

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21945Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	February 3, 2011
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 021945 (Second Complete Response)
Applicant Name	Hologic, Inc.
Date of Submission	July 12, 2010
PDUFA Goal Date	April 13, 2011 (with 3-month extension)
Proprietary Name / Established (USAN) Name	Makena Hydroxyprogesterone caproate injection
Dosage Forms / Strength	Intramuscular (IM) injectable (250 mg/mL)
Indication (Final)	To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth
Proposed Regimen	One mL (250 mg) weekly starting at 16 wks 0 days (16 ⁰ wks) to 20 wks 6 days (20 ⁶ wks) gestation until 36 ⁶ wks or delivery
Action	<i>Approve under Subpart H 21 CRF314.510 (see Section 13.1)</i>

Material Reviewed/Consulted OND Action Package, including:	Names of Discipline Reviewers
Medical Officer Review	Barbara Wesley MD (primary reviewer)
Statistical Review	Lisa Kammerman PhD/Mahboob Sobhan PhD
Pharmacology Toxicology Review	Alexander Jordan PhD/Lynnda Reid PhD
CMC Review/ONDQA	Donna Christner PhD/Moo-Jhong Rhee PhD
Microbiology Review	John Metcalfe PhD/James McVey PhD
Clinical Pharmacology Review	Sandhya Apparaju PhD/Myong-Jin Kim PharmD
DDMAC	Janice Maniwang PharmD/Carrie Newcomer PharmD
DSI	Dylan Dalin Yao MD, PhD/Roy Blay PhD
CDTL	Lisa Soule MD (also clinical Team Leader)
OSE/DMEPA	Lubna Merchant MS, PharmD/Melina Griffis RPh
OSE/DRISK	Robin Duer MSBA, RN/LaShawn Griffiths MSHS-PH, RN

OND	Office of New Drugs
CMC	Chemistry, Manufacturing and Controls
DDMAC	Division of Drug Marketing, Advertising, and Communication
DSI	Division of Scientific Investigations
CDTL	Cross-Discipline Team Leader
OSE	Office of Surveillance and Epidemiology
DMEPA	Division of Medication Errors Prevention and Analysis
DRISK	Division of Risk Management

TABLE OF CONTENTS

1. Introduction.....	4
2. Background.....	5
2.1 Description of Drug Product.....	5
2.2 Regulatory History.....	6
2.2.1 Activities prior to NDA Submission.....	6
2.2.2 Original NDA Submission (First Review Cycle)	6
2.2.2.1 Overview of Study 17P-CT-002	7
2.2.2.2 Efficacy Findings (Study 17P-CT-002).....	8
2.2.2.3 Overall Assessment of Efficacy.....	11
2.2.2.4 Safety Findings from the First Review Cycle.....	11
2.2.2.5 Overall Assessment of Safety Findings	14
2.2.2.6 Advisory Committee Recommendations	15
2.2.2.7 Regulatory Action at End of First Review Cycle	16
2.2.3 Dispute Resolution Request by Applicant.....	18
2.2.4 Applicant's First Complete Response.....	18
2.2.4.1 Overview of Submission.....	18
2.2.4.2 Assessment of the Adequacy of the Complete Response	18
2.2.4.3 Regulatory Action at End of Second Review Cycle.....	18
2.2.5 Applicant's Second Complete Response	19
2.3 Reassessment of the Clinical Significance of Late Preterm Births.....	19
2.4 Recommendations of the Primary Clinical Reviewer, Cross-Discipline Team Leader, and Primary Statistical Reviewer regarding Approvability Based on the Applicant's Second Complete Response.....	21
3. CMC.....	22
3.1 First Complete Response Review Cycle.....	22
3.2 Current Submission.....	22
4. Nonclinical Pharmacology/Toxicology	22
4.1 First Complete Response Review Cycle.....	22
4.2 Current Submission.....	23
5. Clinical Pharmacology/Biopharmaceutics.....	23
5.1 Original Review Cycle.....	23
5.2 Current Submission.....	24
6. Clinical Microbiology.....	24
7. CLINICAL/STATISTICAL-EFFICACY.....	24
7.1 Exploratory Efficacy Analyses	25
7.2 Statistical Reviewer's Overall Assessment.....	28
7.3 Confirmatory Efficacy and Safety Study (Protocol 17P-ES-003 [Original Version])	30
7.3.1 General Study Design	30
7.3.2 Study Objectives and Endpoints	31
7.3.3 Statistical Analyses	31
7.4 Revisions to Protocol 17P-ER-003 (Current Review Cycle).....	32
7.5 Status of Study 17P-ES-003 and Data Safety Monitoring Board.....	32
7.5.1 Status of Study 17P-ES-003.....	32

7.5.2 Data Safety Monitoring Board.....	33
8. Safety (Current Submission).....	33
8.1 Applicant’s Safety Update	34
8.1.1 Overview.....	34
8.1.2 Deaths and Serious Adverse Events	34
8.2 Noninterventional Follow-Up Study of Children of Mothers Treated in Study 17P-ES-003 (Protocol 17P-FU-004 [Original Version]).....	34
8.2.1 Revised Protocol 17P-FU-004.....	35
9. Advisory Committee Meeting.....	36
10. Pediatrics.....	36
11. Other Relevant Regulatory Issues.....	36
12. Labeling	36
13. Decision/Action/Risk Benefit Assessment	37
13.1 Recommended Regulatory Action.....	37
13.2 Risk/Benefit Assessment	38
13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS).....	39
13.4 Recommendation for other Postmarketing Requirements and Commitments.....	39
13.4.1 Postmarketing Requirements	39
13.4.2 Postmarketing Commitments.....	40

1. INTRODUCTION

Preterm birth, defined as birth prior to 37⁰ completed weeks of gestation, is a significant public health problem in the United States (US), with an increasing prevalence currently estimated to affect 12% of all births. Rates of preterm birth in the United States also differ among ethnic groups. Although there are diagnostic tests that purport to identify women at risk for preterm labor and medications used off-label to treat preterm labor, there are no data indicating a definite benefit on neonatal morbidity or mortality from any of these interventions.

Currently there is no approved drug product in the US for prevention of preterm birth. Nevertheless, hydroxyprogesterone caproate (HPC), also known as 17 α -hydroxyprogesterone caproate, is being compounded by pharmacists and is being used widely for prevention of preterm birth in women at high risk. Although several drug products with tocolytic properties (i.e., stopping uterine contractions) are used off-label for treatment of preterm labor, randomized controlled trials have failed to demonstrate that these drugs significantly improve perinatal outcomes.

In 2003, the findings from a multicenter, randomized, vehicle-controlled, double-blind clinical trial of HPC in women at high risk for preterm birth were published.¹ This trial was sponsored by the National Institute for Child Health and Human Development (NICHD). The trial was conducted for the NICHD by the Maternal-Fetal Medicine Units (MFMU) Network, which at that time consisted of approximately 19 university-based clinical centers in the US. This trial (hereafter referred to as Study 17P-CT-002) showed a statistically robust reduction in preterm births < 37 weeks gestation, as well as statistically significant reductions in preterm births at < 35 weeks and < 32 weeks, in women with a prior spontaneous preterm birth (a population at high risk for recurrent preterm birth).

NDA 021945, for the use of HPC for the Applicant's originally proposed indication of *prevention of preterm birth in women with a prior history of at least one spontaneous preterm birth*, was first submitted to the Division of Reproductive and Urologic Products (DRUP) in April 2006. The clinical component of NDA 021945 was based largely on the data from the NICHD clinical trial (Study 17P-CT-002) and a follow-up safety study (Study 17P-FU) that enrolled children whose mothers had participated in Study 17P-CT-002. Following a priority review of NDA 021945, which included discussion of the NDA at the 2006 Advisory Committee for Reproductive Health Drugs (ACRHD), the Application received an Approvable Action in October 2006. The Application was not approved because of clinical, nonclinical toxicology, and chemistry, manufacturing and control (CMC) deficiencies.

In April 2008, the Applicant submitted Complete Response #1. In the Complete Response, the Applicant adequately addressed the nonclinical toxicology and CMC deficiencies, but did not adequately address the clinical deficiencies. The Applicant did not provide sufficient documentation that the proposed confirmatory clinical trial, which would be required to support approval of the NDA under Subpart H regulations for accelerated approval, was feasible and was

1 Meis PJ et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 348: 2379-85, 2003.

likely to be completed successfully. On January 23, 2009, DRUP issued a Complete Response Letter.

In the current submission (Complete Response #2), the Applicant satisfactorily addressed the 2 clinical deficiencies listed in the Division's Complete Response Letter of January 2009. In regard to the first deficiency, the Applicant has provided the requested documentation that the confirmatory safety and efficacy trial (Study 17P-ES-003) has been initiated at both US and non-US sites and has enrolled more than 5% of the planned 1,700 subjects. In regard to the second deficiency, the Applicant had previously submitted an acceptable protocol (Study 17P-FU-004) for developmental assessment at ages 18-24 months of children whose mothers had participated in Study 17P-ES-003. The current submission does not include any new nonclinical, CMC, or clinical pharmacology data. The only significant approvability issue that has been identified during the current review cycle was whether the efficacy findings in Study 17P-CT-002 were sufficient to support approval of the Application under Subpart H regulations. All of the primary reviewers, with the exception of the Statistical Reviewer (who does not believe that the Applicant has provided sufficient evidence of efficacy to support approval, see Section 7.2) have concluded that this Application can be approved. The primary Clinical Reviewer and the Cross Discipline Team Leader (CDTL)/Clinical Team Leader have further recommended that this NDA be approved under Subpart H regulations for accelerated approval. I concur with the recommendations that the Applicant has provided sufficient safety and efficacy data to support approval of NDA 021945 under Subpart H 21 CFR 314.510 (see Section 13).

During the current review cycle, it was decided on January 4, 2011, to treat this Application as if it were an NDA for a new molecular entity (NME) because of (1) the long period that has elapsed since HPC was last marketed as an FDA-approved drug product in the US and (2) the complexity of the review issues. As such, the signatory authority for this NDA has been transferred to the Office of Drug Evaluation III.

2. BACKGROUND

2.1 Description of Drug Product

Hydroxyprogesterone caproate was initially approved by the FDA in 1956 for use in pregnant women (NDA 10-347; Delalutin®). The approved indications included the treatment of habitual, recurrent, and threatened abortion. This approval was based largely on safety considerations in that it occurred prior to the FDA Drug Amendment of 1962, which required that drugs must have substantial evidence of efficacy in addition to evidence of safety in adequate and well-controlled trials. In 2000, the FDA withdrew approval for Delalutin. This action was taken at the request of the holder of the NDA. The action was not taken because of safety concerns.

The proposed drug product that is the subject of this Application (Makena) will be supplied as 5 mL of a sterile solution in a multidose glass vial. Each 5 mL vial will contain HPC USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v). The dosing regimen for the proposed indication is a once-weekly one mL intramuscular injection by a healthcare provider beginning between 16 weeks 0 days (16⁰ weeks) gestation and 20 weeks 6 days (20⁶ weeks) of gestation. Makena is

to be administered once weekly through Week 36⁶ (36 weeks 6 days) of gestation or delivery, whichever occurs first.

2.2 Regulatory History

2.2.1 Activities prior to NDA Submission

After data from Study 17P-CT-002 were published in the New England Journal of Medicine in 2003, Adeza Biomedical (the original Applicant for NDA 021945) met with DRUP to discuss the possibility of using the data supporting the publication as the basis for an NDA for HPC for the indication of prevention of preterm birth in pregnant women with a previous spontaneous preterm birth. Because Study 17P-CT-002 had not been designed as a clinical trial to support marketing approval of HPC, DRUP conveyed several recommendations and concerns to the Applicant during this and subsequent meetings. These recommendations and/or concerns included:

- The lack of follow-up data, beyond the period of initial hospital assessment, of children whose mothers had received HPC for the prevention of preterm birth. DRUP requested that the Applicant obtain follow-up developmental and safety data through at least 2 years of age for children whose mothers had participated in Study 17P-CT-002.
- Clinical trial data supporting the safety and efficacy of HPC for the proposed indication would be derived primarily from only a single adequate and well-controlled trial. The Applicant was informed that generally data from 2 adequate and well-controlled trials were required for marketing approval.

2.2.2 Original NDA Submission (First Review Cycle)

In support of their original NDA submission, the Applicant submitted data from 2 active treatment clinical trials and a follow-up safety study (see Table 1). The primary source of data in support of the efficacy and safety of HPC was Study 17P-CT-002.

