

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205488Orig1s000**

**OTHER REVIEW(S)**

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**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Review:** May 28, 2014

**Requesting Office or Division:** Division of Bone, Reproductive and Urologic Products (DBRUP)

**Application Type and Number:** NDA 205488

**Product Name and Strength:** Natesto (Testosterone) Nasal Gel  
5.5 mg of Testosterone per actuation

**Product Type:** Single Ingredient Product

**Rx or OTC:** Prescription (Rx)

**Applicant/Sponsor Name:** Trimel BioPharma SRL

**Submission Date:** May 28, 2014

**OSE RCM #:** 2013-1239-1

**DMEPA Primary Reviewer:** Denise V. Baugh, PharmD, MBA

**DMEPA Team Leader:** Lisa V. Khosla, PharmD, MHA

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## 1 REASON FOR REVIEW

The Division of Bone, Reproductive and Urologic Products has requested DMEPA assess the container label, carton labeling and insert labeling submitted May 28, 2014 for Natesto (testosterone) Nasal Gel.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Container Label, Carton and Insert Labeling	G

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the recently proposed container label, carton and insert labeling to assess if our recommendations were implemented per our previous review (OSE Review# 2013-1239 dated September 27, 2013 for NDA 205488) and per additional recommendations we made (via e-mail) on May 2, 2014 (for the container label and carton labeling) and on May 13, 2014 (for the insert labeling).

## 4 CONCLUSION & RECOMMENDATIONS

All of the recommendations pertaining to the container label and carton labeling made in our previous review were implemented. Additionally, concerns regarding the efficacy of this product in the event the user has an upper respiratory infection and/or seasonal allergy were discussed with the Division. The bio-adherence of the product to the nasal wall was felt to be such that these conditions would have minimal impact on the efficacy of the product and therefore, DMEPA's concerns were minimized.

However, we have additional comments regarding the instructions in the insert labeling (Section 2, Dosage and Administration of the insert labeling) to promote the safe use of this product. See our comments in Section 4.1.

If you have further questions or need clarifications, please contact Shawnetta Jackson, OSE Regulatory Project Manager, at (301) 796-4952.

#### **4.1 RECOMMENDATIONS TO THE DIVISION**

DMEPA provides the following comments to the Division for consideration prior to approval of this NDA:

##### **A. Insert Labeling**

- a. Revise the statement “Repeat Steps 3 through 6 for the right nostril” to read “Repeat Bullets 3 through 6 for the right nostril using the left index finger”.
- b. Following the statement, “The dispenser should be replaced when . . .” add a statement to assist the user in finding the arrow at the top of the inside label. An example of such a statement would be “The inside label can be found by unwrapping the outer flap from around the container.”
- c. Following the statement, “The dispenser should be replaced when . . .” add a diagram which points to the outer flap. You may consider using the same illustration of the dispenser as that provided in the Patient Package Insert (PPI) section.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Natesto (testosterone) that TrimeI BioPharma SRL submitted on May 28, 2014.

<b>Table 2. Relevant Product Information for Natesto</b>	
<b>Active Ingredient</b>	testosterone
<b>Indication</b>	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone such as congenital or acquired primary hypogonadism and congenital or acquired hypogonadotropic hypogonadism
<b>Route of Administration</b>	nasal
<b>Dosage Form</b>	gel
<b>Strength</b>	5.5 mg per actuation
<b>Dose and Frequency</b>	11 mg of testosterone (2 pump actuations, one per nostril), applied nasally three times daily***.
<b>How Supplied</b>	Metered dose pump containing 11 grams of gel dispensed as 60 metered pump actuations. One pump actuation delivers 5.5 mg of testosterone in 0.122 grams of gel.
<b>Storage</b>	Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted to 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature.
<b>Container Closure</b>	(b) (4), multi-dose metered pump container; supplied (b) (4) with cap attached

## **APPENDIX C. PREVIOUS DMEPA REVIEWS**

### **C.1 Methods**

We searched the shared drive (“L:Drive”) on May 20, 2014 using the term, “Natesto” to identify reviews previously performed by DMEPA.

### **C.2 Results**

Our search resulted in the retrieval of one relevant review:

- OSE Review # 2013-1239 dated September 27, 2013 for NDA 205488 – DMEPA made recommendations to the container label and carton labeling to improve the prominence of important information by clarifying its presentation and re-locating statements; and removing distracting and redundant information.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List and Images of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with postmarket medication error data, we reviewed the following Natesto (testosterone) container labels and carton labeling submitted by Trimel BioPharma SRL. We reviewed the proposed insert labeling provided by the Division on May 28, 2014 and we also received a prototype sample of the product on May 12, 2014 (from the Division) with the proposed container label affixed to the bottle.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/  
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DENISE V BAUGH  
05/28/2014

LISA V KHOSLA  
05/28/2014

505(b)(2) ASSESSMENT

Application Information		
NDA # 205488	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Natesto Established/Proper Name: testosterone nasal gel Dosage Form: nasal gel Strengths: 5.5mg of testosterone		
Applicant: Trimel Biopharma, Inc.		
Date of Receipt: April 29, 2013		
PDUFA Goal Date: May 28, 2014		Action Goal Date (if different):
RPM: Jeannie Roule		
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 by reliance on published literature, or by reliance on a final OTC monograph. *(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 listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<i>Published Literature</i>	<i>Nonclinical toxicology</i>

\*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 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)

The applicant is relying on previous findings of the potential toxicities of testosterone in nonclinical species and provided references that support the current language in Sections 8.1 and 13.1 of their label. The data described in the submitted references is scientifically relevant to this testosterone drug product which was evaluated at or above the proposed human doses.

**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 cited reliance on 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 #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

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

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

- 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 final OTC drug monograph?

YES  NO   
If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

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

Name of drug(s) discontinued from marketing:

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

YES  NO

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

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

This drug application provides for a new route of administration. The application did not rely upon a listed drug for approval.

*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 intended for the same route of administration 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), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

*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?

N/A  YES  NO

*If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

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

Pharmaceutical equivalent(s):

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)?

N/A  YES  NO

*If this application relies only on non product-specific published literature, answer "N/A"*

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):

N020489 ANDRODERM (TESTOSTERONE FILM, EXTENDED RELEASE; TRANSDERMAL);

N021015 ANDROGEL 1% (TESTOSTERONE GEL, METERED; TRANSDERMAL);

N022309 ANDROGEL 1.62% (TESTOSTERONE GEL, METERED; TRANSDERMAL);

N021454 TESTIM (TESTOSTERONE GEL; TRANSDERMAL);

N021543 STRIANT (TESTOSTERONE TABLET, EXTENDED RELEASE; BUCCAL) (b) (4)

(b) (4)

N022504 AXIRON (TESTOSTERONE SOLUTION, metered transdermal)

N021463 FORTESTA (TESTOSTERONE GEL, metered transdermal)

N202763, testosterone gel, Teva Pharmaceuticals

N203098, testosterone gel, Perrigo

#### 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):

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):

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

YES  NO

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

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

YES  NO

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

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

Date(s):

*Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

- (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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/s/  
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JEANNIE M ROULE  
05/28/2014

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

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

**Memorandum**

**Date:** May 22, 2014

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

**From:** Trung-Hieu Brian Tran, PharmD, MBA  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **NDA: 205488**  
**Natesto** (testosterone) nasal gel CIII

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This consult is in response to DBRUP's June 11, 2013 request for OPDP's review on the proposed Package Insert (PI), Patient Package Insert (PPI), and Carton/Container Labeling for Natesto (testosterone) nasal gel CIII.

