

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202763Orig1s000**

**OTHER REVIEW(S)**

## Memorandum

From: Jennifer Mercier  
Chief, project Management Staff  
Division of Reproductive and Urologic Products

To: NDA for Topical Steroid Androgen (NDA # 202763)

Subject: therapeutic equivalence for Teva's Topical Steroid Androgen

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Teva is the applicant of the new drug application (NDA) for Topical Steroid Androgen (NDA # 202763). Teva's NDA was submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Teva's NDA references the listed drug, Androgel (NDA # 022309), an NDA held by Abbott Laboratories. This memorandum is intended to clarify an issue regarding therapeutic equivalence that arose during the review of Teva's product labeling. The Division of Reproductive and Urologic Products (DRUP) initially proposed to add the following Limitations of Use statement in the product labeling:

“Testosterone gel is interchangeable only with approved testosterone gel products that employ the same doses and application instructions.”<sup>1</sup>

A meeting was held on January 27, 2012, to discuss the proposal with representatives from DRUP, the Office of Surveillance and Epidemiology (OSE), the Office of Generic Drugs (OGD), the Orange Book (OB) staff, the Office of Regulatory Policy (ORP), and the Office of Chief Counsel (OCC).

Concerns were expressed from a regulatory perspective regarding whether this text might be read to imply a therapeutic equivalence rating for Teva's product (i.e., that Teva's proposed product is therapeutically equivalent to the reference product, Abbott's Androgel).

DRUP indicated that: (1) a “bioequivalence” study (relative bioavailability study) had been conducted and it was adequate to support the approval of Teva's product; and (2) the statement proposed above is intended to reflect DRUP's judgment that differences between Teva's proposed product and Abbott's product are not clinically significant.

The January 26, 2010, clinical review (p. 79) indicates that “Issues addressed during labeling discussions included, but were not limited to: presentation of the tradename (or lack of tradename), presentation of product strength and dose, presentation of the bioavailability and transfer study data, and reducing the risks of medication errors and interchanging Teva's testosterone gel with testosterone gels other than AndroGel 1%.” (emphasis added). The March 15, 2011, clinical pharmacology review (p. 20) states that “[t]he important limitation of use statement should be added to the Indications and Usage Section of both the Highlights and the Full Prescribing Information of the product label to preclude interchangeable use of Sponsor's T

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<sup>1</sup> The representatives subsequently agreed upon the following text: “Topical testosterone products may have different doses, strengths, or application instructions that may result in different exposure (1, 12.3).”

Gel 1% with any T gel product other than a product with the same dose (i.e., mg) of T and same sites of application, which currently includes only AndroGel® 1%.”

The January 26, 2010, clinical review (p. 10) indicates that “the study design and execution, and the results of this BE study are acceptable, even if the baseline corrected  $C_{max}$  was not completely bioequivalent. The small increase in maximum  $C_{max}$  (126.4% rather than 125%) is not considered to be clinically significant.”

Although the reviews use the term “bioequivalence,” as reflected above, the products would not be considered “completely bioequivalent” -- as that term is used in the context of approvals for abbreviated new drug applications. DRUP’s conclusion -- that differences between the products are not expected to be clinically significant -- is independent of a decision on the therapeutic equivalence rating which has not yet been determined. The OB staff has responsibility for assigning the therapeutic equivalence ratings in consultation with other components, as appropriate.

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/s/  
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JENNIFER L MERCIER

02/14/2012

This document was authored by OCC

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 202763	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: testosterone gel Dosage Form: gel Strengths: 25 and 50 mg		
Applicant: Teva Pharmaceuticals USA		
Date of Receipt: January 14, 2011		
PDUFA Goal Date: February 14, 2012 Original PDUFA: November 14, 2011, Clock extension granted		Action Goal Date (if different): February 14, 2012
Proposed Indication(s): Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES  NO

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

**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

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

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature	Non-Clinical Labeling
Androgel 1%	Efficacy data and some safety data. The Applicant did their own transfer and washing studies which will be reflected in their label.

\*each source of information should be listed on separate rows

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

A multi-center, randomized, single-dose, two way-crossover, pivotal BE study (Study 70343) was conducted in 93 hypogonadal males to compare the Sponsor’s testosterone gel product and the RLD (i.e., AndroGel® 1 %) under fasting condition. The Office of Clinical Pharmacology concludes that the Sponsor has adequately bridged the proposed product to the referenced product.

The Clinical team concurred with Clinical Pharmacology.

**RELIANCE ON PUBLISHED LITERATURE**

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

YES  NO

*If “NO,” proceed to question #5.*

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

YES  NO

*If “NO”, proceed to question #5.*

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

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

YES  NO

**RELIANCE ON LISTED DRUG(S)**

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

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

YES  NO

*If “NO,” proceed to question #10.*

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

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

Androgel 1%	021015	Y

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

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?  
N/A  YES  NO

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

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

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

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

YES  NO

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

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

- b) Approved by the DESI process?

YES  NO

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

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

- c) Described in a monograph?

YES  NO

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

Name of drug(s) described in a monograph:

- d) Discontinued from marketing?

YES  NO

*If "YES", please list which drug(s) and answer question d) i. below.*

*If "NO", proceed to question #9.*

Name of drug(s) discontinued from marketing:

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

YES  NO

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

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

[Redacted] (b) (4)

[Redacted]

[Redacted]

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

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

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

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

(b) (4)

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

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

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

YES  NO

If "NO", proceed to question #12.

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

YES  NO

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

YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

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

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

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

Listed drug/Patent number(s): 6503894 (expires 8/30/20)  
6503894\*PED (expires 3/1/21)

No patents listed  *proceed to question #14*

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

YES  NO

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

Listed drug/Patent number(s):

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

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

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

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

Patent number(s):

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

Patent number(s):

Expiry date(s):

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

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

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

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

Patent number(s):

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

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

(a) Patent number(s): 6503894 and 6503894\*PEDS

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

YES  NO

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

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

YES  NO

On January 3, 2012 the parties entered into a joint stipulation of dismissal regarding the patent.