Table 1 Clinical Studies of HPC in Original Submission of NDA 021945

Study # / Status	Study Design	Study Population	Treatment Dose	Duration of Drug Treatment	Number of Subjects Enrolled	Number of Black/ Non-Black Subjects	Mean Age (Range)
17P-IF-001 Terminated Mar 1999 ^A	Double-blind, Vehicle-controlled, Randomized 2:1 HPC to Vehicle	Pregnant women with previous spontaneous preterm birth	250 mg HPC per week	Weekly injections beginning from 16 ⁰ to 20 ⁶ wks gestation until 36 ⁶ wks gestation or delivery	Total: 150 HPC: 94 Vehicle: 56	Total: 95/55 HPC: 54/40 Vehicle: 41/15	26.2 yr (17, 42)
17P-CT-002 Completed Aug 2002 ^B	Double-blind, Vehicle-controlled, Randomized 2:1 HPC to Vehicle	Pregnant women with previous spontaneous preterm birth	250 mg HPC per week	Weekly injections beginning from 16 ⁰ to 20 ⁶ wks gestation until 36 ⁶ wks gestation or delivery	Total: 463 HPC: 310 Vehicle: 153	Total: 273/190 HPC: 183/127 Vehicle: 90/63	26.2 yr (16, 43)
17P-FU Completed Nov 2005	Observational long-term safety follow-up for Study 17P-CT-002	Infants discharged live in Study 17P-CT-002	None	No study treatment was administered	Total: 278 HPC: 194 Vehicle: 84	Total: 152/126 HPC: 105/89 Vehicle: 47/37	47.4 mo (30, 64)

^A Study 17P-IF-001 was terminated early by the Sponsor when the manufacturer recalled the study drug because of reduced potency. Of the 150 subjects, 104 subjects (65 randomized to HPC and 39 randomized to vehicle) had ended their treatment prior to termination of the study because (1) they had completed treatment with study drugs (i.e., completed study treatment to 36⁶ weeks of gestation or delivery had occurred) or (2) they had withdrawn prematurely for reasons other than recall of study drugs.

^B An independent Data and Safety Monitoring Committee (DSMC) reviewed the study data after 400 subjects had completed the study. Based on that interim dataset, (1) preterm births <37⁰ weeks of gestation (the primary endpoint), were significantly reduced in the HPC-treatment group relative to the control group and (2) the p-value for the difference was below the p-value specified in predefined stopping rules. The DSMC recommended that enrollment in the study be stopped, so that no new subjects would be assigned vehicle. By the time the study was stopped, 463 subjects had been enrolled, which was 92.5% of the proposed sample size of 500 subjects.

Source: Table 2, pg. 20 of the primary Clinical Review for NDA 021945, signed October 19, 2006.

2.2.2.1 Overview of Study 17P-CT-002

Study 17P-CT-002 was the primary Phase 3 clinical trial that assessed the efficacy and safety of HPC for the reduction of the risk of spontaneous preterm birth. Study 17P-CT-002 was a multicenter, randomized, double-blind, vehicle (placebo)-controlled clinical trial. The Study enrolled women (age: 16 to 43 years) with a singleton pregnancy who had a documented history of singleton spontaneous preterm birth (defined as delivery at < 37 weeks of gestation following spontaneous preterm labor or premature rupture of membranes). At the time of randomization (16⁰ to 20⁶ weeks), an ultrasound examination had confirmed gestational age and the absence of a known fetal anomaly. Women were excluded for prior progesterone treatment or heparin therapy during the current pregnancy, a history of thromboembolic disease, or maternal/obstetrical complications (such as current or planned cerclage, hypertension requiring medication, or a seizure disorder).

A total of 463 pregnant women were randomized to receive either HPC (N=310) or vehicle (N=153) at a dose of 250 mg administered weekly by intramuscular (IM) injection starting at 16⁰ to 20⁶ weeks of gestation, and continuing until 36⁶ weeks of gestation or delivery.

Demographics of the HPC-treated women were similar to those in the control group, and

included: 59.0% Black, 25.5% Caucasian, 13.9% Hispanic, and 0.6% Asian. The mean body mass index was 26.9 kg/m².

The primary protocol-defined objective for Study 17P-CT-002 was to determine if treatment with HPC, initiated between 16⁰ and 20⁶ weeks gestation, compared to treatment with vehicle, reduced the risk of preterm birth (birth < 37⁰ weeks gestation) in women who had previously experienced a prior spontaneous preterm birth. At the request of DRUP, the following secondary endpoints were added to the analyses of the study:

- Whether treatment with HPC, compared to vehicle, reduced the risk of preterm birth < 35⁰ and < 32⁰ weeks gestation.
- Whether treatment with HPC reduced overall neonatal morbidity/mortality based on a composite measure of neonatal morbidity and mortality.

Division Director's Comment

- *The Division requested that the Sponsor also evaluate reduction in preterm births at < 35⁰ and < 32⁰ weeks gestation because of the greater morbidity/mortality associated with premature births at these ages as compared to births at < 37⁰ weeks.*

2.2.2.2 Efficacy Findings (Study 17P-CT-002)

Percentages of Subjects with Preterm Births

The percentages of subjects with a preterm birth in the HPC and vehicle (placebo) treatment groups and the mean treatment differences at < 37⁰ weeks gestational age (protocol defined primary endpoint) and at < 35⁰ and < 32⁰ weeks gestational age (secondary endpoints) are listed in Table 2.

Table 2 Percentages (Mean and 95% Confidence Interval) of Subjects with Preterm Births at <37⁰, <35⁰, and, <32⁰ Weeks Gestation (Study 17P-CT-002, FDA and Applicant Analyses)

Gestation Age at Birth	HPC ^A (N=310)	Vehicle (N=153)	Mean Treatment Differences [95% Confidence Interval] ^B
	Percent of Preterm Births		
< 37 ⁰ weeks	37.1	54.9	-17.8% [-28%, -7%]
< 35 ⁰ weeks	21.3	30.7	-9.4% [-18.7%, -0.4%]
< 32 ⁰ weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

^A Four HPC-treated patients were lost-to-follow-up. They are counted as deliveries at their gestational ages at time of last contact (18⁶, 22⁰, 34⁴, and 36⁶ weeks).

^B To preserve the overall type I error rate of 0.05, the adjusted confidence intervals (equivalent to a 96.6% confidence interval) use the final p-value boundary of 0.0345.

Source: Table 3.1, FDA Statistical Review, signed October 19, 2006

(b) (4)

(b) (4)

Division Director's Comments

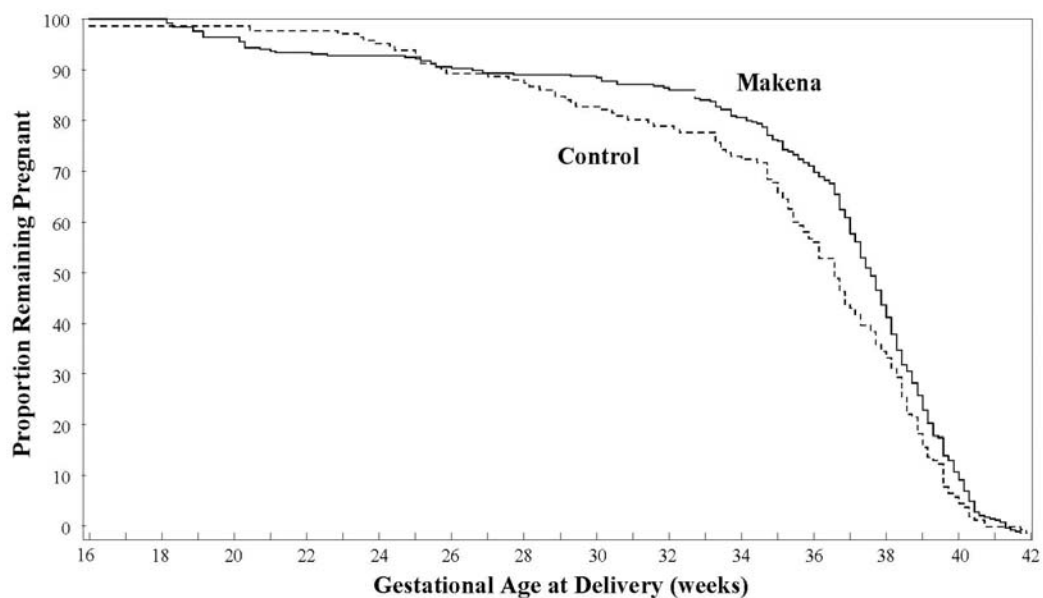
- *There was a statistically significant treatment effect of HPC in reducing the percentage of subjects with a recurrent preterm birth at < 37⁰, < 35⁰, and < 32⁰ weeks gestational age after adjusting for the 2 interim analyses and the final analysis to preserve the overall type I error rate of 0.05.*
- *Based on an analysis by the Applicant, the benefit of treatment for preterm birth of < 37⁰ weeks gestation appeared to remain consistent over varying levels of maternal risk, as*

measured by maternal race, number of prior preterm births, and gestational age of the qualifying preterm birth.

- *The reduction in recurrent preterm births for < 37⁰ weeks gestation was statistically persuasive ($p < 0.001$) and met the level of statistical significance acceptable to support approval of a drug product based on a single adequate and well-controlled trial. The reduction in preterm births at earlier gestational ages (i.e., < 35⁰ weeks and < 32⁰ weeks), although statistically significant, did not meet the level of statistical significance generally expected to support approval of a drug product based on the findings from a single clinical trial.*

The proportion of women remaining pregnant in Study 17-CT-002 as a function of gestational age is shown in Figure 1. Prior to approximately 25 weeks gestation, a numerically greater proportion of subjects randomized to the HPC group delivered prematurely; after 28 weeks gestation, a greater proportion of subjects randomized to the vehicle group delivered prematurely.

Figure 1 Proportion of Women Remaining Pregnant as a Function of Gestational Age (Study 17P-CT-002)



	Number at Risk													
Makena	3	108	215	296	293	286	281	280	273	259	228	141	38	0
Control	2	56	113	152	148	139	137	129	123	114	89	55	11	0

Source: Applicant's submission of July 20, 2006, and to-be-approved Physician Labeling.

Division Director's Comments

- *The increased proportion of preterm births in HPC-treated subjects, relative to the vehicle-treated subjects, up to a gestational age of approximately 25 weeks was due, in part, to 5 miscarriages (spontaneous abortions) in the HPC group (see Section 2.2.2.4 [early pregnancy losses] and Table 6). After adjusting for time in the study, 7.5% of HPC-treated subjects delivered prior to 25-weeks gestation compared to 4.7% of controls subjects. Whether treatment with HPC contributed to these early pregnancy losses is not known and will be investigated further in the Applicant's ongoing post-approval trial.*

- *The mean gestational age at delivery for subjects with available outcome data was one week greater in the HPC group (36.2 weeks vs. 35.2 weeks). The median prolongation of pregnancy (defined as the time from randomization until delivery or date that the subject was last confirmed to be pregnant) was higher in the HPC group compared to the vehicle group (131 days vs. 125 days).*

Because a single center, the University of Alabama, contributed 27% of the subjects in Study 17P-CT-002, FDA requested that the Applicant provide an analysis of the percentages of preterm births by treatment group for the Alabama site alone, for all the other sites excluding Alabama, and for all centers combined. Results of this analysis are presented in Table 3.

Table 3 Percentages of Preterm Births – Effect of University of Alabama (Study 17P-CT-002)

Gestational Age at Birth (weeks)	Percentage of Preterm Births								
	University of Alabama			All Other Centers Combined			All Centers Combined		
	HPC (n=86)	Vehicle (n=40)	Diff.	HPC (n=224)	Vehicle (n=113)	Diff.	HPC (n=310)	Vehicle (n=153)	Diff.
< 37	26.7	45.0	-18.3	41.1	58.4	-17.3	37.1	54.9	-17.8
< 35	17.4	27.5	-10.1	22.8	31.9	-9.1	21.3	30.7	-9.4
< 32	10.5	25.0	-14.5	12.5	17.7	-5.2	11.9	19.6	-7.7

Source: Applicant's submission of October 10, 2006.

Division Director's Comments

- *The rates of preterm birth at < 37⁰ and < 35⁰ weeks gestation were numerically lower in both the HPC and vehicle groups at the University of Alabama compared to the rates at the other centers combined. Nevertheless, the treatment effects (i.e., the differences in the percentages of preterm births between HPC and vehicle groups) at < 37⁰ and < 35⁰ weeks were similar at the Alabama site, the other centers combined, and all centers combined. This analysis indicates that the results from the Alabama site are not responsible for the overall observed treatment effect at < 37⁰ and < 35⁰ weeks gestation.*
- *For < 32⁰ weeks gestation, however, the benefit of treatment at the Alabama site was numerically greater than that at the other centers combined (treatment effect of -14.5% [Alabama] vs. -5.2% [other sites combined]). Thus, it may not be appropriate to extrapolate the mean treatment effect observed at < 32⁰ weeks gestation in Study 17P-CT-002 to the general population of pregnant women at high risk for a recurrent preterm birth. The Applicant, however, submitted several analyses that supported their contention that the overall finding of a treatment benefit for HPC at < 32⁰ weeks gestation was not driven by the effect at the Alabama site.*

Neonatal Outcomes and Morbidities other than Death

Additional endpoints evaluated neonatal outcomes, including the proportions with birth weight of < 2,500 and < 1,500 g. The HPC group had a statistically significantly lower percent of < 2,500 g infants (27% compared to 41% of vehicle-exposed neonates). The trend toward a lower proportion of < 1,500 g infants (8.6% in the HPC group vs. 13.9% in the vehicle group), however, was not statistically significant. Mean birth weight was numerically, but not statistically greater in the HPC treatment group.