OPDP appreciates the opportunity to provide comments on the PI, PPI, and Carton/Container Labeling. OPDP's comments on the PI are based on the substantially complete version of the PI titled, "PI sent to Sponsor May 9 2014," which was received via email from DBRUP on May 9, 2014.

Please see the attached PI with our comments incorporated therein. Comments on the PPI were provided under separate cover on May 14, 2014.

If you have any questions, please contact Trung-Hieu Brian Tran, (240) 402-0281, or [trung-hieu.tran@fda.hhs.gov](mailto:trung-hieu.tran@fda.hhs.gov).

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/s/  
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TRUNG-HIEU B TRAN  
05/22/2014

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

**PATIENT LABELING REVIEW**

Date: May 14, 2014

To: Hylton Joffe, MD  
Director  
**Division of Bone, Reproductive, and Urologic Products (DBRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Trung-Hieu Brian Tran, PharmD, MBA  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)

Drug Name (established name): NATESTO (testosterone)

Dosage Form and Route: Nasal Gel

Application Type/Number: NDA 205488

Applicant: Trimel BioPharma SRL

## 1 INTRODUCTION

On April 29, 2013, Trimel BioPharma SRL, submitted for the Agency's review a New Drug Application (NDA 205488) for Natesto (testosterone) nasal gel indicated for testosterone replacement therapy for adult males with conditions associated with a deficiency or absence of endogenous testosterone.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive, and Urologic Products (DBRUP) on June 11, 2013, and June 11, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Natesto (testosterone) nasal gel.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on September 30, 2013.

## 2 MATERIAL REVIEWED

- Draft Natesto (testosterone) PPI and IFU received on April 29, 2014, and received by DMPP on May 09, 2014.
- Draft Natesto (testosterone) PPI and IFU received on April 29, 2014, and received by OPDP on May 09, 2014.
- Draft Natesto (testosterone) Prescribing Information (PI) received on April 29, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on May 09, 2014.
- Draft Natesto (testosterone) Prescribing Information (PI) received on April 29, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on May 09, 2014.
- Approved Androderm (testosterone) comparator labeling dated April 26, 2012.

## 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 PPI and IFU 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 APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10 and Verdana font, size 11 for the Instructions for Use (IFU) document.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable

#### **4 CONCLUSIONS**

The PPI and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/  
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SHAWNA L HUTCHINS  
05/14/2014

TRUNG-HIEU B TRAN  
05/14/2014

MELISSA I HULETT  
05/14/2014

LASHAWN M GRIFFITHS  
05/14/2014

**M E M O R A N D U M**

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

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DATE: March 13, 2014

TO: Hylton Joffe, M.D.  
Director, Division of Bone, Reproductive, and Urologic  
Products  
Office of New Drugs

FROM: Gopa Biswas, Ph.D., Pharmacologist  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations (OSI)

and

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Addendum to review of EIRs covering NDA 205-488,  
Testosterone Nasal Gel, sponsored by Trimel BioPharma  
SRL, Barbados

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

**Study Number:** TBS-1-2011-03  
**Study Title:** "A 90-day, randomized, dose-ranging study, including potential dose titration, evaluating the efficacy and safety of intranasal TBS-1 in the treatment of male hypogonadism with sequential safety extension periods of 90 and 180 days"

Craig Garmend (ORA, FLA-DO) audited records at Clinical Research of South Florida, Coral Gables, FL, from 8/19 to 8/29/2013.

Yvette LaCour-Davis (ORA CIN-DO) audited records at the Center for Family Medicine, Franklin, OH, from 10/21 to 11/07/2013.

Valerie Grecek Trinh (ORA FLA-DO) audited records at the Jacksonville Impotence Treatment Center, Jacksonville, FL, from 11/05 to 11/14/2013.

Daniel Aisen (ORA NOL-DO) and Gopa Biswas (DBGLPC) audited analytical records for the analytical portions at (b) (4)

DBGLPC provided an initial review of the inspectional findings at the clinical and analytical sites for this study on December 20, 2013.

Additional electronic responses to the observations for the analytical data were received from (b) (4) on January 15, 2014; February 7, 2014 and February 10, 2014 (**Attachments 1-3**). This addendum provides my evaluation of the additional responses for the analytical portion only:

**Analytical Site:** (b) (4)

- 1. Failure to use the appropriate blank matrix for preparing calibrators for testosterone, dihydrotestosterone and estradiol. The calibrators in this study were prepared in artificial matrix prepared with 4% BSA in 0.9% saline in place of serum with low endogenous levels of these analytes.**

**Response:**

(b) (4) provided additional data comparing the responses of calibrators for testosterone (T), dihydrotestosterone (DHT) and estradiol prepared in artificial matrix with calibrators prepared in human serum. The performance of calibrators prepared in both matrices was parallel and showed a linear regression slope of 0.9911, 1.036, and 0.9824 respectively. The firm also evaluated the assay precision and accuracy using QCs prepared in both matrices.

**Evaluation:**

(b) (4) demonstrated that the performance of calibrators prepared in artificial matrix is comparable to calibrators prepared in human serum. The response is acceptable.

**2. Failure to conduct appropriate method validation experiments for testosterone, dihydrotestosterone and estradiol:**

- a) Extraction recovery for testosterone, dihydrotestosterone, and estradiol was not demonstrated appropriately in that an artificial matrix (4% BSA in 0.9% saline) was used in place of serum.
- b) The effects of lipemia on determination of testosterone, dihydrotestosterone and estradiol were not evaluated.
- c) Reinjection reproducibility was not demonstrated. Several analytical runs were reinjected due to interruption of the LC-MS/MS system during the study.
- d) Matrix effects were not evaluated.

**Response:**

(b) (4) conducted additional experiments to provide responses to observations 2.a - 2.d.

2.a) (b) (4) evaluated extraction recovery using human serum. The firm provided new data to show mean extraction recovery at 94.8% for T, 101.75% for DHT and 91.35% for the internal standard. The mean extraction recovery was 96.85% for estradiol and 104.15% for internal standard.

2.b) (b) (4) evaluated effect of lipemia using lipemic serum samples and no significant effect was observed on determination of T, DHT or estradiol.

2.c) (b) (4) provided data demonstrating reinjection reproducibility after storage of samples in autosampler for 146 h for T, DHT and 169 h for estradiol.

2.d) (b) (4) evaluated matrix effect in six different lots of human serum. The results showed no significant matrix effect on determination of T, DHT and estradiol.

**Evaluation:**

This reviewer finds the responses acceptable.

3. Integrity of serum samples was not assured in that sample storage freezers were not locked. The freezers were located in an area with unrestricted access.

**Response:**

(b) (4) acknowledged the concern in observation 3. The response stated that the samples were analyzed after approval of the study director. The use of study samples was always verified by a second person.

As corrective action, (b) (4) plans to install freezer locks with secure electronic access by 03/01/2014.

