone to Reduce Preterm Birth. ACOG Committee Opinion No. 419. American College of Obstetricians and Gynecologists. *Obstet. Gynecol.* 2008;112:963-5.

to vehicle. The study would have 88% power to detect a 15% absolute difference in the rate of screen-positivity on at least one of the questionnaire domains, based on an expected rate of 30% in the HPC-exposed group. The proposed study was found to be acceptable by both clinical and statistical reviewers.

Regulatory action. At the conclusion of this second review cycle, DRUP expressed its concerns about the feasibility of enrollment of US subjects in the placebo-controlled confirmatory clinical trial, 17P-ES-003, in a complete response letter dated January 23, 2009. DRUP stated that adequate assurance of feasibility could only be addressed by actual initiation of the confirmatory trial. In its response, the applicant would need to provide the following: documentation of IRB approval for at least 15 investigational sites (including US sites), enrollment of at least 5% of the total anticipated sample size, enrollment of at least 15 subjects at US sites, and agreement to enroll at least 10% of the total sample from US and Canadian sites.

Cycle 3: July 12, 2010 to February 3, 2011

On July 12, 2010, the applicant (now Hologic Inc.)⁹ submitted a complete response that triggered a third review cycle; receipt of a major amendment extended the review clock by 90 days. Highlights of this review are summarized below.

Clinical and Statistical.

The review during this cycle focused primarily on the evaluation of, and enhancements to, the proposed confirmatory trial, 17P-ES-003, and the infant follow-up study, 17P-FU-004. In addition, the DRUP clinical reviewers reviewed recently published information supporting the concern that preterm births between 34⁰ and 36⁶ weeks (so-called late preterm births) are predisposed to a higher risk of morbidity and mortality than term infants. This evaluation led to the Agency's reconsideration of the positive results seen in the reduction of preterm births < 37⁰ weeks with HPC treatment in the applicant's original clinical trial (17P-CT-002).

Confirmatory trial (17P-ES-003). In this review cycle, several aspects of the confirmatory trial were reviewed and considered acceptable, including recruitment goals and current enrollment in the US and other sites, blinded safety data on maternal, fetal and neonatal outcomes, and the composition and role of the Data Safety Monitoring Board. In addition, given the importance that HPC treatment be demonstrated to reduce neonatal morbidity and mortality as evidence of its clinical benefit, FDA requested and the applicant agreed to analyze preterm delivery < 35⁰ weeks and the composite neonatal morbidity/mortality index as co-primary endpoints.

A Data Safety Monitoring Board (DSMB) has been constituted to review safety data regarding maternal complications, adverse events including serious adverse events, fetal losses, and neonatal morbidity and mortality. The DSMB will meet at least annually, although the Chairperson or the applicant can request additional meetings as necessary. In addition, reviews of neonatal morbidity will be performed when approximately 20%, 40%, and 60% of randomized subjects have delivered. At the request of FDA and the DSMB members, the DSMB Charter was revised on January 6, 2011, to state that DSMB

⁹ Hologic Inc. acquired Cytoc Corporation in October 2007.

members will receive unblinded reports of any serious adverse events that result in the death of the mother, fetus or neonate on an ongoing basis.

The DSMB held its first meeting on December 13, 2010, and reviewed trial data from 17P-ES-003 that were available through November 17, 2010. A total of 179 subjects have been randomized, including 144 in the US, thus exceeding the recruitment goals set forth in DRUP's January 23, 2009, complete response letter. A total of 131 subjects have received at least one injection of trial medication, and there have been 33 live births $\geq 24^0$ weeks. Fourteen serious adverse reactions and four fetal/neonatal deaths have been reported; none were considered related to trial medication. The 4 fetal/neonatal deaths were: a cardio-respiratory arrest related to severe prematurity (delivery at 21 weeks with a birth weight of 340 g; age < 1 day), a report of tight nuchal cord and intrauterine death at 32⁴ weeks, and two miscarriages (both at 19³ weeks).

To date, there have been no maternal deaths and a relatively low rate of maternal complications; none were considered related to trial medication. In particular, there was one report each of the following: pre-eclampsia, gestational diabetes, and oligohydramnios. Injection site reactions were reported in 10% of subjects.