The Applicant, at the request of DRUP, also provided a composite index of neonatal morbidity/mortality that was based on the proportion of neonates who experienced one or more of the following: death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis, or necrotizing enterocolitis (NEC). A lower proportion of neonates in the HPC-group (11.9% HPC group vs. 17.2% vehicle group) experienced at least one event of the composite morbidity/mortality index. This difference, however, was not statistically significant. There also was a numerical decrease in the neonatal mortality rate (2.6% in the HPC group vs. 5.9% in the placebo group), but this difference also was not statistically significant (see Table 6).

Division Director's Comment

- *The clinical trial was not adequately powered to show a reduction in neonatal morbidity/mortality.*

2.2.2.3 Overall Assessment of Efficacy

In a single adequate and well controlled trial (Study 17P-CT-002), treatment with HPC, compared to treatment with vehicle, reduced the percentage of women with a preterm birth < 37⁰ weeks gestation from 54.9% (vehicle group) to 37.1% (HPC group). The effect of HPC treatment in reducing preterm births < 37⁰ weeks gestation was sufficiently persuasive ($p < 0.001$) to meet the level of statistical significance generally expected to support approval of a new drug product based on the findings of a single trial. The proportions of women delivering at < 35⁰ and < 32⁰ weeks also were lower among women treated with HPC compared to those treated with vehicle. These latter changes, although statistically significant, did not meet the level of statistical significance generally expected to support approval of a drug product based on the findings from a single clinical trial.

Additional endpoints evaluated neonatal outcomes that included the proportions of infants with birth weight of < 2,500 and < 1,500 g. There was a statistically significant decrease in infants < 2,500 g in the HPC group (27% HPC group vs. 41% vehicle group). The trend toward a lower proportion of < 1,500 g infants (8.6% in the HPC group vs. 13.9% in the vehicle group), however, was not statistically significant. Mean birth weight was numerically higher in the HPC group, but the difference was not statistically significant.

2.2.2.4 Safety Findings from the First Review Cycle

The safety findings, based on review of the original NDA submission, have been presented in detail in the primary Medical Review of Dr. Wesley (signed on October 19, 2006) of the original submission.

Study 17P-CT-002

Maternal Deaths and Serious Adverse Events

There were no maternal deaths in Study 17P-CT-002. There were 3 reports of a serious adverse event (SAE) in the mothers, all in the HPC group; none were thought by the investigators to be related to the study drug. The SAEs were: one case of a pulmonary embolus 8 days after delivery; one case of cellulitis at the study medication site; and one case that included postpartum hemorrhage, respiratory distress, and endometritis.

Discontinuations Secondary to Adverse Events

In Study 17P-CT-002, 7 (2.2%) of the HPC-treated subjects discontinued therapy prematurely due to adverse events compared to 4 (2.6%) of vehicle-treated subjects. In the HPC-treatment

group, the adverse events and the numbers of subjects reporting them were urticaria (n=3), injection site pain or swelling (n=2), arthralgia (n=1), and weight gain (n=1). In the vehicle-treatment groups, the adverse events and the numbers of subjects reporting them were pruritus (n=2), urticaria (n=1), and injection site pain (n=1).

Common Adverse Reactions

The most common adverse reaction, injection site pain, was reported after at least one injection by 34.8% of the HPC group and 32.7% of the control group. Table 4 lists adverse reactions that occurred in $\geq 2\%$ of subjects and at a higher rate in the HPC group than in the control group.

Table 4 Adverse Reactions Occurring in $\geq 2\%$ of HPC-Treated Subjects and at a Higher Rate than in the Control Subjects (Study 17P-CT-002)

Preferred Term	HPC N=310 %	Vehicle N=153 %
Injection site pain	34.8	32.7
Injection site swelling	17.1	7.8
Urticaria	12.3	11.1
Pruritus	7.7	5.9
Injection site pruritus	5.8	3.3
Nausea	5.8	4.6
Injection site nodule	4.5	2.0

Source: Table 10 of the primary Clinical Review signed on October 19, 2006.

Selected Maternal Complications of Particular Interest

Pregnancy-related maternal complications or events that were numerically increased in the HPC-treated subjects as compared to the control subjects included admission for preterm labor (other than the delivery admission), preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios (Table 5).

Table 5 Selected Maternal Complications of Particular Interest (Study 17P-CT-002)

Pregnancy Complication	HPC N=310 %	Vehicle N=153 %
Admission for preterm labor ¹	16.0	13.8
Preeclampsia or gestational hypertension	8.8	4.6
Gestational diabetes	5.6	4.6
Oligohydramnios	3.6	1.3

¹ Other than delivery admission.

Source: Table 22, primary Clinical Review, signed October 19, 2006 and to-be-approved Physician Labeling.

Division Director's Comment

- The mean gestational age at the time of diagnosis of preeclampsia in the HPC group was 35.6 weeks compared to 33.9 weeks in the vehicle arm. The higher gestational age at birth of infants in the HPC arm could explain, in part, the numerically higher percentage of women with preeclampsia, gestational diabetes, and oligohydramnios in the HPC arm, as the incidence of these complications increases with increasing gestational age.*

Early Pregnancy Losses and Neonatal Deaths

The only clinical finding of significant concern in the original submission was an apparent increase in early pregnancy losses in the HPC-treated subjects in Study 17P-CT-002. The numbers and percentages of miscarriages, stillbirths, and neonatal deaths in each treatment group are listed in Table 6. There was a trend toward an increase in the second trimester miscarriage rate (pregnancy losses prior to 20 weeks of gestation) and a suggestion of a possible increase in the proportion of stillbirths (death of a fetus prior to or during delivery) in the HPC-treatment group. Conversely, the incidence of neonatal deaths was numerically reduced by slightly more than 50% in the HPC group (2.6% vs. 5.9%), although the difference was not statistically significant. The overall incidence of combined fetal and neonatal mortality from the onset of treatment to delivery was similar in the 2 treatment groups (19 of 306 [6.2%] in the HPC group and 11 of 153 [7.2%] in the vehicle group).

Table 6 Miscarriages, Stillbirths, and Neonatal Deaths (Study 17P-CT-002)

Pregnancy Outcome	HPC N=306 n (%) ^A	Vehicle N=153 n (%) ^A	Nominal P-value ^B
Miscarriages <20 weeks gestation	5 (2.4) ^C	0	0.17
Stillbirth	6 (2.0)	2 (1.3)	0.72
Antepartum stillbirth	5 (1.6)	1 (0.6)	---
Intrapartum stillbirth	1 (0.3)	1 (0.6)	---
Neonatal deaths	8 (2.6)	9 (5.9)	0.12
Total Deaths	19 (6.2)	11 (7.2)	0.69

^A Percentages are based on number of enrolled subjects and are not adjusted for time on drug.

^B No adjustment for multiple comparisons.

^C Percentage adjusted for the number of at-risk subjects (n=211) enrolled at < 20 weeks gestation.

Source: Table 11-6 and Table 11-9, Final Report for Study 17-CT-002.

Division Director's Comments

- *A similar trend toward an increase in the rates of miscarriage and possibly stillbirth was not observed in the HPC-treatment group in the smaller supportive Study 17P-IF-001.*
- *These findings were presented to the Advisory Committee for Reproductive Health Drugs in 2006. The recommendation of the majority of the members was that this observation required further investigation, but that the investigation could be conducted post-approval.*
- *Whether treatment with HPC contributed to these early pregnancy losses is not known and will be investigated further in the Applicant's ongoing trial (Study 17P-ES-003).*
- *Other studies in which HPC has been investigated to prevent preterm birth, which for the most part have been published subsequent to the original review of NDA 021945, have had differing findings (i.e., small numeric increases or decreases) in the proportion of early pregnancy losses in women treated with HPC relative to the control group. Most of these studies have been conducted in other populations (e.g., women at risk of preterm birth because of twin or triplet pregnancy or because of a short cervix). One study published in 1990, a meta-analysis of 4 published studies that appears to be based primarily on pregnancy outcomes in women with singleton pregnancies, showed a possible association of*

HPC with miscarriage, demonstrating a non-significant odds ratio of 1.30 (95% confidence interval 0.61 to 2.74).²

Infant Follow-Up Safety Study (Study 17P-FU)

Infants born to women enrolled in Study 17P-CT-002, who survived and were discharged from the nursery, were eligible for participation in a follow-up safety study. Of 348 eligible offspring, 79.9% were enrolled: 194 children of HPC-treated subjects and 84 children of vehicle-treated subjects. The primary assessment was the child's score on the Ages & Stages Questionnaire (ASQ), which evaluates communication, gross motor, fine motor, problem solving, and personal/social parameters. The proportion of children whose scores met the screening threshold for possible developmental delay in each developmental domain was similar for each treatment group (Table 7)

Table 7 Percentages of Children in Each Treatment Group Whose ASQ¹ Scores Met the Screening Threshold for Possible Developmental Delay

	17OHP-C N=193		Vehicle N=82	
	n	%	n	%
Occurrence of score <cutoff on at least one developmental area	53	27.5	23	28.0
Area of Development				
Communication	22	11.4	9	11.0
Gross Motor	5	2.6	3	3.7
Fine Motor	40	20.7	15	18.3
Problem Solving	20	10.4	9	11.0
Personal-Social	7	3.6	1	1.2

¹ Ages & Stages Questionnaire.

Source: Table 12-2, Final Report for Study 17P-FU.

Division Director's Comment

- *Although the follow-up study had data for ASQ Scores from only 275 children whose mothers had been treated with HPC or vehicle, the findings were reassuring and raised no signals of potential concern. Additional follow-up safety data will be obtained post-approval in Study 17-FU-004.*

2.2.2.5 Overall Assessment of Safety Findings

There were no clinical safety findings, with one possible exception (trend to an increased risk of early pregnancy losses), in the original NDA submission of April 2006 that might have precluded approval of HPC for the proposed indication. This assessment was based on data from Study 17P-CT-002 (the primary source of efficacy and safety data), supportive Study 17P-IF-001, Study 17P-FU (follow-up of children whose mothers participated in Study 17P-CT-002), and published medical literature.

2 Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Brit J Obstet Gynecol 97: 149-54, 1990.

There were no maternal deaths in the clinical development program for HPC. The Applicant reported a single case each of pulmonary embolus and injection site cellulitis as serious adverse reactions in HPC-treated subjects. Certain pregnancy-related maternal complications or events were numerically increased in the HPC-treated subjects as compared to control subjects, including preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios. The most commonly reported adverse reactions, reported in $\geq 2\%$ of subjects in Study 17P-CT-002, and at a higher rate in the HPC group than in the control group, were injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), and nausea (6%).

The clinical finding of most concern was a statically non-significant increase in early pregnancy losses in the HPC-treated subjects. This finding was discussed at the 2006 Advisory Committee meeting for HPC. The recommendation of the majority of the members was that this observation required further investigation, but the investigation could be conducted post-approval (see Section 2.2.2.6).

2.2.2.6 Advisory Committee Recommendations

The original Application was presented to the Advisory Committee for Reproductive Health Drugs (ACRHD) on August 29, 2006. The Advisory Committee was asked to vote on several issues that included the following:

Issue 1. Is a reduction in preterm birth prior to 37⁰, 35⁰, or 32⁰ weeks gestation an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity?

- The Committee stated that a reduction in preterm birth < 37⁰ weeks was not an adequate surrogate (yes: 5, no: 16) but that reductions in preterm birth < 35⁰ weeks (yes: 13, no: 8) and < 32⁰ weeks (yes: 20, no: 1) were adequate surrogates.

Division Director's Comment

- *At the time of the Advisory Committee meeting, the general consensus was that the greatest impact on neonatal morbidity and mortality was attributable to early preterm birth, e.g., births at < 35⁰ weeks of gestation. Since the time of the meeting, there has been reconsideration of this view, with new recognition of the impact of "late" preterm birth on infant morbidity and mortality. Late preterm birth is typically defined as birth between 34⁰ and 36⁶ weeks of gestation (see Section 2.3). For this reason, the Advisory Committee's overall opinion regarding the merits of a reduction in preterm births at < 37⁰ week gestation as an adequate surrogate for a reduction in fetal and neonatal morbidity/mortality is not likely to reflect views currently held by most obstetricians and pediatricians.*

Issue 2. Do the data provide substantial evidence that HPC treatment prevented preterm birth earlier than either 35⁰ or 32⁰ weeks gestation?

