CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21945Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021945 SUPPL # HFD # 580

Trade Name Makena

Generic Name hydroxyprogesterone caproate

Applicant Name Hologic, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 010347 Delalutin

NDA# 016911 Delalutin

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 17P-CT-002

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Studies 17P-CT-002

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND (b) (4) YES ☐ ! NO ☒
! Explain:
The study was conducted by NICHD

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐ ! NO ☒
Explain: ! Explain:
The sponsor has not indicated that they had provided substanital support for this study

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Charlene Williamson
Title: Regulatory Health Project Manager
Date: February 3, 2011

Name of Office/Division Director signing form: Scott Monroe, M.D.
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

JENNIFER L MERCIER
02/03/2011

SCOTT E MONROE
02/03/2011

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21-945 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DRUP PDUFA Goal Date: October 24, 2008 Stamp Date: 4/24/2008

Proprietary Name: Gestiva

Established/Generic Name: 17 alpha hydroxyprogesterone caproate 250 mg/ml

Dosage Form: injection

Applicant/Sponsor: CYTYC Corporation

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC #:_____

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☒ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):__
(Attach a completed Pediatric Page for each indication in current application.)

Indication: _____

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☒ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☒ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

CYTYC

16 May 2008

Scott Monroe, M.D., Director
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: Request for Waiver of Pediatric Studies
NDA 21-945: Gestiva® (17 α-Hydroxyprogesterone Caproate Injection 250 mg/mL)
For the Prevention of Preterm Birth in Women with a History of at Least One Spontaneous Preterm Birth

Dear Dr. Monroe,

Cytyc Corporation hereby requests a (b) (4) waiver of pediatric studies for all ages birth to (b) (4) years of age for the above referenced NDA.

Under Section 505B(a)(4)(A)(i) of the Federal Food Drug and Cosmetic Act, Cytyc certifies that necessary studies are impossible or highly impracticable because 17 α-Hydroxyprogesterone Caproate has applicability only to menstruating women. The Division has previously indicated its agreement with (b) (4) waiver status for NDA 21-945 in its September 28, 2005 NDA Presubmission Acknowledgement.

If you have any questions or need any additional information regarding this submission, please contact Robb Hesley at 408-745-5179 or alternatively by email at robb.hesley@cytyc.com.

Sincerely,

Robb Hesley
VP Business Development

cc: Charlene Williamson, DRUP, FDA
Catherine Williams, Director Regulatory Affairs, Cytyc Corporation

CYTYC CORPORATION • 1240 ELKO DRIVE, SUNNYVALE, CA 94089-2212 • TEL: (408) 745-0975 • FAX: (408) 745-0968 • www.cytyc.com

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

/s/

Z. Charlene Williamson
5/21/2008 01:47:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
Building 32-5271
Silver Spring, MD 20993

FEB 1 1 2011

Hologic, Inc.
Attention: Catherine A. Williams
Director Regulatory Affairs
1240 Elko Drive
Sunnyvale, CA 94089

Re: Orphan-drug designation request # 06-2187

Dear Ms. Williams:

Reference is made to your orphan-drug hydroxyprogesterone caproate which was designated an orphan-drug pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) on January 25, 2007, for prevention of preterm birth in singleton pregnancies. We also refer to the letter from the Office of Drug Evaluation III, Center for Drug Evaluation and Research, dated February 3, 2011, granting marketing approval of your New Drug Application for Makena (hydroxyprogesterone caproate).

This letter is to inform you that as the first sponsor of this drug to obtain marketing approval for this indication, you are entitled to seven years of orphan-drug exclusive approval pursuant to Section 527 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360cc) *for the use to reduce the risk of preterm birth in women with singleton pregnancy who have a history of singleton spontaneous preterm birth.* The seven year exclusive approval began on February 3, 2011, the date of approval of your New Drug Application (021945). The scope of orphan-drug exclusive approval is described under 21 C.F.R. 316.31.

Please note that as the holder of exclusivity for Makena (hydroxyprogesterone caproate) you are required to assure the availability of sufficient quantities of this drug to meet the needs of patients. Failure to do so could result in the withdrawal of the drug's exclusive approval as stipulated under 21 C.F.R. 316.36(b).

The entire premise of the orphan products program is based on the realization that the

resources and commitment devoted to the development of drugs for "orphan" populations may not provide financial returns to their sponsors. Therefore, it is with genuine gratitude that we recognize your efforts in developing this drug.

Should you have any questions, please contact Mr. Jeff Fritsch, R.Ph., at (301)796-8682.

Sincerely yours,

Timothy R. Coté, M.D., M.P.H.
Director, Office of Orphan Products Development

Hologic, Inc.

cc:
OCC/EDickinson
OGD/LRB/MHolovac
DRUP/NDA 21-945
DRUP/CWilliamson/PM
OOPD/Chron File
OOPD/OP File # 06-2187
JFritsch 2/9/2011
EXCLUSIVITY

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

/s/

ZETA-MAE C WILLIAMSON
02/23/2011

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

M E M O R A N D U M

DATE: February 3, 2011

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

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

Makena (hydroxyprogesterone caproate injection) is a synthetic progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth. Makena will be supplied as a sterile solution in a multidose vial; each 5 mL contains hydroxyprogesterone caproate (HPC) 250 mg/mL in a castor oil vehicle. One mL (250 mg) should be administered intramuscularly once weekly beginning between 16^0 and 20^6 weeks of gestation and continued until week 37 or delivery, whichever comes first.

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

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

Reference ID: 2900783

Regulatory History, Review Findings and Actions Taken

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

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

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

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

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

Makena. In 2003, the results from a randomized, double-blind, vehicle-controlled trial of HPC in women at risk for preterm birth were published.[2] The trial, conducted by the Maternal-Fetal Medicine Units Network for the National Institute for Child Health and Human Development (hereafter referred to as 17P-CT-002) enrolled 463 US women with a prior spontaneous preterm birth. Women at 16^0-20^6 weeks gestation were randomized in a 2:1 ratio to receive either weekly intramuscular injections of HPC 250 mg or inert oil vehicle until delivery or to 36^6 weeks gestation. The mean duration of gestation at the time of the previous qualifying delivery was 31 weeks, and a third of the women enrolled had had more than one previous preterm delivery. Thus, the trial participants were considered to be at particularly high risk for another preterm delivery.

In 17P-CT-002, treatment with HPC resulted in a statistically significant reduction in preterm births < 37^0 weeks gestation, the primary outcome of the trial. The proportion of HPC-treated women delivering at < 37^0 weeks was 37.1% vs. 54.9% among vehicle-treated women, for a treatment difference of 17.8% (95% CI: -28.0%, -7.4%; $p < 0.001$). The reduction in preterm births < 37^0 weeks was independent of maternal race, number of qualifying preterm births, and gestational age of the qualifying preterm birth. In addition, a 9.4% reduction (95% CI: -19.0, -0.4%) in preterm births was noted at < 35^0 weeks, and a 7.7% reduction (95% CI: -16.1%, -0.3%) at < 32^0 weeks with HPC treatment as compared to vehicle. The reductions observed in preterm births at < 37^0 weeks and < 35^0 weeks were consistent across trial centers; however, for preterm births at < 32^0 weeks there was a greater reduction in HPC-treated women relative to vehicle at the largest accruing site (University of Alabama) compared to all other sites combined.

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

Adeza Biomedical obtained access to the trial data in 2003 and initiated communications with FDA regarding submission of a 505(b)(2) new drug application. On January 25, 2007, Adeza Biomedical was granted orphan designation for the use of HPC (the active ingredient in Makena) for the (b) (4) of preterm birth in singleton pregnancies. The original application, submitted on April 20, 2006, included data from this trial as well as follow-up information on infants born to mothers enrolled in that trial. FDA's review of the NDA encompassed three review cycles, highlights of which are summarized below.

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

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

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

Chemistry, Manufacturing and Controls. The drug product is photosensitive; the applicant needed to address the Agency's concerns regarding the detection of photo-degradation products and the adequacy of secondary packaging to protect the product from light. In addition, it was noted that the limited stability data supported an expiry of no more than (b) (4) (rather than the proposed 24 months).

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

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

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

- *Reduction in preterm births < 37^0 weeks.* Although the reduction in preterm births < 37^0 weeks observed in 17P-CT-002 was statistically persuasive ($p < 0.001$), DRUP expressed concern that this endpoint was not an adequate surrogate for clinical benefit, namely, a reduction in neonatal morbidity and mortality. This view was endorsed by 16 of 21 Advisory Committee members at the 2006 ACRHD meeting. In contrast, 13 of 21 Advisory Committee members indicated that reduction in preterm births < 35^0 weeks would be an adequate surrogate for clinical benefit.
- *Reduction in preterm births < 35^0 weeks.* Twelve Advisory Committee members voted that 17P-CT-002 had provided substantial evidence that HPC reduced preterm births < 35^0 weeks. Although reassuring, this endorsement by expert panelists was not fully shared by the DRUP clinical reviewers or the statistical reviewer, Dr. Lisa Kammerman, who argued that since the evidence for the drug's effectiveness relied on the findings from a single trial, the effect of treatment on preterm births < 35^0 weeks ($p=0.038$)[3] would not meet the level of statistical significance generally expected to support approval based on the findings of a single trial.
- *Generalizability of 17P-CT-002 trial results*. Two concerns were raised regarding the generalizability of trial results to a larger population of women at risk for preterm delivery. First, in contrast to the US population, approximately 59% of trial participants were African American, a population known to have a higher rate of preterm birth than other racial or ethnic groups. In subgroup analyses, however, the

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

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

Second, Dr. Kammerman noted that even if FDA were willing to accept a less robust result (e.g., for preterm births < 35^0 weeks) as the basis for drug approval, she remained concerned that one clinical trial site, the University of Alabama, had enrolled 27% of the total sample size and a disproportionately higher number of subjects at 18 weeks gestation or earlier; both the benefits of HPC and the rate of fetal losses were most pronounced among women who started treatment at or before 18 weeks. DRUP clinical reviewers were reassured by the observation that rates of preterm birth < 37^0 weeks and < 35^0 weeks were similar for the Alabama site and the other sites combined. Divergent (actually better) results for this site were noted only for the rate of preterm birth < 32^0 weeks. Additional analyses performed by the applicant that showed little likelihood that the overall treatment effect at < 32^0 weeks was being driven by the Alabama site were found persuasive by some of the DRUP clinical reviewers.

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

Additional information that was considered during this review cycle included:

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

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[4] For African American women, the proportion of HPC-treated women delivering at < 37^0 weeks was 36.1% vs. 52.2% of vehicle-treated women. For non-African American women, the proportion of HPC-treated women delivering at < 37^0 weeks was 38.6% vs. 58.7% of vehicle-treated women.

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

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

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

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

On the other hand, the DRUP clinical reviewers acknowledged two key recommendations from the ACRHD, namely that reduction in preterm births < 35^0 weeks was an adequate surrogate for clinical benefit in neonates (in terms of morbidity and mortality), and that further evaluation of the product's safety could be performed post-approval. In the end, DRUP concluded that the single clinical trial (17P-CT-002) had demonstrated efficacy with respect to the rate of preterm births < 35^0 weeks and concluded that it would be possible to ultimately approve HPC under Subpart H accelerated approval regulations (21 CFR 314.510), with the requirement that the applicant conduct a second well-controlled trial to verify and confirm the clinical benefit of HPC post-approval. Data from this trial or another trial could further assess the product's safety.

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

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

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

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

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

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

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

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

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

Reproductive Toxicology. The applicant submitted results from a multi-generational reproductive toxicology study in rats that found no evidence for reproductive or developmental toxicity or impaired fertility. When HPC was administered intramuscularly at gestational exposures up to 5 times the recommended human dose, no adverse effects were seen on the parental dams, their developing offspring (F_1), or the latter offspring's ability to produce a viable, normal second generation (F_2). Therefore, the previously identified toxicology deficiency was adequately addressed.

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

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

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

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

[7] Cytyc Corporation acquired Adeza Biomedical on April 2, 2007.

pregnancy who have had a previous spontaneous preterm birth. The primary objective was to determine the effect of treatment on preterm births < 35^0 weeks of gestation. Secondary objectives were to assess whether treatment with HPC compared to vehicle reduced the rates of neonatal morbidity/mortality, as measured by a composite index, as well as rates of preterm births < 32^0 weeks and fetal loss.

In a teleconference held on November 19, 2008, DRUP clinical reviewers and Dr. Kammerman requested that the composite neonatal morbidity/mortality index be evaluated in a hierarchical manner if the primary endpoint of preterm delivery < 35^0 weeks attained statistical significance. This would provide the needed link between the surrogate endpoint of gestational age at delivery and clinical benefit as measured by the neonatal morbidity/mortality index. In response to these requests, the applicant made several protocol revisions, including increasing the proposed sample size to 1707. The proposed trial would have 98% power to detect a 30% reduction (30% to 21%) in the rate of preterm birth at < 35^0 weeks, and 90% power to detect a 35% reduction (17% to 11%) in the composite neonatal morbidity/mortality index, allowing for fetal loss occurring in 2.5% of the pregnancies. The power to rule out a doubling of risk of fetal loss, assuming a rate of 4%, would be 83% (that is, the upper bound of the confidence interval for the relative risk of HPC compared to vehicle would be $\leq$ 2.0).

Although Dr. Kammerman agreed with the above-mentioned protocol revisions, in her review dated January 23, 2009, she reiterated her concern that the level of evidence from the applicant's single trial (17P-CT-002) was not sufficient to support the effectiveness of HPC. Further, she proposed that interim results regarding the reduction in preterm birth in a sufficient number of women from this second controlled trial (17P-ES-003) be submitted for review. If efficacy was established, then in her view, the NDA could be approved under Subpart H regulations. Results for clinical outcomes (such as fetal loss, neonatal morbidity and mortality) could be reviewed post-approval; if efficacy for these endpoints was established, then standard approval could be granted. DRUP did not pursue this proposal with the applicant, intending instead to approve HPC based on its effect on a surrogate endpoint (reduction in preterm births < 35^0 weeks in 17P-CT-002), and accept the proposed second clinical trial as confirmation of the drug's clinical benefit in neonates.

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

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

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

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

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

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

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

Clinical and Statistical.

The review during this cycle focused primarily on the evaluation of, and enhancements to, the proposed confirmatory trial, 17P-ES-003, and the infant follow-up study, 17P-FU-004. In addition, the DRUP clinical reviewers reviewed recently published information supporting the concern that preterm births between 34^0 and 36^6 weeks (so-called late preterm births) are predisposed to a higher risk of morbidity and mortality than term infants. This evaluation lead to the Agency's reconsideration of the positive results seen in the reduction of preterm births < 37^0 weeks with HPC treatment in the applicant's original clinical trial (17P-CT-002).

Confirmatory trial (17P-ES-003). In this review cycle, several aspects of the confirmatory trial were reviewed and considered acceptable, including recruitment goals and current enrollment in the US and other sites, blinded safety data on maternal, fetal and neonatal outcomes, and the composition and role of the Data Safety Monitoring Board. In addition, given the importance that HPC treatment be demonstrated to reduce neonatal morbidity and mortality as evidence of its clinical benefit, FDA requested and the applicant agreed to analyze preterm delivery < 35^0 weeks and the composite neonatal morbidity/mortality index as co-primary endpoints.

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

[9] Hologic Inc. acquired Cytyc Corporation in October 2007.

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

The DSMB held its first meeting on December 13, 2010, and reviewed trial data from 17P-ES-003 that were available through November 17, 2010. A total of 179 subjects have been randomized, including 144 in the US, thus exceeding the recruitment goals set forth in DRUP's January 23, 2009, complete response letter. A total of 131 subjects have received at least one injection of trial medication, and there have been 33 live births $\geq 24^0$ weeks. Fourteen serious adverse reactions and four fetal/neonatal deaths have been reported; none were considered related to trial medication. The 4 fetal/neonatal deaths were: a cardio-respiratory arrest related to severe prematurity (delivery at 21 weeks with a birth weight of 340 g; age < 1 day), a report of tight nuchal cord and intrauterine death at 32^4 weeks, and two miscarriages (both at 19^3 weeks).

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

At a teleconference held on January 5, 2011, FDA requested and the applicant agreed to modify the trial protocol such that preterm delivery $< 35^0$ weeks and the composite neonatal morbidity/mortality index will be co-primary endpoints. With a sample size of 1707, the power to detect significant differences between the treatment groups for both endpoints would be approximately 90%. A revised protocol will be submitted for review in March 2011.

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

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

Reconsideration of the primary efficacy endpoint in 17P-CT-002. The applicant's original clinical trial, 17P-CT-002, demonstrated a significant reduction in the rate of preterm births $< 37^0$ weeks with HPC treatment as compared to vehicle ($p < 0.001$). At the time the trial was initially reviewed, DRUP and the ACHRD members gave this finding less weight because of assumptions that most infants born at 36 or 35 weeks gestation were at little risk for long-term morbidities. In this review cycle, DRUP reviewed recent publications in the literature discussing the developmental and physiologic immaturity of late preterm births.

Late preterm births account for roughly 70% of all preterm births in the US. In 2005, an NIH-sponsored workshop entitled "Optimizing Care and Outcome of the Near-Term Pregnancy and the Near-Term Newborn Infant" recommended that infants born at 34^0 through 36^6 weeks gestation be referred to as "late preterm" to emphasize that these infants are in fact preterm, and at increased risk (compared to term infants) of immaturity-related medical complications. For example, late preterm infants are more likely than term infants to be diagnosed during the birth hospitalization with temperature instability, hypoglycemia, respiratory distress, apnea, jaundice and feeding difficulties. During the first month after birth, late preterm infants are more likely than term infants to be re-hospitalized for jaundice, feeding difficulties, dehydration and suspected sepsis.[10] Compared with term infants, infants born at 36 or 35 weeks were five or nine times as likely to be ventilated as term infants.[11] In addition, the neonatal mortality rate (deaths at 0-27 days) for late preterm infants in the US was 4.6 times higher in 2002 than the rate for term infants (4.1 vs. 0.9 per 1000 live births).[12] Even healthy-appearing late preterm infants carry an increased risk for developmental delays and adverse early school-age outcomes compared with healthy term infants.[13]

Exploration of the effect of maternal race on the safety and effectiveness of HPC. Approximately 59% of enrollees on 17P-CT-002 were African American; 26% were Caucasian, 14% were Hispanic and < 1% were Asian. HPC treatment reduced the rate of preterm birth <37° weeks compared to vehicle for both the African American (36.1 % vs. 52.2%) and the non-African American (38.6% vs. 58.7%) populations.

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

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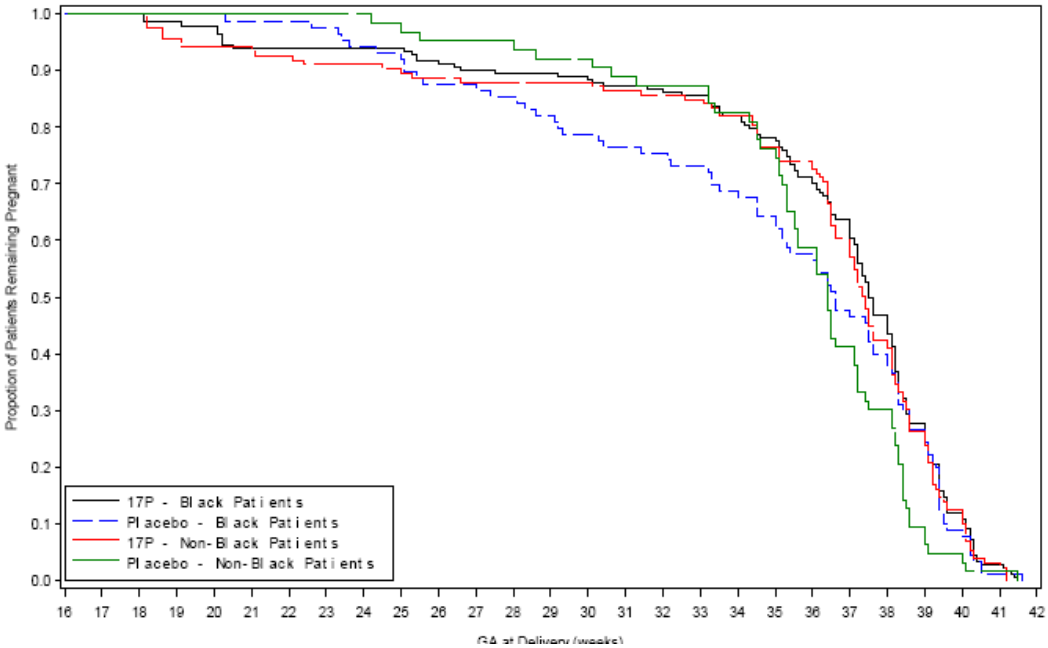
[10] Engle WA, Tomasek KM, Wallman C, and the Committee on Fetus and Newborn. "Late-Preterm Infants: A Population at Risk. Pediatrics 2007;120:1390-1401. McIntire DD, and Leveno KJ. Neonatal Mortality and Morbidity Rates in Late Preterm Births Compared with Births at Term. Obstet. Gynecol. 2008;111:35-41.

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

[12] Engle WA et al. 2007.

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

Proportion Remaining Pregnant by Race and Treatment



Source: Hologic, Inc., February 2, 2011

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

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

Regulatory action. At the conclusion of this third review cycle, acknowledging more recent concerns regarding the increased morbidity and mortality of late preterm births relative to term births, DRUP now recommends and I concur, that reduction in preterm births < 37^0 weeks is an adequate surrogate for clinical benefit (i.e., reduction in neonatal morbidity and mortality). Further, the effect of HPC treatment to reduce preterm births < 37^0 weeks compared to vehicle as observed in 17P-CT-002 was sufficiently persuasive

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

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

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

Clinical Pharmacology

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

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

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

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

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

Safety

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

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

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

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

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

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

Pediatric Considerations

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

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

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

Tradename Review

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

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/s/

JULIE G BEITZ
02/03/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 21945	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Makena Established/Proper Name: 17-α hydroxyprogesterone caproate Dosage Form: Injection (IM) Strengths: 250 mg/ml		
Applicant: Hologic, Inc.		
Date of Receipt: July 12, 2010 (Class 2 Resubmission) April 25, 2008 (Class 2 Resubmission) April 14, 2006 (Original)		
PDUFA Goal Date: April 13, 2011	Action Goal Date (if different): February 3, 2011	
Proposed Indication(s): To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Reference ID: 2900780

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature	**Non-Clinical/Clinical**

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

PK/PD Studies

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

Reference ID: 2900780

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

NOTE: The Sponsor relied on the Agency's previous findings of safety and efficacy.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☐

Reference ID: 2900780

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new indication, "to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth."

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

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YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): N/A

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

Reference ID: 2900780

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): N/A

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

Reference ID: 2900780

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Reference ID: 2900780

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/s/

ZETA-MAE C WILLIAMSON
02/03/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021945 **GENERAL ADVICE LETTER**

Hologic, Inc.
Attention: Robb Hesley
Vice President Business Development
1240 Elko Drive
Sunnyvale, CA 94089-2212

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Makena (hydroxyprogesterone caproate) Injection.

We have the following two postmarketing requirements. Please indicate your agreement to meet the timelines for each, as listed below:

1. To complete the clinical trial of hydroxyprogesterone caproate (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 Date	June 2016
Final Report Submission	December 2016

2. To complete the clinical follow-up study (Protocol #17P-FU-004) of children born to women who participated in Protocol #17P-ES-003:

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

We also have the following three postmarketing commitments with timelines. Please indicate your agreement to these commitments and the timelines as listed below:

3. To submit an academic publication of pharmacokinetic data on hydroxyprogesterone caproate and metabolites in plasma and urine of pregnant women throughout different stages of gestation:

Final Report Submission	December 2011

4. If the publication described in the above postmarketing commitment (Commitment No. 3) 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), you will conduct the following clinical trial:

   A non-randomized clinical pharmacokinetic trial of hydroxyprogesterone caproate and its metabolites in pregnancy. This study will provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine throughout different stages of gestation.

Final Protocol Submission	June 2012
Trial Completion Date	June 2014
Final Report Submission	November 2014

5. To conduct a nonclinical *in vitro* study using 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

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

SCOTT E MONROE
01/13/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021945

REVIEW EXTENSION – MAJOR AMENDMENT

Hologic, Inc.
Attention: Robb Hesley
Vice President Business Development
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

Please refer to your April 14, 2006 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Makena (hydroxyprogesterone caproate) Injection 250 mg/ml.

On January 10, 2011, we received your solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 13, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 3, 2011.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JENNIFER L MERCIER
01/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:	FROM(*Division/Office*)
Charlene Williamson Jennifer Mercier Division of Reproductive and Urologic Products (DRUP)	Carrie Newcomer, PharmD Division of Drug Marketing, Advertising and Communications

DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENTS:
1/10/11		021945	Promotional Press Release and Sales Aid	12/16/10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Makena (hydroxyprogesterone caproate injection)	Yes – launch press release and sales aid		1/24/11

NAME OF FIRM: Hologic, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☑ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

COMMENTS/SPECIAL INSTRUCTIONS:

Please see questions below regarding a launch proposed press release and sales aid for Makena. This consult, along with the promotional material, draft PI, and reference will be entered into DARRTS.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Carrie Newcomer, PharmD	☑ **MAIL (DARRTS)** ☐ FACSIMILE
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 021945

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Hologic, Inc.
1240 Elko Drive
Sunnyvale, CA 94089-2212

ATTENTION: Robb Hesley
Vice President Business Development

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) resubmission dated July 12, 2010, received July 13, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydroxyprogesterone Caproate Injection, 1250 mg/5 mL.

We also refer to your November 29, 2010, correspondence, received November 30, 2010, requesting review of your proposed proprietary name, Makena. We have completed our review of the proposed proprietary name, Makena and have concluded that it is acceptable.

The proposed proprietary name, Makena, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 29, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567.

For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Charlene Williamson, at (301)796-1025.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/20/2010

Merchant, Lubna

From: Merchant, Lubna
Sent: Friday, December 17, 2010 6:42 AM
To: Wasilik, Maria; Griffis, Melina
Cc: Williamson, Charlene
Subject: RE: NDA 21-945 Draft Makena Carton and Vial Labels

Maria,

The container labels and carton labeling are acceptable.

Thanks,
Lubna

Lubna Merchant, M.S., Pharm.D.
Drug Safety Evaluator
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Office 301.796.5162
lubna.merchant@fda.hhs.gov

From: Wasilik, Maria
Sent: Thursday, December 16, 2010 10:34 AM
To: Griffis, Melina; Merchant, Lubna
Cc: Williamson, Charlene; Wasilik, Maria
Subject: FW: NDA 21-945 Draft Makena Carton and Vial Labels

Maria

From: Williamson, Charlene
Sent: Thursday, December 16, 2010 10:24 AM
To: Wasilik, Maria
Subject: FW: NDA 21-945 Draft Makena Carton and Vial Labels

FINAL copies of the carton/container labeling for Makena.

From: Hesley, Robb [mailto:Robb.Hesley@hologic.com]

Sent: Wednesday, December 15, 2010 5:18 PM
To: Williamson, Charlene
Cc: Eckstein, Mary Elizabeth; Williams, Catherine
Subject: NDA 21-945 Draft Makena Carton and Vial Labels

Hi Charlene,
As we just discussed, please disregard the draft Makena carton and vials labels I emailed you from a few minutes ago and use this attachment instead. The difference is [redacted] (b) (4) in this version. I have included the actual print proofs from Baxter (our CMO for Makena).

We will submit these to the NDA tomorrow.
Regards,
Robb

Robb Hesley
Hologic, Inc.
VP Business Development
Office 408 745 5179
Mobile 408 410 5371

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/s/

LUBNA A MERCHANT
01/05/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 021945

PROPRIETARY NAME REQUEST WITHDRAWN

Hologic, Inc.
1240 Elko Drive
Sunnyvale, CA 94089-2212

ATTENTION: Robb Hesley
Vice President Business Development

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) resubmission dated July 12, 2010, received July 13, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydroxyprogesterone Caproate Injection, 250 mg/mL.

We acknowledge receipt of your November 23, 2010 correspondence, on November 24, 2010, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4) This proposed proprietary name request is considered withdrawn as of November 24, 2010.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Charlene Williamson at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DENISE P TOYER on behalf of CAROL A HOLQUIST
12/09/2010

Response to FDA Questions of 6 December 2010

1. *For Study 17P-ES-003, you indicate completion of the study more than 5 years from now. Given that women will only be enrolled for a maximum of about six months, does the current rate of enrollment indicate that it will indeed take this long to complete the study? Please project enrollment goals to see if this timeline might be shortened.*

   In order to completely answer this question, the Sponsor would like to provide some background information on our efforts to date with regard to recruiting sites to conduct the 17P-ES-003 (003) study. In the US, 10,757 OB/GYN physicians were queried by fax to elicit interest. Of those physicians, 352 sites returned a recruitment questionnaire. 173 indicated they were not interested and 179 indicated they were interested. Of those, a total of 49 sites were qualified and agreed to conduct the study. In Canada, 1700 OB/GYN physicians were queried by fax for interest. Of those, 33 sites returned a recruitment questionnaire, 12 indicated they were not interested in participating and 21 indicated they were. Of those, 8 sites were found to be qualified to conduct the study.

