CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022219Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022219 SUPPL # HFD # 580

Trade Name Aveed

Generic Name testosterone undecanoate intramuscular injection

Applicant Name Endo Pharmaceutical Solutions, Inc

Approval Date: March 5, 2014 (PDUFA date: February 28, 2014)

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 at the end 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:

IP157-001 Part C and
IP157-001 Part C2

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"):

IP157-001 Part C and
IP157-001 Part C2

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 # 072297	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 072297	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 ☐ ! NO ☐
Explain: ! Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Jeannie Roule
Title: Senior Regulatory Health Project Manager
Date: February 28, 2014

Name of Office/Division Director signing form: Christine Nguyen, M.D.
Title: Deputy Director for Safety

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
03/05/2014

CHRISTINE P NGUYEN
03/05/2014

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

NDA/BLA#: 22-219 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DRUP PDUFA Goal Date: September 2, 2009 Stamp Date: 3/2/2009

Proprietary Name: Nebido

Established/Generic Name: testosterone undecanoate

Dosage Form: IM injection

Applicant/Sponsor: Endo Pharmaceuticals

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: testosterone replacement in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

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 failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

Not feasible:

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

***** Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be 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).

Check 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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

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

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

* Other Reason: _____

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

If all of the pediatric subpopulations have been covered through 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?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

Note: 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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

If 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)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the 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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

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

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: __

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: 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 failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be 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 Section 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 some or all pediatric subpopulations).

Check 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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

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

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

* Other Reason: _____

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

If all of the pediatric subpopulations have been covered through 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?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

Note: 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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

If 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)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the 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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

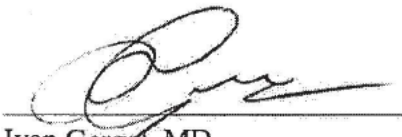
/s/

Jeannie Roule

4/17/2009 01:57:27 PM

3. DEBARMENT CERTIFICATION

Endo Pharmaceuticals Solutions 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.



8/27/13

Ivan Gergel, MD
Executive Vice President R&D and
Chief Scientific Officer

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022219 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Aveed Established/Proper Name: testosterone undecanoate Dosage Form: IM injection		Applicant: Endo Pharmaceuticals Agent for Applicant (if applicable):
RPM: Jeannie Roule		Division: DBRUP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is February 28, 2014, Approved on March 5, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	CR June 27, 2008, December 2, 2009, and May 29, 2013. Approval March 5, 2014
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received N/A
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] 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.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Type 3, New dosage form
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates N/A
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No N/A
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) CR June 27, 2008, December 2, 2009, and May 29, 2013. Approval March 5, 2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	5/13/08, 4/15/09, 7/30/09 5/05/09, 8/07/09, 2/14/14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None DMEPA: ☒ 8/11/09, 8/14/09, 10/18/13, 2/11/14 DMPP/PLT (DRISK): ☒ 8/07/009, 2/05/14 OPDP: ☒ 1/07/09, 7/15/097/23/09, 2/12/14 SEALD: ☒ 02/10/14 CSS: ☐ None Other: ☐ None
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	☐ Not a (b)(2) 03/05/14
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included 03/05/14

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☒ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____	Reviewed by PeRC April 29, 2009 Completed by PeRC July 2, 2009
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	5/30/08, 5/24/10, 6/27/11,
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	April 18, 2013
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 12/02/09, 3/05/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 6/27/08, 11/30/09, 2/28/14
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review See CDTL above
• Clinical review(s) *(indicate date for each review)*	10/25/07, 6/16/08, 02/21/14
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical review 11/10/09

Version: 2/7/2014

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None 04/21/08, 05/28/08, 07/06/09, 11/25/09, 06/13/11, 06/05/12, 02/14/13, 03/22/13, 03/28/13,
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ N/A 08/19/09, 01/24/14, 02/04/14, 02/18/14
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	Included Included ☐ None Included
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 10/17/07, 06/24/08, 07/21/09, 02/04/14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10/17/07, 05/05/08, 07/10/09, 08/17/09, 02/20/1406/26/14
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	None requested N/A
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 04/18/08, 07/09/0308/20/09, 08/20/09, 04/12/13, 10/15/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 10/30/07, 06/26/08, 07/07/09, 08/14/09, 08/27/0902/03/14, 02/25/14
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 06/20/08, 04/23/09
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☒ Review & Environmental Impact Statement *(indicate date of each review)*	See ONDQA review dated06/20/08 pages 30, 31
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 02/24/14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] 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.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done **N/A**
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done **N/A**
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

JEANNIE M ROULE
03/12/2014

From:	Alpert, Meredith
To:	Clark, Paula
Cc:	Roule, Jeannie; Alpert, Meredith
Subject:	REMS comments and REMS-related materials
Date:	Friday, February 21, 2014 3:48:09 PM
Attachments:	Aveed REMS 2-21-14.docx Round 2.zip

Dear Ms. Clark:
Attached are FDA's comments and revised REMS-related materials (in a zip file). Please resubmit the REMS (REMS document and all REMS materials) and the revised REMS Supporting Document as soon as possible. If you have any REMS-related questions, please contact me.

Thank you,

Meredith

Meredith Alpert, M.S.
Safety Regulatory Project Manager
Center for Drug Evaluation and Research
Office of New Drugs
Division of Reproductive and Urologic Products
Phone: 301-796-1218, Fax: 301-796-9897
Email: meredith.alpert@fda.hhs.gov

1 COMMENTS FOR THE APPLICANT

Revise the materials to reflect any additional agreed-upon revisions to the labeling.

Once you have received comments on all the materials, we request that you re-submit the REMS materials via email for a final review.

All final REMS materials can be submitted via the gateway once they have been fully agreed upon by the Agency.

In general, the materials are well done. Please review each document carefully for all our comments and revisions. The sections below include some highlights of our comments.

1. REMS DOCUMENT

We accepted the majority of your edits. Please note the following comments embedded in the REMS document regarding:

- Goals: We revised the goal sub-bullet to state: "… Informing healthcare providers that AVEED can cause POME and anaphylaxis, which have the potential to lead to serious medical consequences (e.g., respiratory distress and syncope);…" this revisions should be a global change (i.e., REMS Supporting Document, HCP Enrollment Form).

- Aveed REMS Program: An Introduction: In addition to the call center, this piece can be provided through other healthcare provider interactions (e.g., sales force, medical information, meeting booths).

- Website: Attach three landing pages to the REMS document. (1) the main, homepage for the Aveed REMS website,(2) the healthcare provider landing page, and (3) the healthcare setting landing pages. No other pages need to be attached to the REMS document. In the REMS document, you do not need to specify that (b) (4)

  Screenshots of the rest of the website should be an appendix to the REMS Supporting Document

- We revised the REMS document and all materials (with the exception of the Patient Guide; please maintain "office") to use "in the healthcare setting" uniformly. Please ensure this is a global change.

- Transferring Aveed to other healthcare facilities (2.b.iv): The revision is acceptable.

Please see the revised REMS Document (track changes; in Word). Please note we did not edit the materials following the REMS document. Comments on the REMS materials are provided in the individual mock-up pdfs.

2. **REMS EDUCATION PROGRAM FOR HEALTHCARE PROVIDERS**

- With regard to the following text on page 2:

(b) (4)

(b) (4)

(b) (4)

Therefore, please delete it. In parallel, delete this text (b) (4)

- Please revise the page breaks in this document to correspond to the different sections of information covered in the piece. The page breaks in the pdf version (compared to the web-based version) are awkward. We recommend incorporating similar breaks in the pdf version to mirror the web-based version.

- Knowledge Assessment Question 8: Revise the question as follows.

  "If patient experiences a hypersensitivity reaction (e.g., angioedema and/or hives) following an Aveed injection, it is appropriate to continue therapy with Aveed."

- Please see the complete set of comments/mark-up in the mock-up pdf.

3. **REMS EDUCATION PROGRAM FOR HEALTHCARE SETTINGS**

- Please apply the applicable comments provided in the "REMS Education Program for HCPs"

- On page 1, revise the "Steps for Healthcare Setting Certification" to include 4 steps. "Step 1: Designate an authorized representative." Maintain the other 3 steps as written.

- Please see the complete set of comments/mark-up in the mock-up pdf.

4. **AVEED REMS PROGRAM: AN INTRODUCTION**

- Please see the complete set of comments/mark-up in the mock-up pdf.

5. WHAT YOU NEED TO KNOW ABOUT AVEED TREATMENT: A PATIENT GUIDE

- Page 1 – Instructions to Patients/Healthcare Providers: Because of the amount of text in this section, the reverse text white font is difficult to read.

  We acknowledge that this color scheme is consistent with the presentation in the other pieces. However, those pieces had less reverse text and more blank space in the orange background.

  We recommend changing to a darker colored font to make the text more legible.

- Please see the complete set of comments/mark-up in the mock-up pdf.

6. HEALTHCARE PROVIDER ENROLLMENT FORM

- Your interim proposal to capture healthcare provider specialty is acceptable.
- We anticipate that this form may be printed in black and white or faxed. We are concerned that some of the light-colored text will not be visible if printed in black and white or if the form is provided via fax.

  We recommend you verify that the text is easily readable by practitioners if provided in black and white. We want to avoid any issues with delays in enrollment due to these type of issues.

- Please see the comments/mark-up in the mock-up pdf.

7. HEALTHCARE SETTING ENROLLMENT FORM

- Your explanation for tracking healthcare provider certification and training for non-prescribing healthcare provider is acceptable.

- Your interim proposal to capture healthcare setting type is acceptable.

- Page 1 – Instructions: Revise to ensure that these steps are consistent with the 4 steps in the Introduction piece and REMS Education Program for Healthcare Settings.

  Because of the amount of text in this section, the reverse text white font is difficult to read.

We acknowledge that this color scheme is consistent with the presentation in the other pieces. However, some of those pieces have less reverse text and more blank space in the orange background.

We recommend changing to a darker colored font to make the text more legible.

- Please see the complete set of comments/mark-up in the mock-up pdf.

8. WEBSITE – SCREEN SHOTS

We reviewed the landing pages included in the REMS supporting document (submitted February 10, 2014) and the website word document submitted via email on February 14, 2014.

- The formatting of the website is acceptable unless otherwise noted. Any *content edits* on the print-version of the educational materials and enrollment forms need to be incorporated into the web-based equivalent.
- Incorporate revisions below to address our comments. A revised version of the screenshots is not attached.

AVEED REMS Homepage Landing Page

- Consider adding the "My Account" tab back to the top of the Landing Page.

Healthcare Provider Certification Landing Page

- We prefer the version of the HCP webpage sent in on Friday February 14, 2014 that allows for non-prescribers to access the training more easily. After the bullet "Non-Prescribing Healthcare Providers must also be trained on the AVEED REMS Education Program for Healthcare Providers," include the following statements: "Enrollment is not required for Non-Prescribing Healthcare Providers. Click below to complete the training online."

- Consider adding the "My Account" tab back to the top of the Landing Page.

Healthcare Setting Certification Landing Page

- Consider adding the "My Account" tab back to the top of the Landing Page.

Healthcare Provider Education Pages

- At the bottom of the "start page," the button to forward to the next page states "Start Education Program." However, the content of the entire "start page" is part of the Education Program.

- Reformat this page so that there is a page break after the section: *What is the AVEED REMS?*
- Rename the button on bottom of both of these pages to "Next."

- Remove the following language under the section (b) (4)

(b) (4)

Healthcare Provider Enrollment Pages

We recognize that in the first submission of your supporting document on August 29, 2013 you included screen shots of the process to become certified, including website registration and enrollment including the electronic signature. However, with the last submission of screen shots of February 14, 2014, the screen shots showing the certification process (attestation, signature, etc) were not included. Therefore we are missing important screen shots to show the process of registration and the complete enrollment process.

- Resubmit screenshots showing the complete process a healthcare provider would be taken through for certification. Include specific screenshots showing website registration, the Education Program including the knowledge assessment, and enrollment including the electronic signature after reviewing the responsibilities. Append these screen shots to the REMS Supporting Document.

- Please note that the phone number on the print form is required, but it is not required on the online version.

Healthcare Setting Education Pages

- At the bottom of the "start page," the button to forward to the next page states (b) (4)
  - Reformat this page so that there is a page break after the section: *What is the AVEED REMS?*
  - Rename the button on bottom of both of these pages (b) (4)

- On the "start page" for Healthcare Settings, the heading [redacted] should be modified to "Steps for Healthcare Setting Certification."
    - Include the additional Step; Step 1- Designate an Authorized Representative and maintain the current steps as Steps 2, 3, and 4 as stated in our comments on the *REMS Education Program for Healthcare Settings* print version.

- Remove the following language under the section [redacted]

[redacted]

Healthcare Setting Enrollment Pages

We recognize that in the first submission of your supporting document on August 29, 2013 you included screen shots of the process to become certified, including website registration and enrollment including the electronic signature. However, with the last submission of screen shots of February 14, 2014, the screen shots showing the certification process were not included. Therefore we are missing important screen shots to show the process of registration and the complete enrollment process.

- Resubmit screenshots showing the complete process an authorized representative would be taken through for certification. Include specific screenshots showing website registration, the Education Program and enrollment including the electronic signature after reviewing the responsibilities. Append these screen shots to the REMS Supporting Document.
- The data fields from the print version of the form and the online version do not match up and some data fields are not included on the online version. For example, "Setting Type" is included under the Authorized Healthcare Setting Representative section on the online version, but under the Healthcare Setting Information section on the print version. Also, the contact information for the Healthcare Setting (phone, fax and email) is missing on the online version of the form.

9. REMS SUPPORTING DOCUMENT

- Page 3 - See revisions to the Background section. These revisions make this section consistent with the Aveed Prescribing Information.
- Page 5 - See revision to the Goals to be consistent with the REMS Document.
- Page 19 – Assessment Plan: See revisions to the Assessment Plan. These revisions are consistent with our previous comments. It does not appear that the assessment was revised to include the scope of the REMS Assessment.

- Please see the revised REMS Supporting Document (track changes; in Word).

10. GENERAL COMMENTS

Resubmission Requirements and Instructions: Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

ATTACHMENTS

- Revised REMS Document (track changes)
- REMS Education Program For Healthcare Providers
- REMS Education Program For Healthcare Settings
- Aveed REMS Program: An Introduction
- Healthcare Provider Enrollment Form
- Healthcare Setting Enrollment Form
- What You Need To Know About Aveed Treatment: A Patient Guide
- Revised REMS Supporting Document (track changes)

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/s/

MEREDITH ALPERT
02/24/2014

From:	Alpert, Meredith
To:	clark.paula@endo.com
Cc:	Roule, Jeannie; Alpert, Meredith
Subject:	Aveed REMS materials
Date:	Wednesday, February 05, 2014 9:08:24 AM
Attachments:	Aveed REMS document revised FDA 2-5-14.doc AVEED REMS Program An Introduction FDA 2-5-14.doc
Importance:	High

Dear Ms. Clark:
Please see the attached 1) revised Aveed REMS Document and 2) "Aveed REMS Program: An Introduction" document drafted by FDA. Note that the revised REMS document is not in track changes. While we have not materially changed the substance of the REMS program that you proposed, we have edited the text of the document to optimally describe the REMS program.

You have received comments on all the REMS materials (REMS document, enrollment forms, and educational pieces). We look forward to receiving an amended REMS submission as soon as possible. Please note, FDA's comments on your assessment plan will be provided under separate cover. You should submit your REMS materials as soon as they are ready; the assessment plan can be revised in your REMS Supporting Document at a later time and should not delay your REMS re-submission. We request that you re-submit the REMS materials via email to facilitate our timely review. All final REMS materials can be submitted via the gateway once they have been fully agreed upon by the Agency.

REMS Document:
To ensure the safe use of Aveed, it is necessary for Aveed only to be available for dispensing and administration by a healthcare provider in a healthcare facility and not dispensed directly to a patient. The REMS, as revised and appended, requires that Endo ensure that Aveed can only be dispensed in healthcare settings that are certified.

How you distribute Aveed to ensure compliance with the Controlled Substance Act is a matter under the purview of the Drug Enforcement Agency.

A. MEDICATION GUIDE
Remove the Medication Guide from the REMS. The Medication Guide will be part of labeling.
Comment on the Medication Guide will be provided under separate cover.
B. COMMUNICATION PLAN
Remove the Communication Plan from the REMS. This will remove the "Dear Healthcare Provider Letter," (b) (4) We recommend a single introductory information piece be distributed as part of the elements to assure safe use to communicate information about the risks and REMS program requirements. Please see the attached "Aveed REMS Program: An Introduction."

The REMS Supporting Document must be consistent with all changes made to the REMS document.
General Comments:
1. Resubmission Requirements and Instructions: Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

2. Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

Thank you,

Meredith Alpert, M.S.
Safety Regulatory Project Manager
Center for Drug Evaluation and Research
Office of New Drugs
Division of Reproductive and Urologic Products
Phone: 301-796-1218, Fax: 301-796-9897
Email: meredith.alpert@fda.hhs.gov

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/s/

MEREDITH ALPERT
02/05/2014

MEMORANDUM

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

DATE: December 19, 2013

TO: NDA 22219, Aveed, testosterone undecanoate with Endo Pharmaceuticals

THROUGH: Jeannie Roule

SUBJECT: Teleconference and Request for Information

DBRUP and DRISK requested a teleconference with Endo to discuss two issues. The first issue discussed was the PI and the second issue was the REMS for AVEED. Regarding the label, FDA provided a proposed Black Box Warning and revisions to the Indication section. Regarding the REMS, the FDA requested Endo provide detailed information on the different methods that Endo plans to use for distribution of AVEED.

The teleconference was held on December 19, 2013.

FDA Participants
Mark Hirsch, Medical Team Lead, DBRUP
Christine Nguyen, Medical Reviewer, DBRUP
Cynthia LaCivita, Senior Drug Risk Analyst, DRISK
Suzanne Robottom, DRISK
Guodong Fang, Medical Reviewer, DBRUP
Alicja Lerner, Medical Reviewer
Jennifer Mercier, Chief, Project Management Staff, DBRUP
Michael Klein, Director, Controlled Substance Staff
Jeannie Roule, Senior Project Manager, DBRUP

Endo Participants
Ivan Gergel, MD, Executive Vice President and Chief Scientific Officer, Research and Development
Bob Barto, Vice President, Regulatory Affairs
Neil Shusterman,, MD, Vice President, Pharmacovigilance and Risk Management and Senior Clinical Advisor
Paula Clark, Senior Director, Regulatory Affairs
Mark Collins, Senior Director, Risk Management, Research and Development
Kevin O'Brien, Senior Director, Managed Markets Trade Distribution, Commercial
Mark Klinger, Director, Promotional Regulatory Affairs

First issue:
The FDA requested that labeling be revised to include a Boxed Warning, as follows:

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNING: SERIOUS PULMONARY OIL MICROEMBOLISM (POME) REACTIONS AND ANAPHYLAXIS

See full prescribing information for complete boxed warning

- **Serious pulmonary oil microembolism (POME) reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur (b) (4) (5.1).**
- **Following each injection of AVEED, observe patients for or at least 30 (b) (4) (5.1).**
- **Because of the risks of serious POME reactions and anaphylaxis, AVEED is available only through a restricted program (b) (4) called the AVEED REMS Program (5.2).**

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS PULMONARY OIL MICROEMBOLISM (POME) REACTIONS AND ANAPHYLAXIS

- **Serious pulmonary oil microembolism (POME) reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur (b) (4) [*Warnings and Precautions* (5.1)].**
- **Following each injection of AVEED, observe patients for or at least 30 (b) (4) *Warnings and Precautions* (5.1)].**
- **Because of the risks of serious POME reactions and anaphylaxis, AVEED is available only through a restricted program (b) (4) [*Warnings and Precautions* (5.2)].**

The FDA also requested that the Indications section of labeling be revised as follows:

1 INDICATIONS AND USAGE

Aveed injection is (b) (4) indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone

- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.

- Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Testosterone undecanoate injection should only be used in patients who require therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis.

Limitations of use:

- Safety and efficacy of Aveed in males less than 18 years old have not been established *[see Use in Specific Populations (8.4)]*.

Conclusion:
Endo provided some additions/edits to the FDA on December 18 before the teleconference(see attached). The FDA will provide its final edits to the Sponsor by January 28, 2014, and further label edits may occur.

Second issue:
The FDA discussed the Sponsor's proposed REMS Document, Implementation System, for Aveed.

In the Sponsor's REM Implementation System the Sponsor states:

(b) (4)

The FDA would like Endo to describe, in detail, the different methods you plan to use to distribute Aveed (beginning with the manufacturer through the precise chain of custody ending with administration to patient). More specifically, explain how you anticipate to operationalize dispensing Aveed based on the scenario created in the above referenced bullet and the requirements and limitations for dispensing a Schedule III substance of the Controlled Substance Act.

Conclusion:
Endo agreed to contact DEA and send FDA a summary of the plan that they share with DEA and a summary of the advice that DEA provides.

After the tcon, DRISK asked that more detailed information be sent to the Sponsor in order to facilitate the Sponsor's correspondence with the DEA.

The following information was sent to the Sponsor on January 3, 2104.

Re: Follow-up to the December 19, 2013, teleconference regarding the distribution plan for Aveed

Dear Ms. Clark,

Controlled Substance Staff suggested you consult with the Drug Enforcement Agency (DEA) regarding the distribution plan that you have outlined in the Aveed REMS to ensure it complies with the Controlled Substance Act (CSA) for the distribution of a controlled substance. Our concern about your distribution plan through specialty pharmacies and our understanding of the CSA is outlined below.

As per our conversation on your proposed distribution plan through specialty pharmacies for Aveed, we understood the following:

- A prescription from a healthcare provider for a specific, named patient would be sent through a "hub" and on to a Specialty Pharmacy

- The Specialty Pharmacy would perform typical pre-dispensing (e.g., billing insurance, determining copay) and REMS –related tasks (e.g., verifying the healthcare provider and facility are certified) then dispense/send (via mail) Aveed to the healthcare provider who wrote the prescription.

- The named patient on the prescription would not receive Aveed directly.

To maximize the safe use of Aveed, we agree that it is necessary for Aveed only to be available for dispensing and administration by a healthcare provider in a healthcare facility and not dispensed directly to a patient. However, because Aveed would be a Schedule III drug subject to the CSA, it is our understanding that a pharmacy filling a prescription must dispense/ship Aveed directly to the patient.

The distribution of Aveed must address both the safe use conditions determined necessary for Aveed ***and*** be in compliance with the CSA.

We suggest you contact Cathy Gallagher, Section Chief, Policy and Liaison, with the DEA at telephone number 202.307.7297, to discuss your proposed distribution plan through specialty pharmacies pertaining to the dispensing of a prescription to the prescriber. We hope the bullets outlined above will be helpful in facilitating your conversation with Ms. Gallagher.
Please provide a summary of your discussion with DEA.

Note: The Sponsor has a teleconference scheduled with the DEA on January 14, 2014, and hope to update the FDA by January 15, 2014.

From: Clark, Paula [Clark.Paula@endo.com]
Sent: Wednesday, December 18, 2013 2:25 PM
To: Roule, Jeannie
Subject: NDA 22219; AVEED - Proposed Modification of Division Labeling Proposal - Black Box Warning/Indications Section

Dear Jeannie:

As discussed, we are providing response below to the Division email dated 12/17/2013 re prescribing information proposed text. Response to the REMS question of 12/18/2013 will come under separate email. We also have extended the meeting time to 1 ½ hours as you have proposed.

Endo appreciates the provided package insert proposals from the Division, which we carefully evaluated. Based on our evaluation, Endo proposes to modify the second bullet point of the proposed Boxed Warning as provided below, for both the Highlights section and Full Prescribing Information. To support our proposed modifications, please note the following:

- The concept of (b) (4) is derived from the parameters for the diagnosis and management of anaphylaxis practice developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) in 2010[1]. As such, it is action-oriented in directing the physician to have the patient remain present in the office. The proposed revision is also consistent with the goals of our proposed REMS and our proposed REMS training for patients and HCPs on the need to remain in the office to allow for recognition and management of symptoms.

- Deletion of "or" is an editorial change.

- Deletion of (b) (4) is to make the text consistent with the recommendation from the AAAAI: "To better recognize and treat anaphylactic reactions, patients should wait after receiving an AIT injection for 30 minutes at the location of the AIT injection."

- Addition of "in order to" links the first message in the sentence with the second message.

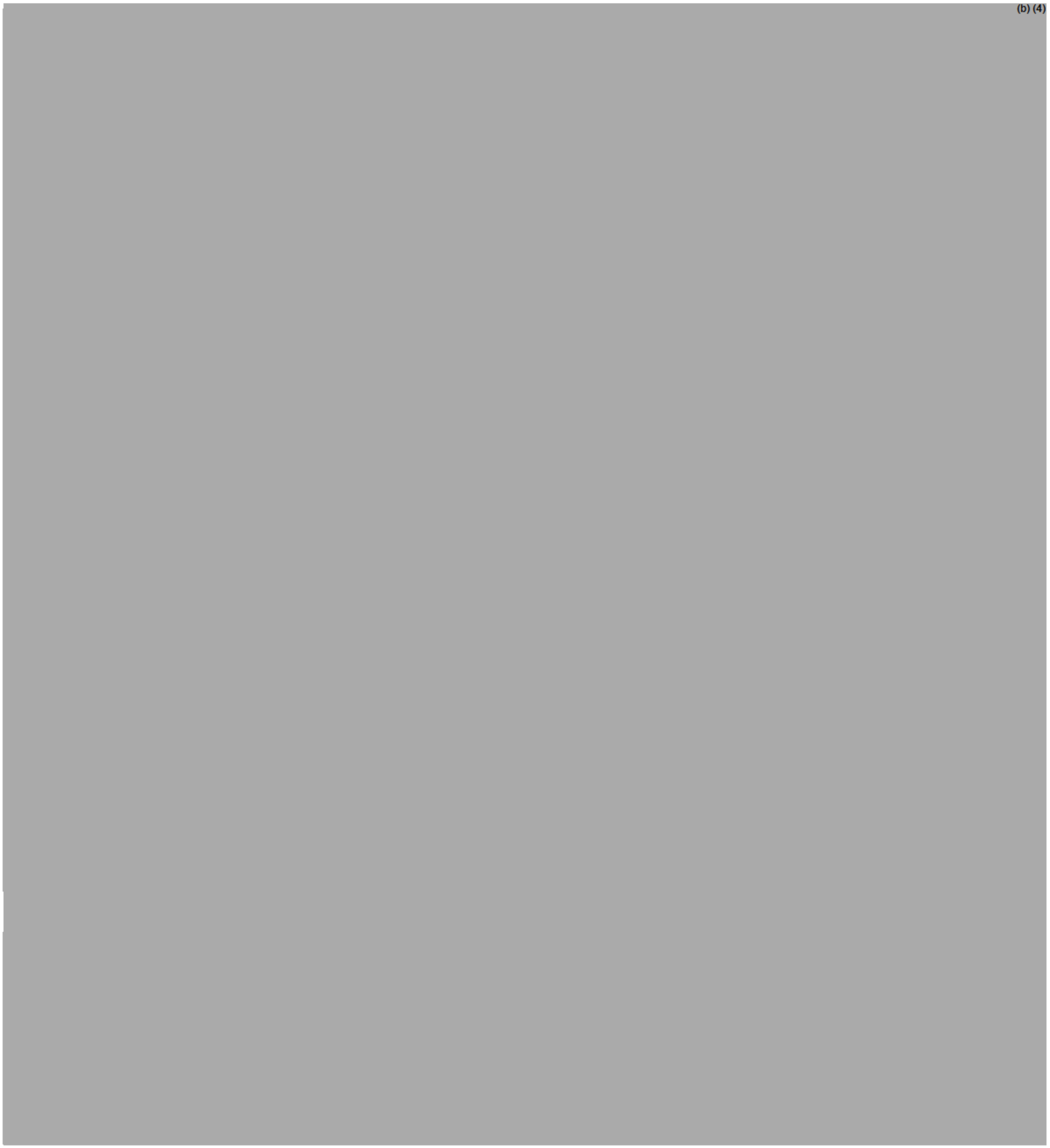
- Substitution of (b) (4) for (b) (4) better expresses the medical process that should be occurring if a patient has symptoms.

- The replacement of (b) (4) with "appropriate medical treatment (b) (4)" is consistent with established FDA labeling for influenza vaccines. The proposed sentence conveys a more holistic and overarching medical concept in that "appropriate medical treatment (b) (4)" encompasses not only (b) (4), but more broadly assessment and evaluation of the entire patient in the context of the evolving medical picture. This change is consistent with our proposed REMS training, which does not dictate medical practice, but describes the available experience with treating these post-injection reactions and provides links to appropriate professional guidelines for anaphylaxis.

1 **Available at** **http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/Anaphylaxis-2010.pdf**.

We look forward our discussion tomorrow. Thank you.

Endo Proposed Text:



Reference ID: 3434062

(b) (4)

Paula Clark
Senior Director, Regulatory Affairs Liaison
1400 Atwater Drive, Malvern, PA 19355
484-216-7397 (b) (6) mobile
clark.paula@endo.com

endo | *AMS Endo Pharmaceuticals HealthTronics Qualitest*

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/s/

JEANNIE M ROULE
01/09/2014

MEMORANDUM

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

DATE: October 21, 2013

TO: NDA 22219, testosterone undecanoate with Endo Pharmaceuticals

THROUGH: Jeannie Roule

SUBJECT: Information Request from DMEPA and CMC Reviewers

The DMEP and CMC reviewers had comments for the Sponsor's carton and container. Please see attached communications.

From:	Roule, Jeannie
To:	"Clark, Paula"
Subject:	NDA 22219
Date:	Monday, October 21, 2013 3:13:00 PM
Attachments:	Carton and Contianer comments for Sponsor Oct 2013.doc

Paula,

Please see attached.

Please send in the newer versions to me via email at your earliest convenience. It will not be necessary for you to submit formally until we have an agreed upon version.

Regards,

Jeannie Roule
Senior Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

October 21, 2013

NDA 22219, Aveed

The DMEPA and CMC reviewers have the following comments regarding the carton and container for Aveed:

1. Revise the presentation of the proprietary name to use title case font (e.g., Aveed). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.

2. Use bold font to make the presentation of the strength per total volume (i.e. 750 mg/3 mL) more prominent on the container label and carton labeling than the strength per milliliter presentation (250 mg/mL). This may prevent confusion when the practitioner is attempting to ascertain the total contents of the vial, thus, mitigating the risk of medication error.

3. Revise the presentation of the concentration to use a capital ‘L’ for the volume (i.e., 250 mg/mL) on the container label.

4. Add a space between "Rx" and "Only" on the carton label.

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/s/

JEANNIE M ROULE
10/21/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219

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 August 29, 2013, of your August 29, 2013, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate injection.

We consider this a complete, class 2 response to our May 29, 2013, action letter. Therefore, the user fee goal date is February 28, 2014.

If you have any questions, call me at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Jeannie Roule
Regulatory Health Project Manager
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JEANNIE M ROULE
09/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22219

MEETING REQUEST CANCELLED

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 undecanoate injection.

We also refer to your June 18, 2013, correspondence requesting a meeting to gain clarification and/or concurrence regarding the content and format of your planned Complete Response.

On July 3, 2013, we provided our draft preliminary responses to the questions presented in your June 18, 2013, meeting request package. After receipt and review of these draft responses, you informed the Division via an e-mail communication on July 9, 2013, that a meeting was not necessary at this time and you requested to cancel the meeting.

In addition, on July 9, 2013, you also requested clarification from the Division on one of the preliminary responses and stated that a response from us via an e-mail communication was acceptable.

The final version of the Division's responses, along with a response to your additional question (in italics), are attached. You are responsible for notifying us of any significant differences in understanding.

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

Sincerely,

{See appended electronic signature page}
Mark Hirsch, M.D.
Medical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

QUESTIONS and RESPONSES

Clinical
Question 1:
In reference to the Safety Update Requirement contained in the May 29, 2013 CR, pages 4-5, there is one additional contraceptive study that has been conducted by Bayer, Germany. This study is the only additional study for AVEED which either was initiated or completed and not included in the November 2012 CR, and is not included in our proposed indication for AVEED. No additional studies are planned for AVEED and no other additional clinical information is available at this time. This additional study was small, with only 40 subjects conducted only in Italy. Out of the 40 subjects, 25 subjects experienced AE's; one SAE, and 2 AE's leading to discontinuation were reported.

The study treatment for this study was a combination of testosterone undecanoate (TU) and norethisterone enanthate (NET-EN). No subjects received TU alone. To fulfill the requirement of a safety update, Endo proposes the following:

- **Not to integrate this study data with the male contraception studies previously submitted**
- (b) (4) [redacted]

Does the Division concur?

Division Response:
We agree with your plan not to integrate the results from the additional clinical study you referenced. However, the following safety data should also be submitted:

- A PSUR covering 01-May-2012 to 30-April 2013;
- CIOMS forms for all possible or probable cases of POME and anaphylaxis during the above period.

Sponsor Comment:
Regarding the first bullet point, Endo and Bayer are in a position to extend the PSUR reporting period to 30-June-2013 to provide a more comprehensive update. This will be the timeframe for the PSUR report included in our response to the CR.

Regarding the second bullet point, Endo has not used a classification scheme of POME or anaphylaxis that includes the categories "possible" or "probable". Instead we propose to use a process similar to that which was included in the Complete Response. Two Endo physicians will review all cases received by Bayer during the interval against the previously agreed definitions of POME and anaphylaxis (Sampson criteria) and submit all cases where both physicians agree. If there is a lack of consensus after discussion between the 2 physicians, a third Endo physician will break the tie.

Division response:
The plan is acceptable with one caveat: in addition to POME and anaphylaxis cases where two Endo physicians agree, submit any POME or anaphylaxis case that involves death or permanent disability.

Regulatory Affairs (REMS)
Question 1:
In the CR Letter dated May 29, 2013, page 2, under Elements to Assure Safe use (ETASU), #1 – there appears to be inconsistent use of the terms "HCP, prescriber and dispenser". Endo will proceed on the assumption that "dispense" is synonymous with "administer" and that all HCPs who prescribe or administer AVEED must undergo the educational training program to be certified.

Does the Division concur?

Division Response:
Yes, we concur. For the purposes of the REMS, the term "prescribe" refers to a medication order filled from an on-site inventory of medication. The term "dispense" refers to the administration of the medication. We remind you that the REMS must provide a controlled distribution system – ensuring a secure distribution chain from the point of manufacture down to distribution only to certified prescribers/healthcare settings.

Sponsor Comment:
We appreciate the feedback; no additional clarification is needed.

Question 2:
In concordance with recent efforts by FDA to improve the functionality and utility of Medication Guides (as was done with those for extended release/long-acting (ER/LA) opioids) , Endo proposes to provide the Medication Guide in a 1 page format to provide enhanced clarity on the content of the proposed Medication Guide.

Does the Division concur?

Division Response:
We recommend that you submit both a "traditional" Medication Guide, and a "one page" version similar to the format you referenced for the opioids. The Agency will review both versions and will determine if the one page format is sufficient to address important information for the patient. For both formats, we remind you to consult the Medication Guide Regulations and to include the specified headings.

Sponsor Comment:
We appreciate the feedback; no additional clarification is needed.

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/s/

MARK S HIRSCH
07/22/2013

JOINT MEETING FOR REPRODUCTIVE HEALTH DRUGS AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

APRIL 18, 2013

NDA 022219: testosterone undecanoate (proposed trade name, Aveed) for intramuscular injection sponsored by Endo Pharmaceuticals Solutions, Inc., for the replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022219

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Endo Pharmaceuticals Solutions, Inc.
1400 Atwater Drive
Malvern, PA 19355

ATTENTION: Paula Clark
Director, Regulatory Affairs

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) dated August 24, 2007, received August 28, 2007, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Testosterone Undecanoate Injection, 250 mg/mL.

We also refer to your correspondence, dated and received December 20, 2012, requesting review of your proposed proprietary name, Aveed. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Aveed, 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 December 20, 2012 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 Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application contact Jeannie Roule, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
03/15/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219

ACKNOWLEDGE CORPORATE NAME/ADDRESS CHANGE

Endo Pharmaceuticals Inc.
Attention: Paula Clark
Director, Regulatory Affairs
1400 Atwater Drive
Malvern, PA 19355

Dear Ms. Clark:

We acknowledge receipt of your February 1, 2013, correspondence notifying the Food and Drug Administration (FDA) that the corporate address has been changed from

Endo Pharmaceuticals Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

to

Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA 19355

for the following new drug application (NDA):

NDA 022219 for testosterone undecanoate injection.

We have revised our records to reflect this change.

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 me at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Jeannie Roule
Senior 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/

JEANNIE M ROULE
02/04/2013

MEMORANDUM

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

DATE: January 10, 2013

TO: NDA 22219, testosterone undecanoate with Endo Pharmaceuticals

THROUGH: Jeannie Roule

SUBJECT: Information Request from DPARP

DPARP had an Information request for the Applicant. Please see emails that are attached.

From: Clark, Paula [Clark.Paula@endo.com]
Sent: Thursday, January 10, 2013 2:37 PM
To: Roule, Jeannie
Subject: RE: NDA 22219, Request for Information
Hi Jeannie – confirm receipt of email.

Kind regards,

Paula Clark
Director, Regulatory Affairs Liaison
100 Endo Boulevard, Chadds Ford, PA 19317
610-459-7397 (b) (6) mobile 484.840.4290 fax
clark.paula@endo.com

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Thursday, January 10, 2013 2:33 PM
To: Clark, Paula
Subject: NDA 22219, Request for Information

Dear Paula,

I have another request for information (see below). Please confirm receipt of this email.

Regards,
Jeannie

Information Request:

We note that the Integrated Safety Summary contains listings of the 416 potential cases of POME (Listing 6.1) and the 90 potential cases of anaphylaxis (Listing 7.1) that occurred in clinical trial subjects based on your search criteria.

Please inform us as to whether the individual case narratives, or other information which you used to adjudicate each case, are included in the NDA submission and let us know their exact location within the NDA submission.

If the information was not included in this most recent NDA submission, please provide the information to us by January 18, 2013.

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Reference ID: 3243417

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/s/

JEANNIE M ROULE
01/10/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219 **INFORMATION REQUEST**

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 undecanoate injection.

