

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021463Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021463

SUPPL #

HFD # 580

Trade Name Fortesta

Generic Name testosterone gel 2%

Applicant Name Endo Pharmaceutical Solutions, Inc.

Approval Date, If Known December 29, 2010

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.

N/A

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?

No

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#

*Please see attachment after the last page of this document

NDA#

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:

FOR01C

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"):

FOR01C

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 # 076634 YES ! NO
! Explain:

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:

Investigation #2

YES

Explain:

!

!

! NO

! 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: Jeannie Roule
Title: Regulatory Health Project Manager
Date: December 29, 2010

Name of Office/Division Director signing form: George Benson, M.D.
Title: Deputy Director

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

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

JEANNIE M ROULE
12/29/2010

GEORGE S BENSON
12/29/2010

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21-463 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: PDUFA Goal Date: Stamp Date: 4/17/2009

Division of Reproductive and Urologic Drug Products October 17, 2009

Proprietary Name: Fortesta 2% gel

Established/Generic Name: testosterone gel

Dosage Form: topical gel

Applicant/Sponsor: ProStrakan

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

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): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, including primary hypogonadism and hypogonadotropic or secondary hypogonadism.

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

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

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

- Yes. Please proceed to Section D.
- 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) (includes new combination); 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.**

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 some or all 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 for the reason(s) selected)

- 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 unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and 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.

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 ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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 unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ 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 complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (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 Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section 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 selected pediatric subpopulations).

Identify the pediatric subpopulation(s) 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)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	yr. mo.	yr. mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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 partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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 there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

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

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	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 all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

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

ote: 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 pediatric subpopulation for which information will be extrapolated. 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. Under the statute, safety cannot be extrapolated.

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?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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 or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

 Jeannie Roule
Regulatory Project Manager

(Revised: 6/2008)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 22, 2010

TO: NDA 021463

THROUGH : Jeannie Roule

SUBJECT: PeRC decision

APPLICATION NUMBER: NDA 021463, Fortesta

This product, Fortesta, was presented to the PeRC committee on August 16, 2009. Their decision is addressed in the attached email.

Roule, Jeannie

From: Greeley, George
Sent: Wednesday, August 26, 2009 11:20 AM
To: Roule, Jeannie
Cc: Stowe, Ginneh D.
Subject: NDA 21-463 Fortesta - Update 8/26/09

Importance: High

Hi Jeannie,

The Fortesta (testosterone gel) full waiver was reviewed by the PeRC PREA Subcommittee on August 19, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable and because the disease/condition does not exist in children and because 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.

Update - August 26, 2009

The PeRC has received an update from OCC that their initial reaction that this product triggered PREA was not correct. Therefore we now ask that you modify the pediatric page to reflect that PREA does not apply.

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

 Please consider the environment before printing this e-mail.

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

/s/

JEANNIE M ROULE
12/22/2010



EN3350 / FORTESTA™ (testosterone) 2% Gel

DEBARMENT CERTIFICATION

Endo Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

A handwritten signature in black ink, appearing to read "Sharon Reinhard".

Sharon Reinhard, MS
Associate Director, Clinical Quality Control
Clinical Operations & Data Management
Endo Pharmaceuticals Inc.

A handwritten date in black ink, "09 DEC 2010".

Date

A handwritten signature in black ink, appearing to read "Eileen M. DiRita".

Eileen M. DiRita RN, BSN
GCP Compliance Manager
Clinical Operations & Data Management
Endo Pharmaceuticals Inc.

A handwritten date in black ink, "09 Dec 2010".

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 021463 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Fortesta Established/Proper Name: testosterone Dosage Form: Gel		Applicant: Endo Pharmaceuticals Solutions, Inc. Agent for Applicant (if applicable):
RPM: Jeannie Roule		Division: Reproductive and Urologic Products
<p><u>NDA's:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p style="padding-left: 20px;">No listed drugs were relied upon</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>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.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p><u>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.</u></p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 30, 2010</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None Complete Response letter issued July 3, 2003 and October 16, 2009

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.

<p>❖ 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 _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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).

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
<p>❖ Copy of this Action Package Checklist³</p>	<p>December 29, 2010</p>
Officer/Employee List	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) Not approvable letter issued July 3, 2003 Complete Response: October 16, 2009 Approval letter: 12/29/10</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p>12/27/10</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>June 30, 2010</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
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<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	12/27/10
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	June 30, 2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	December 13, 2010
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	12/05/02, 02/04/03, 03/27/03, 07/29/09, 11/02/10
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 10/13/09 and 12/17/10 <input checked="" type="checkbox"/> DRISK 10/01/09 and 12/06/10 <input checked="" type="checkbox"/> DDMAC 12/02/03, 10/06/09, 12/03/10 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews SEALD 12/03/10, 12/15/10 and 12/16/10
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2) 12/14/10
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>8/19/09 and they concluded that PREAA does not apply to this product</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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❖ 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 (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 11/30/01
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/3/03, 10/16/09 and 12/29/10
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/3/03, 10/15/09 and 12/29/10
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None One PMR
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	8/01/02, 12/17/02, 7/03/03, 10/16/09 and 12/15/10
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	10/16/09 page 16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not applicable 8/19/09 and 10/20/10
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	June 30, 2010
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	7/28/09 and 12/09/10
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input type="checkbox"/> None 9/02/09 and 11/22/10

⁵ Filing reviews should be filed with the discipline reviews.
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❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested Included
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 8/09/02, 1/08/03, 9/16/09, 10/08/09, 9/27/10, and 11/19/10
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 8/21/02, 7/02/03, 10/14/09, 12/15/10 and 12/28/10
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None Included
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 8/01/02, 8/14/02, 7/13/09, 10/07/09, 11/19/10 and 12/16/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 8/27/02, 1/22/03, 7/02/03, 3/27/03, 10/05/09, and 12/10/10
❖ Microbiology Reviews		<input type="checkbox"/> Not needed 11/08/02
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		01/22/03
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(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 sites⁶)</i>		Date completed: 12/10/10 <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> 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.

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.

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

/s/

JEANNIE M ROULE
12/29/2010



NDA 021463

ACKNOWLEDGE CLASS 2 RESPONSE

Endo Pharmaceuticals Inc.
Attention: Paula Clark
Director, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Ms. Clark:

We acknowledge receipt on June 30, 2010, of your June 30, 2010, resubmission to your new drug application for Fortesta™ (testosterone) 2% Gel.

We consider this a complete, class 2 response to our October 16, 2009, action letter. Therefore, the user fee goal date is December 30, 2010.

If you have any question, call Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21463

ORIG-1

ENDO
PHARMACEUTICA
LS INC

FORTIGEL (TESTOSTERONE
GEL) 2%

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

/s/

JEANNIE M ROULE
07/11/2010



NDA 021463

MEETING MINUTES

Endo Pharmaceuticals Inc.
Attention: Paula Clark
Director, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone 2% Gel.

We also refer to the face-to-face meeting between representatives of your firm and the FDA on June 10, 2010. The purpose of the meeting was to discuss the progress of your reanalysis plan and information that you are planning to include in your Complete Response

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 Jeannie Roule, Regulatory Health Project Manager at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Medical Team Leader
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance
Meeting Date and Time: June 10, 2010@10:30 AM- 12:00 PM
Meeting Location: White Oak, Conference Room #1311
Application Number: NDA 021463
Product Name: testosterone 2% gel
Indication: Testosterone replacement therapy
Applicant Name: Endo Pharmaceuticals, Inc.
Meeting Chair: Mark Hirsch, M.D.
Meeting Recorder: Jeannie Roule

FDA ATTENDEES

George Benson, M.D.	Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D.	Medical Team Leader, DRUP
Guodong Fang, M.D.	Medical Officer, DRUP
Hyunjin Kim, Pharm.D.	Clinical Pharmacology Reviewer, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology (DCP) III
Mahboob Sobhan, Ph.D.	Statistical Team Leader, Division of Biometrics (DB) III, OTS
Jonathan Jarow, M.D.	Medical Officer, DRUP
Sean Kassim, Ph. D.	Pharmacologist, Division of Scientific Investigations (DSI), Office of Compliance (OC)
Carol Rivera-Lopez, Ph.D.	Pharmacologist, DSI, OC
Jennifer Mercier	Chief, Project Management Staff, DRUP
Jeannie Roule	Regulatory Health Project Manager, DRUP

APPLICANT ATTENDEES

Robert Barto, MBA	Vice President, Regulatory Affairs
Paula Clark	Director, Regulatory Affairs
Theodore Danoff, MD, PhD	Vice President, Clinical Development and Medical Affairs, Endocrinology/Urology
Neil Shusterman, MD	Senior Vice President, Clinical Development and Medical Affairs
Lianng Yuh, PhD	Vice President, Biostatistics and Programming
Yusong Chen, Ph.D.	Senior Director, Biostatistics
Frank Diana, Ph.D.	Vice President, Pharmaceutical Development
William Fiske, Ph.D.	Senior Director, Drug Metabolism and Pharmacokinetics
Ian Gordon Duguid	Regulatory Affairs, Prostrakan

BACKGROUND

This NDA was originally submitted on May 31, 2002, and was issued a Not Approvable letter on July 3, 2003. On April 17, 2009, the Applicant submitted a Complete Response to the July 3, 2003, action letter. DRUP issued a Complete Response Letter on October 16, 2009.

The reasons for the Complete Response action were as follows:

The Division of Scientific Investigations (DSI) conducted an audit of the (b) (4) analytical laboratory located in (b) (4). The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from the single phase III clinical study (FOR01C). These deficiencies raised questions regarding the validity of the data needed to determine the efficacy and safety of the drug product.

The Division requested this meeting with the Applicant to discuss the progress of their reanalysis plan and the information that the Applicant is planning to include in their Complete Response

DISCUSSION

Preliminary responses were provided to the Applicant on June 8, 2010, in response to the questions posed in the Applicant's meeting package provided to the Division on May 3, 2010. The Applicant's questions are presented below in **bolded** text, followed by the Division's responses in normal text. Additional discussion held during the meeting is summarized below in *italics*.