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

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

Date(s): 09/23/11

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

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

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

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JEANNIE M ROULE  
02/14/2012

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA #/Product Name: 202763

PMR/PMC Description: testosterone gel

PMR/PMC Schedule Milestones: Final Protocol Submission: May 2012  
Study/Trial Completion: August 2012  
Final Report Submission: November 2012  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The amount of testosterone remaining on the hands after washing is very small. However, the amount of testosterone remaining on application site after washing was not specifically studied. Thus, the potential for secondary exposure to testosterone after washing the application sites was not studied for this product. Therefore, an application site washing trial should be conducted as a PMR.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The application site washing trial is needed to support labeling language indicating that washing the application site will limit the potential for interpersonal transfer.

Secondary exposure to testosterone through interpersonal transfer can lead to clitoromegaly, advanced bone age, and penile enlargement in children, and possibly hypertrophy of clitoris, coarsening of the voice, and excessive hair growth in females.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial that will measure the amount of testosterone on the skin before and after washing the application site.
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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JEANNIE M ROULE  
02/14/2012

CHRISTINE P NGUYEN  
02/14/2012

## SEALD Director Sign-Off Memo and Labeling Review

<b>Product Trade Name (Non-Propriety Name)</b>	<b>TESTOSTERONE gel, for topical use, CIII</b>
Application Number/Supplement Number	NDA 202763
Type of Application	Original Submission
Indication	For replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: <ul style="list-style-type: none"> <li>• Primary Hypogonadism (Congenital or Acquired)</li> <li>• Hypogonadotropic Hypogonadism (Congenital or Acquired)</li> </ul>
Applicant	TEVA Pharmaceuticals USA
Office/Division	ODE III/DRUP
Division Project Manager	Jeannie Roule
Submission Date	January 14, 2011
PDUFA Goal Date	February 14, 2012
SEALD Review Date	February 10, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko, RN, MS
SEALD Director	Laurie B. Burke, RhP, MPH

This memo confirms that a Study Endpoints and Labeling Development (SEALD) review of final agreed-upon prescribing information (USPI) determined that there are **NO** outstanding labeling issues in the USPI. This determination follows active engagement throughout the review process between the Division and the SEALD Labeling Team concerning labeling regulations (21 CFR 201.56 and 201.57), labeling guidances, and best labeling practices. The 46-item Selected Requirements for Prescribing Information (SRPI) checklist contains a subset of these policies that apply to all approved USPIs. At this time, no SRPI deficiencies were found (see below for the SRPI checklist).

This memo also confirms that because there are no outstanding SRPI issues in the USPI, the SEALD Director has **NO OBJECTION** to the approval of the USPI at this time.

# SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Only identified deficiencies are checked (no checks means no deficiencies).

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission. **[JMDCComment: Waiver for ½ page requirement has been granted by DRUP.]**
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

## SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

## SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

# SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

## SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Contraindications**
  - For Pregnancy Category X drugs, list pregnancy as a contraindication.
  
- **Adverse Reactions**
  - Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
  - For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
  - For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”
  
- **Use in Specific Populations**
  - Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for “peds only” indications) are required and cannot be omitted.
  
- **Patient Counseling Information**
  - This section is required and cannot be omitted.
  - Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling ... (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
    - “See FDA-approved patient labeling (Medication Guide)”
    - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
    - “See FDA-approved patient labeling (Patient Information)”
    - “See FDA-approved patient labeling (Instructions for Use)”
    - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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JEANNE M DELASKO  
02/10/2012

LAURIE B BURKE  
02/10/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** January 30, 2012

**To:** Jeannie Roule  
Regulatory Project Manager  
Division of Reproductive and Urologic Products (DRUP)

**From:** Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer  
Division of Professional Drug Promotion (DPDP)  
Jina Kwak, PharmD, Regulatory Review Officer  
Division of Direct-to-Consumer Promotion (DDTCP)

**Subject:** OPDP labeling comments for Testosterone gel for topical use CIII  
NDA: 202763

---

### **Background**

This consult is in response to DRUP's February 1, 2011 request for OPDP's review on draft labeling materials for Testosterone gel for topical use CIII (testosterone gel). OPDP has reviewed the following draft labeling materials for testosterone gel:

#### Healthcare Provider Directed:

- Prescribing Information (PI)

#### Consumer Directed:

- Medication Guide (Med guide)

Please note that our comments are based on the substantially complete version of the draft label sent to OPDP on January 20, 2012. Our comments are attached. OPDP appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)  
301.796.3821 or [janice.maniwang@fda.hhs.gov](mailto:janice.maniwang@fda.hhs.gov)
- Jina Kwak (Consumer directed materials)  
301.796.4809 or [jina.kwak@fda.hhs.gov](mailto:jina.kwak@fda.hhs.gov)

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JANICE L MANIWANG  
01/28/2012

JINA KWAK  
01/30/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: **January 20, 2012**

To: Scott Monroe, MD, Director  
**Division of Reproductive and Urologic Products (DRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Supervisor, Patient Labeling Team  
**Division of Medical Policy Programs (DMPP)**

Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling Team  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling (Medication Guide)

Drug Name (established name): testosterone gel

Dosage Form and Route: For Topical Use

Application Type/Number: NDA 202-763

Applicant: **Teva Pharmaceuticals USA**

## 1 INTRODUCTION

On January 14, 2011 the applicant submitted a New Drug Application (NDA) for testosterone gel (NDA 202-763), indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

This review is written in response to a request by the Division of Reproductive and Urologic (DRUP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for testosterone gel.

The REMS is being reviewed by DRISK and will be provided to DRUP under separate cover.

## 2 MATERIAL REVIEWED

- Draft testosterone gel Medication Guide (MG), received on January 14, 2011 and received by DMPP on January 20, 2012.
- Draft testosterone gel Prescribing Information (PI) received January 14, 2011, revised by the Review Division throughout the current review cycle, and received by DMPP on January 20, 2012.
- Approved ANDROGEL (testosterone gel) comparator labeling dated November 30, 2011.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG, the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

16 Pages of Draft  
Labeling have been  
Withheld in Full as b4  
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01/20/2012

MELISSA I HULETT  
01/20/2012

LASHAWN M GRIFFITHS  
01/20/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: November 2, 2011

Reviewer: Jibril Abdus-Samad, PharmD  
Division of Medication Error Prevention and Analysis

Team Leaders: Todd Bridges, RPh  
Division of Medication Error Prevention and Analysis  
Irene Z. Chan, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name(s): Testosterone Gel 1%  
2.5 gm, 5 gm packet

Application Type/Number: NDA 202763

Applicant: Teva Pharmaceuticals USA

OSE RCM #: 2011-233

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates the proposed container labels, carton and insert labeling for Testosterone Gel 1% (NDA 202763) for areas of vulnerability that can lead to medication errors. Teva Pharmaceuticals USA submitted the proposed labels and labeling on January 13, 2011. Additionally, the Applicant submitted updated insert labeling on May 18, 2011.