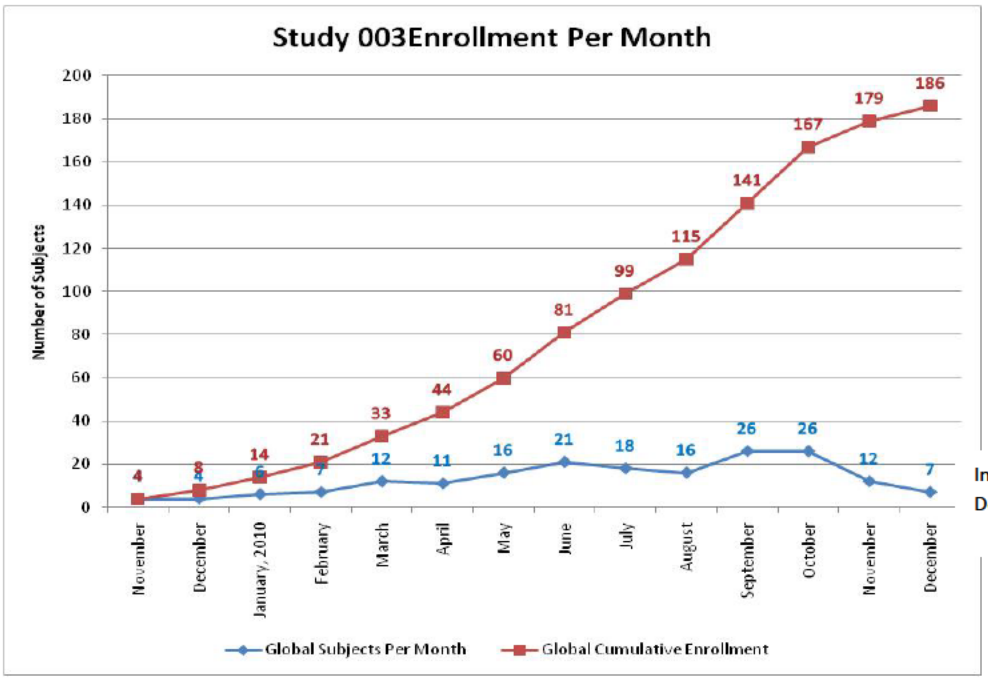
   In Europe, 161 sites from 9 countries (Belgium, Czech Republic, France, Hungary, Italy, Russia, Spain, Ukraine and United Kingdom) were queried for interest in the study. Sites from Belgium, France and United Kingdom had a poor response or showed a lack of interest in the trial participation so no sites in those countries were selected to participate. 35 sites among the remaining countries were interested and found to be qualified to conduct the study.

   The Sponsor notes that one of the most important site qualification criteria was access to a Level III NICU within 30 minutes of the site. This disqualified a large number of sites in both North America and Europe. We felt this was an important criterion to assure that a similar level of care was available for all infants within a reasonable amount of time.

   In an effort to increase enrollment, we have submitted to the Indian and Mexican regulatory authorities for approval to conduct the study in these countries. After one year, we are still awaiting regulatory approval in these countries. Should they be approved, it is possible that enrollment could be completed sooner.

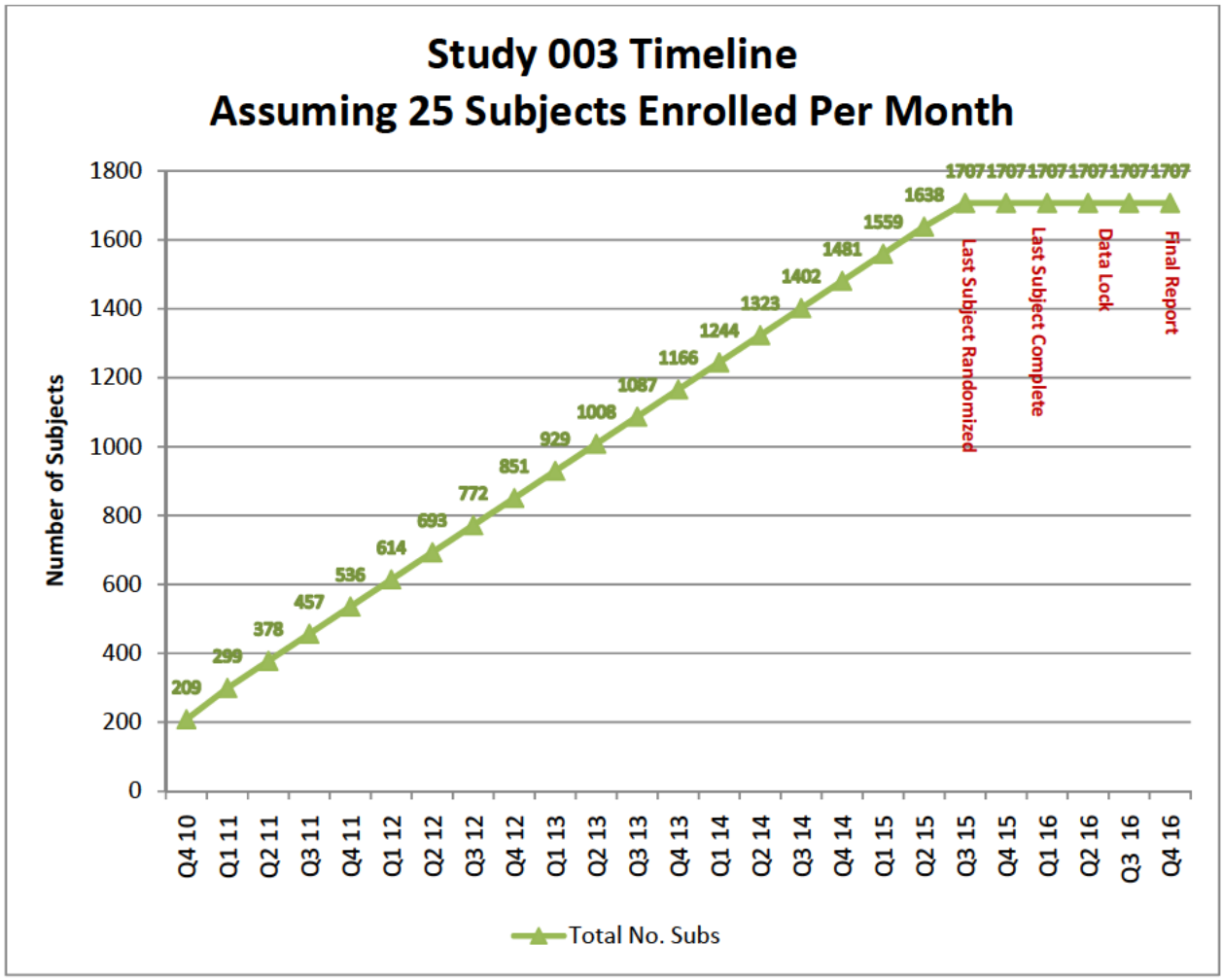
   At present, the Sponsor expects to initiate a total of 92 sites to the study. It is possible that some sites will withdraw upon approval of the product in the US. Therefore, the Sponsor has based forward-looking projections of enrollment on the assumption that 75 sites will participate in the study (40 in the US/Canada and 35 in Europe) in the long term.

   Enrollment into the 003 study began in November of 2009. A graph of enrollment from that time is presented below:



Includes only the 1st six days of December

Since the Resubmission was submitted in July, 2010, an additional 101 subjects have been randomized. This is approximately 20 subjects per month. As can be seen in the graph above, enrollment has fluctuated from a bit below 20 to over 25 subjects each month since July, 2010. The Sponsor believes a recruitment rate of 25 subjects per month is achievable based on these historical data. Note that several sites were initiated in October and November of 2010 and an additional 9 sites will be initiated in December or January. Based on these assumptions, the Sponsor expects the study to follow the timeline denoted in the graph presented below.



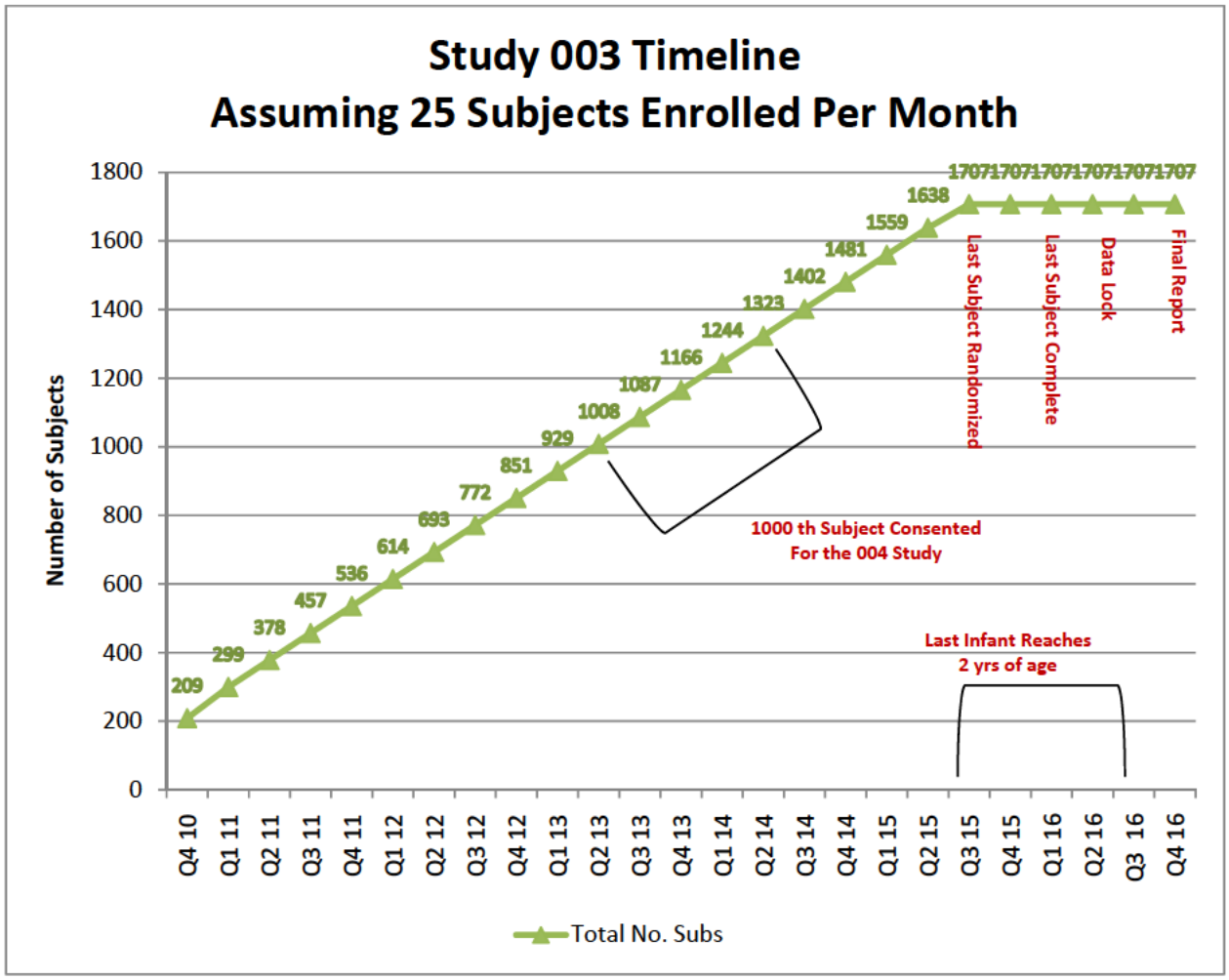
As per the above graph, the last subject is expected to randomize in the 3rd quarter of 2015. This subject would complete the study in approximately the 1st quarter of 2016. Data lock would be expected by Q2 – Q3 of 2016 with the draft final report available by the end of Q4 2016.

The Sponsor is committed to meeting our post approval commitments in this Orphan population. Therefore, the Sponsor has been careful to provide FDA with a realistic estimate of when this study can be completed. If the study is approved and initiated in India and Mexico, it is likely that enrollment can be accelerated.

2. *For Study 17P-FU-004, you indicate the same timelines as the previous study. However, this study will entail follow-up of offspring from Study 17P-ES-003 at 24 months of age, so it would seem that this study needs to be offset by two years from the timelines for Study 003. Please clarify how you arrive at the timelines for Study 17P-FU-004. We would anticipate having the results of Study 17P-ES-003 long before the infant follow-up study is complete.*

Since the infant follow up study, 17P-FU-004 (004) requires 375 subjects to meet its goals, it is anticipated that the Sponsor will attempt to consent the first 1000 subjects to be contacted approximately 2 years after their child is delivered. It is expected that the Sponsor will be able to

contact approximately 500 of these women and they will be sent the ASQ. It is expected that approximately 375 of these women will return the ASQ. As can be seen from the graph presented below, the Sponsor expects that enrollment of approximately 1000 women will occur sometime around the end of 2013 or first part of 2014 (assuming at least 75% of the women randomized in the 003 study consent to be contacted for the 004 study). The infants from the 1000th woman enrolled will reach approximately 2 years of age in late 2015 or early 2016. The ASQ and follow up process will take approximately 3 months. The last subject would therefore complete the 004 study at approximately the same time as the last subject completes the 003 study. Irrespective of when the last subject completes study 004, the Sponsor will not unblind the 004 study until the 003 study database is locked.



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/s/

ZETA-MAE C WILLIAMSON
12/22/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 021945

PROPRIETARY NAME REQUEST WITHDRAWN

Hologic Inc
1240 Elko Drive
Sunnyvale, California 94089-2212

ATTENTION: Mr. Robb Hesley
Vice President, Business Development

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) resubmission dated July 28, 2010, received July 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hydroxyprogesterone Caproate Injection, 250 mg/ml.

We acknowledge receipt of your October 14, 2010 correspondence, on October 15, 2010, notifying us that you are withdrawing your request for a review of the proposed proprietary name Gestiva. This proposed proprietary name request is considered withdrawn as of October 15, 2010.

We acknowledge receipt of your new request for a proposed proprietary name review for Gestene on October 15, 2010.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Charlene Williamson, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/29/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADM NISTRATION	REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**	FROM: Charlene Williamson – Ext. 6-1025 Division of Reproductive and Urologic Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 5, 2010		021945	Paper	July 13,2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gestiva (17α hydroxyprogesterone acetate)	Priority	Progesterone	October 25, 2010

NAME OF FIRM: Hologic, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the labeling for 17 a-hydroxyprogesterone caproate injection 250 mg/ml for the prevention of pre-term birth in women with a history of a least one preterm birth. Please review the AERS database for all AE reports involving any compounded preparations of 17-hydroxyprogesterone caproate used in pregnant women from May 2008 through the present.

SIGNATURE OF REQUESTER Charlene Williamson	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

ZETA-MAE C WILLIAMSON
10/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Charlene Williamson – Ext. 6-1025
Division of Reproductive and Urologic Products

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
September 24, 2010		021945	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Gestiva – 17-α Hydroxyprogesterone Acetate	Standard	Progesterone	December 1, 2010

NAME OF FIRM:
Hologic,Inc

PDUFA Date: January 13, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☒☐ ORIGINAL NDA/BLA (Resubmission)
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: October 14, 2010

Labeling Meetings: November 15, 2010

Wrap-Up Meeting: November 15, 2010

SIGNATURE OF REQUESTER Charlene Williamson

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL ☐ HAND

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/s/

ZETA-MAE C WILLIAMSON
09/24/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021945 **ACKNOWLEDGE CLASS 2 RESPONSE**

Hologic, Inc.
Attention: Robb Hesley
Vice President, Business Development
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

We acknowledge receipt on July 13, 2010 of your July 12, 2010 resubmission to your new drug application for Gestiva™ (hydroxyprogesterone caproate injection) 250 mg/ml.

We consider this a complete, class 2 response to our January 23, 2009 action letter. Therefore, the user fee goal date is January 13, 2011.

If you have any questions, call me, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Z. Charlene Williamson
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21945	ORIG-1	HOLOGIC INC	GESTIVA(17 ALPHA HYDROXYPROGESTERONE CAP

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/s/

ZETA-MAE C WILLIAMSON
07/28/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021945 **MEETING MINUTES**

Hologic, Inc.
Attention: Robb Hesley
Vice President, Business Development
1240 Elko Drive
Sunnyvale, CA 94089-2212

Dear Mr. Hesley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Gestiva (hydroxyprogesterone caproate injection) 250 mg/ml.

A telephone conference call between representatives of your firm and the FDA was scheduled for December 15, 2009. The purpose of the meeting was (1) to discuss CMC issues and questions related to your Complete Response letter received on January 23, 2009, (2) to reach agreement on the clinical protocols and (3) to reach agreement on your plans for addressing the clinical deficiencies described in the Complete Response letter of January 23, 2009.

On December 8, 2009, the Division sent you preliminary comments and responses to your questions submitted in your meeting package. On December 10, 2009, you requested clarification on Question #8, and the Division responded. Based on the Division's responses, you determined that there were no further issues to be resolved, and requested that the scheduled meeting be cancelled.

Therefore, the enclosed document serves as the official minutes of the cancelled meeting. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796 1025.

Sincerely,

{See appended electronic signature page}

Lisa Soule, M.D.
Clinical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

SPONSOR QUESTIONS AND THE DIVISION'S RESPONSES

CMC

Question 1:
Does the Division agree that a 24 month CRT expiry date is acceptable for Gestiva when stored upright and in the secondary carton?

Division Response:
The Division concurs that the data provided in the September 25, 2008 submission support a 24 month expiration dating period when the product is stored upright and protected from light in the secondary carton.

Question 2:
Does the Division agree that a 5 week open-shelf life is acceptable?
Division Response:
The Division concurs that the data provided in the October 31, 2008 submission support a 5 week open-shelf life after first use/penetration of the rubber septum by a syringe.

Clinical

Question 3:
Does the Division agree that the protocols submitted under IND 68,108 are acceptable in design to satisfy the requirements of the Complete Response?

Division Response:
Yes. However, the Division has the following request:

> In addition to using gestational age as a categorical variable, explore the effect of gestational age on outcome by using gestational age as a continuous variable. Further, because the logistic model assumes a multiplicative effect of gestational age on fetal/early infant death, the Division suggests exploring the effect of gestational age using an approach that assumes a linear effect.

Question 4:
Does the Division agree that this presentation of the specified information above is sufficient to demonstrate that the IRB and patient enrollment requirements of the Complete Response have been fulfilled?

Division Response:
Yes, provision of the specified information, including date of IRB approval for at least 15 investigational sites and subject ID and date of randomization to document enrollment of at least 15 US subjects will be sufficient.

Question 5:
Does the Division agree that the information above represents adequate supporting evidence (with acceptable projected enrollment rates) to demonstrate that at least 10% of the study population will be enrolled from US/Canada?

Division Response:
Yes, inclusion of the number of US/Canadian sites, current and projected enrollment rates and description of efforts to assure that at least 10% of total enrollment is from the US/Canada will constitute adequate supporting evidence, provided that the current and projected enrollment rates do not indicate that the goal is unattainable.

Question 6:
Does the Division agree with the proposed geographic distribution and patient enrollment limits as presented as presented above?

Division Response:
Yes, with the understanding that at least 15 subjects will be enrolled at U.S. study sites at the time of the Complete Response submission. It is also understood that the patient enrollment for the initial 85 patients may not reflect the Division's requested distribution of total patient enrollment (no site to enroll more than 15% of the total number of subjects).

Question 7:
Does the Division agree that urine samples do not need to be collected during the Population PK substudy portion of the Confirmatory Study?

Division Response:
The Division agrees that urine samples for pharmacokinetic (PK) analysis do not need to be collected in study 17P-ES-003. However, information on the urinary metabolites is important and will be included as a post-approval commitment, if the product were to be approved. In the resubmission of NDA 21-945 dated 4/24/2008, the Sponsor proposed to submit results from a clinical pharmacology study being conducted by (b) (4) (ClinicalTrials.gov identifier: NCT00409825) when they are published. The study by (b) (4) appears adequate to characterize the PK of hydroxyprogesterone caproate and its metabolites. However, if Dr. (b) (4) decides not to provide access to the results or does not include all relevant findings (e.g., urinary metabolites), then this information would need to be provided to the Agency in some other way (e.g., through a Sponsor-conducted study or by obtaining access to full study results from (b) (4)).

Question 8:
Does the Division agree with the proposed content of the Safety Updates as described above in order to satisfy the requirements from the Complete Response?

Division Response:
The proposal to submit a literature summary for the Safety Update is acceptable; however, the Sponsor should also submit a high-level overview of safety data available for those subjects who have been enrolled in the confirmatory study at the time of the Complete Response submission

(i.e., deaths, serious adverse events, discontinuations due to adverse events and adverse pregnancy outcomes). Depending on the number and nature of such reports, the Division might request that unblinded data be made available (via a third party or by providing the treatment code) without breaking the blind at the level of study personnel.

Additional Question from the Sponsor:
The Sponsor requested clarification that "adverse pregnancy outcomes" referred to miscarriages, stillbirths and congenital anomalies. Assuming the Division is in agreement, the following are the safety data that will be submitted as part of the high-level safety review from the ongoing 17P-ES-003 study:

All Serious Adverse Events and Adverse Pregnancy Outcomes, regardless of whether they are related or expected, including any event that:

1. Results in maternal, fetal (miscarriages, stillbirths [antepartum and intrapartum]), or neonatal death;
2. Is immediately life threatening; requires subject hospitalization for reasons other than pregnancy complications and/or preterm delivery; or prolongation of existing hospitalization;
3. Results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect;
4. Complications requiring the mother to remain hospitalized longer than expected; and
5. Important medical events that may not result in death, be life-threatening, or require hospitalization that in the medical judgment of the investigator may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In addition the Sponsor will provide information on all discontinuations from study drug due to adverse events.

Included with the high-level safety review will be (at least) event onset date, verbatim term and investigator's assessment of relationship to study drug for each event, and copies of all expedited safety reports submitted to the IND.

The Sponsor will provide the above safety information for all randomized patients as of the date of randomization of the last patient needed to satisfy the Complete Response requirement.

The Division agreed.

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	January 15, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21945	GI-1	HOLOGIC INC	GESTIVA(17 ALPHA HYDROXYPROGESTERONE CAP

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/s/

LISA M SOULE
12/17/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Division of Clinical Pharmacology 3** **Office of Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Doanh Tran, R.Ph., Ph.D.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 12/7/2009	IND No.: Serial No.: DARRTS No.:	NDA No. 21-945 **(SDN 048)**	DATE OF DOCUMENT **10/19/2009 (letter date 10/16/2009)**	
NAME OF DRUG **Hydroxyprogesterone caproate Injection, 250 mg/mL**	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Hologic, Inc.

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☒ MEETING PACKAGE (TYPE C)	☐ OTHER *(SPECIFY BELOW):*
☐ PHASE IV RELATED		[ ]

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒ See comments below
☐Medical☐Chemist☐Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
☐Micro☐Pharmacometrics☐Others	meeting/Telecon. see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☒ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

Indication: (b) (4) preterm birth
Objective: Review of meeting package

Regulatory history:
NDA 21-945 for hydoxyprogesterone caproate (17-HPC) was submitted on April 14, 2006. It was found acceptable from a Clinical Pharmacology perspective with a recommendation to obtain additional data post-approval. The original NDA received an Approvable action on October 20, 2006 due to Clinical, Pharmacology and Toxicology, and Chemistry, Manufacturing and Controls deficiencies. The Approvable letter indicated that additional clinical pharmacology information would be needed post approval (if the NDA is to be approved).

The sponsor resubmitted the NDA on 4/24/2008. No new clinical pharmacology studies were done sine the original submission. The resubmission sought the same indication of (b) (4) preterm birth in pregnant women with a history of at least one spontaneous preterm birth and the same dosing regimen of 250 mg 17-HPC intramuscularly once weekly that was sought in the original NDA. In this resubmission, the sponsor proposed to conduct a phase 4 safety and efficacy study. Clinical Pharmacology comments regarding PK sampling time for the proposed protocol

were conveyed to sponsor via Information Request letter on 8/6/2008 and were later updated in a letter to sponsor on 8/21/2008. The sponsor replied on 8/28/2008 and agreed to the protocol design recommendations (See Clinical Pharmacology review NDA 21-945 in DARRTS, date 1/15/2009).

A Complete Response to the NDA resubmission was issued on 1/23/2009. This protocol was submitted to new IND (protocol number 17P-ES-003). The PK samplings were the same as those agreed to by sponsor during the NDA review.

Selected text from NDA 21-945 Complete Response letter dated 1/23/2009:

> "ADDITIONAL ISSUES THAT WOULD NEED TO BE ADDRESSED POSTMARKETING, IF THE PRODUCT WERE TO BE APPROVED:
>
> **Clinical Pharmacology**
>
> 1. Provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine in pregnant women throughout different gestational stages.
>
> 2. Conduct an in vitro study using human hepatocytes to determine whether hydroxyprogesterone caproate induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.

Current submission:

The sponsor has the following question regarding design of study protocol 17P-ES-003:

> Population PK Study
>
> Reference is made to informal telephone and email communications during August of this year between the Division and Hologic confirming that urine samples do not need to be collected during the Population PK sub study portion of the Confirmatory Study. We seek the Division's concurrence of this understanding.
>
> Question 7: Does the Division agree that urine samples do not need to be collected during the Population PK substudy portion of the Confirmatory Study?

Reviewer's comments:

1. It was discussed during the review of NDA 21-945 whether or not urine sampling (in addition to the plasma samplings) was needed in the proposed safety and efficacy study. It was decided that the sponsor would not be required to assess urine metabolite concentration in this study since the study being conducted by the University or Pittsburg and the National Institute of Health (Principle investigator: (b) (4) ClinicalTrials.gov identifier: NCT00409825) would provide substantial data on the PK of 17-HPC and its metabolite in pregnant women – including assessment of metabolites in maternal blood and urine. However, it was noted that the sponsor may not have complete access to all data from the (b) (4) study. Therefore, the CR letter should contain the same commitment to provide PK data in both plasma and urine. The urine data would primarily be used to assess which metabolites are present and in what amount.

Comments for Sponsor:

Question 7: Does the Division agree that urine samples do not need to be collected during the Population PK substudy portion of the Confirmatory Study?

Clinical Pharmacology response:
The Division agrees that urine samples for pharmacokinetic (PK) analysis do not need to be collected in study 17P-

ES-003. However, information on the urinary metabolites is important and will be included as a post-approval commitment, if the product were to be approved. In the resubmission of NDA 21-945 dated 4/24/2008, the Sponsor proposed to submit results from a clinical pharmacology study being conducted by (b) (4) (ClinicalTrials.gov identifier: NCT00409825) when they are published. The study by (b) (4) appears adequate to characterize the PK of hydroxyprogesterone caproate and its metabolites. However, if (b) (4) decides not to provide access to the results or does not include all relevant findings (e.g., urinary metabolites), then this information would need to be provided to the Agency in some other way (e.g., through a Sponsor-conducted study or by obtaining access to full study results from (b) (4)

Additional review notes: *A teleconference with Sponsor was scheduled for 12/15/2009. The Agency's preliminary responses, including the above response to Question 7, were forwarded to Sponsor on 12/8/2009. Subsequently, the Sponsor decided to cancel the teleconference. Please see meeting minutes for further details.*

SIGNATURE OF REVIEWER: _____ **SIGNATURE OF TEAM LEADER:**	Date _____ Date _____
CC.: DCP3; TL: Kim; DD: Bashaw	**Project Manager:**_____ **Date** _____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21945	GI-1	HOLOGIC INC	GESTIVA(17 ALPHA HYDROXYPROGESTERONE CAP

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/s/

DOANH C TRAN
12/15/2009

MYONG JIN KIM
12/15/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Division of Clinical Pharmacology 3** **Office of Clinical Pharmacology** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Doanh Tran, R.Ph., Ph.D.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 12/7/2009	IND No.: Serial No.: DARRTS No.:	NDA No. 21-945 **(SDN 048)**	DATE OF DOCUMENT **10/19/2009 (letter date 10/16/2009)**	
NAME OF DRUG **Hydroxyprogesterone caproate Injection, 250 mg/mL**	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Hologic, Inc.

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☒ MEETING PACKAGE (TYPE C)	☐ OTHER *(SPECIFY BELOW)*:
☐ PHASE IV RELATED		[ ]

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒ See comments below
☐Medical☐Chemist☐Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
☐Micro☐Pharmacometrics☐Others	meeting/Telecon. see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☒ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

Indication: Prevention of preterm birth
Objective: Review of meeting package

Regulatory history:
NDA 21-945 for hydoxyprogesterone caproate (17-HPC) was submitted on April 14, 2006. It was found acceptable from a Clinical Pharmacology perspective with a recommendation to obtain additional data post-approval. The original NDA received an Approvable action on October 20, 2006 due to Clinical, Pharmacology and Toxicology, and Chemistry, Manufacturing and Controls deficiencies. The Approvable letter indicated that additional clinical pharmacology information would be needed post approval (if the NDA is to be approved).

The sponsor resubmitted the NDA on 4/24/2008. No new clinical pharmacology studies were done sine the original submission. The resubmission sought the same indication of (b) (4) preterm birth in pregnant women with a history of at least one spontaneous preterm birth and the same dosing regimen of 250 mg 17-HPC intramuscularly once weekly that was sought in the original NDA. In this resubmission, the sponsor proposed to conduct a phase 4 safety and efficacy study. Clinical Pharmacology comments regarding PK sampling time for the proposed protocol

were conveyed to sponsor via Information Request letter on 8/6/2008 and were later updated in a letter to sponsor on 8/21/2008. The sponsor replied on 8/28/2008 and agreed to the protocol design recommendations (See Clinical Pharmacology review NDA 21-945 in DARRTS, date 1/15/2009).

A Complete Response to the NDA resubmission was issued on 1/23/2009. This protocol was submitted to new IND (protocol number 17P-ES-003). The PK samplings were the same as those agreed to by sponsor during the NDA review.

Selected text from NDA 21-945 Complete Response letter dated 1/23/2009:

> "ADDITIONAL ISSUES THAT WOULD NEED TO BE ADDRESSED POSTMARKETING, IF THE PRODUCT WERE TO BE APPROVED:
>
> **Clinical Pharmacology**
>
> 1. Provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine in pregnant women throughout different gestational stages.
>
> 2. Conduct an in vitro study using human hepatocytes to determine whether hydroxyprogesterone caproate induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.

Current submission:

The sponsor has the following question regarding design of study protocol 17P-ES-003:

> Population PK Study
>
> Reference is made to informal telephone and email communications during August of this year between the Division and Hologic confirming that urine samples do not need to be collected during the Population PK sub study portion of the Confirmatory Study. We seek the Division's concurrence of this understanding.
>
> Question 7: Does the Division agree that urine samples do not need to be collected during the Population PK substudy portion of the Confirmatory Study?

Reviewer's comments:

1. It was discussed during the review of NDA 21-945 whether or not urine sampling (in addition to the plasma samplings) was needed in the proposed safety and efficacy study. It was decided that the sponsor would not be required to assess urine metabolite concentration in this study since the study being conducted by the University or Pittsburg and the National Institute of Health (Principle investigator: (b) (4) ClinicalTrials.gov identifier: NCT00409825) would provide substantial data on the PK of 17-HPC and its metabolite in pregnant women including assessment of metabolites in maternal blood and urine. However, it was noted that the sponsor may not have complete access to all data from the (b) (4) study. Therefore, the CR letter should contain the same commitment to provide PK data in both plasma and urine. The urine data would primarily be used to assess which metabolites are present and in what amount.