Question 1

Based on the data and information provided in this response, Endo believes that the FOR01C Study bioanalytical work is reliable and that the deficiencies identified in the DSI audit of the (b) (4) have been adequately addressed.

Does the Division concur?

Response: The reliability of the recent bioanalytical work and the adequacy of your responses to the deficiencies are review issues. We currently have two major concerns:

1. You will need to clarify how the long-term storage stability of testosterone at -70°C was determined. Ideally, storage stability should be calculated using the concentration of an appropriately stored sample compared to its nominal concentration (a sample prepared with a known amount of analyte in the appropriate matrix). In your meeting package, stability is supported by a comparison of samples at baseline to samples after 951 days at -70°C storage. However, the comparison lacks a nominal value at baseline. You should provide more details of the baseline determination, including how the baseline standards and QCs were prepared, and whether the conditions of analysis were the same for the baseline and recent measurements. Long term storage stability evaluation would be more meaningful using samples prepared at known concentrations and with appropriate storage periods.
2. We note that a total of 128 samples (9.3%) for total testosterone on Day 90 were not available for the re-assay. Missing data are a critical review issue. You need to

submit information in your CR that clarifies the effect of missing data on the primary efficacy outcome. For each patient with missing data on Day 90, provide individual narratives, consisting of (1) text summary related to the missing data, (2) table(s) of all serum testosterone values, and (3) figure(s) showing the testosterone PK curve.

Additional Discussion: In regard to the first concern, the Sponsor stated that there were no spiked samples at [REDACTED] ^{(b) (4)} that had been stored for 951 days. The Division expressed concern regarding the lack of original spiked samples, because without such samples, it is not clear how accuracy of the concentrations of the original samples will be demonstrated. The Sponsor explained that their proposed method to demonstrate accuracy of the concentrations from the original samples did not require original spiked samples. They explained that fresh calibration standards and quality controls were prepared from a control pool and these fresh standards and QC's were prepared according to the original conditions of analysis. The Sponsor further explained that all available clinical study samples that had been stored at -70°C were analyzed, and the results show that the samples were stable for the period of storage. Therefore, the Sponsor believes that their approach is robust, and is valid for determining accuracy and precision of concentrations from the original samples. The Office of Compliance requested that Sponsor provide a clear explanation and detailed information in the Complete Response regarding why their method of reanalysis is as accurate as a "classical" approach.

In regard to the second concern, the Sponsor agreed to submit the requested narratives. These narratives will include detailed information and context for all 128 samples that were not available for re-analysis. The Sponsor stated that all "back-up" samples stored at -70°C at the Cranbury, NJ facility were analyzed for total testosterone. The Sponsor acknowledged that not all original samples were available. The reasons for missing data included insufficient sample remaining and defrosting. The Division noted that back-up samples were not available for nine patients. The Division asked whether any of these patients had original testosterone concentrations that were considered failures (e.g., an excessively high C_{max}). The Applicant stated that there were no predetermined rules for exclusion of samples. The only reason for exclusion was due to the sample being unavailable, and that missing data appeared to be a random phenomenon. The Sponsor stated that only two of the patients with missing data had an excessively high C_{max}, one with a C_{max} of 1930 ng/dL, and one with a C_{max} of 2460 ng/dL. Finally, the Sponsor noted that of the 128 missing samples, 122 of them had valid data from the original assay; that is, these 122 samples came from assay runs that had not been contested by FDA.

Question 2

Based on the statistical analyses, along with the concordance assessment in this response, Endo believes the information is sufficient to support the conclusions in the Clinical Summary Report included in the Original NDA submission.

Does the Division concur?

Response: The adequacy of the information provided to support your conclusions will be a review issue. We have the following comments and requests in this regard:

- 1) We note 13 fewer patients in the re-assayed patient sample (n=125) compared to the original patient sample (n = 138).
 - a. Nine (9) were excluded due to lack of serum samples on Day 90, and four were excluded due to $\text{BMI} \geq 35 \text{ kg/m}^2$. The exclusion of 8 patients with $\text{BMI} < 35 \text{ kg/m}^2$ and insufficient data for re-analysis on Day 90 will be a major review issue. Clarify the reason for excluding these 8 patients.
 - b. Provide individual narratives for each of these 8 patients to include (1) test summary related to missing data, (2) table of testosterone concentrations and (3) testosterone PK curve showing missing testosterone concentrations.

Additional Discussion: The Sponsor noted that of the 8 patients with $\text{BMI} < 35 \text{ kg/m}^2$ and insufficient data for re-analysis on Day 90, there were no “back-up” samples at all for Day 90. The Sponsor believes that the original Day 90 samples were not properly split in these 8 patients. The Division requested that Sponsor investigate this issue further to determine why no back-up samples at all were available for Day 90 for these 8 patients.

- 2) We note that at least one patient with a high serum T concentration on Day 90 (2460 ng/dL) from the original analysis was excluded from the re-analysis. Exclusion of patients with high serum T concentrations on Day 90 from the re-analysis is of concern and will be a review issue.

Additional Discussion: The Sponsor re-iterated that no “back-up” sample for Day 90 was available for this patient. However, the Sponsor noted that the original concentration (2460 ng/dL) came from a valid assay run, one that had not been contested by FDA.

- 3) We note that 236 of the 290 (81.4%) total testosterone values from Days 35 and 90 that did not meet original bioanalytical acceptance criteria had re-assayed values available. Clarify how many of these 54 missing re-assayed values were from Day 35, and how were many from Day 90. If none of these samples are available, then the value of the concordance analysis of only remaining samples is diminished. This will be another critical NDA review issue.

Additional Discussion: The Sponsor stated that the total number of samples from Days 35 and 90 that did not meet original bioanalytical acceptance criteria and were included in the concordance analysis was 250, not 290. The total number of back-up samples available for re-analysis was 236. Therefore, the concordance analysis includes 94% of the original samples, lacking just 14 pairs. The Sponsor stated that 90 of 97 samples from Day 35, and 146 of 153 samples from Day 90 were available for the re-analysis. The Division acknowledged that the percentage of missing data is less than originally stated in the Sponsor’s meeting package. The Sponsor reiterated their belief that the concordance analysis supports the reliability of the original data.

- 4) The exclusion of subjects with $\text{BMI} \geq 35 \text{ kg/m}^2$ from the primary analysis is a potential labeling issue.

Additional Discussion: The Sponsor acknowledged that exclusion of subjects with BMI ≥ 35 kg/m² from the primary analysis is a potential labeling issue. The Division stated that it will review the data with these obese patients excluded and with them included. The Division noted that hypogonadal men may be obese.

Question 3

Endo believes the Table of Contents and the submission plan contains all the required elements to constitute a CR. Does the Division concur?

Response: In addition to the planned elements outlined in the draft Table of Contents, we request the following:

- 1) The Study Report for FOR01C in Section 5 should include:
 - a. A detailed description of the re-analysis.
 - b. Individual patient narratives as requested above.
- 2) SAS transport file comparing original analysis and re-analysis of both individual PK values and total testosterone concentrations.

Additional Discussion: The Sponsor agreed to provide a detailed description of the re-analysis and the individual patient narratives. The Sponsor stated that the final study report for FOR01C would not be "re-opened", but instead it would include an Addendum containing the results of the re-analysis and all information requested by FDA. The Sponsor agreed to provide the SAS transport file as requested. The Sponsor concluded by stating that they are planning to submit the CR by June 30, 2010.

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

The Division will provide meeting minutes to the Applicant within 30 days of the date of the meeting.

ATTACHMENTS AND HANDOUTS

None

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21463

GI-1

ENDO
PHARMACEUTICA
LS INC

FORTIGEL (TESTOSTERONE
GEL) 2%

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

/s/

MARK S HIRSCH
06/30/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021463

MEETING MINUTES

Endo Pharmaceuticals Inc.
Attention: Colleen Murray, MS
Associate Director, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Ms. Murray:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone 2% Gel.

We also refer to the teleconference between representatives of your firm and the FDA on December 1, 2009. The purpose of the meeting was to discuss the timing of your "wash-off" study, clarification of your Complete Response, and your proposed plan for comparison and analysis of your pharmacokinetic (PK) data.

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 Jeannie Roule, Regulatory Health Project Manager at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Suresh Kaul, M.D., MPH
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

Meeting Type: Type A
Meeting Category: Post-Action
Meeting Date and Time: December 1, 2009@ 9-10a.m.
Meeting Location: Teleconference

Application Number: NDA 021463
Product Name: testosterone 2% gel
Indication: Testosterone replacement therapy
Sponsor/Applicant Name: Endo Pharmaceuticals, Inc.

Meeting Chair: Suresh Kaul, M.D., MPH
Meeting Recorder: Jeannie Roule

FDA ATTENDEES:

George Benson, M.D. Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Suresh Kaul, M.D., MPH Medical Team Leader, DRUP
Guodong Fang, M.D. Medical Officer, DRUP
Myong Jin Kim, Pharm.D. Clinical Pharmacology Team Leader, Division of Clinical Pharmacology (DCP) III, Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Hyunjin Kim, Pharm.D. Clinical Pharmacology Reviewer, DCP III, OCP, OTS
Kate Dwyer, Ph.D. Statistical Reviewer, Division of Biometrics III (DBIII), OTS
Sean Kassim, Ph. D. Pharmacologist, Division of Scientific Investigations (DSI), Office of Compliance (OC)
Martin Yau, Ph. D. Pharmacologist, DSI, OC
Carol Rivera-Lopez, Ph.D. Pharmacologist, DSI, OC
Jennifer Mercier Chief, Project Management Staff, DRUP
Margie Kober, R.Ph, M.P.A. Chief, Project Management Staff, DRUP
Jeannie Roule Regulatory Health Project Manager, DRUP

SPONSOR ATTENDEES:

Neil Shusterman, MD Senior Vice President, Clinical Research & Drug Safety
Theodore Danoff, MD, PhD Vice President, Clinical Development
William Fiske, PhD Senior Director, Drug Metabolism & PK
Paula Clark Director, Regulatory Affairs
Colleen Murray Associate Director, Regulatory Affairs
Frank Diana, PhD VP, Pharmaceutical Development
Liang Yuh, Ph.D. Vice President, Biostatistics and Programming
Yusong Chen, Ph.D. Senior Director, Biostatistics and Programming
Simon Lemmy FORTESTA Brand Director, Commercial
Julian Howell Head of Clinical Development at ProStrakan, Inc.

