

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203098Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



PATENT CERTIFICATION [21 CFR 315.50(i)2]

In accordance with the Federal Food, Drug and Cosmetics Act, as amended September 24, 1984, and December 8, 2003, Patent Certification is hereby provided for our 505(b)(2) New Drug Application for Testosterone Gel, (b)(4) (2.5 gm/packet; 5 gm/packet/ and 1.25 gm/activation).

The following patents are listed in the FDA Electronic Orange Book (current through April 2011) for NDA 021015 for Abbott Laboratories.

| US Patent No. | Patent Expiry |
|---------------|-----------------|
| 6,503,894 | August 30, 2020 |
| 6,503,894*PED | March 01, 2021 |

Paragraph IV Certification

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984 and December 8, 2003, Perrigo Israel Pharmaceuticals Ltd. certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 6,503,894 is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Perrigo Israel Pharmaceuticals Ltd.'s Testosterone Gel, (b)(4) (2.5 gm/packet; 5 gm/packet/ and 1.25 gm/activation) for which this application is submitted.

Andrew M. Solomon
Assistant General Counsel
Perrigo Company
On Behalf of

27 May 2011

Date

Perrigo Israel Pharmaceuticals Ltd.



Statement Concerning Notice to Patent Owner and NDA Holder

As required by 21 C.F.R. § 314.52(a) Perrigo Israel Pharmaceuticals Ltd. will give notice to the owner(s) of U.S. Patent No. 6,503,894 and to the NDA holder, that a 505(b)(2) application for Perrigo Israel Pharmaceuticals Ltd.'s Testosterone Gel, ^{(b)(4)} drug product, (2.5 gm/packet; 5 gm/packet/ and 1.25 gm/activation) containing any required bioavailability or bioequivalence data or information has been submitted to obtain the approval to engage in the commercial manufacture, use, and sale of such drug before the expiration of U.S. Patent No. 6,503,894, which expires on August 30, 2020 according to FDA's Orange Book (current through April 2011). This notice will contain all of the information required under 21 C.F.R § 314.52(c). Perrigo Israel Pharmaceuticals Ltd. shall provide proof of such notice to the Agency.

Andrew M. Solomon
Assistant General Counsel
Perrigo Company
On Behalf of
Perrigo Israel Pharmaceuticals Ltd.

27 May 2011

Date

EXCLUSIVITY SUMMARY

NDA # 203098

SUPPL #

HFD # 580

Trade Name N/A

Generic Name testosterone gel

Applicant Name Perrigo Israel Pharmaceuticals Ltd.

Approval Date, If Known January 31, 2013

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?

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

YES NO

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

No

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

*Please see attachment after the last page of this document

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

BE Study # 03-0415-001
Transfer Study # M1IU09001
Hand Washing Study # PRG-806
Skin irritation Study # DS310208

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 <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #2 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #3 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #4 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |

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 <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #2 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #3 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |

Investigation #4

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"):

BE Study # 03-0415-001

Transfer Study # M1IU09001

Hand Washing Study # PRG-806

Skin irritation Study # DS310208

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 # 107130

YES

!
!
! NO
! Explain:

Investigation #2

IND # 107130

YES

!
!
! NO
! Explain:

Investigation #3

IND # 107130

YES

!
!
! NO
! Explain:

Investigation #4
IND # 107130 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: Regulatory Health Project Manager
Date: January 31, 2103

Name of Office/Division Director signing form: Audrey Gassman, M.D.
Title: Deputy Director

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

A083976 TESTRED
A080767 METHYLTESTOSTERONE
A084310 METHYLTESTOSTERONE
A086450 ANDROID 10
A087147 ANDROID 25
N020489 ANDRODERM
N021015 ANDROGEL 1%
N022309 ANDROGEL 1.62%
N021454 TESTIM
A080911 TESTOPEL
N022504 AXIRON
N202763 TESTOSTERONE GEL
N021463 FORTESTA
N021543 STRIANT
A090387 TESTOSTERONE CYPIONATE
A090387 TESTOSTERONE CYPIONATE
A040530 TESTOSTERONE CYPIONATE
A085635 DEPO-TESTOSTERONE
A085635 DEPO-TESTOSTERONE
A040615 TESTOSTERONE CYPIONATE
A040615 TESTOSTERONE CYPIONATE
A040652 TESTOSTERONE CYPIONATE
A086030 TESTOSTERONE CYPIONATE
N009165 DELATESTRYL
A040575 TESTOSTERONE ENANTHATE
A040647 TESTOSTERONE ENANTHATE
A085598 TESTOSTERONE ENANTHATE

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
01/31/2013

AUDREY L GASSMAN
01/31/2013

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 203098 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DRUP PDUFA Goal Date: 05/05/12 Stamp Date: 07-05-11

Proprietary Name: _____

Established/Generic Name: testosterone gel ^{(b) (4)}

Dosage Form: gel

Applicant/Sponsor: Perrigo Israel Pharmacueticals

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

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

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

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

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

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

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

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

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

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

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

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

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

Q3: Does this indication have orphan designation?

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

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

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



DEBARMENT CERTIFICATION STATEMENT

Pursuant to Section 306 (k)(1) of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Perrigo Israel Pharmaceuticals Ltd. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

A handwritten signature in blue ink, appearing to read 'Dalit Fuchs', written over a horizontal line.

Dalit Fuchs
Director of Regulatory Affairs
Perrigo Israel Pharmaceuticals Ltd.

August 1, 2008
Date

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|--|---|---|
| NDA # 203098 BLA # | NDA Supplement # BLA Supplement # | If NDA, Efficacy Supplement Type: |
| Proprietary Name: N/A Established/Proper Name: testosterone Dosage Form: gel | | Applicant: Perrigo Israel Pharmaceuticals Agent for Applicant (if applicable): Valerie Gallagher |
| RPM: Jeannie Roule | | Division: Reproductive and Urologic Products |
| <p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> | <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 21015, Androgel 1%</p> <p>Provide a brief explanation of how this product is different from the listed drug. <div style="background-color: #cccccc; padding: 2px; text-align: center;">(b) (4)</div> <input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input checked="" type="checkbox"/> This application relies on (explain) This drug relied on a RLD and literature</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input checked="" type="checkbox"/> Updated Date of check: 1/14/13</p> <p>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.</p> | |
| ❖ Actions | | |
| <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>February 1, 2013</u> | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR | |
| <ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) | <input type="checkbox"/> None CR, May 3, 2012 | |

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

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).

| | |
|---|---|
| <p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p> | <input type="checkbox"/> Received |
| <p>❖ Application Characteristics ³</p> | |
| <p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p> | |
| <p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p> | <input type="checkbox"/> Yes, dates |
| <p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| <p>❖ Public communications (<i>approvals only</i>)</p> | |
| <ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| <ul style="list-style-type: none"> Press Office notified of action (by OEP) | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| <ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated | <input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |

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.

| ❖ Exclusivity | |
|--|--|
| <ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| <ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____ |
| ❖ Patent Information (NDAs only) | |
| <ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | <input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| <ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | <input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____ |
| <ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> | <input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

| | |
|---|---|
| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
|---|---|

CONTENTS OF ACTION PACKAGE

| | |
|---|--|
| ❖ Copy of this Action Package Checklist ⁴ | 2/6/13 |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |
| Action Letters | |
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | Action(s) and date(s) CR: May 3, 2012 Approval: January 31, 2013 |
| Labeling | |
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| <ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | January 25, 2013 |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | July 5, 2011 |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | |

⁴ Fill in blanks with dates of reviews, letters, etc.

| | |
|--|---|
| <ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) | <input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None |
| <ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | January 25, 2013 |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | July 5, 2011 |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | N/A |
| <ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| <ul style="list-style-type: none"> • Most-recent draft labeling | January 25, 2013 |
| <ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. | N/A |
| <ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) | <input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 1/31/13 and 3/02/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 12/07/12 <input checked="" type="checkbox"/> ODPD (DDMAC) 12/19/12 and 4/23/12 <input checked="" type="checkbox"/> SEALD 1/23/13 <input checked="" type="checkbox"/> CSS 1/02/13 and 4/09/12 <input type="checkbox"/> Other reviews |
| Administrative / Regulatory Documents | |
| <ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) | RPM Filing review: 11/01/11 |
| <ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte | <input type="checkbox"/> Not a (b)(2) |
| <ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) | <input type="checkbox"/> Not a (b)(2) January 31, 2013 |
| <ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) | <input checked="" type="checkbox"/> Included |
| <ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> • Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Not an AP action |
| <ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>PREAA does not apply to this application</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) | <input checked="" type="checkbox"/> Included |