We also refer to your November 29, 2012, submission, containing your complete response and resubmission of your new drug application.

We are reviewing your application and in order to facilitate the safety data review, we request that you collate the CIOMS report narratives for the following adverse reaction categories as defined in your NDA. Submit each narrative in sequential order by case number within each category.

1. Definite POME (228 cases)

2. Definite anaphylaxis according to Sampson and/or special terms criteria (56 cases)

3. Potential POME, not judged to be POME after clinical review (305 cases)

4. Potential anaphylaxis, not judged to be anaphylaxis after clinical review (274 cases)

5. Other reported reactions

We request a written response on or before January 16, 2013, in order to continue our evaluation of your NDA.

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

Sincerely,

{See appended electronic signature page}

Audrey Gassman 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/

AUDREY L GASSMAN
01/08/2013

MEMORANDUM

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

DATE: December 19, 2012

TO: NDA 022219, Endo Pharmaceuticals, testosterone undecanoate

THROUGH: Jeannie Roule

SUBJECT: The Applicant was informed via a telephone conversation on December 12, 2012, that the AC meeting between Endo Pharmaceuticals and the FDA will take place on April 18, 2013.

See Applicant's email that is attached.

From: Clark, Paula [Clark.Paula@endo.com]
Sent: Wednesday, December 19, 2012 3:34 PM
To: Roule, Jeannie
Subject: Re: AC meeting
Thank you!

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Wednesday, December 19, 2012 03:32 PM Eastern Standard Time
To: Clark, Paula
Subject: AC meeting

Paula,

I thought it would be best to also send you an email concerning the AC meeting for NDA 022219.

I informed you (via a telephone conversation) on December 12, 2012, that the AC meeting will take place on April 18, 2013.

More details will follow.

Regards,
Jeannie

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

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/s/

JEANNIE M ROULE
12/19/2012
Notification of AC meeting

From:	Clark, Paula
To:	Jennings, Kerri-Ann
Cc:	Barto, Bob
Subject:	Re: NDA 22219 Aveed
Date:	Friday, December 14, 2012 10:47:26 AM

Thank you. Received voice mail and email. Kind regards.

From: Jennings, Kerri-Ann [mailto:Kerri-Ann.Jennings@fda.hhs.gov]
Sent: Friday, December 14, 2012 10:11 AM Eastern Standard Time
To: Clark, Paula
Cc: Barto, Bob
Subject: NDA 22219 Aveed

Good morning Ms. Clark,

This is a follow-up to my voice message.

To assist with the review of the Quality section of the above NDA, please provide an updated list of all the establishments involved with the NDA as soon as possible. Also, submit the list as an amendment to NDA 22219.

Please confirm receipt of this email.

Thank you.

Regards,

Kerri-Ann E. Jennings, MS, BSN, RN
LT, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment II
Phone (301) 796-2919

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/s/

KERRI-ANN JENNINGS
12/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219

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 of your November 29, 2012, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate injection.

We consider this a complete, class 2 response to our December 2, 2009, action letter. Therefore, the user fee goal date is May 29, 2013.

If you have any questions, call me at (301) 796-3933.

Sincerely,

{See appended electronic signature page}

Jeannie Roule
Senior 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/

JEANNIE M ROULE
12/10/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219

GENERAL ADVICE

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 undecanoate injection.

We also refer to your March 21, 2012, submission, containing a proposal for identification and classification of anaphylaxis and pulmonary oil microembolism (POME) cases.

We have completed our review and in consultation with the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) and the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE) have the following comments:

1. Provide CIOMS line listings as a separate Excel spreadsheet to facilitate organizing the reports. The Excel spreadsheet should include a special code or flag for cases deemed POME or anaphylaxis by adjudication. The Excel spreadsheet should also include both the lower level term (LLT) and the preferred term (PT) for each listing.

2. In Step 1 of the proposed identification and classification process, clarify whether adjudicators are blinded to the drugs used.

3. In Step 2 of the process, clarify how events with an onset greater than 30 minutes are classified. Be aware that we do not agree that cases of anaphylaxis should be limited to reactions occurring within 30 minutes of injection.

4. In Step 2 of the process, clarify what is meant by “medically qualified reporter.”

5. With regard to identifying cases of anaphylaxis, you propose to use the “Rüggeberg” definition, as developed by the Brighton Collaboration Anaphylaxis Working Group to evaluate immunization safety data. In contrast, the Agency currently uses the “Sampson” clinical definition of anaphylaxis developed in 2004 and 2005 by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network to evaluate potential anaphylaxis cases (Sampson HA, Journal of Clinical Immunology 2005 and 2006). We request that the primary analysis of

anaphylaxis in your submission be based on the Sampson definition. If you wish, you may provide a secondary analysis using the Rüggeberg definition.

6. Where the temporal relationship between injection of testosterone undecanoate and POME/ anaphylaxis onset is unknown, we do not agree that an adjudicated case must be reported as related to study drug or that testosterone undecanoate injection must be stated as the suspect product.

7. We remind you that individual CIOMS reports should be provided for all potential cases of POME and anaphylaxis, irrespective of medical review or adjudication.

8. We remind you that because of the marked variability in the quality of data in spontaneous postmarketing adverse event reports, it is possible that some cases not classified as POME or anaphylaxis by your criteria may still represent severe, potentially life-threatening adverse reactions.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

JENNIFER L MERCIER
07/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219

MEETING REQUEST CANCELLED

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 undecanoate injection.

We also refer to your November 10, 2011, correspondence requesting a teleconference to discuss the content and format of your NDA that you are planning on resubmitting

On January 14, 2012, we provided our draft preliminary responses to the questions presented in your December 19, 2012, meeting package. After receipt and review of these draft responses, you informed the Division via an e-mail communication on January 17, 2012, that a teleconference was not necessary at this time and you requested to cancel the meeting.

In addition, you requested clarification from the Division on three of the preliminary responses and stated that a response from us via a written communication is acceptable.

A copy of the preliminary responses, along with responses to your three additional questions, are attached.

If you have any questions, call Jeannie Roule, Senior Regulatory 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 – Memorandum of Meeting Communication

MEMORANDUM OF MEETING MINUTES

SCHEDULED MEETING DATE: January 18, 2012

DATE CANCELLED: January 17, 2012

APPLICATION: NDA 022219

DRUG NAME: testosterone undecanoate injection

SPONSOR'S QUESTIONS AND DIVISION'S RESPONSES:

Question 1
COMPLETION OF CLINICAL STUDY REPORTS (CSRs):
This question provided the Division with clarity regarding completion of the Pivotal CSR IP157- 001, which is divided into 5 parts, denoted as Part A, B, C, C2 and Part D. Endo explained to the Division that complete study reports will be provided in the CR for parts C and C2. Endo further informed the Division that abbreviated CSRs will be provided for Part A (supplementing the interim CSR which had previously been submitted) and Part B. Lastly Endo explained to the Division that a CSR for Part D would not be provided, and that the data for the patients included in Part D would be included in the CSRs for Parts A and C.

The Division concurred with this proposal of completing the CSRs and Endo has no further question.

Question 2
INTEGRATED SUMMARY OF SAFETY (ISS):
In reference to the question included in Endo's briefing book dated May 24, 2011, Endo referenced the CR letter from the Agency, dated December 2, 2009. Endo has reviewed the Safety Update requirements and will comply as requested.

Endo has made appropriate changes to our plan for the ISS, after extensive review of the postmarketing studies performed (ex-US) and a review of all available data. We have made changes to our original question included in the May 24, 2011 briefing book as follows:

(b) (4)

Points 1, 2, 3, 4, and 5 remain the same as presented in the original briefing book; points 6, 7, 8 and 9 are updated.

The ISS in our planned CR will be comprised of all demographic/baseline characteristics, extent of exposure, and adverse experience data presented as:

1. [redacted]

2. [redacted]

3 [redacted]

4. [redacted]

5. [redacted]

6. [redacted]

[redacted]

8. [redacted]

9. [redacted]

[redacted]

[redacted]

Does the Division concur with this proposal for the ISS?

Division Response: No. [redacted] (b) (4)

Question 3
PROVISION OF DATASETS:
To clarify our original proposal which was contained in Endo's briefing book dated May 24, 2011, Endo proposes to provide SAS datasets as follows:

a. ***Integrated Summary of Safety Datasets***
In order to support the safety analyses of testosterone undecanoate, Endo proposes to [redacted] (b) (4)

Does the Division concur with this proposal?

Division Response: No. [redacted] (b) (4)

b. ***US Pivotal Trial IP157-001 Datasets***
In order to support the submission of the complete study reports of the US study, IP157-001, Parts A, B, C and C2, Endo will provide analysis datasets following CDISC ADaM version 2.1 requirements for each part individually. All source/raw data will be represented in the SAS analysis datasets. As such, Endo proposes not to submit separate listing1 or tabulation (SDTM) datasets.

Does the Division concur with this proposal?

Division Response: The proposed analysis datasets are acceptable, provided they are acceptable to the Office of Business Informatics (OBI).

c. ***Datasets for Other Trials***

Endo proposes not to submit SAS analysis datasets for the following studies individually: the 6 European clinical trials (JPH01495, JPH04995, ME98096, ME97029, 306605, and 303934), the 5 male contraception studies (97028, 97173, 98016, 99015 and 42306), and the 2 Post-Marketing Trials [AWB0105 and 39732 (NE0601 IPASS)]. All demography, exposure, and adverse events data will be provided in the integrated safety database (see subsection (a.) above). Further, Endo proposes not to submit legacy listing datasets or tabulation (SDTM) datasets for any of the above mentioned studies.

Does the Division concur with this proposal?

Division Response: Yes.

d. *Post Marketing Experience Datasets*
Endo proposes to (b) (4)

Does the Division concur with this proposal?

Division Response: No. (b) (4)

Question 4
PRESENTATION OF POST MARKETING EXPERIENCE DATA:
(b) (4)

(b) (4)

Does the Division concur with Endo's plan for presentation of the Post Marketing Experience Data?

Division Response: No.

(b) (4)

- In addition, we ask that you provide the following information prior to NDA submission, so that we may provide additional recommendations for your analyses and presentation of postmarketing data:
    - Provide the exact terms you plan to use to search your postmarketing databases for cases of POME and anaphylaxis
    - Provide the specific criteria you plan to use to define POME and anaphylaxis, as well as the specific process you plan to use to adjudicate cases generated by the postmarketing database search.

Question 5
STUDIES TO BE INCLUDED IN THE SUMMARY OF EFFICACY (SCE):
Study IP157-001 is a 5 Part study (A, B, C, C2, and D) in which Parts A, B, C, and C2 contained 2 stages. [Note: Part D was exploratory and studied AVEED via subcutaneous injection.] Part C and C2 were the only 2 parts that examined the dosing regimen under review and are considered pivotal for this study. The previously provided efficacy data (IP157-001 Part C Stage 1, in the original NDA submission) will be augmented with the efficacy data from Part C Stage 2 and Part C2 which have not been previously submitted. These data will be presented in both the SCE, as well as in the CSR's. The previously submitted data for Part C Stage 1 serves as the basis of the pharmacokinetic (PK) data for approval. Part C2 has additional PK data to augment the data from Part C. No pooling of data for the SCE for this CR will be performed; however, an integrated qualitative summary will be provided.

Does the Division concur with the proposed content for the SCE?

Division Response: Yes.

Question 6
PROVISION OF TRANSLATION OF ALL FOREIGN LABELING:
Testosterone Undecanoate (Nebido®, Reandron®) is approved in 94 countries. (b) (4)

(b) (4)

[redacted] (b) (4)

Does the Division concur with this proposal [redacted] (b) (4)

Division Response: No. [redacted] (b) (4)

Additional questions from the Sponsor:

1. **Please refer to the Division's Response to Question #2, Bullet Point #1:**

   To clarify your response to Question 2, bullet point number 1, Endo would like to confirm that you are only interested in subject disposition for the post-marketing clinical trials and not all clinical trials. Due to the differing data collection methods employed in each of the post-marketing clinical trials, e.g., some studies collected only treatment completion status and reason, some collected neither study nor treatment status and some collected both study and treatment status and reason, we propose to submit a qualitative summary of the subject disposition information for each of the studies individually. This qualitative side-by-side summary would report as much information as is available for each of the individual post-marketing clinical trials. In other words, no overall quantitative subject disposition would be provided for the data summary presentation described in Question #2, Item #6 of the briefing book dated 26 May, 2011.

   Does the Agency concur with this proposal?

   Division Response: Yes

2. **Division Response to Question 3, Part b**

   For the US Pivotal Trial IP157-001 Datasets, the analysis datasets will be provided following CDISC ADaM version 2.1 requirements for each part individually. All source/raw data is to be represented in the SAS analysis datasets. As such Endo proposes not to submit separate listings or tabulation (STDM) datasets. The Division responded that the proposed analysis datasets are acceptable, provided they are acceptable to the Office of Business Informatics (OBI).

   Can the Division provide Endo with further details regarding the steps to be taken to receive a response from OBI and the timing associated with their review?

Division Response: In general, the format and documentation is acceptable.

The Agency accepts both CDISC standards and legacy data. The dataset sizes under 1 gigabyte are acceptable in SDTM/ADaM standardized datasets. If the dataset size is larger than 1 gigabyte the Agency prefers that columns be resized to the actual length. The Sponsor should discuss with the review division which datasets should be provided, and the data elements that should be included in each dataset. The Study Data Specifications provide the current specifications for submissions and the structure for submission of study data.

In the Study Data Specifications, the following statement clarifies the best practice for datasets, "Each dataset is provided in a single transport file. The maximum size of an individual dataset is dependent on many factors. In general, datasets other than SDTM datasets should be less than 400 MB; SDTM datasets should not be divided."

While elements of the raw data may be included in the analysis datasets, all source/raw datasets must be submitted in addition to analysis datasets. These can be in listings or tabulation format. Since you are submitting SDTM-formatted datasets, tabulations would be most appropriate. Please see the Study Data Specifications document for additional information on folder structure and content.

If the Sponsor has any further questions, feel free to send an email to cder-edata@fda.hhs.gov.

3. **Division Response to Question 4**

In response to Question 4, Endo is requested to provide the Division with the specific criteria we plan to use to define POME and anaphylaxis, as well as the specific process we plan to use to adjudicate cases generated by the post-marketing database search. We appreciate your offer to provide recommendations on this review strategy.

In order to properly plan our timeline, we would how long (estimated) will the Division take to review our proposed strategy?

Division Response: We estimate that this review will take approximately 6 weeks. We remind the Sponsor to provide the exact terms that will be used to search the postmarketing databases for cases of POME and anaphylaxis.

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/s/

MARK S HIRSCH
02/21/2012

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22219

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 undecanoate injection.

We also refer to the meeting between representatives of your firm and the FDA on June 27, 2011. The purpose of the meeting was to present clarifying data and to discuss a path forward for an NDA resubmission.

A copy of the official minutes of the meeting is enclosed 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:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**Type C**
Meeting Category:	**Guidance**
Meeting Date and Time:	**June 27, 2011**
Meeting Location:	**White Oak, Building 22, room 1309**
Application Number:	**NDA 22-219**
Product Name:	**testosterone undecanoate injection**
Indication:	**testosterone replacement therapy**
Sponsor/Applicant Name:	**Endo Pharmaceuticals, Inc**
Meeting Chair:	**Mark Hirsch, M.D.**
Meeting Recorder:	**Jeannie Roule**

FDA ATTENDEES

Scott Monroe, M.D.	Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D.	Medical Team Leader, DRUP
Harry Handelsman, D.O.	Medical Officer, DRUP
Jonathan Jarow, M.D.	Medical Officer, DRUP
John Stinson, M.D.	Medical Officer, DRUP
Anthony Durmowicz, M.D.	Medical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Eric Andreasen, Ph.D.	Pharmacology Reviewer, DRUP
Hyunjin Kim, Pharm.D	Division of Clinical Pharmacology (DCP) III, Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Amarilys Vega, M.D.,	Risk Management Analyst, Division of Risk Management (DRISK), Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology (OSE)
Cynthia LaCivita, Pharm.D.	Risk Management Analyst, DRISK, Office of Medication Error Prevention and Risk Management, OSE
Jennifer Mercier	Chief, Project Management Staff (CPMS), DRUP
Jeannie Roule	Regulatory Health Project Manager, DRUP

SPONSOR ATTENDEES

Endo Pharmaceuticals Attendees:

Robert Barto, MBA	Vice President, Regulatory Affairs
Paula Clark	Director, Regulatory Affairs
Theo Danoff, M.D., Ph.D	Vice President, Clinical Development, Endocrinology/Urology
Susan Potts	Associate Director, Quantitative Sciences
Neil Shusterman, M.D.	Senior Vice President, Clinical Development
Ivan Gergel	Executive Vice President, Research and Development

Bayer Schering Pharma, AG Attendee:

Heidrun Hildebrand	Global Product Leader, General Medicine, Global Project Management, Bayer Schering Pharma AG

(b) (4)

BACKGROUND

On December 2, 2009, the Division issued a Complete Response (CR) Letter for AVEED™ (testosterone undecanoate) intramuscular injection. AVEED was not approved because the Division concluded that the Applicant had not demonstrated that the benefits of the drug outweigh the additional potential risks associated with the use of testosterone undecanoate injection (AVEED). The Division's primary safety concern with AVEED was the occurrence of serious, immediate, potentially life threatening post-injection reactions.

In the CR Letter, the Division proposed two approaches to demonstrate that the benefits outweigh the potential risks associated with the use of AVEED as follows:

1. Identify which component(s) of the drug product may be contributing to the serious, immediate post-injection adverse reactions, reformulate the product, and demonstrate that these reactions have been reduced or mitigated; or
2. Identify a population of adult males who require testosterone replacement therapy and in whom the additional potential risks associated with the use of testosterone undecanoate injection as currently formulated would be acceptable.

On May 24, 2010, the Division met with Endo Pharmaceuticals to discuss Endo's proposed path to approval for AVEED.

The Applicant requested on February 16, 2011, another meeting with the Division to present clarifying data and to discuss a possible path forward for a resubmission and ultimate approval of testosterone undecanoate injection.

DISCUSSION

Preliminary responses were provided to the Applicant on June 22, 2011, in response to the questions posed in the Sponsor's meeting packages provided to the Division on February 16, 2011, and May 26, 2011. The Sponsor'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: With an appropriate REMS program which includes a restricted distribution system and HCP attestation as elements of the ETASU, a Communication Plan and a Medication Guide, does FDA agree that AVEED's benefit-to-risk profile is acceptable for men with conditions associated with a deficiency or absence of endogenous testosterone? Could a submission containing such a REMS program, in light of our clarification of the safety data, be approved for the wider male hypogonadal population? If not, please be specific regarding your concerns.

Response: After further consideration and consultation, we have determined that the proposed REMS program with ETASU is not appropriate for AVEED and is therefore unacceptable. Currently, we do not agree that AVEED's benefit-to-risk profile is acceptable for the proposed

indication, primarily due to the risk of life-threatening post-injection reactions (Pulmonary Oil Microembolism [POME] and/or anaphylaxis) that have been reported continuously in the postmarketing period. We remind you that a decision concerning benefit/risk will be made as part of the Division's review of a Complete Response (CR), taking into consideration all the submitted data, including postmarketing adverse events reported prior and subsequent to the previous CR action.