BACKGROUND:

This NDA was originally submitted on May 31, 2002, and was issued a Not Approvable letter on July 3, 2003. On April 17, 2009, the Applicant submitted a Complete Response to our July 3, 2003, action letter. We issued another Complete Response to the Applicant on October 16, 2009. The reasons for the Complete Response action were as follows:

The Division of Scientific Investigations (DSI) conducted an audit of the (b) (4) analytical laboratory located in (b) (4). The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from your single phase III clinical study (FOR01C). These deficiencies raised serious questions regarding the validity of the data needed to determine the efficacy and safety of the drug product.

In addition, no information has been submitted regarding whether the testosterone gel 2% can be removed from the skin by washing.

DISCUSSION:

The following preliminary draft responses were provided to the sponsor on November 25, 2009, in response to the questions posed in the sponsor's meeting package. The sponsor's questions are presented below in **bolded** text, followed by the Division's responses in normal text. All additional discussion is summarized in *italics*.

Question 1:

If the Agency is in agreement that the "Wash Off" Study can be conducted as a PMR, then the expected data to be submitted will be a small package related to correction of the deficiencies at (b) (4) and a very brief safety update. (b) (4)

Does the Agency concur?

FDA Response to Question 1:

(b) (4)
(b) (4) The resubmission should address all issues listed in the CR letter.

Additional Discussion:

The Applicant confirmed that they had no additional comments or questions pertaining to this issue.

Question 2:

Does the Agency concur that the proposed Hand Wash Study design is appropriate (b) (4)

FDA Response to Question 2:

No. The design of the “wash off” study requires further discussion.

(b) (4)

In addition, the following aspects of the study should be pre-defined in the study protocol and kept consistent across all subjects:

- Specify and control the size of the drug application site
- Specify and control the time of washing relative to dosing (e.g. 30 minutes post-dose)
- Specify and control the duration and method of washing/showering with soap and water
- Specify and control the process for wiping the application site

We recommend that you submit the full revised protocol for our review.

The timing of the submission of the “wash off” study will be further discussed at the meeting. If the complete response will be submitted prior to the completion of the “wash off” study, the “wash off” study can be performed as a post-marketing requirement.

Additional Discussion:

The Applicant stated that their study design for the hand washing study was discussed during a prior teleconference that was held on October 1, 2009. The Applicant had agreed that a hand washing study (b) (4) would be performed. The Applicant had prepared a protocol synopsis based on the guidance that the Division provided during that meeting. The Applicant stated that the Division’s preliminary response to question number 2 is substantially different from what was discussed during the October 1, 2009, teleconference and the Division agreed.

Currently, the Division believes that there is a greater potential for transference from the application site than from the fingers. Further discussion concerning using the fingertips, hands or application site for the “wash off” study ensued.

The Division suggested that the Applicant submit a White Paper that justifies (b) (4)

The Applicant explained that they are willing to amend the study design as needed. The Applicant agreed and confirmed that they would provide the revised study protocol with their Complete Response.

Question 3:

Endo proposes using the equivalence analysis method to compare the previously submitted total testosterone values to the newly generated values. This method is derived from FDA's

Guidance for Industry: Bioanalytical Method Validation. As this approach reflects accepted FDA Guidance, does the Agency concur that this approach is acceptable?

FDA Response to Question 3:

More detailed information is required in order to evaluate this approach. Specifically:

- The source and selection of the samples being re-assayed for testosterone are not specified. We assume that these samples are from Study FOR01C. If so, which samples are to be re-assayed and how does their selection represent the remaining 3400+ samples not being re-assayed?
- How does this approach address the absence of audit trails for 246 of the 259 total testosterone batches?
- How does establishing the reproducibility of 280 samples address the 291 total testosterone samples (from 65 subjects) rejected due to batch failure (unacceptable QCs)?
- The 15% rule cited in the Bioanalytical Method Validation Guidance is intended to evaluate the accuracy and precision of quality controls and standards, not to establish equivalence between old and re-assayed samples. What is the rationale supporting this “equivalence analysis method”?
- Incurred sample reproducibility and sample stability for the elapsed storage time were not addressed in your proposal.

Additional Discussion:

The Applicant explained that the (b) (4) will reanalyze samples from the pivotal study. These samples were identified by DSI and reported in observation 5 of the FDA-483. The Applicant further stated that the runs not included in observation 5 will not be re-analyzed. The Applicant explained that (b) (4) provided 13 audit trails in their response to the last FDA inspection. The Applicant further stated that they plan to reestablish the integrity and reliability of the results. They will rerun 280 total testosterone samples, as there are backups for only 280 of the 291 failed samples identified in observation 5. The Applicant believes that their Bioanalytical Validation (including stability data) will be sufficient.

The Division inquired if the Applicant intends to reanalyze the total testosterone samples that did not meet the original quality control (QC) criteria and, if that is the case, the Division would prefer reassay of all samples from the 65 subjects that had samples originally analyzed in the failed total testosterone analytical runs.

The Applicant believes that the samples from the other runs were considered valid and had met the QC criteria.

The Division stated that, at a minimum, the Applicant needs to reanalyze study samples in the failed batches, but, in addition, should reanalyze all of the total testosterone samples from the 65

subjects to minimize run to run data variabilities. This approach would be more effective to re-establish the accuracy and integrity of the data. Because the study is more than two years old, longer stability data will need to be provided. In addition, the Division would like the Applicant to reanalyze other analytes as well. By presenting all of the analytes, the Applicant will have an opportunity to further establish that all results are consistent and reliable.

The Division stated that, if the Applicant's plan is to compare the reassayed data to the failed run data, such an approach would not be acceptable and a different approach would be needed. The Division stated that the Applicant needs to reanalyze and then re-evaluate all of the data. It is not acceptable to compare new data with old data for which you cannot establish validity. This approach might be considered a secondary method but it cannot be the primary approach. All failed and rejected data must be excluded from your report.

The Division inquired about the audit trails for all of the runs. The Applicant explained that not all of the audit trails are available but they would like to submit some other type of information, such as bar code readings. The Division stated that they will evaluate this information but we do not currently think that this will take the place of an audit trail.

The Division recognizes that the Applicant had submitted a second response to DSI's initial report but the Division still has concerns about the laboratory. The Division still questions how some of the data is being generated. The Division reminded the Applicant that it is unclear how the data from the freeze/thaw stability experiment were generated and that the details of the DHT validation experiment submitted in the first response were not provided by the laboratory.

The Applicant stated that all of the pertinent data will be provided and that they would like to discuss the problem concerning the audit trails with us at a teleconference in the near future.

The Division reiterated that since the Applicant does not have the audit trails, we will need to evaluate other supportive data. The Division also inquired about incurred sample reproducibility (ISR) assessments.

ISSUES REQUIRING FURTHER DISCUSSION:

The Division informed the Applicant that they will need to submit the following information:

- "Wash off" Protocol so that it can be reviewed and further discussed
- Statistical Analysis Plan (SAP)
- Details of how results were obtained for freeze/thaw stability study, DHT measurements, and long-term stability study

ACTION ITEMS:

Meeting minutes will be provided to the Sponsor within 30 days.

ATTACHMENTS/HANDOUTS:

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21463	GI-1	ENDO PHARMACEUTICA LS INC	FORTIGEL (TESTOSTERONE GEL) 2%

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

/s/

SURESH KAUL
01/07/2010



NDA 21-463

Cellegy Pharmaceuticals
Attention: William Schary, Ph.D., RAC
Vice President, Regulatory Affairs and Quality
349 Oyster Point Blvd., Suite 200
South San Francisco, CA. 94080

Dear Dr. Schary:

Please refer to your May 31, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tostrex 2% (testosterone gel).

We also refer to the submission sent via facsimile on July 30, 2002.

We are reviewing the clinical section of your submission and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please provide patient number, dose, and the study day that the pharmacokinetics (PK) was performed for all patients with a C_{max} of testosterone of greater than 1800 ng/dL. In addition, please provide a discussion of the safety implications of these supraphysiologic testosterone levels.
2. In response to Questions 1 and 2 contained in your faxed document on July 30, 2002:
 - a) Regulatory action for each NDA amendment will be determined by the Division at the time of receipt of that amendment. Safety updates are required 120 days after the NDA submission and at least 91 days prior to final regulatory action.
 - b) Please provide the limited interim report (adverse events and concomitant medications) with the 120-day safety update.
 - c) Please provide the interim report once all subjects have reached the 6-month point with the 7-month safety update.
3. In response to Question 3:

The Division prefers submission of these graphs electronically.
4. In response to Question 4:

Please provide one desk copy, in addition to the archival copy. Please refer the to the guidance for industry titled *Formatting, Assembling and Submitting New Drug and Antibiotic Applications*. The guidance can be found at <http://www.fda.gov/cder/regulatory/applications/NDA.htm>

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products,
HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research



NDA 21-463

ACKNOWLEDGE TRANSFER NDA OWNERSHIP

Endo Pharmaceuticals Inc.
Attention: Colleen Murray, MS
Associate Director, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Ms. Murray:

We acknowledge receipt on September 9, 2009, of your September 8, 2009, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product: Fortesta™ (testosterone) 2% Gel

NDA Number: 21-463

Name of New Applicant: Endo Pharmaceuticals Inc.