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

| | |
|--|--|
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i> | <input checked="" type="checkbox"/> Verified, statement is acceptable |
| ❖ Outgoing communications <i>(letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons)</i> | 4/05/12, 3/23/12, 3/08/12, 2/24/12, 2/23/12, 2/22/12, 2/09/12, 1/10/12, 12/27/11, 12/21/11, 9/16/11, 8/04/11, 7/13/11, and 9/06/11 |
| ❖ Internal memoranda, telecons, etc. | N/A |
| ❖ Minutes of Meetings | |
| • Regulatory Briefing <i>(indicate date of mtg)</i> | <input checked="" type="checkbox"/> No mtg |
| • If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i> | <input checked="" type="checkbox"/> N/A or no mtg |
| • Pre-NDA/BLA meeting <i>(indicate date of mtg)</i> | <input checked="" type="checkbox"/> No mtg 05/19/10 |
| • EOP2 meeting <i>(indicate date of mtg)</i> | <input checked="" type="checkbox"/> No mtg |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i> | |
| ❖ Advisory Committee Meeting(s) | <input checked="" type="checkbox"/> No AC meeting |
| • Date(s) of Meeting(s) | |
| • 48-hour alert or minutes, if available <i>(do not include transcript)</i> | |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo <i>(indicate date for each review)</i> | <input checked="" type="checkbox"/> None |
| Division Director Summary Review <i>(indicate date for each review)</i> | <input type="checkbox"/> None 5/03/12 |
| Cross-Discipline Team Leader Review <i>(indicate date for each review)</i> | <input type="checkbox"/> None 1/31/13 and 5/02/12 |
| PMR/PMC Development Templates <i>(indicate total number)</i> | <input checked="" type="checkbox"/> None |
| Clinical Information⁶ | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) <i>(indicate date for each review)</i> | See CDTL above |
| • Clinical review(s) <i>(indicate date for each review)</i> | 1/30/13, 5/02/12 and 9/01/11 |
| • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i> | <input checked="" type="checkbox"/> None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i> | See Clinical Review, dated 5/02/12, page 10 |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> | <input checked="" type="checkbox"/> None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i> | <input type="checkbox"/> Not applicable 1/02/13 and 4/09/12 |

⁶ Filing reviews should be filed with the discipline reviews.

| | |
|---|--|
| ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | 1/25/13 and 12/12/11 1/31/13 <input type="checkbox"/> None 11/20/12 and 3/02/12 |
| ❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) | <input checked="" type="checkbox"/> None requested |
| Clinical Microbiology <input type="checkbox"/> None | |
| ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Microbiology Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Statistical Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Statistical Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None 4/26/12 (2) |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None 1/25/13, 12/20/12, 5/01/12 and 8/24/11 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>) | <input type="checkbox"/> None 12/28/12 and 5/02/12 |
| Nonclinical <input type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| • Supervisory Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| • Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | <input type="checkbox"/> None 1/25/13, 1/27/12 and 9/01/11 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | <input checked="" type="checkbox"/> None Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>) | <input checked="" type="checkbox"/> None requested |

| Product Quality | | <input type="checkbox"/> None |
|--|--|---|
| ❖ Product Quality Discipline Reviews | | |
| • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> | | <input checked="" type="checkbox"/> None |
| • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> | | <input checked="" type="checkbox"/> None |
| • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> | | <input type="checkbox"/> None 1/08/13, 4/11/12, 3/06/12 and |
| ❖ Microbiology Reviews | | <input checked="" type="checkbox"/> Not needed |
| <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> | | |
| <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i> | | |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> | | <input checked="" type="checkbox"/> None |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | | |
| <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> | | See Quality review dated, 3/06/12, page 67 |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i> | | |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i> | | |
| ❖ Facilities Review/Inspection | | |
| <input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i> | | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable |
| <input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i> | | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i> | | <input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review) |

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

JEANNIE M ROULE
02/06/2013

Roule, Jeannie

From: Roule, Jeannie
Sent: Thursday, January 31, 2013 8:31 AM
To: CDER EXSEC
Subject: NDA approval action

Hello,

DRUP is taking an approval action on NDA 203098, testosterone gel with Perrigo on Thursday, January 31, 2013.

There are no press related issues.

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



NDA 203098

DEFICIENCIES PRECLUDE DISCUSSION

Perrigo Company
Attention: Valerie Gallagher
U.S. Agent for Perrigo Israel Pharmaceuticals Ltd.
502 Eastern Avenue
Plant 6
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your New Drug Application (NDA) dated July 4, 2011, received July 5, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for testosterone gel.

We also refer to our September 16, 2011, letter in which we notified you of our target date of April 5, 2012, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

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 Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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
04/05/2012

MEMORANDUM

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

DATE: March 8, 2012

TO: NDA 203098

THROUGH: Jeannie Roule

SUBJECT: ONDQA

APPLICATION NUMBER: NDA 203098 (testosterone gel)

Comments and requests for information from the ONDQA reviewers were emailed to the Sponsor on March 7 and 8, 2012.

Please see attached email correspondences for all of the details.

From: Roule, Jeannie
Sent: Wednesday, March 07, 2012 11:39 AM
To: 'Dalit Fuchs'
Subject: RE: NDA 203098 and Information Request
Dalit,

The reviewer has the following comment:

We believe when you calculated 90% CI, you did not take into consideration the square root of n. Please use the right formula which is mean +/- 1.645 (St Dev/sq root of n).

Regards,
Jeannie

From: Dalit Fuchs [mailto:Dalit.Fuchs@Perrigo.co.il]
Sent: Wednesday, March 07, 2012 8:38 AM
To: Roule, Jeannie
Subject: RE: NDA 203098 and Information Request
Importance: High

Jeannie,

Statistical evaluation of the mean slopes from the bio-batch (T06P033) and primary stability batches 038366, 034424, 034414,034421 was performed in order to set the specifications. The in vitro slopes are summarized in the table below:

| Slopes Slope (ug/(cm ² * hr ^{1/2}))of Perrigo Batches | | | | |
|--|--------|--------|--------|--------|
| T06P033 | 038366 | 034424 | 034414 | 034421 |
| 768.00 | 613.05 | 907.77 | 406.37 | 704.13 |
| 662.74 | 615.84 | 724.43 | 680.02 | 809.07 |
| 477.29 | 649.19 | 667.21 | 485.67 | 852.18 |
| 813.42 | 707.37 | 871.02 | 755.25 | 883.44 |
| 848.29 | 758.73 | 876.97 | 721.85 | 920.19 |
| 830.55 | | 797.90 | 527.42 | 877.63 |

Descriptive Statistics:

Testosterone Gel, (b) (4)

Variable Mean StDev
Testosterone Gel, (b) (4) 731.5 137.5
Distribution plot with 90% confidence intervals.

Following the Agency's approach to get a range based on mean +/- 90% confidence interval, Perrigo's proposed specifications are (b) (4)

Could you please let me know if this is acceptable and we will update the specification table and the NDA via the gateway.

Thanks and best regards
Dalit

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Tuesday, March 06, 2012 4:50 PM

Reference ID: 3099439

To: Dalit Fuchs
Subject: NDA 203098 and Information Request

Dalit,

Your proposed range of [REDACTED] (b) (4) is too wide. It appears that you derived this range based on data from 82 batches of your proposed formulations at different stages (not all of them are final to be marketed) and based on your statistical approach.

The Agency's approach is to get a range based on mean +/- 90% confidence interval. We need the data from the bio-batches (PK and clinical) and primary stability batches only.

Provide us with data from the stability and other batches conducted with the final to be marketed formulations and propose a spec. range based on mean +/- 90% confidence interval. If you can provide us a table identifying the batch numbers and in which study they were used, that will be very helpful.

If possible, a response by Wednesday (3/7/12) will be helpful.

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

From: Roule, Jeannie
Sent: Thursday, March 08, 2012 3:37 PM
To: 'Dalit Fuchs'
Subject: NDA 203098
[Dalit,](#)

[Sorry but I accidentally put the wrong NDA number in the subject line.](#)

[Thanks,](#)
[Jeannie](#)

From: Roule, Jeannie
Sent: Thursday, March 08, 2012 10:38 AM
To: 'Dalit Fuchs'
Subject: NDA 22309 and CMC

Dalit,

The CMC reviewer has the following comment for you:

[We have reviewed the amendment dated 5-MAR-2012, and the real time stability data to support 18 months of expiration dating period for your product can not be located. In the absence of the stability data to determine the fate of isostearic acid, only 12 months of expiration dating period can be granted. However, it is possible to extend the expiration dating period via an Annual Report, when more real time stability data become available.](#)

[Please respond to this email by 12-MAR-2012.](#)

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

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
03/08/2012

MEMORANDUM

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

DATE: February 24, 2012

TO: NDA 203098

THROUGH: Jeannie Roule

SUBJECT: Carton and Container edits

APPLICATION NUMBER: NDA 203098 (testosterone gel)

Comment from DMEPA reviewer concerning the cartons and containers were emailed to the Sponsor.

Please see attached email correspondences for all of the details.

From: Roule, Jeannie
Sent: Friday, February 24, 2012 3:31 PM
To: 'Dalit Fuchs'
Subject: Cartons and containers/Addition
Dalit,

DMEPA has reviewed post marketing cases of medication errors associated with inappropriate interchanging of topical testosterone products due to confusion of similar dosages, strengths, and application instructions.

Thus, upon further review of your NDA, the DMEPA reviewer has requested an additional change to all labels and labeling. Please add the following language to the principal display panels of the container labels and carton labeling for the metered-dose pump and 25 mg and 50 mg unit-dose packets:

Topical testosterone products may have different doses, strengths, or application instructions that may result in different exposure.

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
02/24/2012

MEMORANDUM

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

DATE: February 23, 2012

TO: NDA 203098

THROUGH: Jeannie Roule

SUBJECT: CMC request for Information

APPLICATION NUMBER: NDA 203098 (testosterone gel)

The CMC reviewer had a request for information from the Sponsor concerning acceptance criterion of isostearic acid as a functional excipient.