**Evaluation:**

Although the sample storage freezers were not locked, there was no evidence of improper use of study samples during the study. The corrective action proposed in (b) (4) response is acceptable. In my opinion, observation 3 should not have an impact on study outcome.

**Conclusion:**

My conclusion for the clinical portion of study TBS-1-2011-03 remains the same as provided in the first review:

- The OCP reviewer should assess the impact of early dose adjustments from BID to TID for subject #051-036 (clinical site #2) on the safety and efficacy of the treatment.
- Abnormal results for subject #051-014 ((b) (6)) during visit #6 should be reviewed for safety evaluations.

After evaluation of additional responses for the analytical portion of the above inspections, I recommend that the study data are acceptable for further review.

Gopa Biswas, Ph.D.  
Bioequivalence Branch, DBGLPC, OSI

**Final Classifications:**

VAI-Clinical Research of South Florida, Coral Gables, FL  
(FEI: 3000719761)

VAI-Center for Family Medicine, Franklin, OH  
(FEI: 3010408388)

VAI-Jacksonville Impotence Treatment Center, Jacksonville, FL  
(FEI: 3010375351)

VAI [REDACTED] (b) (4)

CC:

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OSI/DBGLPC/Taylor/Dejernett/CF

OSI/DBGLPC/BeB/Haidar/Choi/Biswas

OSI/DBGLPC/GLP/Bonapace/Mada

CDER/OND/ODEIII/DBRUP/Joffe/Roule

CDER/OTS/OCP/DCPIII/Bashaw/Yu

ORA/FLA-DO/Craig Garmendia

ORA/CIN-DO/Yvette LaCour-Davis

ORA/FLA-DO/Valerie Grecek Trinh

ORA/NOL-DO/Aisen

Draft: GB 2/12/2014

Edit: YMC 2/20/2014; SHH 2/21/14; WHT 3/13/2014

OSI: BE File # 6468; O:\BE\EIRCOVER\205488tri.tes.add.doc

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/ANALYTICAL  
SITES/ [REDACTED] (b) (4)

Cabinets/CDER OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL  
SITES

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GOPA BISWAS  
03/13/2014

WILLIAM H TAYLOR  
03/14/2014

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

---

DATE:            December 20, 2013

TO:              Hylton Joffe, M.D.  
Director, Division of Bone, Reproductive, and Urologic  
Products  
Office of New Drugs

FROM:           Gopa Biswas, Ph.D., Pharmacologist  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH:      Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations (OSI)

and

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT:       Review of EIRs Covering NDA 205-488, Testosterone  
Nasal Gel, sponsored by Trimel BioPharma SRL, Barbados

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

**Study Number:**    TBS-1-2011-03  
**Study Title:**     "A 90-day, randomized, dose-ranging study,  
including potential dose titration, evaluating  
the efficacy and safety of intranasal TBS-1 in  
the treatment of male hypogonadism with  
sequential safety extension periods of 90 and 180  
days"

Craig Garmendia(ORA, FLA-DO) audited records at Clinical Research of South Florida, Coral Gables, FL, from 8/19 to 8/29/2013.

Yvette LaCour-Davis (ORA CIN-DO) audited records at the Center for Family Medicine, Franklin, OH, from 10/21 to 11/07/2013.

Valerie Grecek Trinh (ORA FLA-DO) audited records at the Jacksonville Impotence Treatment Center, Jacksonville, FL from 11/05 to 11/14/2013.

Daniel Aisen (ORA NOL-DO) and Gopa Biswas (DBGLPC) audited analytical records for the analytical portions at [REDACTED] (b) (4)

The inspections included a thorough review of study records, examination of facilities and equipment, and interviews and discussions with firms' management and staff.

At the conclusion of the inspections, Form FDA-483 was issued at each site (**Attachments 1-4**). DBGLPC received written responses to the inspectional observations from each site (**Attachments 5-8**).

My evaluation of the observations and the responses from the clinical sites follows:

**Clinical Research of South Florida, Coral Gables, FL**

A written response to the inspectional observations was received on 9/25/2013 (**Attachment 5**).

- 1.A. In all versions of the protocol under Visits 4 and 6 it states that "Once the subject has been administered the TBS-1 dose and has completed an additional 2 hours of fasting post-dose, provide a standardized meal." In discussions with both the Clinical Investigator and the Site Administrator Director it was indicated that subjects were not given a standardized meal. This applied to all subjects, including the 11 out of 11 subjects fully reviewed during this inspection.

**Response:**

The principal investigator (PI) agreed that a standardized meal was not given during the study; instead pizza was given.

However, the PI provided the sponsor's statement that the standardized meal was not necessary to the protocol because the route of drug administration was intranasal (pages 3-5, Attachment 5).

The site proposed a corrective action for future studies, by training the staff to strictly follow the protocol and changes must be included as protocol amendments (page 2, Attachment 5).

**Evaluation:**

In my opinion, the clinical pharmacology reviewer should evaluate the impact of this protocol violation.

**1.B. In all versions of the protocol under Visits 1, 2, and 4 it states to "obtain a blood sample for fasting morning (900 h  $\pm$  30 min)." The blood draws were taken outside of the protocol specified window of  $\pm$ 30 minutes for the following subjects and visits:**

- i. Subject 001 - Visit 1
- ii. Subject 005 - Visit 1
- iii. Subject 017 - Visit 4
- iv. Subject 019 - Visits 1 and 2
- v. Subject 050 - Visit 1

**Response:**

The PI acknowledged the protocol violation, and commented that the deviations in blood draw timings were errors by the staff. To prevent similar protocol violations in future studies, the staff has been trained to adhere to study protocols.

**Evaluation:**

The deviations in blood draw timings were reported to the sponsor and included in the study report. In my opinion, this observation is not likely to impact the study outcomes because the actual times of collection were used for calculation of testosterone, dihydrotestosterone, and estradiol pharmacokinetics. I recommend that the OCP reviewer should evaluate the impact of these deviations on study outcomes.

**1.C. In all versions of the protocol it states that "all visits are to occur within  $\pm$  3 days." The visits occurred outside of the protocol specified window of  $\pm$  3 days for the following subjects and visits:**

- i. Subject 001 - Visit 9
- ii. Subject 004 - Visits 6 and 10

- iii. Subject 005 - Visit 9, 10, 11, 12, and 13
- iv. Subject 015 - Visits 6, 10, 11, 12, 14, and 15
- v. Subject 017 - Visits 6 and 12
- vi. Subject 019 - Visits 6 and 7
- vii. Subject 021 - Visit 9
- viii. Subject 041 - Visits 6, 8, and 9
- ix. Subject 043 - Visits 4 and 8
- x. Subject 048 - Visits 6 and 9
- xi. Subject 050 - Visits 4 and 6

**Response:**

The PI provided evidence that the deviations were reported to the CRO (b)(4) and the sponsor (Pages 3, 15-27). As a corrective action, the staff has been retrained to adhere to protocols for future studies.

**Evaluation:**

I recommend that the Review Division should evaluate the protocol deviations.

- 2. You failed to document in the source documentation both what was fed to the subjects and when the subjects were fed. This applied to all subjects, including the 11 out of 11 subjects fully reviewed during this inspection.