Name of Previous Applicant: Prostrakan, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Endo Pharmaceuticals, Inc. as the applicant of record for this application.

All changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation except that changes in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor may be reported in the next annual report. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

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 questions, call Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

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

cc: Prostrakan, Inc.
1430 US Highway 206, Suite 110
Bedminster, NJ 07921-2652

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
JDA-21463	GI-1	PROSTRAKAN LTD	FORTIGEL (TESTOSTERONE GEL) 2%
NDA-21463	GI-1	PROSTRAKAN LTD	FORTIGEL (TESTOSTERONE GEL) 2%

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
09/17/2009



NDA 21-463

INFORMATION REQUEST

Endo Pharmaceuticals Inc.
Attention: Colleen Murray, MS
Associate Director, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Ms. Murray:

Please refer to your April 17, 2009, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fortesta™ (testosterone) 2% gel.

We also refer to your submission dated August 19, 2009.

After review of your proposed REMS and REMS supporting document, and in consultation with the Division of Risk Management (DRISK), Office of Surveillance and Epidemiology (OSE), we have the following requests and comments.

1. Revise the REMS document incorporating the changes indicated in Appendix A.
2. The Medication Guide distribution plan is generally acceptable.
3. We remind you of the requirement to comply with 21 CFR 208.24(d):

A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

“Dispense the accompanying Medication Guide to each patient” or
“Dispense the enclosed Medication Guide to each patient”

4. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable. You will need to prominently identify the submission containing the REMS assessments with the following wording in bold capital letters at the top of the first page of the submission:

NDA 21-463 REMS ASSESSMENT

5. Submit for review a detailed plan to evaluate patients' understanding about the safe use of FORTESTA™ (testosterone) 2% Gel. Your detailed plan should be submitted as part of the REMS supporting document. This information **does not** need to be submitted for FDA

review prior to approval of your REMS, however, it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS-Other."

6. If you plan to conduct this assessment using a survey, your submission should include all methodology and instruments that will be used to evaluate the patients' understanding about the safe use of FORTESTA™ (testosterone) 2% Gel. This should include, but not be limited to:
- Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)
 - The expected number of patients to be surveyed
 - How the participants will be recruited
 - How and how often the surveys will be administered
 - Explain controls used to minimize bias
 - Explain controls used to compensate for the limitations associated with the methodology

The submission should also include the survey instruments (questionnaires and/or moderator's guide) and any background information on the testing survey questions and how they correlate to the messages in the Medication Guide.

7. Resubmit the revised REMS document as soon as possible. The REMS supporting document may also be submitted at this time for our review, but it is not required for approval. Provide the documents in Word format and include a track changes and clean version.

If you have questions, call Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IDA-21463

ORIG-1

PROSTRAKAN LTD

FORTIGEL (TESTOSTERONE
GEL) 2%

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/s/

GEORGE S BENSON

09/16/2009



NDA 21-463

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

ProStrakan Inc.
1430 US Highway 206, Suite 110
Bedminster, New Jersey 07921-2652

ATTENTION: Mary E. Norvitch, Ph.D.
Vice President, US Regulatory Affairs

Dear Dr. Norvitch:

Please refer to your New Drug Application dated May 31, 2002, received June 3, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Gel 2%.

We also refer to your June 3, 2009, correspondence, received June 4, 2009, requesting review of your proposed proprietary name, Fortesta. We have completed our review of the proposed proprietary name, Fortesta, and have concluded that it is acceptable.

The proposed proprietary name, Fortesta, 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 June 3, 2009, 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, Jeannie Roule, at (301) 796-3993.

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

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21463	ORIG 1		FORTIGEL (TESTOSTERONE GEL) 2%

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/s/

CAROL A HOLQUIST
08/13/2009



NDA 21-463

INFORMATION REQUEST LETTER

ProStrakan, Inc.
Attention: Mary Norvitch, Ph.D.
Vice President, US Regulatory Affairs
1430 US Highway 206
Suite 110
Bedminster, NJ 07921-2652

Dear Dr. Norvitch:

Please refer to your April 17, 2009, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone 2% gel.

We are reviewing your application and have the following Chemistry and Manufacturing Controls (CMC) comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. It is not acceptable to wait until 12 months after approval to set a specification for components of the (b) (4) or for in-vitro release. As per **ICH Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances**, it is recognized that limited data may be available at the time of filing and an interim specification may be set that can be modified after more data are available. We have the following specific comments concerning these tests:
 - a. For isopropanol, oleic acid and propylene glycol, the limits should be set at (b) (4) of target unless data are available to justify different limits.
 - b. For in-vitro release, the test should be validated and performed on all primary stability batches of drug product. The data should be submitted no later than July 31, 2009, in order to set an interim specification prior to approval.
2. There are insufficient data available to set an expiry for drug product manufactured at the (b) (4) site since only release data are provided. Provide at least three months of both long term and accelerated stability data on the three batches of drug product packaged in the proposed commercial container closure system. The data must also include values for the following tests: Content of Isopropanol, Propylene Glycol and Oleic Acid, and In-vitro Release. Additional stability data on the primary stability batches manufactured at (b) (4) should also be updated at the same time and should include the tests listed above. In order to allow adequate time for review and to make a determination on expiry during this review cycle, the information should be submitted by July 31, 2009.

If you have any questions, call Jeannie Roule, Regulatory Health Project Manager, at 301-796-3993.

Sincerely,

{See appended electronic signature page}

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

George Benson

5/29/2009 01:55:12 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-463

ProStrakan, Inc.
Attention: Mary Ellen Norvitch, Ph.D.
Vice President, Regulatory Affairs, US
1430 US Highway 206, Suite 110
Bedminster, NJ 07921-2652

Dear Dr. Norvitch:

We acknowledge receipt on April 17, 2009, of your April 17, 2009, resubmission to your new drug application for Fortigel™ (testosterone) 2% Gel.

We consider this a complete, class 2 response to our July 3, 2003, action letter. Therefore, the user fee goal date is October 17, 2009.

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 acknowledge receipt of your request for a partial waiver and a partial deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have waived and/or deferred the pediatric study requirement for this application.

If you have any question, call Jeannie Roule, Regulatory Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff Director
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
5/1/2009 03:20:33 PM



NDA 21-463

ProStrakan, Inc.
Attention: Mary Ellen Norvitch, Ph.D.
Vice President, US Regulatory Affairs
1430 US Highway 206, Suite 110
Bedminster, NJ 07921-2652

Dear Dr. Norvitch:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fortigel™ (testosterone) 2% gel.

We also refer to your March 7, 2008, correspondence, received March 10, 2008, requesting a meeting to discuss and reach agreement on the content and format of the Resubmission (Complete Response to the July 3, 2003, Non-Approvable Letter).

On June 23, 2008, we provided our draft preliminary responses to the questions presented in your May 22, 2008, meeting package. After receipt and review of these draft responses, you informed the Division via email communication that a meeting is not necessary at this time and you requested to cancel the meeting.

The final version of our responses is enclosed. You are responsible for notifying us of any significant differences in understanding.

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

Sincerely,

{See appended electronic signature page}

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Memorandum of Meeting Communication

Scheduled Date of Meeting: June 26, 2008

Date Cancelled: June 23, 2008

NDA 21-463

Drug Name: Fortigel (testosterone) 2% Gel

Proposed Indication: treatment of male hypogonadism

Sponsor's Questions and Division Responses:

Question 1: During the course of the Original NDA review, the invented names "TOSTREX" and "TOSTRAN" were ruled unacceptable by the Agency. Is FORTIGEL an acceptable name for this product?

Division's Response:

A consultation will be submitted to the Division of Medication Errors and Technical Support (DMETS) at the time of NDA re-submission to determine the acceptability of the proposed tradename "Fortigel."

Question 2: ProStrakan will provide the Resubmission dossier in the same format as that of the Original NDA, i.e. as a hybrid Common Technical Document where most of the NDA is supplied as a paper copy and the following items are supplied as PDF files on CD ROMs:

- a) **Clinical Study Patient Data Listings**
- b) **Case Report Forms (including copies of the data clarification sheets and clinical laboratory printouts)**
- c) **Copies of the published references**

SAS transport files will also be provided.

Is this acceptable to FDA?

Division's Response:

Your proposal is acceptable.

Question 3: ProStrakan will present in the Resubmission a point-for-point response to the 03 Jul 2003 Non Approvable and 19 Jul 2007 IND 76,634 Advice Letters. The Resubmission will include new data only with cross reference to the Original NDA and previous submissions, i.e. Clinical Study Reports and Case Report Forms for older studies will not be resubmitted. Is this acceptable to FDA?

Division's Response:

Yes.

Question 4: In response to Chemistry, Manufacturing and Controls (CMC) questions raised in the 19 Jul 2007 IND 76,634 Advice Letter (provided in Appendix 7.1), ProStrakan will provide a point-for-point response in Module 1.12 *Other Correspondence* of the Resubmission together with the following information:

- a) Tests developed and implemented to quantitate all components of the [REDACTED] (b) (4) [REDACTED] in the gel at the time of release as well as shelf life.
- b) Test developed and implemented for *in vitro* release testing of the drug substance from the gel at the time of release as well as shelf life.
- c) Justification of the drug product specification acceptance limit for butylated hydroxytoluene (BHT).
- d) Updated drug product stability data, including determination of degradation products listed in the specification.

Is this acceptable to FDA?