The request was emailed to the Sponsor.

Please see attached email correspondences for all of the details.

From: Roule, Jeannie
Sent: Thursday, February 23, 2012 1:22 PM
To: 'Dalit Fuchs'
Subject: Information requests

Dalit,

Upon further review of your NDA 203098, testosterone gel, the CMC reviewer has the following request for information:

We have reviewed the acceptance criterion of isostearic acid as a functional excipient. The acceptance criterion should be tightened to 90.0-110.0%. Provide a revised specification table (release and stability).

Please respond by 29-FEB-2012.

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
02/23/2012

Tran-Zwanetz, Catherine

From: Tran-Zwanetz, Catherine
Sent: Friday, February 17, 2012 3:09 PM
To: 'Dalit Fuchs'
Cc: McKnight, Rebecca
Subject: RE: NDA 203098

Hello Ms. Fuchs,

Thank you for the t-con.

The following people were at the t-con:
 Donna Christner, CMC Lead
 Rajiv Agarwal, CMC Reviewer
 Tapash Ghosh, Biopharm Reviewer
 Cathy Tran-Zwanetz, ONDQA Project Manager

Here are the key points from our t-con:

1. *Your proposal of using (b) (4) as the routine quality control test to evaluate the in vitro drug release of your product does not seem appropriate for a semi-solid gel dosage form like your Testosterone gel product under review. You cited the reference of Guidance for industry "Dissolution testing of Immediate Release Solid Dosage Forms" which is not applicable for a topical gel. For a topical gel, you need to demonstrate the release of the active drug from the dosage form in the surrounding medium through a membrane, rather than directly in the testing surrounding medium. Therefore, we suggest that you adopt the IVRT method used in the bridging studies, as the quality in vitro routine test to evaluate the drug release of your proposed Testosterone Gel product. If you agree, please provide a proposal for the "release rate acceptance criterion" based on slope of the release profile for your IVRT method.*
2. *Alternatively, if you believe that the (b) (4) method is appropriate, you need to demonstrate the discriminatory ability of the method. Traditionally the discriminatory ability of a chosen method is demonstrated by showing how the method can pick up differences in the formulation and the process. That needs to be shown with variation of manufacturing conditions and formulations. After you submit the additional information with the specific details of the methodology ((b) (4) amount of sample used, place from where and how routine sample will be withdrawn with a diagram which will be your official document to be followed in future, etc.), as well as the complete drug release profile data showing its discriminatory ability, etc., we will review for acceptability of the method.*

Additionally, please note that for this test, your proposed dissolution approach of having a single acceptance criterion time point of Q (b) (4) in 60 minutes is not appropriate and it needs to be change to a multi-point release criteria. The selection of the specification-time points and specification-range should be based on the overall drug release profile data from the bio-batches (PK and clinical) and 1l primary stability batches. For the setting of the product acceptance criteria, the following point should be considered:

- *The in vitro drug release profiles should encompass the timeframe over which at least (b) (4) of the drug is released or where the plateau of drug being released is reached if incomplete release is occurring.*

- *Propose at least three specification time-points covering the initial, middle, and terminal phases of the complete drug release profile. The specification ranges should be based on the overall drug release data generated at these times.*
- *In general, the selection of the specification ranges is based on mean target value $\pm 10\%$ and NLT ^{(b) (4)} for the last specification time-point.*
- *The in vitro drug release acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any batches with drug release profiles outside those that were tested clinically.*

Please respond by February 29, 2012.

Thanks!
Cathy

From: Dalit Fuchs [mailto:Dalit.Fuchs@Perrigo.co.il]
Sent: Thursday, February 16, 2012 2:44 PM
To: Tran-Zwanetz, Catherine
Subject: NDA 203098
Importance: High

Dear Catherine,

Following our telephone conversation please feel free to send me emails

Best regards

Dalit Fuchs
Head of Regulatory Affairs
Perrigo Israel Pharmaceuticals Ltd.

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/s/

CATHERINE A TRAN-ZWANETZ
02/21/2012

TAPASH K GHOSH
02/22/2012

MEMORANDUM

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

DATE: February 9, 2012

TO: NDA 203098

THROUGH: Jeannie Roule

SUBJECT: Comments from DMEPA and CMC

APPLICATION NUMBER: NDA 203098 (testosterone gel)

Comments from DMEPA and CMC concerning the carton and container that were emailed to the Sponsor.

Please see attached email correspondences for all of the details.

From: Dalit Fuchs [Dalit.Fuchs@Perrigo.co.il]
Sent: Thursday, February 09, 2012 1:39 PM
To: Roule, Jeannie
Cc: Valerie Gallagher
Subject: RE: NDA 203098 carton/container

Importance: High

Hello Jeannie,

Sorry I missed your call, I didn't notice your comment at the bottom it was a crazy week.
I did received your email and already requested the change from our Art department.
I will submit it via they gateway as soon as it is available.

Thanks for following up
Have a great weekend
Dalit

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: ג 07 פברואר 2012 16:10
To: Dalit Fuchs
Cc: Valerie Gallagher
Subject: NDA 203098 carton/container

Dear Dalit,

The CMC and DMEPA reviewers have reviewed your latest versions of your carton and containers and have the following comments:

The container labels and carton labeling for your 2.5 gram and 5 gram packets utilize two colors, (b) (4) formatted into a reverse color scheme to differentiate the two strengths.

The appearance of both colors in similar formats on the labels and labeling for both strengths makes them appear similar and difficult to differentiate, especially for people who are color blind.

DMEPA and CMC recommend using color schemes which do not overlap to differentiate between the two strengths. For instance, the 25 mg strength could use (b) (4), and the 50 mg strength could use (b) (4)

Please acknowledge receipt of this email and let me know if you have any questions.

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

Reference ID: 3085263

file:///C:/Documents and Settings/roulej/Desktop/RE NDA 203098 cartoncontainer.htm[2/9/2012 1:48:10 PM]

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/s/

JEANNIE M ROULE
02/09/2012



NDA 203098

INFORMATION REQUEST

Perrigo Israel Pharmaceuticals Ltd.
c/o Perrigo Company
Attention: Valerie Gallagher, Associate Director, ANDA/NDA Regulatory Affairs
Eastern Ave., Plant 6
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your New Drug Application (NDA) dated July 4, 2011, received July 5, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone Gel, (b) (4)

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, submitted by January 18, 2011, in order to continue our evaluation of your NDA. Please also submit your responses via email to rebecca.mcknight@fda.hhs.gov.

IVRT

You used IVRT using vertical diffusion cell and Nylon membrane to bridge formulation changes and scale-up. In a previous IR, you were asked to submit development and validation report of the IVRT study. You were specifically asked to address the criteria for membrane selection (membrane binding, membrane resistance, membrane stability), membrane equilibrium, medium solubility, method precision, method sensitivity, method reproducibility, selection of time points, etc. While you did address some of them in the document (#56186-v1) submitted on Nov 8, 2011, the following elements are still missing as part of development, optimization and validation of the method:

- Choice of diffusion medium
- Choice of rotation speed
- Choice of diffusion membrane
- Membrane binding
- Choice of sampling times and temperature
- Choice of amount of sample to be used

Please submit responses in these regards.

Dissolution:

You proposed dissolution method for the gel product using (b) (4) .
(b) (4)
(b) (4) . Evaluation of release/dissolution of a semi-solid product using (b) (4) method is not usual. While you discussed little bit about choice of medium, agitation speed, pH etc, you did not give any scientific rationale for choosing this apparatus over the traditional Franz cell or enhancer cell etc where there is a rate controlling membrane present. You also did not discuss the discriminatory ability of the method. Obviously, the release from the product, as anticipated, is very quick.

Please explain why you chose (b) (4) your choice of apparatus for this purpose. You did use vertical cell for the IVRT methods which could very well be used for this purpose.

Also, you should include the specification for dissolution in the drug product specifications for bottles with non-aerosol metered dose pumps and provide the updated drug product specifications table. If you do not intend to, please provide your justification.

If you have any questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

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

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/s/

MOO JHONG RHEE
01/10/2012
Chief, Branch IV



NDA 203098

INFORMATION REQUEST

Perrigo Company
Attention: Valerie Gallagher
U.S. Agent for Perrigo Israel Pharmaceuticals Ltd.
502 Eastern Avenue
Plant 6
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your New Drug Application (NDA) dated July 4, 2011, received July 5, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for testosterone gel (b) (4).

In collaboration with the Division of Medication Errors Prevention and Assessment (DMEPA) in the Office of Surveillance and Epidemiology (OSE), we have the following comments related to your proposed container/carton labeling. Your prompt response to these comments is requested.

1. The strength of the product in the packets should be changed (b) (4) to “25 mg (or 50 mg) of testosterone per packet”. The name, dosage form and strengths on the labels should be displayed as following:

TESTOSTERONE GEL

*25 mg (or 50 mg) of testosterone per packet**

For immediate container label, the following should display:

** each packet contains 2.5 grams (or 5 grams) of gel*

For carton label, the following should display:

30 unit-dose packets (2.5 grams/or 5 grams) of gel each packet

2. Revise the container labels and carton labeling of your 2.5 grams and 5 grams packets to provide more differentiation between the two packet sizes. As currently presented with the identical layout and color schemes the labels and labeling of the two sizes appear identical and could lead to selection of the wrong packet. You can increase the differentiation between the two products by using different colors on the labels and labeling of one of the packet sizes.