At a teleconference held on January 5, 2011, FDA requested and the applicant agreed to modify the trial protocol such that preterm delivery < 35⁰ weeks and the composite neonatal morbidity/mortality index will be co-primary endpoints. With a sample size of 1707, the power to detect significant differences between the treatment groups for both endpoints would be approximately 90%. A revised protocol will be submitted for review in March 2011.

Infant follow-up study (17P-FU-004). At a teleconference held on January 5, 2011, FDA requested that the applicant maximize the number of infants that would be evaluated in this follow-up study of developmental milestones. The applicant agreed to offer enrollment in this study to all subjects who are randomized into 17P-ES-003 at the sites participating in the infant follow-up study. With this change, the applicant estimates that ASQ questionnaires may be received from as many as 584-750 subjects (as opposed to the previous target of 375). A revised protocol will be submitted in March 2011. The applicant also agreed to submit a preliminary report on infants who have completed the 2-year follow-up period at the time when the last subject completes 17P-ES-003, and a subsequent final report of the outcomes of all infants approximately two years later.

As of October 29, 2010, 59 US subjects have consented to be contacted at month 23 following their child's birth to consent for this follow-up study.

Reconsideration of the primary efficacy endpoint in 17P-CT-002. The applicant's original clinical trial, 17P-CT-002, demonstrated a significant reduction in the rate of preterm births < 37⁰ weeks with HPC treatment as compared to vehicle ($p < 0.001$). At the time the trial was initially reviewed, DRUP and the ACHRD members gave this finding less weight because of assumptions that most infants born at 36 or 35 weeks gestation were at little risk for long-term morbidities. In this review cycle, DRUP reviewed recent publications in the literature discussing the developmental and physiologic immaturity of late preterm births.

Late preterm births account for roughly 70% of all preterm births in the US. In 2005, an NIH-sponsored workshop entitled “Optimizing Care and Outcome of the Near-Term Pregnancy and the Near-Term Newborn Infant” recommended that infants born at 34⁰ through 36⁶ weeks gestation be referred to as “late preterm” to emphasize that these infants are in fact preterm, and at increased risk (compared to term infants) of immaturity-related medical complications. For example, late preterm infants are more likely than term infants to be diagnosed during the birth hospitalization with temperature instability, hypoglycemia, respiratory distress, apnea, jaundice and feeding difficulties. During the first month after birth, late preterm infants are more likely than term infants to be re-hospitalized for jaundice, feeding difficulties, dehydration and suspected sepsis.¹⁰ Compared with term infants, infants born at 36 or 35 weeks were five or nine times as likely to be ventilated as term infants.¹¹ In addition, the neonatal mortality rate (deaths at 0-27 days) for late preterm infants in the US was 4.6 times higher in 2002 than the rate for term infants (4.1 vs. 0.9 per 1000 live births).¹² Even healthy-appearing late preterm infants carry an increased risk for developmental delays and adverse early school-age outcomes compared with healthy term infants.¹³

Exploration of the effect of maternal race on the safety and effectiveness of HPC.

Approximately 59% of enrollees on 17P-CT-002 were African American; 26% were Caucasian, 14% were Hispanic and < 1% were Asian. HPC treatment reduced the rate of preterm birth <37⁰ weeks compared to vehicle for both the African American (36.1 % vs. 52.2%) and the non-African American (38.6% vs. 58.7%) populations.

In this review cycle, Dr. Kammerman evaluated Kaplan Meier curves depicting the proportion of women remaining pregnant as a function of gestational age at delivery for African American and non-African American women. Although the overall curves for the racial subgroups mimicked those for the overall trial population, some differences were noted. Among African American women, there was a small difference in the proportion of women remaining pregnant between 20-24 weeks that favored vehicle treatment; after 24 weeks, women receiving HPC were more likely to remain pregnant than women receiving vehicle, suggesting a treatment benefit. Among non-African American women, there was a difference in the proportion of women remaining pregnant between 18-33 weeks that favored vehicle treatment; after 34 weeks, women receiving HPC had higher rates of remaining pregnant than women receiving vehicle. These patterns suggest that treatment benefit in non-African American women may be greatest at later gestational ages. However, when the Kaplan Meier curves are displayed simultaneously, the curves for African American and non-African American women receiving HPC are super-imposable. In contrast, curves for the vehicle treated women suggest differences in the rates of preterm delivery that are independent of race. See figure below.