### 1.1 PRODUCT INFORMATION

Testosterone Gel 1% has a proposed indication for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: Primary Hypogonadism (Congenital or Acquired) and Hypogonadotropic Hypogonadism (Congenital or Acquired). The recommended starting dose of Testosterone Gel 1% is 5 g once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt). Testosterone gel is supplied (b) (4) in individual packets. Testosterone gel is supplied (b) (4) in individual packets. After applying the gel, the application site should be allowed to dry for a few minutes prior to dressing. Hands should be washed with soap and water after testosterone gel has been applied. (b) (4)

Additionally, Testosterone Gel 1% is also supplied in unit-dose foil packets in cartons of 30. Each packet of 2.5 g or 5 g gel contains 25 mg or 50 mg testosterone, respectively.

### 1.2 REGULATORY HISTORY

Testosterone Gel 1% is the subject of a 505(b)2 NDA submission that notes Androgel (Testosterone Gel) 1% (NDA 021015) as the reference listed drug, which was originally approved February 28, 2000. Topical Testosterone gel is currently marketed in the United States in two package configurations (packets and metered-dose pumps), dosage forms (gel and solution), and various strengths. For this application, the Applicant proposes a Testosterone 1% Gel to be marketed as the established name, Testosterone Gel. (b) (4)

Additionally, the Agency revised the strength presentation of topical testosterone products from percentage strength to milligrams of testosterone per packet (b) (4)

Additionally, the strength presentation of milligrams of testosterone per packet (b) (4) allows the health care practitioner to communicate the appropriate dose based on the strength presentation.

## 2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis<sup>1</sup> and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted January 13, 2011 (Appendix A)
- Carton Labeling submitted January 13, 2011 (Appendix B)
- Insert Labeling submitted May 18, 2011 (no image)

Additionally, because topical Testosterone is currently marketed by other manufacturers, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving topical Testosterone. The AERS search conducted on July 13, 2011, using the following search terms: trade names “Androgel, Axiron, Fortesta, Testim”, and verbatim terms “Androg%”, “Axir%”, “Fortes%”, and “Testi%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. The time frame was limited from previous OSE Review 2010-2433 date of the AERS search, January 14, 2011 until July 13, 2011.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error.

Following exclusions we evaluated a total of 12 cases relevant to this review. Some cases contained more than one medication error.

### Secondary Exposure (7)

The seven cases that involved secondary exposure to testosterone are described in Appendix D. There was no evidence in these cases that directly linked the labeling of the product to these medication errors. In fact, in three of the seven cases, patients and caregivers did not read or adhere to the labeling instructions. In two of the remaining four cases, the cause of exposure was undetermined. One case involved secondary exposure after the patient’s daughter slept on same sheets as the patient.

FDA released a press announcement on May 7, 2009, entitled *Testosterone Gel Safety Concerns Prompt FDA to Require Label Changes, Medication Guide*<sup>2</sup>, that addressed accidental exposures, subsequent adverse events, and the newly required labeling changes

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

<sup>2</sup> <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149580.htm>, last accessed September 16, 2011

for the currently approved topical testosterone gel products. The Applicant has submitted insert labeling with the appropriate warnings and a Medication Guide to comply with aforementioned labeling requirements for testosterone gel.

#### Prescribing Error (3)

There were three cases of prescribing errors in which the physician instructed patients to apply testosterone to the chest. One patient experienced his upper chest looking “blue and purple” and nipples were “bigger and yellow in color”, the second patient experienced increased irritability, anxiety and depression, and the last patient experienced pins and needles sensation, redness, feels lethargic, no energy and shoulders feel heavy. There were no further details explaining why the physician recommended the upper chest area as an application site. The chest area is not recommended for application of any topical testosterone products.

#### Wrong Site of Administration (2)

Two cases of patients applying testosterone gel to the wrong administration sites. One patient applied Testim to his shoulders correctly, however sometimes he applied Testim to his stomach. He experienced enlarged breasts due to the therapy and had undergone a surgery for removal. Testim should be applied to the shoulders and upper arms. Only Androgel 1% Gel can be applied to the abdomen.

The second patient applied testosterone gel to his face to treat poison ivy. The stomach and face are not recommended for application of any topical testosterone products and testosterone is not indicated for treatment of poison ivy.

#### Accidental Exposure (1)

One patient experienced eye burns, impaired vision when squeezing contents of an Androgel packet, some of the Androgel flew up into his right eye. The patient was treated in the emergency room.

### **3 DISCUSSION OF DEFICIENCIES**

#### **3.1 STRENGTH PRESENTATION**

The strength presentation for these products should be the milligrams of testosterone per packet. The strength presentation as a percentage does not directly inform practitioners how much drug, testosterone, is contained in each packet. In OSE Review 2010-2433, we identified confusion in the marketplace due to the strength presentation for existing topical testosterone products, which have percentage strength presentations only. Additionally, we identified medication errors due to interchange of topical testosterone products because healthcare professionals believed that 1% strength of one product was equivalent to 1% strength of another topical testosterone product.

### **3.2 ADMINISTRATION SITE**

Topical testosterone products have different applications sites (see Appendix C) and bioavailability. Interchanging topical testosterone products may result in wrong administration site errors. For example, Androgel 5 gram packet can be applied to the shoulder, upper arms, and abdomen; however Testim 5 gram tube can be applied to shoulders and upper arms but not the abdomen. Thus, to prevent wrong administration site errors, the labels and labeling should clearly state that testosterone products are not interchangeable with one another.

### **3.3 DEVELOPMENT OF TOPICAL TESTOSTERONE PRODUCTS**

The development and approval of newer topical testosterone products submitted as NDA 505(b)2 and ANDA may bring additional confusion with interchanging topical testosterone products. Typically, it is common practice for health care practitioners to safely interchange topical drug products of the same active ingredient and percentage strength, mainly because the effects of the topical drug were localized with limited systemic absorption. However, topical testosterone products achieve systemic absorption with the use of different penetration enhancers, application sites, and resulting in different bioavailability profiles. This change in technology and product design of a topical drug product requires a change in common practice habits for health care practitioners.