3. The Bar code should be provided on all container closure labels.
4. Provide "Net Quantity 88 g" on metered dose pump labels.
5. The strength of the product in the metered-dose pump should be changed (b) (4) "12.5 mg testosterone per pump actuation". The name, dosage form and strengths on the labels should be displayed as following:

TESTOSTERONE GEL

*12.5 mg of testosterone per pump actuation**

For immediate container and carton labels, the following should display:

- *each pump actuation dispenses 1.25 grams of gel*

6. Delete (b) (4) which appears above the established name and strength on the principal display panel of all labels and labeling. The (b) (4) (b) (4) competes with the established name and product strength for prominence. Additionally, (b) (4) is also duplicative because this information appears on the on either the back or side panels of all labeling.
7. Delete (b) (4) which also appears above the established name and strength on the principle display panel of all labels and labeling. The (b) (4) also competes with the established name and product strength for prominence.
8. The word "Pump" on the pump label and pump carton labeling matches the prominence of the established name and thus appears to be part of the name. Decrease the prominence of the word "Pump" by decreasing the size of the font, using unbolded font, and locating the word away from the established name.
9. Include the statement "Dispense the enclosed Medication Guide to each patient" on the principal display panel of all labels and labeling per 21 CFR 208.24 (d) which states:

The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.
10. We recommend revising the dosing chart on the principal display panel of the gel pump label to specify the dose in milligrams of testosterone (b) (4). The dosing of testosterone products should be based on the amount of testosterone that is applied. We recommend revising the table from:



To:

| Prescribed Daily Dose | Number of Pump Depressions |
|-----------------------|----------------------------|
| 50 mg | 4 (once daily) |
| 75 mg | 6 (once daily) |
| 100 mg | 8 (once daily) |

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

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/s/

JENNIFER L MERCIER
12/27/2011



NDA 203098

INFORMATION REQUEST

Perrigo Company
Attention: Valerie Gallagher
U.S. Agent for Perrigo Israel Pharmaceuticals Ltd.
502 Eastern Avenue
Plant 6
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your New Drug Application (NDA) dated July 4, 2011, received July 5, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for testosterone gel (b) (4)

We are continuing our review of the Clinical Pharmacology and the Chemistry, Manufacturing and Controls sections 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.

Clinical Pharmacology:

1. Regarding your Bioequivalence (BE) Study 03-0415-001:
 - Incurred sample reanalysis (ISR) is recommended to evaluate the accuracy of the incurred samples analyzed. We note that there is no information regarding ISR in the study report. The number of ISR samples should be 5-10% of the total sample size including a sample near C_{max} and a sample at the elimination phase for each individual included in ISR. We request that you submit ISR results to ensure the reliability of the study data.
2. Regarding your Transfer Study M1IU09001:
 - Provide the dataset of the 24-hour baseline concentrations for all individuals.
 - The names of the xpt files do not match with the content of the data. Provide a table with the file name and the description of the data that is included in each file.

- We cannot locate the dataset for Treatments C and D in the current NDA. We request that you submit the dataset for Treatments C and D.

If the information above has been previously submitted in your current application package, inform us about the location of the report and/or dataset.

Chemistry, Manufacturing and Controls:

3. We have reviewed your justification that isostearic acid is not (b) (4) (b) (4). However, we deem that isostearic acid acts as a (b) (4) in your formulation. Therefore, revise the function of isostearic acid from (b) (4) and provide an updated drug product composition table.
4. Include the specification for isostearic acid in the drug product specifications for both packets and bottles with non-aerosol metered dose pumps at both release and during stability. Provide the updated drug product specifications table. The fate of isostearic acid should be monitored during stability and should be added to your stability protocol.
5. Include the specification for dissolution in the drug product specifications for Bottles with non-aerosol metered dose pumps and provide the updated drug product specifications table.
6. The Executed batch record can not be located in the submission. Identify the location of this document in the application or provide the Executed batch record.

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

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/s/

JENNIFER L MERCIER
12/21/2011



NDA 203098

FILING COMMUNICATION

Perrigo Company
Attention: Valerie Gallagher
U.S. Agent for Perrigo Israel Pharmaceuticals Ltd.
502 Eastern Avenue
Plant 6
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your New Drug Application (NDA) dated July 4, 2011, received July 5, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for testosterone gel (b) (4).

We also refer to your amendments dated July 28, August 4, 8, 11, 25, and September 14, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 5, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 5, 2012.

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

1. In the BE study (Study 03-0415-001), the use of two time points for testosterone baseline measurement (-12hr & 0hr) will be a review issue.

We are providing the above comment to give you preliminary notice of potential review issue. 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. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We also request that you submit the following information:

Biopharmaceutics:

In-Vitro Release Test (IVRT)

1. Describe (preferably in a tabular format) the number of times that the *in-vitro* release test (IVRT) was performed to support this submission, including the rationale for performing this test at each time.
2. The SUPAC SS guidance clearly mentions that the *IVRT* methodology should be appropriately validated. In reviewing the information you provided, the development and validation report for the *IVRT* study could not be found. Submit the complete development and validation report for the *IVRT* method, including the criteria for membrane selection (membrane binding, membrane resistance, and membrane stability), membrane equilibrium, medium solubility, method precision, method sensitivity, method reproducibility, selection of time points, etc. Also, provide the details of analytical validation parameters including linearity, range, detection limit, specificity, precision, sensitivity, robustness, etc. If you have already provided this information in your NDA submission, specify where it is located (section, page/link, etc.).
3. For the submitted *IVRT* results, provide the computation of ordering the 36 individual T/R ratios from lowest to highest to identify the 8th and the 29th ordered individual ratios.

Dissolution

4. In reviewing the information provided by you, the development and validation report for the dissolution method (# 30701304-06) could not be found. Submit full development and validation report for the dissolution method including the criteria for apparatus selection, medium selection, rotational speed, temperature, sampling time point, method precision, method sensitivity, method reproducibility, selection of time points, etc. Also, provide the details of analytical validation parameters including linearity, range, detection limit, specificity, precision, sensitivity, robustness, etc. If you have previously provided this information, direct us to the section/link.
5. Submit full release profiles (with data) at different time points instead of release at 60 minutes.

Clinical Pharmacology:

6. In the BE study, both baseline corrected and baseline uncorrected testosterone pharmacokinetic (PK) parameters will be assessed for the bioequivalence (Refer to the meeting minutes on May 19, 2010). Provide the PK parameters (i.e., C_{max} and AUC) and

the corresponding BE evaluation based on total testosterone concentrations without baseline subtraction. If the requested information has been provided in the application, provide the location of the information.

7. Concerning the inter-personal transfer study, provide the comparison between the baseline and post-transfer PK parameters (i.e., C_{\max} and AUC) of testosterone in female partners for both test and reference products. This information should include the percent calculation of difference between the baseline vs. post-transfer PK parameters (i.e., C_{\max} and AUC) for each individual. If the requested information has been provided in the application, provide the location of the information.

We remind you to provide labeling in Physician Labeling Rule (PLR) format with information specific to your drug product.

We request that you resubmit labeling that addresses these issues by October 10, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for 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.

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

Because none of these criteria apply to your application, you are exempt from this requirement

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

Sincerely,

{See appended electronic signature page}

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

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/s/

GEORGE S BENSON
09/16/2011



NDA 203098

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Perrigo Israel Pharmaceuticals Ltd.
c/o Perrigo Company
Attention: Valerie Gallagher
Associate Director, ANDA/NDA Regulatory Affairs
502 Eastern Avenue
Plant 6
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone gel, (b) (4).

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

¹ These violations include studies conducted by (b) (4) specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Jeannie Roule, Regulatory 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

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/s/

MARGARET M KOBER
09/06/2011
signed for Scott Monroe

MEMORANDUM

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

DATE: July 28, 2011

TO: NDA 203098

THROUGH: Jeannie Roule

SUBJECT: IR request from the Clinical and Clinical Pharmacology Review teams

APPLICATION NUMBER: NDA 203098 (testosterone gel)

The Clinical and Clinical Pharmacology Review reviewers requested that the attached Information Request be emailed to the Applicant.

Please see attached email correspondences for all of the details.

Roule, Jeannie

From: Roule, Jeannie
Sent: Thursday, July 28, 2011 11:57 AM
To: 'Dalit Fuchs'
Subject: RE: Information request

Dalit,

As per our conversation, please provide the following information to your NDA:

1. Updated Debarment Certification for a New Drug Application (not generics)
2. Updated financial disclosure form
3. List of all Cetero locations that were used for any studies that you performed (transfer, washing, BE)
Include dates that studies were initiated and completed
Include all sites where data may have been analyzed or reports generated and dates that the data was generated

Let me know if you have any questions.

Regards,
Jeannie

From: Dalit Fuchs [mailto:Dalit.Fuchs@Perrigo.co.il]
Sent: Thursday, July 28, 2011 11:25 AM
To: Roule, Jeannie
Subject: RE: Information request
Importance: High

Jeannie,

We are not sure what the reviewer meant in the second comment when he asked us to provide "clear definitions for the data files". We would like to contact our CRO, but are not sure what to request. Could the reviewer please provide us with more details.