Division's Response:

An overview of the responses may be submitted in Module 1.12 **Other Correspondence**. Full information on each point should be included in the appropriate section of Module 3 and a summary provided in Module 2. If no changes are made in specific sections of the CTD format, reference can be made to the original NDA noting that no changes have been made, with the following exceptions:

- 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 for an individual at the site, detailed responsibilities of that facility and a date of when the facility was last inspected by FDA. This information will help to facilitate inspection requests. This comprehensive table should be attached to the 356h. Full information should still be provided in the appropriate sections of Modules 2 and 3.
- Provide an updated drug product specification sheet.
- Provide updated color carton and immediate container labels, including any logos, in order to allow full review of these labels.

Question 5: An application for Deferral of Pediatric Studies was filed in the Original NDA. Can you please advise on the status of the deferral application?

Divisions' Response:

The request for deferral of pediatric studies will re-submitted to the Pediatric Review Committee (PeRC) at the time of NDA re-submission.

Question 6: In response to Clinical questions raised in the 03 Jul 2003 Non- Approvable Letter (provided in Appendix 7.1), ProStrakan will provide a point-for-point response in

Module 1.12 *Other Correspondence of the Resubmission with cross reference to new Modules 2.5, 2.7 and 5. Is this acceptable to FDA?*

Division's Response:

Yes.

General Clinical Comments:

- Data should be submitted to justify using the 2 hour post dose serum testosterone concentration for dosage adjustment.
- Skin safety data obtained in studies in females should be submitted.

General Clinical Pharmacology Comments:

- Confirm that the formulation and manufacturing sites of Fortigel employed in the study FOR01C are the same as that of the to-be-marketed Fortigel.
- Provide subgroup analyses of testosterone concentrations based on Body Mass Index (BMI, e.g. 22-25, 25-30, and 30-35) and ethnicity.
- Submit the following information in table format:
 - Serum total testosterone concentration vs. body weight
 - Testosterone concentration at 2-hour post dose at each visit where this was measured for each individual

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/s/

George Benson
6/27/2008 02:58:23 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-463

ProStrakan, Inc.
Attention: Mary Ellen Norvitch, Ph.D.
Vice President, US Regulatory Affairs
1430 US Highway 206, Suite 110
Bedminster, NJ 07921-2652

Dear Dr. Norvitch:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fortigel™ (testosterone) 2% gel.

We also refer to your March 7, 2008, correspondence, received March 10, 2008, requesting a meeting to discuss and reach agreement on the content and format of the Resubmission (Complete Response to the July 3, 2003, Non-Approvable Letter).

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B 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: May 15, 2008

Time: 10:00 – 11:30 AM

Location: 10903 New Hampshire Ave., White Oak Building, Conference Room 1309
Silver Spring, MD 20995-0002

The following attendees are invited to the meeting:

Scott Monroe, M.D. – Director, Division of Reproductive and Urologic Products (DRUP)

George Benson, M.D. – Acting Deputy Director, DRUP

Guodong Fang, M.D. – Medical Officer, DRUP

Jennifer Mercier – Chief, Project Management Staff, DRUP

Krishan Raheja, DVM – Pharmacology/ Toxicology Reviewer, DRUP

Lynnda Reid, Ph.D. – Pharmacology Supervisor, DRUP

Donna Christner, Ph.D. – Pharmaceutical Lead, Division of Pre-Marketing II, Office of New Drug Quality Assessment (ONDQA)

Hyunjin Kim, Ph.D. – Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III, Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)

Myong Jin Kim, Pharm.D. – Clinical Pharmacology Team Leader, DCP III, OCP, OTS

Mahboob Sobhan, Ph.D. – Team Leader, Office of Biometrics, OTS

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 eufrecina.deguia@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 my phone number so I can pick you up from the lobby and escort you to the conference room.

Provide the background information for this meeting (three copies to the NDA and 10 desk copies to me) at least one month 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 April 15, 2008, we may cancel or reschedule the meeting.

If you have any questions, please call me at (301)796-0881.

Sincerely,

{See appended electronic signature page}

Eufrecina P. DeGuia
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/

Eufrecina deGuia
3/24/2008 01:54:40 PM



NDA 21-463

ACKNOWLEDGMENT LETTER

ProStrakan, Inc.
Attention: Mary Ellen Norvitch, Ph.D.
Vice President, US Regulatory Affairs
1430 State Highway 206, Suite 110
Bedminster, NJ 07921

Dear Dr. Norvitch:

We acknowledge receipt of your January 29, 2008, correspondence notifying the Food and Drug Administration that the corporate address has been changed from

1005 Radley Drive
West Chester, PA 18392

to

1430 State Highway 206
Suite 110
Bedminster, NJ 07921

for the following new drug application:

NDA 21-463 for Fortigel™ (testosterone) 2% Gel.

We have revised our records to reflect this change.

If you have any questions, call me at (301) 796-0932.

Sincerely yours,

{See appended electronic signature page}

John C. Kim, R.Ph., J.D.
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/

John C. Kim
2/22/2008 08:20:04 PM



NDA 21-463

Cellegy Pharmaceuticals, Inc.
Attention: David A. Karlin, M.D.
Vice President, Clinical Research
349 Oyster Point Blvd., Suite 200
South San Francisco, CA 94080

Dear Dr. Karlin:

Please refer to your New Drug Application (NDA) for Fortigel™ (testosterone gel) 2% submitted June 3, 2002, not approved July 3, 2003, and your Investigational New Drug Application (IND) (b) (4) submitted under section 505(b) and 505(i) of the Federal Food, Drug, and Cosmetic Act, respectively.

We also refer to both of your January 12, 2004, submissions. The first submission asked the Division to comment on your plans to prepare and submit a Class 2 resubmission based on the final report of a Phase 3 study, CP601B 02-02-01, submitted under this NDA. The second submission was the referenced Clinical Study Report, CP601B 02-02-01, submitted under IND (b) (4)

We have reviewed your submissions and the Division has continued concerns relating to the high supraphysiologic C_{max} serum testosterone levels achieved in a significant proportion of patients. There continues to be insufficient information provided to demonstrate that the dose of this product can be adjusted to preclude these high serum testosterone levels. The Division also cannot agree to a dose adjustment regimen predicated on the Monte Carlo simulation because C_{max} levels of testosterone are not predictable based on dose and there are no clinical data for doses lower than 40 mg. The bases for the Division's concerns are summarized below.

1. The percentage of patients with a C_{max} of testosterone ≥ 1500 ng/dl on Day 56 (20/65, 31%) is not substantially improved over the previous study T 00-02-01 in which 65/146 (45%) patients had a C_{max} value of ≥ 1500 on Day 56.
2. Exclusion of patients with $C_{max} > 2500$ on Day 14 would not significantly reduce the percentage of patients with a $C_{max} \geq 1500$ on Day 56. If the 7 patients with a $C_{max} > 2500$ on Day 14 were excluded, 18/58 (31%) of the remaining patients had a $C_{max} \geq 1500$ on Day 56; 4/58 had $C_{max} > 2500$, and one had $C_{max} > 4500$. A substantive number of patients whose Day 14 C_{max} was < 1500 had a C_{max} at Day 56 that exceeded 1500. In fact, on Day 56, 4/65 (6%) had C_{max} values ≥ 2500 ng/dl.
3. It is not clear why the C_{max} values at Days 14 and 56 are disparate when steady state should have occurred by Day 14. In the patients who remained on 3 grams of the drug, although none had $C_{max} \geq 1500$ on Day 14, 8/23 (35%) had testosterone levels ≥ 1500

on Day 56. One patient in this group had a C_{\max} value of > 4500 on Day 56. In the group that dose escalated from 3 grams to 4 grams at Day 14, none of the patients had $C_{\max} \geq 1500$ on Day 14, but 9/31 had $C_{\max} \geq 1500$ on Day 56 (3 patients had $C_{\max} > 2500$).

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel

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NDA 21-463

Cellegy Pharmaceuticals, Inc.
Attention: Daniel L. Azarnoff, M.D., F.A.C.P.
Senior Vice President, Clinical and Regulatory Aff
349 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080

Dear Dr. Azarnoff:

Please refer to the meeting between representatives of your firm and FDA on July 30, 2003. The purpose of the meeting was to obtain clarification on the deficiencies identified in the Not Approvable letter and to explore what additional information is necessary to remedy the identified deficiencies.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

Date: July 30, 2003 **Time:** 3:00 – 4:15 PM **Location:** Parklawn, 17-05
NDA: 21-463 **Drug Name:** Fortigel™ (testosterone gel) 2%
Sponsor: Cellegy Pharmaceuticals
Type of Meeting: “Post-Action” Meeting
Meeting Chair: Dr. Daniel Shames **External Lead:** Michael Forrest
Meeting Recorder: John Kim

FDA Attendees:

Daniel Shames, M.D. – Director, Division of Reproductive and Urologic Drug Products (HFD-580)
Donna Griebel, M.D. – Deputy Director, DRUDP (HFD-580)
George Benson, M.D. – Urology Team Leader, DRUDP (HFD-580)
Guodong Fang, M.D. - Medical Officer, DRUDP (HFD-580)
Margie Kober, R.Ph. – Chief, Project Management Staff, DRUDP (HFD-580)
Eufrecina DeGuia - Regulatory Health Project Manager, DRUDP (HFD-580)
Dhruba Chatterjee, Ph.D. – Clinical Pharmacology Reviewer, DRUDP (HFD-580)
John Kim, R.Ph., J.D. – Regulatory Project Manager, DRUDP (HFD-580)
Donna Christner, Ph.D. – Chemistry Reviewer, DNDC II @ DRUDP
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics, OCPB@DRUDP (HFD-580)
Leslie Kenna, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

External Attendees:

Michael Forrest - CEO and President, Cellegy Pharmaceuticals, Inc.
Daniel Azarnoff, M.D. – Sr. Vice President, Regulatory and Medical Affairs, Cellegy Pharmaceuticals, Inc.
David Karlin, M.D. – Vice President, Clinical Research, Cellegy Pharmaceuticals, Inc.
Vivien Mak, Ph.D. – Vice President, Research, Cellegy Pharmaceuticals, Inc.
William Schary, Ph.D., RAC –Vice President, Regulatory Affairs & Quality, Cellegy Pharmaceuticals, Inc.
Jack Chandler – Vice President, Corporate Development, Cellegy Pharmaceuticals, Inc.