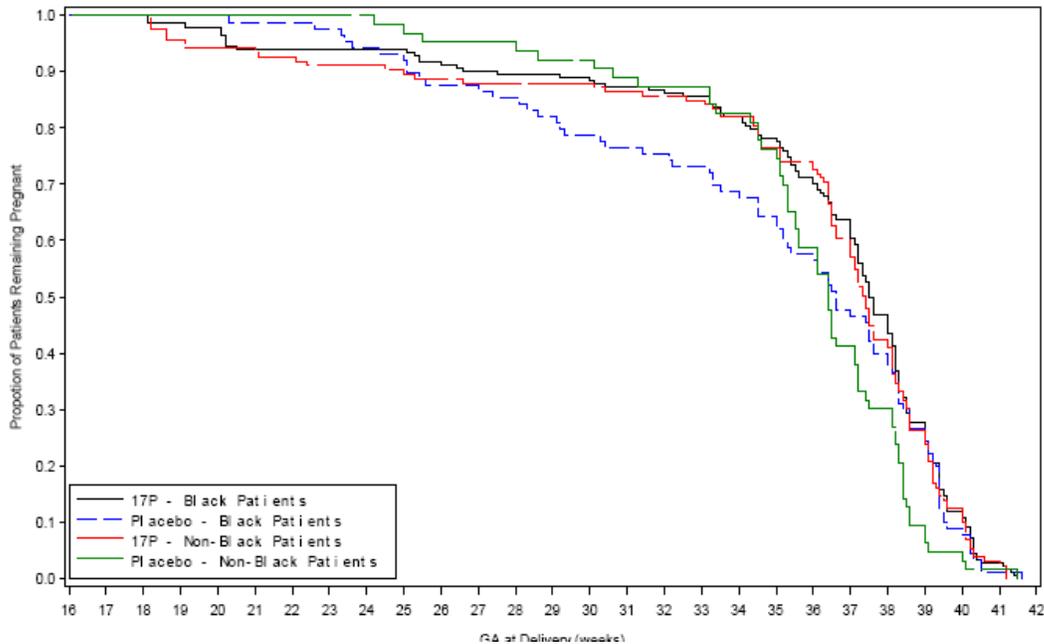
¹⁰ Engle WA, Tomasek KM, Wallman C, and the Committee on Fetus and Newborn. “Late-Preterm Infants: A Population at Risk. *Pediatrics* 2007;120:1390-1401. McIntire DD, and Leveno KJ. Neonatal Mortality and Morbidity Rates in Late Preterm Births Compared with Births at Term. *Obstet. Gynecol.* 2008;111:35-41.

¹¹ Escobar GJ, Clark RH, and Greene JD. Short-Term Outcomes of Infants Born at 35 and 36 Weeks Gestation: We Need to Ask More Questions. *Semin. Perinatol.* 2006;30:28-33. *See also* Kitsommart R, Janes M, Mahajan V et al. Outcomes of Late-Preterm Infants: A Retrospective, Single-Center, Canadian Study. *Clinical Pediatrics* 2009;48:844-850.

¹² Engle WA et al. 2007.

¹³ Morse SB, Zheng H, Tang Y, and Roth J. Early School-Age Outcomes of Late Preterm Infants. *Pediatrics* 2009;123:e622-e629.

Proportion Remaining Pregnant by Race and Treatment



Source: Hologic, Inc., February 2, 2011

Further exploration of gestational age at randomization suggested that among African American women, those who enrolled at < 18 weeks gestation derived the greatest benefit of HPC treatment. In contrast, among non-African American women, those who enrolled between 18-20 weeks gestation derived the greatest benefit of HPC treatment. This observation may be explained by varying rates of preterm delivery among vehicle-treated women. The confirmatory trial (17P-ES-003) will stratify subjects by gestational age at randomization and should allow for a better assessment of the impact, if any, of gestational age at randomization on the effect of HPC treatment.