We already have the datasets ready to be submitted, it was inadvertently omitted in the original submission. Would you prefer that we submit those now and later amend the NDA with the definitions for the data files.

Thanks
Dalit

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Thursday, July 28, 2011 6:05 PM
To: Dalit Fuchs
Subject: RE: Information request

Dalit,

Try to state in an email the questions you have about the information that we requested.

Regards,
Jeannie

Roule, Jeannie

From: Roule, Jeannie
Sent: Wednesday, July 27, 2011 4:20 PM
To: 'Dalit Fuchs'
Subject: Information request

Dear Dalit,

I have a question from the Medical Officer:

We cannot find any data sets for your BE study (03-0415-001), the skin sensitization study (DS102308), or the skin irritation study (DS310208). You will need to submit these data sets as soon as possible so that we can verify that it is sufficient to file the NDA.
Keep in mind that your filing date is September 3.

Also, you need to provide clear definitions for the data files and the data within the files for studies PRG-812, PRG-806 and M11U09001 (data sets were provided).

Regards,
Jeannie

From: Dalit Fuchs [mailto:Dalit.Fuchs@Perrigo.co.il]
Sent: Wednesday, July 13, 2011 2:33 PM
To: Roule, Jeannie
Cc: Valerie Gallagher; Dalit Fuchs
Subject: US Agent contact information
Importance: High

Hello Jeannie,

Following our telephone conversation below are Valerie Gallagher contact details:

valerie.gallagher@perrigo.com

Telephone : 269-290-5125 and 269-673-9367

Let me know if you need any additional information

Best regards

Dalit

Roule, Jeannie

From: Dalit Fuchs [Dalit.Fuchs@Perrigo.co.il]
Sent: Thursday, July 28, 2011 11:25 AM
To: Roule, Jeannie
Subject: RE: Information request
Importance: High

Jeannie,

We are not sure what the reviewer meant in the second comment when he asked us to provide "clear definitions for the data files". We would like to contact our CRO, but are not sure what to request. Could the reviewer please provide us with more details.

We already have the datasets ready to be submitted, it was inadvertently omitted in the original submission. Would you prefer that we submit those now and later amend the NDA with the definitions for the data files.

Thanks
Dalit

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Thursday, July 28, 2011 6:05 PM
To: Dalit Fuchs
Subject: RE: Information request

Dalit,

Try to state in an email the questions you have about the information that we requested.

Regards,
Jeannie

From: Dalit Fuchs [mailto:Dalit.Fuchs@Perrigo.co.il]
Sent: Thursday, July 28, 2011 11:01 AM
To: Roule, Jeannie
Subject: RE: Information request

Jeannie,

I just left you a voice message. 11:30 works fine for me, I will be waiting for your call.

Regards,
Dalit

From: Roule, Jeannie [mailto:Jeannie.Roule@fda.hhs.gov]
Sent: Thursday, July 28, 2011 5:58 PM
To: Dalit Fuchs
Subject: RE: Information request

Dalit,

I am going to call you around 11:30 am today. My supervisor, Jennifer Mercier will be in my office as well.

Regards,
Jeannie

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
08/04/2011



NDA 203098

NDA ACKNOWLEDGMENT

Perrigo Company
Attention: Valerie Gallagher
U.S. Agent for Perrigo Israel Pharmaceuticals Ltd.
502 Eastern Avenue
Plant 6
Allegan, MI 49010

Dear Ms. Gallagher:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: testosterone gel, (b) (4)

Date of Application: July 4, 2011

Date of Receipt: July 5, 2011

Our Reference Number: NDA 203098

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 September 3, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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 Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JEANNIE M ROULE
07/13/2011



IND 107130

MEETING MINUTES

Perrigo Israel Pharmaceuticals Ltd.
Attention: Valerie Gallagher
Associate Director Regulatory Affairs
502 Eastern Avenue, Plant 6
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Testosterone Gel (b) (4) Multi-dose Pump and Unit Dose Pack.

We also refer to the face-to-face meeting between representatives of your firm and the FDA on May 19, 2010. The purpose of the meeting was to discuss your clinical study plan and approval requirements for a 505(b)(2) NDA for Testosterone Gel (b) (4) Multi-dose Pump and Unit dose Packet.

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 C
Meeting Category: Guidance
Meeting Date and Time: May 19, 2010 @ 10-11:30 a.m.
Meeting Location: Conference Room 1415

Application Number: IND 107130
Product Name: testosterone gel (b) (4)
Indication: Testosterone replacement therapy
Sponsor Name: Perrigo Israel Pharmaceuticals Ltd.
Meeting Chair: Mark Hirsch, M.D.
Meeting Recorder: Jeannie Roule

FDA ATTENDEES

| | |
|----------------------------|---|
| George Benson, M.D. | Deputy Director, Division of Reproductive and Urologic Products (DRUP) |
| Mark Hirsch, M.D. | Medical Team Leader, DRUP |
| Guodong Fang, M.D. | Medical Officer, DRUP |
| Lynnda Reid, Ph.D. | Pharmacology Supervisor, DRUP |
| Jeffrey Bray, Ph.D. | Pharmacology Reviewer, DRUP |
| E. Dennis Bashaw, Pharm.D. | Division Director, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III (DCP III) |
| Myong Jin Kim, Pharm.D. | Clinical Pharmacology Team Leader, OTS, OCP, DCP III |
| LaiMing Lee, Ph.D. | Clinical Pharmacology Reviewer, OCP, OTS, DCP III |
| Mahboob Sobhan, Ph.D. | Statistical Team Leader, Division of Biometrics III (DB III), OTS |
| Xin Fang, Ph.D. | Statistical Reviewer, DB III, OTS |
| Donna Christner, Ph.D. | CMC Lead, Division of New Drug Quality II (DNDQA II), Office of Pharmaceutical Sciences (OPS), Office of New Drug Quality Assessment (ONDQA) |
| Danuta Gromek-Woods, Ph.D. | Chemistry Reviewer, DNDQA II, OPS, ONDQA |
| Audrey Gassman, M.D. | Deputy Director for Safety, DRUP |
| Martin Kaufman, DPM, MBA | Safety Regulatory Health Project Manager, DRUP |
| Maria Walsh, RN, MS | Associate Director for Regulatory Affairs, Office of Drug Evaluation III (ODE III) |
| John Peters, M.D. | Office of Pharmaceutical Science (OPS), Office of Generic Drugs (OGD) |
| Michael Bernstein | Director, Division of Regulatory Policy II (DRPII) |
| Jane Baluss | Regulatory Counsel, DRPII |
| Roger Weiderhorn, M.D. | Medical Officer, DRUP |
| Jonathan Jarow, M.D. | Medical Officer, DRUP |
| Jennifer Mercier | Chief, Project Management Staff, DRUP |
| Jeannie Roule | Regulatory Health Project Manager, DRUP |

SPONSOR ATTENDEES

| | |
|--------------------|---|
| Jatin Shah, Ph.D. | Senior Vice President & Chief Scientific Officer |
| Amira Zeevi, Ph.D. | Vice President, Pharmaceutical R&D |
| Brian Schuster | Associate Director, Technical Advisor, Regulatory Affairs |
| Jonathan Schwartz | Senior Project Manager, Clinical Affairs |

BACKGROUND

The Sponsor has developed a generic Testosterone Gel, (b) (4) formulation that contains different inactive ingredients from that specified in the reference listed drug (RLD), Androgel® (testosterone gel) 1%. On June 15, 2007, and December 16, 2008, the Sponsor submitted two (b) (4) for the multi-dose pump and unit dose packets (2.5 and 5 gram) to the Office of Generic Drugs (OGD). On August 28, 2009, the Sponsor received written communication from OGD that, due to the differences in the Sponsor's formulation, clinical safety studies would be required to support the regulatory approval of the product. The Sponsor would like to discuss the filing requirements, including the clinical study plan, related to a planned 505(b)(2) NDA for Testosterone Gel (b) (4), Multi-dose Pump and Unit-dose Packet.

PRELIMINARY COMMENT:

The Division recommends that Sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf> . In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>) .

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

DISCUSSION

The following preliminary draft responses were provided to the Sponsor on May 18, 2010, in response to the questions posed in the sponsor's meeting package. The Sponsor's questions are

presented below in **bolded** text, followed by the Division's responses in normal text. All additional discussion is summarized in *italics*.

I. Clinical

Perrigo proposes to demonstrate efficacy and safety of the new drug product with the following data and information:

i) Study to Support Efficacy - A pharmacokinetic bioequivalence study of the test versus the reference drug AndroGel®

Question #1

Perrigo seeks concurrence that the results of this PK study fulfill the data requirements to demonstrate efficacy of the proposed Testosterone ^{(b) (4)} gel formulation and that an additional Phase 3 study will not be required. If any additional efficacy studies are required, we request that basic information on the study design be provided in this meeting.

Response: We concur. In addition to the baseline-corrected serum testosterone (T) concentrations, provide comparisons of total testosterone without baseline subtraction. We note that two different Perrigo products were used (Lot T06P030 and Lot T06P033) in the BE study. Are these considered 2 different lots or 2 different formulations? Which one will be the basis for your new drug application?

Additional Discussion: The Sponsor indicated that Lot T06P030 and T06P033 are different formulations. The Sponsor verified that Lot T06P033 will be the basis for their new drug application.