Additional Discussion: The Sponsor made an opening statement that it appeared to them that the Division had already made a decision concerning approval, and that an impasse had been reached. The Division stated that decisions concerning drug approval are not made in advance of the submission of an NDA (in this case a CR), and that the Division is amenable to additional discussion of the AVEED risk/benefit issues both prior to and after submission of the CR.

Additional discussion ensued in three major areas: the incidence of serious post-injection reaction, the Agency's position on a REMS with ETASU for AVEED, and possible dispute resolution:

<u>Regarding the incidence of serious post-injection reactions:</u>
The Sponsor remarked that this drug remains on the market in 70 other countries. They stated that there is an established postmarketing reporting rate of serious post-injection reactions and it has been consistent over several years. There was discussion of how to calculate the reporting rate for serious post-injection reactions, as well as the effect of underreporting The Sponsor distributed a handout containing their calculations of the postmarketing reporting rates for POME and anaphylactic reactions. The Sponsor further stated that a large number of patients have been treated with AVEED in controlled trials without a single reported case of anaphylactic reaction. Further, if you compare the incidence rate of POME in clinical trials to the reporting rate for POME in the postmartketing experience, the results are similar.

The Division remarked that the Sponsor had previously stated that there were no cases of anaphylactic reaction in the postmarketing experience, and yet now there appears to be as many as 23 cases (as derived from the Sponsor's analysis of 240 total reports of anaphylaxis). The Division further stated that all relevant postmarketing cases should be submitted with the CR, including the 160 cases of POME. The Division stated that the CR review would focus heavily on the postmarketing safety experience.

The Sponsor noted that there have been no reported deaths from serious post-injection reactions to AVEED. The Division stated that deaths could be expected if this product is continued to be used. The Sponsor stated that there are many products, including common foods, that can cause fatal anaphylactic reactions. The Sponsor gave peanuts as an example, and emphasized that anaphylaxis is quite common, but it is rarely a cause of death.

<u>Regarding the Agency's position on a REMS with ETASU:</u>
The Sponsor stated that in May 2010, the Sponsor was seeking a path towards approval, and at that time, the Division suggested that the Sponsor might consider a REMS program with Elements to Assure Safe Use (ETASU). Based on the Division's suggestion, the Sponsor planned a REMS with ETASU and sought the Division's concurrence to this program at today's meeting. Therefore, the Sponsor was surprised by the Division's lack of agreement to the proposed REMS with ETASU. The Division stated that the Sponsor's proposed REMS with ETASU for AVEED

was presented within FDA, including discussion with senior management. A decision was reached that a REMS with ETASU was not appropriate in this particular situation. The Division provided a rationale for this decision. The Division explained that a REMS with ETASU has been previously employed in situations where a product was intended for a serious or life-threatening indication, the product was shown to provide an important clinical benefit over existing products, or there was no existing product for the indicated use, and safety issues required an ETASU. The situation with AVEED does not meet these criteria. It was decided, therefore, that the plan to restrict distribution of AVEED under a REMS with ETASU was not an acceptable pathway to possible approval.

Regarding potential dispute resolution:
Based on the Division's current position concerning the Sponsor's proposed REMS with ETASU, as well as the Sponsor's belief that reformulation of the product was not possible, the Sponsor stated that an impasse appears to have been reached, and therefore, they were considering a formal dispute resolution process.

The Division stated that the Sponsor might want to consider submitting another CR rather than proceeding with dispute resolution based on the Division's December 2009, CR action. The Division reminded the Sponsor that a regulatory decision on approval is always a balance of the risks and benefits of the drug. Serious and life-threatening post-injection reactions have been reported for AVEED, and these clearly remain a major concern. Despite this, the Division continued to recommend that Sponsor submit another CR, inclusive of all postmarketing safety information. In response, the Sponsor stated that the Division reviewed the NDA in 2009 and a CR was issued. In the Sponsor's opinion, the overall risk-benefit for AVEED for the testosterone replacement indication has not changed since that time; therefore, the Sponsor was reluctant to submit another CR for the Division's review.

The Sponsor stated that they would consider their options and that they would make a decision in the near future.

Postmeeting Comment
If the Sponsor resubmits a Complete Response, it is likely that the Division's review of the Complete Response will include discussion at an Advisory Committee meeting.

Question 2: Study IP157, the study of AVEED conducted by Indevus and Endo Pharmaceuticals in the United States, was done in 5 parts, denoted as Part A, Part B, Part C, Part C2 and Part D. Parts A, B, C and C2 utilized deep intramuscular injection delivery of TU while Part D utilized subcutaneous injection delivery of TU. Only Parts C and C2 used the proposed dose and route of administration for which Endo is seeking approval. Part C, which was previously submitted in part in NDA 22-219, serves as the basis of the pharmacokinetic (PK) data for approval. Part C2 has additional PK data to augment the data from Part C.

Endo proposes to author complete study reports (CSR's) for Parts C and C2,which utilize the proposed dosing strength (750 mg) and dosing regimen (initial injection followed by an additional injection at 4 weeks and every 10 weeks thereafter).

We propose to submit abbreviated CSR's because they utilized dosing strengths and regimens which differed from the proposed dosing strength and regimen. These abbreviated CSR's will contain demographic data/baseline characteristics, extent of exposure, patient disposition and full safety evaluations. PK concentration data for total testosterone will also be presented as it the safety of the formulation. The Part A abbreviated CSR will supplement the interim Part A CSR which was previously submitted.

Part D was comprised of 2 subsets of patients, approximately 20 patients who crossed over from Part A and approximately 20 patients who crossed over from Part C. These subsets of patients received their 8th and 9th injections via subcutaneous injection during their participation in part D. These patients' Part D injection data will be included in the CSR's for Parts A and C and a separate Part D CSR is not planned due to the limited data that were collected. The injection site reaction data from Part D have been included in separate tabular summaries in both aforementioned CSR's.

Does the Agency concur with this proposal of completing the CSR's?

Response: Yes.

Additional Discussion: The Sponsor informed the Division prior to the meeting that additional discussion of this response was not necessary.

Question 3: In reference to the complete response letter, dated 2 December 2009, Endo has reviewed the Safety Update requirements and will reply as requested. The integrated Summary of Safety (ISS) in our planned complete response will be comprised of all demographic/baseline characteristics, extent of exposure, patient disposition and adverse experience date presented as:

(b) (4)

(b) (4)

Does the Agency concur with this proposal for the ISS?

Response: No. The proposed ISS submission is not sufficient. (b) (4)

Additional Discussion: The Sponsor informed the Division prior to the meeting that additional discussion of this response was not necessary.

Question 4: Endo proposes to provide SAS analysis datasets following CDISC ADaM version 2.1 requirements (b) (4)

Endo also proposes that data tabulation datasets will not be submitted in CDISC and ADaM format but instead submitted in Case Report Tabulation format as it was data based from the CRF.

Does the Agency concur with this proposal for submission of datasets for the complete response?

Response: We agree with the proposal for the first part of the question. Please clarify the second part of the question. Did you mean to say that CRF's will not be in CDISC or Adam format? If that's the case, then we agree.

Additional Discussion: The Sponsor informed the Division prior to the meeting that additional discussion of this response was not necessary.

Additional Clinical Comments

1. We note that postmarketing cases of serious post-injection reactions continue to be submitted since the May 24, 2010, Type A meeting. The May 25, 2011, version of your meeting package describes a total of 400 postmarketing cases of post-injection reaction (160 POME and 240 anaphylactic reactions), which is substantially greater than the 106 cases we had previously identified.

2. We note that in several newly submitted cases, the post-injection reaction resulted in medically significant sequelae, such as acute coronary syndrome, syncope, arrhythmia, and significant decrease or increase in blood pressure.

3. We note that several patients (including Case DE-2004-037302) experienced post-injection reactions upon re-challenge, and most were treated with corticosteroid and antihistamines as for anaphylactic reaction.

4. In addition to POME and anaphylactic reactions, there were other serious adverse events reported among the new postmarketing cases, including:

    - Polycythemia and cerebrovascular accident
    - Gynecomastia and breast pain
    - Muscle and joint pain syndromes
    - Purpuric rash and hematuria syndrome (with positive re-challenge)
    - Severe injection site reaction
    - Azoospermia
    - Acute psychiatric reactions, including mania and aggression.

5. The proposed "Management Algorithm" may not be capable of supporting health care professionals, especially urologists, in dealing with serious post-injection reactions.

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
Meeting minutes will be conveyed to Sponsor within 30 days.

ATTACHMENTS AND HANDOUTS
See attached

Updated Table 7: Ampoules Sold and Number of Injection Based Pulmonary Oil Microembolism Reactions and Anaphylaxis Events as Reported by BSP in PSURs

	Launch thru PSUR7 (11/25/03-11/24/08)	PSUR8 (11/25/08-11/24/09)		PSUR9 (11/25/09-11/24/10)		Total (11/25/03-11/24/10)
Ampoules	(b) (4)					
Cumulative Ampoules						
Injection-based pulmonary oil microembolism reactions (% of ampoules)						
Serious	31	10		23		64
	(b) (4)					
Non-serious	40	36[1)]		20		96
	(b) (4)					
Total Injection Reactions	71	46		43		160
	(b) (4)					
Anaphylaxis						
Cumulative SMQ (pre-review)	119			121		240
Rüggeberg	5	3		3[2)]		11
	(b) (4)					
Preferred Term[3)]	0	6		6		12
	(b) (4)					
Total Anaphylaxis Reactions	5	9		9[2)]		23
	(b) (4)					
Grand Total Immediate Post Injection Reactions	76	55		52		183
	(b) (4)					
Deaths	0	0		0		0

[1)] Includes 22 reported by one HCP.

[2)] One case from the allergy study (IP157-003) was also reported in this period but was recruited based on a report from 2004 (case DE-2004-037302) and so is reported in the column 'launch thru PSUR7' (to prevent double-counting).

[3)] Cases which did not meet any level of Rüggeberg diagnostic certainty criteria but coded to a preferred term of 'anaphylaxis' or 'anaphylactic shock' based on reported terms.

At the time that the FDA generated the list of 106 cases (PSUR8), the number of cases identified in the PSUR was 131 (=76+55)

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/s/

MARK S HIRSCH
08/01/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219

MEETING REQUEST GRANTED

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 undecanoate injection.

We also refer to your February 16, 2011, correspondence requesting a meeting to present clarifying data and to discuss a path forward for a resubmission and ultimate approval of testosterone undecanoate injection. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: June 27, 2011
Time: 12: 30 -2:00 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

FDA participants:

Scott Monroe, M.D.	Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D.	Medical Team Leader, DRUP
Harry Handelsman, D.O.	Medical Officer, DRUP
Lynnda Reid, Ph.D.	Pharmacology Supervisor, DRUP
Eric Andreasen, Ph.D.	Pharmacology Reviewer, DRUP
Myong Jin Kim, Pharm.D.	Clinical Pharmacology Team Leader, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology (DCP) III
Hyunjin Kim, Pharm .D.	Clinical Pharmacology Reviewer, OCP, OTS, DCP III
Mahboob Sobhan, Ph.D.	Statistical Team Leader, Division of Biometrics (DB) III, OTS
Donna Christner, Ph.D.	Pharmaceutical Assessment Lead, Office of Pharmaceutical Sciences (OPS), Office of New Drug Quality Assessment (ONDQA), Division of Pre-Marketing Assessment (DPA) II

Audrey Gassman, MD	Director for Safety, DRUP
Anthony Durmowicz, M.D.	Medical Team Leader, Division of Pulmonary and Allergy Products (DPARP)
Jennifer Mercier	Chief, Project Management Staff, DRUP
Jeannie Roule	Regulatory Health Project Manager, DRUP

Please e-mail me any updates to your attendees at jeannie.roule@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Jeannie Roule (301) 796-3993 or Victor Browne (301) 796-2130.

We acknowledge that you have already submitted your background information for the meeting. Submit 15 desk copies at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting, we may cancel or reschedule the meeting.

Submit the 15 desk copies to the following address:

Jeannie Roule
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building #22, Room: 5369
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, call Jeannie Roule, Regulatory 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

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	June 27, 2011 @ 12: 30 PM
MEETING ENDING DATE AND TIME	June 27, 2011 @ 2:00 PM
PURPOSE OF MEETING	Industry Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	White Oak Building #22 Room 1309
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	Jeannie Roule Regulatory Project Manager White Oak, Building #22 Room 5369 301-796-3993
ESCORT INFORMATION (If different from Hosting official)	Victor Browne, 301-796-3943

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/s/

JENNIFER L MERCIER
03/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219

MEETING MINUTES

Endo Pharmaceuticals Inc.
Attention: Robert Barto, MBA
Vice President, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Barto:

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

We also refer to the meeting between representatives of your firm and the FDA on May 24, 2010. The purpose of the meeting was to discuss the possibility of a path forward for the drug development of testosterone undecanoate injection.

A copy of the official minutes of the meeting 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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**Type A**
Meeting Category:	**Guidance**
Meeting Date and Time:	**May 24, 2010@ 2:30-4:00 p.m.**
Meeting Location:	**White Oak Conference Room 1309**
Application Number:	**NDA 022219**
Product Name:	**testosterone undecanoate injection**
Indication:	**Testosterone replacement therapy**
Applicant Name:	**Endo Pharmaceuticals, Inc.**
Meeting Chair:	**Mark Hirsch, M.D.**
Meeting Recorder:	**Jeannie Roule**

FDA ATTENDEES

Scott Monroe, M.D.	Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D.	Medical Team Leader, DRUP
Harry Handelsman, D.O.	Medical Officer, DRUP
Roger Wiederhorn, M.D.	Medical Officer, DRUP
Jonathan Jarrow, M.D.	Medical Officer, DRUP
Eric Andreasen, Ph.D.	Pharmacology Reviewer, 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
Audrey Gassman, MD	Deputy Director for Safety, DRUP
Martin Kaufman, D.P.M., M.B.A	Safety Regulatory Project Manager, DRUP
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	Directory, Regulatory Affairs
Theodore Danoff, MD, PhD	Vice President, Clinical Development and Medical Affairs, Endocrinology/Urology
Ivan Gergel, MD	Executive Vice President, Research and Development
Neil Shusterman, MD	Senior Vice President, Clinical Development and Medical Affairs
Nova Silver, RN	Associate Director, Clinical Development and Medical Affairs
Lianng Yuh, PhD	Vice President, Biostatistics and Programming
Heidrun Hildebrand, M.D.	Global Product Leader General Medicine, Global Project Management

BACKGROUND

On December 2, 2009, the Division issued a Complete Response (CR) Letter for AVEED™ (testosterone undecanoate) intramuscular injection. AVEED was not approved because the Division concluded that the Applicant had not demonstrated that the benefits of the drug

outweigh the additional potential risks associated with the use of testosterone undecanoate injection (AVEED). The Division's primary safety concern with AVEED was the occurrence of serious, immediate, potentially life threatening post-injection reactions.

In the CR Letter the Division proposed two approaches to demonstrate that the benefits outweigh the potential risks associated with the use of AVEED as follows:

1. Identify which component(s) of the drug product may be contributing to the serious, immediate post-injection adverse reactions, reformulate the product, and demonstrate that these reactions have been reduced or mitigated; or
2. Identify a population of adult males who require testosterone replacement therapy and in whom the additional potential risks associated with the use of testosterone undecanoate injection as currently formulated would be acceptable.

The Applicant requested a meeting to discuss the possibility of a path forward for the drug development of their product.

DISCUSSION

Preliminary responses were provided to the Applicant on May 21, 2010, in response to the questions posed in the Applicant's meeting package provided to the Division on April 21, 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*.

1. **Does the FDA agree** (b) (4)

   Response: In response to Questions 1, 2 and 3a:

(b) (4)

The goals of such a strategy would be to ensure that appropriate patients are prescribed AVEED, that patients and prescribers are made aware of the risks, and that patients are adequately monitored. Mechanisms for prescriber reporting of adverse events could also be implemented. Further guidance can be provided following internal discussion with the Office of Surveillance and Epidemiology.

Additional Discussion: The Applicant provided the Division with a 1-page handout entitled "Reimbursement and Distribution Flow," containing a schematic for the possible postmarketing distribution of Aveed (see attachment).

In this handout, the Applicant proposed that their product would be supplied to physicians from either a Specialty Distributor or a Specialty Pharmacy.

The Division stated that it envisioned a restricted distribution program where the physician would serve as a certified "gatekeeper" to the product. The physician would "sign up" with the Applicant. The physician would receive detailed education concerning the indications for, and risks of AVEED. The physician would attest that they understood the indications for, and the risks of AVEED, and that they were capable of, and medically equipped to manage serious post-injection reactions. The Division further emphasized the importance of capturing and reporting the adverse events of interest. The Division stated that the program would need to be capable of assessing compliance and also acting upon those compliance assessments.

The Applicant expressed the opinion that the Division's proposal was unduly burdensome. They further stated that the Division's proposal was "discordant" with the demonstrated risks of AVEED, especially in regard to the need for a physician attestation. The Applicant stated that their original risk mitigation proposal, coupled with the proposed new distribution model, was more appropriate, more consistent with clinical practice, and would adequately address the Division's concerns, without the need for a physician attestation. They stated that their current proposal was a "de facto" restricted distribution program as the drug would not be available via retail pharmacies.

The Division stated that it is not familiar with the details of the Applicant's plan but was willing to discuss the plan further. The Division suggested that the Applicant submit all of the details of their plan to the IND.

2. Does the FDA agree (b) (4)

Response: See response to Question 1.

3a. Does the FDA agree (b) (4)

Response: See response to Question 1.

(b) (4)

Additional Discussion: The Applicant asked whether this study was necessary. The Division stated (b) (4)

The Applicant asked (b) (4)

The Division voiced a concern (b) (4)

however, the Division agreed to consider this issue further.

Post meeting Comment: (b) (4)

3c. Does the FDA agree that (b) (4)

Response: No. See our response to Question 3b. .

4. Endo believes (b) (4)

[redacted] (b) (4)

Does the FDA agree that this study would no longer be required?

Response: We believe that the precise incidence of serious, immediate, post-injection reactions is still undefined due to the lack of complete information for potential incident cases in the studies submitted as part of the your previous Complete Response submitted in July 2008. Therefore, we believe that the proposed post-marketing study will yield useful information and should be conducted.

If AVEED were to be approved with restricted distribution of the product, adverse event reporting mechanisms could be implemented to provide sufficient information regarding the likely incidence of serious, immediate, post-injection reactions, and obviate the need for the proposed study described under Protocol number [redacted] (b) (4)

Additional Discussion: The Applicant believes that their proposed plan for a "de facto" restricted distribution plan [redacted] (b) (4) *would also be capable of capturing the likely incidence of serious, immediate post-injection reactions, and would obviate the need for this study. The Division reiterated that it was unfamiliar with the details of the Applicant's plan, but was willing to review the plan, once it was submitted to the IND.*

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

ATTACHMENTS AND HANDOUTS
See attached handout

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	GI-1	ENDO PHARMACEUTICALS INC	NEBIDO

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/s/

MARK S HIRSCH
06/22/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022219

Endo Pharmaceuticals, Inc.
Attention: Robert Barto
Vice President, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Barto:

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

We are providing you, per your request, with a list of 115 post marketing safety reports for individual cases for which adverse reactions were reported immediately or soon after an injection of intramuscular testosterone undecanoate. We identified these reports in the Bayer/Schering post marketing safety update reports (PSURs) for Nebido, which were submitted in your original NDA and in your subsequent Complete Response received on March 2, 2009. This list also includes (1) nine reports for individual cases submitted by you on August 29, 2009, in response to our request for a final safety update and (2) one additional report that you submitted after your final safety update.