- The Committee (by a small majority) indicated that the data provided substantial evidence that HPC treatment prevented preterm birth < 35⁰ weeks (yes: 12, no: 9) but did not provide substantial evidence for < 32⁰ weeks (yes: 7, no: 14).

Division Director's Comment

- *The percent difference (and associated 95% confidence interval [CI]) for the proportion of preterm births at < 32⁰ weeks gestation between the HPC- and vehicle-treated subjects was incorrectly presented to the Committee as -7.7% (95% CI: -15.5%, 0.1%), indicating that the change was not statistically significant. Had the correct 95% CI of (-16.1%, -0.3%)*

been presented, it is likely that the vote for < 32⁰ weeks would have been similar to that for the effect of treatment on preterm births < 35⁰ weeks (yes: 12, no: 9). A change in the vote for < 32⁰ weeks is likely because the 95% CIs for the differences between the HPC- and vehicle-treatment groups at < 35⁰ and < 32⁰ weeks were virtually the same (see Table 2).

Issue 3. Is further study needed to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth and if so, should this information be obtained prior to approval for marketing or post-approval?

- The Committee was unanimous in its recommendation that further study was needed (yes: 21, no: 0), but a majority felt that this information could be obtained post-approval (pre-approval: 8, post-approval: 13).

Issue 4. Are the overall safety data obtained in Studies 17P-CT-002 and 17P-IF-001 and Study 17P-FU (long-term follow-up study) adequate and sufficiently reassuring to support marketing approval of HPC without the need for additional pre-approval safety data?

- A majority of the Committee voted that the existing safety data were sufficient to support marketing approval of HPC without the need for additional pre-approval safety data (yes: 13, no: 8).

Division Director's Comments

- *Overall, a majority of the Committee members indirectly expressed support for approval of HPC based on their votes regarding the following 3 issues:*
 - *Thirteen (13) of the 21 members voted that a reduction in preterm birth < 35⁰ weeks was an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity;*
 - *Twelve (12) of the 21 members voted that the Applicant's data provided substantial evidence that HPC treatment prevented preterm birth < 35⁰ weeks gestation; and*
 - *Thirteen (13) of the 21 members voted that the existing safety data were sufficient to support marketing approval of HPC without the need for additional pre-approval safety data.*
- *The Committee also was unanimous in recommending that further study was needed to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth, but a majority (13 of 21 members) stated that this information could be obtained post-approval.*

2.2.2.7 Regulatory Action at End of First Review Cycle

Approvable Action

An Approvable Letter was issued on October 20, 2006, that described clinical, CMC, and nonclinical toxicology information that would be required to obtain approval to market HPC for reducing the risk of preterm birth. The Approvable Letter conveyed to the Applicant that if outstanding deficiencies were satisfactorily addressed, approval under Subpart H 21 CFR 314.510 could be a possibility because a reduction in preterm births, the primary endpoint of Study 17P-CT-002, was a surrogate for a reduction in neonatal morbidity and/or mortality.

Content of Approvable Letter

The deficiencies and information needed to address the deficiencies outlined in the Approvable Letter included the following:

Clinical Deficiencies

1. Further study is needed to provide confirmatory evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly, or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation.
2. There are insufficient data to evaluate a potential association of HPC with an increased risk of early fetal loss (second trimester miscarriage and stillbirth).

Information Needed to Address the Clinical Deficiencies

1. Submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of HPC for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510.
2. Provide a draft protocol to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth. This could be assessed as a part of the confirmatory efficacy study referred to in Item No. 1 above.

Pharmacology and Toxicology Deficiency

There is a lack of nonclinical data from a multi-generational reproductive toxicology study for this product.

Information needed to address the toxicology deficiency

A GLP-compliant, multigenerational reproductive toxicology study needs to be performed, evaluating all stages of pregnancy during which dosing will be administered in humans. The study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior, and reproductive function, in offspring exposed in utero.

The letter also outlined additional issues that would need to be addressed postmarketing, if the product were to be approved:

Clinical (postmarketing requests)

1. Completion of the additional efficacy and safety study(ies) requested above under the description of clinical deficiencies will be required as a condition of an approval under Subpart H 21 CFR 314.510 (Item No. 1 above under clinical deficiencies) or as a formal phase 4 commitment (Item No. 2 above under clinical deficiencies).
2. Long-term post treatment safety data (at least through puberty) from children whose mothers had been treated with HPC is lacking in the NDA.
3. Additional developmental assessment is needed of children at ages 18-24 months whose mothers had been treated with HPC. This assessment could be obtained from the offspring of women enrolled in the confirmatory efficacy study or the safety study addressing early fetal loss.

Division Director's Comment

- *Postmarketing request No. 2 listed above was subsequently determined to be unnecessary, based on the findings from the Applicant's multigenerational reproductive toxicology study in rodents that showed no evidence of adverse effects of HPC treatment during pregnancy on future reproductive potential of the off-spring (see Section 4.1). If results of concern should be obtained in follow-up Study 17-FU-004, DRUP might decide to request a longer-term follow-up study under its FDAAA authorities, based on identification of a new safety signal.*

2.2.3 Dispute Resolution Request by Applicant

Following receipt of the Approvable Letter, the Applicant filed a Formal Dispute Resolution Request to the Office of Drug Evaluation III (ODE III) on March 16, 2007. Three requirements in the Approvable Letter were disputed: the need for a reproductive toxicology study, the need for a multicenter confirmatory efficacy trial, and the need for preapproval submission of a protocol to evaluate the potential increased risk of early fetal loss. Dr. Daniel Shames, Deputy Director of ODE III, reviewed the Applicant's arguments and concurred fully with the Division's decisions and requests as described in the Approvable Letter. This decision was conveyed to the Applicant on April 12, 2007.

2.2.4 Applicant's First Complete Response

2.2.4.1 Overview of Submission

In April 2008, the Applicant (now Cytec Corporation) submitted a Complete Response to the Division's Approvable Letter of October 2006. The Applicant's submission included (1) a draft clinical protocol (Study 17-ES-003) to confirm and expand upon the efficacy and safety findings from Study 17P-CT-002, (2) a draft protocol (Study 17-FU-004) for a follow-up study of the children whose mothers had participated in Study 17-ES-003, (3) a final report from a non-clinical multi-generational reproductive toxicology study in rodents, and (4) additional CMC information.

2.2.4.2 Assessment of the Adequacy of the Complete Response

The information provided in the original Complete Response submission or during the review cycle adequately addressed the CMC (see Section 3.1) and the nonclinical toxicology (see Section 4.1) deficiencies, but did not adequately address the clinical deficiencies. Although agreement was reached with the Applicant on the design of the confirmatory safety and efficacy clinical trial (Protocol 17-ES-003) during the review cycle (see Section 7.3 for a description of Protocol 17-ES-003), DRUP was concerned that the Applicant had not provided sufficient documentation that the trial was likely to be completed successfully, particularly if the trial was to be conducted primarily in the US. Largely because of this concern, a Complete Response letter was issued by DRUP on January 23, 2009. The basis for this concern is provided in Section 2.2.4.3 below.

2.2.4.3 Regulatory Action at End of Second Review Cycle

The Complete Response Letter identified the following clinical deficiencies and the steps that would need to be taken to resolve the deficiencies.

Clinical Deficiencies

1. You have not provided adequate documentation that it will be feasible for you to conduct and successfully complete the Confirmatory Study. The American College of Obstetrics

and Gynecology (ACOG) Committee Opinion³, issued in October 2008, on use of progesterone in women with a history of spontaneous preterm birth has raised our concern that successful completion of the placebo-controlled study that you have proposed is not likely to be feasible if the trial is conducted primarily in the US. We believe that the ACOG opinion has virtually established offering treatment with progesterone to such high-risk patients as a de facto standard of care. ... We believe that adequate assurance of feasibility can only be addressed by actual initiation of the trial.

2. Additional developmental assessment at ages 18-24 months is needed for children whose mothers participate in the Confirmatory Study.

Resolution of Clinical Deficiencies

1. The Confirmatory Study will need to enlist investigators at a sufficient number of US and non-US sites to support target enrollment of 1,700 subjects; ... Acceptable documentation of feasibility would include the following elements:
 - Documentation of IRB approval for at least 15 investigational sites (including US and non-US sites).
 - Enrollment of at least 5% of the total anticipated sample size.
 - Enrollment of at least 15 subjects at US study sites.
 - Agreement (with supporting evidence) to enroll at least 10% of the total sample of 1,700 subjects from US and Canadian sites.
2. Submit a final clinical protocol for a study that will provide additional data to address whether treatment of mothers with HPC has a detrimental effect on early infant/child development. For those children whose initial screening examination suggests a developmental delay, the protocol should include formal psychometric and developmental assessments as well as an assessment by a pediatric neurologist.

2.2.5 Applicant's Second Complete Response

On July 12, 2010, the Applicant (now Hologic, Inc.) submitted Complete Response #2 that addressed DRUP's Complete Response Letter of January 23, 2009. Complete Response #2 included (1) an update on the status of ongoing Study 17P-ES-003, (2) a Safety Update that included blinded safety data from Study 17P-ES-003 and an update on publications not previously submitted concerning the use of HPC for the prevention of preterm births, and (3) proposed product labeling. The Complete Response did not include any new CMC, nonclinical toxicology, or clinical pharmacology information. Late in the review cycle, the Applicant submitted additional publications describing morbidity/mortality associated with late preterm births that was not fully recognized at the time of the 2006 Advisory Committee meeting.

2.3 Reassessment of the Clinical Significance of Late Preterm Births

At the time of the Advisory Committee meeting in 2006, the general consensus was that the greatest impact on neonatal morbidity and mortality was attributable to early preterm birth, e.g., births at < 35⁰ weeks of gestation. Since the time of the meeting, there has been

3 ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 419, October 2008.

reconsideration of this view, with new recognition of the impact of “late” preterm birth on infant morbidity and mortality. Late preterm births are on the rise and 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 are at increased risk (compared to term infants) of immaturity-related medical complications. Late preterm infants are more likely than term infants to be diagnosed during their 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.^{4,5,6} In addition, infant mortality rates in 2002 were 3 times higher in late-preterm infants than term infants (7.9 versus 2.4 deaths per 1,000 live births).⁷ Similarly, 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 1,000 live births). Even healthy-appearing late preterm infants carry an increased risk for developmental delays and adverse early school-age outcomes compared with healthy term infants.⁸

Division Director's Comments

- *Based on their review and assessment of these and other publications regarding the impact of “late” preterm birth on infant morbidity and mortality, both the primary Clinical Reviewer (Dr. Wesley) and the CDTL (Dr. Soule), now believe that reduction in preterm births < 37⁰ weeks gestation is an adequate surrogate for clinical benefit (i.e., reduction in neonatal morbidity and/or mortality). I concur with their assessment.*
- *The reduction in the proportion of preterm births < 37⁰ weeks in HPC-treated subjects, compared to that in the vehicle-treated subjects in Study 17P-CT-002 was sufficiently persuasive ($p < 0.001$) to meet the level of statistical significance generally expected to support approval of a drug product based on the findings of a single trial.*
- *I therefore believe that Study 17P-CT-002 is an adequate and well-controlled trial that established the effect of HPC treatment on a surrogate endpoint (reduction in preterm births < 37⁰ weeks gestation) that is reasonably likely to predict clinical benefit.*

4 Engle WA, Tomasek KM, Wallman C, and the Committee on Fetus and Newborn. Late-Preterm Infants: A Population at Risk. *Pediatrics* 120:1390-1401, 2007.

5 ACOG Committee on Obstetric Practice. Late-Preterm Infants. No. 404, April 2008.

6 McIntire DD and Leveno KJ. Neonatal Mortality and Morbidity Rates in Late Preterm Births Compared with Births at Term. *Obstet. Gynecol.* 111:35-41, 2008.

7 Tomasek KM, Shapiro-Mendoza CK, Davidoff MJ, et al. Differences in Mortality between Later-Preterm and Term Singleton Infants in the United States, 1995-2002. *Pediatrics* 151(5):450-6, 2007.