Taken together, there were a total of 30 pregnancy losses on 17P-CT-002, including miscarriages, stillbirths and neonatal deaths; 19 (6.2%) occurred on HPC treatment and 11 (7.2%) on vehicle treatment. Among African American women, there were 11 such losses in 181 HPC-treated women (6.1%) and 8 losses in 90 vehicle-treated women (8.9%); among non-African American women, there were 8 losses in 125 HPC-treated women (6.4%) and 3 losses in 63 vehicle-treated women (4.8%). These are crude rates and do not account for time on trial medication. No definitive conclusions can be drawn given the small numbers of events in these subgroups. Further exploration of the effect of race on fetal and neonatal outcomes may be accomplished in the larger confirmatory trial, 17P-ES-003.

Regulatory action. At the conclusion of this third review cycle, acknowledging more recent concerns regarding the increased morbidity and mortality of late preterm births relative to term births, DRUP now recommends and I concur, that reduction in preterm births < 37⁰ weeks is an adequate surrogate for clinical benefit (i.e., reduction in neonatal morbidity and mortality). Further, the effect of HPC treatment to reduce preterm births < 37⁰ weeks compared to vehicle as observed in 17P-CT-002 was sufficiently persuasive

($p < 0.001$) to meet the level of statistical significance generally expected to support approval based on the findings of a single trial. I therefore concur with the conclusion that 17P-CT-002 was an adequate and well-controlled trial that established the effect of HPC treatment on an adequate surrogate that is reasonably likely to predict clinical benefit, and that the trial findings support approval of HPC in accordance with Subpart H accelerated approval regulations (21 CFR 314.510). The applicant has further demonstrated the feasibility of conducting the ongoing confirmatory clinical trial, 17P-ES-003, and preliminary results from this trial do not raise any new safety or efficacy concerns.

Product labeling for Makena (hydroxyprogesterone caproate) will reflect the findings of 17P-CT-002, including the statistically significant reduction in preterm births $< 37^0$ weeks, as well as trends in favor of HPC treatment in lowering the risk of preterm births $< 35^0$ and $< 32^0$ weeks. Labeling will reflect the uncertainty around the treatment effects at $< 35^0$ and $< 32^0$ weeks, and the limited number of preterm births at $< 32^0$ weeks. Maternal complications, fetal losses, neonatal deaths and neonatal morbidity will be described. Available data regarding development milestones in children born to mothers from this trial will also be described. A patient package insert will inform women of the risks associated with the use of the product.

Although Dr. Kammerman continues to articulate her concern that the level of evidence from the applicant's single controlled trial (17P-CT-002) is not convincing to support the effectiveness of HPC, her comments regarding product labeling and the applicant's protocols for the required postmarketing studies have been considered fully and substantially incorporated. Additionally, it is anticipated that the ongoing large confirmatory trial (17P-ES-003) and infant follow-up study (17P-FU-004) will address many of her concerns. Should the clinical and statistical reviewers conclude that further revisions to the statistical analysis plans of these studies are needed, these recommendations will be conveyed to the applicant.

Clinical Pharmacology

Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which HPC reduces the risk of preterm birth is not known. Following a single intramuscular injection of 1000 mg HPC, peak serum levels appeared after 3-7 days in non-pregnant female subjects.

The pharmacokinetics of the 250 mg dose of HPC has not been evaluated. There is currently no pharmacokinetic information for HPC in pregnant women available for FDA review. The applicant has agreed to submit the final publication of results from an ongoing NIH-sponsored trial at the University of Pittsburgh evaluating the pharmacokinetics of HPC and its metabolites in pregnant women throughout different gestational stages. If this trial does not sufficiently address FDA's concerns, the applicant has agreed to conduct a post-approval trial in pregnant women to characterize the pharmacokinetics of HPC and its metabolites in plasma and urine throughout the different gestational stages (see **Cycle 2: April 25, 2008 to January 23, 2009**). In addition, the applicant will obtain sparse pharmacokinetic samples from approximately 450 pregnant women enrolled in the ongoing 17P-ES-003 trial to assess exposure-

response relationships and the effect of body weight and other covariates on the pharmacokinetics of HPC.