**Response:**

The PI acknowledged observation 2 and provided receipts for pizza meals purchased for the subjects as evidence that the subjects were fed. (pages 6-9, Attachment 5)

**Evaluation:**

Please refer to the review and recommendations under the Observation 1.A. In my opinion, observation 2 relates to documentation of the meals, not to whether the site followed the protocol.

**Center for Family Medicine, Franklin, OH (Gary Bedel, M.D.)**

A written response to the inspectional observations was received on 11/21/2013 (Attachment 6).

- 1.A. Section 10.1 of Protocol, Amendment #3, version date (24 April 2012), under the header Adverse Events, paragraph 5 states: "Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at

baseline and significantly worsen will be reported as adverse events." The following was observed:

- (1) Subject #051-114 ((b) (6)) had abnormal laboratory findings of increased ALT/SGPT, AST/SGOT, GGT and Creatine Kinase after being randomized into the study at Visit #4 and Visit #6, that were not reported as adverse events as illustrated in the table below:

Visit	ALT/SGPT {6-41 U/L}	AST/SGOT (9-34 U/L)	GGT (11- 52 U/L)	Creatine Kinase {25- 210 U/L}
Visit #1(Screen) (21 Apr 12J)	50 U/L	37 U/L	169 U/L	385 U/L
Visit #3 (Randomization/Day!) (OS May 12)	57 U/L	37 U/L	207 U/L	199 U/L
Visit #4 /Day #30 (23 Jun 12)	77 U/L	50 U/L	301 U/L	549 U/L
Visit #6 /Day 90 (25 Aug 12)	93 U/L	189 U/L	185 U/L	7070 U/L

**Response:**

The PI Dr. Bedel noted that the correct subject number was 051-014 ((b) (6)). He stated that at the time of the study, he reviewed the abnormal laboratory results in observation 1 and decided that they were not clinically significant. He said that he did not consider the elevated creatine kinase (CK) result during visit #6 as an adverse event because the subject was involved in strenuous physical exercise before the visit.

**Evaluation:**

I recommend that the reviewing division should consider the abnormal test results in safety evaluations.

- 1.A. (2) Two subjects randomized into the study had abnormal laboratory findings of increased thyroid stimulating hormone (TSH) that were not reported as adverse events illustrated in the table below:

Subject #/ Initials Randomization Date	Visit/Date Laboratory Collected	Thyroid Stimulating Hormone (TSH) Reference Range 0.40 -4.00 µIU/mL
Subject #051-012 ((b) (6)) 13 May 2012	Visit # 1/Screen (18 Apr 2012)	2.691 µIU/ml
	Visit #6 (06 Aug 2012)	5.44 µIU/mL

<b>Subject #051-037</b> (b) (6) 21 Jun 2012	Visit # 1/Screen (29 May 2012)	3.021 $\mu$ IU/mL
	Visit #6 (16 Sep 2012)	4.33 $\mu$ IU/mL

**Response:**

In his response, Dr. Bedel stated that the subjects did not have indications of hypothyroidism at other visits and he considered that the increased TSH results were not clinically significant.

**Evaluation:**

The study protocol allowed accepting TSH results that are  $\leq 1.5$  times the ULN. The values listed in observation 2 were within this limit. In my opinion, the safety of the subjects was not compromised and observation 1.A. (2) should not have a significant impact on study outcomes.

- 1.A. (3) Two subjects randomized into the study had abnormal urine laboratory findings that were not reported as adverse events, illustrated in the table below:**

Subject#/Initials	Visit Abnormal Laboratory Finding Collected
Subject #051-016 (b) (6)	Visit #9 collected on 27 Nov 2012
Subject #051-028 (b) (6)	Visit #6 collected on 10 Aug 2012

**Response:**

Dr. Bedel noted that the subject #051-016 was related to visit #6 and subject #051-028 was related to visit #9. He did not consider the findings as adverse events because the subjects were clinically symptom-free. He described that the high bacteria count (4+ Bacteria) in urine shown in Subject #051-016 during visit #6 was initially considered clinically significant, but later it appeared that the bacteria were attributable to contamination. As correction for future studies, Dr. Bedel will note whether a finding is an adverse event or not, and also provide an explanation for his decision.

**Evaluation:**

I find the response acceptable. Subject safety was not likely compromised and observation 1.A. (3) will not have significant impact on study outcomes.

- 1.B. Section 5.1.1. of Protocol, Amendment #3, version date (24 April 2012), the last bullet point of "Visit 4 (Day 30/31)" states, "On Day 45, if applicable, based on the results of the PK profile**

of serum testosterone obtained at Visit 4, contact subjects in the BID group and instruct subject to increase their daily dose to TID (see Section 6.1.1)."

A review of subjects "Patient Daily Diary Protocol TBS-1-2011-03" revealed the following subjects randomized to the BID treatment group whose Visit 4 serum total testosterone concentrations C avg < 300 ng/dL were titrated to TID prior to Day 45 as specified in the protocol illustrated in table below:

Subject#/Initals	Randomization Date to BID Dosaging/Time 1st Dose Administered	Date Dosage Increased to TID Per Daily Diary
(b) (4)		

**Response:**

Dr. Bedel stated that the study protocol was followed and the dose adjustments were up-titrated and calculated for 15 days ±3 days after visit #4 on day 30/31 (see table on page 4, Attachment 6). The dose was increased at 15 days ±3 days after visit #4 for all subjects listed in observation 1.B., except subject #051-036. For subject #051-036, the dose was increased after 11 days instead of 15 ±3 days. As a correction, the staff has been retrained to follow the protocol schedule.

**Evalaution:**

The response is acceptable. In my opinion, the OCP reviewer should evaluate the protocol deviation for when dose was increased in subject #051-036.

2. For the following subjects, data recorded on/in source documents and other study related records did not match the data as reported on the electronic case report forms (eCRFs):

1. Subject #051-001 ((b) (6)): The source document, dated 5-6-12, lists the time of first study drug administration as "20:55" and the eCRF list the time as "21:01."

2. Subject #051-004 ( (b) (6) ): The weight of study drug dispenser #3 is listed as "27.98 g" on the "Individual Study Drug Log," dated 6/9/12 and visit source document dated 6/9/12; however the weight on the eCRF, dated 9/Jun/2012 of dispenser #3 is listed as "29.98 g."
3. Subject #051-007 ( (b) (6) ): The return weight of two study drug dispensers on the Individual Drug Log," dated 9/1/12, for dispenser #1 is listed as "17.86 g" and dispenser #2 as "18.32 g"; however the return weight on the eCRF, dated 1/Sep/2012 for dispenser #1 is listed as "19.28 g" and dispenser #2 as "19.64 g."

**Response:**

Dr. Bedel acknowledged the observation and stated that these were transcription errors. He said that the staff has been retrained to verify transcribed information during future studies.

**Evaluation:**

I find the response acceptable. Observation 2 is not likely to have significant impact on study outcomes.

**Jacksonville Impotence Treatment Center, Jacksonville, FL (Roger Miller, Jr., M.D.)**

A written response to the inspectional observation was received on 11/29/2013 (Attachment 7).