We considered different methods for preventing inappropriate interchange of topical testosterone products. Different proprietary names for topical testosterone products provides some distinction between these products, however the proprietary name does not inform the user of the differences between these products and the lack of interchangeability. Therefore, labeling topical testosterone products with the revised strength presentation (milligrams of testosterone per packet or per actuation) and highlighting these products are not interchangeable should minimize the risk of inappropriate product exchange. Additionally, the topical testosterone products must comply with the required Medication Guide to provide further instructions for patients and caregivers.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

The proposed labels and labeling introduce vulnerability that can lead to medication errors because the strength presentation and lack of statement concerning non-interchangeability increases the likelihood of inappropriate product substitution. Additionally, the presentation of other information on the labels and labeling requires improvement. We provide recommendations for the professional labeling in section 4.1, *Comments to the Division*. Section 4.2, *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

#### 4.1 COMMENTS TO THE DIVISION

##### Insert Labeling

###### A. General Comments

1. [REDACTED] (b) (4)
2. Replace the [REDACTED] (b) (4) with the revised strength presentation of 25 mg per packet and 50 mg per packet.

###### B. Dosage and Administration, Highlights of Prescribing Information and Full Prescribing Information – section 2

1. Add the following statement to address appropriate washing of hands and application site to prevent secondary exposure.

Patients should wash hands immediately with soap and water after applying Testosterone Gel and cover the application site with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated.

2. Dosage and Administration, Highlights of Prescribing Information and Full Prescribing Information - Section 2

Add the following statement:

Testosterone Gel is not interchangeable with other topical testosterone products

3. Revise dosage instructions for Testosterone Gel to read in terms of milligrams of testosterone [REDACTED] (b) (4)

###### C. Dosage Forms and Strengths, Highlights of Prescribing Information and Full Prescribing Information - Section 3

1. Revise to read as follows:

Testosterone Gel for topical use only, is supplied in packets.

25 mg of testosterone per packet

50 mg of testosterone per packet

###### D. How Supplied/Storage and Handling - Section 16

Revise to read as follows:

Testosterone Gel is available in unit-dose packets in cartons of 30.

25 mg - each packet contains 25 mg of testosterone in 2.5 g of gel

50 mg - each packet contains 50 mg of testosterone in 5 g of gel

## 4.2 COMMENTS TO THE APPLICANT

### A. Container Labels and Carton Labeling

1. Revise the presentation of the established name from all UPPERCASE letters to Title Case to improve readability and revise the presentation of the strength, [REDACTED] (b) (4). Thus the presentation of the established name and strength to appear as follows:

Testosterone Gel  
xx mg of testosterone per packet\*

\*Each packet contains x g of gel

2. Add a statement to the principal display panel that Testosterone Gel is not interchangeable with other topical testosterone products. Refer to package insert for dosing instructions.
3. Decrease the prominence of the schedule III symbol (CIII) by decreasing the font size and changing the font color. The CIII symbol has more prominence than the strength because of the larger font size and similar color.

### B. Container Label

1. Revise the statement, [REDACTED] (b) (4)

Discard used packets in household trash

2. Add the statement, *For Topical Use Only*, to the principal display panel.
3. Add a bar code to be in compliance with 21 CFR 201.25.

### C. Carton Labeling

1. Relocate the statement, *For Topical Use Only*, [REDACTED] (b) (4) to the principal display panel.
2. Revise the Medication Guide Statement to read:

*Dispense the enclosed Medication Guide to each patient.*

**5 REFERENCES:**

Toombs, L. Shenee'. OSE Review 2010-2433: DMEPA Label and Labeling Review for Androgel 1.62%, March 2, 2011

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**Appendix C:** Topical Testosterone product characteristics

Product	Strength	Dose	How Supplied	Application Site
Testosterone Gel	1%  25 mg, 50 mg per packet**	5 g to 10 g gel daily  25 mg to 100 mg testosterone daily**	2.5 g, 5 g packets  25 mg, 50 mg per packet**	shoulders, upper arms, abdomen
Androgel (Testosterone) Gel	1%	5 g to 10 g daily	75 g Multi-dose Pump (1.25 g per actuation) 2.5 g, 5g packet	shoulders, upper arms, abdomen
Androgel 1.62%, (Testosterone) Gel	20.25 mg Testosterone per actuation	20.25 mg to 81 mg (1 to 4 pumps) daily	metered-dose pump (20.25 mg testosterone per actuation)	shoulders, upper arms
Testim (Testosterone Gel)	1% (50 mg)	5 g gel containing 50 mg testosterone	5 g tube	shoulders, upper arms
Fortesta (Testosterone) Gel	10 mg testosterone per actuation	10 mg to 70 mg testosterone (1 to 7 pump actuations)	metered-dose pump (10 mg testosterone per actuation)	front and inner thighs
Axiron (Testosterone) solution	30 mg Testosterone per actuation	30 mg to 120 mg testosterone (1 to 4 pump actuations)	metered-dose pump (30 mg testosterone per actuation)	axilla

\*\* DMEPA's proposed strength presentation

**Appendix D:** Secondary Exposure cases

<b>ISR number</b>	<b>Date of Report</b>	<b>Drug</b>	<b>Description</b>	<b>Outcome</b>
7508177-6	5/13/2011	Testim	Per physician instructions, patient applied Testim to shoulders upper arms and upper chest area. Sometimes wife applied Testim to help patient. Wife applied Testim, wife did not read package insert.	No adverse events to wife.
7516719-x	5/09/2011	Testim	Mother smelled the “nice floral smell from product” was also on her 8 year old daughter’s arms. Father covered areas with clothing.	No reported adverse reactions to 8 year old daughter.
7516718-8	5/09/2011	Testim	5 year old daughter shows signs exposure to testosterone such as . However other daughter does not show signs. Patient thinks exposure was through bathtub.	5 year old daughter with enlarged clitoris, body hair, underarm odor, acne, genitalia hair growth, increased libido, self-stimulation.
7516707-3	5/09/2011	Testim	Patient noticed his 14 year old daughter is growing sideburns. Daughter sleeps on father’s bed sheets occasionally.	14 year old daughter facial hair growth.
7473331-9	4/25/2011	Testim	Patient did not cover application sites with clothing. Girlfriend exposed to testosterone. Patient did not cover application site with clothing.	More aggressive, headache, nausea, facial acne, missed menstrual period.
7403662-x	3/25/2011	Testim	50 year patient’s wife reports a miscarriage, however husband is very careful regarding application to upper arms and shoulders. Wife felt she was in contact with Testim during intercourse.	Miscarriage.
7267519-x	1/18/2011	Testim	Pregnant daughter accidentally touched the application site of her 55 year old father 4 hours after application. Application site not covered with clothing.	Placenta previa, child born 37 weeks gestational age.