Comments for Sponsor:

Question 7: Does the Division agree that urine samples do not need to be collected during the Population PK substudy portion of the Confirmatory Study?

Clinical Pharmacology response:
The Division agrees that urine samples for pharmacokinetic (PK) analysis do not need to be collected in study 17P-

ES-003. However, information on the urinary metabolites is important and will be included as a post-approval commitment, if the product were to be approved. In the resubmission of NDA 21-945 dated 4/24/2008, the Sponsor proposed to submit results from a clinical pharmacology study being conducted by (b) (4) (ClinicalTrials.gov identifier: NCT00409825) when they are published. The study by (b) (4) appears adequate to characterize the PK of hydroxyprogesterone caproate and its metabolites. However, if (b) (4) decides not to provide access to the results or does not include all relevant findings (e.g., urinary metabolites), then this information would need to be provided to the Agency in some other way (e.g., through a Sponsor-conducted study or by obtaining access to full study results from (b) (4)).

Additional review notes: *A teleconference with Sponsor was scheduled for 12/15/2009. The Agency's preliminary responses, including the above response to Question 7, were forwarded to Sponsor on 12/8/2009. Subsequently, the Sponsor decided to cancel the teleconference. Please see meeting minutes for further details.*

SIGNATURE OF REVIEWER: **SIGNATURE OF TEAM LEADER:**	Date Date
CC.: DCP3; TL: Kim; DD: Bashaw	**Project Manager:** **Date**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21945	GI-1	HOLOGIC INC	GESTIVA(17 ALPHA HYDROXYPROGESTERONE CAP

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/s/

DOANH C TRAN
12/15/2009

MYONG JIN KIM
12/15/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021945 **MEETING GRANTED**

Hologic, Inc.
Attention: Robb Hesley
Vice President Business Development
1240 Elko Drive
Sunnyvale, CA 94089-2212

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gestiva (hydroxyprogesterone caproate injection) 250 mg/ml.

We also refer to your October 16, 2009, correspondence requesting a teleconference to discuss CMC issues and questions related to your Complete Response letter received on January 23, 2009. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: December 15, 2009
Time: 3:00 – 4:00 PM EST
Phone Arrangements: Call-in arrangements will be made at a later date

CDER Participants:
Scott Monroe, M.D. Director, Division of Reproductive and Urologic Products (DRUP)
Lisa Soule, M.D., Clinical Team Leader, DRUP
Barbara Wesley, M.D., Medical Officer, DRUP
Doanh Tran, Ph.D., Clinical Pharmacologist, Office of Clinical Pharmacology (OCP)
Jennifer Mercier, Chief, Project Management Staff, DRUP
Charlene Williamson, Regulatory Health Project Manager, DRUP

If you have any questions, call me at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Z. Charlene Williamson
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21945	GI-1	HOLOGIC INC	GESTIVA(17 ALPHA HYDROXYPROGESTERONE CAP

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/s/

ZETA-MAE C WILLIAMSON
11/03/2009

MEMORANDUM OF MEETING MINUTES

Meeting Date: August 6, 2009

Meeting Time: 3:30 p.m. to 4:00 p.m.

Application Number: NDA 21-945

Product Name: Gestiva (hydroxyprogesterone caproate injection), 250 mg/mL

Indication: (b) (4) preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth

Applicant Name: Hologic, Inc.

Meeting Chair: Barbara Wesley, M.D.

Meeting Recorder: Meredith Alpert

FDA ATTENDEES

Barbara Wesley, M.D., M.P.H. – Medical Officer, DRUP
Meredith Alpert, M.S.– Regulatory Health Project Manager, DRUP

SPONSOR ATTENDEES

Mr. Robb Hesley, Vice President, Business Development

BACKGROUND

The purpose of the meeting was to confirm that the sponsor was planning to obtain urine samples from another pharmacokinetics (PK) study.

DISCUSSION

The Sponsor had called to get clarification from a sentence in the Complete Response letter regarding the collection of PK urine samples. Specifically, they wanted to know if the Division expected them to collect urine samples in addition to blood samples. After speaking with the Clinical Pharmacologist (Dr. Doanh [Donny] Tran), Dr. Wesley clarified the Division's understanding that the Sponsor is expected to provide PK data based on urine samples (as stated in the Complete Response letter), but this data could be obtained from publications of the studies done by (b) (4), if these data are made available.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21945	ORIG-1	HOLOGIC INC	GESTIVA(17 ALPHA HYDROXYPROGESTERONE CAP

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/s/

MEREDITH H ALPERT
08/27/2009

BARBARA D WESLEY
09/20/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Hologic, Inc.
Attention: Robb Hesley
Vice President, Business Development
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of Federal Food, Drug, and Cosmetic Act for Gestiva (hydroxyprogesterone caproate injection 250 mg/ml).

We also refer to the teleconference between representatives of your firm and the FDA on June 17, 2009. The purpose of the meeting was to discuss an alternate contract manufacturing organization and modified container closure system.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Charlene Williamson, Regulatory Health Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Donna Christner, Ph.D.
Pharmaceutical Assessment Lead
Office of New Drug Quality Assessment
Pre-Marketing Division II, Branch III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MEETING MINUTES

MEETING DATE: June 17, 2009
TIME: 12:00 – 1:00 PM
APPLICATION: NDA 21-945
SPONSOR: Hologic, Inc.
DRUG NAME: Gestiva (hydroxyprogesterone caproate), 250 mg/ml, (17P)
TYPE OF MEETING: CMC – Type C
MEETING CHAIR: Donna Christner, Ph.D.
MEETING RECORDER: Charlene Williamson

FDA ATTENDEES:
Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment (ONDQA), Pre-Marketing Division II, Branch III
Lisa Soule, M.D., Clinical Team Leader, Division of Reproductive and Urologic Products (DRUP)
Barbara Wesley, M.D., Medical Officer, DRUP
Charlene Williamson, Regulatory Health Project Manager, DRUP

EXTERNAL CONSTITUENT ATTENDEES:
Hologic, Inc.
Robb Hesley, Vice President Business Development
Mark D'Andrea, CMC Consultant
Catherine Williams, Director Regulatory Affairs

KV Pharmaceuticals, Inc.
Gerald McCarthy, Project Management

BACKGROUND:
The Sponsor submitted a meeting request to seek FDA's input on proposed changes to their contract manufacturing site. The Sponsor recently was informed by Baxter that they would be (b) (4). The Sponsor has started discussions with (b) (4) to replace Baxter as their contract manufacturer. In addition to the site change, the Sponsor also would like to change the stopper used for the container closure system, since the original stopper was shown to cause an increase in particulate matter over time. Information was submitted in the meeting package on the types of studies to be performed to support the changes. The preliminary responses were forwarded to the Sponsor prior to the teleconference in order to facilitate discussion.

SPONSOR'S QUESTIONS AND THE DIVISION'S RESPONSE

1. *Does the Division agree that the outline comparability study described above will be sufficient to qualify (b) (4) as an alternate commercial manufacturer and to qualify an alternate stopper for the 17P drug product?*

FDA Response:
Taking into account the history of your product and the multiple changes you propose to both the manufacturing site and container closure system, 6 months of stability data should be submitted in the Complete Response. The current on-going 6-month stability study comparing the two alternate stoppers should also be submitted as supporting data. We have the following additional comments:

- Full manufacturing information will need to be provided for the (b) (4) site and will need to be reviewed by the microbiologist during the review cycle.

- The (b) (4) site will require an inspection. In the NDA Complete Response, provide a comprehensive table/list of all facilities involved in production of the drug product with full street address of the actual manufacturing and/or testing site (not the corporate office), contact information of an individual at the site, detailed responsibilities of that facility and a date of when the facility was last inspected by FDA. This comprehensive table should be attached to the 356h form. Full information should still be provided in the appropriate sections of Modules 2 and 3. Due to a recent software update, inspections cannot be requested unless all the above information is provided. If this information is not provided when the NDA is submitted, it will delay inspection requests and may adversely affect the outcome of the review decision during this cycle.

- Information will need to be provided on the new stopper for review. This can be provided in a DMF with the appropriate Letter of Authorization provided in the submission.

<u>Discussion Points:</u>
- The Division agreed that the five-arm study was acceptable to support the qualification of (b) (4) as a secondary manufacturer for 17P and the qualification of the stopper.
- The Division agreed that it seemed reasonable to change the stopper used in the container closure system during the manufacturing transfer.
- If the (b) (4) site is submitted in the Complete Response, this would require an inspection request to be submitted. While it is anticipated that the inspection would be finished and a decision made prior to the PDUFA date, there is no guarantee that the inspection could be performed significantly earlier than the goal date.

2. *Does the Division agree that the new CMC information to qualify (b) (4) as an alternate manufacturer can be submitted with three months of accelerated stability data with a commitment from Hologic to submit the six month stability data during the review cycle?*

FDA response:
As outlined above, we recommend that 6 months of accelerated and room temperature data be submitted in your Complete Response in order to support the changes and to allow adequate time for review.

<u>Discussion Points:</u>
- The Sponsor needs to submit the CMC information with six months of accelerated and room temperature stability data

- If the six months of stability data is equal to or better than the stability results on Baxter's 17P product, the Division would establish an expiry date for (b) (4) product based on both the (b) (4) and the Baxter data.
- Since the Baxter site will be (b) (4), the Sponsor also has the option of submitting the Complete Response with Baxter as the manufacturer, and then, assuming the NDA is approved, submitting the change to (b) (4) as the manufacturer in a Post-Approval Supplement. This would be a Prior Approval Supplement, which would have a four month review clock.

ACTION ITEMS:
The meeting minutes are due to the Sponsor within 30 days.

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/s/

Donna Christner
7/15/2009 08:43:16 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

HOLOGIC, Inc.
Attention: Robb Hesley
VP Business Development
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

We acknowledge receipt on March 10, 2009 of your March 9, 2009 correspondence notifying the Food and Drug Administration that the corporate name has been changed from

CYTYC CORPORATION

to

HOLOGIC, INC.

for the following new drug application:

NDA 21-945 for Gestiva® (hydroxyprogesterone caproate injection, 250mg/ml).

We have revised our records to reflect this change.

We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Charlene Williamson
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Z. Charlene Williamson
3/23/2009 11:36:28 AM

Charlene,

The Gestiva (17 α-Hydroxyprogesterone caproate) (b) (4) was reviewed by the PeRC PREA Subcommittee on September 10, 2008. The Division recommended a full waiver because studies would be impossible or highly impracticable because there are too few children with the disease/condition to study. The PeRC agreed to a partial waiver for pre-menarchal females and to extrapolate efficacy for post-menarchal females.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

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/s/

Z. Charlene Williamson
1/14/2009 12:01:24 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: January 9, 2009

To: Robb P Hesley	**From:** Charlene Williamson
Company: Cytyc Corporation	Division of Reproductive and Urologic Products
Fax number:	**Fax number:** 301-796-9897
Phone number: 408-745-5179	**Phone number:** 301-796-1025

Subject: Gestiva Protocol Updates .01.09.09

Total no. of pages including cover: 3

Comments:

Document to be mailed: ❑ YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2130. Thank you.

Requested Protocol Revisions

Follow-up of children from the pregnancy study:
Obtain consent from all women who enter the trial to be recontacted and asked for consent for their child to be evaluated in the infant/toddler follow-up study. Actual enrollment of exposed off-spring would entail a second consent process; this initial consent to be recontacted would simply notify women of the planned additional study and ensure that adequate contact information was obtained to allow tracking of the participants several years after conclusion of the maternal trial. Women who decline would still be eligible to participate in the pregnancy study; however, the Applicant would need to ensure that sufficient numbers who are agreeable to participating in the follow-up study are enrolled in each arm.

The number/percent of subjects to be enrolled in the infant/toddler study will be negotiated during the next cycle when the protocol (development of outcome measures) for that study is completed.

Women should remain blinded to the treatment/study group they were assigned to until after the completion of the infant/toddler study.

Eliminate the sections that address the adolescent study from the protocol. The need for further study of the *in utero*-exposed children at adolescence is less pressing in light of the reassuring multigenerational reproductive toxicology study. If findings from the infant/toddler study raise concerns about long-term safety of *in utero* exposure, further follow-up may be requested.

Composite neonatal morbidity index:
Change bronchopulmonary hypertension (BPH) to bronchopulmonary dysplasia (BPD)

Qualitative Evaluation of Stillbirths:
Remove this sentence in the protocol:

(b) (4)

Replace with this sentence:
"Every attempt will be made to investigate the cause of stillbirth/fetal death/in-utero fetal loss according to the recommendations from the Stillbirth Collaborative Research Network of the NICHD, which consist of the following assessments:"

Adverse events:
Remove this sentence in the protocol:

(b) (4)

Replace with these sentences:

"For the purposes of this study, hospitalization due to preterm labor/pPROM that does not result in delivery, is expected and will be recorded on the subject's CRF and not reported as an SAE. Other pregnancy complications requiring hospitalization such as preeclampsia, chorioamnionitis, uncontrolled diabetes, etc. will be reported as an SAE."

Castor Oil/Pulmonary Oil Microemboli:
Other drugs which contain a castor oil-based vehicle have been associated with rare cases of pulmonary oil microemboli (POME). In most cases the injected castor oil solution was 4mL; therefore, we do not expect this to be a problem with Gestiva. However, we would like you to specifically monitor for the transient symptoms associated with this condition that occur within 10 minutes of the injection: transient coughing or dyspnea. Please add this to the protocol and to the Case Report Form.

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/s/

Z. Charlene Williamson
1/9/2009 01:23:05 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Cytyc Corporation
ATTENTION: Robb Hesley
Vice President, Business Development
1240 Elko Drive
Sunnyvale, California 94089

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) dated April 14, 2006, received April 20, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 17 α-Hydroxyprogesterone Caproate Injection, 250 mg/mL.

We also refer to your January 30 and October 16, 2008, correspondence received January 31, and October 17, 2008, respectively, requesting reconsideration of your proposed proprietary name, GESTIVA. We have completed our review and have concluded that the proprietary name, GESTIVA, is acceptable.

The proprietary name will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 16, 2008, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Cherye Millburn, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Scott Monroe, MD
Director
Division of Reproductive and Urologic Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Scott Monroe
12/18/2008 03:37:49 PM

MEMORANDUM OF TELECON

DATE: December 18, 2008

APPLICATION NUMBER: NDA 21-945

BETWEEN:

Name: Robb Hesley, Vice President, Business Development
Catherine Williams, RAC, Director, Regulatory Affairs
Mary Eckstein, Clinical Research Manager
(b) (4)
Cynthia Kirk, PhD, RAC, VP Regulatory Affairs Branded Products
KV Pharmaceuticals

Representing: CYTYC, Inc.

AND

Name: Scott Monroe, M.D., Director
Lisa Soule, M.D., Clinical Team Leader
Barbara Wesley, M.D., Medical Officer
Charlene Williamson, Regulatory Health Project Manager

Representing: Division of Reproductive and Urologic Products

SUBJECT: December 12, 2008 Submission:

- Acceptability of international study sites
- Acceptable evidence of feasibility
- Protocol revision in response to Division's requests

The Division appreciates the effort the Sponsor has undertaken to address the Division's concerns, and acknowledges both the challenges and possibilities apparent in conducting a post-approval study in the U.S. The Division is therefore agreeable to including non-U.S. study sites, although inclusion of some sites in the U.S. is requested. To date, the Sponsor has primarily contacted investigators in Western Europe and North America, and intends to seek participation from U.S. and Canadian investigators.

The Division had previously discussed with the Sponsor the need for greater assurance that the study would actually be able to be undertaken post-approval, such as initiating enrollment of a portion of the total sample prior to regulatory action. The Division remains concerned that an indication of interest by individual investigators does not necessarily imply that a study could be completed, and requests a higher level of assurance. One possibility would entail providing documentation of IRB approval for U.S. study sites (and the equivalent commitment for ex-U.S.

sites); however, the Division may need a greater level of assurance, such as enrollment of 10% of the sample. In the latter case, the Division would not require that every site enroll 10% of its expected subjects, but that, over all sites, a total of 10% of the sample is enrolled. The Sponsor believes that there will be no difficulty enrolling subjects at international sites and challenged the need for pre-submission enrollment of subjects abroad. However, the Division continues to be concerned that the study must be shown to be feasible on three levels (investigator participation, IRB approval and participation by local physicians and patients). The Division is aware of significant obstacles to participation in a placebo-controlled trial in the U.S., but is unable to concede that no such obstacles would pertain in an international setting.

The Sponsor raised the possibility of alternative designs to a placebo-controlled study, such as using a historical control. The Division continues to believe that a randomized controlled trial is needed, particularly because approval under Subpart H requires providing further evidence for efficacy. In the absence of approved comparator drugs for this indication, a randomized, placebo-controlled trial would be necessary. In addition, the atypical preterm delivery rate in the control arm of the National Institute of Child Health and Human Development (NICHD) trial may be partially responsible for the significance of the efficacy results in that trial. Failure to obtain a concurrent comparison to an untreated control would make interpretation difficult.

The Sponsor remains concerned about the delay in approval inherent in requiring study initiation and partial enrollment prior to action, and is uncertain whether management will continue the investment in further development prior to approval. The Sponsor may seek an informal discussion with the Office of Drug Evaluation (ODE) or the Office of New Drugs (OND) regarding the Division's recommendations.

The Division's review of the revised protocol is ongoing, but it appears that the Sponsor has been responsive to the Division's requests for modification. If any further protocol comments remain, the Division will try to convey them by early January.

_____

Lisa Soule, M.D.
Clinical Team Leader

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/s/

Lisa Soule
1/22/2009 10:04:20 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: December 2, 2008

To: Robb P Hesley	**From:** Charlene Williamson
Company: Cytyc Corporation	Division of Reproductive and Urologic Products
Fax number: 408-745-5179	**Fax number:** 301-796-9897
Phone number: 408-745-5179	**Phone number:** 301-796-1025

Subject: Gestiva Protocol

Total no. of pages including cover: 3

Comments:

Document to be mailed: ❑ YES ☑ NO

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Requested Revisions to Gestiva Protocol

We request that the following revisions be made to the revised protocol submitted on August 28, 2008. While suggested wording for specific sections is provided here, we ask that you review the entire protocol to ensure that all areas address the following changes in a consistent manner.

3.5.2 Secondary Outcomes

This section currently states that secondary outcomes include:

(b) (4)

Revise this to define "Fetal/early infant death" as

> Spontaneous abortion/miscarriage (delivery from 16° through 19[6] weeks of gestation) or death (from minutes after birth until 28 days of life) occurring in liveborns born at less than 24 weeks gestation or stillbirth (antepartum or intrapartum death from 20 weeks gestation through term).

(This will also entail revision of 2.2 Secondary Objectives, which currently states:

> *Determine if the rate of fetal/early infant death, defined as spontaneous abortion/miscarriage (delivery from 16° through 19° weeks of gestation) or death (from minutes after birth until 28 days of life) occurring in liveborns born at less than 24 weeks gestation, in the 17P group is not inferior (i.e., higher) to that in the placebo group.*)

9.1 Sample Size

We ask that the study be sized to achieve 90% power to detect a 35% reduction (from the anticipated placebo rate of 17%) in the Neonatal Composite Index. Revise the sample size discussion and Table 3 to reflect this.

We further request a redefinition of the safety endpoint concerning the fetal/early infant death rate (see 2.2 and 9.4.2). State the anticipated power for detecting a treatment effect on this endpoint, based on the sample size required by the calculations for the Neonatal Composite Index. Insufficient power to demonstrate success on this safety endpoint will be a review issue, and we encourage you to size the study to allow for adequate power on this endpoint as well as on the primary and key secondary endpoints.

We believe that including stillbirths as well as cases of spontaneous abortion/miscarriage and neonatal death in liveborn infants born at less than 24 weeks of gestation will appropriately address the concern about possible fetal harm, and will also provide more events of interest, such that the power to detect change in this endpoint will be enhanced.

9.4.1 Primary Efficacy Outcome Measure

Regarding the planned hierarchical analysis, the current protocol reads:

> *The primary efficacy outcome measure will be the proportion of subjects who deliver prior to 35° weeks of gestation. The primary efficacy analysis will utilize the ITT Population. The percentage of subjects with a preterm birth < 35° weeks of gestation will be determined as the point estimate of the survival function from a staggered entry Kaplan-Meier analysis (which adjusts for gestational age at randomization) using time from randomization until delivery as the analysis variable. Subjects with missing outcome data will be censored on the date last known pregnant. Significant differences between the 17P and placebo group in the proportion of subjects who deliver prior to 35° weeks gestation will be determined using a Z-test where the variance of the point estimates is determined from Greenwood's formula.*[22]

A hierarchical testing approach will be utilized.[23] *Statistical significance will be determined for the primary outcome of preterm birth <35° weeks of gestation (ITT Population) at the 0.05 significance level.* (b) (4)

Please revise the last sentence of the first paragraph to read:

"Significant differences between the17P and placebo group in the proportion of subjects who deliver prior to 35^0 weeks gestation will be determined using a Cochran-Mantel-Haenszel test stratified by gestational age at randomization, where the effective sample sizes for each treatment group within strata will be derived from Greenwood's formula.[22]"

Please revise the second paragraph to read:

"A hierarchical testing approach will be utilized.[23] Statistical significance will be determined for the primary outcome of preterm birth <35° weeks of gestation (ITT Population) at the 0.05 significance level. If and only if the primary outcome is significant, the secondary outcome of the percent of subjects in each treatment arm whose neonates had a score > 0 on the composite neonatal index (ITT Population) will be tested for significance at the 0.05 level."

9.4.2 Secondary Outcomes

The second paragraph describes the key safety analysis, and currently states:

(b) (4)

Please revise this to describe (instead of a non-inferiority analysis) an analysis of the fetal/early infant death rate such that a successful outcome will exclude a doubling of the risk of fetal/early infant death in the Gestiva group as compared to the placebo group (i.e., the upper bound of the two-sided confidence interval around the relative risk should be ≤ 2.0). Also, determine the relationship, if any, between gestational age at the time of randomization and the risk of fetal/early infant death in the Gestiva group as compared to the placebo group.

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/s/

Z. Charlene Williamson
12/2/2008 12:18:20 PM
CSO

From: Greeley, George
Sent: Tuesday, December 02, 2008 3:27 PM
To: Williamson, Charlene
Cc: Mathis, Lisa
Subject: NDA 21-945 Gestiva (17 a-Hydroxyprogesterone caproate)

Importance: High

Charlene,

The Gestiva (17 α-Hydroxyprogesterone caproate) waiver was reviewed by the PeRC PREA Subcommittee on September 10, 2008. The Division recommended a full waiver because studies would be impossible or highly impracticable because there are too few children with the disease/condition to study. The PeRC agreed to a partial waiver for pre-menarcheal females and to extrapolate efficacy for post-menorrheal females.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

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/s/

ZETA-MAE C WILLIAMSON
01/12/2011

MEMORANDUM OF TELECON

DATE: November 19, 2008

APPLICATION NUMBER: NDA 21-945

BETWEEN:

Name: Robb Hesley, Vice President, Business Development
Catherine Williams, RAC, Director, Regulatory Affairs
Mary Eckstein, Clinical Research Manager
(b) (4)
Cynthia Kirk, PhD, RAC, VP Regulatory Affairs Branded Products
KV Pharmaceuticals

Representing: CYTYC, Inc.

AND

Name: Scott Monroe, M.D., Director
Lisa Soule, M.D., Clinical Team Leader
Barbara Wesley, M.D., Medical Officer
Lisa Kammerman, Ph.D., Statistician
Charlene Williamson, Regulatory Health Project Manager

Representing: Division of Reproductive and Urologic Products

SUBJECT: ACOG Committee Opinion

The Division noted that the October 2008 publication of a revised ACOG Committee Opinion (#419) on use of progesterone for prevention of recurrent preterm birth had engendered concern and much internal discussion within DRUP regarding the feasibility of the proposed post-approval placebo-controlled trial of 17 α-hydroxyprogesterone caproate (17-HPC). The Division is worried that the ACOG statement may appear to bring premature closure to the evaluation of the safety and efficacy of 17-HPC. The specific concerns focus on three levels of feasibility necessary for successful completion of a trial:

- Whether investigators will still agree that the safety and efficacy of 17-HPC are sufficiently open questions as to induce them to enroll subjects in such a placebo-controlled study
- Whether institutional review boards (IRBs) will approve a placebo-controlled trial after 17-HPC has FDA approval and given the clinical standard of care at their institution ensuing from the ACOG statement

- Whether patients will consent to randomization that might result in assignment to the placebo arm

The Division's October 2006 approvable letter requested that the Sponsor submit a draft protocol and evidence of feasibility for an additional, post-approval, multicenter, well-controlled trial to provide confirmatory evidence of efficacy and to address a potential safety signal of early fetal loss. The ramifications of the current ACOG opinion have led the Division to consider that the "evidence of feasibility" needs to exceed the currently provided letters of interest from several potential U.S. and Canadian investigators. It may be that nothing short of actual trial initiation, with enrollment of approximately 10% of the planned sample size, will provide sufficient reassurance that a post-approval trial can reasonably be expected to succeed. Given that the first cycle review found that, in addition to the single NICHD study submitted, the Division needed confirmatory evidence of efficacy as well as further exploration of a potential safety signal of early fetal loss, the Division cannot in good conscience approve Gestiva now if there is reasonable doubt that such a confirmatory study would ever be conducted.

The Sponsor believes that the 2008 ACOG opinion is not very different from the original opinion issued in 2003, and noted that their initial discussions with potential investigators about the feasibility of a placebo-controlled trial were favorable, even within the context of ACOG's initial permissive statement about use of progesterone as a treatment option for women with previous preterm birth. Many in the Division believe that the ACOG 2008 opinion is much stronger than the 2003 opinion in setting the standard of care for women with previous preterm birth, such that it may be difficult or impossible to conduct a placebo-controlled study post-approval. In fact, several investigators have reported difficulty in getting research projects studying progesterone products for the prevention of preterm birth approved by their IRBs in the wake of the new opinion. The Division recommended that the Sponsor re-contact the thought leaders and potential investigators and discuss whether their interest in and support for the trial has changed since the ACOG opinion, and whether they are aware of difficulty in conducting similar clinical trials.

The Division acknowledges that a request that the Sponsor actually initiate enrollment in the trial prior to receiving approval would pose a significant logistical and financial hurdle. However, the Division is not considering a request that the Sponsor submit final data prior to taking an approval action.

The Sponsor asked about two alternative options that might sidestep difficulties facing a placebo-controlled trial in the U.S.:

- Conduct of a study in which all subjects are enrolled outside of the U.S.

  The Division agreed that the Sponsor will likely need to explore additional ex-U.S. sites, but cautioned that it is necessary that at least some of the data come from the U.S., or at least from other sites with somewhat similar population demographics to the U.S.

- Conduct of an alternative design, which had been discussed in the first review cycle, of two active treatment arms to evaluate the effect of staggered entry onto active drug. Instead of having one active and one placebo arm, such a study would initiate one

arm immediately onto active drug, while the other arm would receive placebo until a specified gestational age, at which time they would also receive active drug.

A staggered entry study might provide useful data on the potential safety signal, but would be unlikely to provide confirmatory efficacy data, or none that would be as incisive as that obtained against a placebo comparator.

The Division has some additional revision requests for the draft protocol that it will communicate to the Sponsor within the next week. These include:

- Change in the "key secondary" endpoint that would be analyzed in a hierarchical manner if the primary efficacy endpoint (% deliveries at <35 weeks) demonstrates statistical significance. Rather than the currently specified key secondary endpoint of deliveries at <32 weeks, the Division requests that the composite neonatal mortality and morbidity index be evaluated in a hierarchical manner. This will provide the needed link between the surrogate endpoint of gestational age at delivery and a clinical benefit as measured by the index. The Sponsor should size the study so as to provide adequate power for evaluating the index.
- Revising the safety endpoint analysis to describe ruling out a doubling of risk of early fetal loss in the 17-HPC arm rather than determining a non-inferiority margin in the rate of early fetal loss.
- Revise the analysis plan to include an analysis that reflects the stratified randomization scheme, such as a Cochran-Mantel-Haenszel analysis.

The Sponsor inquired about progress in reviewing the proprietary name, the label, and the data supporting the shelf-life labeling. Review of the latter two issues is ongoing; DMEPA has not submitted a formal review, but has indicated that the name Gestiva is likely to be acceptable.

ACTION ITEMS:

- Meeting minutes to Sponsor within 30 days
- Proposed protocol revisions to Sponsor within one week
- Sponsor will discuss with potential investigators feasibility in light of the 2008 ACOG Committee Opinion

_____

Lisa Soule, M.D.
Clinical Team Leader

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/s/

Z. Charlene Williamson
1/22/2009 04:36:17 PM
CSO

Lisa Soule
1/22/2009 04:49:14 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Pharmaceutical Science/NDMS
Attention: Jim McVey

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Charlene Williamson, Project Manager, DRUP
6-1025

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 5, 2008		21-945	Paper	October 31, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gestiva	Priority		November 14, 2008

NAME OF FIRM: Hologic, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Attached is the sponsor's response to our review of the post-penetration shelf life for Gestiva.

SIGNATURE OF REQUESTOR
Charlene Williamson

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

CYTYC

31 October 2008

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-945
17 α-Hydroxyprogesterone Caproate Injection, 250 mg/mL (17P)
Post-Penetration Shelf Life

Dear Dr. Monroe,

This letter serves to summarize the interactions to date and provides Cytyc Corporation's (Cytyc) reasoning to support the proposed 5-week post-penetration shelf life (shelf life after the first puncture through the stopper) for 17 α-Hydroxyprogesterone Caproate Injection, 250 mg/mL.

As way of background regarding the interactions to date on this issue, the proposed prescribing information which was originally submitted to the NDA did not contain a restriction regarding the post-penetration shelf life. As part of labeling review, the Division stated via emails on 02 October 2008 and on 03 October 2008 that, among other comments, the following statements should be added to the carton, vial and prescribing information labels:

(b) (4)

On 04 October 2008 Cytyc responded to this request with an email to Ms. Freshnie Deguia (see Attachment 1) briefly summarizing the reasons why we believe a (b) (4) is not appropriate given the antimicrobial effectiveness data that had been submitted and the expected use of the product. Consequently, we made the suggestion for a 5-week post-penetration shelf life as more appropriate if the Division wanted to add such a limitation to the label. In this same email we also explained why we thought a requirement for (b) (4) storage after the first use was not appropriate. Also, in our response

(b) (4)

1240 ELKO DRIVE • SUNNYVALE, CA 94089 • TEL: (408) 745-0975 • FAX: (408) 744-1905

dated 16 October 2008 to FDA Comments #1 of the Prescribing Information we included the 5-week post penetration shelf life.