1. The site did not follow the protocol for Visit 4 in that the PK samples were not collected within the required time frames following administration of the initial (2100 h) study drug dose for 5 subjects (Subjects 052-002, 052-009, 052-012, 052-013, and 052-033). In addition, the protocol indicates that the study drug is to be administered at plus or minus 5 minutes from the indicated time (2100 h and 0700 h); however, of these 5 subjects, the initial doses for 3 (Subjects 052-002, 052-009, and 052-012) and the morning dose for 1 (Subject 052-033) were not administered within that appropriate time frame.

**Response:**

The PI Dr. Miller acknowledged the observation. He stated that the deviations were communicated to the sponsor and the IRB. As a corrective action, an additional medical assistant was hired

to help with blood draws at 24 h times and the staff was retrained to adhere to study protocols for future studies.

**Evaluation:**

In my opinion this observation is not likely to have significant impact on study outcomes because the actual times of collection were used for calculation of testosterone, dihydrotestosterone and estradiol pharmacokinetics.

**Analytical Site:**

(b) (4)

An electronic response to the inspectional observations was received from the firm on 12/05/2013 (**Attachment 8**).

- 1. Failure to use the appropriate blank matrix for preparing calibrators for testosterone, dihydrotestosterone and estradiol. The calibrators in this study were prepared in artificial matrix prepared with 4% BSA in 0.9% saline in place of serum with low endogenous levels of these analytes.**

**Response:**

(b) (4) acknowledged the observation and stated that additional validation experiments will be performed to evaluate comparability of calibrators prepared in the artificial matrix with calibrators prepared in human serum. The firm will also compare the accuracy and precision of assays using QCs prepared in both matrices. (b) (4) promised to provide the additional data by 1/15/2014.

**Evaluation:**

The study samples were extracted by derivatization from human serum and the firm did not ensure that extraction efficiency was comparable in both matrices (see observation 2a). Also, during the study, (b) (4) did not establish that the use of calibrators prepared in artificial matrix would not impact the accuracy of determination of the analytes in serum. In my opinion, the accuracy of testosterone, dihydrotestosterone and estradiol concentrations in serum samples is not assured. (b) (4) should demonstrate that the performance of calibrators prepared in artificial matrix is comparable to calibrators prepared in human serum.

- 2. Failure to conduct appropriate method validation experiments for testosterone, dihydrotestosterone and estradiol:**

- a) **Extraction recovery for testosterone, dihydrotestosterone, and estradiol was not demonstrated appropriately in that an artificial matrix (4% BSA in 0.9% saline) was used in place of serum.**
- b) **The effects of lipemia on determination of testosterone, dihydrotestosterone and estradiol were not evaluated.**
- c) **Reinjection reproducibility was not demonstrated. Several analytical runs were reinjected due to interruption of the LC-MS/MS system during the study.**
- d) **Matrix effects were not evaluated.**

**Response:**

(b) (4) acknowledged the concerns listed in observation 2 and stated that additional experiments will be done to address them. (b) (4) promised to submit the additional data by 1/15/2014.

**Evaluation:**

An addendum to this review will follow when the additional data arrive. The following is my preliminary evaluation of the observations.

2.a) (b) (4) used calibrators spiked into artificial matrix before and after extraction to evaluate extraction recovery. This method did not account for contributing factors from serum matrix. (b) (4) should provide data for extraction recovery and its variability in human serum.

2.b) Lipemic blood or serum samples were not identified by either the clinical sites or (b) (4). In my opinion, because this was a fed study it is important to evaluate the impact of lipemia on the accuracy of determinations of testosterone, dihydrotestosterone, and estradiol.

2.c) None of the interrupted and reinjected runs failed due to QC failure. Therefore, observation 2c is not likely to have significant impact on study results.

2.d) (b) (4) should have evaluated matrix effects including variability among sources of serum. However, no significant variability in internal standard signals was apparent during the analysis of serum samples. Therefore, observation 2d should not have significant impact on study results.

- 3. Integrity of serum samples was not assured in that sample storage freezers were not locked. The freezers were located in an area with unrestricted access.**

**Response:**

(b) (4) acknowledged observation 3. The response claimed that samples were analyzed only after approval by the study director, and that use of study samples was always verified by a second person. As a corrective action, (b) (4) plans to install freezer locks with secure electronic access by 03/01/2014.

**Evaluation:**

Although the sample storage freezers were not locked, there was no evidence of improper use study samples during the study. The corrective action proposed by (b) (4) is acceptable. In my opinion, observation 3 is not likely to have an impact on study outcome.

**Conclusion:**

After evaluation of inspectional observations and the responses for the above inspections for study TBS-1-2011-03, I recommend the following:

- a) The OCP reviewer should assess the impact of early dose adjustments from BID to TID for subject #051-036 (clinical site #2) on the safety and efficacy of the treatment.
- b) Abnormal results for subject #051-014 ((b) (6)) during visit #6 should be reviewed for safety evaluations.

Analytical data should not be accepted until the following additional data are provided:

- a) Data that performance of calibrators prepared in artificial matrix is comparable to calibrators prepared in human serum, after adjustment for endogenous hormone concentrations; and
- b) Data for extraction recovery and matrix effects in human serum and the impact of lipemia on the accuracy of determinations of testosterone, dihydrotestosterone, and estradiol concentrations.

Gopa Biswas, Ph.D.  
Bioequivalence Branch, DBGLPC, OSI

**Final Classifications:**

VAI-Clinical Research of South Florida, Coral Gables, FL  
(FEI: 3000719761)

VAI-Center for Family Medicine, Franklin, OH  
(FEI: 3010408388)

VAI-Jacksonville Impotence Treatment Center, Jacksonville, FL  
(FEI: 3010375351)

VAI [REDACTED] (b) (4)

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Dejernett/CF

OSI/DBGLPC/BeB/Haidar/Choi/Biswas

OSI/DBGLPC/GLP/Bonapace/Mada

CDER/OND/ODEIII/DBRUP/Joffe/Roule

CDER/OTS/OCP/DCPIII/Bashaw/Yu

ORA/FLA-DO/Craig Garmendia

ORA/CIN-DO/Yvette LaCour-Davis

ORA/FLA-DO/Valerie Grecek Trinh

ORA/NOL-DO/Aisen

Draft: GB 11/26/2013

Edit: YMC 12/18/2013; MFS 12/19/2013; WHT 12/19/2013

OSI: BE File # 6468; O:\BE\EIRCOVER\205488tri.tes.doc

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/ANALYTICAL  
SITES/ [REDACTED] (b) (4)

Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL  
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/s/  
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GOPA BISWAS

12/20/2013

Dr. Haidar will sign on behalf of Dr., Taylor.

SAM H Haidar

12/20/2013

**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, Labeling and Packaging Review**

Date	September 27, 2013
Reviewer	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Drug Name & Strength	Natesto (Testosterone) Intranasal Gel 5.5 mg of Testosterone per actuation
Application Type/Number	NDA 205488
Applicant	Trimel BioPharma SRL
OSE RCM #	2013-1239

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

## Contents

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## 1 INTRODUCTION

This review evaluates the proposed packaging, container label, carton and insert labeling for Natesto<sup>1</sup> for areas of vulnerability that could lead to medication errors.

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested this review as part of their evaluation of the 505(b)(2) submission for Natesto (NDA 205488).