In vitro data indicate that the metabolism of HPC is predominantly mediated by CYP3A4 and CYP3A5. The effect of renal or hepatic impairment on the pharmacokinetics of HPC has not been evaluated.

An *in vitro* metabolism study using human liver microsomes and CYP isoform-selective substrates indicated that HPC increased the metabolic activity of CYP1A2, CYP2A6, and CYP2B6. Product labeling will state that the clearance of drugs metabolized by CYP1A2 (e.g., theophylline, tizadine, clozapine), CYP2A6 (e.g., acetaminophen, halothane, nicotine), or CYP2B6 (e.g., efavirenz, bupropion, methadone) may be increased during treatment with HPC. The applicant has agreed to conduct a post-approval *in vitro* study in human hepatocytes to determine whether HPC induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.

Safety

A total of 463 pregnant women at risk for spontaneous preterm delivery were enrolled in trial 17P-CT-002; 310 subjects received weekly injections of 250 mg HPC and 250 received injections of a castor oil vehicle. The most common adverse reactions reported in women receiving at least one injection were: injection site pain, injection site swelling, and urticaria. Serious maternal and fetal complications observed in this trial are discussed above (under **Cycle 1: April 20, 2006 to October 20, 2006**). No new safety concerns have been identified in preliminary analyses of blinded adverse events reported on the applicant's ongoing confirmatory clinical trial.

Use in pregnancy. There are no adequate and well-controlled studies of HPC in women during the first trimester of pregnancy. Safety data from trial 17-P-CT-002 in women exposed to weekly HPC in their second and third trimesters, as well as long-term follow-up information in 194 of their infants did not demonstrate any teratogenic risks to infants from *in utero* exposure. The pregnancy risk category for HPC will be designated as category B. Hydroxyprogesterone caproate is not intended for use to stop active preterm labor.

Use in nursing mothers. Hydroxyprogesterone caproate should be discontinued at 37 weeks gestation or upon delivery. Although detectable amounts of progestins have been identified in the milk of mothers receiving progestin treatment, no adverse effects have been observed in breastfeeding performance, or on the health of the infant.

Labeled contraindications and warnings. Labeling for HPC will carry several contraindications and warnings consistent with the known effects of progestins. Hydroxyprogesterone caproate should not be used in women with: current or history of thrombosis or thromboembolic disorders; known or suspected breast cancer, other hormone-sensitive cancer or history of these conditions; undiagnosed abnormal vaginal bleeding unrelated to pregnancy; cholestatic jaundice of pregnancy; liver tumors or active liver disease; or uncontrolled hypertension.

Treatment with HPC should be discontinued if an arterial or deep venous thrombotic or thromboembolic event occurs. Pre-diabetic and diabetic women should be carefully monitored for evidence of decreased glucose tolerance. Women with conditions that might be influenced by fluid retention (such as pre-eclampsia) should be carefully monitored as progestins may cause some degree of fluid retention. Women with a history of clinical depression should be monitored and treatment discontinued if clinical depression recurs. Healthcare providers should consider whether the benefits of treatment warrant continuation of use in women who develop jaundice or hypertension while receiving HPC.

In addition, there is a labeled warning for allergic reactions, since the castor oil vehicle has been associated with reports of urticaria, pruritus and angioedema.

Pediatric Considerations

Pediatric Use. The safety and effectiveness of HPC have not been established in pediatric patients less than 16 years of age. A small number of women under age 18 years have been studied. Safety and efficacy are expected to be the same in women aged 16 years and above as for users 18 years and older.

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 11 years because necessary studies are impossible or highly impracticable. This is because premenarcheal patients are not at risk of becoming pregnant, and the use of this product before menarche is not indicated. The applicant has fulfilled the pediatric study requirement for post-menarcheal pediatric patients by extrapolation of adult efficacy data.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Division of Drug Marketing, Advertising, and Communications (DDMAC), have concluded that the tradename "Makena" is acceptable. The applicant was notified of this determination on December 20, 2010.

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/s/

JULIE G BEITZ
02/03/2011