Earlier this week, on 28 October 2008, we received an email from Ms. Williamson with the following comment from the CMC reviewer(s):

> *"In order to justify a 5-week post-penetration shelf life, demonstrate the long range effectiveness of the preservative by challenging the preservative over time as would occur in use, i.e., challenge penetrated containers each week with a battery of organisms consistent with the product use (skin and environmental isolates, etc.) and compendial organisms. Storage would be according to the label recommendations. Tests should be conducted for 10 weeks."*

After consultation with several advisors, including microbiologists, and vendors with specific knowledge of multidose vial requirements and a review of various publications, we believe that the appropriate and industry standard test for a preservative-containing, multiple dose injectable such as Gestiva with a limited open container shelf life of 5 weeks is the USP<51>, Antimicrobial Effectiveness Testing. The protocol suggested by FDA is not consistent with the USP compendial test and appears to add little meaningful value to the antimicrobial effectiveness test (AET) data already submitted for the 17P drug product. We believe that if the 17P product required a post-penetration shelf life of several months or greater, additional AET data as suggested by FDA would be warranted.

For the purposes of release and long term stability, as required by ICH Guidelines and USP<51> multidose injectables, AET was performed on one of the primary stability batches of 17P drug product (Lot 901379) manufactured by Baxter Pharmaceutical Solutions, LLC. AET has been performed and reported in the various submissions and amendments to NDA 21-945 on both the time zero release and thirty (30) month CRT (25° C/ ± 2° C/60% ± 5% RH) and three (3) and six (6) month accelerated temperature conditions (40° C/ ± 2° C/75% ± 5% RH) both in the upright and inverted orientations (see Attachment 2, Tables 1 and 2, respectively). Please note that the AET results reported to date have been described in the Quality Control Master Documents as 'conforms to USP <51>'. Tables 1 and 2 of Attachment 2 present the raw data generated for each of the seven (7) AET evaluations and clearly demonstrate the effectiveness of the 2% (v/v) benzyl alcohol used as a preservative in the 17P drug product formulation at days 7, 14 and 28 post inoculations.

USP<51> states that *"In the case of sterile articles packaged in multiple-dose containers, antimicrobial preservatives are added to inhibit the growth of microorganisms that may be introduced from repeatedly withdrawing individual doses."* The introduction concludes by stating *"This chapter provides tests to demonstrate the effectiveness of antimicrobial protection. Added antimicrobial preservatives must be declared on the label. The tests and criteria for effectiveness apply to a product in the original, unopened container in which it was distributed by the manufacturer."* The description of the intended application of USP<51> supports the validity of using this procedure for assuring a drug product is protected from microbial contamination potentially introduced during administration from a multiple dose container.

In addition to the AET microbiological evaluation that has been performed, HPLC analyses performed during the 17P stability studies confirm the benzyl alcohol chemical content to remain essentially the same as the time zero release value of 2.1% (v/v) through at least 30 months storage at CRT and 6 months 40°C when stored in both the upright and inverted orientations.

A publication from the PDA Journal of Pharmaceutical Science and Technology (Sutton, V. W. S. and Porter, D., Vol 56, No. 6, November/December 2002), *Development of the Antimicrobial Effectiveness Test as USP Chapter <51>*, attests to the ability of AET to determine *"...the level of biological activity possessed by the preservative system of a pharmaceutical product..."*. The authors state that a previous review *"... stressed the point that both the Ph. Eur. and USP AET tests are designed to demonstrate 'adequate protection from adverse effects that may arise from microbial contamination or proliferation during storage or* <u>*use*</u> (emphasis added) *of the preparation.'"* In situations where the chemical stability is not likely to be compromised by in-use procedures (e.g. chemical oxidation) the authors conclude that *"It is unclear that there is any real value gained in terms of safety to the patient from* [in-use] *additional microbiological testing on all products."* The article is provided as Attachment 3.

During the NICHD clinical trial, the Manual of Operations (IND #53,730) instructed clinical trial personnel to not use the vial if more than 5 weeks has passed from when the vial was initially "punctured (entered)" (see excerpt from NICHD Manual of Operations included as Attachment 4). It is based on this document that we proposed the 5-week post-penetration shelf life as Gestiva and the drug product tested in the NICHD study are *identical* in both chemical formulation and container closure system.

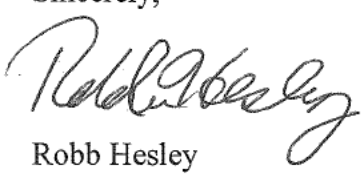
With regard to the suggested storage temperature of (b) (4) we do not believe that storage at refrigerated temperatures after initial stopper penetration is needed due to presence of the 2% benzyl alcohol preservative and the USP conforming AET results. A requirement for storage at refrigerated conditions could cause unnecessary issues with office patient flow as the vial would need to be warmed to room temperature before injection because of the viscous nature of the product. Also, patients who are bringing the product in for administration would need to carry it on ice packs during transport.

(b) (4)

(b) (4) We believe, as has been confirmed by our numerous consultations this week with advisors and vendors, that the AET that has been submitted to the NDA support our proposed 5-week post-penetration shelf life with storage at room temperature. We would welcome an opportunity to discuss this issue further.

I can be reached at 408-745-5179 or at robb.hesley@cytyc.com.

Sincerely,



Robb Hesley
Vice President, Business Development

cc: Charlene Williamson, Regulatory Project Manager, DRUP, Food and Drug Administration
Catherine Williams, Director, Regulatory Affairs, Cytyc Corporation
Mark D'Andrea, Project CMC Consultant

Attachment 1

Hesley, Robb

From: Hesley, Robb
Sent: Saturday, October 04, 2008 1:51 PM
To: Deguia, Eufrecina P
Subject: Follow-up to phone call

Freshnie,
As a follow-up to our conversation regarding the request to add language to the Gestiva label instructing the user to: *"Store* [redacted] (b) (4) I thought it would be helpful to provide you with a brief explanation of why the request does not make sense to us.

1. The product is preserved with 2% benzyl alcohol and all USP antimicrobial effectiveness testing (AET) submitted in the CMC portion of the NDA has demonstrated passing results for the product stored under accelerated conditions (40°C) for up to 6 months. Also, the long term storage conditions for the product is controlled room temperature (25° C) for which we have submitted passing stability results through 30 months.

2. The product is packaged in a multidose vial (5 doses) with injections to be given once a week. Since the vial will be prescribed to a specific patient in most cases, [redacted] (b) (4) [redacted] (b) (4) This would cause a tremendous amount of waste of the product.

3. For the NICHD clinical trial, the Manual of Operations (IND #53,730) instructed clinical trial personnel to not use the vial if more than 5 weeks has passed from when the vial was initially "punctured (entered)". Perhaps adding a "Use within 5 weeks" statement to the label would be more appropriate.

4. With regard to the storage temperature, we do not believe that storage at refrigerated temperatures after initial stopper penetration is needed due to presence of the 2% benzyl alcohol preservative and the USP conforming results of the AET testing. A requirement for storage at refrigerated conditions could cause unnecessary issues with office patient flow as the vial would need to be warmed to room temperature before injection because of the viscous nature of the product. Also, patients who are bringing the product in for administration would need to carry it on ice packs during transport.

Let me know if we need to submit to the NDA a more comprehensive explanation of why we think the [redacted] (b) (4) statements should not be required. I wanted to send you this quick email just to make sure you understood the points I was bringing up today on the phone.

I've let the team know about the extension to the PDUFA date. Let me know if you are able to get a call set up with the CMC reviewer(s) for this week.

Best regards,
Robb

Robb Hesley
VP Business Development
Hologic, Inc.
1240 Elko Drive
Sunnyvale, CA 94089
Direct: 408-745-5179
Cell: 408-410-5371

Attachment 2

USP<51> AET Results Performed to Date

Table 1: Summary of Controlled Room Temperature (25ºC/60% relative humidity) Stability AET Results for Lot No. 901379

	Upright								Inverted			
	0 Months (Release)				30 Months[1]				30 Months[1]			
Challenge Organism (ATCC#)	Inoculated Log CFU/mL	Days[2] Post Inoculation			Inoculated Log CFU/mL	Days[2] Post Inoculation			Inoculated Log CFU/mL	Days[2] Post Inoculation		
		7	14	28		7	14	28		7	14	28
S. aureus (6538)	5.4	1.0	<1.0	<1.0	5.6	<1.0	<1.0	<1.0	5.6	<1.0	<1.0	<1.0
P. aeruginosa (9027)	5.5	<1.0	<1.0	<1.0	5.9	<1.0	<1.0	<1.0	5.9	<1.0	<1.0	<1.0
E. coli (8739)	5.9	<1.0	<1.0	<1.0	5.9	<1.0	<1.0	<1.0	5.9	<1.0	<1.0	<1.0
C. albicans (10231)	5.8	4.4	3.7	2.8	5.7	<1.0	<1.0	<1.0	5.7	<1.0	<1.0	<1.0
A. niger (16404)	5.7	4.9	4.7	4.7	5.6	4.9	4.8	3.9	5.6	4.9	4.7	3.5

[1] AET results for 36 month stored samples are pending
[2] All results reported as Log CFU/mL product

Table 2: Summary of Accelerated (40ºC/75% relative humidity) Stability AET Results for Lot No. 901379

	Upright								Inverted							
	3 Months				6 Months				3 Months				6 Months			
Challenge Organism (ATCC#)	Inoculated Log CFU/mL	Days[1] Post Inoculation			Inoculated Log CFU/mL	Days[1] Post Inoculation			Inoculated Log CFU/mL	Days[1] Post Inoculation			Inoculated Log CFU/mL	Days[1] Post Inoculation		
		7	14	28		7	14	28		7	14	28		7	14	28
S. aureus (6538)	6.3	<1.0	<1.0	<1.0	5.7	<1.0	<1.0	<1.0	6.3	<1.0	<1.0	<1.0	5.7	<1.0	<1.0	<1.0
P. aeruginosa (9027)	6.1	<1.0	<1.0	<1.0	5.6	<1.0	<1.0	<1.0	6.1	<1.0	<1.0	<1.0	5.6	<1.0	<1.0	<1.0
E. coli (8739)	6.2	<1.0	<1.0	<1.0	6.0	<1.0	<1.0	<1.0	6.2	<1.0	<1.0	<1.0	6.0	<1.0	<1.0	<1.0
C. albicans (10231)	5.5	<1.0	<1.0	<1.0	5.9	4.3	3.5	<1.0	5.5	1.3	<1.0	<1.0	5.9	3.9	1.9	<1.0
A. niger (16404)	5.8	3.7	4.4	2.7	5.7	4.7	3.6	2.8	5.8	3.5	2.8	<1.0	5.7	4.6	3.2	2.0

[1]All results reported as Log CFU/mL product

Attachment 3

12 Pages Have Been Withheld In Full As Copyright Material

Attachment 4

2 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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/s/

Z. Charlene Williamson
11/5/2008 06:05:28 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 22, 2008
To:	Scott Monroe, MD, Director Division of Reproductive and Urologic Products
Through:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Felicia Duffy, RN, BSN, MSEd, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Response to Gestiva Trade Name Rebuttal
Drug Name:	Gestiva (17 α-Hydroxyprogesterone Caproate) Injection 250 mg/mL
Application Number:	NDA 21-945
Applicant:	Cytyc Corporation
OSE RCM #:	2008-832

EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis (DMEPA) previously evaluated the name, Gestiva, in OSE Review 06-0134, dated August 7, 2006, and found the name unacceptable due to orthographic and phonetic similarity to the name Sustiva. In response to this rejection, the Applicant provided supportive data to demonstrate that Gestiva would not be distributed via the normal pharmacy distribution channel. Upon evaluation of the aforementioned information, we reverse our initial decision, and find the proprietary name, Gestiva, acceptable.

1 INTRODUCTION

This memorandum is written in response to a May 21, 2008, request from the Division of Reproductive and Urologic Products to reconsider the acceptability of the proposed proprietary name, Gestiva. The Division also requested a review of all adverse event reports involving any compounded preparation of 17 α-hydroxyprogesterone Caproate used in pregnant women from June 2003 through the present. This request was completed by the Division of Pharmacovigilence (formerly known as the Division of Adverse Event Analysis) in OSE review #2008-833 dated June 23, 2008.

2 REGULATORY HISTORY

DMEPA found the proprietary name, Gestiva, unacceptable in OSE Review 06-0134, signed September 13, 2006, based on the name Sustiva.

The Applicant submitted a rebuttal in a letter dated January 30, 2008, to support the use of Gestiva. Within the rebuttal letter, the Applicant provided a general description of a distribution plan for Gestiva. This information was not provided in the initial submission of the application. DMEPA and representatives from the review Division participated in a telephone conference on September 24, 2008, at the request of DMEPA in order to obtain more specific information about the proposed distribution plan. As a result of the telephone conference, the Applicant submitted a more detailed description of the distribution plan and a pre-printed referral form for Gestiva.

Additionally, the applicant submitted a Medication Error Prevention Analysis Report from the (b) (4) on October 16, 2008. However, this documentation was received too late in the review cycle for us to include comments in this review. Furthermore, this documentation does not affect the outcome of our decision to reverse our initial decision and find the proprietary name, Gestiva, acceptable.

3 MATERIAL REVIEWED

We reviewed the Applicant's rebuttal letter dated January 30, 2008 and the previous OSE review 06-0134, in which we expressed concerns with the potential for confusion of Gestiva with Sustiva.

Additionally, we reviewed the detailed distribution plan submitted to the Agency on October 1, 2008, which includes a Gestiva referral form (see Appendix A).

4 DISCUSSION

The Applicant's rationale submitted in support of the name Gestiva is based on four main points: 1) The differentiating product characteristics between Gestiva and Sustiva address the concern regarding look-alike/sound-alike confusion between the two drugs; 2) Gestiva will be (b) (4) (b) (4) 3) names do not meet the Agency's criteria for the likelihood of confusion; and 4) the Applicant is willing to add a protective disclaimer statement to the product

labeling in order to avoid confusion. Our risk assessment differs from the applicant's rationale which is discussed below.

4.1 Differentiating Product Characteristics

We maintain our position that Gestiva and Sustiva share orthographic and phonetic similarities. We also acknowledge that Gestiva and Sustiva have several differentiating product characteristics such as indication for use (prevention of preterm birth vs. HIV treatment), strength (250 mg/mL vs. 50 mg, 100 mg, 200 mg, and 600 mg), route of administration (intramuscular vs. oral), dosage form (injection vs. tablets/capsules), and frequency of administration (beginning with week 16-20, once weekly until week 37 vs. once daily). Although an achievable dose of 250 mg may occur with Gestiva and Sustiva, the conditions are minimized by the fact that in order to achieve a 250 mg Sustiva dose, the medication would be prescribed to a child weighing 15 kg to <20 kg (33 lb to 44 lb). Additionally, the Applicant's inclusion of a pre-printed order form for Gestiva, which specifically includes the instructions for use, will also help to minimize confusion between Gestiva and Sustiva.

4.2 (b) (4)

(b) (4)

4.3 The Names Do Not Meet FDA's Criteria for the Likelihood of Confusion

The Applicant uses information from a presentation given in June 2003 by a former DMEPA Associate Director to make the case that the names Gestiva and Sustiva do not meet FDA's criteria for the likelihood of confusion based on a list of potential contributing factors to medication errors including these differentiating product characteristics: indication, patient population, formulation, overlapping strength or directions, and storage conditions. We acknowledge that product characteristics contribute to medication errors. However, when two names have strong orthographic and phonetic similarities (as seen with Gestiva and Sustiva), confusion may occur even though they lack overlapping product characteristics. As mentioned in the previous sections, the Applicant's distribution plan will minimize the potential for confusion when distributing Gestiva. Thus, we believe the names Gestiva and Sustiva may co-exist in the marketplace with minimal potential of confusion.

4.4 Adding a Disclaimer Statement to Product Labeling in Order to Avoid Confusion

The Applicant states that they are amenable to the addition of a proactive statement in the Gestiva product labeling such as "Attention Healthcare Professionals: To reduce the potential for

medication errors with Gestiva, please write and say "Gestiva" clearly". We do not recommend the Applicant utilize such as statement on any of the labeling for Gestiva. With the proposed distribution plan we do not believe such a statement is necessary.

5 CONCLUSIONS AND RECOMMENDATIONS

Although we maintain our belief that the names Gestiva and Sustiva are orthographically and phonetically similar, the proposal and implementation of the Applicant's specialized distribution plan minimizes the potential for confusion between the two drugs. Therefore, DMEPA reverses its initial decision on the acceptability of the proprietary name Gestiva, and find the proprietary name acceptable. We would be willing to meet with the Division for further discussion, if needed. Also, please copy the Division of Medication Error Prevention and Analysis on any correspondence to the applicant pertaining to this consult. If you have any questions or need clarification, contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

Appendix A: Gestiva Referral Form

Gestiva™
hydroxyprogesterone
caproate injection

Telephone 800-847-3418 • www.gestivacare.com • Fax 800-847-3413

GESTIVA REFERRAL FORM

PRESCRIBER INFORMATION

Prescriber Name		Phone No.	
Street Address	City	State	Zip
Office Contact Name	Office Phone	Office Fax	

PATIENT INFORMATION (*Required Fields)

Patient Name*			Date of Birth*
Street Address	City	State	Zip
Home Phone No.*	Alternate Phone No.*		
Primary Insurance*			
PHARMACY BENEFIT INFORMATION* Phone	Group Policy #	RxBIN #	

❑ **Gestiva Injection** (hydroxyprogesterone caproate injection)
250 mg/mL 5 mL vial — _1_ To be dispensed
Sig: Inject 1 mL IM each week — ___ Refills
❑ 18 g 1½" needle & 3 mL syringe — _5_ # — ____ Refills
❑ 21 g 1½" needle — _5_ # — ____ Refills

Fax completed form to: 800-847-3413

Submitted by: _____ **Today's Date:** _____ **Anticipated Start Date:** _____

Physician's Signature: _____ **DEA #:** _____

Patient Authorization and Release to Collect, Use, and Disclose Medical Information

By signing below, I authorize KV Pharmaceuticals, Inc. and agents operating the above described Program (collectively, "KV Pharmaceuticals") to use and disclose any and all of my individually identifiable health information, including, but not limited to, any and all spoken or written facts about my health, medications, insurance benefits, and all records maintained by KV Pharmaceuticals in connection with the Program ("Health Information"), as described in this Authorization. I understand that my medical treatment and/or payment is not conditioned upon signing this Authorization. I agree that I may be contacted by the Authorized Persons by phone, by mail, by e-mail or through other means with respect to the Information. I understand that KV Pharmaceuticals does not sell my Health Information to the Authorized Persons but that the Authorized Persons may receive remuneration from KV Pharmaceuticals in connection with their involvement with the Program, including the dissemination of the Information I know and agree that the Authorized Persons may use and see my Health Information as described above. I understand that my Health Information may also be given out as needed to deal with safety, my treatment, adverse events, and related issues to the extent allowed under applicable law or as previously consented to in writing by me. I understand that if my Health Information is given out as allowed in this Authorization, federal and state privacy laws may not protect it if those laws do not apply to the recipients. I agree that a copy of this Authorization may be treated as a signed original.

Signature of Patient: _____ Date: _____

Personal Representative Section: If this form is signed by someone who is not the participant listed at the top of this Authorization, describe the signer's legal authority to act for the participant:

_____

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/s/

Laura Pincock
10/21/2008 05:02:14 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Felicia Duffy and Kellie Taylor

Denise Toyer
10/22/2008 12:41:42 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/22/2008 02:10:06 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Cytyc Corporation
Attention: Robb Hesley
Vice President, Business Development
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

Please refer to your new drug application (NDA) dated April 14, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 17 α-Hydroxyprogesterone Caproate Injection, 250 mg/mL (17P).

We also refer to your submission dated April 24, 2008, which constituted a Complete Response to our Approvable Letter issued on October 20, 2006.

On September 26, 2008, we received a major Chemistry, Manufacturing and Controls (CMC) amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 25, 2009.

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 796-0881.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
10/6/2008 02:25:47 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945 **INFORMATION REQUEST LETTER**

Cytyc Corporation
Attention: Robb P. Hesley
Vice President Business Development, Strategic Projects
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

Please refer to your April 14, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gestiva (hydroxyprogesterone caproate).

We are reviewing your submission dated April 24, 2008, which constituted a complete response to our approvable letter of October 20, 2006, and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We also refer to your email dated August 8, 2008, in which you asked the Division for clarification on your post-marketing efficacy protocol.

> "*The first bullet point of Number 2 of the clinical reviewer comments indicates to compare fetal and infant deaths using: Deaths (from minutes after birth until 28 days of life) occurring in liveborns born at <24 weeks gestation. Spontaneous abortions/miscarriages (16-20 weeks gestation) should also be included in the group.*
>
> *The above definition does not include stillbirths from 20-23.6 weeks gestation. Should stillbirths from 20-23, 6 weeks gestation also be included in the definition of the outcome above? If not, please ask the clinical reviewer to explain why so we understand the reasoning."*
>
> **Response**
>
> No. Stillbirths from 20 - 23.6 weeks are included in the third bullet point of number 2 of the clinical reviewer comments: "All stillbirths/ fetal deaths/in-utero fetal losses, from *20 weeks gestation until term".*
>
> Newborns born *alive* at < 24 weeks gestation often have a different cause of death (e.g., inflammation) than *stillbirths* (e.g. congenital anomalies, viral infections etc.). It is too difficult to distinguish stillbirths from other births at less than 20 weeks gestation, so we think at this very early gestation, they should be combined.

Clinical Pharmacology

In the Advice letter dated August 6, 2008; we made the following request regarding the design of the Phase 4 safety and efficacy study protocol:

- Collection of the 3rd pharmacokinetic (PK) sample at 1 to 4 days post Dose 8, 9, or 10 should be stratified such that the numbers of samples collected are evenly distributed among days 1, 2, 3, and 4 post-dose. This would ensure that there will be appropriate data for the population PK modeling.

We would like to revise our previous request listed above to the following:

- Collection of the 3rd pharmacokinetic (PK) sample at 1 to 4 days post Dose 8, 9, or 10 should be expanded to capture the entire dosing interval of 7 days. We recommend that the 3rd PK sampling be stratified such that the samples collected are evenly distributed among the following 5 time intervals: day 1, day 2, day 3, day 4, and days 5-6 post-dose. Each patient is still required to provide only 3 PK samples.

Additional Clinical Pharmacology comment

- In vitro metabolism study with human liver microsomes (Study report 304-1177-02) indicated that 17-alpha hydroxyprogesterone caproate (17-HPC) increased the metabolic activity of CYP1A2, CYP2A6, and CYP2B6. We recommend that you conduct follow up studies in human hepatocytes in vitro to determine whether 17-HPC induces or alters the metabolic activities of these CYP isoforms.

CMC Comments

1. Based on analysis of the submitted data, and taking into account the particulate matter results under intermediate conditions, an expiry of 24 months can be granted when stored at controlled room temperature. In addition to storing the vial in the container to afford protection from light, the vial should also be stored upright to minimize contact with the stopper, and the appropriate Caution Statement added to the label.
2. Expiry can be extended upon submission of additional real-time data. If an expiry of 30 months is sought, a 30-month time-point must be added to the stability protocol.
3. Any change in the stopper after approval should be submitted as a Prior Approval Supplement and should include detailed information on the issue of particulate matter.
4. The following labeling changes should be made throughout the Physician's Insert and the container and carton labels, where applicable. Please resubmit updated carton and container labels for review after the changes are made.
    - The phrase "… (b) (4) should be deleted and replaced with "…contains…"
    - The established name should be changed to "Hydroxyprogesterone caproate" for consistency with the USP monograph.
    - The established name should be in letters at least one half the size of the proprietary name to conform with 21 CFR 201.10(g)(2).

- The comma should be removed from 1,250 mg.
- The "Manufactured for" statement should be changed to reflect the current NDA holder. (b) (4)
- The storage statement should be as follows. All "Caution" statements should be included on the container and carton labels. Store at controlled room temperature [15º-30ºC (59º-86º F)]. Protect vial from light. Store vial in its box. Store upright.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-796-1025.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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 /s/
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Jennifer L. Mercier
8/21/2008 12:22:52 PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945 **ADVICE LETTER**

Cytyc Corporation
Attention: Robb P. Hesley
Vice President, Business Development, Strategic Projects
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gestiva (17 α-hydroxyprogesterone caproate).

We have the following requests and recommendations regarding the design of the phase 4 safety and efficacy study protocol:

1. Collection of the 3rd pharmacokinetic (PK) sample at 1 to 4 days post Dose 8, 9, or 10 should be stratified such that the numbers of samples collected are evenly distributed among days 1, 2, 3, and 4 post dose. This would ensure that there will be appropriate data for the population PK modeling.

2. Sponsor should consider storing a separate aliquot of each PK blood sample from the phase 4 safety and efficacy study for potential future analysis of any important metabolite(s) that may be identified following completion of the phase 1 PK study (i.e., the study being conducted by Dr. Steve Caritis).

Provide a response to these comments as soon as possible to allow a timely review of the NDA.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-796-1025.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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Jennifer L. Mercier
8/6/2008 10:51:30 AM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945 **ADVICE LETTER**

Cytyc Corporation
Attention: Robb P. Hesley
Vice President Business Development, Strategic Projects
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 17α-hydroxyprogesterone caproate injection (250 mg/ml).

We are providing you with the following preliminary comments to assist you in revising your postmarketing study protocol.

Clinical Reviewer Comments

(b) (4)

2. *Discontinue the use of the term* (b) (4) *and compare fetal and infant deaths between the treatment and placebo arms in the in the following ways:*
    - Deaths (from minutes after birth until 28 days of life) occurring in *liveborns* born at *less than 24 weeks gestation*. Spontaneous abortions/miscarriages (16-20 weeks gestation) should also be included in this group.
    - Deaths (from minutes after birth until 28 days of life) occurring in liveborns born at *24 weeks gestation or greater*.
    - All stillbirths/fetal deaths/in-utero fetal losses occurring from *20 weeks gestation until term.*

A death following a live birth may have a different etiology than that of a stillbirth/fetal death/in-utero fetal loss.

3. *Every attempt should be made to determine a cause for each stillbirth/fetal death/in-utero fetal loss. These cases should have, at a minimum, the following work-up (recommended by the Stillbirth Collaborative Research Network of the National Institute of NICHD [scrn.rti.org]):*
   - Perinatal autopsy and placental evaluation by a pathologist with expertise in perinatal pathology
   - Karyotype
   - Antibody screen
   - Serologic test for syphilis
   - Screen for fetal-maternal hemorrhage (Kleihauer-Betke or other)
   - Urine toxicology screen
   - Parvovirus serology

   These tests are also recommended if there is clinical suspicion:
   - Lupus anticoagulant screen
   - Anticardiolipin antibodies
   - Factor V Leiden mutation
   - Prothrombin G20210A mutation
   - Screen for protein C, protein S, and Antithrombin III deficiency
   - Uterine imaging study

This information will be essential to the evaluation of the safety of 17α-hydroxyprogesterone caproate injection.

Statistical Reviewer Comments

1. Subject withdrawal: A distinction between withdrawal from study and withdrawal from study medication needs to be made. Except in the case of withdrawal of consent, all subjects should remain on-study regardless of treatment status, i.e., full determination of pregnancy outcome should be made. Adverse events thought to be due to study medication may warrant discontinuation of the medication, but the subject should remain in the study. Non-compliance is not a sufficient reason to withdraw a subject from the study.
2. (b) (4) In order to assess the impact of treatment, analyses need to account for *time from randomization*. Assuming that study drug starts at the time of randomization, such analyses will account for duration of treatment.
3. Previous studies have shown that efficacy may be related to the *gestational age at the onset of treatment*. The analysis needs to account for the gestational age at which the subject is randomized. In addition, consider stratifying randomization according to gestational age; for example, 16^0 to 17^6 weeks gestation at randomization and 18^0 to 20^6 weeks gestation at randomization.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-796-1025.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Scott Monroe
7/30/2008 05:00:21 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945 **INFORMATION REQUEST LETTER**

Cytyc Corporation
Attention: Robb P. Hesley
Vice President, Business Development, Strategic Projects
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

Please refer to your August 30, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 17 α-Hydroxyprogesterone Caproate Injection, 250 mg/ml (17 P).

We also refer to your submission dated April 24, 2008 which constituted a complete response to our Approvable Letter dated October 20, 2006.

We are reviewing your submission and have the following comments. We request a written response by July 8, 2008 in order to continue our evaluation of your NDA.

In the letter conveying FDA's "Approvable" action, dated October 20, 2006, we asked that the confirmatory study provide "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 [bolding added]." We request that you add preterm birth prior to 32 weeks gestation as a co-primary endpoint.

Also, in the above referenced letter, we requested that in your confirmatory study you provide sufficient data to assess early fetal loss (second trimester miscarriage and stillbirth). We request that you evaluate fetal loss from 16^0 to 23^6 weeks and all stillbirths regardless of their gestational age.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-796-1025.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
6/27/2008 04:04:39 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Drug Marketing, Advertising and Communications (DDMAC) Attention: Lisa Hubbard	FROM (*Name, Office/Division, and Phone Number of Requestor*): Charlene Williamson, Project Manager, DRUP x 6-1025

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 21, 2008		21-945	Resubmission	April 24, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gestiva (17 alpha hydroxyprogesterone caproate, 250 mg/ml)	Standard	Progesterone	September 1, 2008

NAME OF FIRM: CYTYC Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review the labeling for 17 alpha-hydroxyprogesterone caproate injection 250mg/ml for the (b) (4) preterm birth in women with a history of at least one spontaneous preterm birth. Attached are PI, carton and vial labeling.