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

2.4 Recommendations of the Primary Clinical Reviewer, Cross-Discipline Team Leader, and Primary Statistical Reviewer regarding Approvability Based on the Applicant's Second Complete Response

The primary Clinical Reviewer, Barbara Wesley MD, stated the following in her primary Clinical Review signed on February 3, 2011:

"As the primary reviewing Medical Officer for this application, I recommend an approval action under the Subpart H regulation (21 CFR 314.510) [also referred to as Subpart H] for 17 α -hydroxyprogesterone caproate [hereafter referred to as 17-HPC, but also known as HPC and 17P] for the reduction of the risk of preterm birth (PTB) in women with a singleton pregnancy who have a history of a singleton spontaneous preterm birth. I make this recommendation because the Applicant has fully addressed the clinical deficiencies that are listed in the January 23, 2009 Complete Response letter to my satisfaction."

Dr. Wesley also recommended the postmarketing requirements and commitments that are listed in Section 13.4.

The Cross Discipline Team Leader, Lisa Soule MD (who also was the Clinical Team Leader), stated the following in her Review signed on February 3, 2011:

"I recommend that Makena receive an Approval action under Subpart H, 21 CFR 314.510 for the indication "to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth." This recommendation is based on data from a single study that demonstrated efficacy on a surrogate endpoint (delivery < 37 weeks) as well as on additional endpoints of delivery < 35 and <32 weeks."

Dr. Soule also recommended the postmarketing requirements and commitments that are listed in Section 13.4.

The primary Statistical Reviewer, Lisa Kammerman PhD, stated the following in her Statistical Review signed on February 3, 2011:

"From a statistical perspective, the information and data submitted by the Applicant do not provide convincing evidence regarding the effectiveness of 17 α -hydroxyprogesterone, caproate injection (17P) for the prevention of preterm deliveries among women with a history of at least one spontaneous preterm delivery."

In this review of the second Complete Response, I have done additional analyses to address whether the data are sufficient to support approval if the endpoint of deliveries <37 weeks gestation is used as the surrogate endpoint. I have also done additional analyses exploring the effect of race on the efficacy results. However, the results from these analyses do not support the efficacy of 17P based on a single study."

Division Director's Comments

- I agree with the recommendations of Dr. Wesley and Dr. Soule that HPC (Makena) be approved for the indication of reducing the risk of preterm birth in women with a singleton pregnancy who have a history of a singleton spontaneous preterm birth. See Section 13.1 and Section 13.2 for the basis of my agreement.*
- Although I acknowledge the concerns expressed by Dr. Kammerman in her Statistical Review, I do not agree with her overall recommendation or several of the issues that she raises for the reasons discussed in Section 7.2.*

3. CMC

3.1 First Complete Response Review Cycle

In the Approvable Letter of October 20, 2006, 3 CMC deficiencies were listed. These deficiencies concerned (1) failure to detect photo-degradation products by the Applicant's HPLC method, (2) failure to demonstrate that the secondary packaging provided adequate light protection for the drug product, and (3) lack of adequate data to support a product expiration date of 24 months. In her review of Complete Response #1, the primary Chemistry Reviewer, Donna Christner PhD, stated that the 3 deficiencies were adequately addressed, and she recommended Approval from a CMC perspective.

3.2 Current Submission

The primary Chemistry Reviewer, Donna Christner PhD, made the following recommendations in her Review, signed on December 1, 2010.

"This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have adequate information as required (the trade name is still under review by DMEPA, but is not a CMC issue). The final overall "Acceptable" recommendation has been made from the Office of Compliance."

"Therefore, from a CMC perspective, this NDA is still recommended for APPROVAL as was recommended in Review #2 dated 22-Dec-2008."

Dr. Christner did not recommend any postmarketing commitments. Dr. Christner updated her Review with a memo signed on January 31, 2011, in which she stated that *"from a CMC standpoint, the labels are acceptable and the NDA is still recommended for Approval."*

Division Director's Comment

- *I concur with the assessment/recommendation made by Dr. Christner. There are no outstanding CMC issues.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

4.1 First Complete Response Review Cycle

The Approvable Letter of October 20, 2006, listed "a lack of nonclinical data from a multi-generational reproductive toxicology study" as a deficiency that would need to be resolved prior to approval of HPC for the proposed indication. A submission to the NDA, received on June 16, 2008, contained the final Report for a multigenerational study in rats in which offspring exposed *in utero* were evaluated for potential effects on development, learning, and behavior. The study was conducted under Good Laboratory Procedures and was also audited by FDA inspectors. The study did not find any potential adverse effects on neurologic or reproductive development of offspring exposed to HPC *in utero*.

The primary Pharmacology/Toxicology Reviewer, Alexander Jordan PhD, made the following recommendations in his Review signed on October 14, 2008:

- Recommendation on approvability: *"I recommend approval of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth."*
- Recommendation for nonclinical studies: *"none."*

Division Director's Comments

- *Unrelated to the multi-generational reproductive toxicology study was a report of embryoletality in rhesus monkeys receiving HPC at doses equivalent to the human dose. Similar findings were not observed in cynomolgus monkeys or rodents receiving HPC. The Pharmacology/Toxicology Team Leader, Dr. Reid, stated in her separate NDA memo, dated October 14, 2008, that this finding of embryoletality “does not appear to be a risk factor in humans.”*

4.2 Current Submission

Dr. Jordan made the following statements and recommendation in his primary Pharmacology/Toxicology Reviewer signed on November 24, 2010:

“This NDA was submitted previously and was given a complete response letter dated January 23, 2009 due primarily to clinical deficiencies. There were no nonclinical studies requested or submitted in this Class 1 Resubmission.

Following our recommendations, Sponsor changed the label in section 13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility, to reflect the correct exposure multiple of the rat multi-generational study. Also, under 8.1 Pregnancy, Sponsor moved the clinical data to the beginning of the section followed by the animal data.

Recommendation: *The label for 17-alpha hydroxyprogesterone caproate for the prevention of recurrent preterm birth is satisfactory from the standpoint of pharm/tox.”*

Division Director's Comment

- *I concur with the assessments and recommendations of Drs. Jordan and Reid that from a nonclinical pharmacology/toxicology perspective this NDA can be approved. There are no outstanding nonclinical pharmacology/toxicology issues.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

5.1 Original Review Cycle

The original submission included limited pharmacokinetic data from non-pregnant women that the Applicant compiled from the public literature. Following a single IM injection of 1,000 mg HPC in 5 non-pregnant women, the mean (\pm SD) C_{\max} was estimated to be 27.8 (\pm 5.3) ng/mL, and the T_{\max} was estimated to be 4.6 (\pm 1.7) days. The elimination half-life was 7.8 (\pm 3.0) days. The pharmacokinetics of the 250 mg dose of HPC has not been evaluated. HPC binds extensively to plasma proteins including albumin and corticosteroid binding globulins. In vitro studies have shown that HPC can be metabolized by human hepatocytes and that the metabolism is predominantly mediated by CYP3A4 and CYP3A5. The in vitro data indicate that the caproate group is retained during metabolism of HPC. Both conjugated metabolites and free steroids are excreted in the urine and feces.

The Approvable Letter of October 20, 2006, included 3 clinical pharmacology requests that could be addressed as postmarketing studies.

5.2 Current Submission

No additional clinical pharmacology data were included in the current submission. The primary Clinical Pharmacology Reviewer, Sandhya Apparaju PhD, stated the following in her review, signed on December 9, 2010:

“NDA 021945/SDN # 51 [submitted on 07/12/2010] is acceptable from a Clinical Pharmacology perspective provided that a satisfactory agreement is reached with the Sponsor regarding the labeling language.

The two Clinical Pharmacology Phase IV Commitments (PMC) listed below should be communicated to the sponsor as part of the NDA action letter:

PMC #1: Provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine in pregnant women throughout different gestational stages.

PMC #2: Conduct an in vitro study using human hepatocytes to determine whether hydroxyprogesterone caproate induces the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.”

Dr. Apparaju concurred in an Addendum, signed on February 3, 2011, with final labeling submitted by the Applicant.

Division Director's Comments

- The Applicant has agreed to conduct the 2 clinical pharmacology studies as postmarketing commitments (see Section 13.4.2).*
- A third request from Clinical Pharmacology that was conveyed to the Applicant in the Approvable Letter of 2006 (to evaluate HPC exposure-response relationships and the effect of body weight on the pharmacokinetics of 17-HPC via sparse sampling) is being addressed in clinical Trial 17P-ES-003..*
- I concur with Dr. Apparaju's overall assessment. There are no outstanding Clinical Pharmacology issues.*

6. CLINICAL MICROBIOLOGY

No new microbiology data were provided in the current submission. The microbiological stability of the product once the product (sterile vial) is penetrated was reviewed during the prior review cycle. The microbiology reviewer, James McVey PhD, concluded in his review signed on December 12, 2008, that the microbiology data provided by the Applicant were adequate to support an in-use shelf-life of 5 weeks once the vial stopper was penetrated in actual use.

Division Director's Comment

- I concur with the assessment of Dr. McVey. There are no outstanding microbiology issues. Labeling will clearly state that the product must be used within 5 weeks after first use.*

7. CLINICAL/STATISTICAL-EFFICACY

The current submission did not contain any new efficacy data. The efficacy findings from Study 17P-CT-002 that support approval of this Application were submitted during the original review cycle and are summarized in Section 2.2.2.2 of this Summary Review. During the current review cycle, however, both the FDA Statistician and the Applicant (at the request of

FDA) conducted additional exploratory analyses of the efficacy data from Study 17P-CT-002. These analyses, as well as concerns raised by the primary Statistical Reviewer (Dr. Kammerman) regarding the overall strength of the efficacy findings, are discussed below in Sections 7.1 and Section 7.2.

To address the clinical issues in the Approvable Letter of October 20, 2006, the Applicant's first Complete Response (submitted in April 2008) contained the protocol for a confirmatory efficacy and safety study (Protocol 17P-ES-003). Agreement with the design of the trial, planned sample size, primary and secondary endpoints, and proposed analysis plan was reached during the review of the Applicant's first Complete Response. The Applicant also provided in their first Complete Response a draft protocol for an infant follow-up study (Protocol 17P-FU-004). In accordance with DRUP's request in the Complete Response Letter of January 23, 2009, the Applicant has initiated Trial 17P-ES-003 and has provided a status report of enrollment into the trial. A summary of Protocol 17P-ES-003 is provided in Section 7.3.

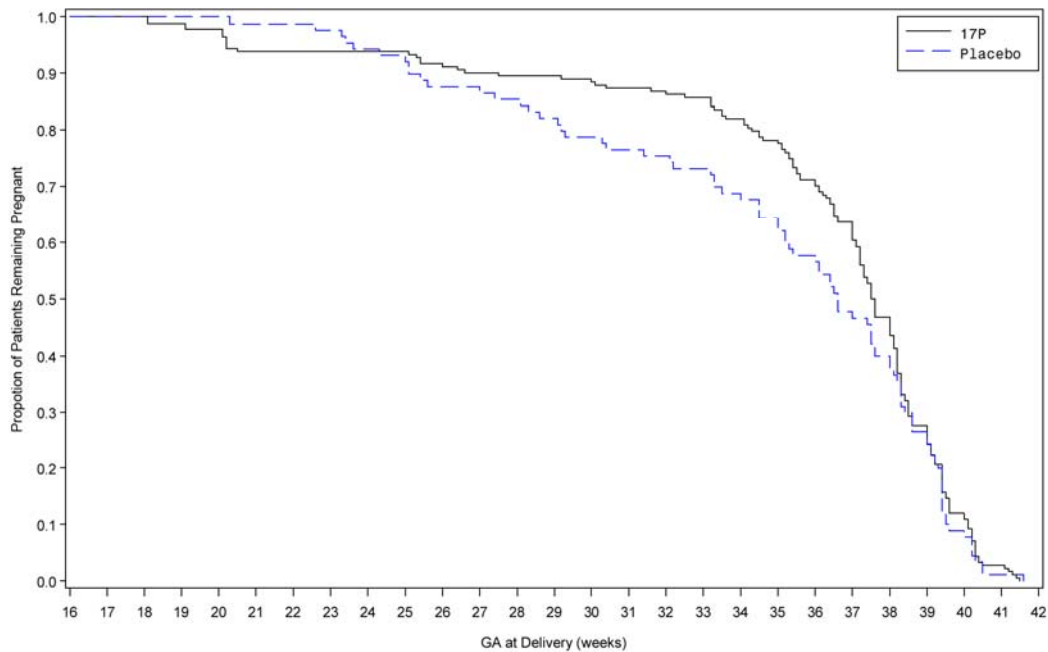
7.1 Exploratory Efficacy Analyses

During this review cycle, the Applicant was asked to conduct several exploratory analyses based on the data from Study 17P-CT-002, primarily to address issues that were raised by the primary Statistical Reviewer. These exploratory analyses are described more fully in Dr. Soule's CDTL review (see Section 7.1.3 of her Review signed on February 3, 2011). Among the analyses that I consider to be most important and relevant to the safe and effective use of HPC is the possible effect of race (defined as Black or non-Black in these analyses) on the efficacy and safety findings from Study 17P-CT-002.