(b) (4)

Wayne Meikle, M.D. – Professor of Medicine, School of Medicine, University of Utah, Clinical Consultant

Background:

NDA 21-463 Fortigel™ (testosterone gel) 2% was submitted on June 3, 2002. The indication is for testosterone replacement therapy in males with a deficiency or absence of endogenous testosterone.

Because of a major amendment submitted on January 30, 2003, the User Fee Goal Date was extended for three months to July 3, 2003. A not approvable letter was issued on July 3, 2003.

Meeting Objectives:

- To obtain clarification on the deficiencies identified in the Not Approvable letter, specifically:
 - lack of evidence to support that high supraphysiologic daily C_{max} is safe for chronic administration.
 - lack of information to support that dosage can be adjusted to prevent high supraphysiologic testosterone levels.
- To explore what additional information is necessary to remedy the identified deficiencies.

Discussion:

- Agency is concerned with high C_{max} because it is unknown whether long term exposure to daily high testosterone levels is safe. The supraphysiologic levels seen with Fortigel™ are too high for replacement therapy.
- There was continued disagreement as to the importance of the high C_{max} which had been discussed during the Pre-NDA meeting. (see Pre-NDA Meeting Minutes, dated October 29, 2001) The sponsor stated that they were unaware of Agency's concerns over C_{max} , and its importance in relationship with C_{min} and $C_{average}$ data.
- Sponsor presented a slide presentation. Key points presented by the sponsor were:

(b) (4)

- Agency suggested that the sponsor's anticipated dose response may not be borne out in prospective data due to the power of the penetration enhancers present in

Fortigel™. In addition, Agency expressed concerns that peak to trough ratio may be too high and asked whether the sponsor is planning to propose a lower dosage.

- Sponsor responded that by increasing surface area, rotating site and using several dose adjustments, the peak/trough ratio would be reduced and would improve pharmacokinetic profile. Sponsor emphasized that they believe that the benefit of Fortigel™ is the ability to dose adjust it with the dispenser, a feature currently unavailable with other testosterone products.
- Sponsor asked whether a reduction of the proportion of patients with $C_{max} > 1500$ from 31% to 17.5% in the additional Study 02-02-01 would have an effect on approval. Agency stated that they could not make such a determination without reviewing the additional data to determine if dose optimization is effective. In addition, the Agency stated their reservations that the data from this study may at best establish a dose to be studied in a new prospectively designed, adequate and well controlled trial.

Action Items:

- PM will send official minutes of the meeting to the Sponsor within 30 days.
- Sponsor will submit results from their analysis of dose adjustment from their additional study with a dose adjustment schedule proposal.

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

{See appended electronic signature page}

Daniel Shames, M.D.
Meeting Chair

Attachment

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/s/

Donna Griebel

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-463

Cellegy Pharmaceuticals, Inc.
Attention: William Schary, Ph.D., RAC
Vice President, Regulatory Affairs and Quality
349 Oyster Point Boulevard, Suite 200
South San Francisco, CA 94080

Dear Dr. Schary:

Please refer to your May 31, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone gel 2%.

On January 31, 2003, we received your January 30, 2003 major 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 July 3, 2003.

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
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/

Margaret Kober
3/19/03 02:45:59 PM
Chief, Project Management Staff

Teleconference Minutes

Date: 25-FEB-2003 **Time:** 3:45-4:05 PM **Location:** 17B45 Conference Room

NDA: 21-463 **Drug Name:** Testosterone 2% gel

Indication: Androgen Replacement

Sponsor: Cellegy Pharmaceuticals

Reason for teleconference: To discuss FDA request that *in vitro* release testing be performed at release and stability, and the sponsor's 18-FEB-2003 Amendment indicating they want to perform this test only for a manufacturing change.

FDA Attendees: Moo-Jhong Rhee, Ph.D.-Chemistry Team Leader, DNDCII @ DRUDP
Donna F. Christner, Ph.D.-Chemistry Reviewer, DNDCII @ DRUDP
Margie Kober, Supervisory Project Manager DRUDP

Sponsor Attendees: Daniel Azarnoff, M.D.
J. C. Lee, Ph.D.
Chuck Lee

Discussion: Dr. Christner started the discussion with the request that *in vitro* release testing be performed at product release and for stability studies.

The sponsor maintained that this is unnecessary unless there is a manufacturing change involved. They also stated that obtaining a standard would be difficult due to the fact that over a long period of time the gel standard would change. (In our SUPAC-SS CMC-7 Guidance, the test is run as a side-by-side analysis of a standard gel batch and a new batch manufactured under any changes.) They were also concerned about the reproducibility with commercially available membranes for Franz cells.

Dr. Rhee stated that manufacturers of other gel products in our Division have agreed to the inclusion of routine *in vitro* release testing. He stated that a statistically significant number of lots could be used to establish the reference standard and that this historical data could be used as acceptance criteria. A reference slope could be established, and slope variation would be dependant on the manufacturing capabilities of future batches. Dr. Rhee did not share the sponsor's concerns about commercially available membranes.

The sponsor wanted clarification on the requirements for stability studies since inclusion of *in vitro* release testing for stability would involve a large number of samples. Dr. J.C. Lee wanted to know if the stability studies would just be on samples held at 25°C/60% RH and if they could be done yearly.

Dr. Rhee replied that the studies on the first three commercial batches would need to be done at the typical timepoints for stability at 25°C/60% RH (0, 3, 6, 9, 12, 18, 24 months and up to expiry), but the annual batches after that would be done yearly up to expiration.

The sponsor agreed. In a follow-up conversation with Dr. Azarnoff, he agreed to submit the commitment as an Amendment to the NDA.

Moo-Jhong Rhee, Ph.D.
Meeting Chair

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/s/

Donna Christner
3/10/03 12:49:53 PM
CHEMIST

Tcon minutes incorporating your change.

Moo-Jhong Rhee
3/10/03 01:42:59 PM
CHEMIST
I concur

Teleconference Minutes

Date: 13-FEB-2003 **Time:** 1PM **Location:** 17B45

NDA: 21463 **Drug Name:** Testosterone Gel 2%

Indication: Androgen replacement

Sponsor: Cellegy Pharmaceuticals

Dr. William Schary

Reason for teleconference: Discussion of data needed in response to Amendment #3 (13-FEB-2003)/Deficiency Responses

FDA Attendee: Donna F. Christner, Ph.D.

Discussion:

The reviewer called Dr. Schary to discuss points concerning the review of the 13-FEB-2003 Amendment. Discussion centered on the deficiencies, Cellegy's response to them, and our review. Not all deficiencies were discussed.

Deficiency 11: Density and Viscosity

The reviewer confirmed that the specifications set were acceptable as long as the sponsor agreed to their commitment to (b) (4)

The sponsor agreed.

Deficiency 12: In vitro Release Testing

The reviewer requested that this testing be performed on release and for stability, and not only when there was a manufacturing change. Validation data for the method was also requested and the sponsor was informed that this is a Review Issue.

The sponsor agreed.

Deficiency 15: Metered-dose Delivery

The reviewer requested that data be submitted, and that this was a Review Issue. Also, confusion about terminology between **dose** and **discharge** should be cleared up in the method.

The sponsor agreed to submit any data that is available. Dr. Schary would check with Dr. J.C. Lee to determine what is available. Dr. Lee is traveling today, but should be available on 14-FEB-2003.

Deficiency 22: Acceptance criteria for Impurities

The reviewer confirmed that the criteria for (b) (4) and Total Impurities (NMT (b) (4)) were acceptable, but for the other impurities, the limit should be set at NMT (b) (4) to reflect the stability data found to date and to agree with the drug substance manufacturers' criteria.

The sponsor agreed.

Deficiency 25: New stability protocols

The reviewer noted that the protocols would need to be updated to include changes discussed in the other deficiencies.

Deficiency 26: Freeze-thaw studies

The reviewer requested information on the inconsistent assay results, and wanted to know if studies were being conducted to determine the reason for the results, such as (b) (4). Also, the reviewer confirmed that there were plans to initiate studies with cycling between 4°C-40°C and that this should be a Phase IV commitment if it is not completed before the review. The reviewer stated that a caution statement of "Do not store below 10°C" should be included on the label instead of "Do Not Freeze" until the data for the 4°C studies are available and the stability at low temperature could be evaluated. The reviewer requested that all raw data for all studies be submitted for review because of the inconsistencies in the freeze-thaw studies. The reviewer also requested data for the impurity profile if it is available and if it shows an increase in degradation products is responsible for the inconsistent assay results.

The sponsor stated that they were looking at the data to try to determine why the assay values were low. Dr. Schary was not sure what stage they were on concerning the 4°C studies, but would check with Dr. Lee. Dr. Schary agreed with the new cautionary statement. He agreed to forward the requested data, although he needed to check with either Dr. Lee or the personnel at (b) (4) to find out how soon that could be accomplished. He agreed to forward any relevant data on impurity profiles or crystallization when they were available.

Dr. Schary stated that Cellegy was submitting a package today of requested material (Note: CMC request for info on pump system, in addition to information for the BioPharm reviewer). He stated that he did not think he could get all the information for our discussion by tomorrow, but would let me know the status on Tues. before the Division's Wed. meeting.

The reviewer confirmed receipt of a fax of the LOA for DMF (b) (4) on 12-FEB-2003, but requested that Cellegy either determine when the LOA for DMF (b) (4) had been submitted to the NDA previously or just to the CDR, or submit a copy when information is sent to the NDA. The sponsor agreed.