SIGNATURE OF REQUESTOR Charlene Williamson	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

14 pages of draft labeling have been withheld in full as B(4) CCI/TS immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE CONSULTS

FROM: Charlene Williamson, DRUP 6-1025

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 21, 2008		21-945	Resubmission	April 25, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gestiva (17 HP)	Priority	Progesterone	September 1, 2008

NAME OF FIRM: CYTYC Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the trade name Gestiva® and the labeling (PI, PPI, carton/container) for 17 a-hydroxyprogesterone caproate injection 250 mg/ml for [redacted] (b) (4) of pre-term birth in women with a history of a least one preterm birth. The review division is requesting that you review the AERS database for all adverse event reports involving any compounded preparations of 17OHP-C used in pregnant women from June, 2003 through the present.

PDUFA DATE: October 24, 2008
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 21-945
HFD- /Division File
HFD-580/RPM
HFD- /Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER
Charlene Williamson

METHOD OF DELIVERY (Check one)
☒ DFS ONLY ☐ MAIL ☐ HAND

SIGNATURE OF RECEIVER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

CYTYC
Attention: Robb Hesley
Vice President, Business Development
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

We acknowledge receipt on April 26, 2008, of your April 24, 2008 resubmission to your new drug application (NDA) for 17 ά-hydroxyprogesterone caproate injection, 250 mg/ml (17P).

We consider this a complete, class 2 response to our October 20, 2006 action letter. Therefore, the user fee goal date is October 24, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. We will notify you whether we have waived the pediatric study requirement for this application.

If you have any question, call me at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Charlene Williamson
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Z. Charlene Williamson
5/8/2008 05:23:01 PM

CYTYC

January 30, 2008

Scott Monroe, MD, Director
Division of Reproductive & Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Complex
10903 New Hampshire Ave
Bldg. 22, Rm. 5380
Silver Spring, MD 20993

Re: NDA 21-945
DMETS' Comments on Proposed Trade Name Gestiva

Dear Dr. Monroe,

I am writing today in response to your letter of September 28, 2006, in which you forwarded comments from the Division of Medication Errors and Technical Support (DMETS) on the proposed proprietary name "Gestiva" for 17 α-hydroxyprogesterone caproate, 250 mg/mL. Cytyc Corporation ("Cytyc"), formerly Adeza Biomedical, will incorporate all of DMETS' general and specific comments relating to the container label, carton labeling and package insert (A, B1-B7, C1-C2, D1-3) and will submit the revised labeling in the Complete Response to the Approvable Letter. Cytyc also notes the Division of Drug Marketing, Advertising and Communications (DDMAC) comment that use of the proposed trade name Gestiva may (b) (4)

(b) (4)

(b) (4)

2 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

1240 ELKO DRIVE, SUNNYVALE, CA 94089 PHONE: 408 745-0975 FAX: 408 744-1905

I can be reached at 408-745-5179 or at robb.hesley@cytyc.com should you have questions.

Sincerely,

Robb Hesley
Vice President, Business Development

cc: (b) (4)
Catherine A. Williams, Director, Regulatory Affairs

Attached: Letter dated 9/28/2006 from Dr. Scott Monroe

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Adeza Biomedical
Attention: Durlin Hickok, M.D., M.P.H.
Vice President, Medical Affairs
1240 Elko Drive
Sunnyvale, CA 94089

Dear Dr. Hickok:

Please refer to your April 14, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 17-alpha hydroxyprogesterone caproate, 250mg/mL.

We, in consultation with Division of Medical Error and Technical Support (DMETS), have completed review of your proposed tradename. DMETS has the following comments regarding your proposed proprietary name "Gestiva":

DMETS does not recommend the use of the proprietary name, Gestiva. In reviewing the proprietary name, the primary concern relating to look-alike and sound-alike confusion with Gestiva is Sustiva. Sustiva contains efavirenz and is indicated for the treatment of HIV-1 infection. Sustiva and Gestiva may look similar as they both contain 7 letters and have identical endings (-stiva). The letters "S" and "G" may also resemble one another when scripted (see below). Additionally, the letter "u" in Sustiva looks similar to the letter "e" in Gestiva if either letter is not prominently scripted. Sustiva and Gestiva are phonetically similar as they both contain 3 syllables, and the last two syllables are the same ("-tiva").

Gestiva 250mg
Sustiva 250mg

Sustiva and Gestiva have several differentiating product characteristics such as indication for use (HIV treatment vs. prevention of preterm birth), strength (50 mg, 100 mg, 200 mg, and 600 mg vs. 250 mg/mL), route of administration (oral vs. intramuscular), dosage form (tablets/capsules vs. injection), and frequency of administration (once daily vs. beginning with week 16-20, once weekly until week 37).

Although both drug products differ in route of administration, dosage form, and frequency of administration, the potential exists for Sustiva and Gestiva to be written with "as directed" instructions, which eliminates the majority of these differences and contributes to the products' similarities. Due to insurance billing in the US, and the potential cost of Gestiva, patients may receive outpatient prescriptions for Gestiva to be filled at a retail pharmacy and the patient will

bring the medication to their appointment. Since Gestiva may potentially be prescribed on an outpatient basis, prescriptions may be written as "Gestiva 250 mg, use as directed". In this case, the potential exists for "Gestiva 250 mg, use as directed" to be confused as "Sustiva 250 mg, use as directed." If Sustiva is dispensed in place of Gestiva or vice versa, the expectation is that the error will be caught prior to administration because the patient would likely question the dosage form. However, if the patient has not been educated, the patient may not be aware of which form the drug will be supplied, which could compound confusion. Additionally, Sustiva is in pregnancy category D (positive evidence of fetal risk) because of neural tube defects in infants born to women with first trimester exposure to Sustiva. Although Gestiva is to be initiated in the second trimester, the risk still exists for unnecessary fetal exposure *in utero* if Sustiva is dispensed in error. In either case, even if the error is caught prior to administration, an error has still occurred. The introduction of the name Gestiva will create a window for confusion and potential for error. We anticipate reports of potential error with this name pair, especially since the names appear almost identical and they share an overlapping dose. Thus, due to the similarity in spelling and pronunciation, DMETS believes we can object to name based on 21 CFR 201.10(c)(5):

> "The labeling of a drug may be misleading by reason (among other reasons) of: (5) Designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient."

DMETS questions whether it is appropriate to introduce a proprietary drug name that may potentially generate confusion in high risk patient populations such as pediatric HIV patients and pregnant women with a history of preterm births. It is likely that the patient will recognize the error when the drug is dispensed and verification will prevent the actual administration of the wrong drug. However, the name confusion would have occurred and resulted in the medication error. If such an error goes undetected and the medication is somehow administered, there is a significant risk for harm. In contrast, if the error is detected prior to administration, a medication error would have occurred, but would not result in patient harm. Despite the lack of a negative outcome, DMETS believes that the goal of patient safety is to prevent the medication error from occurring in the first place, if at all possible. DMETS believes the potential for error between names goes beyond the context of use (indication, dosage form, etc.) when the names are very similar, and therefore, DMETS does not recommend the use of the proposed proprietary name, Gestiva.

Additionally, DMETS reviewed the container labels, carton and insert labeling from a safety perspective. We have identified the following areas of improvement, which may minimize potential user error.

A. GENERAL COMMENT

(b) (4)

(b) (4) Delete the diagrams from the carton labeling to avoid distracting the reader. Also, refer to the comment below from Division of Drug Marketing, Advertisement and Communications (DDMAC) in reference to disseminating

(b) (4)

[redacted]

B. CONTAINER LABEL (5mL multiple dose vial: 250 mg/mL)

1. The gray/purple color of the proprietary name appears light and may be difficult to read in brightly lit areas (e.g., hospital pharmacies, inpatient units, and clinics). Additionally, it is less prominent than the NDC number, dosage form, route of administration, and product strength. Darken the shade of the proprietary name in order to improve visibility and to increase its prominence.

2. The established name appears in a light gray color which is very difficult to read. Additionally, the current font of the established name makes it appear crowded on the label. Consider revising the established name to appear in the same font and color as the dosage form (injection).

3. Ensure the established name is at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).

4. Relocate the product strength to appear in closer proximity to the proprietary and established names, preferably beneath the established name.

5. Medication errors resulting in overdoses and underdoses have occurred because labels of small volume parenteral drug products do not list the total milligram content of the drug contained in the vial. Thus, in order to avert dosing errors with this product, we recommend expressing the strength in terms of total drug content. For example:

   1,250 mg/5 mL
   (250 mg/mL)

6. Relocate the net quantity (5 mL Multiple Dose Vial) from the side panel to appear on the primary display panel, away from the product strength.

7. De-bold the "Rx Only" statement as it detracts attention from the product name, strength, and route of administration.

C. CARTON LABELING (5mL multiple dose vial: 250 mg/mL)

1. See comments B1-B5, and B7.

2. Decrease the prominence of the sponsor's name (Adeza) at the bottom of the carton as it appears almost as prominent as the proprietary name.

D. PACKAGE INSERT

1. Delete [redacted] (b) (4) Refer to DDMAC's comment in reference to disseminating reminder advertisements or labeling.

2. The dosage form (injection) does not appear in conjunction with the established name at the top of the package insert. Include the dosage form with the established name.

3. In step 2 of the "Instructions for Administration" section, do not use the abbreviation "cc" to describe the volume of the 3 "cc" syringe. The abbreviation "cc" appears on the ISMP error prone abbreviations, symbols and dose designations list (http://www.ismp.org/Tools/errorproneabbreviations.pdf#search=%22ismp%20dangerous%20abbreviations%22), and has been misinterpreted as "u" (units). The FDA launched a campaign in June 2006, warning health care providers and consumers not to use error - prone abbreviations. Thus, we request that the Office of New Drugs not approve or use abbreviations in their labels and labeling as they can be misinterpreted. Therefore, revise "3 cc" to appear as "3 mL".

If you have any questions, call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 796-2130.

Sincerely,

(See appended electronic signature page)

Scott Monroe, M.D.
Acting Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Scott Monroe
9/28/2006 11:21:54 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Cytyc Corporation
Attention: Catherine Williams
Director, Regulatory Affairs
1240 Elko Drive
Sunnyvale, CA 94089

Dear Ms. Williams:

We acknowledge receipt on April 30, 2007, of your April 27, 2007, correspondence notifying the Food and Drug Administration that the corporate name and/or address has been changed from

Adeza Biomedical Corporation

to

Cytyc Corporation

for the following new drug application: NDA 21-945 for Gestiva™ (17 α-hydroxyprogesterone caproate injection, 25- mg/ml).

We have revised our records to reflect this change. We request that you notify your suppliers and contractors who have Drug Master Files [DMF(s)] referenced by your application of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Charlene Williamson
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Z. Charlene Williamson
11/30/2007 06:33:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Cytyc Corporation
Attention: Robb P. Hesley
Vice President Business Development, Strategic Projects
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 17 α-hydroxyprogesterone caproate injection 250 mg/ml.

We also refer to your submission dated June 15, 2007, containing your protocol entitled "*17 Alpha-Hydroxyprogesterone Caproate: An Intramuscular Multi-Generation Toxicity Study in Rats Following In-Utero Exposure*."

We have completed the pharmacology/toxicology review of the referenced material and have the following comments:

- The protocol is acceptable.
- As discussed during the November 9, 2006 meeting, it will be acceptable to submit initially a non-audited report of the Multi-Generation Toxicity Study as a component of your Complete Response for NDA 21-945.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-796-1025.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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 /s/
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Scott Monroe
7/17/2007 05:26:11 PM
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MEMORANDUM OF TELECON

DATE: April 13, 2007

APPLICATION NUMBER: NDA 21-945

BETWEEN:

Name: Robb Hesley, VP business Development, Strategic Projects
Durlin Hickok, MD, MPH, Senior VP Medical Affairs
Catherine Williams, Director Clinical and Regulatory Affairs
Phone: 408-745-5179
Representing: Cytec (formerly Adeza Biomedical)

AND

Name: Daniel Shames, MD, Deputy Director
Bronwyn Collier, Associate Director for Regulatory Affairs
Office of Drug Evaluation III

SUBJECT: Gestiva™ (17-αhydoxyprogesterone caproate): Response to March 14, 2007, Formal Request for Dispute Resolution

Background: NDA 21-945 was submitted April 14, 2006 and received on April 20, 2006. The application was discussed by the Reproductive Health Drugs Advisory Committee (RHDAC) on August 29, 2006 and the Division of Reproductive and Urologic Products (DRUP) subsequently issued an approvable letter on October 20, 2006. Several deficiencies were stated in the letter including the need for an additional study to confirm evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality, data to evaluate a potential association of 17-αhydoxyprogesterone caproate (17HPC) with increased risk of early fetal loss (second trimester miscarriage and still birth) and the need for, at minimum, preliminary data from multi-generational reproductive toxicology studies pre-approval. The sponsor submitted a request for formal dispute resolution on March 14, 2007, that stated their position that the pre-approval requirements cited in the approvable letter exceeded the recommendations of the RHDAC. The response to the request for dispute resolution, issued and faxed to the sponsor April 13, 2007, agreed with DRUP that the cited deficiencies needed to be addressed pre-approval.

Call: Dr. Shames explained that the purpose of the call was to confirm that the sponsor had received the response to their request for dispute resolution and to provide an opportunity for clarification, as needed, regarding the response. Mr. Hesley confirmed that they had received the fax with sufficient time to read and discuss it. The following key points were discussed:

1. The requirement for a multi-generation reproductive toxicology study in rodents:

   - The sponsor stated that they agreed that such a study is needed and that they have met with DRUP to work on developing an appropriate protocol.

- The sponsor questioned whether the Pushpalatha study could be used instead to represent the "worst case scenario" in rats. Dr. Shames explained that because the Pushpalatha study did not mimic the method of proposed clinical use, the data would potentially present misinformation regarding 17HPC and thus an appropriate study needed to be conducted.
- The sponsor questioned how labeling would be handled if the new study results do not match the Pushpalatha results. Dr. Shames stated that this would need to be discussed when the data are available for review.
- The sponsor questioned what level of negative data would result in a not approvable action should the study provide negative results. Dr. Shames responded that the agency would likely seek expert input through an advisory committee discussion if the study results were negative.
- Dr. Shames acknowledged that DRUP would accept preliminary data from the multi-generation rodent study pre-approval.

2. The requirement for a confirmatory multi-center efficacy clinical trial including evaluation of the potential for increased risk of second trimester miscarriage and stillbirth:

   - The sponsor asked what level of significance would be required. Dr. Shames commented that the current data submitted to support efficacy are not substantial and that DRUP agreed with the RHDAC that another clinical trials was necessary to provide more robust data. Although, generally p=.05 with two trials is the accepted level of significance, other factors will be taken into consideration such as the nature of the condition treated.
   - The sponsor noted the requirement to include the confirmatory efficacy study protocol and evidence of study feasibility in their response to the approvable letter. They said that they've already received word that the National Institutes of Health would not sponsor a placebo-controlled trial. They commented that gathering feasibility evidence will take some time and asked whether the protocol and feasibility evidence could be submitted post-approval. Dr. Shames responded that the response to the approvable letter would be reviewed under the regulations for accelerated approval and that in the interest of ensuring that appropriate information is available to support safety and efficacy, the protocol should be submitted and agreed-upon pre-approval. He also recommended that the sponsor discuss the difficulties they have already encountered regarding study feasibility and any proposed approaches with DRUP. Ms. Collier suggested that the sponsor request a special protocol assessment when they submit the protocol.

In conclusion, Dr. Shames explained that the sponsor's options were to work with DRUP on the necessary studies to support safety and efficacy for (b) (4), or, to pursue their request for dispute resolution to the next organizational level (Office of New Drugs). Mr. Hesley acknowledged the options and stated the company's commitment to pursuing appropriate development towards approval for (b) (4)

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/s/

Bronwyn Collier
4/30/2007 09:30:00 AM
CSO

Daniel A. Shames
4/30/2007 11:31:19 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Adeza Biomedical Corporation
Attention: Robb P. Hesley
Vice President Business Development, Strategic Projects
1240 Elko Drive
Sunnyvale, California 94089

Dear Mr. Hesley:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gestiva™ (17 α-hydroxyprogesterone caproate injection).

Your March 14, 2007, request for formal dispute resolution, received on March 16, 2007, concerned the October 20, 2006 approvable letter for the Gestiva™ NDA in which several deficiencies were stated including the need for an additional study to confirm evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality, data to evaluate a potential association of 17 α-hydroxyprogesterone caproate (17HPC) with increased risk of early fetal loss (second trimester miscarriage and stillbirth) and the need for, at minimum, preliminary data from multi-generational reproductive toxicology studies pre-approval. Your request for dispute resolution states your position that the above requirements exceed the recommendations of the Reproductive Health Drugs Advisory Committee (RHDAC) discussed at the August 29, 2006 meeting of this committee.

I have reviewed your appeal and conclude that the requirements stated in the October 20, 2006 approvable letter are appropriate. The rationale for this conclusion is detailed in the following responses to the points made in your appeal:

1. The requirement for a multi-generation reproductive toxicology study in rodents.

Your request stated two issues of concern relating to toxicological information required for approval. The first was that during initial and subsequent communications with the Division of Reproductive and Urologic Products (DRUP) regarding preclinical safety data, Adeza believed that the division explicitly indicated that the scope of information proposed for inclusion in NDA 21-945 was sufficient and that notification that a multi-generational reproductive toxicology study in rodents would be a pre-approval requirement was conveyed late (October and November 2006) in the review of the NDA. You asserted in your request that "…substantive and relevant toxicology studies were provided to the NDA and subsequent amendments to the NDA." and that the reproductive toxicology study is not required for approval. However, you also propose that if such a study is determined to be necessary, it should be permitted to be conducted post-approval. Your second concern is that, in fact, (b) (4) can be administered safely and be appropriately labeled based on evaluation of the submitted published toxicology studies.

After review of the relevant documents, I agree that Adeza was informed late in the review process that a new pre-approval toxicology study would be required. I also acknowledge that DRUP communicated to Adeza on multiple occasions during the development of the NDA application that no toxicology data beyond what was proposed for the application appeared necessary. As flawed as the communications may have been, however, this process in itself cannot negate the need for full information necessary to assure safe use and appropriate labeling of (b) (4) In addition, after review of the submitted information, the FDA toxicologists determined that there were significant deficiencies in the scope and quality of the reported nonclinical studies. Most of the nonclinical studies did not comply with either Good Laboratory Practices (GLP) or conform to current CDER and ICH guidances. Although exact conformance to guidances is not required, they do convey information on how to address data that is needed to support safety and efficacy. A particular concern of the FDA toxicologists focused on data found in a series of articles by Pushpalatha that culminated in a paper published in 2005. In this study, 17HPC was administered to pregnant rats early in gestation. The effect of gestational exposure to 17HPC on fertility was assessed by breeding F1 male rats with control females as well as analyzing sperm quality and quantity in the F1 males. The number of implantation sites and viable fetuses was significantly reduced in females mated with F1 males that were exposed to 17HPC during embryonic development. The decrease in sperm function was associated with a decrease in sperm motility, sperm viability and sperm count in the F1 rats. The conclusion was that in utero exposure to 17HPC affects fertility in male rats.

I agree with DRUP that a multi-generational study in rats conducted according to GLPs will provide important information that is needed in labeling to properly inform healthcare practitioners and patients regarding the potential risks of (b) (4) I further agree with DRUP that the preliminary results of this study, as described in the approvable letter, should be available pre-approval. The Pushpalatha studies have significant flaws and are not useful for labeling because the results may misinform patients and prescribers regarding the risks of (b) (4) A multi-generational reproductive toxicology study in rats performed according to GLPs that closely mimics the clinical administration of (b) (4) will be best suited for generating the information needed for labeling.

2. The requirement for a confirmatory multi-center efficacy clinical trial.

The approvable letter suggested that the requirement for a confirmatory multi-center efficacy trial could be conducted post-approval under the regulations for accelerated approval at 21 CFR 314.510. Such a trial would evaluate evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly or through a well-established surrogate. DRUP also specified in the letter that the draft protocol for and evidence of feasibility of conducting this trial be included in any response to the approvable action. In addition, if Adeza determined that a placebo-controlled trial would not be feasible, an alternative study design should be submitted. Your dispute resolution request states that a confirmatory clinical trial should not be required even post-approval as outlined by DRUP. You also request that if it is determined that a clinical trial is required, the draft protocol and evidence of feasibility be permitted to be provided post-approval. You also point out that the Advisory Committee recommended that a clinical trial to investigate further safety and/or effectiveness could be conducted post-approval.

The data generated by the single clinical trial provided in the NDA did not provide evidence of a statistically significant effect on a composite endpoint of major neonatal morbidities and mortality.

However, a majority of the members of the Advisory Committee believed that preventing preterm birth at less than 32 and less than 35 weeks of gestation does represent an adequate surrogate for a reduction in neonatal morbidity and mortality. A majority of committee members also thought that there was a significant reduction in preterm births at less than 35 weeks gestation in Study 17-CT-002. However, the level of statistical significance for the treatment effect at less than 32 weeks and less than 35 weeks gestation did not meet the level of statistical significance generally accepted by FDA to support approval of a drug product based on the findings from a single clinical trial.

I have concluded that although Adeza has demonstrated efficacy of (b) (4) for reducing the risk of preterm birth at gestational ages (surrogate measures) that correlate with increased neonatal morbidity and mortality in a single trial, the data are not sufficiently robust or compelling to support approval without the requirement for conduct of an additional clinical study(ies) as described in the approvable letter. I have also concluded that the accelerated approval regulations at 21 CFR 314.510 are applicable in this situation. DRUP exhibited appropriate prudence by requesting submission of a draft protocol and evidence of feasibility for a study to verify the observed clinical benefit of (b) (4) for the prevention of recurrent preterm birth. Therefore, I concur with DRUP's position as communicated in the approvable letter.

3. The requirement for a pre-approval protocol to evaluate the potential association of 17HPC with increased risk of second trimester miscarriage and still birth.

DRUP recommended in the approvable letter, that the risk of second trimester miscarriages and stillbirth could be assessed as part of the confirmatory efficacy study described above. In addition, the division specified that the draft protocol be included in Adeza's response to the approvable action, again as stated above. Your dispute resolution request acknowledged that continued study of second trimester miscarriages and still birth rates associated with 17HPC is important but reiterated the request that the draft protocol be provided post-approval.

An increase in early pregnancy loss in the (b) (4) treated subjects was a particular concern. There was a trend towards an increase in second trimester miscarriage rate (pregnancy loss prior to 20 weeks of gestation) and a suggestion of an increase in stillbirth rate (death of the fetus prior to or during delivery) in the (b) (4) group. These findings were presented at the RHUAC meeting and the recommendation of the majority of the members was that this observation required further investigation (yes=21, no=0), but that the investigation could be conducted post approval (pre-approval=8, post-approval=13). A majority of the committee members also voted that no additional clinical safety data were required prior to approval.

DRUP again exhibited appropriate prudence in requiring submission of a draft protocol to evaluate the association of (b) (4) with second trimester miscarriages and stillbirths. I agree that this safety concern could be studied as part of the efficacy trial described above and that the accelerated approval regulations at 21 CFR 314.510 are applicable in this situation. Therefore, I concur with DRUP's position as communicated in the approvable letter.

If you have any questions, call Ms. Grace Carmouze, Formal Dispute Resolution Project Manager, at (301) 796-1654.

Sincerely,

{See appended electronic signature page}

Daniel A. Shames, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
4/13/2007 09:56:15 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Adeza Biomedical Corporation
Attention: Robb P. Hesley
Vice President Business Development, Strategic Projects
1240 Elko Drive
Sunnyvale, CA 94089

Dear Mr. Hesley:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gestiva (17 α-hydroxyprogesterone caproate injection, 250 mg/ml) for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth.

We acknowledge receipt on March 16, 2007, of your March 14, 2007, request for formal dispute resolution concerning the approvable letter dated October 20, 2006. Specifically, you are disputing the requirements for a multi-generation reproductive toxicology study in rodents, a confirmatory multi-center efficacy clinical trial, and a pre-approval protocol to evaluate the potential association of 17HPC with increased risk of second trimester miscarriage and stillbirth.

Pursuant to the CDER/CBER draft Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," we have thirty (30) calendar days from the receipt date of the formal request to respond to the appeal. Therefore, our response to this appeal is due on or before April 13, 2007.

This appeal has been forwarded for review to Daniel Shames, MD, Deputy Director, Office of Drug Evaluation III, Center for Drug Evaluation and Research. We will contact you should we have any questions or require additional information.

If you have any questions, please call me at (301) 796-1654.

Sincerely,

{See appended electronic signature page}

Grace N. Carmouze
Formal Dispute Resolution Project Manager
Lead Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Grace Carmouze
3/21/2007 02:29:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Adeza Inc.
Attention: Robb Hesley
VP Strategic Projects
1240 Elko Drive
Sunnyvale, CA 94089-2212

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 17-alpha hydroxyprogesterone caproate injection, 250 mg/mL (Gestiva).

We also refer to the meeting between representatives of your firm and the FDA on November 9, 2006. The purpose of the meeting was to discuss the deficiencies listed in the October 20, 2006 Approvable Letter and the information needed to resolve the deficiencies.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcome.

If you have any questions, call Kassandra Sherrod, R.Ph., Regulatory Project Manager, at (301) 796-0997.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Division Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE	November 9, 2006
TIME	9:00 a.m. – 10:30 a.m.
LOCATION	White Oak Conf. Rm. 1417
APPLICATION	21-945
DRUG NAME	17-hydroxyprogesterone caproate injection
TYPE OF MEETING	A
MEETING CHAIR	Scott Monroe, M.D., Acting Director, Division of Reproductive and Urologic Products (DRUP), HFD-580
MEETING RECORDER	Kassandra Sherrod, R.Ph., Regulatory Project Manager, DRUP HFD-580

FDA ATTENDEES
Daniel Shames, M.D. - Acting Deputy Director, Office of Drug Evaluation III, HFD-103
Scott Monroe, M.D. - Acting Director, DRUP, HFD-580
Lisa Soule, M.D. - Clinical Team Leader, DRUP, HFD-580
Barbara Wesley, M.D. - Medical Officer, DRUP, HFD-580
Lynnda Reid, Ph.D. - Pharmacology Team Leader, DRUP, HFD-580
Alexander Jordan, Ph.D. - Pharmacologist, DRUP, HFD-580
Kassandra Sherrod, R.Ph. - Regulatory Project Manager DRUP, HFD-580
Jennifer Mercier, - Chief, Project Management Staff, DRUP, HFD-580
Monica Cooper, Ph.D. - Chemist, Office of New Drug Quality Assessment (ONDQA), Division of Premarketing Assessment II (DPMA II), Branch III
Lisa Kammerman, Ph.D. - Biostatistics Team Leader, Division of Biostatistics II, HFD-715

ADEZA ATTENDEES
Emory Anderson - President and CEO
Durlin Hickok, M.D. - VP Medical Affairs
Robb Hesley, V.P. - Strategic Products
James L. Schardein, M.S., Fellow ATS - Reproductive and Development Toxicology Consultant
Natasha Leskovsek - Regulatory Counsel, Heller Ehrman
Mark D'Andrea - CMC Consultant, via teleconference

BACKGROUND
Adeza submitted NDA 21-945 for 17-hydroxyprogesterone caproate injection 250 mg/mL (Gestiva) for prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth. The sponsor was issued an approvable letter dated October 20, 2006.

MEETING OBJECTIVES
The purpose of the meeting was to discuss the deficiencies listed in the October 20, 2006 Approvable Letter and the information needed to resolve the deficiencies.

SPONSOR'S QUESTIONS AND THE FDA'S RESPONSES

Toxicology

1. *Does the study design and dosing outlined above meet the Division's requirements for a multigenerational reproductive toxicology study as outlined in the Division's letter of October 20, 2006?*

   DRUP Response

   Yes. However, DRUP has the following additional recommendations:

   - Consider adding an additional arm that would begin active treatment at a stage of development comparable to that of the proposed human dosing regimen (i.e., after the gonads are developed)
     - Use 2 dosing regimens with the active drug and the appropriate control.
     - Dose pregnant rats on:
       - Gestational days 6, 13, and 20
       - Gestational days 13 and 20
   - Mate the F1 pups (when mature) with untreated animals.
   - Prior to the study, do a separate pharmacokinetic (PK) study in rats to determine if the half-life of 17-hydroxyprogesterone caproate is the same in rats as it is in humans to support the dosing regimen. If not, alter the dosing regimen accordingly in the reproductive toxicology study.
   - Submit the PK data and the protocol for the reproductive study for review by the Division prior to study initiation.

   The Division would allow submission of an abbreviated toxicology study report that included, at a minimum, the results of mating the F1 generation pups (i.e., number and weight of live offspring) with the Complete Response to the Approvable Letter. The final study report could be submitted during review of the Complete Response.

2. *How will the results of this additional preclinical reproductive toxicology study affect the potential approval of this NDA?*

   DRUP Response

   - The Division cannot answer this question until the outcome of the preclinical reproductive toxicology study has been reviewed.
   - The impact of the outcome of the study could range from (a) inclusion of the study findings in labeling and no other action to (b) not approving the NDA.

3. *If the study results replicate the findings from the Pushpalatha studies will this prevent the NDA from being approved*?

   DRUP Response

   - The Division cannot provide a definitive answer. If the findings of such a preclinical study also showed significant impairment of male reproductive function, even if drug were started later in fetal development of the rodent, this would be a very significant adverse finding.

- The consequences of such a finding would also need to be considered in light of any additional clinical data that the Sponsor might be able to provide that demonstrated that children of pregnant women treated with 17-hydroxyprogesterone caproate for the proposed or other indications, who had reached the age of reproductive competence, did not exhibit any impairment of reproductive potential. The Division would likely attribute more significance to any human data if the data were highly relevant and readily interpretable.

4. *Is it acceptable that the placebo material needed for the study be prepared under non-GMP conditions and be contained in sterile polypropylene screw cap tubes?*

   DRUP Response
   Yes, this is acceptable.

(b) (4)

[redacted]

Clinical

1. *Does the survey process described meet the Division's requirements for "Information needed address the clinical deficiencies" as described in the Division's letter of October 20, 2006? Are there any specific suggestions from the Division regarding how the survey should be conducted or what should be specifically asked?*

   DRUP Response
   - The Division's preference is that the clinical study about which the survey will assess feasibility replicate the NICHD study submitted in the NDA. If the Sponsor's conclusion is that such a study will be feasible, it is important that the survey document who will participate and the projected timeframe for enrollment. If the Sponsor concludes that a randomized, placebo-controlled study is not feasible, it will be important to document what questions were asked in the survey and how the Sponsor reached this conclusion.