These cases were selected on the basis of the following criteria:

- A close temporal relationship to the injection of testosterone undecanoate, occurring during or shortly after the injection.
- The sudden onset of respiratory, cardiovascular, or allergic signs or symptoms.

We made an effort to identify all serious reactions meeting these basic criteria. We also included non-serious reactions if we believed they were of clinical importance.

Among these 115 individual cases, our consultants have determined that some represent anaphylactic reactions, possible anaphylactic reactions, or allergic reactions. These cases are delineated in the accompanying list using the following codes:

A = anaphylactic reaction or probable anaphylactic reaction
B = possible anaphylactic reaction
C = allergic reaction

In the listing, we also provide the individual assessments of each of our consultants. These consultants were Medical Officers (either allergists or pulmonologists from the FDA's Division of Pulmonary and Allergy Drug Products [DPAP]) and two non-FDA consultants (identified in the listing as SGE [Special Government Employee] #1 and #2. Both of the non-FDA consultants are well-respected academic allergists. The criteria that DPAP used to categorize cases as anaphylaxis or possible anaphylaxis were those described in (1) Sampson HA et al, J Allergy

Clin Immunol 115 (3):584-591, 2005, and (2) Sampson HA et al, J Allergy Clin Immunol 117 (2):391-397, 2006.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

Testosterone Undecanoate IM Injection
Immediate Post-Injection Adverse Reactions (Postmarketing Reports)

	List of Patients	FDA	SGE Consultant #1	SGE Consultant #2
1	2009 32012 GPV	A	A	A
2	2009 10048 BNE	A	B	
3	2009 10221 BNE	B		
4	2009 12293 BNE	A	B	
5	2009 12294 BNE	A	B	
6	2009 16799 LA	A	B	
7	2009 19013 LA	C	B	
8	2009 19765 LA	A	B	
9	2009 24735 GPV	A	B	
10	2009 12132 GPV	B		
11	2008 15625 LA	A	A	
12	2008 18230 LA	A	B	
13	2008 28604 GPV	B	B	
14	2008 12947 GPV	B		
15	DE 2005 008181	B		
16	DE 2005 008140	C		
17	DE 2005 008146			
18	DE 2005 008154			
19	DE 2005 008161			
20	DE 2005 008193			
21	DE 2005 008199			
22	NO 2007 008557			
23	NO 2007 008581			
24	DE 2005 014372			
25	DE 2007 004748			
26	DE 2006 009799			
27	2008 21776 GPV		B	
28	2008 13805 LA			
29	BR 2006 019257			
30	2007 11462 BNE			
31	AT 2006 001317			
32	SE 2007 002541			
33	SE 2006 039053			
34	SE 2007 002515			A
35	CH 2005 002386			
36	FR 2007 035024			
37	2008 16799 GPV			
38	2008 15181 GPV	B	A	
39	2008 19576 LA	B		
40	2008 12881 BNE	A		
41	2008 11461 BNE	C		
42	2008 20307 GPV			
43	2008 21519 GPV		B	
44	2008 26527 GPV			

FDA
A = Anaphylaxis
B = Possible Anaphylaxis
C = Allergic

Consultant # 1
A = Probable Anaphylaxis
B = Possible Anaphylaxis

Consultant # 2
A = Anaphylaxis

Testosterone Undecanoate IM Injection
Immediate Post-Injection Adverse Reactions (Postmarketing Reports)

	List of Patients	FDA	SGE Consultant #1	SGE Consultant #2
45	2008 26556 GPV			
46	2008 11355 GPV	B		
47	2008 12136 GPV			
48	2008 25110 GPV			
49	2008 21057 GPV			
50	2008 22564 GPV			
51	2008 12867 LA			
52	2008 19842 GPV			
53	2007 11268 BNE			
54	2007 11270 BNE	B		
55	2007 11462 BNE		B	
56	2007 18455 GPV			
57	AT 2007 035468			
58	AU 2007 014016			
59	BR 2007 005496		B	
60	BR 2007 010933			
61	CH 2007 042227			
62	DE 2004 037302	A		
63	DE 2005 004016		B	
64	DE 2005 005199		B	
65	DE 2005 008181			
66	DE 2005 009283		B	
67	DE 2006 003298		B	
68	DE 2006 008415			
69	DE 2007 004747			
70	DE 2007 023890			
71	DE 2007 030464			
72	GB 2006 006197	B	B	
73	GB 2007 000740		A	
74	GB 2007 023826	A	B	A
75	SE 2006 014505			
76	SE 2006 017516			
77	SE 2006 022330	B	B	
78	ZA 2007 035469	A	B	
79	2008 10157 GPV			
80	2008 10357 GPV			
81	AR 2006 008403			
82	AT 2006 020143			
83	AU 2007 008333			
84	AU 2007 035848			
85	BR 2006 032646			
86	DE 2005 007589			
87	DE 2005 008140			
88	DE 2005 008199			

FDA
A = Anaphylaxis
B = Possible Anaphylaxis
C = Allergic

Consultant # 1
A = Probable Anaphylaxis
B = Possible Anaphylaxis

Consultant # 2
A = Anaphylaxis

Testosterone Undecanoate IM Injection
Immediate Post-Injection Adverse Reactions (Postmarketing Reports)

	List of Patients	FDA	SGE Consultant #1	SGE Consultant #2
89	DE 2005 011567			
90	DE 2005 015256			
91	DE 2005 016985			
92	DE 2005 01795			
93	DE 2005 019516			
94	DE 2006 002815			
95	DE 2006 009799			
96	DE 2006 010466			
97	DE 2006 021129			
98	DE 2006 021339			
99	DE 2006 022513			
100	DE 2007 004748			
101	DE 2007 004750			
102	DK 2005 009832			
103	DK 2005 018395			
104	DK 2006 002013			
105	DK 2007 030285			
106	DK 2007 031980			
107	GB 2006 036061			
108	GB 2007 036451			
109	NO 2007 008557			
110	NO 2007 038349			
111	SE 2005 021116			
112	SE 2006 027304			
113	SE 2007 002541	C		
114	SE 2007 038495			
115	SE 2007 038496			

FDA
A = Anaphylaxis
B = Possible Anaphylaxis
C = Allergic

Consultant # 1
A = Probable Anaphylaxis
B = Possible Anaphylaxis

Consultant # 2
A = Anaphylaxis

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	ORIG-1	ENDO PHARMACEUTICALS INC	NEBIDO

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/s/

SCOTT E MONROE
12/22/2009

MEMORANDUM

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

DATE: December 3, 2009

TO: NDA 022219

FROM: Jeannie Roule, Regulatory Health Project Manager

SUBJECT: Response from outside consultation

APPLICATION/DRUG: NDA 022219, Aveed™ (testosterone undecanoate) injection

The Division of Reproductive and Urologic Products (DRUP) in the Office of New Drugs (OND) is actively reviewing the new drug application (NDA) for AVEED™ (testosterone undecanoate) injection and we seek your input. We consulted Thomas A.E. Platts-Mills, M.D., Ph.D., Professor of Medicine and Microbiology, Division Head, Division of Allergy and Clinical Immunology at the University of Virginia Health System in Charlottesville, VA.

His response is attached.

Request for Consultation

Date: November 2, 2009

To: Thomas A.E. Platts-Mills, M.D., Ph.D.
Professor of Medicine and Microbiology
Division Head, Division of Allergy and Clinical Immunology
University of Virginia Health System
Charlottesville, VA

From: Mark S. Hirsch, M.D.
Medical Team Leader in Urology
Division of Reproductive and Urologic Products
Office of New Drugs
Center for Drug Evaluation and Research
United States Food & Drug Administration
Silver Spring, MD

In regard to: New Drug Application 22-219
Aveed™ (testosterone undecanoate) injection
Endo Pharmaceuticals
Lexington, MA

1. Background

The Division of Reproductive and Urologic Products (DRUP) in the Office of New Drugs (OND) is actively reviewing the new drug application (NDA) for AVEED™ (testosterone undecanoate) injection and we seek your input. We are profoundly grateful for your willingness to help on this project.

AVEED is a depot preparation of testosterone undecanoate intended for the replacement of testosterone in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The drug product contains three components: testosterone undecanoate (an unapproved ester of testosterone), castor oil, and benzyl benzoate. It is administered as a deep intramuscular injection into the gluteus muscle, and dosed as 750mg (3mL) at initiation, at 4 weeks, and then (b) (4)

The product has been marketed since 2004 by Bayer/Shering Plough in Europe as a 4mL injection (under the tradename "Nebido"). The drug is approved for sale in other parts of the world as well.

Our main safety concern for AVEED has been reports of immediate post-injection reactions, characterized as an urge to cough, cough, dyspnea, wheezing, shortness of breath, difficulty breathing, respiratory distress, bronchospasm, chest pain, flushing of the skin, sweating, throat pain, throat burning, throat tightening, laryngospasm, choking, occasional urticaria, occasional rash, occasional syncope and loss of consciousness, and

occasional circulatory collapse. The majority of these cases have been reported spontaneously from the worldwide postmarketing experience. The Sponsor attributes these events, some of which were serious and life-threatening, to a phenomenon called "*pulmonary oily microembolism*", or POME. There has been considerable debate, however, between FDA and Sponsor as to whether these cases are wholly attributable to the phenomenon that Sponsor refers to as "POME", or whether some reflect anaphylactic reactions. Most cases were reported and treated as acute systemic allergic reactions. In addition, it is of note that the European marketer, Bayer Schering, has stated their opinion that at least several of the cases reflect anaphylaxis, but in many cases, the differentiation between anaphylaxis and POME may be impossible.

With this in mind, we ask that you provide an opinion on these events, individually and as a group. The enclosed package consists of the individual case reports of interest and this cover letter.

2. Specific Request to Consultants

Our major request for this consult is for you to review 116 individual postmarketing adverse event reports for Nebido. These cases are derived from:

a. A single CIOMS report submitted on September 21,2009 (*n=1*) - **BIN #1**
b. Medwatch reports submitted on August 29, 2009 (*n=9*) - **BIN #2**
c. Listings in Appendix 8 of the Bayer Post-Marketing Safety Update Report (PSUR) for the time period November 2007-November 2008 (*n=31*) submitted on March 2, 2009 - **BIN #3**
d. Listings in the body of the Bayer PSUR for the time period November 2007-November 2008 submitted on March 2, 2009 (*n=12*) - **BIN #4**
e. An Executive Summary submitted on February 12, 2008 (*n=63*) – **BIN #5**

An additional case of interest is provided for your review (MFR Report # 200910 189GPV - skin test positive reaction to benzyl benzoate). All 117 cases are provided in narrative form.

3. Specific Questions for the Consultant

1. Of the 116 cases submitted for your review, how many meet clinical criteria for anaphylaxis? In how many of these cases can anaphylaxis not be ruled out?

2. Many of the cases describe skin flushing as well as throat symptomatology (throat pain, throat ticking, throat tightening, throat swelling, laryngeal edema, etc). DRUP is unable to find evidence that skin flushing and throat tightening reflect pulmonary oily microembolism (POME). Can these skin and throat-related symptoms reflect anaphylaxis?

3. Do you agree with Bayer Shering-Plough that it can be impossible to differentiate anaphylaxis from POME?

4. Is benzyl benzoate an allergen, and if so, can it be playing a role in the immediate post-injection reactions reported with the product?

5. Is castor oil an allergen, and if so, can it be playing a role in the immediate post-injection reactions reported with the product?

6. Do you have any general thoughts or comments on the pulmonary/allergy risks demonstrated for the product, or for those risk in relation to the product indication?

UNIVERSITY of VIRGINIA HEALTH SYSTEM

The DEPARTMENT *of* INTERNAL MEDICINE

ASTHMA & ALLERGIC DISEASES CENTER

Thomas A. E. Platts-Mills, MD, PhD
Oscar Swineford JR Professor of Medicine

November 16, 2009

Mark S. Hirsch
Medical Team Leader in Urology
Center for Drug Evaluation and Research
United States Food & Drug Administration
Silver Spring, MD

Dear Dr. Hirsch:

Re: New Drug Application 22-219
Aveed™ (testosterone undecanoate) injection
Endo Pharmaceuticals
Lexington, MA

Thank you for asking me to have a look at these incident/reaction reports related to injections of testosterone undeconate. First, let me state that I only found three cases that I would regard as anaphylaxis. The consistency of the reports is remarkable with tickling of the throat, urge to cough and dyspnea in a large majority of the cases. Furthermore, these responses are very rapid. Indeed, the speed of these response is reminiscent of the reactions to intramuscular immunoglobulin and also those to IV contrast media. Classical IgE mediated anaphylaxis to venom, penicillin, food, or allergy shots is slower than this. Furthermore, anaphylaxis in patients who do not have asthma generally does not include chest symptoms. The rarity of "hives" or "urticaria" or equivalent words in these reports is striking.

Please don't take my opinion that these cases are not anaphylactic as arguing that they are not severe. There are multiple descriptions here that are very severe including collapse, with apnea, severe chest pain, coughing sufficient to put patients in the intensive care unit, etc. I am assuming that no patient is known to have died during or rapidly following one of these injections.

In your letter you state that skin flushing and throat tightening are not known to reflect POME. There is no doubt that symptoms of this kind can occur in anaphylaxis, but skin flushing in particular is not diagnostic and we would only accept that as evidence of anaphylaxis in the context of other changes. Throat tightening is a highly subjective symptom and I did not identify any reports where objective evidence for "throat tightening" was provided. Again, I stress that the very low prevalence of urticaria in these cases argues, strongly against histamine release as a significant mechanism. When

PO Box 801355. Charlottesville, Virginia 22908-1355
Office: 434-924-5917. Fax: 434-924-5779. E-mail: tap2z@virginia.edu

you ask the question "how many of these cases can anaphylaxis be ruled out?", you are asking a question that cannot be answered by chart review. The main problem being that one would need to examine the cases at the time of these reactions. If you use rapid onset of two of the following:

- Skin itching and hives,
- Airway obstruction,
- Fall in blood pressure,

as the definition of anaphylaxis, clearly any of the cases that report itching and cough or throat tightening cannot strictly be ruled out? However, it is the rarity of convincing cases that argues against it.

Detailed Comments:

1. In these cases, there seems to be a random distribution of first case reactions, and reactions occurring after several previous injections. Without knowing what proportion of total injections are first injections, it is difficult to evaluate this. However, there is not a consistent pattern that this drug needs repeated exposure for sensitization or that the reactions reflect pre-sensitization (as we found with cetuximab, Chung CH, et al, Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med 2008;358:1109-1117.

2. I was not given a full description of the product. In case #3 in Bin #3, there is a list of ingredients including (b) (4)

3. Do you think speed of injection is relevant? The term "very slow" appears repeatedly, but seems to be defined as anything from 1 minute to 7 minutes. Only once did I see a specific statement that 2 min was the recommended time for injection.

4. Detailed investigation of these cases was reported in only 3-4 cases: Case #1 in Bin #1 where skin tests were positive: Extra case in Bin #4 where skin test showed type IV delayed reaction ? to (b) (4) and case #18 in Bin 5 where testing fo (b) (4) and castor oil were negative.

5. Judging severity by either need for urgent treatment or by the decision to stop treatment with testosterone undeconate it is clear that these reactions were almost all severe.

6. I was truly impressed by the confused nature of these reports: In particular trying to sort out which of the cases had been given a subsequent dose was not possible.
   - Case #4 in Bin #4 "This view is supported by positive dechallenge for the Nebido"
   - Case #6 in Bin #4 states: "Rechallenge for the events except for "short scratching in the throat" was considered to be positive."

   But my favorite case reports were:

- Case #7 Bin 5, part 1 who reported being "ventilated in the drug store".
- And Case 8, Bin 5, Part I who reported collapsing after giving 3 ml of Nebido and then completing the injection when he recovered consciousness.

7. The speed of these reactions is remarkable and could be taken as an argument **against** an anaphylactic reaction. Thus in case #11 of Bin #5 part I the reaction is stated to have started "15 seconds" after the injection with circulating collapse and unconsciousness. It is important to remember that "fainting" ie circulatory collapse is an important early feature of pulmonary embolus. In this case, I would agree with the companies' assessment that this time interval is very short for allergy or anaphylaxis.

8. I would regard three cases as including criteria for anaphylaxis or an IgE mediated allergic responses :
    - Case #1, Bin 1. Progressive development of respiratory distress combined with generalized urticaria, in a patient who was, subsequently shown to have positive skin tests. It would be interesting to know what part of Australia this boy comes from because there are regional causes of anaphylaxis in Australia.
    - Case #22, Bin 4, part 1: Rapid onset of coughing and airway closure accompanied by a "raised rash" on the abdomen.
    - Case #25, Bin 4: "Urticaria over the whole body and itching"

I have written comments about each of the serious cases and would gladly try to classify them; however, I am sending this report now because I think it is responsive to most of your questions. I look forward hearing from you.

Yours sincerely,

Thomas A.E. Platts-Mills, MD, PhD, FRCP
Oscar Swineford JR Professor of Medicine
Asthma and Allergic Diseases Center
University of Virginia

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	ORIG-1	ENDO PHARMACEUTICALS INC	NEBIDO

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/s/

JEANNIE M ROULE
12/08/2009

MEMORANDUM

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

DATE: December 3, 2009

TO: NDA 022219

FROM: Jeannie Roule, Regulatory Health Project Manager

SUBJECT: Response from outside consultation

APPLICATION/DRUG: NDA 022219, Aveed™ (testosterone undecanoate) injection

The Division of Reproductive and Urologic Products (DRUP) in the Office of New Drugs (OND) is actively reviewing the new drug application (NDA) for AVEED™ (testosterone undecanoate) injection and we seek your input. We consulted Dr. James Li, M.D., Chairman, Division of Allergic Diseases in the Department of Internal Medicine at the Mayo Clinic in Rochester, MN.

His response is attached.

Request for Consultation

Date: November 2, 2009

To: James T.C. Li, M.D.
Chairman, Division of Allergic Diseases
Department of Internal Medicine
Mayo Clinic
Rochester, MN

From: Mark S. Hirsch, M.D.
Medical Team Leader in Urology
Division of Reproductive and Urologic Products
Office of New Drugs
Center for Drug Evaluation and Research
United States Food & Drug Administration
Silver Spring, MD

In regard to: New Drug Application 22-219
Aveed™ (testosterone undecanoate) injection
Endo Pharmaceuticals
Lexington, MA

1. Background

The Division of Reproductive and Urologic Products (DRUP) in the Office of New Drugs (OND) is actively reviewing the new drug application (NDA) for AVEED™ (testosterone undecanoate) injection and we seek your input. We are profoundly grateful for your willingness to help on this project.