7.1.1 Effect of HPC Treatment on Preterm Births < 37⁰ Weeks Gestation in Black and non-Black Subjects

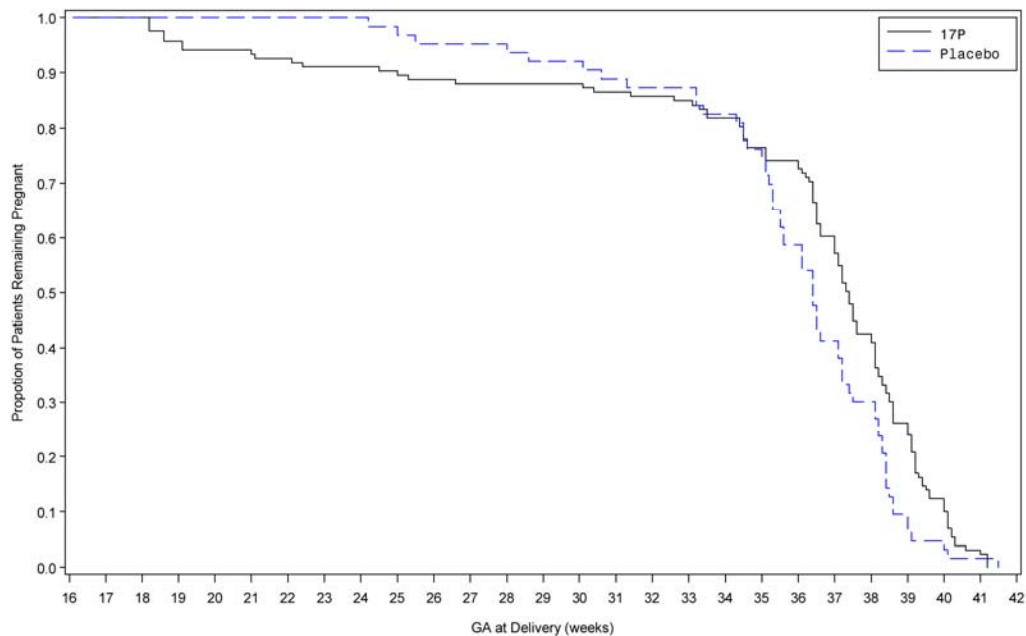
The proportion of Black subjects remaining pregnant as a function of gestational age in Study 17P-CT-002 is shown in Figure 2. The proportion of non-Black subjects remaining pregnant as a function of gestational age in Study 17P-CT-002 is shown in Figure 3. The most obvious difference between the figures is the gestational ages at which the curves representing the placebo and HPC treatment groups cross. For the Black subjects, the curves cross at approximately gestational weeks 23-25. After Week 25 and through approximately Week 38, the proportion of subjects remaining pregnant is greater in the HPC-treatment group. For the non-Black subjects, the curves cross at approximately gestational weeks 33-35. After Week 35, the proportion of subjects remaining pregnant is greater in the HPC-treatment group.

Figure 2 Proportion of Subjects Remaining Pregnant as a Function of Gestational Age (Black Subjects Only, Study 17P-CT-002)



Source: Figure K-M #1 of Applicant's submission of January 18, 2011.

Figure 3 Proportion of Subjects Remaining Pregnant as a Function of Gestational Age (Non-Black Subjects Only, Study 17P-CT-002)



Source: Figure K-M #2 of Applicant's submission of January 18, 2011.

Division Director's Comment

- The differences in the gestational ages at which the curves representing the placebo (vehicle) and HPC groups cross in the Black and the non-Black subjects appears to be due primarily to the differences in the proportion of placebo-treated subjects remaining pregnant as a function of gestational age. In the non-Black placebo group, a greater proportion of subjects remained pregnant, compared to subjects in the Black placebo group, at most gestational ages. The proportions of Black and non-Black subjects remaining pregnant as a function of gestational age, however, were similar in the HPC-treatment groups.*

Table 8 lists preterm births < 37⁰ weeks gestation (the primary efficacy endpoint in Study 17P-CT-002) by race and treatment group. The percentage of Black patients in Study 17P-CT-002 was 59% in both the HPC (183/310) and the vehicle (90/153) groups. HPC treatment reduced the rate of preterm birth < 37⁰ weeks gestation compared to vehicle in both the Black (36.1 % vs. 52.2%) and the non-Black (38.6% vs. 58.7%) populations.

Table 8 Preterm Births < 37⁰ Weeks Gestation by Race and Treatment Group (Study 17P-CT-002)

Race	HPC Group n/N (%) ^A	Vehicle Group n/N (%)
Black	66/183 (36.1%)	47/90 (52.2%)
Non-Black	49/127 (38.6%)	37/63 (58.7%)

A: N represents the number of patients overall in a specific category.
n represents the number of patients in a specific category who delivered the study pregnancy < 37⁰ weeks gestation.

Source; Table 11-4 of Applicant's Final Report for Study 17-CT-002.

Division Director's Comment

- The extent to which treatment with HPC reduced the percentage of subjects with a preterm birth < 37⁰ weeks gestation, compared to treatment with vehicle, was similar in both the Black and non-Black subjects.*

7.1.2 Perinatal Mortality

The findings from Study 17P-CT-002 were also explored to determine if perinatal mortality (defined as miscarriages, stillbirths, and neonatal deaths) differed in Black and non-Black subjects. The numbers and percentages of perinatal deaths in the Black and non-Black subjects in the HPC and vehicle groups are listed in Table 9. There was a total of 30 perinatal deaths in Study 17P-CT-002. Across the 2 treatment groups, 19 (6.2%) occurred on HPC treatment and 11 (7.2%) occurred on vehicle treatment. Among Black subjects, there were 11 such losses in 181 HPC-treated subjects (6.1%) and 8 losses in 90 vehicle-treated subjects (8.9%); among non-Black subjects, there were 8 losses in 125 HPC-treated subjects (6.4 %) and 3 losses in 63 vehicle-treated subjects (4.8%).

Table 9 Miscarriages, Stillbirths, and Neonatal Deaths by Maternal Race (Study 17(-CT-002) ^A

	Black		Non-Black	
	HPC (N=181)	Vehicle (N=90)	HPC (N=125)	Vehicle (N=63)
	n (%)	n (%)	n (%)	n (%)
Miscarriages	2 (1.5%)	0	3 (3.9%)	0
Stillbirths	3 (1.7%)	1 (1.1%)	3 (2.4%)	1 (1.6%)
Neonatal Deaths	6 (3.3%)	7 (7.8%)	2 (1.6%)	2 (3.2%)
Total Deaths	11 (6.1%)	8 (8.9%)	8 (6.4%)	3 (4.8%)

^A: Values are not adjusted for time-on-treatment.

Source: Table 4 of Applicant's Submission of February 1, 2011.

Division Director's Comment

- No meaningful conclusions can be drawn given the small numbers of events in these subgroups and the small difference in the percentage of deaths in the HPC and vehicle groups. One additional death in the non-Black vehicle group would have increased the percentage of deaths to 6.3% compared to 6.4% in the HPC group. Further information regarding the effect of race on perinatal mortality will be obtained in the larger confirmatory trial (Study 17P-ES-003).*

7.2 Statistical Reviewer's Assessment of Efficacy

Throughout the review of NDA 021945, the primary Statistical Reviewer (Dr. Kammerman) has been opposed to approval of HPC, even under Subpart H regulations. Throughout the review of this Application, Dr. Kammerman has expressed concerns about the generalizability of the findings from Study 17P-CT-002. Her major concerns expressed at the conclusions of each of the 3 review cycles are summarized and discussed in this Section.

7.2.1 Original Review Cycle

At the conclusion of the original (first) review cycle, Dr. Kammerman stated the following in her Statistical Review dated October 19, 2006:

"From a statistical perspective, the level of evidence from Study 17P-CT002 is not sufficient to support the effectiveness of 17P. The primary reason is the absence of a second, confirmatory study. Without a second study, the generalizability of the study results to a larger population cannot be assessed.

When compared with all other centers, one center, the University of Alabama, is disproportionately represented in the study. The University of Alabama accounts for about 25% of all subjects enrolled (126/463) and is about three times the size of the next largest center, the University of Tennessee (45/463 = 9.7%).

When two studies are submitted, the chance of both studies yielding a false positive result is 1/1600. In the case of a single study, the results must be less than a nominal p-value of 0.00125 to ensure the same false positive rate. In Study 17P-CT-002, the only endpoint that meets this criterion is Delivery <37 weeks gestation. Deliveries at times earlier than 37 weeks gestation were not statistically significant at 0.001. The results of the analyses of the 32 and 35 week endpoints suggest their false positive rates could be as great as 1/40."

Division Director's Comments

- At the end of both the first and second review cycles, DRUP reviewers were focusing on the clinical finding of a reduction in preterm births at < 35⁰ weeks gestation as a possible basis*

for approval under subpart H regulations. Based on the new recognition of the impact of late preterm births on infant morbidity and mortality, the DRUP reviewers now believe that a reduction in preterm births at < 37⁰ weeks gestation is an adequate surrogate for clinical benefit to support approval of HPC under subpart H regulations. The effect of HPC treatment to reduce preterm births < 37⁰ weeks gestation, compared to the effect of vehicle, 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.

- The Applicant conducted several analyses to determine if the findings from the University of Alabama were primarily responsible for the observed benefit of treatment with HPC. Although some question remains as to whether the Alabama site may have had a disproportionate effect on the finding at < 32⁰ weeks gestation, the DRUP clinical reviewers and I do not believe that there is evidence that this site had a disproportionate effect on the findings at < 35⁰ and < 37⁰ weeks gestation.*

7.2.2 First Complete Response Review Cycle

At the conclusion of the first Complete Response (second) review cycle, Dr. Kammerman stated the following in her Statistical Review signed January 23, 2009:

“Study 17P-CT002, which was the single study included in the original NDA, showed statistically significant reductions in preterm deliveries at <35 weeks and at <32 weeks. The medical team concluded these results were sufficient to support the efficacy of 17 α -hydroxyprogesterone caproate injection.

However, from a statistical perspective, the effect of 17 α -hydroxyprogesterone caproate injection on preterm births has not been established by adequate and well-controlled clinical trials.”

Division Director's Comments

- DRUP is no longer basing their recommendation for approval on the reduction of preterm births at < 35⁰ weeks gestation. The efficacy findings, based on the reduction of preterm births at < 37⁰ weeks gestation, are statistically persuasive ($p < 0.001$).*
- Dr. Kammerman also proposed in her Review that possible approval of the Application be deferred until interim results from the Applicant's planned confirmatory study (Study 17P-ES-003) were available for the endpoint of reduction in preterm births < 35⁰ weeks. 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. DRUP did not pursue this option with the Applicant.*

7.2.3 Current Review Cycle

At the conclusion of the current review cycle, Dr. Kammerman stated the following in her Statistical Review signed February 3, 2011:

“From a statistical perspective, the information and data submitted by the Applicant do not provide convincing evidence regarding the effectiveness of 17 α -hydroxyprogesterone, caproate injection (17P) for the prevention of preterm deliveries among women with a history of at least one spontaneous preterm delivery.

In this review of the second Complete Response, I have done additional analyses to address whether the data are sufficient to support approval if the endpoint of deliveries <37 weeks

gestation is used as the surrogate endpoint. I have also done additional analyses exploring the effect of race on the efficacy results. However, the results from these analyses do not support the efficacy of 17P based on a single study.”

Division Director's Comments

- The primary clinical Reviewer (Dr. Wesley), the CDTL (Dr. Soule), and I do not concur with Dr. Kammerman's overall assessment that the data from Study 17P-CT-002 are not adequate to support the effectiveness of HPC for reducing the risk of preterm labor or her recommendation that this Application not be approved at this time. Study 17P-CT-002 was an adequate and well-controlled clinical trial in which the effectiveness of HPC treatment in reducing preterm births < 37⁰ weeks gestation, compared to the effect of vehicle, 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.*
- Although all of Dr. Kammerman's concerns regarding the effect of race on HPC-treatment outcomes have not been fully addressed during the current review cycle, I believe that treatment with HPC has been shown to be effective in both Black and non-Black subjects as discussed in Section 7.1 of this Summary Review. Dr. Soule also has addressed the issue of treatment outcomes and race as well as time of randomization on treatment outcomes in Section 7.1.3 of her CDTL review.*
- Dr. Kammerman's comments regarding product labeling and the Applicant's protocols for the required postmarketing studies have been considered fully and many have been incorporated. Additionally, it is anticipated that the ongoing large confirmatory trial (Study 17P-ES-003) and infant follow-up study (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.*

7.3 Confirmatory Efficacy and Safety Study (Protocol 17P-ES-003 [Original Version])

The description of the protocol that follows is based upon the final Protocol dated June 15, 2009, that is entitled “*A Phase 3 B, Multi-Center, Randomized, Double-Blind Study of Hydroxyprogesterone Caproate Injection, 250 mg/mL, Versus Vehicle for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous Preterm Delivery.*”

7.3.1 General Study Design

Study 17P-ES-003 is a multicenter, international, randomized, double-blind, vehicle-controlled study. The study will enroll 1,707 women aged 16 and above with a singleton gestation and a history of a previous singleton spontaneous preterm birth. Subjects will be randomized in a 2:1 ratio to treatment with HPC (250 mg) or vehicle (castor oil). Subjects will receive once weekly IM injections of Study Drug from the time of randomization (which will occur between 16⁰ to 20⁶ weeks of gestation) through 36⁶ weeks of gestation or delivery, whichever occurs first. Maternal subjects will be followed until the later of 30 days after the last dose of study drug or discharge from the delivery hospitalization; neonates will be followed until 28 days of life, with those remaining hospitalized at 28 days post birth to be followed until the earlier of discharge or 120 days of life. Maternal subjects who discontinue study drug will remain in the study, and, at a minimum, delivery outcome data will be obtained.