- Parameters that should be addressed in the survey include:
  - Physicians' perception as to whether the study would be feasible and appropriate
  - IRB/site likelihood of approving the study
  - Patient access (including number likely to be eligible at each site and how long the potential investigator anticipates it would take to enroll the target number of subjects)
  - Likelihood of patient consent (this could be asked of physicians and could also be explored with potential subjects in a focus group setting)
- Potential groups that might be asked to participate in the survey include members of the current MFMU Network, obstetricians from community hospitals, and patient groups from both of these settings.

2. *With respect to the FDA's request No. 2 above, is FDA requesting that Adeza conduct a study powered to detect differences in miscarriage and stillbirth rates?*

DRUP Response

- Yes; the Division believes that the study should be adequately powered to define with "reasonable precision" the miscarriage/early fetal loss and stillbirth rates in placebo and 17-hydroxyprogesterone caproate-treated women or to rule out a specific potential increase in the rate of miscarriage and stillbirth rates. The Sponsor should propose a difference that they believe should be ruled out, based, at least in part, on the assessment of the benefits of treatment on overall neonatal morbidity and mortality.
- The Division has considered possible study designs that would address the issues of miscarriage/early fetal loss and stillbirth rates as well as overall efficacy in terms of demonstrating a reduction in the rates of PTB at gestational ages of < 35 and < 32 weeks.
  - The optimal study design would be a randomized, placebo controlled study similar to the Phase 3 study in the original NDA submission, adequately powered to show a reduction both in the rates of PTB at gestational ages of < 35 and < 32 weeks and a reduction in overall morbidity/mortality (e.g., the composite morbidity index that was used in original NDA 21-945).
  - If placebo treatment through Week 36 were found to be an unacceptable design, active treatment could be introduced in the arm initially assigned to placebo treatment, after the period of potential concern for early fetal loss (e.g., after weeks 24-25 gestational age). Such a study is likely to be feasible and might also provide information about effectiveness as well as safety, as the effects of different times of treatment onset could be evaluated.

(b) (4)

[redacted]

4. *If this NDA is approved under Subpart H, 21 C.F.R. § 314.510, would the Agency refuse to approve an ANDA until Adeza has fulfilled its postmarketing study requirements? We note for the Division's additional consideration that there is a petition (06P-0144) pending before the Office of Generic Drugs to permit submission and approval of an ANDA to Delalutin, which would put a potentially interchangeable product on the market under a different route*.

DRUP Response

- If Delalutin (17-hydroxyprogesterone caproate) is found not to have been withdrawn for reasons of safety or efficacy, an applicant can submit a 505(j) application for the listed drug.
- If 17-hydroxyprogesterone caproate (Gestiva) is approved for prevention of PTB and receives 3 years exclusivity, this would only block an ANDA for this drug for the PTB indication. This would not prevent an ANDA from being filed and approved for a generic version of Delalutin for previously approved indications.
- Delalutin does not hold the same indication as proposed for 17-hydroxyprogesterone caproate in NDA 21-945 so this would not block approval of an ANDA for other previously approved indications.
- The Division strongly recommends that the Sponsor confirm this response with the Office of Generic Drugs.

Chemistry

1. If the timeline to resolve the non-CMC comments from the Approvable Letter can be shortened and the results from the repeated ICH Q1B Stage 2 testing are acceptable, would FDA allow Adeza to make a post-marketing commitment to evaluate and develop a new method to detect photodegradants, if one is determined to be necessary?

Chemistry Response

Chemistry recommends that evaluation and development of a new method to detect photodegradants not be deferred to a post-marketing commitment. Adeza should provide the data in the Complete Response that has been collected up to that point. If the Sponsor can justify why a new photodegradants method is not needed based on the available data (e.g., results of the repeated ICH Q1B Stage 2 study), the Sponsor's proposed justification will be considered during the review of the Complete Response and a decision will be made at that time.

ACTION ITEMS

- The meeting minutes will be sent to the sponsor within 30 days.
- Sponsor will submit a preclinical study protocol, results of the feasibility study for conducting a placebo-controlled clinical trial(s) to address clinical deficiencies, and draft protocol(s) for clinical trials.

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/s/

Scott Monroe
12/8/2006 05:38:47 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Adeza Biomedical
Attention: Robb Hesley
Vice President, Business Development
1240 Elko Drive
Sunnyvale, CA 94089-2212

Dear Mr. Hesley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gestiva™(17-alpha hydroxyprogesterone caproate injection), 250 mg/mL.

We also refer to your October 30, 2006, correspondence, received October 31, 2006, requesting a meeting to discuss necessary actions in response to the October 20, 2006 approvable letter.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date:	November 9, 2006
Time:	9:00 a.m. – 10:30 a.m.
Location:	White Oak Conference Rm. #1417 10903 New Hampshire Avenue, Silver Spring, MD 20993
CDER participants:	Drs. Monroe, Soule, Wesley, Jordan, Kammerman, Reid, Cooper, and Mrs. Mercier and Sherrod

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at Kassandra.sherrod@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Kassandra Sherrod, (301) 796-0997; the division secretary, (301) 796-2130.

Provide the background information for this meeting (three copies to the NDA and 15 desk copies to me) at least one week prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by November 6, 2006, we may cancel or reschedule the meeting.

If you have any questions call me at (301) 796-0997.

Sincerely,

{See appended electronic signature page}

Kassandra Sherrod, R.Ph.
Senior Regulatory Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Kassandra C. Sherrod
11/2/2006 03:13:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Adeza Biomedical
Attention: Durlin E. Hickok, M.D., M.P.H.
Vice President, Medical Affairs
1240 Elko Drive
Sunnyvale, CA 94089

Dear Dr. Hickok:

Please refer to your April 14, 2006, new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Gestiva™ (hydroxyprogesterone caproate injection), 250mg/mL.

We also acknowledge receipt of your presubmissions dated August 30, 2005, January 10, March 28, and April 7, 2006.

We further acknowledge receipt of your submissions dated April 20, June 23, July 14, 21, 28 and 30, August 14 (2), 22 (2) and 23, September 7, 12, 19 (2) and 25, October 10 and 15, 2006.

This application proposes the use of Gestiva™ for (b) (4) preterm birth in pregnant women with a history of at least one spontaneous preterm birth.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, it will be necessary for you to address the following deficiencies:

Clinical

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 hydroxyprogesterone caproate (HPC) with 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. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals.
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

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*. At the time of a Complete Response submission to this approvable letter, provide, at a minimum, an unaudited interim final report of the requested study.

Chemistry, Manufacturing and Controls (CMC)

1. Significant degradation was observed for the light-stressed drug product sample with respect to content (assay) during the HPLC method validation studies. Thus, the drug product appears to be photosensitive; however, the resulting photodegradation products are not detectable by your HPLC method.
2. Given the results from your photostability study in which both the Stage 1 (fully exposed to light) and Stage 2 (enclosed in a chipboard box) samples showed decreases in content (assay) from that of the control (wrapped in foil) without corresponding increases in impurities by your HPLC method, you have not demonstrated that the secondary packaging provides adequate light protection for the drug product.
3. Your proposed expiration date of 24 months for the drug product is not acceptable based on the stability data included in your application to date.

Information needed to address the CMC deficiencies

1. Since you cannot account for the degradation of the active ingredient under light-stress conditions by your HPLC method, you should develop a supporting method that can adequately detect and quantitate the potential photodegradation products. The drug product specifications should include limits for any potential impurities observed using the new method, and a detailed description of the new analytical procedure with appropriate validation should be provided.
2. Alternative primary and/or secondary packaging should be used to protect the drug product from light. A description and justification for the new packaging system should be submitted with appropriate letters of authorization. In addition, you should revise the drug product labeling to state that the vials should be protected from light.
3. Based on the limited stability data provided in the application and the out-of-specification (OOS) results for particulate matter observed at accelerated conditions, an expiration date of NMT (b) (4) would be appropriate for the drug product when stored at controlled room temperature, protected from light. You are encouraged to determine the cause of the OOS results for particulates under accelerated conditions, and if necessary, you should consider a different container closure for storage of your drug product.

Additional issues that would need to be addressed postmarketing, if the product were to be approved:

Clinical

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. This information is requested and could be obtained through the establishment of a surveillance program (e.g., registry) to evaluate the effects of prenatal exposure in adolescents and young adults. Submit your proposal as to how these data would be obtained.
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. Children who screen positive for developmental delay should have a formal psychometric assessment and an additional assessment by a neurologist.

Clinical Pharmacology

In planning your subsequent clinical trial(s), the following pharmacokinetic elements should be considered as part of the design to allow for better understanding of HPC pharmacokinetics and optimal dosing:

- Characterize the pharmacokinetics of HPC and its metabolites in pregnant women (including both plasma and urine concentrations) at several periods throughout the pregnancy.
- Assess the HPC exposure-response relationship and the effect of body weight on the pharmacokinetics of HPC via sparse sampling of all subjects.
- Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on HPC pharmacokinetics.

Further comments on labeling are deferred until the above deficiencies are addressed.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration, regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Reproductive and Urologic Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this Division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 796-2130.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Scott Monroe
10/20/2006 03:48:19 PM

Deguia, Eufrecina P

From: Colangelo, Kim M
nt: Thursday, October 12, 2006 5:04 PM
: Deguia, Eufrecina P
Cc: Mercier, Jennifer L
Subject: RE: Questions regarding Gestiva

Freshnie,

I discussed your application yesterday with ORP and OCC. Please note the following (some of these issues have previously been identified to you, but for completeness, I am including them again):

(b) (5)

Please DFS your filing review once revised. You are cleared for action on this one! (Note - we will need to reclear this upon resubmission.)

Please let me know if you have any questions.

From: Deguia, Eufrecina P
Sent: Tuesday, October 03, 2006 12:40 PM
To: Colangelo, Kim M
Cc: Mercier, Jennifer L
Subject: RE: Questions regarding Gestiva

Hi Kim,

(b) (6)

From my review of old files and original submissions of these 2 NDAs (10-347 and 16-911), which I requested from CDER archives, NDA 10-347 was approved in 1956
for the treatment of habitual and recurrent abortion, threatened abortion and post-partum after pains. In 1972, it was also approved for the treatment of endometrial cancer,
management of amenorrhea and abnormal uterine bleeding as NDA 16-911. NDA 16-911 was submitted as a supplement but according to the Acknowledgement
Letter issued by the Agency on March 18, 1970, the application was regarded as an original NDA because of the entirely new indication so it was assigned a new NDA #.

The proposed product is similar to the Delalutin, same formulation (per CMC Final Review).

After notification by Bristol-Myers Squibb that Delalutin was no longer marketed, NDAs 10-347 and 16-911 were withdrawn without prejudice by the Agency
(Federal Register 2000). From what I gathered from previous minutes, the review team must have gone back to the regulatory history of the Delalutin and determined
that the products were not withdrawn due to safety concerns. From the old records, the reason for withdrawal was solely due to the discontinuance of marketing of

the product, no mention of efficacy concerns whatsoever.

Kim, I hope I came close to answering your questions. As you know, this is not in my drug group at all. Jen asked me to help out when this came because of heavy workload for her group. I had no idea at all about this drug. The information I am providing is a result of digging in the archives.

Please let me know if you have further questions and when I can finalize my Filing Review (incorporating your edits).

Thank you so much again for your input.

Warm Regards.

Freshnie

From: Colangelo, Kim M
Sent: Monday, October 02, 2006 3:20 PM
To: Deguia, Eufrecina P
Subject: Questions regarding Gestiva

Freshnie,

Adeza references two applications for the Delalutin product: NDA 10-347 for treatment of benign gynecological abnormalities, and NDA 16-911 for use in advanced adenocarcinoma of the uterus corpus. Can you please tell me what the difference is in these two applications? I ask because if it were solely a new indication, we would not need a second NDA (16-911); the advanced adenocarcinoma indication would have been an efficacy supplement to NDA 10-347.

If the products differ somehow, how does the currently proposed product compare to the products approved in these applications? Are there differences in formulation between them? Both Delalutin products are listed in the Orange Book (in the discontinued products section) as being 125 mg/mL and 250 mg/mL (with the proposed product at 250 mg/mL), but there is no additional information.

Also, can you tell me if, during the team's review of the available documents for the two Delalutin applications, you also ascertained whether the product/applications were withdrawn for reason of efficacy? (You explicitly state in your filing review that the team determined that the product(s) was/were not withdrawn due to safety concerns.) I know that the efficacy of Delalutin isn't directly applicable to Gestiva (I know Adeza did at least one trial to demonstrate efficacy). (b) (5) [redacted])

Please call if you have questions, and thank you in advance!
Kim

Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs
CDER/FDA

10903 New Hampshire Ave.
Bldg #22, Room 6300
Silver Spring, MD 20993-0002

301-796-0700 (OND IO main)
301-796-0140 (direct)
301-796-9856 (facsimile)

Kim.Colangelo@fda.hhs.gov

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 10, 2006

TO: File

FROM: Eufrecina DeGuia, Regulatory Health Project Manager

SUBJECT: **NDA 21-945, Gestiva (17-alpha hydroxyprogesterone caproate) 250mg/mL**

See attached request for additional information for NDA 21-945 that was discussed during the teleconference of October 5, 2006 with the sponsor. This Information Request was sent via email on October 6, 2006, from Dr. Scott Monroe, Acting Director, Division of Reproductive and Urologic Products to Mr. Robb Hesley, Vice President, Business Development, Strategic Projects, Adeza Biomedical.

October 6, 2006

NDA 21-945

Robb Hesley
V.P. Business Development
Adeza Biomedical

We are requesting the following information as part of our on-going review of NDA 21-945.

1. Provide for each center in clinical trial 17-CT-002 the number and proportion of preterm births in each treatment group for gestational ages <37 weeks, <35 weeks, and <32 weeks. In addition to providing the center by center data, provide a summary of the same outcome data for the study as a whole excluding the data from the Alabama center.

   Provide the data in a format identical or similar to that shown below, in both PDF and Excel or SAS transport files.

Center Name	**Delivery**	**17OHP**	**Vehicle**
		n (%)	**n (%)**
Alabama			
	$<37^0$		
	$<35^0$		
	$<32^0$		
Tennessee (etc.)			
	$<37^0$		
	$<35^0$		
	$<32^0$		
All Centers minus Alabama			
	$<37^0$		
	$<35^0$		
	$<32^0$		

2. Provide in a listing format the following information for each subject randomized into study 17-CT-002 (the ITT population): center, subject ID, treatment group, gestational age at delivery or last visit, outcome of the pregnancy, and whether lost to follow up. Provide this information in a SAS transport or Excel data file in the following format.

Center	Subject ID	Treatment Group	Gestational age at delivery or last visit (for subjects lost to follow up)		Outcome [B]	Lost to Follow Up [C]
			Weeks [A]	Days		

A. Express as a whole number and decimal (i.e., 27 wks 2 days = 27.29)
B. Survived or died
C. Identify the 4 subjects lost to follow up

3. Provide the rationale for your conclusion that the outcome of the clinical trial is not being driven by an especially positive outcome at the Alabama center.

Please submit your response to both the NDA and directly to me by e-mail (scott.monroe@fda.hhs.gov) as soon as possible and no later than COB on October 12, 2006. Should you need additional clarification, please contact me either by e-mail or at 301-796-0959.

Please acknowledge receipt of this request.

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/s/

Eufrecina deGuia
10/11/2006 09:15:19 AM
CSO

Deguia, Eufrecina P

From: Blay, Roy A
Sent: Thursday, September 21, 2006 11:19 AM
To: Deguia, Eufrecina P
Subject: RE: DSI inspection for NDA 21-945 Gestiva

Dear Freshnie,

Current status of the inspections for NDA 21-945 is as follows:

Dr. Hauth: the inspection was classified NAI and a letter has been sent to the investigator

Dr. Sibai: several delays in this inspection due to the lack of availability of the investigator and/or the study coordinator. The inspection should be conducted in the second week of October. I have asked that the results of this inspection be forwarded to me ASAP.

Dr. Varner: the inspection is complete, I have received the Form 483 and am awaiting the actual inspection report. The 483 indicates a number of deficiencies that I cannot fully assess until I can review the inspection report. I've asked the field office to forward the inspection report ASAP.

I hope this is helpful. Pleas call me if you have any questions or concerns.

Roy
(301) 827-7389

From: Deguia, Eufrecina P
Sent: Thursday, September 21, 2006 8:26 AM
To: Blay, Roy A
Subject: DSI inspection for NDA 21-945 Gestiva

Hi Roy,

Any update on the status of the audits? We are having our 5th month status meeting at 12:30 and it would be nice to update Scott on the progress of the inspection.

Thanks. I look forward to hearing from you.

Freshnie

MEMO **FOOD AND DRUG ADMINISTRATION**

Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research

Date:	September 21, 2006
Reviewer:	Lynnda Reid, Ph.D. Supervisory Pharmacologist
NDA #/SS#/date:	21-945 / N000 / April 20, 2006
Sponsor:	Adeza Biomedical
Drug Product:	17 alpha-hydroxyprogesterone caproate
Indication:	Prevention of recurrent preterm birth

Drug History: The subject of this NDA is 17 Alpha-Hydroxyprogesterone Caproate Injection, 250 mg/mL for the proposed indication of (b) (4) recurrent preterm birth. The use of 17 alpha-hydroxyprogesterone caproate will be limited to pregnant women with a history of at least one spontaneous preterm birth at less than 37 weeks of gestation.

17 alpha-hydroxyprogesterone caproate, hereafter referred to as 17-HPC, was first approved and marketed as Delalutin (NDA 10-347) in 1956 for the treatment of habitual and recurrent abortion, threatened abortion and post-partum after pains. In 1972 it was also approved for the treatment of endometrial cancer, management of amenorrhea and abnormal uterine bleeding, and for the production of secretory endometrium and desquamation (NDA 16-911). After notification by Bristol-Myers Squibb Co. that Delalution was no longer marketed, NDAs 10-347 and 16-911 were withdrawn without prejudice by the FDA (Federal Register 2000). 17-HPC continues to be used in women at high risk for recurrent preterm birth and is available through compounding pharmacies in the U.S.

Meetings were held between Adeza Biomedical and DRUP on 30 January 2004, 5 April 2004 and 16 July 2004 under IND 68,108 to discuss the overall drug development program leading to a submission of a 505(b)(2) NDA. A Pre-NDA meeting with the applicant was held on 27 June 2005. At these meetings Adeza was told that no additional nonclinical studies would be needed to file a NDA. At that time, it was thought that there was sufficient clinical and nonclinical safety data to support the safety of 17-HPC.

After a review of the published nonclinical data it was found that there were significant deficiencies in the scope and quality of the reported nonclinical studies. Most of the nonclinical studies were old and did not comply with either Good Laboratory Practices or

conform to current CDER and ICH guidances. The primary deficiencies in the nonclinical studies included insufficient numbers of animals, use of unconventional species, lack of any PK/ADME data, correlation between gestational timing of exposures and pregnancy outcome, and lack of developmental studies in offspring exposed in utero. In addition there were conflicting findings in the studies, regarding 17-HPC embryolethality and potential differences in species sensitivity, which have not been adequately addressed and remain safety concerns.

Teratogenicity: There were no published reports of teratogenic effects in any species studied including non-human primates. However, potential adverse effects on learning and behavior have not evaluated in any of the reviewed nonclinical literature.

Supranormal doses of 17-HPC (100 to 200 times the MRHD), delivered by various routes of administration, have been associated with impairment of reproductive performance in male rats exposed to 17-HPC in utero, maternal and fetal deaths in mice and rats, retarded fetal growth in rats, and fetal deaths in monkeys.

Impairment of reproductive performance in adult male rats exposed in utero may be associated with decreased enzyme activity levels (3 ß-hydroxysteroid dehydrogenase and 17 ß-hydroxysteroid dehydrogenase) of the testis. Decreases in cauda epididymal sperm counts and motility were observed, as well as decreased serum testosterone levels. Serum FSH and LH levels were increased.

There was no reported evidence of androgenic or glucocorticoid activity at supranormal doses in rats or rabbits.

Non-human primate Studies:

1) In a retrospective study performed by Courtney and Valerio (1968) in breeding colonies of Rhesus monkeys routinely treated with 17-HPC for threatened abortions, there were no findings of adverse effects on development. The results of treatment with 17-HPC were reported for a total of 15 monkeys: 14 dosed at 125 mg/day and 1 at 250 mg/day for 1-10 days during various stages of gestation.

Copyright Material

The nine normal births all resulted in viable neonates which survived for at least seven months. There were no signs of masculinization in the four female offspring,

and the mean weight of the nine offspring at birth was 458g, comparable to historical control birth weights. The mean gestation length, 160 days, was also comparable to controls.

2) In a prospective study by Hendrickx et al. (1987), pregnant Rhesus (*Macacca mulatta*) and Cynomologous (*Macacca fasicularis*) monkeys (n=?/group) were administered 17-HPC (i.m.) alone or combined with estradiol valerate (EV) at 7-day intervals between 20 and 146 days of gestation. Fetuses were examined after Caesarean delivery at 150±2 days. The 17-HPC dose administered was only given in relationship to the human dose as 0.01 to 10 times the human equivalent dose (HED). The pregnant animals were observed regularly for adverse clinical signs, food intake and vaginal bleeding. Immediately after delivery all fetuses were weighed, morphometrically measure, and examined for malformations. All visceral organs were examined in situ prior to removal, then weighed and preserved in 10% formalin.

   Embryolethality was observed in all groups including controls, but was significantly increased (100% lethality) only in the Rhesus monkeys treated at 1X and 10X 17-HPC.

Copyright Material

Abortions/resorptions occurred between gestational days 20 and 146. No anomalies were found in any of the surviving fetuses examined at Caesarean-section. All fetal weights and measurements were within the normal range for control fetuses. There were no dose-related malformations noted.

There was no discussion by the authors regarding the apparent increase in sensitivity to 17-HPC in the Rhesus monkeys. Since PK/ADME parameters were not measured,

it is not possible to determine which strain of monkeys may be more relevant to human exposures.

Unresolved Toxicology Issues:

- Based on the information available in the published literature, it appears that high doses of 17-HPC are associated with increased embryolethality in several species. The nonclinical data provided is insufficient to calculate a no adverse effect level (NOAEL) in animals.
- There is insufficient nonclinical information on potential adverse effects on postnatal development including learning, behavior, and reproduction.

Conclusions and Recommendations: From a Pharmacology/Toxicology standpoint, this NDA is approvable. There is insufficient nonclinical data on which to base the safety of 17-HPC, especially in regards to long-term effects in offspring exposed in utero. We recommend that a thorough reproductive and developmental study be performed in accordance with ICH S5A "Guideline for Industry: Detection of toxicity to Reproduction for Medicinal Products". A multigenerational 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.

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/s/

Lynnda Reid
10/5/2006 03:16:54 PM
PHARMACOLOGIST

MEMORANDUM OF TELECON

DATE: September 6, 2006

APPLICATION NUMBER:
NDA 21-945 - 17α-hydroxyprogesterone caproate injection (17OHP-C), 250mg/mL

BETWEEN:

Robb Hesley, V.P. – Business Development, Strategic Projects
Durlin Hickok, M.D., M.P.H. – Vice President, Medical Affairs
Catherine Williams, M.P.H., RAC – Director, Clinical and Regulatory Affairs
Phone: (b) (4)
Representing: Adeza Biomedical Corporation

AND

Scott Monroe, M.D. – Acting Director
Barbara Wesley, M.D. – Medical Officer
Eufrecina DeGuia – Regulatory Health Project Manager
Lisa Soule, M.D. – Medical Team Leader
Representing: Division of Reproductive and Urologic Products

SUBJECT: Exchange of information post-Advisory Committee (AC) Meeting - The following summarizes the Division's comments made during the teleconference and also includes some additional information not provided during the teleconference.

- The Division agrees with the Committee's recommendation that further study is needed to evaluate the potential association of 17OHP-C with increased risk of second trimester miscarriage and stillbirth. The Applicant is strongly encouraged to explore with potential investigators clinical trial designs to determine whether these pregnancy losses are related to the use of 17OHP-C.
- The Division also agrees with the Committee that long-term safety data from children (at least through puberty), whose mothers were treated with 17OHP-C, should be obtained, with a particular emphasis on the status of the reproductive system.
- The Applicant is strongly encouraged to explore potential study designs to provide additional statistical support for the effectiveness of 17OHP-C to reduce the incidence of preterm birth (PTB) particularly at <35 and <32 weeks gestational age. Ideally, the study would also provide statistical support for the effectiveness of 17OHP-C to reduce morbidity and possibly mortality associated with PTB. The Division recognizes the challenges of such a study, particularly the use of a placebo arm. The Applicant should discuss with potential investigators, either individually or in small groups, potential study designs that would provide further evidence of effectiveness of 17OHP-C. The content of these discussions should be fully documented, particularly whether investigators would be willing to

participate in a clinical trial that included a placebo arm. These discussions should be conducted with investigators within the Maternal-Fetal Medicine Network Units and with investigators who are not within this network.

- If a clinical trial with a placebo arm is judged to be not feasible, based on discussions with potential investigators, the Applicant should explore the feasibility of other adequate and well-controlled clinical trial designs that could provide statistically significant information supporting the effectiveness of 17OHP-C in reducing the incidence of PTB at <35 and <32 weeks gestational age.
- The Division requests that the sponsor conduct a multi-generation reproductive toxicology study for 17OHP-C. This is a standard regulatory requirement for drugs that are indicated for use in pregnant women.

Some of the issues listed above will need to be resolved before this Application could be approved.

(See attached appended electronic signature page)

Scott Monroe, M.D.
Meeting Chair

Concurrence: LSoule 091506; JMercier091706; SMonroe9.28.06

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/s/

Scott Monroe
9/29/2006 07:12:13 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 15, 2006

TO: File

FROM: Eufrecina DeGuia, Regulatory Health Project Manager

SUBJECT: **NDA 21-945, Gestiva (17-alpha hydroxyprogesterone caproate) 250mg/mL**

See below for the request for additional information for NDA 21-945 sent via email on October 6, 2006 to Mr. Robb Hesley, Vice President, Business Development, Strategic Projects, Adeza Biomedical.

Information Request to Adeza for NDA 21-945 (17α hydroxyprogesterone caproate)

This is a request for additional safety information from studies 17P-IF-001 and 17P-CT-002 to aid us in our review of the above referenced NDA:

1. For each of studies 17P-IF-001 and 17P-CT-002, provide a listing of each patient who developed preeclampsia and include the following information for each patient:
   - Which study patient enrolled in
   - Patient identifier
   - Gestational age when preeclampsia was first diagnosed
   - Gestational age of infant at delivery
   - Other pregnancy complications (including miscarriages or stillbirths)
   - Other Adverse events

2. Provide a listing of each patient who developed diabetes and include the information detailed in question 1, (including gestational age when diabetes was first diagnosed). In addition, specify whether the patient developed gestational diabetes or newly diagnosed type II diabetes.

3. Provide a list of each patient who had a diagnosis of oligohydramnios and include information detailed in question 1, (including gestational age when oligohydramnios was first diagnosed).

4. Provide a list of each patient who became pregnant as a result of any artificial reproductive technology and include information detailed in question 1. In addition, specify what type of reproductive technology was used.

5. Please provide narratives for the 11 patients who discontinued in study 17P-CT-002.

As a follow-up to your e-mail regarding the conference call, we are requesting that you provide us with the total number of patients who received the "screening injection without enrolling in the study, and further detail the number/percent who experienced injection site reactions and the number/percent who subsequently declined enrollment into the study due to injection site reactions.

Please provide us with the information requested above by close of business, Aug 23, 2006.

October 6, 2006

NDA 21-945

Robb Hesley
V.P. Business Development
Adeza Biomedical

We are requesting the following information as part of our on-going review of NDA 21-945.

1. Provide for each center in clinical trial 17-CT-002 the number and proportion of preterm births in each treatment group for gestational ages <37 weeks, <35 weeks, and <32 weeks. In addition to providing the center by center data, provide a summary of the same outcome data for the study as a whole excluding the data from the Alabama center.

   Provide the data in a format identical or similar to that shown below, in both PDF and Excel or SAS transport files.

Center Name	**Delivery**	**17OHP**	**Vehicle**
		n (%)	**n (%)**
Alabama			
	$<37^0$		
	$<35^0$		
	$<32^0$		
Tennessee (etc.)			
	$<37^0$		
	$<35^0$		
	$<32^0$		
All Centers minus Alabama			
	$<37^0$		
	$<35^0$		
	$<32^0$		

2. Provide in a listing format the following information for each subject randomized into study 17-CT-002 (the ITT population): center, subject ID, treatment group, gestational age at delivery or last visit, outcome of the pregnancy, and whether lost to follow up. Provide this information in a SAS transport or Excel data file in the following format.

Center	Subject ID	Treatment Group	Gestational age at delivery or last visit (for subjects lost to follow up)		Outcome [B]	Lost to Follow Up [C]
			Weeks [A]	Days		

A. Express as a whole number and decimal (i.e., 27 wks 2 days = 27.29)
B. Survived or died
C. Identify the 4 subjects lost to follow up

3. Provide the rationale for your conclusion that the outcome of the clinical trial is not being driven by an especially positive outcome at the Alabama center.

Please submit your response to both the NDA and directly to me by e-mail (scott.monroe@fda.hhs.gov) as soon as possible and no later than COB on October 12, 2006. Should you need additional clarification, please contact me either by e-mail or at 301-796-0959.

Please acknowledge receipt of this request.

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/s/

Eufrecina deGuia
10/11/2006 09:11:11 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

DISCIPLINE REVIEW LETTER

Adeza Biomedical
Attention: Durlin E. Hickok, M.D., M.P.H.
Vice President, Medical Affairs
1240 Elko Drive
Sunnyvale, CA 94089

Dear Dr. Hickok:

Please refer to your April 14, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gestiva (17α-hydroxyprogesterone caproate injection), 250mg/mL.

Our review of the Chemistry, Manufacturing and Controls section of your submission is ongoing and we have identified the following deficiencies:

1. Confirm that each in-coming excipient batch is tested for identity (at a minimum) before use in the manufacture of the 17P drug product.

2. Revise your impurity specifications to conform to ICH format: specified impurities, any individual unspecified impurity (with a limit of not more than the ICH Q3B identification threshold), and total impurities (including specified and unspecified impurities).