AVEED is a depot preparation of testosterone undecanoate intended for the replacement of testosterone in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The drug product contains three components: testosterone undecanoate (an unapproved ester of testosterone), castor oil, and benzyl benzoate. It is administered as a deep intramuscular injection into the gluteus muscle, and dosed as 750mg (3mL) at initiation, at 4 weeks, and then (b) (4)

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Our main safety concern for AVEED has been reports of immediate post-injection reactions, characterized as an urge to cough, cough, dyspnea, wheezing, shortness of breath, difficulty breathing, respiratory distress, bronchospasm, chest pain, flushing of the skin, sweating, throat pain, throat burning, throat tightening, laryngospasm, choking, occasional urticaria, occasional rash, occasional syncope and loss of consciousness, and

occasional circulatory collapse. The majority of these cases have been reported spontaneously from the worldwide postmarketing experience. The Sponsor attributes these events, some of which were serious and life-threatening, to a phenomenon called "*pulmonary oily microembolism*", or POME. There has been considerable debate, however, between FDA and Sponsor as to whether these cases are wholly attributable to the phenomenon that Sponsor refers to as "POME", or whether some reflect anaphylactic reactions. Most cases were reported and treated as acute systemic allergic reactions. In addition, it is of note that the European marketer, Bayer Schering, has stated their opinion that at least several of the cases reflect anaphylaxis, but in many cases, the differentiation between anaphylaxis and POME may be impossible.

With this in mind, we ask that you provide an opinion on these events, individually and as a group. The enclosed package consists of the individual case reports of interest and this cover letter.

2. Specific Request to Consultants

Our major request for this consult is for you to review 116 individual postmarketing adverse event reports for Nebido. These cases are derived from:

a. A single CIOMS report submitted on September 21,2009 (*n=l*) - **BIN #1**
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c. Listings in Appendix 8 of the Bayer Post-Marketing Safety Update Report (PSUR) for the time period November 2007-November 2008 (*n=31*) submitted on March 2, 2009 - **BIN #3**
d. Listings in the body of the Bayer PSUR for the time period November 2007-November 2008 submitted on March 2, 2009 (*n=12*) - **BIN #4**
e. An Executive Summary submitted on February 12, 2008 (*n=63*) – **BIN #5**

An additional case of interest is provided for your review (MFR Report # 200910 189GPV - skin test positive reaction to benzyl benzoate). All 117 cases are provided in narrative form.

3. Specific Questions for the Consultant

1. Of the 116 cases submitted for your review, how many meet clinical criteria for anaphylaxis? In how many of these cases can anaphylaxis not be ruled out?

2. Many of the cases describe skin flushing as well as throat symptomatology (throat pain, throat ticking, throat tightening, throat swelling, laryngeal edema, etc). DRUP is unable to find evidence that skin flushing and throat tightening reflect pulmonary oily microembolism (POME). Can these skin and throat-related symptoms reflect anaphylaxis?

3. Do you agree with Bayer Shering-Plough that it can be impossible to differentiate anaphylaxis from POME?

4. Is benzyl benzoate an allergen, and if so, can it be playing a role in the immediate post-injection reactions reported with the product?

5. Is castor oil an allergen, and if so, can it be playing a role in the immediate post-injection reactions reported with the product?

6. Do you have any general thoughts or comments on the pulmonary/allergy risks demonstrated for the product, or for those risk in relation to the product indication?

Testosterone undecenoate
November 19, 2009
James T. Li MD

Specific Questions for Consultant

1. Given the lack of detail in many of the reports, I wouldn't use defined "clinical criteria" to establish a diagnosis of anaphylaxis. There are at least 4 cases that I suspect as "probable anaphylaxis" (Bin #1, 1; Bin #3, 1,29; Bin#5, serious, 21). There are 22 cases of what I will call "possible anaphylaxis" (Bin #2 1,3,4,5,6,7,8; Bin#3, 2,3,18,29; Bin#4, 3; Bin #5 Serious, 3,7,11,12,14,15,20,22,25,26).
2. Skin flushing, throat tickling or tightness can be symptoms of a systemic allergic reaction. These symptoms are fairly common in patients experiencing systemic reactions ("anaphylaxis") to allergen immunotherapy injections and food.
3. Allergic reactions and POME may have some elements in common, such as development of symptoms immediately after exposure, cough and shortness of breath. Isolated cough may be more suggestive of POME. Pruritus, flushing, rash or urticaria, hypotension, wheezing, angioedema, are more characteristic of anaphylaxis. Throat symptoms would seem to suggest an allergic reaction rather than POME.
4. I have no information on benzyl benzoate as an agent that can cause anaphylaxis. It is possible that benzyl benzoate could be a cause of contact dermatitis.
5. Plant oils per se are not common causes of anaphylaxis. However, as a plant-derived product, castor bean oil could theoretically contain toxins, allergenic proteins or contaminants. Castor bean protein and pollen can be highly allergenic.
6. Several of the cases resulted in epinephrine administration, emergency department visits or brief hospitalizations, or were characterized as life-threatening. For the cases of "probable" and "possible" anaphylaxis noted above, as well as for some additional cases, I would not be comfortable attributing the adverse events to POME. A handful of cases seem consistent with anaphylaxis (immediate development of symptoms, shortness of breath, flushing or urticaria, upper airway obstruction and/or hypotension) treated with epinephrine. Other cases are suggestive, but are milder or self-limited. Known systemic reactions ("anaphylaxis") to insect stings, food and allergen immunotherapy injections do vary in severity. Some are life-threatening, but others can resolve without treatment. There seems to be some risk of allergic-type reactions to this product distinct from POME.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	ORIG-1	ENDO PHARMACEUTICALS INC	NEBIDO

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/s/

JEANNIE M ROULE
12/08/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-219 **INFORMATION REQUEST**

Endo Pharmaceuticals
Attention: Mark Roessel
Associate Vice President, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Roessel:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aveed™ (testosterone undecanoate) injection.

We continue to review the Clinical section of your submission, specifically the adverse event reports of immediate post-injection reaction, including events reported during clinical trials. We have an additional request for information on five specific patients who experienced immediate post-injection reactions in clinical trials. We request a prompt written response in order to continue our evaluation of your NDA.

For each of the patients listed below, provide detailed narratives and case report forms. Provide as much information as possible including but not limited to, the investigator's verbatim term, the adverse event terms to which the verbatim terms were coded, and the investigator's narrative of the event. If the available data are insufficient to provide a clear explanation for the post-injection reaction, provide a specific reason why the information is not sufficient.

- Patient Number 011-6089 from Study Number IP157-001 – This 52 year old male with hypertension, heart murmur, sinus bradycardia and excessive yawning experienced shortness of breath at each at each of his two injections. The investigator's verbatim terms for these events included shortness of breath, as well as "erythema – neck". The subject was subsequently diagnosed with left ventricular hypertrophy. The subject's shortness of breath led to his discontinuation from the study.

- Patient Number 001-036010 from Study Number 39732 (NE0601 IPASS) - This 60 year old male with diabetes mellitus, hypertension, and hyperlipidemia experienced flushing, sensation of warmth, "oro-pharyngeal discomfort", and heartburn (investigator verbatim terms) immediately after injection. The subject continued in the study and received four additional injections without additional adverse events being reported.

- Patient Number 001-0011 from Study Number 97173 – This 26 year old male with a history of convulsions experienced convulsions starting after his first injection. The investigator's verbatim terms also include "he looses urine". The patient was referred to a neurologist. The subject received subsequent injections without additional adverse events being reported.

- Patient Number 001-0017 from Study Number 97173 – This 38 year old male collapsed after receiving an injection. The event resolved in five minutes and the subject successfully completed his semen sample 20 minutes later. The subject received subsequent injections without additional adverse events being reported.

- Patient Number 001-0004 from Study Number JPH04995 – This 49 year old male experienced two separate episodes of circulatory collapse (investigator verbatim term) over the course of the four year study. The first event occurred immediately after his fifth injection. Low blood pressure was detected (95/60 mmHg). The second event occurred six weeks following the subject's 14th and final injection.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	ORIG-1	ENDO PHARMACEUTICALS INC	NEBIDO

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/s/

JENNIFER L MERCIER
10/14/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-219 **INFORMATION REQUEST**

Endo Pharmaceuticals
Attention: Mark Roessel
Associate Vice President, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Roessel:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aveed™ (testosterone undecanoate) injection.

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

Provide full Council for International Organizations of Medical Sciences (CIOMS) reports for each of the 43 cases listed below:

Cases from the November 2007 – November 2008 Bayer Periodic Safety Update Report (PSUR) submitted with the Complete Response, from the listings in Attachment A to Appendix 8 [n=31]

1. 2008 15625 LA- 60 y/o, reported as "anaphylactic reaction" immediately after injection (cough, throat itching, glottis spasm, glottis edema).

2. 2008 18230 LA- 58 y/o, reported as "anaphylactic reaction" within 24 hours of dose. No further information.

3. 2008 28604 GPV- 41 y/o with Klinefelter's, reported as "anaphylactic reaction" during injection (feeling of tightness in region of thorax, burning eyes, flushing, tingling sensation in lungs ascending to nose, dry cough). Allergy testing planned.

4. 2008 12947 GPV- 38 y/o with acute lymphoblastic leukemia, status post radiotherapy, with two episodes. The first episode was reported as "mild allergic reaction" after first dose. The second episode six months later was reported as "severe allergic reaction/potential heart failure" (severe throat swelling).

5. DE 2005 008181- 67 y/o obese patient, "deep IM injection may have been difficult", reported as "allergic reaction" (circulatory collapse, hypotension, nausea, retching, and "fever attacks").

6. DE 2004 037302- 38 y/o, reported as “allergic reaction” two minutes after the injection (hyperventilation during injection, red face, shivers, tachycardia, hypertension, feeling heat in thighs and upper arms, indisposition”).

7. DE 2005 008140- 56 y/o, reported as “allergic reaction” immediately after removal of needle (immediate ticking of throat, allergic reaction).

8. DE 2005 008146- 57 y/o, reported as “allergic reaction” (headache, temporary visual field defect, injection site hemorrhage).

9. DE 2005 008154- 65 y/o, reported as “allergic reaction” (“pressing complaints after injection”, “allergic reaction”, injection site discomfort).

10. DE 2005 008161- 70 y/o, reported as “allergic reaction” (“sensitive skin reaction”, “allergic reaction”).

11. DE 2005 008193- 69 y/o, reported as “allergic reaction” (headaches, hot head, pain at injection site, “allergic reaction”).

12. DE 2005 008199- 68 y/o, reported as “allergic reaction” (“short term cough with allergic sound”). The patient had the opinion that it was more likely due to use of alcohol for disinfection than the injection.

13. NO 2007 008557- age not specified, reported as “hypersensitivity” (dry cough, itching, tingling sensation). No further information.

14. NO 2007 008581- age not specified, reported as “hypersensitivity” (itching all over).

15. DE 2005 014372- age not specified, reported as “edema attributed to allergic reaction”. No further information.

16. DE 2007 004748- age not specified, reported as “suspicion of allergic event” (urge to cough, dyspnea).

17. DE 2006 009799- age not specified, reported as “suspected allergic reaction, no local symptoms” shortly after injection (dyspnea, cold sweat).

18. 2008 21776 GPV- 33 y/o with nonseminoma testicular cancer, status-post unilateral orchiectomy, radiotherapy to remaining testicle reported as “allergic reaction” directly after injection (breathing problems, cough, felt bad, blood pressure increased to 147/89).

19. 2008 13805 LA- 53 y/o with three episodes. After the first 2 injections there was injection site pain, injection site mass, injection site warmth, and injection site pruritis. After the third injection, injection site pain, warmth and pruritis, dry throat, sinusitis, nocturnal dyspnea, breathlessness at night, and increased blood pressure were reported.

20. BR 2006 019257- age not specified, reported as “allergic reaction”. No further information.

21. 2007 11462 BNE- 44 y/o with cough, shortness of breath and flushing immediately after injection.

22. AT 2006 001317- 64 y/o with severe hot flush, dyspnea, anxiety, tachycardia (>109 bpm), fatigue, depression and sleep disorder after the second injection.

23. SE 2007 002541- age not specified, with cough, redness of face, feeling warm over chest and head. No further information provided.

24. SE 2006 039053- age not specified, with palpitations, rash, whole body itching, trembling, erection failure, intensive migraine for the first week, and weight gain.

25. SE 2007 002515- age not specified, with urticaria over whole body, itching. Other suspected drug: Plaxix (clopidrogel sulfate).

26. CH 2005 002386- 33 y/o, with patchy reddening of the whole integument and mild pruritis after the first injection. Rash abated immediately with cortisone injection.

27. FR 2007 035024- age not specified, with redness on face and chest, and pruritis on face and chest after the first injection. No further information.

28. 2008 16799 GPV- age not specified, with nervousness, hot flushes, sweats, rash around neck, unusual head hair, excessive hair growth, headache, difficulty sleeping, rosacea, slight depression and no sex drive one week after the first dose.

29. 2008 15181 GPV- 52 y/o, reported as "assumed microfat embolization" (severe dyspnea, heat sensation in neck, muscle twitching, ticking in throat, loss of consciousness). CT scan: no pathological findings, no infarction, no bleeding.

30. 2008 19576 LA- age not specified, with sweating, cough, face redness, and dizziness during injection. No further information.

31. 2008 12881 BNE- 27 y/o with Noonan syndrome, primary testicular failure, asthma, with cough, flushing, wheezing and bronchopasm immediately after the second injection. Recovered after salbutamol nebulizer.

Cases from the November 2007 – November 2008 Bayer PSUR, submitted with the Complete Response, from text and line listings in the PSUR [n=12]

1. 2008 1141 BNE- 55 y/o history of hypopituitarism, with sharp increase in blood pressure ('soared to 275/175"), heavy sweating, metallic taste in mouth, "burning up" sensation immediately after the third injection.

2. 2008 20307 GPV- 2 y/o with cyanosis, coughing continuously, dizziness, numbness of face, immediately after the fourth injection.

3. 2008 21519 GPV- 21 y/o with sudden chest pain radiating towards neck and throat, light cough, and cold sweating.

4. 2008 26527 GPV- 72 y/o with severe coughing, temporary palsy of mouth and face, facial dysesthesia, and choking fit during injection.

5. 2008 26556 GPV- 76 y/o reported as POME (severe coughing, dyspnea, choking fit during injection. Stated similar reactions previously.

6. 2008 11355 GPV- 30 y/o with dry cough episode, severe burning in throat, scratching in throat, moderate dyspnea, and sensation of heat.

7. 2008121366 GPV- 40 y/o with cough, sweating, dizziness and prickly feeling in fingers and toes after each of two injections.

8. 2008 25110 GPV- 21 y/o with chest pain, cold sweat, pain in throat and chest treated with adrenaline and betamethasone.

9. 2008 21057 GPV- 50 y/o with rash on whole body three days after injection. Treated with antihistamine and recovered.

10. 2008 22564 GPV- 30 y/o with urticaria at an unknown time after injection. Treated with antihistamine and not recovered. Also using Testogel.

11. 2008 12867 LA- 22 y/o with red eyes, cough, malaise, and diarrhea 24 hours after injection. Previously using Durateston.

12. 2008 19842 GPV- age not specified, with pituitary hypogonadism, with sweating, light fall in blood pressure, and “severe reaction” at unknown time after injection.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	ORIG-1	ENDO PHARMACEUTICALS INC	NEBIDO

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/s/

JENNIFER L MERCIER
09/30/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-219

PDUFA GOAL DATE EXTENSION

Endo Pharmaceutical Solutions, Inc.
Attention: Mark Roessel
Vice President, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Roessel:

Please refer to your August 27, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AVEED™ (testosterone undecanoate) injection.

On August 31, 2009, we received your August 29, 2009, major amendment to this application, containing additional clinical safety information. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 2, 2009.

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

Sincerely yours,

{See appended electronic signature page}

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

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/s/

SCOTT E MONROE
09/02/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-219

INFORMATION REQUEST

Endo Pharmaceuticals
Attention: Mark Roessel
Vice President, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Roessel:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aveed (testosterone undecanoate) intramuscular injection.

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 Goals section is acceptable with the edits noted in Appendix A. We deleted the (b) (4) [redacted]

3. We have determined that the REMS will require a Medication Guide rather than a Patient Package Insert. A new Medication Guide section, with recommended wording, was added to replace the Patient Package Insert section. The REMS document should clarify whether the Medication Guide will be packaged with the product or provided separately.

4. We deleted the proposed instructional video and educational brochure from the REMS communication plan because the technique for intramuscular injection is adequately explained in the Prescribing Information and is well known to healthcare professionals. We recommend that you utilize these materials outside of the REMS and that you submit them to the Division of Drug Marketing, Advertising, and Communication (DDMAC) for their review.

5. Revise the Dear Healthcare Professional letter incorporating the changes indicated in Appendix B.

6. Delete all references to “allergic reactions” throughout the REMS (including references in the Dear Healthcare Professional letter) and the REMS supporting document. Replace these references with “anaphylactic reactions” to reflect clinical safety information provided in the proposed final product labeling.

7. The proposed timetable for assessments, (b) (4) 3 years, and 7 years, is acceptable. However, the specific dates of the reporting intervals that each assessment will cover and the planned date of submission of the assessment to the FDA also should be included. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31 should conclude no earlier than June 1.

8. Resubmit the revised REMS document and the REMS supporting document. 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}

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

10 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

JEANNIE M ROULE
08/18/2009

SCOTT E MONROE
08/18/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-219

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, Pennsylvania 19317

ATTENTION: Mark C. Roessel
Vice President, Regulatory Affairs

Dear Mr. Roessel:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Undecanoate Injection, 750 mg/3 mL.

We also refer to your May 12, 2009, correspondence, received May 13, 2009, requesting review of your proposed proprietary name, Aveed. We have completed our review of the proposed proprietary name, Aveed, and have concluded that it is acceptable.

The proposed proprietary name, Aveed, 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 May 12, 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 22219	ORIG 1		NEBIDO

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/s/

CAROL A HOLQUIST
08/07/2009

MEMORANDUM

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

DATE: July 31, 2009

TO: NDA 22-219

FROM: Jeannie Roule

SUBJECT: Pediatric Review of NDA 22-219, Aveed (testosterone undecanoate) IM injection

PeRC agreed with the Division of Reproductive and Urologic Products to grant a full waiver for Aveed.

Please see attached email.

Roule, Jeannie

From: Greeley, George
Sent: Thursday, July 02, 2009 8:31 AM
To: Roule, Jeannie
Cc: Stowe, Ginneh D.
Subject: NDA 22-219 Aveed

Importance: High

Hi Jeannie,

The Aveed (testosterone undecanoate) full waiver was reviewed by the PeRC PREA Subcommittee on April 29, 2009. The Division recommended a full waiver because too few children with disease/condition to study. The PeRC agreed with the Division to grant a full waiver for this product.

However, the PeRC has asked that the Division change the pediatric page to reflect the only reason for waiver as being too few children with disease/condition to study. The PeRC also recommends having a discussion with the sponsor to determine if a Written Request is feasible.

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

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22219	ORIG 1	ENDO PHARMACEUTICALS INC	NEBIDO

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/s/

JEANNIE M ROULE
07/31/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-219

INFORMATION REQUEST LETTER

Endo Pharmaceutical Solutions, Inc.
Attention: Mark Roessel
Vice President, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Roessel:

Please refer to your March 2, 2009, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aveed (testosterone undecanoate) intramuscular injection.