7.3.2 Study Objectives and Endpoints

The **primary objective** of Study 17P-ES-003 is to determine if treatment with HPC, compared to vehicle, reduces the rate of preterm birth < 35⁰ weeks of gestation.

The **key secondary objective** is to determine if treatment with HPC, compared to vehicle, reduces the rate of neonatal morbidity/mortality, if and only if, the rate of preterm birth < 35⁰ weeks of gestation is statistically significant (i.e., hierarchical; testing approach). Neonatal mortality or morbidity is measured by a composite index comprised of the following elements:

- Neonatal death
- Grade 3 or 4 intraventricular hemorrhage (IVH)
- Respiratory distress syndrome (RDS)
- Bronchopulmonary dysplasia (BPD)
- Necrotizing enterocolitis (NEC)
- Proven sepsis

Additional secondary objectives include:

- **Exclude a doubling of the risk of fetal/early infant death, defined as spontaneous abortion/miscarriage (delivery from 16⁰ through 19⁶ weeks of gestation) or death (from minutes after birth until 28 days of life) occurring in live born infants < 24⁰ weeks gestation or stillbirths (antepartum or intrapartum death from 20⁰ weeks gestation through term), in the HPC group compared to the vehicle group.**
- Determine if HPC reduces the rate of preterm birth < 37⁰ and < 32⁰ weeks of gestation.
- Determine if HPC reduces the rate of neonatal death (from minutes after birth until 28 days of life) occurring in live births ≥ 24 weeks gestation.
- Evaluation of PK/PD parameters for HPC in a subset of approximately 450 subjects (300 HPC subjects) stratified by pre-pregnancy BMI (≤ 28 and > 28). A total of 3 blood samples will be drawn from each subject in the PK substudy. In addition, for the third blood sample, subjects will be stratified so that an even distribution of samples will be drawn on Day 1, Day 2, Day 3, Day 4, or Day 5/6 post-dose.

7.3.3 Statistical Analyses

The primary statistical analysis is hierarchical to protect against type 1 error. The statistical analysis for the key secondary objective will therefore be performed only if the primary endpoint of preterm birth < 35⁰ weeks attains statistical significance.

According to the Applicant, the proposed sample size will provide 98% power to detect a 30% relative reduction (30% to 21%) in the rate of preterm birth at < 35⁰ weeks with an alpha level of 0.05%. The study will also have 90% power to detect a 35% relative reduction (17% to 11%) in the rate of adverse outcomes, based on the composite neonatal index. The power to rule out a doubling of risk of fetal/early infant death, assuming a rate of 4%, would be 83%. A doubling of the risk of fetal/early infant loss will be ruled out if the upper bound of the 95% confidence interval for the relative risk of HPC, compared to vehicle, is < 2.0.

Division Director's Comments

- *The objectives and key endpoints of the clinical trial were revised in accordance with comments made by the clinical and statistical reviewers during the second review cycle.*

- *The inclusion of a clinical endpoint, the neonatal morbidity/mortality index as the key secondary endpoint, analyzed in a hierarchical manner, was considered by DRUP during review of the Applicant's first Complete Response as adequate to address Subpart H regulations of extending initial findings based on a surrogate endpoint to the demonstration of an actual clinical benefit.*
- *The confirmatory clinical trial also addresses DRUP's concern regarding a possible increase in early pregnancy loss in women treated with HPC.*
- *Dr. Kammerman (primary Statistical Reviewer) stated the following in an Addendum, signed on January 14, 2009, to her primary Review:*

"Since completing my statistical review of the applicant's complete response to the approval letter for NDA 21-945, the medical division and I have had numerous discussions with the applicant regarding their draft study protocol:

'A Phase 4, multi-center, randomized, double-blind study of 17 a-hydroxyprogesterone caproate (17P) versus placebo for the prevention of preterm birth in women with a previous singleton spontaneous preterm delivery.'

This study represents a confirmatory study of the findings from Study 17P-CT-002.

As a result of these discussions, the applicant submitted a revised protocol on 12/12/2008. I agree with changes made to the protocol and do not have any additional statistical comments."

7.4 Revisions to Protocol 17P-ES-003 (Current Review Cycle)

Although it is widely believed that a reduction in preterm births at $< 35^0$ weeks would be associated with a clinically meaningful reduction in neonatal morbidity/mortality, this endpoint is still considered by some as a surrogate of an actual clinical benefit. Therefore, the Applicant was requested during the current review cycle to amend Protocol 17P-ES-003 and to elevate the key secondary objective (the neonatal mortality/morbidity index) to a co-primary endpoint. This request was made to address more precisely the Subpart H regulations that state that the purpose of the confirmatory clinical trial is to "verify and describe" the drug's "clinical benefit." In an e-mail communication on January 7, 2011, the Applicant agreed to this change. In the communication, the Applicant also stated that the power to detect significant differences between the treatment groups for both outcome measures (reduction in preterm births at $< 35^0$ weeks gestation and an improvement in the neonatal morbidity/mortality index "is expected to be close to 90%."

7.5 Status of Study 17P-ES-003 and Data Safety Monitoring Board

7.5.1 Status of Study 17P-ES-003

In the submission of July 12, 2010, the Applicant provided a status update on recruitment of study centers and enrollment of subjects into Study 17P-ES-003. In the US, 43 investigational sites have received IRB approval, and IRB approval was pending at an additional 10 US sites. Outside of the US, 29 sites have received Ethics Committee (EC) approval, and EC approval was pending at an additional 19 non-US sites. At the time of the submission, 89 subjects (5.2%) of the anticipated sample size of 1,700 patients had been randomized in Study 17P-ES-003. Of the 89 subjects, 82 were randomized at US sites.

Division Director's Comments

- *The Applicant has recruited a diverse group of US sites, including academic centers, military medical centers, and private practices. The Applicant anticipates that about half of all sites will be in the US and Canada. The Applicant has also engaged a specialty contract research organization to provide support in recruiting patients and referring physicians.*
- *In a later submission dated December 6, 2010, the Applicant provided an update on enrollment and stated that 186 subjects (> 10 % of the total) had been enrolled into Study 17P-ES-003. Of these subjects, at least 145 have been enrolled at US/Canadian sites.*
- *Based on enrollment of subjects, to date, there is a high likelihood that Study 17P-ES-003 will be successfully completed by mid 2016, as projected by the Applicant. I conclude that the Applicant has acceptably addressed the deficiencies relating to the confirmatory efficacy and safety study that were noted in the Complete Response Letter of January 2009.*

7.5.2 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) has been constituted to review safety data regarding maternal complications, adverse events, fetal losses, and neonatal morbidity and mortality. Based on the DSMB Charter of November 3, 2010, the DSMB was to meet annually. Review of neonatal morbidity data was to occur no more than 3 times during the course of the study and only when approximately 20%, 40%, and 60% of randomized subjects had delivered.

Division Director's Comment

- *At the request of the FDA, the Charter was amended on January 6, 2011. The most significant modifications/additions to the Charter were:*
 - *The Chairperson or the Applicant can now request additional meetings as necessary in addition to the required annual meeting.*
 - *Between meetings, copies of the initial and final MedWatch and/or CIOMS reports for each reported serious adverse event resulting in the death of a mother, fetus, or neonate and the treatment assignment will be sent to the DSMB members as they become available.*

8. SAFETY (CURRENT SUBMISSION)

The safety findings that support approval of this Application were submitted during the original review cycle for NDA 021945 and are summarized in Section 2.2.2.4 of this Summary Review. With the exception of data, blinded as to treatment assignment, that were provided in the Safety Update for ongoing Study 17P-ES-003, the current submission did not contain any new safety data from clinical studies with HPC sponsored by the Applicant.

The submission also included an update of publications that relate to the use of HPC or progesterone for the prevention of preterm birth. Review of these articles, as well as previously submitted publications, did not identify any new safety issues that (1) would affect the approvability of HPC for the proposed indication or (2) are not adequately addressed in to-be-approved product labeling.

8.1 Applicant's Safety Update

8.1.1 Overview

The Applicant submitted a Safety Update (with a cut-off date of October 29, 2010) on November 5, 2010. The update was based on blinded safety reports received by the Applicant for the Applicant's only ongoing Study with HPC (Study 17P-ES-003). According to the Applicant, 167 subjects had been randomized into the study and 8 subjects had received a trial injection but were not randomized. Partial adverse event data were available for 31 subjects (6 who received only the "trial injection" (pre-randomization injection of vehicle) and 25 who were randomized). Of 123 treatment-emergent adverse events (AEs) reported as of October 29, 2010, the only AEs that were reported in more than 2 subjects and the numbers of subjects reporting them were: injection site pruritus (n=6), injection site nodule (n=4), vaginal discharge (n=6), and nausea (n=4). One subject was reported to have discontinued for an AE unrelated to a pregnancy-related event (i.e., rash at the injection site).

8.1.2 Deaths and Serious Adverse Events

There have been no maternal deaths. A total of 12 serious adverse events (SAEs), involving 8 subjects, have been reported. Three of the SAEs were fetal/neonatal deaths. The non-fetal/neonatal SAEs include one case each of pneumonia, inadvertent overdose, pancreatitis (relapsing), peripheral edema, migraine, and increased blood glucose. None of these SAEs were attributed to treatment with Study Drug by the Investigators.

The 3 fetal/neonatal deaths were one case each of (1) cardio-respiratory arrest related to severe prematurity (delivery at 21 weeks gestation), (2) an intrauterine death at 32⁴ weeks gestation, and (3) a miscarriage at 19³ weeks gestation. As of 29 October 2010, the Applicant stated that it had documentation from site logs that 55 of the 167 subjects had delivered.

Division Director's Comments

- *An additional case of miscarriage (also at 19³ weeks gestation) was reported to have occurred on (b) (6) (after the cut-off date of the Safety Update).*
- *The reported AEs/SAEs in the Safety Update are consistent with those observed in Phase 3 Study 17P-CT-002 and do not raise any new safety concerns.*

8.2 Noninterventional Follow-Up Study of Children of Mothers Treated in Study 17P-ES-003 (Protocol 17P-FU-004 [Original Version])

In DRUP's Complete Response Letter of January 2009, the Applicant was informed that additional developmental assessment at ages 18-24 months will be needed for children whose mothers had participated in Study 17P-ES-003. This information would be needed to provide additional reassuring data that treatment of mothers with HPC did not have a detrimental effect on early infant/child development. The Letter stated further that for those children whose initial screening examination suggested a developmental delay, the protocol should include formal psychometric and developmental assessments as well as an assessment by a pediatric neurologist.

The final clinical protocol for Study 17P-FU-004, entitled "*A Prospective, Noninterventional Follow-Up Study of Children Aged 23 to 25 Months, Born to Mothers Who Received Hydroxyprogesterone Caproate Injection, 250 mg/mL, or Vehicle for the Prevention of Preterm Birth,*" was submitted to IND 68,108 in June 2009.

The primary objective of Study 17P-FU-004 is to determine whether there is a difference in developmental status between offspring of women who received HPC in Study 17P-ES-003 (the confirmatory efficacy and safety study), as compared to developmental status of offspring of women who received vehicle. Sufficient children will be enrolled to assure that approximately 375 children (250 exposed in utero to HPC and 125 exposed to vehicle) complete the Ages and Stages Questionnaire (ASQ), the same measure used in the initial infant follow-up study (Study 17P-FU). Children who screen positive for developmental delay will be referred for additional follow-up using the Bayley Scales of Infant and Toddler Development and an evaluation by a pediatric neurologist. Mothers will be requested at the time of their enrollment into Study 17P-ES-004 to consent to the participation of their children at the age of 23 to 25 months. The sample size, according to the Applicant, should provide 88% power to detect an absolute difference of 15% in the rate of developmental delay using an alpha of 0.05, assuming a rate of 30% in the HPC group.