## 2 PRODUCT INFORMATION

The Applicant provided the following information in their April 29, 2013 submission:

- Active Ingredient: Testosterone
- Indication of Use: Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).
- Route of Administration: Intranasal
- Dosage Form: Gel
- Strength: 5.5 mg per actuation
- Dose and Frequency: The recommended starting dose is 11 mg of testosterone applied intranasally twice daily for a total daily dose of 22 mg. (b) (4)  
[REDACTED]
- How Supplied and Packaging Configuration: Multiple dose dispenser inherent with a metered dose pump. Each multiple dose dispenser contains 11 gram of gel dispensed as 60 metered pump actuations. One pump actuation delivers 5.5 mg of testosterone in 122.5 mg of gel. (b) (4)  
[REDACTED] The product will not be supplied in any physician samples or starter packs.
- Storage: Controlled Room Temperature
- Container and Closure Systems: Product is supplied in a (b) (4), multi-dose, metered pump container. The containers are supplied separately as (b) (4) with cap attached.

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<sup>1</sup> DMEPA found the proposed proprietary name, Natesto acceptable (OSE Review 2013-957 and 2013-1182 dated July 11, 2013)

### **3 METHODS AND MATERIALS REVIEWED**

This section describes the methods and materials we reviewed to better understand the potential for medication errors with the proposed product.

#### **3.1 PRODUCT DESIGN, LABELS, AND LABELING**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with post marketing medication error data, we evaluated:

- Container labels submitted April 29, 2013 (Appendix A)
- Carton labeling submitted April 29, 2013 (Appendix B)
- Natesto Container closure system diagram submitted via email on May 7, 2013 (Appendix C)
- Insert labeling submitted April 29, 2013 (no image)

### **4 RESULTS AND ASSESSMENT**

This section provides our findings from the review of the Natesto product design, labels, and labeling.

#### **4.1 PRODUCT DESIGN, LABELS, AND LABELING REVIEW**

The Applicant is proposing a bio-adhesive testosterone gel intended for intranasal application as another option for testosterone replacement therapy. According to the Applicant, one advantage of the proposed intranasal testosterone gel, when compared to other formulations, includes the lack of transference to other family members. Furthermore, the Applicant states that the bio-adhesive characteristics of the gel ensure that it does not run or drip out of the nasal cavity. The DBRUP Medical Officer's review of the phase 3 study protocol concluded that no adverse events of either secondary exposure or drug product administration issues due to patient mishandling of the study drug were reported.

DMEPA also expressed concerns with the bio-availability and transference of this product in the presence of upper respiratory infections (URI's) and seasonal allergies. In an e-mail dated September 3, 2013, DBRUP shared this concern and determined it could be addressed in the labeling. Pending their additional statements addressing this issue, we would suggest repeating this information in strategic areas of the insert labeling to alert users to the proper and safe use of this product.

The Applicant did not conduct a usability or label comprehension study to demonstrate that patients can use the proposed pump safely. We acknowledge that requesting the Applicant to conduct such a study may not be feasible at this stage of product development. However, we reviewed responses from the Applicant's participant survey for comments that could inform our views about the effectiveness of the proposed IFU

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<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004

and/or if improvements were necessary. Our assessment reinforced the necessity to address how to use this product in the presence of URI's and seasonal allergies. Specifically, the following comments were made: "With cold and flu season there is sometimes drainage", "Difficult to use in AM due to nasal drip", and "Having a cold".

Our review of the proposed insert labeling, instructions for use, container labels, and carton labeling concluded that improvements are needed to promote the safe use of the product, to mitigate any confusion, and to clarify information. We make recommendations in Section 5 below.

## **5 RECOMMENDATIONS**

Based on this review, DMEPA provides the following comments and recommendations prior to approval of this NDA:

### **A. Comments to the Division**

DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA:

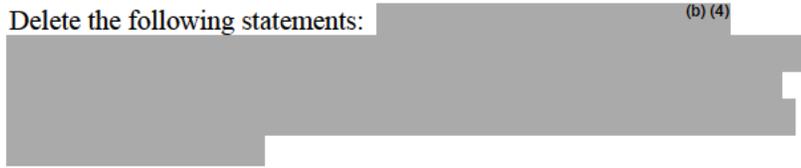
1. We defer the following items to the Division to consider for this testosterone product:
  - a. Consider if a boxed warning or limitation of use statement addressing secondary exposure would be appropriate for this product. Although the Applicant states the bio-adhesive nature of the gel prevents the product from running or dripping out of the nasal cavity, the risk may still exist. Additionally, the possibility of the product being accidentally transferred to the hands of the patient by touching the tip of the pump after administering the product, or being transferred to any other areas to which others may come in contact, cannot be ruled out. If you agree, consider adding the same warnings and cautionary statements that are used with other FDA approved topical testosterone products (e.g., Androgel, Axiron, Fortesta) as appropriate. We recommend that the chosen statements appear in the Administration subsection of 'Dosage and Administration', in Section 17.3 (titled "Patients Should be Advised of these Administration Instructions"), and in the Patient Information section under the statement "What is the most important information I should know about Natesto"?
  - b. Consider the potential for the interchangeability of Natesto with other testosterone products. Statements such as "Topical testosterone products may have different doses, strengths, or application instructions that may result in different system exposure" may be used. This may be added to the dosing subsection of the Dosing and Administration section of the insert labeling. (See Comment in the Dosing Section.)
  - c. If Natesto is determined to be non-child resistant, consider adding the following statement to help minimize the risk of accidental exposure to children: "This package is not child resistant. Keep out of reach of children" to the Storage and Handling section.
  - d. The appropriateness of labeling instructions for patients experiencing upper respiratory infections (URI's) and/or seasonal allergies while using

this product. Consider repeating such statements in the Administration (2.2), Patient Counseling Information (17.3) and the Patient Instruction (“How should I use TBS-1?”) Sections of the insert labeling to maximize patient awareness of how they should use the product in the event of URI’s/seasonal allergies.

2. The Dosage and Administration (Highlights and the Full Prescribing Information), Dosage Forms and Strengths (Full Prescribing Information), How Supplied/Storage and Handling, and Patient Counseling Sections of the insert labeling as well as the Patient Labeling should be revised to improve clarity, to include statements warning against interchangeability between Natesto and other testosterone products as well as accidental exposure. Please also note the comments and recommendations in the subsection titled “Applying TBS-1” in the Patient Information section of the insert labeling (See Appendix D).