**Appendix D:** ISR numbers of all cases

7508177    7516719    7473331    7327766    7478995  
7302410    7516718    7403662    7455966  
7516097    7516707    7267519    7600504

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TODD D BRIDGES  
11/04/2011

CAROL A HOLQUIST  
11/04/2011



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** September 14, 2011

**To:** Scott Monroe, M.D., Director  
Division of Reproductive and Urologic Products

**Through:** Michael Klein, Ph.D., Director  
Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff

**From:** James M. Tolliver, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** NDA 202-763 Testosterone Gel, 1%  
**Indication:** Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: Primary hypogonadism (congenital or acquired); Hypogonadotropic hypogonadism (congenital or acquired).  
**Dosages:** Transdermal Gel, 5 mg, (b)(4) mg strengths  
**Sponsor:** Teva Pharmaceuticals

**Materials reviewed:** Proposed Labeling for Testosterone Gel 1% submitted under NDA 202-763

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**I. Summary**

A. Background

This memorandum is in response to a consult request dated January 28, 2011, from the Division of Reproductive and Urologic Products (DRUP) for CSS to review the "9. Drug Abuse and Dependence" section of the proposed label for Testosterone Gel 1% under NDA 202-763,

submitted by Teva Pharmaceuticals. CSS has reviewed the labeling and provides the comments and recommendations listed below.

B. Conclusions:

1. The language under section "9. DRUG ABUSE AND DEPENDENCE" should be modified to be consistent with the recently revised abuse section for [REDACTED] (b) (4), as CSS previously proposed. This would include modifying section "9.1 Controlled Substance" and adding sections "9.2 Abuse" and "9.3 Dependence."

C. Recommendations:

1. The proposed language under section "9 DRUG ABUSE AND DEPENDENCE" should be modified (deletions in strikeout and additions in italic) as follows:

**9.1 Controlled Substance**

Testosterone Gel 1% contains testosterone, a Schedule III controlled substance ~~as defined by the Anabolic Steroids Control Act in the Controlled Substances Act.~~

~~Oral ingestion of Testosterone Gel, 1% will not result in clinically significant serum testosterone concentrations due to extensive first pass metabolism.~~

**9.2 Abuse**

*Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.*

**9.3 Dependence**

*Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:*

- *Taking more drug than intended*
- *Continued drug use despite medical and social problems*
- *Significant time spent in obtaining adequate amounts of drug*
- *Desire for anabolic steroids when supplies of drug are interrupted*
- *Difficulty in discontinuing use of the drug despite desires and attempts to do so*
- *Experience of withdrawal syndrome upon discontinuation of anabolic steroid use*

## II. Discussion

A. Chemistry

1. Product information

Testosterone Gel 1% is a transdermal testosterone formulation indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. It is a clear, colorless hydroalcoholic gel containing 1% testosterone. Inactive ingredients include carbomer homopolymer type C, dehydrated alcohol 67%, isopropyl palmitate, purified water, and sodium hydroxide. Topical administration of Testosterone Gel 1% 5 g. (b) (4) contains 50 mg, (b) (4) testosterone, respectively. The product would be available as: (b) (4) individual 2.5 g testosterone packets or 5 g testosterone packets. The recommended starting dose is 5 grams for adult males, applied topically once daily to the shoulders, upper arms, or abdomen. If with the starting dose, the serum testosterone level is below the normal range, the dose may be adjusted from 5 grams to 7.5 grams and from 7.5 grams to 10 grams.

#### B. Integrated assessment

CSS reviewed the proposed language under Section 9 DRUG ABUSE AND DEPENDENCE of the label for Testosterone Gel 1%. The language proposed by the Sponsor is as follows:

##### **9.1 Controlled Substance**

Testosterone Gel 1% contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act.

Oral ingestion of Testosterone Gel, 1% will not result in clinically significant serum testosterone concentrations due to extensive first-pass metabolism.

The Anabolic Steroid Control Act of 1990 amended the Controlled Substances Act (CSA) to place testosterone in Schedule III (21 U.S.C. 802(41)(A)(xlvii)). As such, Testosterone Gel 1%, which contains testosterone, is a product in Schedule III of the CSA. The language of section "9.1 Controlled Substance" should be changed to reflect this. (b) (4)

Sections "9.2 Abuse" and "9.3 Dependence" are currently missing from the labeling proposed by the Sponsor. (b) (4)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAMES M TOLLIVER  
09/14/2011

SILVIA N CALDERON  
09/16/2011

MICHAEL KLEIN  
09/16/2011

MEMORANDUM

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

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DATE: July 29, 2011

TO: Scott E. Monroe, M.D.  
Director, Division of Reproductive and Urologic  
Products (DRUP), Office of Drug Evaluation III

Edward D. Bashaw, Pharm.D.  
Director, Division of Clinical Pharmacology III,  
Office of Clinical Pharmacology

FROM: Sripal R. Mada, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.  
Acting Team Leader - Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202-763, Testosterone Gel,  
1%, from Teva Pharmaceuticals, USA

At the request of the Division of Reproductive and Urologic Products (DRUP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of clinical and analytical portions of the following study:

**Study: 70343**: "Randomized, Open-Label, Two-Way Crossover, Bioequivalence Study of Testosterone 1% Topical Gel Formulation and Androgel (Reference) Following a 100 mg Dose in Hypogonadal Male Volunteers"

DBGC sent the inspection summary memo for the above audit to DRUP on July 1, 2011. DBGC received (b) (4) (b) (4) response to the Form FDA-483 (see **Attachment**) on July 11, 2011 after the DBGC inspection summary memo was forwarded to DRUP.

DBGC recommended the following in the July 1, 2011 Inspection Summary Memo:

- Runs # 58PQM and 71PQM containing plasma sample data from subjects # 60, 61, 62, 92, 93 and 94, and Run # 74PQM containing plasma sample data after repeat analysis is not assured. DBGC recommends that data from subjects # 60, 61, 62, 92, 93 and 94 and the re-assayed samples in Run #74PQM be excluded from final BE evaluation (see **Form FDA-483, item 1**).
- (b)(4) should re-process all chromatograms for both validation and subject samples using integration parameters established in the method SOP (see **Form FDA-483, item 3**).
- The data in the clinical portion are acceptable for your review.