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

Clinical Pharmacology

- Analysis of data from study IP157-001 Part C indicated that baseline body weight and body mass index (BMI) were inversely correlated with serum total T exposure. Additionally, the primary safety and efficacy analysis of study IP157-001 Part C excluded patients weighing less than 65 kg. You indicated that the rationale for this exclusion was that the intended population for treatment with testosterone undecanoate is men with a body weight of at least 65 kg. One excluded patient (patient 031-7021, body weight 59 kg) had serum T concentration data available from the primary PK third injection interval. He exhibited high C_{max} and C_{avg} serum total T concentrations of 2888 ng/dL and 1164 ng/dL, respectively. We are concerned about the safety of administering your testosterone undecanoate drug product to patients weighing less than 65 kg. This concern will need to be addressed in the product label.

Nonclinical

- We have identified areas of labeling that should be addressed. The following sections need to be added: use in women (5.11), affects on spermatogenesis (5.12), drug interactions with anticoagulants (7.5), use in pregnant or nursing women (8.1, 8.3), use in pediatrics (8.4), and use in patients with impaired renal or hepatic function (8.6).

- Comments regarding hepatocellular carcinoma and prostatic hypertrophy and prostatic carcinoma in humans (b) (4) should be moved to the warnings and precautions section 5.5 (cancer, prostatic hyperplasia and prostatic carcinoma).

Chemistry, Manufacturing, and Controls

- Lot number and expiration date should be added to the container and carton labels.

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

Sincerely,

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

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/s/

Scott Monroe

5/19/2009 09:41:08 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-219

PROPRIETARY NAME REQUEST
- UNACCEPTABLE

Endo Pharmaceuticals, Inc.
Attention: Mark Roessel
Vice President, Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Roessel:

Please refer to your New Drug Application (NDA), dated and received August 24, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate 750 mg/3 mL.

We also refer to your March 2, 2009, correspondence, received March 3, 2009, requesting review of your proposed proprietary name (b) (4) We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable (b) (4)

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated March 2, 2009. In order to initiate the review of the alternate proprietary name, Aveed, submit a

new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Darrell Jenkins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0558. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

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

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/s/

Scott Monroe

5/5/2009 05:15:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-219

Endo Pharmaceuticals
Attention: Mark Roessel
Vice President Regulatory Affairs
100 Endo Boulevard
Chadds Ford, PA 19317

Dear Mr. Roessel:

We acknowledge receipt on March 30, 2009, of your March 27, 2009, correspondence notifying the Food and Drug Administration that the corporate name and address has been changed from

Indevus Pharmaceuticals, Inc.
33 Hayden Avenue
Lexington, MA 02421-7971

to

Endo Pharmaceuticals, Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

for the following new drug application:

NDA 22-219 for Nebido (testosterone undecanoate) intramuscular injection.

We have revised our records to reflect this change.

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

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

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

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

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/s/

Jennifer L. Mercier
4/2/2009 11:40:49 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-219

Indevus Pharmaceuticals, Inc.
Attention: Mark C. Roessel
Vice President Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421

Dear Mr. Roessel:

We acknowledge receipt on March 2, 2009, of your March 2, 2009, resubmission to your new drug application for Nebido® (testosterone undecanoate) intramuscular injection.

We consider this a complete, class 2 response to our June 27, 2008, action letter. Therefore, the user fee goal date is September 2, 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 (b) (4)

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

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/s/

Jennifer L. Mercier
3/11/2009 03:43:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-219

PROPRIETARY NAME REQUEST WITHDRAWN

Indevus Pharmaceuticals, Inc.
Attention: Mark C. Roessel
Vice President Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421-7971

Dear Mr. Roessel:

Please refer to your New Drug Application (NDA) dated August 24, 2007, received August 28, 2007, submitted under section505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate.

We acknowledge receipt of your February 11, 2009, correspondence, received on February 12, 2009, notifying us that you are withdrawing your request for review of the proposed proprietary name (b) (4) This proposed proprietary name request is considered withdrawn as of February 12, 2009.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, please contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Jeannie Roule at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

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

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/s/

Scott Monroe

3/9/2009 05:33:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-219

Indevus Pharmaceutical, Inc.
Attention: Mark C. Roessel
Senior Director, Regulatory affairs
33 Hayden Avenue
Lexington, MA 02421

Dear Mr. Roessel:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nebido® (testosterone undecanoate) intramuscular injection.

We also refer to the meeting between representatives of your firm and the FDA on September 24, 2008. The purpose of the meeting was to discuss further the manner by which the three clinical deficiencies outlined in the June 27, 2008, approvable letter could be adequately addressed and to reach agreement with the Division on necessary data to be provided for responding to the three requests for information needed to resolve the clinical deficiencies.

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

If you have any questions, please 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 Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 24, 2008

TIME: 9-10:30 AM

LOCATION: White Oak Conference Room #1313

APPLICATION: NDA 22-219

DRUG NAME: Nebido (testosterone undecanoate)

TYPE OF MEETING: End of Review Conference (Type A)

MEETING CHAIR: Mark Hirsch, M.D.

MEETING RECORDER: Jeannie Roule

FDA ATTENDEES:

Scott Monroe, M.D.	Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D.	Medical Team Leader, DRUP
Harry Handelsman, M.D.	Medical Officer, DRUP
Jennifer Mercier	Chief Project Management Staff (CPMS), DRUP
Freshnie DeGuia	Regulatory Health Project Manager, DRUP
Jeannie Roule	Regulatory Health Project Manager, DRUP
Eric Andreasen, Ph.D.	Pharmacology Reviewer, DRUP
Audrey Gassman, M.D.	Acting Associate Director for Safety, DRUP
Anthony Durmowicz, M.D.	Medical Team Leader, Division of Pulmonary and Allergy Products (DPAP)
Charles Lee, M.D.	Medical Reviewer, DPAP
Lynne Wu, M.D.	Medical Reviewer, DPAP
Mahboob Sobhan, Ph.D.	Statistical Team Leader, Division of Biometrics II, Office of Biometrics, Office of Translational Sciences (OTS)
Martin Kaufmann, D.P.M., M.B.A.	Safety Regulatory Health Project Manager, DRUP
Mary Willy, Ph.D.	Team Leader, Division of Risk Management (DRISK) Office of Surveillance and Epidemiology (OSE),

EXTERNAL CONSTITUENT ATTENDEES:

Indevus Attendees:

Bobby W. Sandage, Jr., Ph.D.	EVP of Research and Development
James E Shipley, M.A., M.D.	Sr. VP Clinical Development, Medical and Regulatory Affairs
LuAnn Sabounjian, BSN	VP Clinical Development
Nova Silver, RN	Associate Director Clinical Development

Mark Harnett, M.S.	VP Biostatistics, Data Management and Medical Writing
Albert Profy, Ph.D.	VP Preclinical and Pharmaceutical Sciences
Mark Roessel	Senior Director, Regulatory Affairs
Steven Lyons	Sr. VP, Program Management

From Bayer Schering Pharma, AG:

Heidrun Hildebrand	Global Project Manager, Bayer Schering Pharma AG
Sven Oechsner	Global Regulatory Strategist, Bayer Schering Pharma AG

Consultants:

(b) (4)

BACKGROUND:

Nebido (testosterone undecanoate) is indicated for testosterone replacement in hypogonadal men. It was submitted under NDA 22-219 on August 27, 2007, and was issued an Approvable Letter on June 27, 2008. The letter described reports of serious post-injection respiratory and allergic adverse reactions in men who had received testosterone undecanoate intramuscular injections. These reports raised significant safety concerns regarding the risk/benefit profile for the use of testosterone undecanoate intramuscular injection for the proposed indication. The drug-related respiratory events, generally described as a sudden need to cough in the immediate post-injection period, had been reported in two patients in the testostersone undecanoate intramuscular injection clinical trials and in approximately 60 patients in the post marketing period in Europe. In some cases, laryngeal tightness, respiratory distress, circulatory collapse, cyanosis and loss of consciousness were also reported as part of the event. Pulmonary oil microembolism (POME), based upon the castor oil in the depot injection, appears to be causative for most of these cases. In at least four other cases, however, signs and symptoms of a clinically serious systemic allergic reaction have been reported, including two cases believed to meet criteria of anaphylaxis.

The likely incidence of these serious POME and allergic reactions in men who would be treated with testosterone undecanoate intramuscular injection, was not known. Therefore, the Division requested that Sponsor provide a precise estimate of the likely incidence of these serious adverse events so that a meaningful risk/benefit assessment for the proposed indication could be made.

The original application also did not include information regarding the underlying etiology of the anaphylaxis reactions. Therefore, the Division also requested information from investigations intended to discern a mechanism.

Finally, the application did not include an adequate plan to minimize or manage the risk of developing these potentially life-threatening events (both POME and anaphylaxis-like events).

MEETING OBJECTIVES:

- To discuss the manner by which the three clinical deficiencies outlined in the June 27, 2008, Approvable letter may be resolved.

- Reach agreement with the Division on necessary data to be provided for responding to the three requests for information needed to resolve the clinical deficiencies.

The following preliminary draft responses were provided to the sponsor on September 22, 2008, in response to the questions posed in the sponsor's meeting package update provided to the Division on September 4, 2008. The sponsor'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*.

DISCUSSION POINTS:

1. **Does the Agency agree that this database is of sufficient size to determine with reasonable and acceptable confidence the incidence of POME, and further, that this database offers adequate precision to the estimate of the incidence of post-injection POME?**

   Response: If the quality of the study reports is acceptable, then the proposed database would be of sufficient size. We wish to raise concerns about "study synopses" planned for ongoing studies, especially since the ongoing studies contain approximately 1100 of the 2620 total patients treated through October 1, 2008. For the ongoing studies, we request detailed interim study reports, rather than study synopses. Each study report should contain sufficient data to determine quality of study design as well as adequacy of the adverse events collection and reporting methods. This will be a review issue.

   Additional Discussion: In response to the Division's concern about study synopses, the Sponsor stated that individual reports will be provided for each study. In addition to the individual study reports, the Sponsor will also provide an integrated summary. The Sponsor noted that these reports will focus on the safety results, as well as the quality of the safety data. The Division agreed with that focus.

2. **Does the Agency concur that the data from this investigation is sufficient to characterize the nature and etiology of these anaphylaxis-like events?**

   Response: No. (b) (4)

(b) (4)

Additional Discussion: (b) (4) *In conjunction with the Division of Pulmonary and Allergy Products (DPAP), the Division reiterated its position that the reports in question reflect anaphylaxis, in temporal association to injection of intramuscular testosterone undecanoate. Thus, the Division continues to be concerned that the product played a role in causing those events.*

Based upon the Division's response to Question #2, (b) (4) *the Sponsor asked whether their proposed skin testing/re-challenge study was still required.*

In response, the Division asked whether the Sponsor accepted that anaphylaxis was a potential risk of Nebido. The Sponsor stated that that they do, in fact, accept that anaphylaxis is a potential risk of Nebido and that they are willing to address this potential risk in labeling and risk management. With this in mind, the Division agreed that the proposed skin testing/re-challenge study was not a requirement, but nonetheless, we encourage its conduct since additional helpful information may be gleaned if there are positive skin tests or positive re-challenges.

Based upon the difficulties associated with conducting this study, and the Division's position that the study was not a requirement, the Sponsor asked specifically whether the Complete Response would be acceptable without results from this study. The Division responded that

[1] Sampson HA, et. al. J Allergy Clin Immunol. 115(3):584-591, 2005.
[2] Sampson HA, et. al. J Allergy Clin Immunol. 117(2):391-397, 2006.

this question required further internal discussion and would be addressed in the final meeting minutes.

The Sponsor suggested that if the study was still needed by the Division, but not as requirement for the Complete Response, it could be conducted post-marketing, perhaps as part of a Phase 4 commitment. The Division stated that it could not agree at this time that the study can become part of a Phase 4 commitment. Additional internal discussion was required and this would be addressed in the final meeting minutes.

***Post-meeting Addendum**: While we continue to encourage the Sponsor to conduct the proposed skin testing/re-challenge study, we do not require that those results be provided in the Complete Response. It would not be unreasonable to propose the study as a Phase 4 commitment.*

3. Does the Agency have comments or suggestions on the proposed Risk Evaluation and Mitigation Strategy?

Response: We believe that plans are also warranted to manage the risk of anaphylaxis, including efforts to increase awareness of such reactions as well as their proper treatment. Part of this plan should include patient observation for at least 30 minutes after each injection of Nebido. In addition, you might consider a MedGuide as part of your risk management program.

The Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE) has the following additional comments:

We have reviewed your briefing package which contains an outline of your proposed risk mitigation and assessment activities targeting the POME reactions. This includes labeling, education and outreach, and a Phase 4 study. While these activities represent a good starting point for minimizing and assessing the risk of POME reactions, it should be noted that anaphylaxis and allergic reactions were also of concern to the Agency. These risks are not addressed in your strategy to minimize and assess the product's risks.

The final risk management efforts will largely depend on the risk assessment from your proposed analyses.

The meeting package prepared by the sponsor states that there have been 2 POME events in clinical studies of testosterone undecanoate (Nebido) for a frequency of 1 in 14,000 injections. The observational study proposed by the sponsor (10,000 patients / 42,000 injections) would appear to be powered to detect a POME frequency as low as 7 per 100,000, however, detailed information is needed to assess the adequacy of the sample size.

A final protocol with more detail about the type of data that will be collected and how these data will be collected, particularly in relation to "peri-injection" data would be needed to determine if this study addresses the Agency's concerns.

Additional Discussion: The Sponsor stated that while the 30 minutes post-inject observation period is not included in their European label, they will agree to add it to the proposed U.S. label.

The Sponsor asked for the Division's rationale for a MedGuide. The Division responded that a MedGuide provides additional information to patients as compared to a Patient Package Insert (PPI). The risks are explained in a MedGuide in a very specific format in patient friendly language. This is particularly important if the product being approved raises significant safety concerns. In addition, it may be useful to periodically assess understanding of the MedGuide to assess how well the risks of the product are being understood by patients. It is possible that a MedGuide would be required by the Division for Nebido, after review of the additional safety data.

The Sponsor stated that the final protocol for the proposed observational study will include details about the type of data to be collected, procedures for collecting that data, and sample size justification.

The Sponsor asked for an overall assessment and specific comments about their risk management proposal. The Division responded that if indeed the Sponsor accepted the potential risk of anaphylaxis and addressed that risk in their plan, then the overall proposal was very reasonable. No additional specific comments could be made at this time, although there may be additional comments and requests at a later date.

Additional Clinical Comments

1. Despite the proposed (b) (4) drug product volume (b) (4) 3mL, the serious post-marketing adverse events observed with NEBIDO remain a concern.

2. We offer the following preliminary comments about the targeted package insert. These do not comprise all potential labeling issues:

   a. The Warnings re: hypersensitivity and POME should not include (b) (4)

   Additional Discussion: The Sponsor asked (b) (4) *The Division responded* (b) (4) .

   b. The Warning re: hypersensitivity reactions omits (b) (4) and thus, will need to be revised.

c. The Warning re: POME reactions will need to be revised. POME reactions have lasted up to several hours, not [redacted] (b) (4) In addition, some patients required emergency treatment and some, hospitalization, in order to mitigate more serious complications.

d. The Adverse Reaction section contains information [redacted] (b) (4) This section will need to be revised. [redacted] (b) (4)

e. Additional sections of the package insert (e.g., Warnings, Geriatric Use, Clinical Studies, etc) will require further discussion during the review.

DECISIONS (AGREEMENTS) REACHED: None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

The Division requested additional time to discuss whether the proposed skin testing/re-challenge study was a required element of the Complete Response and if not, whether a protocol for that study should be submitted as part of a Phase 4 commitment. In follow-up, we offer the following response:

While we continue to encourage Sponsor to conduct the proposed skin testing/re-challenge study, we do not require that those results be provided in the Complete Response. It would not be unreasonable to propose the study as a Phase 4 commitment.

ACTION ITEMS:

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

ATTACHMENTS/HANDOUTS: None

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/s/

Mark S. Hirsch

10/23/2008 02:06:28 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-219

Indevus Pharmaceuticals, Inc.
Attention: John Berryman
Vice President, Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421-7971

Dear Mr. Berryman:

Please refer to your August 28, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate intramuscular injection.

We acknowledge receipt of your submissions dated October 8 and December 5, 20, and 28, 2007, February 8, 11, 15, and 26, March 12 and 31, April 2 and 30, May 13, 15, 19, 23, 27, and 28, and June 10 and 13(2), 2008.

We further refer to your amendment dated February 22, 2008, containing your request (b) (4) for us to use the 750 mg loading dose regimen, used in Part C of Study IP157-001, as the primary basis for our review of your application.

This application proposes the use of testosterone undecanoate intramuscular injection for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

1. Primary hypogonadism (congenital or acquired) – testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range.
2. Hypogonadotropic hypogonadism (congenital or acquired) – idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. These patients have low serum testosterone levels, but have gonadotropins in the normal or low range.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, it will be necessary for you to address the following deficiencies.

Clinical Deficiencies

Reports of serious post-injection respiratory and allergic adverse reactions in men who have received testosterone undecanoate intramuscular injection raise significant safety concerns regarding the risk/benefit profile for the use of testosterone undecanoate intramuscular injection for the proposed indication. The drug-related respiratory events, generally described as a sudden need to cough in the immediate post-injection period, have been reported in two patients in the testosterone undecanoate

intramuscular injection clinical trials and in approximately 60 patients in the postmarketing period in Europe. In some of the cases, laryngeal tightness, respiratory distress, circulatory collapse, cyanosis, and loss of consciousness were also reported as part of the event. Pulmonary oil microembolism (POME), based upon the castor oil in the depot injection, appears to be causative for most of these cases. In at least four other cases, however, signs and symptoms of a clinically serious systemic allergic reaction have been reported, including two cases meeting criteria for anaphylaxis.

1. The likely incidence of these serious POME and allergic reactions in men who would be treated with testosterone undecanoate intramuscular injection, should the drug product be approved for marketing, is not known. A precise estimate of the likely incidence of these serious adverse events is needed to make a meaningful risk/benefit assessment for the use of testosterone undecanoate intramuscular injection for the proposed indication.
2. The application does not include information regarding the underlying etiology of the anaphylaxis-like reactions. It is not known if these reactions are secondary to the active drug substance or excipients in the drug product, including the castor oil vehicle.
3. The application does not include an adequate plan to minimize or manage the risk of developing these potentially life-threatening events (both POME and anaphylaxis-like events).

Chemistry, Manufacturing, and Controls (CMC) Deficiency

Deficiencies were identified in the Drug Master File (DMF) # (b) (4) for the drug product. A letter outlining the deficiencies has been provided to the DMF holder.

Information Needed to Resolve the Clinical Deficiencies

1. *Detailed safety information from clinical studies to determine the incidence of serious post-injection POME and allergic reactions.*

   At a minimum, the safety database should include (1) all subjects treated in Stage 2 of all parts of Study IP157-001, (2) all subjects in (a) Study NE0601 (IPASS), (b) the Non-Interventional Study (NIS), and (c) Study 42306, and (3) all additional foreign data of which you are aware. We consider the information that you provided in your submissions of June 10 and 13, 2008, to be preliminary. Depending on the findings and the number of subjects and the number of injections of testosterone undecanoate from the studies listed above, the safety database may need to include data from additional clinical studies. You should propose the size of the safety database (i.e., total number of subjects exposed to testosterone undecanoate intramuscular injection and total number of injections) and the rationale for the size of the proposed safety database.