3. Provide a commitment date for the completion of the HPLC method validation for benzyl benzoate purity and for the establishment of acceptance criteria for impurities in the benzyl benzoate raw material. Until that time, your proposed "alert" limits should be used as the specification limits for impurities in the benzyl benzoate raw material.

4. Provide a commitment date for completion of the method validation for *Benzyl Alcohol Content by HPLC*. You stated that robustness data would be generated at a later date (prior to process validation and commercial batch production).

5. Provide a commitment date for completion of the method validation for *Hydroxyprogesterone Caproate Content, Purity, and Identity Determination in In-Process and Final Drug Product Samples by HPLC*. You stated that robustness and forced degradation data would be generated at a later date (prior to process validation and commercial batch production).

6. In the table on page 230, Vol. 2 (page 201 of 485), two impurities (b) (4) (b) (4)) are observed (b) (4) at levels at or above (b) (4) in the three drug product batches tested (Lots 901357, 901379, and 901431). In addition, in your report entitled "*Discussion of 17 alpha-Hydroxyprogesterone Caproate Injection, USP, 250 mg/mL, Observed Individual Unidentified Impurities*" on page 347 of 374 in Vol. 3, impurities at (b) (4) showed levels above the ICH Q3B identification and qualification thresholds within the first 3 months of storage at 25°C/60% RH and 40°C/75% RH in the three drug product batches (Lots 901357, 901379, and 901431). Since these impurities are present at levels at or above the ICH Q3B identification and qualification thresholds, please identify and specify these impurities or provide justification for not doing so.

7. Provide an explanation for the decrease in assay for the drug product photostability test samples versus the control samples after exposure to light (both Stage 1 and Stage 2). If the decrease in assay cannot be explained, alternative drug product packaging should be considered to provide additional light protection.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 796-0881.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
7/31/2006 05:39:44 PM
Chief, Branch III

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: CDER ODE CONSULTS
Or Office of Surveillance and Epidemiology (OSE)
Attention: Sammie Beam, Project Manager

FROM: **Freshnie DeGuia, Regulatory Project Manager**
Division of Reproductive and Urologic Products
(301) 796-0881

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 20, 2006		21-945	New NDA	April 20, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gestiva (17-α hydroxyprogesterone caproate), 250 mg/mL	**PRIORITY**		August 20, 2006

NAME OF FIRM: ADEZA BIOMEDICAL

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- x ADVERSE REACTION REPORTS
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- X REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **This is a consult request from the Division of Reproductive and Urologic Products. NDA 21-945 Gestiva (17-α hydroxyprogesterone caproate, 17OHP-C), a priority review NDA, is for the use of 17OHP-C for (b) (4) recurrent pre-term birth. The review division is requesting that you review the AERS database for all adverse event reports involving any compounded preparations of 17OHP-C used in pregnant women from June, 2003 through the present. Because this application is going to be presented to an Advisory Committee on August 29, 2006, we request that the consult review be completed on or before August 20, 2006. See attachment for additional information. Contact Dr. Barbara Wesley for additional information.**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

The National Institute of Child Health and Development (NICHD) created the Maternal Fetal Medicine Units (MFMU) Network in 1986 to focus on clinical questions in maternal fetal medicine and obstetrics. The MFMU Network conducted a multicenter, randomized placebo-controlled, double-masked study on the efficacy and safety of 17alpha-hydroxyprogesterone caproate (17OHP-C) in pregnant women with a previous preterm birth. The results of this study were published in the New England Journal of Medicine on June 12, 2003. Women were enrolled at 19 clinical centers at 16 to 20 weeks of gestation and randomly assigned in a 2:1 ration to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil (castor oil) placebo; the primary outcome was preterm delivery before 37 weeks of gestation. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks by almost 30%.

The drug substance (17OHP-C) used in this study was previously approved under the trade name of Delalutin® for gynecologic indications. In the 1970s and 1980s this drug was also used off-label to prevent miscarriage in early pregnancy (prior to 20 weeks gestation); however the data to support this use was sparse and the practice discontinued. Marketing of Delalutin® was discontinued in the early 1990s because of the decrease in use. Although several generic versions of Delalutin were also marketed at one time, none are currently marketed in the U.S. Immediately after the publication of the above referenced study, physicians began to prescribe this drug for preterm labor prevention using compounded preparations prepared by various pharmacies around the nation. This practice occurred in part because the study received major publicity and in part because this practice was supported by the American College of Obstetricians and Gynecologists

NDA 21-945 was submitted to the Agency by Adeza using the clinical trial conducted by the MFMU Network. The proposed name is Gestiva. The applicant has been granted a priority review with a goal date of October 20, 2006. This application will be taken to the Division's Advisory Committee on Aug. 29, 2006.

The review division is requesting that you review the AERS database for *all adverse event reports* involving any compounded preparations of 17OHP-C used in pregnant women from June, 2003 through the present. We are requesting that you submit your findings to us by Aug. 20, 2006.

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/s/

Eufrecina deGuia
7/20/2006 11:39:18 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945 **FILING COMMUNICATION**

Adeza Biomedical
Attention: Durlin E. Hickok, M.D., M.P.H.
Vice President, Medical Affairs
1240 Elko Drive
Sunnyvale, CA 94089

Dear Dr. Hickok:

Please refer to your April 14, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gestiva (17-α hydroxyprogesterone caproate injection), 250 mg/mL.

We also refer to your presubmissions dated August 30, 2005, January 10, March 28, April 7 and 14, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on June 19, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Clinical

1. The quantity of data submitted with your application may be insufficient to enable us to adequately determine the risk/benefit ratio of your proposed drug therapy.

2. The primary protocol-defined efficacy endpoint of your clinical trial (reduction of premature birth less than 37-weeks gestation) is a surrogate endpoint for neonatal morbidity and mortality. This endpoint may not be adequate to perform a true risk/benefit analysis of your proposed therapy.

3. There appears be a potential safety signal regarding a trend towards an increase in fetal wastage (miscarriages and stillborns) in the active treatment arm. Assessing the clinical significance of this observation is difficult because of the limited number of subjects in your clinical trial.

Nonclinical Pharmacology and Toxicology

The paper entitled "Drug Efficacy Study" by the National Academy of Sciences - National Research Council, Division of Medical Sciences, dated March 13, 1956 is illegible. Please contact the Academy to obtain a legible copy.

Clinical Pharmacology

1. The submitted *in vivo* pharmacokinetic (PK) study by Onsrud et al. (1985) was done in non-pregnant, endometrial carcinoma patients using a 4-fold higher dose of 1000 mg and in limited sample size. It is not known if 17-α hydroxyprogesterone caproate (17-HPC) PK in these patients can be used to estimate the PK in the targeted population of pregnant women.

2. The metabolic pathway for elimination of 17-HPC is not established either in vitro or in vivo. Data from a drug metabolizing enzyme identification study will help to better label Gestiva for safe and effective use.

3. 17-HPC in vitro caused inhibition of several important CYP enzymes. Since 17-HPC PK in pregnant women is not known, the clinical significance of these findings is not clear. Therefore, the safety risk to both mother and fetus due to the potential drug interactions is also not known. In addition, the effect of 17-HPC on induction of CYP enzyme activity has not been examined.

4. You requested a waiver for bioavailability requirements. One method to satisfy the requirement for evidence of bioavailability as listed in 21 CFR 320.24(b)(4) is to provide "well-controlled clinical trials that establish the safety and effectiveness of the drug product". A waiver is not needed if the clinical trials submitted in the NDA are determined during the review to meet the above criteria.

Chemistry, Manufacturing and Controls

No filing issues identified.

Statistics

No filing issues identified.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Eufrecina DeGuia, Regulatory Health Project Manager, at (301)796-0881.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Scott Monroe
6/29/2006 11:31:36 AM

MEMORANDUM OF TELECON

DRAFT

(Sent to Scott 7/24. Still waiting for Concurrence.

DATE: June 20, 2006

APPLICATION NUMBER: NDA 21-945 - 17α-hydroxyprogesterone caproate injection, 250mg/mL

BETWEEN:

Robb Hesley, V.P.- Business Development, Strategic Projects
Durlin Hickok, M.D., M.P.H. – Vice President, Medical Affairs
Catherine Williams, M.P.H., RAC – Director, Clinical and Regulatory Affairs

Phone: (b) (4)
Representing: Adeza Biomedical Corporation

AND

Scott Monroe, M.D. – Acting Director
Barbara Wesley, M.D. – Medical Officer
Eufrecina DeGuia – Regulatory Project
Lisa Soule, M.D. – Medical Team Leader
Jennifer Mercier – Chief, Project Management Staff
Division of Reproductive and Urologic Products

SUBJECT: Advisory Committee Meeting Questions

The sponsor requested this teleconference to discuss and seek some clarification/guidance on the following questions regarding the upcoming Advisory Committee scheduled for August 29, 2006:

Question #1. Does the FDA have a basic agenda in mind at this time for the Advisory Committee?
Response: *As a general rule, the agenda is not disclosed prior to making it available to other members of the public on the day of the meeting. The Division, however, believes that the basic agenda will include concerns and issues about 17α-hydroxyprogesterone caproate injection, 250mg/mL, its level of effectiveness and the limited clinical data.*

Question #2. What will be the order of presenters? FDA first or Adeza first?
Answer: The *sponsor will make their presentation first before the Agency. The usual order of presentation is as follows: FDA will give a brief background, the Speakers will give an overview, followed by the sponsor, and FDA will present last.*

Question #3. Will Dr. Romero and (b) (4) be giving any presentation?
Answer: *It is not appropriate to disclose this information.*

Question #4. Should Adeza plan on presenting the medical need presentation?
Answer: *It would be helpful to present a "medical need" argument. At the moment, FDA has no plans to do so.*

Question #5. Will FDA be presenting information regarding Delalutin's previous approval and subsequent voluntary withdrawal from the market?
Answer: *FDA will not be presenting this information. The sponsor should include this in their presentation.*

Question #6. Is there a need for either FDA or Adeza to explain the regulatory requirements for a 505(b)(2) application?
Answer: *If there is a need, FDA will address this issue, not the sponsor.*

Question #7. Should Adeza provide the draft labeling for Gestiva as part of the Briefing Package?
Answer: *This is not necessary. It is premature to be mentioning or discussing labeling-related issues.*

Question #8. With regard to Post Marketing Surveillance, we are not sure what to include in the Briefing Package or prepare for Q&A since FDA and Adeza have not discussed any potential need for PMS yet.
Answer: *The sponsor is encouraged to present if they have some proposals in mind. The Division agrees to review any proposal but would need time to review any proposal that would be presented to the Committee. The sponsor indicated that they will submit their proposal in mid-July.*

Question #9. We believe there is ample precedent for NICHD to participate in the meeting (please see examples below). We would still like to consider (b) (4) (b) (4)
Answer: *Advisors and Consultants Staff reiterated that with the exception of Roberto Romero in 1998, all the individuals on the list Adeza provided were representing FDA and not the sponsor. The current regulations are less permissive that in 1998. Ethics believes* (b) (4) *participation would not be permitted under current federal statute.*

(See attached appended electronic signature page)

Scott Monroe,M.D.
Meeting Chair

Concurrence: LSoule 071506; JMercier071706

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Adeza Biomedical
Attention: Durlin E. Hickok, M.D., M.P.H.
Vice President, Medical Affairs
1240 Elko Drive
Sunnyvale, CA 94089

Dear Dr. Hickok:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Gestiva (17-α hydroxyprogesterone caproate injection, 250 mg/mL)
Review Priority Classification:	Priority
Date of Application:	April 14, 2006
Date of Receipt:	April 20, 2006
Our Reference Number:	NDA 21-925

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 19, 2006 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 20, 2006.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Belstville, MD 20705-1266

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 796-2130.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
6/1/2006 01:00:51 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Division of Drug Marketing, Advertising and Communications (DDMAC), OMP**
Attention: Corrinne Kulick, Senior Regulatory Scientist
WO Bldg 22, Room 1465

FROM: Freshnie DeGuia, Regulatory Health Project Manager
Division of Reproductive and Urologic Products
(301) 796-0881

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 11, 2006		NDA-21-945	New NDA (electronic)	April 14, 2006

NAME OF DRUG:	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
17-alpha hydroxyprogesterone caproate injection, 250mg/mL	PRIORITY	progesterone	July 10. 2006

NAME OF FIRM: Adeza Biomedical

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the label and carton and vial labeling. The review package will be hand delivered to DDMAC today. The NDA can be accessed in EDR. This NDA was submitted as a Priority Review NDA. Advisory Committee Meeting is scheduled for August 29, 2006. Reviews are encouraged to be done prior to the AC.

Thank you.
PDUFA GOAL DATE: October 20, 2006

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL x HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Eufrecina deGuia
5/11/2006 10:30:56 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Office of Pharmaceutical Science/NDMS
Attention: Jim McVey, Microbiologist
Building 21, Room 3657

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Freshnie Deguia, Project Manager
Division of Reproductive and Urologic Products
(301) 796-0881

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 2, 2006		21-945	New NDA	April 14, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
17 -Hydroxyprogesterone Caproate Injection, 2350mg/mL	PRIORITY		June 2, 2006

NAME OF FIRM: Adeza Biomedical

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This is a priority review NDA. PDUFA Goal date is October 20, 2006. Advisory Committee meeting is scheduled for August so all reviews should be near completion by that time. The NDA is available in EDR. Please review and evaluate:

For Drug Substance, the sponsor has included tests for Endotoxins and Bioburden in the NDA. The DMF (b) (4) holder plans to submit them to the DMF, but they are included in the NDA for review.

For Drug Product, manufacture is via (b) (4) Evaluation/review is needed for the manufacturing process and the release/stability specifications and acceptance criteria. Two DMFs (b) (4) are involved for which LOAs are provided. Review package will be hand delivered to Micro.

SIGNATURE OF REQUESTOR Deguia	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☒ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Eufrecina deGuia
5/2/2006 02:44:57 PM

ADEZA®

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ORIG AMENDMEN

ORIGINAL

April 20, 2006

RECEIVED

APR 21 2006

CDER White Oak DR 1

Ms. Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Update to NDA 21-945 CMC Section with Revised Drug Product Carton and Vial Labeling

Dear Ms. Mercier:

Please find enclosed 5 color copies of the drug product carton and vial labeling which has been updated since the submission of the CMC Section on March 28, 2006 to reflect the proposed GESTIVA™ trade name and product logo.

Sincerely,

Catherine A. Williams, MPH, RAC
Director, Clinical and Regulatory Affairs

enclosure

ADEZA BIOMEDICAL
1240 Elko Drive
Sunnyvale, CA
94089, U.S.A.
Tel:(408)745-0975
Fax:(408)745-0968

8 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22; Mail Stop 4447)

DATE RECEIVED: 5/4/2006 **DATE OF DOCUMENT**: 4/14/2006	**DESIRED COMPLETION DATE:** 7/2/2006 **PDUFA DATE:** 10/20/2006	**OSE REVIEW #:** 06-0134

TO: Scott Monroe, MD
Acting Director, Division of Reproductive and Urologic Products
HFD-580

THROUGH: Nora Roselle, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Felicia Duffy, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Gestiva™** (17 α-Hydroxyprogesterone Caproate) Injection 250 mg/mL **NDA #**: 21-945	**SPONSOR:** Adeza Biomedical

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Gestiva.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC has no objections to the proposed name, Gestiva, from a promotional perspective. However, DDMAC has the following comment:

(b) (4)

[redacted]

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Pre-marketing Project Manager, at 301-796-0538.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

INFORMATION REQUEST LETTER

Adeza Biomedical
Attention: Durlin Hickok, M.D., M.P.H.
Vice President, Medical Affairs
1240 Elko Drive
Sunnyvale, CA 94089
US

Dear Dr. Hickok:

Please refer to your August 30, 2005 new drug application (NDA) presubmission submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 17 hydroxyprogesterone caproate Injection (17P).

We also refer to your submission dated January 10, 2006.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. You stated that there was a 13% incidence of Bacterial Vaginosis (BV) in the study population (13% in the active treatment arm and 13% in the control arm), but there was a higher use of metronidazole in the treatment arm (10.3% vs. 5.2%).
   - What clinical/laboratory procedures were used to diagnose BV in the study?
   - What percent of the subjects who were treated with metronidazole had BV vs. trichomonas?
   - Provide a listing of subjects who had a diagnosis of BV and who had a spontaneous abortion, stillborn, preterm premature rupture of the membranes (pPROM), neonatal sepsis, or cerebral palsy.
   - Populate the table below:

Study Subjects with Bacterial Vaginosis

Outcome	17 P Subjects with BV n (%)	Placebo Subjects with BV n (%)
Spontaneous Abortion		
Stillborn		
pPROM		
Neonatal Sepsis		
Cerebral Palsy		

2. How do you explain the following:
   Of the total subjects in the 17P arm: 21.6 % delivered at <35 wks but only 12.9% received tocolytic therapy and only 14.2% received parental corticosteroids; Of the total subjects in the control arm: 30.7% delivered at < 35 wks but only 11.8% received tocolytic therapy and only 13.7% received parental steroids?

3. Why does the article published in the New England Journal of Medicine on June 12, 2003 (348;24) have different values than those in the NDA submission for total tocolytic use (17% in the 17P arm and 15.9% in the control arm) and total parental steroid use (17.3% in the 17P arm and 19.7% in the control arm)? Were there any other indications for parental steroid use other than to enhance fetal lung maturity?

4. Populated the table below:

Preterm Deliveries (PTD) < 34 weeks in Study Pregnancy

Preterm Deliveries (PTD)	17P (N=310) n (%)	Placebo (N=153) n (%)
Total (PTD) (due to any cause) $32^{0/7}$-$33^{6/7}$ wks $30^{0/7}$-$31^{6/7}$ wks $28^{0/7}$-$29^{6/7}$ wks $26^{0/7}$-$27^{6/7}$ wks $24^{0/7}$-$25^{6/7}$ wks <24 wks		
*SPTD due to **PTL $32^{0/7}$-$33^{6/7}$ wks $30^{0/7}$-$31^{6/7}$ wks $28^{0/7}$-$29^{6/7}$ wks $26^{0/7}$-$27^{6/7}$ wks $24^{0/7}$-$25^{6/7}$ wks <24 wks		
SPTD due to pPROM $32^{0/7}$-$33^{6/7}$ wks $30^{0/7}$-$31^{6/7}$ wks $28^{0/7}$-$29^{6/7}$ wks $26^{0/7}$-$27^{6/7}$ wks $24^{0/7}$-$25^{6/7}$ wks <24 wks		
Indicated Deliveries $32^{0/7}$-$33^{6/7}$ wks $30^{0/7}$-$31^{6/7}$ wks $28^{0/7}$-$29^{6/7}$ wks $26^{0/7}$-$27^{6/7}$ wks $24^{0/7}$-$25^{6/7}$ wks <24 wks		

*SPTD= Spontaneous Preterm Deliveries
**PTL = Preterm Labor

If you have any questions, call me at 301-796-0957.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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 /s/
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Jennifer L. Mercier
3/24/2006 08:54:17 AM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA PRESUBMISSION ACKNOWLEDGEMENT

NDA 21-945

Adeza Biomedical
Attention: Durlin E. Hickok, M.D., M.P.H.
Vice President, Medical Affairs
1240 Elko Drive
Sunnyvale, CA 94089

Dear Dr. Hickok:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product:	17 α-Hydroxyprogesterone Caproate Injection, 250/mg/mL
Date of Submission:	August 30, 2005
Date of Receipt:	September 1, 2005
Our Reference Number:	NDA 21-945

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete. Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 796-0933.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
9/28/2005 12:06:30 PM

Teleconference Meeting Minutes

Date: June 27, 2005 **Time:** 1:00 1:50 PM **Location:** Parklawn 17B-43

Application: PIND 68,108 **Drug Name:** 17-hydroxyprogesterone caproate

Indication: Prevention of recurrent preterm birth

Sponsor: Adeza Biomedical

Type of Meeting: Pre-NDA Meeting (Clinical)

Meeting Chair: Scott Monroe, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees

Donna Griebel, M.D. Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Scott Monroe, M.D. Clinical Team Leader, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. Clinical Team Leader, DRUDP (HFD-580)
Barbara Wesley, M.D. Medical Officer, DRUDP (HFD-580)
Phill Price, M.D. Medical Officer, DRUDP (HFD-580)
Lisa Soule, M.D. Medical Officer, DRUDP (HFD-580)
John Hunt, Ph.D. Deputy Director, Division of Pharmaceutical Evaluation II, Office of Clinical Pharmacology and Biopharmaceutics (OCPB; HFD-870)
Kate Meaker, M.S Statistical Reviewer, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Jennifer Mercier Chief, Project Management Staff, DRUDP (HFD-580)

External Participants

Emory Anderson President and CEO, Adeza Biomedical
Durlin Hickok, M.D., M.P.H. VP Medical Affairs, Adeza Biomedical
Robb Hesley Vice President Strategic Projects
(b) (4)
(b) (4)
(b) (4)
Catherine Williams Director, Clinical and Regulatory Affairs
(b) (4)

Objective

To provide guidance for the Sponsor regarding the clinical section of their planned NDA for the prevention of recurrent preterm birth.

Background
Adeza is planning to submit a 505(b)(2) NDA for the use of 17-hydroxyprogesterone caproate (17P) for the prevention of recurrent preterm birth. The NDA will be based upon (1) information available in the literature regarding preclinical safety findings for 17P and clinical safety finding when 17P has been used for the treatment or prevention of gynecological or obstetrical disorders and (2) data from a NIH sponsored clinical trial for the prevention of recurrent preterm birth.

SPONSOR'S QUESTIONS AND THE DIVISION'S RESPONSES

Human Pharmacokinetics and Bioavailability

1. ***With reference to Information Package section 2.6, does the Division agree that available published pharmacokinetic information can be provided in the Clinical Pharmacology subsection, and that a separate NDA section for Human Pharmacokinetics and Bioavailability is not required***?

Division Response

- According to 21 CFR 314.50 (d)(3), a Human Pharmacokinetics and Bioavailability section is required for an NDA application. A primary component of this section should include addressing the similarity between the drug product used in the NIH sponsored clinical trial and the to-be-marketed formulation.
- In addition, to understand the drug pharmacokinetics (PK) and for appropriate information for the package insert, this section should include available PK information addressing the Absorption, Distribution, Metabolism, Excretion, PK in Target and Special Populations, and Drug Interactions. Studies that provide the following kinds of information for 17P can be obtained from the literature. For submitted publications, the Sponsor should provide, in addition to a full copy of each publication, a brief summary of what each publication addresses.
  - PK in the target population (e.g. single/multiple doses, accumulation)
  - In vitro metabolism characterization
  - PK in special populations (e.g., hepatic/renal insufficiency)
  - Exposure-response analyses (e.g., concentration-response analysis) to identify the optimal dose(s) for safety & efficacy
  - The potential for QT prolongation

Additional Comments and Discussion

- There should be an assessment of the formulation similarity between the product used in the Norwegian PK study published in 1985 (and for any other formulations that were used in other submitted publications) and the proposed to-be-marketed formulation.
- In the event that additional safety/efficacy studies are conducted, sparse PK sampling may be needed to address unanswered PK issues.

- The Sponsor was asked if they had information about the disposition of the caproate portion of the proposed drug product.
  Sponsor's Response. The Sponsor stated that they do not know the pharmacokinetics or disposition of the caproate portion of the 17P molecule and that they are not aware of any PK data for the ADME section of the label.

Clinical Efficacy

2. ***Does the Division agree with Adeza's plan to provide an abbreviated report for the 133 patients who received an initial formulation (i.e., the drug product manufactured by (b) (4) which was subsequently recalled) of 17P in the NICHD study?***

Division Response

- You may follow the FDA Guidance for Industry: "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications" with the additional inclusion of line listings, which you have indicated that you will provide.
- We may request additional analyses based on our review.

Clinical Safety

3. ***Can the Division recommend any drug class specific labeling considerations for use in developing draft labeling for Adeza's 17P product?***

Division Response

- We cannot make any recommendations at present.

4. ***Does the Division agree with Adeza's plan to provide the table of adverse events from the NICHD study by MedDRA higher level and preferred term instead of system organ class and preferred term?***

Division Response

- The Division prefers that you include system organ class headers as well as "higher level" and preferred terms.
  Sponsor's Response. The Sponsor stated that they would do this.
- The proposed format for Adverse Events Listings is not adequate. Listing No. 7 (Appendix 3) should include the following additional information for each reported adverse: (1) start and stop dates (expressed as calendar date, study day (i.e., treatment day), and gestational age; (2) relationship to treatment; (3) severity; (4) treatment for adverse event; and (5) outcome of adverse event.
  Sponsor's Response. The sponsor stated that the NICHD did not collect this additional data for adverse events.
  - The Division stated that the absence of this data would be a review issue.

5. ***Does the Division agree with Adeza's plan to discuss fetal/infant morbidity and mortality in both the safety and efficacy sections of the report and summaries?***

   Division Response
   - Yes.

6. ***With reference to Section 2.8.2, does the Division agree with Adeza's definition of all undesirable treatment outcomes?***

   Division Response
   - Yes for the treatment and immediate post treatment phases of the clinical trial.
   - For the 2-year post treatment follow up component, the Division requests that the Sponsor provide information regarding all clinically significant post discharge adverse events, including all outcomes related to neurodevelopmental delay (sensory, motor, or early cognitive) through the end of 2 years or at the last infant assessment.

Additional Information

7. ***Does the Division agree that the literature on the effects of 17P in other indications, such as use for luteal phase support during in vitro fertilization-embryo transfer (IVF-ET) procedures, contraception in conjunction with estradiol, or the treatment of endometrial or breast cancer, are not applicable to this submission, and will not be included in the NDA?***

   Division Response
   - Yes with the following exceptions. The Division requests that the Sponsor include all articles that discuss any outcomes of pregnancy such as studies related to luteal phase support (during either spontaneous menstrual cycles or IVF-ET procedures) and prevention of early pregnancy loss. This information is needed to support the safety of 17P for the proposed indication.

8. ***With reference to Section 2.8.2, will the Division file and review the NDA without the salivary progesterone and estradiol results***?

   Division Response

   - Yes, but the Division seeks additional information about these samples. When during the course of the study were these samples collected and could they be assayed for 17 OH progesterone (17OHP) concentrations?
     Sponsor's Response. The Sponsor stated that the salivary samples were obtained at baseline and that they did not have an assay for salivary 17OHP. The Sponsor also stated that there were no retained blood samples that could be used for the measurement of 17OHP concentrations.

Statistical

9. ***The protocol for the NICHD study was not designed to provide statistical power for a determination of efficacy at <32 weeks of pregnancy. With reference to Appendix 3, Statistical Analysis Plan, does the Division agree with Adeza's analysis of this FDA proposed additional endpoint?***

   Division Response
   - Yes, but we have the option to request additional analyses and tables.

10. ***Adeza plans to submit electronic clinical data and analysis datasets for clinical studies as SAS transport files, along with annotated case report forms and the define PDF.file, but will not be following the CDISC format. Does the Division have any issues with accepting the 17P clinical data in this format?***

    Division Response
    - The Division requests that the Sponsor submit electronic data in accordance with the Guidance for Electronic Documents.

11. ***With reference to Appendix 3, Statistical Analysis Plan and mock tables for the final clinical study report, ISE, and ISS; are these tables sufficient to permit NDA review, or are additional data tables required***?

    Division Response
    - The proposed tables appear to be adequate for submission with the following exceptions:
      - Table 2 should be more detailed in terms of reasons for subject withdrawal (e.g., categories labeled "non-clinical reason" and "physician stopped" should be supported by a listing of the actual reasons for withdrawal.
      - In regard to adverse events, the Division requests separate tables for all adverse events, drug-related adverse events, serious adverse events, and adverse events leading to premature termination.
      - The Division also requests that the Sponsor provide listings and summary tables for chemistry and hematology values. The tables should provide (1) mean, median and range values at each time point as well as (2) changes from baseline.
    - During its review of the NDA, the Division is likely to request additional analyses and tables.
      Sponsor's Response. The Sponsor stated that most of the requested adverse event data and laboratory safety data could not be provided because the data had not been collected as part of the NIH sponsored clinical trial.

12. ***With reference to Section 2.11.1, does the Division agree with the definition and organization of the case report tabulations? Does the Division require Adeza to provide Patient Profiles for patients in 17P-CT-002 (Section 2.11.2)?***

Division Response

- The Division will not require case report tabulations assuming that all of the data of interest (e.g., demographic data, pregnancy outcomes, adverse events, laboratory data, and reasons for termination) are provided electronically in SAS transport format.
- The Division requests that the Sponsor provide narratives for patients who experienced a serious adverse event, terminated prematurely because of an adverse event, or had a pregnancy outcome that was associated with neonatal death, significant neonatal morbidity, or an intrauterine death.
- The Division also requests narratives for all neonates who had significant morbidity.

Pediatric Studies

13. Does the Division agree that the Pediatric Studies section is not applicable to 17P NDA and that Adeza should request a Waiver from the Agency?

Division Response

- The Division agrees that the Sponsor should submit a request for a pediatric waiver.

NDA Submission and Review Process

14. Does the Division agree with the proposed schedule for submission of NDA Reviewable Units discussed in Section 3? Can the Division provide an NDA number to facilitate identification and tracking of these Reviewable Units?

Division Response

- The schedule for submission of the NDA components is acceptable. NDA numbers are assigned through the Central Document Room. The Sponsor can contact the Central Document Room to obtain a NDA number.

15. Will the Division review and comment on submitted Reviewable Units prior to submission of the last Reviewable Unit/complete NDA?

Division Response

- (b) (4) The Division is willing to grant Fast Track designation and will try to review and provide comments on complete sections of the NDA that are submitted. The Division is not likely to provide comments on the clinical section of the Application until the post-delivery 2 year follow-up data have been reviewed. Under the Fast Track program, the

Division is not bound by a review clock for individual sections of the NDA that have been pre-submitted.

16. Does the Division agree that 17P should be reviewed as a Priority submission?

Division Response

- If the NDA meets the requirements for Priority Review at the time of submission of the final component (i.e., the submission is complete), the Division will consider granting priority status.

<u>NDA Overall Content and Format:</u>

17. With reference to the Table of Contents for the planned NDA for 17P included in Appendix 2, does the Division agree that the content proposed in the Table of Contents will support filing and review of the NDA? Are any additional data or information required for filing of the NDA?

Division Response

- Other than the need for the addition of a Human Pharmacokinetics and Bioavailability section as discussed previously, the Table of Contents appears to be acceptable for submission and filing.