Our evaluation of the response to Form FDA-483 observations follows:

**Item 1: Failure to train properly a technician who was responsible for sample processing in the bioanalytical laboratory. Specifically, repeated long-term freezer stability studies for testosterone failed during the partial validation-6 (5 of 6 runs containing long-term freezer stability data was failed). An investigation of the failures concluded that the technician who processed samples in the failed runs made an error during sample handling. Further, training records ('spiking check' conducted after the investigation) indicated that technician who handled the failed runs could not handle the pipettes properly. A total of 11 validation runs (run # 01SVT, 02SVT, 06SVT, 07SVT, 08SVT, 09SVT, 10SVT, 01FTY, 02FTY, 03FTY and 04FTY), and 4 production runs (run # 58PQM, 67PQM, 71PQM and 74PQM) were affected by this technician's practice.**

In their response to Form FDA-483, (b)(4) said the pipetting technique used by the technician (technician-1 in response to Form FDA-483) was different from the standardized technique used in (b)(4), and this technique can result in a bias when quality control (QC) results from this technician are compared to those from another technician. Also, (b)(4) said that technician was re-trained on November 19, 2008 followed by an evaluation run (spiking test). However, (b)(4) did not provide any document in support of the re-training of the technician.

Regarding (b)(4) explanation that the original technique of technician would not introduce bias if she prepared both the standard curve and QCs in a run, this is an assumption and the

evidence (i.e., passing QC results generated in runs processed by technician) to confirm this is not provided in the written response. Furthermore, passing QC results do not assure that no bias was introduced into the results of subject samples.

Regarding the additional evidence provided in Table-A on pages 3-4 of the written response, it is unclear under what circumstances the re-analyses were conducted as no source documentation was provided.

Furthermore, as the subject samples listed in Table-A were not QC samples (i.e., samples with known concentration), it is not possible to evaluate with certainty if the results from these samples were biased, especially in 8 of the 26 samples where the same technician conducted both the original sample analysis and re-analysis. Overall, DBGC is of the opinion that (b) (4) written response is not adequate. DBGC recommends that data from Runs # 58PQM and 71PQM containing plasma samples from subjects # 60, 61, 62, 92, 93 and 94, and data from Run # 74PQM containing plasma sample after repeat analysis can not be assured.

**Item 3: Integration parameters from most chromatographic runs in the validation and production were modified and were different from the method SOP. These changed integration parameters were not applied to all samples in the respective runs.**

In their response to Form FDA-483, (b) (4) re-integrated all chromatograms generated during method validation and production runs using integration parameters from the method SOP. In addition, (b) (4) upon sponsor's request conducted bioequivalence assessment using re-integrated concentration datasets.

**Conclusion:**

Following our evaluation of (b) (4) response to the Form FDA-483, DBGC's recommendation to DRUP in our July 1, 2011, EIR review remained unchanged.

DBGC recommends that data from subjects # 60, 61, 62, 92, 93 and 94 and the re-assayed samples in Run #74PQM be excluded from final BE evaluation with the newly re-integrated data.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.  
Bioequivalence Branch, DBGCC, OSI

**Final Classifications:**

**Analytical:**

**VAI** - [REDACTED] (b) (4)

The current FEI # for [REDACTED] (b) (4) is not available

**Clinical:**

**VAI** - [REDACTED] (b) (4)

The current FEI # for [REDACTED] (b) (4) is not available

**VAI** - [REDACTED] (b) (4)

The current FEI # for [REDACTED] (b) (4) is not available

**NAI** - [REDACTED] (b) (4)

The current FEI # for [REDACTED] (b) (4) is not available

cc:

OSI/Ball

OSI/DBGCC/Salewski/Dejernet

OSI/DBGCC/BB/Mada/Yau/Haidar

OCP/DCP3/Bashaw/Kim/Yu

ODE3/DRUP/Monroe/Roule

HFR-SW350/Kuchenthal

Draft: SRM 07/28/2011

Edit: MKY 07/29/2011

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/s/  
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SRIPAL R MADA  
07/29/2011

MARTIN K YAU  
07/30/2011

MEMORANDUM

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

---

DATE: July 01, 2011

TO: Scott E. Monroe, M.D.  
Director, Division of Reproductive and Urologic  
Products (DRUP), Office of Drug Evaluation III

Edward D. Bashaw, Pharm.D.  
Director, Division of Clinical Pharmacology III,  
Office of Clinical Pharmacology

FROM: Sripal R. Mada, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.  
Acting Team Leader - Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202-763, Testosterone Gel,  
1%, from Teva Pharmaceuticals, USA

At the request of the Division of Reproductive and Urologic  
Products (DRUP), the Division of Bioequivalence and GLP  
Compliance (DBGC) conducted inspections of clinical and  
analytical portions of the following study:

**Study: 70343**: "Randomized, Open-Label, Two-Way Crossover,  
Bioequivalence Study of Testosterone 1% Topical Gel  
Formulation and Androgel (Reference) Following a  
100 mg Dose in Hypogonadal Male Volunteers"

**CLINICAL AND ANALYTICAL SITE INSPECTIONS:**

The clinical portions of Study 70343 were conducted at (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

Before the inspections, DBGC was informed by (b)(4) that the clinical site located in (b)(4) was already closed on September 17, 2010. The clinical site located in (b)(4) (b)(4) is scheduled to be closed by June 30, 2011. Thus, all the clinical study source documents at the (b)(4)

(b)(4) The analytical portion of study 70343 was conducted at (b)(4). Due to the closing of the clinical sites, all the inspections (i.e, both clinical and analytical portions of study 70343) were conducted at (b)(4)

Following the inspections (June 6-21, 2011), Form FDA-483 was issued (**Attachment 1**). Our evaluation of the Form FDA-483 observations follows:

**1. Failure to train properly a technician who was responsible for sample processing in the bioanalytical laboratory.** Specifically, repeated long-term freezer stability studies for testosterone failed during the partial validation-6 (5 of 6 runs containing long-term freezer stability data was failed). An investigation of the failures concluded that the technician who processed samples in the failed runs made an error during sample handling. Further, training records ('spiking check' conducted after the investigation) indicated that technician who handled the failed runs could not handle the pipettes properly. A total of 11 validation runs (run # 01SVT, 02SVT, 06SVT, 07SVT, 08SVT, 09SVT, 10SVT, 01FTY, 02FTY, 03FTY and 04FTY), and 4 production runs (run # 58PQM, 67PQM, 71PQM and 74PQM) were affected by this technician's practice.