The Sponsor asked the Division if baseline corrected or baseline uncorrected testosterone concentrations will be the Division's primary endpoint for the determination of bioequivalence.

The Division stated that both baseline corrected and baseline uncorrected testosterone concentrations will be reviewed. The Division has not determined which set of data will be used to evaluate establishment of bioequivalence.

ii) Studies to Support Safety

Literature Review

Perrigo intends to confirm the safety of the proposed drug product through a thorough evaluation of the available preclinical and clinical literature on the active ingredient. In addition, a survey of the postmarketing adverse event data related to the active ingredient will be conducted using U.S. (AERS) and international (WHO) regulatory databases.

Question #2

Please confirm that this proposal is acceptable, or if more specific evaluation is necessary.

Response: From the Nonclinical perspective, your proposal to rely upon the Agency's previous finding of safety for AndroGel may be acceptable to meet the requirements for nonclinical safety assessments, provided that bioequivalence to AndroGel is demonstrated. Alternatively, your proposal to conduct a literature review is acceptable. You should submit complete reprints of all

cited literature. Safety should be assessed for adverse effects following chronic administration, genotoxicity, carcinogenicity, and potential effects on fertility and development.

From the Clinical perspective, your proposal is acceptable.

Additional Discussion: The Sponsor stated that if their BE information is acceptable then they will assume that no new nonclinical data will be needed. The Division confirmed that no further nonclinical studies would be needed.

Dermal Irritation Studies

Perrigo has performed a Repeat Insult Patch Test (RIPT) and a Cumulative Irritant Patch Test utilizing the comparator product Androgel®, in the context of support for the filing of the original ANDAs. Summaries of these studies are enclosed in Attachment 7. These studies were performed at the request of OGD for the purpose of demonstrating that the proposed product, which differs in inactive ingredients from the reference drug, does not have any greater potential to cause dermal irritation or sensitization.

Question #3

FDA comments are requested regarding the acceptability of these studies to support NDA approval.

Response: From the Nonclinical perspective, no further nonclinical studies are necessary since dermal irritation and sensitization studies were conducted in humans.

From the Clinical perspective, the contact sensitization study (repeat insult patch test) is acceptable. For the cumulative irritation study, however, provide justification that 0.2 gm when applied to a 2 x 2 cm area of skin is representative of 10 gm (the maximum clinical dose) when applied to the arms and shoulders as per labeling.

Additional Discussion: The Sponsor inquired if it was acceptable to use the 0.2 gm and not the full 10 gm for their contact sensitization study and if the Division recommends a standard size area that should be used.

The Division stated that it is the Sponsor's responsibility to provide evidence that the 0.2 gm dose applied to a 2 x 2 cm area provides a comparable skin safety assessment to 10 gm applied to the approved application sites. The Sponsor stated that they would provide the requested information.

Hand washing study

Perrigo has performed a pilot hand washing study. The protocol is provided in Attachment 8.

Question #4

Perrigo seeks Agency concurrence, or further discussion, on the following points:

- 1) The proposed dose of (b) (4) will be acceptable in pivotal study.

Response: We do not concur. The dose for use in the hand washing study should be the maximum clinical dose (10 gm), applied by the subject to the arms and shoulders as per the label. After the per label application, swab assessment of residual should be conducted before and after hand washing.

Also, you should be aware that our primary focus will be the residual amount of the Perrigo test product remaining on the hands, not the comparison of test product to reference product.

Additional Discussion: The Sponsor asked the Division how conclusions would be drawn from the hand washing study without a concurrent AndroGel control group. The Division stated it is primarily interested in the safety of the Perrigo product itself, specifically whether the product could be washed off the hands. The Sponsor needs to demonstrate that the Perrigo product is largely removed from the hands by washing. The Sponsor might consider a confidence interval approach and set a lower bound for acceptability.

The Sponsor stated that they would like to submit a hand washing protocol for the Division's review. The Sponsor asked whether this protocol would qualify for a Special Protocol Assessment (SPA). The Division encouraged the Sponsor to submit a proposed protocol but stated that protocols for safety studies do not meet the criteria for a SPA..

2) The study design requires the subject to wait 5 minutes before initiating the washing step to allow the gel to dry on the hands, simulating a worse case effect.

Response: We propose a slightly different study design, whereby subjects will use the product as per the labeled instructions (application of 10 gm to the arms/shoulders). The hands will then be swabbed for residual after the application to arms/shoulders and then swabbed again following hand washing. With this design, waiting for 5 minutes is unnecessary and is not recommended.

Additional Discussion: The Sponsor inquired if the Division prefers any particular waiting period between each step of the hand washing procedure. The Division stated that it prefers that the hand washing procedure follow a real life scenario and that no specific waiting periods have been set by the Division. The Sponsor suggested implementing some set times for washing, drying, and waiting between steps, so that there would be consistency with the procedure.

The Division remarked that a uniform scenario would be helpful but the hand washing procedure should mimic a real life situation. The Division further stated that the Sponsor could research various hand washing techniques and then submit a protocol with an exact plan. The Division would then be able to make more specific comments.

The Division stated that the Sponsor should submit a rationale and justification that they will use for their swabbing technique and show that there is a consistency with the study.

3) The study design incorporates a washing procedure whereby subjects will wet their hands with warm tap water for 10 seconds, have 2 mL of liquid soap dispensed onto the hands, wash their hands with a controlled hand scrubbing motion for 15 seconds, followed by a 15 second rinse with warm tap water, then dry their hands with a dry cotton towel for 30 seconds.

Response: The hand washing procedure is considered reasonable. However, the total time of 1 minute 10 seconds may be longer than expected in a real-life setting. Additional discussion is required, especially in regard to shortening the duration of hand drying.

Additional Discussion: *The Sponsor asked whether the duration of hand drying could be 20 seconds. The Division stated that details of the hand washing procedure, such as this, would be part of our review of the final protocol.*

The Sponsor stated that the hand washing procedure would be consistent with the patient instructions in the AndroGel label (e.g., apply 10gms to the palms, then apply to the arm and shoulder area). The Division stated that the Sponsor should submit a rationale and justification for the hand washing procedures, especially for the swabbing technique itself.

4) The overall proposed design and sample size.

Response: See our previous responses (and the additional request below) in regard to the proposed design. Since our focus is on the residual amount of Perrigo test product, a comparison to reference product is not required. Therefore, the proposed sample size (n=24) could be made smaller.

Additional Discussion: *The Division stated that the primary focus on the Perrigo product itself. Safety of the Perrigo product could be analyzed based on the desired lower bound of the 95% confidence interval for testosterone residual estimate. The Division expects to see that the product is largely removed by hand washing. The Division stated that although fewer than 24 subjects may be possible, the effect of variability may be reduced by keeping the sample size at 24.*

From the Biometrics perspective, the absolute residual and percentage of testosterone remaining from before washing (the “wash-off” percentage) should be presented for both testing drug and reference drug (if reference is maintained in the study design). If you still plan to compare test to reference groups, the same ANOVA model may be used for both absolute residual and percentage of residual, if the model assumptions are valid. In addition, handling of missing data needs to be specified in the protocol. An expected drop-out rate should be incorporated into the final sample size analysis.

Additional Request Related to Washing Off T-Gel

In addition to demonstrating that the product is removed from the hands by washing, you will need to demonstrate that the product is also removed *from the application site* (arms/shoulders) by washing. This request is based upon the potential for secondary exposure of T-gel to another individual from contact with the application site, as well as to support labeling which instructs patients to wash the application site prior to unclothed, close physical contact. The objective of this part of the study is to demonstrate that washing the application sites precludes transfer of T-gel to non-treated individuals during close, unclothed, physical contact.

We believe that this *application site* investigation could be conducted at the same time as the hand-washing study. We recommend the following general procedures be followed in this part of the study: Gel that has been applied to the arms/shoulders is allowed to dry for some time

(e.g., 2 hours). Swabbing of the application sites is done prior to and following a complete washing of the application sites (e.g., a body shower). The absolute residual and the “wash-off percentage are determined. An alternative to this swabbing procedure is to conduct an in vivo study, for example: Following the male user’s body shower, female subjects are asked to engage in 15 minutes of contact with the application sites in males. Blood is sampled for serum testosterone in the females and compared to their own baseline serum testosterone levels, which have been drawn sometime previously. Changes-from-baseline are calculated. If the swabbing procedure is conducted, then the results of the swabbing investigation may necessitate further follow-up with the in vivo study.

Additional Discussion: The Sponsor stated that the application site washing investigation was logistically feasible. The Sponsor further stated that they simply wanted to conduct the safety studies required by the Division for product approval.

At first glance, the Sponsor proposed to use a swabbing technique to determine residual percentage at the application site, as in the hand washing study. The Sponsor asked how it will be determined that additional studies would be needed. The Division stated that when it reviews the results, if it is decided that the residual percentages were too high, then additional studies might be needed. The Division further stated that at this time it is not able to provide an acceptable percentage. The Division expects to see that the product is largely washed off from the application site.

Post-meeting Comment: The Division requested that the Sponsor provide information that supports the sensitivity and reliability of the swabbing technique in detecting testosterone (e.g., information to support the validity of the swabbing technique). The Division prefers that this information be submitted with the revised protocols.