2. *Information from clinical investigations intended to characterize the nature and etiology of the anaphylaxis-like events with testosterone undecanoate intramuscular injection.*

   This information could be obtained by (1) skin testing procedures to the product and its excipients and (2) *in vitro* testing for the presence of specific IgG and IgE antibodies to both active and excipient components of the drug product.

3. *A plan to minimize the risks associated with the clinical use of testosterone undecanoate intramuscular injection, namely, to reduce the incidence and/or severity of the serious POME and anaphylaxis-like adverse events.*

Information Needed to Resolve the CMC Deficiency

All deficiencies identified in DMF # (b) (4) must be satisfactorily resolved and submitted to the DMF to support your application.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required. When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or a telephone conference with us to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Scott Monroe

6/27/2008 04:06:19 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 30, 2008
TIME: 9:15 a.m. – 10:00 a.m.
LOCATION: Teleconference (877-491-7415)
APPLICATION: NDA 22-219
DRUG NAME: Nebido
TYPE OF MEETING: Guidance

MEETING CHAIR: Mark Hirsch, M.D.

MEETING RECORDER: Martin Kaufman, D.P.M., M.B.A.

FDA ATTENDEES:
Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Products (DRUP)
Suresh Kaul, M.D., Acting Medical Team Leader, DRUP
Harry Handelsman, D.O., Medical Officer, DRUP
Eric Andreasen, Ph.D., Pharmacologist, DRUP
Charles E. Lee, M.D., Medical Officer, Division of Pulmonary and Allergy Products (DPAP)
Martin Kaufman, D.P.M., M.B.A., Science Policy Analyst, DRUP

EXTERNAL CONSTITUENT ATTENDEES:
Bobby Sandage, Executive Vice President, Research & Development
Jim Shipley, Senior Vice President, Clinical Development and Medical Affairs
Ute Schwiderski, Vice President, Biostatistics and Data Management
John Berryman, Vice President, Regulatory Affairs
(b) (4)

BACKGROUND:
The Division requested this teleconference in response to the Sponsor's request for feedback regarding the review of the NDA.

MEETING OBJECTIVES:
- To provide the Sponsor with an update regarding the current status of the NDA review
- To discuss any outstanding review issues

DISCUSSION POINTS:
- The Division acknowledged the Sponsor's request for feedback on the status of the Nebido NDA review. It stated that at this time, the issue of immediate post-injection "cough reaction" remains unresolved for the review team. This issue, which was identified early in the review process, was initially conveyed to the Sponsor in the Division's November 9, 2007, Filing Communication letter. The issue was discussed with the Sponsor during a teleconference held on January 15, 2008, and was reiterated in the Discipline Review letter sent on May 5, 2008. The Division has reviewed the additional information submitted by the Sponsor, including its response to the Discipline Review letter. However, this information is not sufficient to resolve the review team's concerns. Therefore, we are left with a product with an unresolved safety concern.

- The Division explained that the issue of immediate post-injection "cough reaction" is an unresolved medical risk which has not been fully assessed, quantified, or adequately managed. The cases of most concern to the review team were medically significant events. Some were described as severe and some required interventions to prevent patient harm. While most of the reactions reported are consistent with Pulmonary Oil Microembolism (POME), several appear to be cases of anaphylaxis.
- The Sponsor stated that it had assessed information from postmarketing surveillance and clinical trials and believes that the reported reactions are cases of POME. If there are hypersensitivity reactions, they are rare. It believes that the reactions are self limiting and can be managed.
- The Sponsor's proposals to address this safety concern through labeling or with a postmarking study were discussed.
- The Division does not believe that the submitted data are adequate to inform labeling that would mitigate the safety concern. In addition, it does not believe that a phase 4 study could be done in such a way that the benefit of the product would outweigh the risk to patients.
- The Sponsor proposed submission of two observational studies which were done by their marketing partner. However, these studies could not be submitted before the June 27, 2008, goal date for the NDA.
- The Division stated that it plans on taking an action on the NDA by the goal date. The action letter will specify what information is needed to resolve this issue. After reviewing the action letter, the Sponsor can determine the appropriate path forward, and can decide if the observational studies provide the information requested by the Division.
- The Division provided the Sponsor with the opportunity to ask any additional questions concerning the NDA review.

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/s/

Martin Kaufman
6/25/2008 11:20:13 AM

Mark S. Hirsch
6/25/2008 11:45:41 AM

MEMORANDUM

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

DATE: June 23, 2008

TO: **NDA 22-219, NEBIDO (testosterone undecanoate) Intramuscular injection**

FROM: Freshnie DeGuia, Regulatory Health Project Manager

SUBJECT: **CMC/DMETS comments provided to Indevus on May 13, 2008**

The attached email documentation provided to the sponsor contained CMC and DMETS comments regarding the most recent submission of proposed container and carton labeling.

Additional information is also attached regarding linear bar code requirements on the vial.

Deguia, Eufrecina P

From: Deguia, Eufrecina P
Sent: Tuesday, May 13, 2008 3:15 PM
To: Berryman, John
Subject: RE: CMC comments
Sensitivity: Confidential

Here are the comments from CMC and DMETS regarding your most recent submission of the carton and container labeling. Please bear in mind that the review of the NDA is still very much ongoing.

Container label:

1. Use a darker font to display the proprietary name, established name, dosage form, the strength, the route of administration, as well as other important information.

2. Delete [redacted] (b) (4)

3. Include the product concentration, 250 mg/mL, in parentheses on a separate line immediately following the total drug content statement.

4. Delete the word [redacted] (b) (4) from the dosage form statement below the established name.

5. Relocate and increase the prominence of the route of administration statement. [redacted] (b) (4)

6. Revise the [redacted] (b) (4) statement to read: 'Single Use Vial – Discard Unused Portion'. Relocate this statement to appear below the route of administration statement and above the 'Store at room temperature' statement.

Carton Labeling

1. See comments 1-6 above.

2. Include a quantitative statement following each inactive ingredient in accordance with 21CFR 201.100 (b)(5)(iii).

3. Decrease the prominence of the name of the Applicant, [redacted] (b) (4) located at the bottom portion of the principal display panel.

John, please refer to your most recent May 9, 2008 submission that you sent me via email containing your response to the Discipline Review letter. Please provide blood pressure readings and the "details later confirmed by the physician" for case ZA-2007-035469. In addition, we also need reference to "tightness in the throat as an expected symptom of POME" for case GB-2006-006197.

Thank you so much for your help.

Warm Regards,

Freshnie

From: Berryman, John [mailto:JBerryman@indevus.com]
Sent: Tuesday, May 13, 2008 8:47 AM
To: Deguia, Eufrecina P
Subject: RE: CMC comments
Sensitivity: Confidential

Thanks Freshnie – have a nice day!
John

From: Deguia, Eufrecina P [mailto:eufrecina.deguia@fda.hhs.gov]
Sent: Tuesday, May 13, 2008 7:52 AM
To: Berryman, John
Subject: RE: CMC comments
Sensitivity: Confidential

I should have them to you shortly, hopefully later today or tomorrow. DMETS and CMC teams finished their reviews but still in draft. I'll keep you posted.

Regards.
Freshnie

From: Berryman, John [mailto:JBerryman@indevus.com]
Sent: Monday, May 12, 2008 9:56 AM
To: Deguia, Eufrecina P
Subject: RE: CMC comments
Sensitivity: Confidential

Freshnie,
Good Monday morning to you!
Any review/response yet on the (b) (4) carton and vial label drafts?
John

From: Berryman, John
Sent: Wednesday, April 30, 2008 5:20 PM
To: 'Deguia, Eufrecina P'
Subject: RE: CMC comments
Sensitivity: Confidential

Freshnie,
Welcome back!
I hope you have had a restful (though short) vacation.
Attached, please find a revised color mock-up of the (b) (4) vial label and carton following the comments you so kindly provided.
If the reviewer(s) can check these over by the end of the week (May 9) or early next week, that would be great!
Thanks!
John

From: Berryman, John
Sent: Monday, April 28, 2008 10:47 AM
To: 'Deguia, Eufrecina P'
Subject: RE: CMC comments
Sensitivity: Confidential

Thanks Freshnie!
I will also (hopefully) have revised draft vial label and carton mock ups for you later today.
Yours,
John

From: Deguia, Eufrecina P [mailto:eufrecina.deguia@fda.hhs.gov]
Sent: Monday, April 28, 2008 10:45 AM
To: Berryman, John
Subject: RE: CMC comments
Sensitivity: Confidential

Hi John.

I have discussed the bar code issue with the CMC team. According to the regs, the bar code requirement on the label can be exempted if compliance is not technically feasible. Your proposal, therefore, is acceptable. Please send your justification below via correspondence to your NDA so we have it on record that you requested (sort of) an exemption from the bar code requirement.

Please let me know if you have any questions.

Kind Regards,

Freshnie

From: Berryman, John [mailto:JBerryman@indevus.com]
Sent: Friday, April 25, 2008 4:46 PM
To: Deguia, Eufrecina P

Subject: RE: CMC comments
Sensitivity: Confidential

Dear Freshnie,
One more (last, I promise) item for today.
In the comments you very kindly sent on Monday, the last item under Container Label asks that we provide a linear barcode on the container [vial] label.
We have made measurements on this item and found that the linear barcode, if printed along the horizontal axis, would be too curved for consistent barcode resolution. Alternatively, the barcode if printed along the vertical axis, is too long to fit on this small vial label (and if compressed, again loses scanning resolution).
As such, we propose that only the human-readable NDC number be presented on the vial label, while both the linear barcode and human-readable NDC be printed on the carton (in which the vial is always to be packaged until use).
Yours,
John

From: Berryman, John
Sent: Thursday, April 24, 2008 4:59 PM
To: 'Deguia, Eufrecina P'
Subject: CMC comments
Sensitivity: Confidential

Dear Freshnie,
Regarding the vial size (b) (4), it is in fact a (b) (4) vial.
The original development of testosterone undecanoate (b) (4) was (b) (4)
I believe there may have been some preliminary vial development work done in a (b) (4) vial, but the (b) (4) vial was ultimately selected.
The reported stability data was generated using the 750 mg / 3 mL fill in (b) (4) vials.

On that note, the 24-month stability data is soon to be filed (sometime in May) to the DMF.
As explained in the NDA and per ICH guidelines Q1A(R2) and Q1E, the expiry of lots produced after this date will be based upon this new data, as will future lots from the data generated going forward.
Changes to the expiration period will be reported in the NDA annual report.
Yours,
John

From: Deguia, Eufrecina P [mailto:eufrecina.deguia@fda.hhs.gov]
Sent: Tuesday, April 22, 2008 11:37 AM
To: Berryman, John
Subject: RE: Thank you!

Sensitivity: Confidential

Hi John,

I want you to know that I set up a meeting with the CMC and DMETS teams yesterday to get a better feel of the status of their reviews and to make sure that both teams are aligned in terms of the comments that I now send to you. DMETS has no objection to your proposed tradename, (b) (4) Although they have yet to finalize their reviews, I am sending the attached as preliminary comments to assist you as you work with your labels. We will ask you to send us your mock-ups when available. In addition, see also request from CMC regarding your drug product.

Please bear in mind that clinical review is still very much ongoing and evaluation of the result of the Pulmonary consult still has to be done. I will keep you posted on that too as things progress.

Please see attached. Let me know if you need further discussion.

Sincerely,

Freshnie

Freshnie DeGuia
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Office: (301) 796-2130
Direct Line: (301) 796-0881
Fax: (301) 796-9897
Email: eufrecina.deguia@fda.hhs.gov

From: Berryman, John [mailto:JBerryman@indevus.com]
Sent: Wednesday, April 16, 2008 1:19 PM
To: Deguia, Eufrecina P
Subject: Thank you!
Sensitivity: Confidential

Thank you for the excellent summary - this very helpful!
Very appreciatively yours,
John

From: Deguia, Eufrecina P [mailto:eufrecina.deguia@fda.hhs.gov]
Sent: Wednesday, April 16, 2008 12:31 PM

To: Berryman, John
Subject: RE: Welcome!
Sensitivity: Confidential

Thank you, John, for the warm welcome! I will try my best.

Just a brief update to where some of the things are at this point:

CMC is currently reviewing your latest amendment. I was informed that they will have comments and questions that are forthcoming to you hopefully by Monday. They may include comments and questions to the DMF holder too.

I also have contacted DMETS to get the status of their review and I have not heard from them yet. John sent them the carton and vial labeling amendment too. I will let you know as soon as I hear from them. I cc'd the Team Leader so she is aware that I'm seeking some sort of a timeline and to remind them that the review is winding down.

With regards to the POME consult, the primary review is done and is now with the Director in Pulmonary for his secondary review and sign off. Once the consult is finalized and sent to DRUP, the clinical team will then review and discuss the result of the consult. The Division still has the final say on all consults.

We have an 8-month status meeting coming up on April 28 for this NDA and hopefully I will be able to give you a better update after that meeting. Meanwhile, I will try my best to follow on all pending consults and reviews.

I will definitely keep you posted.

Sincerely.

Freshnie

Freshnie 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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Office: (301) 796-2130
Direct Line: (301) 796-0881
Fax: (301) 796-9897
Email: eufrecina.deguia@fda.hhs.gov

From: Berryman, John [mailto:JBerryman@indevus.com]
Sent: Tuesday, April 15, 2008 5:50 PM
To: Deguia, Eufrecina P
Subject: Welcome!
Sensitivity: Confidential

Dear Freshnie,

Welcome to your first official (I think) full day as the Regulatory Health Project Manager for NDA 22-219!! How exciting for both of us!

At your convenience, could you kindly provide me with a brief update on the status of things?

For example, we need to settle ~~on the carton text and vial label,~~ which are to be printed by our German partner (Bayer Schering Pharma), preferably within the next 2 weeks.

Likewise, I have provided you a draft PI (email last week) that we think is a fair starting point for discussion, but the status of the Pulmonary Oil Microembolism ("POME") review was unfinished last I heard (consult to Pulmonary & Allergy Division) – any change in status?

In my experience with NDA reviews at the Agency, no news is generally good news, so I don't expect that you will have too much to report, but I wanted to get the two of us onto the same page – that is, whenever it's convenient for you.

Thanks and again my fondest welcome!

John

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/s/

Eufrecina deGuia

6/23/2008 04:07:27 PM

CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-219

DISCIPLINE REVIEW LETTER

Indevus
Attention: John Berryman
Vice President, Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421-7971

Dear Mr. Berryman:

Please refer to your August 28, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NEBIDO® (testosterone undecanoate).

We also refer to your submissions dated February 22, and March 26, 2008, containing an Executive Summary of "Immediate Post-Injection Reactions Suspect of Being Pulmonary Oil Microembolism (POME)" and Expert Opinion paper regarding the two adverse event reports in controlled trials and 66 adverse events reported in the post-marketing period.

We have completed the review of your submissions and, in consultation with the Division of Pulmonary and Allergy Products (DPAP), we have the following comments:

> We agree that the majority of the 66 suspect cases of respiratory adverse events are likely secondary to POME. However, we continue to have concerns that almost half (28/66) of the cases were reported as serious, some were life-threatening and required hospitalization, and others, according to your consultants, were "suggestive of a hypersensitivity response."
>
> In fact, DPAP concluded that two of the 66 individual adverse events reported in the post-marketing period met diagnostic criteria for anaphylaxis, another case was consistent with acute urticaria and angioedema, and in an additional case anaphylaxis could not be excluded.
>
> Based on our review of the available data, we continue to have serious concerns that severe and/or life-threatening adverse events have been reported following administration of NEBIDO and these risks require further assessment in order to eliminate or to substantially mitigate them.

We are providing this comment to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final

decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Jennifer L. Mercier

5/5/2008 02:26:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-219

INFORMATION REQUEST LETTER

Indevus Pharmaceuticals, Inc.
Attention: John B. Berryman
Vice President, Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421

Dear Mr. Berryman:

Please refer to your August 24, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nebido® (testosterone undecanoate) intramuscular injection.

We also refer to your submissions dated February 11, 2008, containing draft carton and container labels.

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

1. Provide bar codes on both container and carton labels.
2. Provide quantitative excipient information on the carton label.

Please note that Information Request Letters have been sent to the Drug Master File (DMF) Holder for DMFs (b) (4) and (b) (4)

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center of Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
2/29/2008 11:20:41 AM
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-219

Indevus Pharmaceuticals, Inc.
Attention: John B. Berryman
Vice President, Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421

Dear Mr. Berryman:

Please refer to your new drug application (NDA) dated August 24, 2007, received August 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for NEBIDO® (testosterone undecanoate for injection).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on October 26, 2007, in accordance with 21 CFR 314.101(a).

During our filing review of your application, we identified the following potential review issues:

1. It is not clear if steady state was reached during the 4th dosing interval in Part A of Study IP157-001. Mean trough concentrations (C_{trough}) increased with each dose, including the 4th dose. Assessment of the maximal testosterone concentration with continued dosing will be a review issue.

2. The data for NEBIDO® 750 mg also will be reviewed during this review cycle. Testosterone values above the normal range for both the 750 mg and 1000 mg doses will be a review issue.

3. Immediate post-injection "cough reactions," including symptoms of cough, urge to cough, dyspnea, and respiratory distress, are of concern.

4. Demonstration of comparability of the drug substance manufactured at the [redacted] (b) (4) sites will be necessary. Any questions that arise during the review will be conveyed to you and the Drug Master File (DMF) holders.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. To assess whether steady state was reached by the 4th dosing interval, submit a pharmacokinetic (PK) modeling and simulation report (based on the final PK dataset from Part A of Study IP157-001) that provides estimates for maximum serum testosterone concentration (C_{max}), AUC, and C_{trough} during each dosing interval. This simulation should be carried out through at least the 8th injection. Include a plot of the simulation for serum testosterone concentrations and a table of the predicted PK parameters. The report should be submitted as soon as possible, but no later than the 4-month safety update.

2. State what expiration dating you are requesting for this product.

3. Submit color mock-ups for the carton and immediate container labels, including any logos.

4. Clarify which drug product will be commercially available ((b) (4) 3 (b) (4) ml in vials).

5. Provide a table with the Certificates of Analysis for each of the batches used in both the nonclinical and clinical studies.

6. Submit a case narrative and complete set of case report forms (CRFs) for the single subject who reported post-injection "cough reaction" among the 422 subjects treated in the clinical development program.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for male pediatric patients under the age of 18 years. We will communicate our decision regarding this request under separate cover.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

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

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/s/

Scott Monroe

11/9/2007 10:39:01 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-219

NDA ACKNOWLEDGMENT

Indevus Pharmaceuticals, Inc.
Attention: John B. Berryman
Vice President, Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421

Dear Mr. Berryman:

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: NEBIDO® (testosterone undecanoate for injection)

Review Priority Classification: Standard (S)

Date of Application: August 24, 2007

Date of Receipt: August 28, 2007

Our Reference Number: NDA 22-219

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 October 26, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 27, 2008.

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

Please cite the NDA number listed above at the top of the first page of 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 me at (301) 796-0932.

Sincerely,

{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

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