During method validation, long-term frozen stability studies for testosterone failed in 5 of 6 runs. An investigation of the failed runs by (b)(4) found that (1) the same analyst was involved in all the failed runs, and (2) this analyst failed to handle the pipettes properly, thus causing the validation runs to fail. During the inspection, (b)(4) said this analyst was given further training in pipetting thereafter, but no training records were available for audit (see **Attachment 2**). Based on this finding, the precision and accuracy of data generated by this analyst cannot be assured.

A total of 11 validation runs (run # 01SVT, 02SVT, 06SVT, 07SVT, 08SVT, 09SVT, 10SVT, 01FTY, 02FTY, 03FTY and 04FTY) and 4 production runs (run # 58PQM, 67PQM, 71PQM and 74PQM) were conducted by this analyst.

DBGC recommends that data from these validation and production runs be not accepted for review (see **Attachment 3** to identify samples analyzed in these runs). However, please note that validation runs conducted by this analyst included mostly intra-run, short term, and long-term stability data, which were evaluated by other analysts in other validation runs. Regarding the production runs, Run # 67PQM was rejected as both replicates at LQC samples were out of the acceptance range. Runs # 58PQM and 71PQM utilized subject plasma sample for subjects # 60, 61, 62, 92, 93 and 94. Run # 74PQM utilized subject plasma sample analysis for repeats (see Attachment 3 for more details).

DBGC recommends that Runs # 58PQM and 71PQM containing plasma sample data from subjects # 60, 61, 62, 92, 93 and 94, and Run # 74PQM containing plasma sample data after repeat analysis is not assured. DBGC recommends that data from subjects # 60, 61, 62, 92, 93 and 94 and the re-assayed samples in Run #74PQM be excluded from the final BE evaluation.

**2. Failure to provide adequate security for electronic source records, Specifically,**

**(a) A common access procedure is used to access the computer workstation and the 'Analyst' software used for analytical data integration.**

**(b) Technical writers who do not work in the bioanalytical laboratory were given inappropriate permission to edit chromatograms in 'Analyst' software.**

DBGC explained to (b)(4) that these practices were not recommended during the conduct of any bioequivalence studies. This objectionable practice is related to DBGC's concern discussed below under Form FDA-483, Item 3, regarding modifying chromatographic integration parameters. Currently, (b)(4) has updated their operating procedures to restrict the common computer access procedure and not granting permission to technical writers edit chromatograms in future studies.

**3. Integration parameters from most chromatographic runs in the validation and production were modified and were different from the method SOP. These changed integration parameters were not applied to all samples in the respective runs.**

Integration parameters for many chromatograms in validation and analytical runs were modified. The reasons for modifying the integration parameters were neither documented nor captured in the audit trail. To assure the data provided in the study report were unbiased, (b)(4)

should re-process all chromatograms generated during method validation and production runs using integration parameters from the method SOP. When modifications are necessary, justification for the changes in integration parameters should be documented and/or captured in the audit trial.

**4. Failure to use appropriate informed consent forms (ICF) during study # 70343. Specifically, Testosterone ICF dated June 12, 2008 was used in place of ICF dated December 6, 2008 for subjects # 1, 3, 5, 6, 19, 28, 41, 71 and 73.**

This observation applies to (b)(4) clinical sites. (b)(4) was informed not to make these errors in future studies. This observation should not have effect on testosterone study data.

**Conclusions:**

Following the inspection, DBGCC recommends the following:

- Runs # 58PQM and 71PQM containing plasma sample data from subjects # 60, 61, 62, 92, 93 and 94, and Run # 74PQM containing plasma sample data after repeat analysis is not assured. DBGCC recommends that data from subjects # 60, 61, 62, 92, 93 and 94 and the re-assayed samples in Run #74PQM be excluded from final BE evaluation (see **Form FDA-483, item 1**).
- (b)(4) should re-process all chromatograms for both validation and subject samples using integration parameters established in the method SOP (see **Form FDA-483, item 3**).
- The data in the clinical portion are acceptable for your review.

Please note that DBGCC has not yet received the written response to the Form FDA-483 from (b)(4). DBGCC will update DRUP if our review of the response upon receipt resulted in a change of our recommendation.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.  
Bioequivalence Branch, DBGCC, OSI

**Final Classifications:**

**Analytical:**

**VAI** - [REDACTED] (b) (4)

The current FEI # for [REDACTED] (b) (4) is not available

In light of the significant procedural deficiency for training of analysts and computer security issues DBGC is considering sending an untitled letter to [REDACTED] (b) (4)

**Clinical:**

**VAI** - [REDACTED] (b) (4)

The current FEI # for [REDACTED] (b) (4) is not available

**VAI** - [REDACTED] (b) (4)

The current FEI # for [REDACTED] (b) (4) is not available

**NAI** - [REDACTED] (b) (4)

The current FEI # for [REDACTED] (b) (4) is not available

cc:

OSI/Ball

OSI/DBGC/Salewski/Dejernet

OSI/DBGC/BB/Mada/Yau/Haidar

OCP/DCP3/Bashaw/Kim/Yu

ODE3/DRUP/Monroe/Roule

HFR-SW350/Kuchenthal

Draft: SRM 06/30/2011

Edit: MKY 07/01/2011

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/s/  
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SRIPAL R MADA  
07/01/2011

MARTIN K YAU  
07/01/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 202763 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: None Established/Proper Name: testosterone gel Dosage Form: gel Strengths: 1%		
Applicant: Teva Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: January 13, 2011 Date of Receipt: January 14, 2011 Date clock started after UN:		
PDUFA Goal Date: November 14, 2011		Action Goal Date (if different):
Filing Date: March 15, 2011		Date of Filing Meeting: February 24, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i></b>		
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s):				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the Electronic Orange Book at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>NDA 21463</td> <td>Fortesta</td> <td>NP</td> <td>Dec 29, 2013</td> </tr> <tr> <td>NDA 22504</td> <td>Axiron</td> <td>NP</td> <td>Nov 23, 2013</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	NDA 21463	Fortesta	NP	Dec 29, 2013	NDA 22504	Axiron	NP	Nov 23, 2013					<p>X</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
NDA 21463	Fortesta	NP	Dec 29, 2013																	
NDA 22504	Axiron	NP	Nov 23, 2013																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i> <i>February 1, 2011</i></p>	X			