Body transfer study

Perrigo has engaged a CRO that has prior experience with performing testosterone body transfer studies. A draft protocol for this study is provided in Attachment 10, and was also submitted in IND (#107130) to initiate the safety review in December 2009.

Question #5

Perrigo seeks Agency concurrence, or further discussion, on the following points:

- 1) Maximum dose (2x5grams) to be used in the study.**

Response: The maximum dose (2x 5 grams) is acceptable.

- 2) Initiation of direct skin contact two hours after dosing will be adequate to compare test to reference product safety. If not, what is the recommended time elapsed prior to contact?**

Response: We concur with direct skin contact 2 hours after dosing but our primary focus is on transfer potential of the Perrigo test product itself, not the comparison of test product to reference product.

Additional Discussion: The Sponsor inquired about the use of a t-shirt and no t-shirt as part of this study.

The Division is primarily interested in the ability of a t-shirt to block transfer of the Perrigo product itself. The percentage transferred is of interest when the male user is without a t-shirt and when the same male user wears a t-shirt. The Division further noted that the Sponsor's original proposal was considered reasonable.

Given that female partners will be participating in the transfer study, it should be noted that premenopausal and postmenopausal women have different baseline testosterone concentrations. In addition, potential menstrual cycle effects on baseline testosterone concentrations should be taken into consideration if the Sponsor plans to enroll premenopausal women.

The Sponsor remarked that they will take all of the Division's suggestions into consideration.

- 3) A direct skin contact period of 15 minutes between male and female partners (with and without a t-shirt worn by the male) is adequate to compare test to reference product safety. If not, what duration of contact is recommended?**

Response: We concur with a direct skin contact period of 15 minutes, but our primary focus is on transfer potential of the Perrigo test product itself, not the comparison of test product to reference product. In addition, the 15 minutes of contact should be continuous at one application site, not divided in half (7.5 min on each side) as proposed.

- 4) Body rubbing methodology between male and female partner as detailed in the study protocol.**

Response: We concur.

- 5) The body transfer study design requires subjects apply drug to the shoulder and upper arm target areas (trunk is excluded) to maximize the surface to surface contact during the rubbing phase. Application of the drug to the shoulder and upper arm target areas will be adequate.**

Response: We concur.

- 6) A wash out period of 7-days between treatment periods will be adequate.**

Response: We concur.

- 7) The use of AUC_{0-t} and C_{max} for the non-inferiority assessment of safety.**

Response: We concur with the use of AUC and C_{max} to assess safety but our primary focus is on demonstrating that a T-shirt blocks transfer of the Perrigo test product from a treated male to a non-treated female, not a comparison of test product to reference product.

- 8) The proposed sampling times pre-dose application (0, 2, 4, 6, 8, 10, 12, and 16 hours) and post-dose application (0, 2, 4, 6, 8, 10, 12, 16, and 24 hours) for females.**

Response: We concur. However, a 24-hour baseline testosterone level is recommended, not 16 hours as proposed.

- 9) Discuss the recommended normal range of testosterone in males. The AndroGel package insert states the normal range is between 298-1043 ng/dL for males.**

Response: We concur that this is a generally acceptable normal range. However, it is unclear how this normal range in males affects the transfer study.

- 10) The overall proposed design and sample size.**

Response: We concur with the overall proposed design and sample size; however, our primary focus is on demonstrating that a T-shirt blocks transfer of the Perrigo test product from a treated male to a non-treated female, not a comparison of test product to reference product.

From the Biometrics perspective, the same comments apply as for our response to Question #4, Item 4 (e.g., handling of missing data, accounting for discontinuations in the sample size calculation, etc).

Showering Study (if required based on hand washing study outcome)
A draft showering study protocol is provided in Attachment 11.

Question #6

Perrigo seeks Agency concurrence, or further discussion, on the following points:

- 1) Confirm that showering study is not necessary if the results of the pivotal hand washing study confirm those of the pilot study, considering that the PK study successfully met standard bioequivalence criteria. A showering study would only be required if the pivotal hand washing study were to demonstrate that the test product behaved differently from the RLD (significantly more residual testosterone remained after washing).**

Response: A showering study may or may not be necessary. One purpose of a showering study is to provide useful information to patients and prescribers as to when a patient can shower, swim, or immerse the application site(s) without affecting the efficacy of the product (testosterone concentrations). We require additional time to review this issue; specifically, in regard to the showering experience for the reference listed drug and how it might affect the need for a showering study for your product.

Additional Discussion: The Sponsor inquired if the Division might decide that a hand and application site washing study, a transfer study, and the appropriate pharmacokinetics data, are sufficient and that a showering study might not be needed. The Division stated that that might be true. A key issue in this decision is related to the showering experience for the reference drug and how that will affect the need for a separate showering study using the Perrigo product. The Division further stated that it might be to the Sponsor's advantage to conduct their own showering study.

- 2) The approved labeling for AndroGel® instructs patients to shower 6 hours after drug application. Perrigo has replicated this parameter into the showering study design following a single dose of the drug. The showering step of the study will be performed prior to subjects reaching "steady state" blood levels of the drug.**

Response: See our response to the previous question. If a showering study is ultimately determined to be necessary, the timing of showering relative to gel application (e.g., 2 hours) will require additional discussion.

- 3) The protocol currently states that we will enroll hypogonadal subjects, discuss whether it may be possible to conduct the study with healthy subjects rather than hypogonadal subjects.**

Response: See our response above.

- 4) The study incorporates a 7 day wash out period.**

Response: See our response above.

- 5) The study proposes 21 blood samples per subject each period. Pharmacokinetic sampling will occur at -12, -6, -1, and -0.5 hours, just prior to dosing (0 hour) to capture baseline testosterone levels, and after dose administration at 1, 2, 3, 4, 6, 8, 10, 12, 14, 17, 20, 24, 30, 36, 48, and 72 hours.**

Response: See our response above. If a showering study is ultimately determined to be necessary, a 24-hour baseline testosterone level in women is recommended, not 12 hours as proposed.

- 6) The proposed non-inferiority criteria will be adequate for approval. To demonstrate noninferiority of the test product compared to the reference product with regard to the pharmacokinetic parameters (AUC_{0-t} and C_{max}), the upper bound of the one-sided 95% CI of the geometric mean test-to-reference ratio must be less than or equal to 1.25.**

Response: See our response above.

- 7) The study design requires subjects to apply the formulations to each upper outer arm and shoulder prior to showering.**

Response: See our response above.

- 8) The definition of a hypogonadal subject is as follows: Subjects must have an average of two morning (between 7:00-10:00 AM) serum testosterone levels (measured on two separate days) < 300 ng/dL.**

Response: See our response above.

- 9) Use of the following Pharmacokinetic parameters:
Testosterone will be calculated based on serum total testosterone concentrations and baseline-corrected serum concentrations.**

For each subject and treatment period, baseline testosterone value will be defined as the mean of the -12, -6, -1, -0.5, and 0 hour samples obtained prior to gel application.

For baseline correction, the mean of the 5 pre-dose concentrations will be attributed to the pre-dose sample. All concentrations, including the pre-dose concentration for each subject and period, will be corrected for the mean of the 5 pre-dose concentrations. If, after correction, any negative concentrations result, they will be set equal to zero.

If the baseline testosterone serum concentration mean for any study period is more than 350 ng/dL (3.50 ng/mL), all of the data from that subject will be excluded from the pharmacokinetic analysis.

Response: See our response above.

10) The overall proposed design and sample size.

Response: See our response above.

II. CMC Related Questions

Question #7

- 1) For purposes of data consistency, Perrigo proposes to perform any required additional clinical studies with the initial development phase formulation noted in Table 1, containing Carbomer 940, and with dehydrated alcohol at a level of (b) (4). Concurrence is requested on the acceptability of this proposal.**

Response: From the CMC perspective, this would be acceptable. See the response to the following question for information on what would be required to bridge the two Perrigo formulations.

From the Nonclinical perspective, your proposal is acceptable.

Additional Discussion: See Question #7 Item 2 for additional discussion.

- 2) Does the agency agree that the “initial Perrigo formulation” as described in Table 1, can be changed to the “revised Perrigo formulation” as described in Table 2, with adequate supporting stability data, either during the NDA review period, or as a post-approval change without the need for additional safety or efficacy studies?**

Response: The proposed change should be done prior to the NDA submission and all supporting data submitted at the time of the initial NDA submission. **It is not acceptable to make this change during the NDA review cycle.** For the formulation containing Carbomer 940, a drug product specification should be added for (b) (4).

From a CMC standpoint, based on the *Guidance for Industry: Nonsterile Semisolid Dosage Forms: Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm0649>)

[79.htm](#)), the change in the amount of alcohol would be designated as a Level 1 change and the change in the grade of Carbomer is designated as a Level 2 change. This would require submission of the following information to link the two formulations:

Additional Discussion: The Sponsor stated that the amount of (b) (4) for the Carbomer 940 formulation would be at NMT (b) (4). They, therefore, will be using Carbomer 980 for commercialization.

The Division further stated that short term clinical studies could be conducted with the formulation containing Carbomer 940, even though the formulation using Carbomer 980 was planned for commercialization. The Division stated that this was acceptable because of the limited use and exposure to the product during planned clinical trials.

- **Stability:**

At a minimum, 6 months accelerated and room temperature stability data for one batch of the revised formulation would need to be submitted. The long term stability studies would need to be continued to support the proposed expiration dating period. The stability studies should be performed in all to-be-marketed container closure systems (both sachets and metered dose container).