**B. Recommendations for the Applicant**

DMEPA recommends the following be implemented prior to the approval of this NDA:

1. General Comments for Container Labels and Carton Labeling
  - a. Replace ‘Tradename’ with ‘Natesto’ because we found the proposed proprietary name acceptable. Additionally, revise the presentation of the proprietary name from all capital letters (i.e., TRADENAME) to mixed case (i.e., Tradename) to increase readability.
  - b. Ensure the controlled substance schedule ‘CIII’ appears on the container labels and carton labeling [21 CFR 1302.03 and 1302.04]. Additionally, ensure ‘CIII’ is displayed prominently, and separated from the proprietary or established names by white space, not directly juxtaposed.
  - c. Revise the established name ‘(b) (4)’ to read ‘(Testosterone) Gel’ for consistency with other FDA approved testosterone products.
  - d. Ensure the established name (i.e., the active ingredient, ‘Testosterone’ and the finished dosage form, ‘Gel’) is printed in letters that are at least ½ as large as the letters comprising the proprietary name and that the established name has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)].
  - e. Delete the following statements: (b) (4)  


- f. Place the statement ‘5.5 mg of testosterone per pump actuation\*’ immediately below ‘(Testosterone) Gel’ as this statement is considered the statement of strength and should appear below the active ingredient and dosage form statements. This statement should then be followed by ‘\*Each actuation delivers 0.122 grams of gel’ and ‘Multi-dose pump capable of dispensing 60 metered pump actuations’.
- g. Revise the net quantity statement ‘Total Contents = 11.0 g/dispenser’ to read ‘11 g’. Additionally, relocate ‘11 g’ to appear at the bottom portion of the container labels and carton labeling.
- h. Increase the prominence of the route of administration ‘for intranasal use only’ by bolding and increasing the font size.
- i. Add the statement ‘This package is not child resistant’ to appear before the statement ‘Keep out of reach of children.’
- j. Relocate the NDC number to appear above the proprietary name and ensure that the font size does not compete with the name.
- k. Remove the Medication Guide statement, (b) (4) since a Medication Guide is not being proposed for this product.
- l. Following the revisions recommended in 1a through 1k above, the presentation of the proprietary and established names, dosage form, strength, route of administration, child safety warning, and the net quantity on the principal display panel of the container label and carton labeling would appear as such:

**Natesto CIII**

(testosterone) Gel

5.5 mg of testosterone per pump actuation\*

\*Each actuation delivers 0.122 g of gel  
Multi-dose pump capable of dispensing  
60 metered pump actuations.

**For intranasal use only**

Warning: This package is not child resistant. Keep out of reach of children.

11 g

## 2. Container Label

- a. Delete the large background image as well as the smaller image that appears on the left hand side of the proprietary name. These graphics distract from important information (i.e., Proprietary and established names, product strength information, and route of administration) and clutter the label. Additionally, superimposed text over the large background image is difficult to read.
- b. Reduce the prominence of the company name (i.e., TRIMEL) and logo to appear less prominent than the proprietary name.
- c. Include the statement, 'Patient: see enclosed patient information leaflet.' on the side panel. The statement may be placed below 'See package insert for full prescribing information.'
- d. Revise Step 1 (under the heading "Instructions for the use of TRADENAME") to be Prime the pump so that this important step is not overlooked.
- e. Ensure that the *Priming instructions* and the *Instructions for Use* sections of the container label follow our recommendations for the 'Applying *Natesto*' section of the Patient Information leaflet. All of the instructions should be identical to minimize any confusion that may lead to mishandling of the product or medication errors.

## 2. Carton Labeling

- a. Delete the storage information as well as the active and inactive ingredients that appear on the principal display panel. This information is already included on the side panels and is repetitive.
- b. Ensure the proprietary and established names, dosage form, and the strength statement appear above the horizontal gold line and the remaining information appears below it.

If you have further questions or need clarifications, please contact Shawnetta Jackson, OSE Project Manager, at 301-796-4952.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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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DENISE V BAUGH  
09/27/2013

JAMES H SCHLICK  
09/30/2013

# Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

All of the “NO” sections of this review were told to the Sponsor via their 74 day letter.

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## Highlights (HL)

### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

## Selected Requirements of Prescribing Information (SRPI)

**YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

*Comment:*

**NO** 7. A horizontal line must separate HL and Table of Contents (TOC).

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

*Comment:*

#### Highlights Limitation Statement

**YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

*Comment:*

#### Product Title

**YES** 10. Product title in HL must be **bolded**.

*Comment:*

#### Initial U.S. Approval

**NO** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

*Comment:*

## Selected Requirements of Prescribing Information (SRPI)

### Boxed Warning

12. All text must be **bolded**.

Comment:

YES

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

### Recent Major Changes (RMC)

N/A

17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

### Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

### Dosage Forms and Strengths

## Selected Requirements of Prescribing Information (SRPI)

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

**YES**

## Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

**Comment:**

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

**Comment:**

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

**Comment:**

- YES** 34. When a section or subsection is omitted, the numbering does not change.

**Comment:**

- YES** 35. If a section or subsection from 201.56(d)(1) 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.”

**Comment:**

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

**Comment:**

- YES** 37. All section and subsection headings and numbers must be **bolded**.

**Comment:**

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>

## Selected Requirements of Prescribing Information (SRPI)

8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

**Comment:**

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

## Selected Requirements of Prescribing Information (SRPI)

- YES** 45. If no Contraindications are known, this section must state “None”.

**Comment:**

### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), 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.”*

**Comment:**

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“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.”*

**Comment:**

### Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “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)”

**Comment:**

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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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JEANNIE M ROULE  
08/07/2013

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: August 2, 2013

TO: Chief,  
Medical Products & Tobacco Trip Planning Branch  
Division of Medical Products and Tobacco Inspections  
Office of Medical Products and Tobacco Operations

Director, Investigations Branch  
Florida District Office  
555 Winderley Place, Suite 200  
Maitland, FL 32751

Director, Investigations Branch  
Cincinnati District Office  
6751 Steger Drive  
Cincinnati, OH 45237

FROM: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGLPC)  
Office of Scientific Investigations (OSI)

SUBJECT: Amendment to FY 2013, **CDER High Priority User Fee NDA, Pre-Approval Data Validation Inspection**, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 205-488  
DRUG: Testosterone nasal gel  
SPONSOR: Trimel BioPharma SRL  
Barbados

This memo requests that you arrange for inspections of the clinical and analytical portions of the following safety/efficacy and pharmacokinetic study. **These inspections should be completed prior to November 22, 2013**. Our earlier memo requested inspection of the analytical portions only.

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) to schedule the inspections. A DBGLPC scientist will participate in the inspection of the analytical

site to provide scientific and technical expertise. Background materials will be available in ECMS under the ORA folder.

**Study #:** TBS-1-2011-03  
**Study Title:** "A 90-day, randomized, dose-ranging study, including potential dose titration, evaluating the efficacy and safety of intranasal TBS-1 in the treatment of male hypogonadism with sequential safety extension periods of 90 and 180 days"

**Clinical Site #1:** Clinical Research of South Florida  
275 Alhambra Circle  
Coral Gables, FL 33134  
**Investigator:** Jeffrey Rosen, MD

**Clinical Site #2:** Center for Family Medicine  
333 Conover Drive, Suite D  
Franklin, OH 45005  
**Investigator:** Gary Bedel, MD

**Clinical Site #3:** Jacksonville Impotence Treatment Center  
2950 Halcyon Lane, Suite 706  
Jacksonville, FL 32223  
**Investigator:** Roger Miller, Jr., MD

**Do not reveal the application number, the study to be inspected, the drug name, or the study investigators to the sites prior to starting the inspections.** The sites will receive this information during the inspection opening meetings. The inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

Once the inspections are completed, **please send a scanned copy of the completed Section A of this memo to the DBGLPC POC.**

#### **SECTION A - CLINICAL DATA AUDIT**

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

**During the clinical site inspection, please:**

- Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.