Division Director's Comments

- *In Meeting Minutes dated 17 December 2009, DRUP agreed that Protocol 17P-FU-004 was acceptable and that the Protocol adequately addressed Clinical Deficiency #2 in DRUP's Complete Response Letter issued on January 23, 2009.*
- *The FDA statistical reviewer recommended that all US/Canadian subjects should be requested to enroll their children in the follow-up study. The Applicant committed to this and will ask all eligible US/Canadian subjects to consent to inclusion of their children in Study 17P-FU-004.*
- *The FDA statistical reviewer also requested that Study 17P-FU-004 be powered to rule out a doubling of the risk of developmental delay in the children exposed to HPC in utero. The Applicant has stated that, based on the 28% rate of screen positives on the ASQ in the previous follow-up study (Study 17P-FU), the planned study will have 95% power to rule out a doubling of risk. If the rate of screen positives in the vehicle arm is as low as 18%, the study will have 80% power to rule out a doubling of risk. According to the CDTL Review, the Applicant proposes to add a secondary analysis to the Statistical Analysis Plan to determine the relative risk of the primary outcome and the 95% confidence interval (CI). If the upper bound of the CI is ≤ 2.0 , a doubling of risk will have been ruled out. The CDTL Review finds this proposal acceptable, and I agree with her assessment.*

8.2.1 Revised Protocol 17P-FU-004

Based on a request by DRUP, the Applicant agreed in their communication of December 7, 2010, to offer all subjects who are randomized into the 17P-ES-003 study at sites participating in Study 17P-FU-004 enrollment into Study 17P-FU-004. The Applicant estimates that this modification could increase total enrollment in Study 17P-FU-004 from 375 subjects to between 584–750 subjects depending on various assumptions.

Division Director's Comment

- *This revision to Protocol 17P-FU-004 will increase further the power of the study to determine whether there is a difference in developmental status between offspring of women who received HPC, compared to the children of women who received vehicle, in Study 17P-ES-003 (the confirmatory efficacy and safety study).*

9. ADVISORY COMMITTEE MEETING

As noted earlier (see Section 2.2.2.6), the original Application was discussed at the Advisory Committee for Reproductive Health Drugs (ACRHD) in August 2006. During the review of this submission, it was determined that further guidance from the ACRHD was not needed or warranted to reach a regulatory decision regarding the approvability of NDA 021945 during the current review cycle.

10. PEDIATRICS

The Applicant requested a (b) (4) of pediatric studies, and DRUP concurred, as studies would be impossible or highly impractical because there are too few children with the condition to study. The Pediatric Review Committee (PeRC), on September 10, 2008, agreed to a partial waiver for premenarcheal females and to extrapolate efficacy for postmenarcheal females.

11. OTHER RELEVANT REGULATORY ISSUES

DSI Audits. Audits of 3 of the highest enrolling clinical sites were conducted by the Division of Scientific Investigation (DSI) during or shortly after the first review cycle. The overall assessment from DSI stated that *“the inspections ... did not identify any regulatory violations that would appear to have a significant impact on data reliability or patient safety. ... Overall, the data appear acceptable in support of the respective indication.”*

An audit of the site that conducted the non-clinical multi-generational reproductive toxicology study also was conducted by DSI. Although some issues were identified, DSI did not believe they warranted a Form 483 and the audit was classified as No Action Indicated (NAI).

12. LABELING

The proprietary name Gestiva had been found to be acceptable by the Division of Medication Error, Prevention, and Analysis (DMEPA) on October 22, 2008. During the current review cycle, however, DMEPA determined that Gestiva was no longer an acceptable name because of possible name confusion with the approved drug Sustiva. DMEPA found the Applicant's proposed name Makena to be acceptable.

DMEPA found the final carton and container labeling submitted on December 16, 2010, acceptable.

Consults on the Applicant's proposed physician and patient labeling were obtained from the Study Endpoints and Label Development (SEALD) team, the Division of Drug Marketing and Advertising Communications (DDMAC), and the Division of Risk Management (DRISK). Their comments were incorporated into the label as appropriate.

Major revisions/additions to the Applicant's originally proposed labeling included the following:

- Revisions of the proposed indication from “prevention of preterm birth” to “reduction of the risk of preterm birth.”
- Addition of the following subpart H language to the indication: “The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.”

- Addition of the following limitation of use statement to the indication: “While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth.”

-  (b) (4)

- Development of patient labeling

In summary, physician and patient labeling for Makena (hydroxyprogesterone caproate) will reflect the findings of Study 17P-CT-002, including the statistically significant reduction in preterm births < 37⁰ weeks gestation, as well as trends in favor of HPC treatment in lowering the risk of preterm births < 35⁰ and < 32⁰ weeks gestation. Labeling also will reflect the uncertainty around the treatment effects at < 35⁰ and < 32⁰ weeks gestation as well as the limited number of preterm births at < 32⁰ weeks gestation. Maternal complications, fetal losses, neonatal deaths and neonatal morbidity also will be described. Patient labeling will inform women of the risks associated with the use of the product.

Physician and patient labeling submitted by the Applicant on February 3 was found to be acceptable.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Recommended Regulatory Action

I recommend that hydroxyprogesterone caproate injection (HPC, Makena) be approved in accordance with Subpart H accelerated approval regulations (21 CFR 314.510) for the indication “to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.” This recommendation is based primarily on the findings from Study 17P-CT-002, in which treatment with HPC was shown to reduce the percentage of subjects with a preterm birth < 37⁰ weeks gestation from 54.9% (vehicle group) to 37.1% (HPC group) ($p < 0.001$). Subpart H states that:

“FDA may grant approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathologic, or other evidence, to predict clinical benefit. ... Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed benefit to ultimate outcome. Postmarketing studies would usually be studies already underway.”

In Study 17P-CT-002, the effectiveness of HPC treatment in reducing preterm births < 37⁰ weeks gestation, compared to the effect of vehicle, 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. Furthermore, recent studies (see Section 2.3) provide strong evidence that late preterm infants (i.e., those born between 34⁰ and 36⁶ weeks gestation) are at significantly greater risk, compared to infants born $\geq 37^0$ weeks gestation, of experiencing immaturity-related medical complications, including death. I therefore believe that a reduction in preterm births < 37⁰ weeks gestation is an adequate surrogate to support approval of HPC under subpart H regulations.

Lastly, in accordance with Subpart H accelerated approval regulations, the Applicant is currently conducting an international multicenter, double-blind, vehicle controlled clinical trial to confirm the clinical benefit of HPC treatment (Study 17P-ES-003). Preliminary results from this ongoing trial do not raise any new safety concerns.

The Applicant has fully addressed the clinical deficiencies that were listed in the January 23, 2009 Complete Response letter.

13.2 Risk/Benefit Assessment

Efficacy

In a single adequate and well controlled trial (Study 17P-CT-002), treatment with HPC, compared to treatment with vehicle, reduced the percentage of women with a preterm birth < 37⁰ weeks gestation from 54.9% (vehicle group) to 37.1% (HPC group). The effect of HPC treatment in reducing preterm births < 37⁰ weeks gestation was sufficiently persuasive ($p < 0.001$) to meet the level of statistical significance generally expected to support approval of a new drug product based on the findings of a single trial. The proportions of women delivering at < 35⁰ and < 32⁰ weeks gestation also were lower among women treated with HPC compared to those treated with vehicle. These latter changes, although statistically significant, did not meet the level of statistical significance generally expected to support approval of a drug product based on the findings from a single clinical trial.

In the past few years, there has been increasing recognition that late preterm infants (i.e., infants born between 34⁰ and 36⁶ weeks gestation) are at significantly greater risk of experiencing immaturity-related medical complications, including death, compared to infants born full-term ($\geq 37^0$ weeks gestation). In contrast to my earlier belief, expressed in my 2006 Memorandum for my original review for NDA 021945, I now believe that a reduction in preterm births < 37⁰ weeks gestation is an adequate surrogate endpoint that is reasonably likely to predict clinical benefit in terms of a reduction in neonatal morbidity and/or mortality. In summary, I believe that the efficacy findings from Study 17P-CT-002 are adequate to support approval of HPC under subpart H regulations for accelerated approval.

Safety

There were no safety findings from Study 17P-CT-002, supportive Study 17P-IF-001, and follow-up Study 17P-FU that would preclude approval of HPC for the proposed indication. There were no maternal deaths in the clinical development program for HPC. The Applicant reported a single case each of pulmonary embolus and injection site cellulitis as serious adverse reactions in HPC-treated subjects. Certain pregnancy-related maternal complications or events were numerically increased in the HPC-treated subjects as compared to control subjects, including preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios. The most commonly reported adverse reactions, reported in $\geq 2\%$ of subjects in Study 17P-CT-002, and at a higher rate in the HPC group than in the control group, were injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), and nausea (6%). The safety finding of most concern was a statistically non-significant increase in early pregnancy losses in the HPC-treated subjects. This finding was discussed at the 2006 Advisory Committee (AC) meeting for HPC. The recommendation of the majority of the members of the AC was that this observation required further investigation, but the investigation could be conducted post-approval.

Overall Assessment

The public health importance of preterm birth and the lack of an approved efficacious treatment for preterm labor must be considered in assessing the overall benefit/risk profile for a drug product for the indication of reduction of the risk of recurrent preterm birth.

Hydroxyprogesterone caproate is currently available only through compounding pharmacies and is widely used for reduction of preterm birth, based, in part, on the endorsement of the American College of Obstetricians and Gynecologists (ACOG) in 2008.

The safety and efficacy findings from Study 17P-CT-002 support approval of HPC under Subpart H accelerated approval regulations (21 CFR 314.510) for the indication “*to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.*” My recommendation for approval is based primarily on a statistically persuasive ($P < 0.001$) reduction in preterm births at $< 37^0$ weeks gestation. The required confirmatory efficacy and safety study (Study 17P-ES-003) is ongoing and is designed to provide efficacy data on a possible reduction in neonatal morbidity and mortality, the ultimate clinical outcome of interest. In addition, the study will evaluate the potential safety signal of a possible increased risk of early pregnancy loss. Although approval of HPC at this time would be based on a surrogate endpoint, I believe it is of greater service to the public health to provide an FDA-regulated drug product at this time, with labeling that will promote safe use, than to delay approval for several more years awaiting completion of the confirmatory efficacy and safety study.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

No postmarketing risk evaluation and mitigation strategies, beyond the to-be-approved physician and patient labeling and standard postmarketing pharmacovigilance monitoring are recommended at this time.

Approval under Subpart H regulations will also ensure that advertising accurately reflects labeling as one of the requirements of approval under subpart H is that advertising materials be submitted to DDMAC at least 30 days prior to the intended time of initial dissemination.

13.4 Recommendation for other Postmarketing Requirements and Commitments

13.4.1 Postmarketing Requirements

The Applicant has agreed to the following timelines for the required postmarketing studies:

1. To complete the clinical trial of HPC in women with a singleton pregnancy who had a previous spontaneous preterm birth (Protocol #17P-ES-003):

Revised Protocol Submission:	March 2011
Trial Completion:	June 2016
Final Report Submission:	December 2016
2. To complete the clinical follow-up safety study (Protocol 17P-FU-004) of children born to women who participated in Protocol #17P-ES-003:

Revised Protocol Submission:	March 2011
Final Interim Report Submission:	December 2016
Study Completion Date:	July 2018
Final Report Submission:	October 2018

13.4.2 Postmarketing Commitments

The Applicant has agreed to the following timelines for the following studies:

1. Submission of an academic publication of pharmacokinetic data on HPC and its metabolites in plasma and urine of pregnant women throughout different stages of gestation:
Final Report Submission: December 2011
2. If the publication referenced in the above postmarketing commitment is not submitted by December 31, 2011, or if the results from the publication do not include all the relevant findings (e.g., urinary metabolites), the Applicant will conduct the following clinical trial:
A non-randomized clinical pharmacokinetic trial of HPC and its metabolites in pregnant women. This trial will provide data characterizing the pharmacokinetics of HPC and its metabolites in plasma and urine throughout different gestational stages:
Final Protocol Submission: June 2012
Trial Completion: June 2014
Final Report Submission: November 2014
If the publication in support of postmarketing commitment #1 is submitted on time and deemed adequate, then postmarketing commitment #2 may be released.
3. An in vitro study in human hepatocytes to determine whether HPC induces or alters the metabolic activities of CYP1A2, CYP2A6, and CYP2B6:
Final Protocol Submission: June 2011
Study Completion Date: March 2012
Final Report Submission: July 2012

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

/s/

SCOTT E MONROE
02/03/2011