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?				
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>		X		Submitted but not needed
<b>BPCA (NDAs/NDA efficacy supplements only):</b> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>	X			
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>		X		No meeting held

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>		X		No meeting held
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 24, 2011

BLA/NDA/Supp #: NDA 202763

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: testosterone gel 1%

DOSAGE FORM/STRENGTH: gel

APPLICANT: Teva Pharmaceuticals

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone

**BACKGROUND:**

Teva Pharmaceuticals submitted an ANDA (b) (4) on December 29, 2008, and received a Refuse to Receive Letter on April 7, 2009. The basis for the letter was that Teva's formulation contained different ingredients than those contained in the RLD. (b) (4)

[Redacted text block]

Please note that there were no IND submitted previous to this NDA application and no pre-NDA meetings were held.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeannie Roule	Y
	CPMS/TL:	Jennifer Mercier	N
Cross-Discipline Team Leader (CDTL)	Mark Hirsch		Y
Clinical	Reviewer:	Guodong Fang	Y

	TL:	Mark Hirsch	
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Chongwoo Yu	Y
	TL:	Myong-Jin Kim	Y
Biostatistics	Reviewer:	Jia Guo	Y
	TL:	Mahboob Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jeffrey Bray	Y
	TL:	Lynnda Reid	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Zhing Fang Ge	Y
	TL:	Donna Christner	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		

OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	Y
	TL:	Carlos Mena Grillasca	N
OSE/DRISK (REMS)	Reviewer:	Shawna Hutchins	N
	TL:	Melissa Hulett	N
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Sripal Mada	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	James Tolliver	N
	TL:	Michael Klein	N
Other reviewers	Robert Dean (DDMAC observer)		Y
Other attendees	Samantha Burgess (PM)		Y

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	
<p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no</b>, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIostatistics</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p><b>Comments:</b></p>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority: George Benson</b></p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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

JEANNIE M ROULE  
05/04/2011

JENNIFER L MERCIER  
05/06/2011

## DSI CONSULT: Request for Inspections – Clin Pharm

**Date:** February 22, 2011

**To:** Dr. Sam Haidar, Branch Chief  
Division of Scientific Investigations  
Office of Compliance, CDER  
WO Bldg 51, Room 5210  
FDA

**Through:** Chongwoo Yu, Ph.D.  
Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3 (DCP3),  
Office of Clinical Pharmacology (OCP)

Myong Jin Kim, Pharm.D.  
Clinical Pharmacology Team Leader, DCP3, OCP

Dennis Bashaw, Pharm.D.  
Director of DCP3, OCP

**From:** Jeannie Roule, Regulatory Project Manager, DRUP

**Subject:** **Request for Clinical Pharmacology (pivotal bioequivalence [BE] study clinical and bioanalytical) Sites Inspection**

### **I. General Information**

Application#: NDA 202763

Teva Pharmaceuticals USA  
Attention: Robert S. Vincent  
400 Chestnut Ridge Road  
Woodcliff Lake, NJ 07677

Phone: 1-201-930-3610  
Fax: 1-201-489-1403  
Email: rob.vincent@tevausa.com

Drug Proprietary Name: Testosterone (T) gel, 1%  
NME or Original BLA: No  
Review Priority: Standard

Study Population includes < 17 years of age: No  
Is this for Pediatric Exclusivity: No

Proposed New Indication(s): Treatment of hypogonadism

PDUFA:  
Action Goal Date: November 14, 2011  
Inspection Summary Goal Date: July 29, 2011

**II. Protocol/Site Identification**

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID <sup>a</sup>	Number of Subjects	Indication
(b) (4)	70343	93 (90 completed)	Treatment of hypogonadism
(b) (4)	70343	93 (90 completed)	Treatment of hypogonadism

**III. Site Selection/Rationale**

The selected clinical and bioanalytical sites are the sites that the pivotal BE study was conducted. Therefore, DSI inspection is warranted.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply): NA

- \_\_\_\_\_ There are insufficient domestic data
- \_\_\_\_\_ Only foreign data are submitted to support an application
- \_\_\_\_\_ Domestic and foreign data show conflicting results pertinent to decision-making
- \_\_\_\_\_ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- \_\_\_\_\_ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**IV. Tables of Specific Data to be Verified (if applicable)**

*If you have specific data that needs to be verified, please provide a table for data verification, if applicable.*

Should you require any additional information, please contact Jeannie Roule at 301-796-3993.

Concurrence: (as needed)

\_\_\_\_\_ Medical Team Leader  
\_\_\_\_\_ Medical Reviewer  
\_\_\_\_\_ Division Director (for foreign inspection requests or requests for 5 or more sites only)

**Additional Information:**

Teva Pharmaceuticals USA submitted New Drug Application (NDA) 202763 for T gel, 1% in accord with Section 505 (b)(2) on January 13, 2011 to seek an approval for the treatment of hypogonadism.

T gel, a clear colorless gel, is a T replacement therapy formulation for transdermal application has been developed with the aim of achieving and establishing Pharmaceutical equivalence with the Innovator's product namely, Androgel® (1 % w/w) marketed by Solvay Pharmaceuticals Inc. T gel was manufactured, packaged, and tested at Cipla Ltd., India, a contract manufacturer for the Sponsor.

The active ingredients, route of administration, dosage form, and strength for the proposed drug product are the same as those of the Reference Listed Drug (RLD). The only difference between Sponsor's formulation and that of the RLD is the substitution of isopropyl myristate (RLD) with isopropyl palmitate (Sponsor).

## Appendix

Clinical Study subject to DSI Consult Request:

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Bioequivalence	70343	Determine the bioequivalence between a new (generic) drug product and a marketed reference product under fasting conditions	Multiple-centre, Bioequivalence, Open-label Randomized, 2-way crossover study.	Testosterone 1% Topical Gel	93 (90 Completed)	Hypogonadal Adult Male Subject	Single-Dose	Completed

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHONGWOO YU  
02/24/2011

EDWARD D BASHAW  
03/07/2011