18. Does the Division agree that, other than PDFs of the NDA Overall Summary and labeling, and SAS Transport files of the clinical data and analysis datasets for the clinical studies, no other electronic data will be required for this NDA?

Division Response

- Although additional electronic files (other than labeling in Microsoft Word format) are not required, the Division requests that the Sponsor also provide PDF files for Sections 8.3, 8.5 (only narrative portion of final reports), 8.7, 8.8, and 8.10. These PDF files will facilitate review of the Application.

19. Does the Division agree with Adeza's plan to submit the CMC section, and Nonclinical Pharmacology and Toxicology Summary and Synopsis Tables in CTD format, and the remainder of the NDA in NDA format?

Division Response

- This plan is acceptable to the Division.

20. Can the Division provide any other recommendations or comments to facilitate the successful filing and review of the Adeza 17P NDA?

Division Response

- No. However, we remind you of the potential review issues that could impact on approvability that were discussed in prior meetings.
  - The study was not powered to determine if 17P would reduce the number of births at gestational ages of less than 32 weeks.
  - The study protocol did not include a predefined composite assessment for neonatal or infant outcome
  - The sample size of the study was not sufficiently large to make a meaningful determination of the likely incidence of serious adverse events such as fetal death, miscarriage, neonatal sepsis, or subsequent adverse neurodevelopmental outcomes.
- The Application will most likely be presented to an Advisory Committee for their recommendation regarding approvability.

Action Items:
Meeting minutes will be sent to the Sponsor within 30 days.

(*See appended electronic signature page)*

Scott Monroe, M.D.
Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

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/s/

Scott Monroe
7/26/05 11:12:48 AM

Meeting Minutes

Date: April 18, 2005 **Time:** 1:00 2:30 PM **Location:** Conference Room "C"

PIND 68,108 **Drug Name:** 17 hydroxyprogesterone caproate

Indication: Treatment of preterm labor

Sponsor: Adeza

Type of Meeting: Chemistry Pre-NDA Meeting

Meeting Chair: Moo-Jhong Rhee, Ph.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Moo-Jhong Rhee, Ph.D. Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Rajiv Agarwal, Ph.D. Chemist, DNDCII @ DRUDP (HFD-580)
Jennifer Mercier Regulatory Health Project Manager, DRUDP (HFD-580)

External Participants:
Emory Anderson President and CEO, Adeza Biomedical
Durlin Hickok, M.D., M.P.H. VP Medical Affairs, Adeza Biomedical
(b) (4)
Robb Hesley Vice President Strategic Projects
(b) (4).

Objective: To discuss the sponsor's proposal of the chemistry section of their planned NDA for the treatment of preterm labor in patients who have previously experienced preterm labor.

Background: Adeza has planned a 505(b)(2) literature-based NDA based upon (i) the longstanding history of safety associated with the use of 17 hydroxyprogesterone caproate (17P), (ii) the recent findings confirming the efficacy of this drug for the prevention of recurrent preterm delivery, and (iii) the public health policy need to facilitate the availability of an approved drug product manufactured under cGMP conditions for clinicians and vulnerable patients.

Questions:

Active Pharmaceutical Ingredient

1. Does the Agency agree that the API section of the planned NDA can be supported in large part by referencing the supplier (b) (4) Drug Master File (DMF)?

   Answer: Yes, The Letter of Authorization (LOA) to review (b) (4) DMF should be provided in the NDA and the (b) (4) DMF should be active and current. The physico-chemical properties, specifications and stability data should be the part of the NDA.
   - The sponsor stated the DMF is current.

2. Does the Agency agree with the proposed API specifications shown in Table 2.1 of the information package?

   Answer: The proposed API specifications are acceptable, however, the acceptance criteria of each test described in the API specifications will be a review issue. The certificate of analysis will be needed as part of the NDA.

Drug Product

3. Does the Agency agree that the existing stability data for one lot of 17P stored in the upright vial position, generated by (b) (4) and included in Appendix 5, are sufficient to permit filing and review of the planned NDA?

   Answer: No. The stability data provided in Appendix 5 is done on one batch and did not test the appropriate stability indicating attributes such as assay, degradation products, and free caproic acid in upright and inverted vial positions. Therefore, the data presented in the Appendix 5 is not considered to be sufficient for filing NDA.
   - The sponsor indicated that the Appendix 5 was not for the drug product, but for the placebo.

   If you provide three months real time and accelerated data from three primary batches (with two API batches) at the time of submission of NDA, and further update the data with up to six months real time and accelerated data during the review cycle, it would be acceptable. The stability data should include the stability indicating attributes and the update data should be submitted at least 90 days before the PDUFA goal date.
   - The sponsor asked if free caproic acid test can be waived based on the use of the validated HPLC method and quantification of the 17P. The Division informed the sponsor to propose this in writing for a formal response.
   - The sponsor asked if only one API batch can be used in the primary batches and the Division informed the sponsor that they propose it in writing with rationale for a formal response.

(b) (4)

5. Does the Agency have any other recommendations on Adeza's plans for stability testing of the 17P product (discussed in section 2.2.7 of the Information Package,) to facilitate review and approval of the NDA?

   Answer: Yes. According to the stability protocol in section 2.2.7 (table 2.6), the drug product will be tested for physical appearance, assay and sterility. It is recommended that the product be also tested for benzyl alcohol content, volume recovery, free caproic acid, particulate matter (every six months), (b) (4), degradation product of the API and for bacterial endotoxin at ICH storage conditions. Please refer to "Guidance for Industry (Draft): Stability Testing of Drug Substances and Drug products, June 1998.

   - The sponsor raised questions as to whether tests for volume recovery, particulate matter, (b) (4) can be waived from the stability testing. Agency said these are deemed necessary, but will reassess the necessity of these tests.

6. Does the Agency agree that Adeza's plan for demonstrating pharmaceutical equivalence between the Meis study formulation and the planned commercial formulation, discussed in Section 2.2.8 of the Information Package, is acceptable for filing and review of the NDA?

   Answer: Yes. You should also submit quantitative and qualitative composition of the clinical study formulation and to-be marketed formulation.

7. It is anticipated that the CMC section of the NDA will be submitted prior to the actual performance of the process validation runs. A protocol for the process validation runs will be included in the CMC section of the NDA for the Agency's review and comment.

Adeza recognizes that three successful process validation runs will need to be performed prior to marketing approval. Does the Agency agree with this approach?

Answer: Yes. Process validation information including the adequacy and efficacy of (b) (4) (b) (4) (b) (4) should be submitted at the time of NDA filing.

8. Does the Agency agree that the final product release specifications and associated analytical methods described in Section 2.2.5 of the Information Package are acceptable for the product approval?

   Answer: Yes, provided that the tests and acceptance criteria for degradation products, free caproic acid and particulate matter are in the final product release specifications. The acceptance criteria of each test described in the drug product specifications will be evaluated during the review cycle. The acceptance criterion of Physical Examination should read " Clear, yellow color, free of any **particulate matter**, viscous and oily solution with an organic odor".

   - The sponsor asked the Agency to reconsider the phrase "free of any particulate matter", and Agency asked the sponsor to propose new language.

   The use of HPLC system as an alternate analytical method is acceptable to identify the 17P drug product. To validate the analytical procedure, please refer to the following guidances for industry:

   - Guidance for Industry: Q2A Text on Validation of Analytical Procedures, March 1995.
   - Guidance for Industry: Q2Bvalidation of Analytical Procedures: Methodology, November 1996.

9. Adeza proposes an alternative 17P container closure system in section 2.2.4 of the Information Package. Provided the results are equivalent, does the Agency agree that a three month accelerated stability study will be adequate to justify the use of the alternative container closure system while retaining the demonstrated expiry dating of the current container closure system?

   Answer: Agency agrees that three months accelerated stability will be adequate to justify the use of the alternative container closure system as long as the stability data are submitted 90 days before the PDUFA goal date. Relevant DMFs, LOAs for each alternate packaging component should be provided.

   - The sponsor informed the Division that they will not change the stopper.

10. As discussed in section 2.2.6 Analytical Methods, provided the appropriate validations are performed (i.e. LOD, LOQ, range of linearity, selectivity, system precision and accuracy, repeatability and ruggedness) using the product solution as the starting material for identity and drug content, does the Agency have any objection to the use of an alternative methodology HPLC assay method for drug product release?

    Answer: Agency has no objection to the use of the alternative HPLC assay method for drug product release, if it is the same method as the validated (b) (4) HPLC method.

NDA Content and Format

11. With reference to the Table of Contents for the planned NDA CMC section for 17P shown in Section 2.3 (Table 2.7), does the Agency agree that the content proposed in the Table of Contents will support filing and review of the NDA? Are any additional data or information required for filing?

    Answer: Yes, one batch record for primary stability batch and COAs of the three stability batches should be included under section 4.4.7. Additionally, if the CMC section of NDA is submitted in the CTD format then the Table of Contents for the planned NDA CMC section for 17P should follow the following CTD guidances:

    - Guidance for Industry: M4Q: The CTD-Quality, August 2001.
    - Guidance for Industry: M4Q: The CTD-Quality, Questions and Answers/Location issues, June 2004.

12. Does the Agency agree that, other than the electronic versions of the CMC Technical section Summary and Overall Summary, an electronic submission of the CMC data will not be required for the NDA?

13. Does the Agency agree that the CMC section of the NDA can be submitted in CTD format while the remaining sections of the NDA can be submitted in a non-CTD format?

    Answer to both 12 and 13: If you plan to submit your application in CTD format you should be aware that if you submit any portion of that application electronically the entire application must be submitted electronically. This is not a Division policy. It is an Agency policy.
    - The sponsor informed the Division that the chemistry section of the NDA would be the only item in CTD format and nothing in that section would be electronic.

14. Can the Agency provide any other recommendations or comments to facilitate the successful filing and review of the CMC section of the Adeza 17P NDA?

    Answer: We have the following additional recommendation for a successful filing and review of the CMC section:

    At the time of filing, the drug substance and drug product manufacturing sites should be ready for cGMP inspection.

    Relevant references to the DMFs and Letter of Authorizations to review the DMFs (API, container/closure etc.) should be provided. DMFs should be active and current.

Action Items:

- Meeting minutes will be sent to the sponsor in 30 days.
- The sponsor will submit the stability protocols prior to their use.
- the sponsor will submit to the Pre-IND proposals for the following:
  - use of the HPLC testing
  - preservative testing
  - wording regarding the physical examination.
- The sponsor will submit a request and rationale to allow only one API batch to be used in the primary batches for stability.

(*See appended electronic signature page)*

Moo-Jhong Rhee, Ph.D.
Concurrence, Chair

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/s/

Moo-Jhong Rhee
5/4/05 10:43:39 AM

Meeting Minutes

Date: July 26, 2004 **Time:** 1:00 1:45 PM **Location:** Parklawn; Conference Room "C"

Pre-IND: 68,108 **Drug Name:** 17-hydroxyprogesterone caproate

Indication: Prevention of recurrent preterm birth

Sponsor: Adeza

Type of Meeting: Guidance

Meeting Chair: Scott Monroe, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees

Daniel Shames, M.D. Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Donna Griebel, M.D. Deputy Director, DRUDP (HFD-580)
Scott Monroe, M.D. Clinical Team Leader, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. Clinical Team Leader, DRUDP (HFD-580)
Barbara Wesley, M.D. Medical Officer, DRUDP (HFD-580)
Phill Price, M.D. Medical Officer, DRUDP (HFD-580)
Lisa Soule, M.D. Medical Officer, DRUDP (HFD-580)
Karen Hoover, M.D. Medical Intern, DRUDP (HFD-580)
Jennifer Mercier Regulatory Health Project Manager, DRUDP (HFD-580)

External Participants

Emory Anderson President and CEO, Adeza Biomedical
Durlin Hickok, M.D., M.P.H. VP Medical Affairs, Adeza Biomedical
(b) (4)
(b) (4)
Rob Hesley Project Consultant
(b) (4)

Meeting Objective: To discuss the Sponsor's proposal for the Infant Follow-up Study.

Sponsor's Questions and the Division's Responses

1. **Does the FDA agree that the proposed, validated instrument to be used in the infant follow up study is sufficient to support approval of 17 alpha-hydroxyprogesterone caproate for the prevention of recurrent preterm birth**?

   It appears that the instruments that will be used in the infant follow up study, based on the questionnaires that were submitted in your meeting package, will provide us with adequate follow up information for a specific infant. We cannot comment at this time on whether the total body of data that you plan to provide will be adequate to support approval of 17 alpha-hydroxyprogesterone caproate (17-OH-P) for the prevention of recurrent preterm birth until we have an opportunity to review all the data.

2. **Does the Division have any comments on study design or deployment of the study questionnaire?**

   The study design and deployment of the questionnaire are acceptable to the Division with one possible exception. We previously requested that you obtain follow-up data on infants through at least 2 years of age. You have indicted in your submission that at the time of planned distribution of the questionnaires the infants will range from 18 months to 40 months of age. If infants < 2 years of age represent more than a few subjects or if the total percentage of infants from whom data are obtained is less than 50% of the eligible infants, we will likely request that you include follow up data through 2 years of age for all infants.

   We have previously informed you that normally either 2 adequate and well controlled studies or a single study with a robust and compelling outcome and strong supporting data are required to support approval of a new drug product. In the case of your proposed product, however, we have indicated that we would consider for review an NDA based primarily on the NICHD study that was reported in the NEJM on June 12, 2003, if actual data listings and 2-year follow up data for the infants were provided. There is a risk, however, that the data may be considered insufficient to demonstrate that 17-OH-P is safe and effective for the prevention of preterm delivery. The Division also will most likely seek the advice of the Advisory Committee on Reproductive Health Drugs in its deliberations concerning your proposed NDA.

3. **Will the Division allow Adeza to submit the intended NDA on a "rolling" basis?**

   You should submit a request for "Fast Track" designation for this application. This request can be submitted at any time once you have an active IND or have submitted your NDA. You need to know that "Fast Track" designation can be rescinded at any time if another drug product is approved prior to approval of your application. The review clock for your application, if it receives "Fast Track" designation, would start when the last component that constitutes a complete NDA package is submitted to the NDA.

Other Discussion Items

- The Sponsor indicated that the Steering Committee for the NICHD study on prevention of premature delivery will release the actual study data to Adeza so that Adeza will be able to include the data listings in their NDA submission.
- The Sponsor clarified the number of sites that will participate in the infant follow-up study. The Sponsor indicated that they were pleased by the number of centers that have remained in the Network and the by proportion of patients surveyed who have agreed to participate in the follow-up study. The Sponsor, however, could not provide the total number of subjects who would participate in the follow-up study.
- The Division asked the Sponsor to include in the NDA data from the patients who were treated in the first phase of the study (the phase that used a different lot/formulation of 17-OH-P).
- The Division requested that the Sponsor include in their NDA all additional information that they could find in the literature on the use of 17-OH-P for prevention of premature delivery.
- The Sponsor stated that they did not believe that their study included a sufficient number of deliveries at or before 31 weeks of gestation to show a statistically significant benefit of treatment with 17-OH-P for this gestational age group.

Action Items

- Meeting minutes will be sent to the Sponsor in 30 days
- The Sponsor will request a meeting with the FDA Chemistry Group to discuss chemistry issues concerning their proposed New Drug Application.

(*See appended electronic signature page)*

Scott Monroe, M.D.
Concurrence, Chair

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/s/

Scott Monroe
8/5/04 11:20:41 AM

Meeting Minutes

Date: April 5, 2004 **Time:** 1:00 2:00 PM **Location:** Parklawn; 17B-43

IND 68,108 **Drug Name:** 17-hydroxyprogesterone caproate

Indication: Prevention of preterm labor

Sponsor: Adeza

Type of Meeting: Guidance

Meeting Chair: Scott Monroe, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Scott Monroe, M.D. Clinical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Phill Price, M.D. Medical Officer, DRUDP (HFD-580)
Martin Kaufman Project Manager, DRUDP (HFD-580)
Jennifer Mercier Regulatory Health Project Manager, DRUDP (HFD-580)

External Participants:
Emory Anderson President and CEO, Adeza Biomedical
Durlin Hickok, M.D., M.P.H. VP Medical Affairs, Adeza Biomedical
Martha Charney, Ph.D. Piedmont Consulting Group
Natasha Leskovsek, RN, M.B.A., J.D. Heller Ehrman
Catherine Spong, M.D. - Chief, Pregnancy and Perinatology Branch, Institute of Child Health and Human Development, National Institutes of Health

Objective: To discuss the sponsor's progress in obtaining additional clinical data in support of a NDA for the prevention of preterm labor.

Discussion:
- Adeza informed the Division that the supplier of the drug product for the NICHHD sponsored trial for the prevention of recurrent preterm delivery (RPD) has agreed to work with Adeza and will provide Adeza with authorization to access/reference their Drug Master File (DMF).
- Dr. Spong informed the Division that the Steering Committee of the Network that conducted the trial for prevention of RPD is considering whether to release the data from the trial directly to Adeza or only to the FDA. The Division informed Dr. Spong of the difficulties that would likely result during the review process if Adeza were the sponsor of the NDA but did not have direct access to the clinical data from the trial.

- Dr. Spong also stated that additional analyses of the data from the prevention of RPD trial are being conducted.
- The remainder of the discussion focused on the need to obtain follow-up data from the babies from the prevention of RPD trial.
  - At the meeting with Adeza on January 30, 2004, the Division had expressed concern that no follow-up safety data for the babies from the prevention of RPD trial had been obtained after discharge from the hospital. The Division had recommended at the meeting that the babies from this trial be followed through two years of age to identify any adverse effects of treatment with 17-hydroxy progesterone caproate.
  - Adeza indicated during the teleconference that they would likely be able to obtain some follow-up safety data on the babies, but it would be limited because of HIPPA regulations. HIPPA regulations would limit the amount of information that could be collected at the present time because provisions for post discharge data collection were not incorporated into the original study protocol and consent for obtaining such data had not been obtained.
  - Dr. Spong indicated that the Network was conducting a pilot survey to see how many of the patients in the NICHD study could be located and how many would likely participate in a follow-up study concerning the health of their child.
  - The Division again expressed concern regarding the limited scope of the safety data that would likely be available for review if a NDA were submitted for 17 hydroxy-progesterone caproate for prevention of recurrent preterm delivery, particularly if a high percentage of patients from the completed NICHHD trial did not provide post treatment safety follow-up data.

Action Items:

- Meeting minutes will be sent to the sponsor in 30 days
- The sponsor will request a meeting with the Chemistry group to discuss the chemistry issues for a NDA submission.
- The sponsor will keep the Division updated on progress in obtaining follow-up safety data through 2 years post delivery from the babies whose mothers had participated in the NICHHD sponsored prevention of RPD clinical trial.

(*See appended electronic signature page)*

Scott Monroe, M.D.
Concurrence, Chair

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/s/

Jennifer L. Mercier
4/29/04 02:33:18 PM
CSO

Scott Monroe
4/29/04 07:08:21 PM
MEDICAL OFFICER

Meeting Minutes

Date: January 30, 2004 **Time:** 2:00 3:30 PM **Location:** Conference Room "C"

IND 68,108 **Drug Name:** 17 hydroxyprogesterone caproate

Indication: Treatment of preterm labor

Sponsor: Adeza

Type of Meeting: Guidance

Meeting Chair: Scott Monroe, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Daniel Shames, M.D. Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Donna Griebel Deputy Director, DRUDP (HFD-580)
Scott Monroe, M.D. Clinical Team Leader, DRUDP (HFD-580)
Barbara Wesley, M.D. Medical Officer, DRUDP (HFD-580)
Lesley Furlong, M.D. Medical Officer, DRUDP (HFD-580)
Lisa Soule, M.D. Medical Officer, DRUDP (HFD-580)
Shahla Farr, M.S. Statistical Reviewer, Division of Biometrics (HFD-715)
Moo-Jhong Rhee, Ph.D. Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
DJ Chatterjee, Ph.D. Clinical Pharmacology and Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Leslie Kenna, Ph.D. - Clinical Pharmacology and Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Suzanne Thornton, Ph.D. Pharmacologist, DRUDP (HFD-580)
Margaret Kober Chief, Project Management Staff, DRUDP (HFD-580)
Jennifer Mercier Regulatory Health Project Manager, DRUDP (HFD-580)

External Participants:
Emory Anderson President and CEO, Adeza Biomedical
Durlin Hickok, M.D., M.P.H. VP Medical Affairs, Adeza Biomedical
Paul Meis, M.D. Professor, Wake Forest University, School of Medicine, Department of OB/GYN. Principal Investigator, NICHD Maternal-Fetal Medicine Units Network Study "Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate"
(b) (4)
(b) (4)

Objective: To discuss the sponsor's proposal of a 505(b)(2) application for the treatment of preterm labor in patients who have previously experienced preterm labor.

Background: Adeza has planned a 505(b)(2) literature-based NDA based upon (i) the longstanding history of safety associated with the use of 17 hydroxyprogesterone caproate (17P), (ii) the recent findings confirming the efficacy of this drug for the prevention of recurrent preterm delivery, and (iii) the public health policy need to facilitate the availability of an approved drug product manufactured under cGMP conditions for clinicians and vulnerable patients.

Questions:

1. Given the well-characterized nature of this drug, does the Division have any specific concerns or suggestions regarding the manufacture or packaging of 17P?

   Answer:
   - You will need to submit in your NDA full Chemistry, Manufacturing, and Controls information for the drug product.
   - If the clinical reviewers accept the efficacy and safety data from the NICHD sponsored clinical trial reported by Meis et al., you will need to establish pharmaceutical equivalency between the 17P product used in that study and the to-be-marketed formulation of 17P.
   - You may want to consider opening a Drug Master File (DMF) for the drug substance, if it is manufactured by a contractor.
   - We encourage you to submit 12-months stability data at the time of NDA submission. This would include 12-months real time and 6-months accelerated stability on 3 commercial batches.

2. Does the FDA agree that its prior findings of safety for Delalutin, together with current published preclinical information on 17P are sufficient to support approval of the proposed 505(b)(2) NDA? Is there any specific additional preclinical information that would be required for approval of the NDA?

   Answer:
   - The Division agrees with you that FDA's prior findings of safety for Delalutin with current published preclinical information on 17P would be sufficient to support a NDA. The Division requests that you submit in your NDA all literature, including journal articles, and the Summary Basis of Approval (SBA) for 17P, and all available toxicology information in the literature for benzyl benzoate to support this application.

3. Does the Division agree that adequate replicate evidence of 17P's safety and effectiveness for the prevention of recurrent preterm delivery exists in the literature and is sufficient to support approval of the proposed NDA for this orphan population?

Answer:

- The Division does not believe that adequate evidence of safety and effectiveness exists in the literature to support approval of the proposed NDA submission for the use of 17P to prevent recurrent preterm delivery.
- The Division's main concern is the lack of follow-up data, beyond the period of initial hospital assessment, of babies in which the mother received 17P for the prevention of preterm labor.
- Without such data, the Division cannot make a meaningful assessment of the benefit/risk ratio.
- You will need to submit actual data listings from the NICHD clinical trial. The information provided in the New England Journal of Medicine (NEJM) publication is not sufficient for us to assess either the effectiveness or safety of the treatment.
- The NEJM publication did not include any long-term outcome data in the babies. We will require such data from a substantial number of babies (at least 35-50% of babies in each treatment arm of the study) through at least 2 years of age from the NICHD trial or a comparable number of babies from another trial of similar design using the same drug product.
- The Division also has some concerns about the actual conduct of the NICHD study, the outcomes, and the analyses. These concerns include:
    - The drug product(s) that was used during the trial. Complete CMC information about the drug product, including its purity and potency will need to be provided.
    - The findings and actual analyses from the 133 or so patients that received the initial formulation of 17P, who apparently were not included in the NEJM analysis or described in the publication.
    - The outcome analyses if one considered the 5 deaths that occurred prior to week 20 as treatment failures.
- The Division believes that reducing the number of deliveries at ≤ 32 weeks gestational is a clinically important outcome.
- The Division does not believe that reducing the number of deliveries at ≥ 33 weeks would be an adequate endpoint by itself, since the literature does not support substantial mortality or morbidity in this age group.
- In a risk/benefit assessment, the Division would likely consider all undesirable outcomes in both study arms as treatment failures.
- The Division would also focus on what it believes to be the most important outcomes (i.e., overall survival of fetuses/infants and a significant reduction in serious morbidities from the time of enrollment rather than an increase in gestational age only without other accompanying clinical benefits).
- Normally, the Division would request that a Sponsor conduct two adequate and well controlled studies. It is possible that the NICHD study,

with other strong supporting data and studies (which to our knowledge are likely to be of limited value because of differences in study design, entry criteria, and use of different study drug preparations) might suffice to support safety for the mother. However, neither the NICHD study nor other reported studies will address the Division's concerns about the safety and efficacy of 17P treatment for the babies (i.e., follow up data on the babies).

- DRUDP does not designate Orphan Drug status under section 526 of the Federal Food, Drug and Cosmetic Act. The required information to be included in an application for Orphan Designation is found under 21 CFR 316.20(b) and the application should be submitted to :

  Marlene E. Haffner, M.D., M.P.H.
  Director, Office of Orphan Products Development
  Food and Drug Administration, HF-35
  5600 Fishers Lane, Room 6A55
  Rockville, MS 20857

- Any questions regarding Orphan Drug status should be addressed to the Office of Orphan Products Development. For questions specific to Designations, contact Jeffrey Fritsch, RPh at (301)827-0989 or by e-mail at: jfritsch@oc.fda.gov
- The Office of Orphan Products Home page can be accessed at: http://www.fda.gov/orphan/index.htm

Action Items:

- meeting minutes will be sent to the sponsor in 30 days

(*See appended electronic signature page)*

Scott Monroe, M.D.
Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Concurrences:

HFD-580/Mercier, Shames, Griebel, Monroe, Wesley, Furlong, Farr, Kenna, Thornton, Chatterjee, Soule

drafted: Mercier/2.4.04
concurrences: Thornton2.6.04/Rhee2.4.04/Chatterjee2.4.04/Kenna2.4.04/Furlong2.4.04/Monroe2.17.04
final: February 18, 2004

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

/s/

Scott Monroe
2/18/04 01:34:14 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 021945 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Makena Established/Proper Name: 17-α Hydroxyprogesterone caproate Dosage Form: Injection		Applicant: Hologic, Inc. Agent for Applicant (if applicable):
RPM: Williamson		Division: DRUP

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☒ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is April 13, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None 10/20/2006 - CR, 01/23/2009- CR

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Reference ID: 2905640

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☒ Received
❖ Application Characteristics [2]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☒ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ REMS not required

Comments:

BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

Reference ID: 2905640

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 02/03/2011; 01/23/2009; 10/20/2006
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	February 3, 2011
• Original applicant-proposed labeling	April 14, 2006
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

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Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	February 3, 2011
• Original applicant-proposed labeling	April 14, 2006
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	December 15, 2010
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 Accepted - December 20, 2010 December 20, 2010
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA November 12, 2010; 11.24.2008; 09.30.2008; 09/13/2006 ☒ DRISK January 5, 2011 ☒ DDMAC 02/03/11;07/10/2006 ☐ CSS ☒ Other reviews Feb. 3, 2011

Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) January 31, 2011 ☐ Not a (b)(2) January 31, 2010
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 09/10/2008 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	 ☒ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 06/27/2005
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	CMC - 04/18/2005
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None February 3, 2011
Division Director Summary Review *(indicate date for each review)*	☐ None February 3, 2011; 01.23.2009; 10.21.2006
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None February 3, 2011; 01.23.2009;10.20.2006
PMR/PMC Development Templates *(indicate total number)*	☐ None 5
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	February 3, 2011
• Clinical review(s) *(indicate date for each review)*	February 3, 2011; 01.23.2009; 10.12.2006
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical Review Page 32
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None February 3, 2011
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None February 3, 2011; 01.23.2009
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None February 3, 2011
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None February 3, 2011
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None February 3, 2011; 12.15.2009; 08.26.2008; 09.20.2006
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None January 6, 2011; 10.05.2006
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None August 11, 2010; 10.14.2008; 09.21.2006
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

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Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None January 10, 2011
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None December 1, 2010; January 31, 2011; 12.22.2008; 09.22.2006
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed December 18, 2008; 06.19.2008; 08/10/2006
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Septembe 22, 2006
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: October 26, 2010 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Reference ID: 2905640

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 21-945 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Gestiva Established/Proper Name: 17-alpha hydroxyprogesterone caproate) 250 mg/ml Dosage Form: Injection		Applicant: Cytyc Corporation Agent for Applicant (if applicable):
RPM: Charlene Williamson		Division: Division of Reproductive and Urologic Products

NDAs: NDA Application Type: X 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	January 25, 2009
❖ Actions	
• Proposed action	☐ AP ☐ TA ☐ AE ☐ NA X CR
• Previous actions *(specify type and date for each action taken)*	☐ None Approvable
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Reference ID: 2905640

Application[2] Characteristics	
Review priority: X☐ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	September 10, 2008
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	X☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	X None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	X☐ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
✓ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	X☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes,**" skip to question (4) below. If "**No,**" continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "**No,**" continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No,**" the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No,**" continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☐ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Complete Response 01/25/2009
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	April 25, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use X☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

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• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	April 25, 2008
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM X DMEDP November 24, 2008 ☐ DRISK DDMAC ☐ CSS ☐ Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	 DMEPA – October 22, 2008 Acceptable
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing 10/16/2006
NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes X No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	X Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	X None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	X None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

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• Incoming submission documenting commitment	
Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	Included
Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable 09/10/2008
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable
• Regulatory Briefing *(indicate date)*	☐ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☐ None Pending
Cross-Discipline Team Leader Review *(indicate date for each review)*	X None
Clinical Information[5]	
Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Pending
• Clinical review(s) *(indicate date for each review)*	Pending
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	X None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	See Clinical Review –
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See Clinical Review –
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	X Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☐ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
Clinical Microbiology X☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None

[5] Filing reviews should be filed with the discipline reviews.

Reference ID: 2905640

Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	X☐ None Pending
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 08/21/08
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 10/14/08
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 10/05/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
ECAC/CAC report/memo of meeting	X None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	X None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 12/22/08
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	X 0617/08 & 12/18/08
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
X☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC Review # 1 dated 09/22/06
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

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NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested X Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: **X** Acceptable ☐ Withhold recommendation
• BLAs: ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	 Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Reference ID: 2905640