Donna F. Christner
Meeting Chair

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/s/

Donna Christner
3/7/03 10:08:32 AM
CHEMIST

Teleconference Minutes

Date: 12-FEB-2003 **Time:** 1 PM **Location:** 17B45

NDA: 21-463 **Drug Name:** Testosterone gel 2%

Indication: Androgen replacement

Sponsor: Cellegy

Reason for teleconference: Question on LOA for DMF (b) (4)

FDA Attendee: Donna F. Christner, Ph.D., Chemistry Reviewer

Sponsor Attend: Dr. J.C. Lee

Discussion: Dr. J.C. Lee initiated the phone conversation in response to a request by Freshnie DeGuia to Dr. Azarnoff in an unrelated phone call. There were three main topics of conversation:

1. LOA for DMF (b) (4)

Dr. Lee stated that the LOA for DMF (b) (4) had been submitted on approximately 03-OCT-2002, but he agreed to fax a copy for my records.

2. Information from Valois

I requested any additional information on the pump assembly that (b) (4) had sent him in response to the FDA 09-SEP-2002 tcon with (b) (4) and he agreed to forward the package they had sent to him. He stated he was not aware it was to be forwarded.

3. (b) (4)

I asked him to clarify if (b) (4) is the standard alcohol used in the production of the gel product. He stated that due to Canadian regulations, if they use (b) (4) in production they need to pay impound fees that would average \$5-6 million. This is not required if they use (b) (4)

(b) (4) He stated that if at some point manufacture would be done in the US, then (b) (4) would probably be used.

Donna F. Christner
Meeting Chair

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Donna Christner
3/7/03 10:05:09 AM
CHEMIST

Teleconference Minutes

Date: 03-MAR-2003 **Time:** 1:30 PM **Location:** 17B45

NDA: 21-463 **Drug Name:** Testosterone gel 2%

Indication: Androgen replacement

Sponsor: Cellegy Pharmaceuticals
Dr. J.C. Lee

Reason for teleconference: Timeline for setting of *in vitro* release specification.

FDA Attendee: Donna F. Christner, Ph.D.

Discussion: Dr. Lee initiated the phone call in response to a call to Dr. Azarnoff concerning the time line for setting specifications for *in vitro* release. In the Amendment dated 26-FEB-2003, point #2 stated that the "specification will be established by using the data generated from a statistically significant number of commercial lots..." The FDA requests a firm date for setting the specifications.

Dr. Lee stated that because they would do the test routinely, instead of only for a manufacturing change, they were planning to purchase an automated system. They have contacted (b) (4)) and were told that it would take 4-6 weeks to build the equipment. Dr. Lee stated that the first commercial batch of product would probably be manufactured in May 2003. He stated that once the equipment was on site, they would validate it with the three registration batches of gel and then analyze the first three commercial batches. He felt that it would be possible to have specifications by July 2003, if all went as planned. Because there is some uncertainty to the actual delivery date of the equipment and the date of commercialization, it was decided that Cellegy would agree to a Phase IV Post-Approval Commitment to set the specifications within 6 months of approval. Dr. Lee was informed this should be submitted as an amendment to the NDA.

Donna F. Christner
Meeting Chair

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/s/

Donna Christner
3/7/03 10:12:04 AM
CHEMIST

Teleconference Minutes

Date: 09-SEP-2002 **Time:** 9:00-9:10 AM **Location:** Parklawn 17B45

NDA: 21-463 **Drug Name:** Tostrex 2%

Indication: Testosterone Replacement in hypogonadal men

Sponsor: Cellegy

Reason for teleconference: Sponsor requested that pump manufacturer contact the FDA chemist to answer questions on the container closure system.

Industry Attendee: (b) (4)

FDA Attendee: Donna F. Christner, Ph.D., DRUDP, HFD-580, chemistry reviewer
Eufrecina De-Guia, Project Manager

Discussion: Dr. Christner requested copies of the DMFs for the container closure system. (b) (4) stated that (b) (4) did not have a DMF that was specific for this pump, but had a general DMF for a number of products. (b) (4) offered to send all relevant information to Cellegy so that they could include it in an amendment to the NDA. It was agreed that this would be the easiest way to access the information.

Dr. Christner also asked some general questions about the role of (b) (4) and the pump. (b) (4)

Dr. Christner also asked about the mechanism of the pump. (b) (4)

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/s/

Donna Christner
3/7/03 10:01:09 AM
CHEMIST



NDA 21-463

Cellegy Pharmaceuticals
Attention: William Schary, Ph.D., RAC
Vice President, Regulatory Affairs and Quality
349 Oyster Point Blvd., Suite 200
South San Francisco, CA. 94080

Dear Dr. Schary:

Please refer to your May 31, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tostrex 2% (testosterone gel).

We also refer to the teleconference held on December 17, 2002, between your Staff and the Division wherein you were informed that the use of the tradename Tostrex is not recommended.

We have reviewed your tradename proposal and in consultation with the Division of Medication and Technical Support (DMETS) we have the following comments:

DMETS does not recommend the use of the name "Tostrex". DMETS believes that the

(b) (4)

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/s/

George Benson
12/26/02 03:45:29 PM
signed for Dan Shames



NDA 21-463

Cellegy Pharmaceuticals
Attention: William Schary, Ph.D., RAC
Vice President, Regulatory Affairs and Quality
349 Oyster Point Blvd., Suite 200
South San Francisco, CA. 94080

Dear Dr. Schary:

Please refer to your May 31, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tostrex 2% (testosterone gel).

We are reviewing the Chemistry, Manufacturing and Controls (CMC) section of your submission and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

P.2.1.2 Excipients

1. Please provide complete chemistry information on (b) (4). Please clarify if it is the standard alcohol used for production batches. Please provide the GC method (b) (4) used for the assay of this excipient, and its method validation. Please provide the name and address of the source of this non-compendial excipient.
2. Tests should be developed and implemented to quantitate the components of the (b) (4) the gel at the time of release as well as during the shelf life because these components are deemed to increase penetration of testosterone into the skin.

P.2.2.1 Formulation Development

3. Please confirm if the formulation for (b) (4) contains (b) (4) and/or oleic acid to address discrepancies found in the tables in Section P.2.2.1.

P.3.3 Description of Manufacturing Process and Process Controls

4. Please address the discrepancy found between the narrative and the manufacturing direction sheet in (b) (4).
5. Please provide complete information on equipment and conditions (i.e., mixing speed ranges, mixing time, etc.) used for the batches to date and those proposed for future commercial batches.

6. Please provide information on sampling techniques to acquire samples from the top, middle and bottom of the compounding vessel for bulk product release.
7. Please provide information on filling equipment used and the in-process tests performed.
8. Please provide information on bulk gel retained and on the conditions for storage and release testing.
9. Please provide information on the number of canisters filled/batch.
10. Please provide information on the quality control sampling plan for filled canisters.

P.3.4 Controls of Critical Steps and Intermediates

11. Acceptance criteria should be set for Density and Viscosity.
12. Tests should be developed and implemented for *in vitro* release testing of the drug substance from the gel.

P.3.5 Process Validation and/or Evaluation

13. Information should be provided on process validation and cleaning procedures used to date.

P.4.1 Specifications for Control of Excipients

14. Please indicate the specific identity tests performed to release excipients.

P.5.1 Specifications

15. Metered-dose delivery should be revised to determine the total number of discharges from the container and the dose uniformity over the entire contents.

P.5.2 Analytical Procedures

16. Please provide analytical methods and validation for any requested tests developed, and resubmit 3 copies of the updated method validation.

P.5.3 Validation of Analytical Procedures

17. Please provide copies of the chromatograms from stress studies of the placebo and drug product that show new peaks for (b) (4)

18. Please indicate if (b) (4) are routinely used in HPLC analyses for (b) (4) or only during method validation. If routinely used, the method should reflect this.
19. Please update the submitted HPLC methods used for analyses to reflect the increase in run time developed during method validation for (b) (4)
20. Please clarify which detector will be used for BHT analysis, and change the submitted (b) (4) if necessary.

P.5.4 Batch Analyses

21. Please address the lack of data for Anti-microbial Effectiveness for batches manufactured before Oct. 2000.

P.5.5 Characterization of Impurities

22. Acceptance criteria should be set for each individual impurity. The limit for total impurities should be narrowed to take into account levels found to date. The following acceptance criteria are proposed:

Impurity	Submitted Acceptance criteria	FDA proposed Acceptance Criteria
(b) (4)	None set	NMT (b) (4)
(b) (4)	None set	NMT
(b) (4)	None set	NMT
(b) (4)	None set	NMT
Total Impurities	NMT (b) (4)	NMT

P.8.1 Stability Summary and Conclusions

23. Only 18 months of expiry can be given until more real time data is available for registration lots.

P.8.2 Postapproval Stability Protocol and Stability Commitment

24. Please set criteria for weight loss during the stability studies.
25. Please add additional tests to stability protocols to reflect new release specifications/tests implemented.

P.8.3 Stability Data

26. Freeze-thaw studies should be performed to determine the effects of high and low temperature variations on drug product quality and performance (for example, (b) (4) [redacted])
27. Please supply stability data for intermediate studies (30°C/60% RH) due to the significant change in testosterone assay seen in the accelerated stability samples.

R1 Executed Batch Records

28. Please establish the stability specifications under specific conditions for bulk product returned to storage. Please establish release criteria for the stored bulk product before it can be used in a subsequent filling campaign. Please provide data for any stability testing of bulk gel performed to date.
29. Please identify the site for storage and testing of stability samples for the packaged product. Please provide the storage conditions and site for packaged drug product.
30. Please address steps taken to minimize trapped air in the gel. Please provide procedures for rejection of low weight canisters.

Labeling

31. Please revise the storage statement for both the package insert and the primary and secondary packaging as follows:

Store at controlled room temperature 20-25°C (68-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP].