Additional Discussion: The Division acknowledged that 6 months accelerated stability data would not be able to be generated on the Carbomer 940 formulation and that six month accelerated stability data would be needed for the formulation containing Carbomer 980. The Sponsor asked whether it was acceptable to provide 3 months accelerated stability data at the time of NDA filing or whether the 6 month data would need to be submitted in the initial NDA. The Division stated that additional stability data will need to be submitted by month four of the review cycle (see response to Question #7 Item 2).

The Division had some questions concerning the actual packaging systems for the Perrigo product. The Sponsor stated that the sachet and the pouch of the metered-dose pump were made of the same material. The Division reminded the Sponsor that extractable/leachable studies will be needed on all product-contact surfaces (pouch and/or pump components). The Division also requested stability data for all packing configurations.

- **In Vitro Release testing:**

Compare the in vitro release rate of the revised formulation with the initial formulation containing Carbomer 940. The median in vitro release rates of the two formulations must be within acceptable limits using the testing procedure described in Section VII of the SUPAC-SS guidance.

From the Nonclinical perspective, if you satisfy CMC requirements, your plan is acceptable.

Additional CMC comments:

1. Include an assay for isostearic acid in drug product specification with a proposed

acceptance criterion, along with method validation data.

Additional Discussion: The Sponsor inquired as to why they would be required to include an assay for isostearic acid, since isostearic acid is a small portion of the formulation and the Sponsor believes that isostearic acid acts [REDACTED] (b) (4).

The Sponsor stated that that they were aware of a study which compared the performance of two compounds containing different percentages of isostearic acid (0.3% and 0.45%). According to the Sponsor, this study showed no difference in the performance of the two different compounds, which they believe supports the contention that isostearic acid [REDACTED] (b) (4).

The Division stated that excipient functionality depends on the presence of other excipients and the entire formulation system. The Division currently believes that isostearic acid is a [REDACTED] (b) (4) and the Sponsor must include enough data for review so that the Division can evaluate the contention that isostearic acid does not act as a [REDACTED] (b) (4) in the product.

The Sponsor stated that they did not wish to include isostearic acid in the specification. The Division stated that during the review cycle the Sponsor will need to provide justification for items that were not included in the specification, as well as all acceptance criteria for items included in the specification.

2. Tighten the limit for individual unspecified impurity [REDACTED] (b) (4) in the drug product stability specification to comply with ICHQ3B. Alternatively, identify individual unspecified impurities above [REDACTED] (b) (4) label claim.
3. Since testosterone is systemically absorbed, include the in vitro release test in drug product specification.

Additional Discussion: The Sponsor requested additional information regarding in vitro test release. The Division informed the Sponsor to develop a plan and submit it for review.

4. Stability studies should be performed in all container closure systems in order to set an expiration dating period. Data on drug product stored in the metered dose pump will be used as supportive data for drug product packaged in sachets. For NDA applications, a minimum of three batches of drug product should be placed on stability in each proposed container closure system and accelerated stability studies should be performed for at least 6 months (as opposed for 3 months for drug products submitted to OGD).

Additional Discussion: The Sponsor inquired why drug product stored in the metered dose pump would be used as supportive data, since the sachet and the pouch in the metered dose bottle are made from the same material. The Division stated that it was unclear from the meeting package what stability data were available, but stability considerations included not only the material of construction but also the amount of drug product packaged in each container and the contact surface area. In addition, interactions of the gel with the pump components would also need to be considered. See the Additional Discussion above concerning extractable/leachable testing on all product-contact surfaces.

III. Regulatory

Question #8

- 1) **Confirm acceptability to file one NDA to include both the pump and unit dose packets. Note that the Androgel® NDA 21-015 includes the 2.5 gr and 5 gr packet and the metered dose pump.**

Response: According to FDA's "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" (bundling policy), found online at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079320.pdf>, different dosage forms should be submitted in separate original applications unless the products are identical in quantitative and qualitative composition (e.g., a sterile liquid in a single dose vial that is intended for use as either an injectable or an inhalation solution). Your proposed packets and metered dose pump are considered different dosage forms according to the Orange Book, Appendix C [i.e., gel (packets) and metered gel (pump)] and are not identical in quantitative and qualitative composition. Therefore, you should submit two NDAs, one for the packets and one for the pump.

If you have any further questions regarding the bundling policy, please contact Michael Jones in CDER's Office of Regulatory Policy at 301-796-3602.

Additional Discussion: The Sponsor stated that their product is qualitatively and quantitatively the same and therefore they believe that only one NDA should be submitted for both the packets and the pump.

The Division stated that the Agency's current thinking is that the proposed dosage forms (packet and pump) are not quantitatively the same. The Division advised the Sponsor to contact Mike Jones at the phone number provided in the Division's original response if they have any further questions.

The Sponsor asked whether two sets of data were needed in the event that two applications were required. The Division responded that only one set of data was needed even if two applications were required.

- 2) **Confirm that an AB Therapeutic Equivalency rating may be granted from the Office of Generic Drugs for a drug product approved under Section 505(b)(2) of the FDCA. Discuss the potential for the proposed product to receive such an equivalence rating.**

Response: An AB Therapeutic Equivalency rating may be granted for a drug product following approval of an application submitted pursuant to section 505(b)(2) of the FDCA if bioequivalency to a pharmaceutical equivalent product has been demonstrated for the same conditions of use.

Additional Discussion: The Sponsor asked which FDA Office grants an AB rating and at what point in the process would this decision be made. The Division stated that the Office of Generic Drugs (OGD) determines whether an AB rating is applicable following approval of a product.

The Sponsor asked whether performing the requested safety studies without a comparison to Androgel as well as whether any differences in the labeling between their product and Androgel would effect the AB rating determination.

The Division stated that any studies that the Sponsor has performed should be described in the labeling. The Division further stated that clarification would be obtained from OGD as to whether any differences in the labeling or a lack of AndroGel control groups in the requested safety studies would affect the AB rating determination.

Post meeting Comment:

The Perrigo T-gel product may be granted an AB rating after approval even if there are minor differences between the Perrigo labeling and the AndroGel labeling as long as the conditions of use are determined to be the same. Whether or not an AndroGel control group is needed in the requested safety studies in order for the Perrigo product to be considered for an AB rating is still under discussion in OGD.

3) Discuss in overview, the acceptability of the draft labeling and medication guide provided in Attachment 2.

Response: The labeling will need to include results of all studies conducted in support of your application, including the bioequivalence and transfer studies.

In regard to the Medication Guide, please refer to our response to Question #8 Item 4.

4) Discuss any special requirements for post-approval safety evaluation or monitoring. It is anticipated that a REMS program will be required at the time of approval similar to that followed by the sponsor of Androgel®.

Response: Post-approval evaluations (studies and clinical trials) that involve safety issues are considered postmarketing requirements (PMRs). Decisions regarding PMRs are made during NDA review. If the review team determines that a PMR is necessary for approval of your NDA, you will be notified during the review cycle.

Decisions regarding REMS are also made during NDA review. If a REMS is required for approval of your NDA, you will receive a REMS notification letter instructing you to submit a proposed REMS. The REMS notification letter will also specify the elements that need to be included in the REMS.

Currently, all approved testosterone gel products are required to have a REMS consisting of the following elements: a Medication Guide and a timetable for assessments.

5) Would this 505(b)(2) NDA potentially qualify to receive exclusivity based on any of the studies required to support the approval?

Response: Your 505(b)(2) application may qualify for three years of exclusivity if new clinical studies, essential for approval, have been conducted by you or for you. Please be advised that FDA does not make exclusivity determinations pursuant to Section 505(c)(3)(E) and (j)(5)(F) of

the Federal Food, Drug and Cosmetic Act, and 21 CFR 314.108, until approval of an NDA. As described in 21 CFR 314.50(j), you should include in your application, a description of the exclusivity to which you believe you are entitled. FDA will consider your assertions regarding exclusivity in the review of the application.

6) The labeling of Androgel® (issued Sept 2009) contains the following boxed warning:

| |
|---|
| <p>WARNING: SECONDARY EXPOSURE TO TESTOSTERONE</p> <ul style="list-style-type: none">• Virilization has been reported in children who were secondarily exposed to testosterone gel (5.2, 6.2).• Children should avoid contact with any unwashed or unclothed application sites in men using testosterone gel (5.2).• Healthcare providers should advise patients to strictly adhere to recommended instructions for use (5.2). |
|---|

Section 8.4 Pediatric Use, contains the statement:

Safety and efficacy of AndroGel in males < 18 years old has not been established. According to the Draft Guidance for Industry, *How to Comply with the Pediatric Research Equity Act*, (Sept 2005)

In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and pediatric populations.

Please comment on whether this product would be subject to the Pediatric Research Equity Act (PREA), and if so, the potential requirement to perform any pediatric studies under PREA, or to obtain a waiver under section 505B(a) of the Act.

Response: If your application does not propose a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, it is not subject to PREA.

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

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

ATTACHMENTS AND HANDOUTS

None

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-107130

GI-1

PERRIGO ISRAEL
PHARMACEUTICA
LS LTD

TESTOSTERONE (b) (4) GEL

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

/s/

MARK S HIRSCH
06/30/2010