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

(Please see appended electronic signature page)

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products,
HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
10/31/02 12:23:34 PM



NDA 21-463

Cellegy Pharmaceuticals
Attention: William Schary, Ph.D., RAC
Vice President, Regulatory Affairs and Quality
349 Oyster Point Blvd., Suite 200
South San Francisco, CA. 94080

Dear Dr. Schary:

Please refer to your May 31, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tostrex 2% (testosterone gel).

We also refer to the submission sent via facsimile on July 30, 2002.

We are reviewing the clinical section of your submission and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please provide patient number, dose, and the study day that the pharmacokinetics (PK) was performed for all patients with a C_{max} of testosterone of greater than 1800 ng/dL. In addition, please provide a discussion of the safety implications of these supraphysiologic testosterone levels.
2. In response to Questions 1 and 2 contained in your faxed document on July 30, 2002:
 - a) Regulatory action for each NDA amendment will be determined by the Division at the time of receipt of that amendment. Safety updates are required 120 days after the NDA submission and at least 91 days prior to final regulatory action.
 - b) Please provide the limited interim report (adverse events and concomitant medications) with the 120-day safety update.
 - c) Please provide the interim report once all subjects have reached the 6-month point with the 7-month safety update.
3. In response to Question 3:

The Division prefers submission of these graphs electronically.
4. In response to Question 4:

Please provide one desk copy, in addition to the archival copy. Please refer to the guidance for industry titled *Formatting, Assembling and Submitting New Drug and Antibiotic Applications*. The guidance can be found at <http://www.fda.gov/cder/regulatory/applications/NDA.htm>

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products,
HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
8/9/02 01:48:24 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-463

Cellegy Pharmaceuticals, Inc.
Attention: William Schary, Ph.D., RAC
Vice President, Regulatory Affairs and Quality
Oyster Point Blvd., Suite 200
South San Francisco, CA 94080

Dear Dr. Schary:

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: Tostrex™ (testosterone) 2% gel

Review Priority Classification: Standard (S)

Date of Application: May 31, 2002

Date of Receipt: June 5, 2002

Our Reference Number: NDA 21-463

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 August 4, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 5, 2003.

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:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products
Attention: Division Document Room, 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-463

Page 2

Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Reproductive and Urologic Drug Products, HFD-580

Attention: Document Room 17B-20

5600 Fishers Lane

Rockville, Maryland 20857

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.

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/

Margaret Kober
6/7/02 04:09:39 PM

Meeting Minutes

Date: October 29, 2001 **Time:** 10:00 – 11:30 AM

Location: Potomac Conference Room

IND: (b) (4) **Drug:** Tostrex testosterone gel

Indication: Treatment of male hypogonadism

Sponsor: Cellegy Pharmaceuticals, Inc.

Type of Meeting: Pre-NDA Meeting

Meeting Chair: Daniel Shames, M.D., Acting Division Director

External Participant Lead: Daniel Azarnoff, M.D., FACP

Meeting Recorder: Archana Reddy, MPH

FDA Attendees:

Daniel Shames, M.D., Acting Division Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)

Mark Hirsch, M.D., Medical Team Leader, DRUDP (HFD-580)

George Benson, M.D., Medical Officer, DRUDP (HFD-580)

Jeanine Best, M.S.N., RN, Senior Regulatory Associate, DRUDP (HFD-580)

Archana Reddy, MPH, Project Manager, DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)

DJ Chatterjee, Ph.D., Pharmacokinetic Reviewer, DRUDP (HFD-580)

Mike Welch, Ph.D., Statistical Team Leader, Division of Biometrics II @ Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160) and Division of Reproductive and Urologic Drug Products (HFD-580)

External Participants:

Cellegy Pharmaceuticals

William Schary, Vice President, Regulatory Affairs and Quality

Daniel L. Azarnoff, Senior Vice President, Clinical and Regulatory Affairs

Delphine Imbert, Research Scientist

Ken Phillips, Statistician

Michael Forrest, CEO

Consultants

(b) (4), Consultant

(b) (4), Consultant

A. Wayne Meikle, Consultant

(b) (4), Consultant

(b) (4), Ph.D., Consultant, (b) (4)

Meeting Objectives: To discuss the sponsor's proposal to submit an NDA for Tostrex testosterone gel and the meeting questions raised by the sponsor in their pre-NDA meeting package dated August 23, 2001.

Background: The sponsor is proposing to submit an NDA for Tostrex testosterone gel for the treatment of hypogonadal men. A guidance meeting was held with the sponsor on May 25, 2000.

Discussion:

- the sponsor is planning to submit the NDA in the first quarter of 2002
- the sponsor was informed that the information available appears to be adequate for filing of the NDA

Clinical

- the sponsor presented an algorithm for determining first dose (based on BMI) and for adjusting the dose (based on 2 hour post-dose T level on day 14); sponsor will justify this algorithm in the NDA
- DRUDP expressed concern with C_{max} values over 5,000 ng/dl; sponsor indicated that the levels are high in the 60 mg group before titration and that the C_{max} decreases after dose adjustment; sponsor cited studies using injectable testosterone in which the serum testosterone levels remain high for several days; Division clarified that outliers with testosterone levels that are elevated and remain elevated are of concern due to possible adverse clinical events
- Division emphasized to sponsor that each patient with high supraphysiological levels will be reviewed including the CRFs, hemoglobin, blood chemistry levels (including lipids) and adverse events; sponsor cited long-term experience with injectable testosterone products where there is evidence of high supraphysiological levels of T for several days with no increased evidence of clinical adverse events
- sponsor will provide CRFs on a CD

Biopharmaceutics and Clinical Pharmacology

- C_{max} values were high in many patients
- the transfer study was not acceptable since it did not address the "worst case scenario"
- the exposure to T may not be proportional to the doses administered
- the washing protocol and the showering protocol are acceptable

Biometrics

- an Information Request letter was sent to the sponsor on August 21, 2001, requesting clarification of the 80 % responder threshold, sample size, and planned analysis; the sponsor's reply (October 8) provided some justification for not meeting an 80 % threshold for the per protocol endpoint and indicated a full statistical plan will be forthcoming
- the sponsor proposed to submit the statistical analysis plan using C_{avg} as the primary endpoint with a 90 % threshold; the Division recommends that the sponsor plan for a threshold of 30 – 40 % lower confidence bound using (the percentage of patients with

both C_{avg} and C_{min} within normal range) as the primary endpoints; it was decided that any other endpoints (e.g., C_{avg} , C_{max} , C_{min} , number of hours per day within normal range, etc.) would be considered secondary endpoints

- the Division recommends that the sponsor propose a method for handling dropouts in the statistical plan; the sponsor will address this issue in the statistical plan

Questions:

Efficacy/PK

- 1. Is the study design of the Phase 3 trial, with pharmacokinetic profiles at baseline (Day 0), 2 weeks, 6 weeks, and 180 days on the final dose, appropriate to determine the effects of continued dosing on testosterone levels?**
 - Yes, the study design is acceptable
- 2. Are the number of patients included in the Phase 3 trial, approximately 160, in combination with the other pharmacokinetic study and Phase 2 results, adequate to provide a reliable estimate of the pharmacokinetic profile and testosterone serum levels in this population?**
 - Yes, these numbers are acceptable
- 3. Is the use of C_{avg} as the primary pharmacokinetic parameter acceptable to assure testosterone levels are within the desired therapeutic window?**
 - this is not the per-protocol primary endpoint; C_{avg} should be analyzed as one of several secondary endpoints, including C_{max} and C_{min}
 - the Division recommends that the plan for a threshold of 30 – 40 % lower confidence bound using (the percentage of patients with both C_{avg} and C_{min} within normal range) serve as the primary endpoint
 - the sponsor believes that bone mineral density data suggests a physiological/pharmacological effect and will submit data to show this; the Division will review all the pharmacokinetic data in its totality to assess efficacy

Safety

- 1. Is the total number of patients exposed for 6 months adequate for approval?**
 - The number of patients exposed for 6 months appears adequate; the incidence of adverse events (AE's) and laboratory abnormalities, as well as the PK profile of the drug are review issues
- 2. Is the total number of patients studied in this clinical program adequate to support the application?**
 - See #1 above
- 3. Is the safety profile (skin irritation and other adverse events, hematology, serum lipids, hepatic enzymes) adequately addressed?**

- this will be a review issue; the discontinuation rate due to skin irritation is concerning. Individual laboratory results will be a review issue; high C_{max} values may be problematic; need complete data in Case Report Forms (CRFs)

4. Is the rationale for not performing a formal skin sensitization study acceptable?

- the rationale was not provided to the Division for review; the sponsor clarified with the Division that some patients received continuous treatment for 18 months and such experience should provide adequate data to assess skin irritation
- the sponsor has undertaken a guinea pig sensitization study in which the results were negative; the Division stated that this rationale is acceptable and that another human study would not be needed
- the sponsor agreed to provide the results of the guinea pig sensitization study for review

Decisions made:

- on its face, there appears to be enough data to file an NDA
- the sponsor agreed to submit a statistical analysis plan
- the Division will consider a follow-up tcon with the sponsor to discuss the design of the transfer study

Action Items:

1. The PM will send the official minutes of the meeting to the sponsor within 30 days.
2. The PM will set up a follow-up tcon to discuss the design of the transfer study.
3. The sponsor will fax a copy of the 1996 article from the Journal of Clinical Endocrinology (Meikle et al).

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Meeting Minutes

Page 5 of 5

Cc:

Original IND (b) (4)

HFD-580/Division Files

HFD-580/Reddy/Rumble/Shames/Benson/Hirsch/Chatterjee/Parekh/Raheja/Jordan/De-Guia/Best

Drafted by: Archana Reddy, November 5, 2001

Concurrence: jb/November 6, 2001, djc/November 29, 2001, mw/November 6, 2001, kr/November 7, 2001, gb/November 28, 2001, mh/November 29, 2001, das/November 30, 2001

Finalized: Archana Reddy, November 30, 2001

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/s/

Daniel A. Shames
11/30/01 01:18:51 PM