- Compare the study records in the NDA submission to the original documents at the site.
- Check for evidence of under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
  - o Number of subject records reviewed during the inspection: \_\_\_\_\_
  - o Number of subjects screened at the site: \_\_\_\_\_
  - o Number of subjects enrolled at the site: \_\_\_\_\_
  - o Number of subjects completing the study: \_\_\_\_\_
- Verify from source documents that case report forms accurately report evaluations related to the primary endpoint.
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocol.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports.
- Check the accuracy of the actual time of drug administration (morning dose) and blood sampling around that morning dose (scheduled to be 1 hour pre-dose and 20 minutes post-dose) on days 30 and 90.**
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**SECTION B - AUDIT OF ANALYTICAL DATA**

**Analytical Site:**

**Investigator:**

**Contact person:**

**Methodology:**

LC-MS/MS

(b) (4)

**Please complete the following items during the inspection:**

- Examine all pertinent items related to the analytical method used for the measurement of testosterone and dihydrotestosterone (DHT) concentrations in human serum.
- Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.
- Determine if the site employed a validated analytical method to analyze the subject samples.
- Compare the assay parameters observed during the study sample analysis with those obtained during method validation. These parameters may include variability between and within runs, accuracy and precision, etc.
- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.
- Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.
- Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.
- Examine correspondence files between the analytical site and the applicant for their content.

**Additional instructions to ORA Investigator:**

The DBGLPC POC will provide you with compliance program elements, and in certain situations, additional study specific instructions prior to the inspections. Please contact the DBGLPC POC for inspection-related questions and clarifications before, during, and after the inspections.

**If you issue Form FDA 483**, please remind the inspected firm of the 15 business-day timeframe for submission of a written response to observations listed on the form. Promptly fax or email a copy of the form to the DBGLPC POC. If it appears that the site violations may warrant an OAI classification, notify the respective DBGLPC POC as soon as possible. Fax or email any written response to Form FDA 483 as soon as you receive it to the DBGLPC POC.

DBGLPC POC foreign site: Arindam Dasgupta, Ph.D.  
Email: [arindam.dasgupta@fda.hhs.gov](mailto:arindam.dasgupta@fda.hhs.gov)  
TEL: (301)796-3326  
FAX: (301)847-8748

DBGLPC POC domestic sites: Ruben Ayala, Pharm.D.  
Email: [ruben.ayala@fda.hhs.gov](mailto:ruben.ayala@fda.hhs.gov)  
TEL: (301)796-2018  
FAX: (301)847-8748

cc:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Bonapace/Haidar/Skelly/Choi/Ayala/Dejernett  
ORA/OMPTO/DMPTI/BIMO/Turner/Arline/Carrion/Alexis/Johnson/Braswell/Colon

HFR-SE250/Sinninger, Kathleen (DIB)/Torres, Brunilda (BIMO)

HFR-CE450/Miser, David (DIB)

HFR-CE4525/Harriger, Mishelle (BIMO)

CDER/OND/ODEIII/DBRUP/Joffe/Roule

CDER/OTS/OCP/DCPIII/Bashaw/Yu

Draft: RCA 6/18/2013, 8/2/2013

Edit: MFS 6/18/13, 8/2/13

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB

ECMS: Cabinets/ORA/OMPTO/BIMO/FY'13/CDER/DMPTI

ECMS: Cabinets/ORA/OMPTO/BIMO/FY'13/CDER/FLA-DO

ECMS: Cabinets/ORA/OMPTO/BIMO/FY'13/CDER/CIN-DO

OSI file #: BE6468; O:\BE\assigns\bio205488\_amended.doc

**FACTS: 8680622**

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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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RUBEN C AYALA  
08/02/2013

CHARLES R BONAPACE  
08/03/2013

## 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 # 205488 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Natesto Established/Proper Name: testosterone nasal gel Dosage Form: gel Strengths: 5.5 mg		
Applicant: Trimel Biopharma SRL Agent for Applicant (if applicable): John Dubeck		
Date of Application: April 29, 2013 Date of Receipt: April 29, 2013 Date clock started after UN:		
PDUFA Goal Date: February 28, 2014		Action Goal Date (if different):
Filing Date: June 28, 2013		Date of Filing Meeting: June 13, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5		
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)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review 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>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<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"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <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 Designation <input type="checkbox"/> Breakthrough Therapy Designation <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)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 070512

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
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		Emailed Document room to change
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 New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
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>  If yes, explain in comment column.		X		
If affected by AIP, has OC/OMPQ been notified of the submission? <b>If yes</b> , date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<b>User Fee Status</b>  <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>		<b>Payment for this application:</b>  <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			
<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>		<b>Payment of other user fees:</b>  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
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)].				X	
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)]?				X	
<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 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		X			
<b>Check the Electronic Orange Book at:</b> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>					
<b>If yes, please list below:</b>					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
NDA 21463	Fortesta	NP	Dec 29, 2013		
NDA 22504	Axiron	NP	Nov 23, 2013		
NDA 202763	Testosterone gel	NP	Feb 14, 2014		
<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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
<b>Exclusivity</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug</b>			X		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<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)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  <b>If yes</b> , # years requested: (b) (4)  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?			X	
<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)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<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)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
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:	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?			X	
<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>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> 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 FD&amp;C Act 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>	X			
<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	
<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: June 11, 2013</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</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</i></p>	X			PeRC meeting scheduled for 11/20/13

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

<i>requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
<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>			X	
<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			
<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/OSI/DSC/PMSB via the CDER OSI RMP 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 checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input 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				

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

format?	X			
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	X			
<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 applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> 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)			X	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<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> March 14, 2011	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b>	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

**DATE:** June 13, 2013

**BLA/NDA/Supp #:** 205488

**PROPRIETARY NAME:** NATESTO

**ESTABLISHED/PROPER NAME:** testosterone nasal gel

**DOSAGE FORM/STRENGTH:** 5.5 mg

**APPLICANT:** Trimel Biopharma

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

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

**BACKGROUND:**

**Dose and formulation:** 5.5 mg as a single dose into each nostril BID (b) (4)

The primary study objective is to determine the efficacy of 4.5% TBS- 1 gel, administered as 2 (b) (4) daily intranasal doses of 5.5 mg per nostril

Trimel Pharma outlining its drug development program for a 4.5% testosterone gel for intranasal installation. The proposed indication is for testosterone replacement in hypogonadal males. The product would be instilled into the nose two (b) (4) times daily on a chronic basis.

The nasal formulation under development by Trimel Pharma will represent the first nasal formulation of testosterone for the treatment of male hypogonadism.

The drug product contains (b) (4) of 4.5% testosterone gel as the active ingredient and castor oil, oleoyl polyoxylglycerides, and colloidal silicon dioxide as excipients. The excipients have not been used in any approved nasal formulation in the U.S; however, they are used in other topical formulations.

The sponsor's formulation is contained in a multiple dose dispenser with an actuator that when pressed (b) (4).

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Jeannie Roule	Y
	CPMS/TL:	Jennifer Mercie	Y
Cross-Discipline Team Leader (CDTL)	Mark Hirsch		Y
Clinical	Reviewer:	Harry Handelsman	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:	Sonia Castillo	Y
	TL:	Mahboob Sobhan	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Lynnda Reid	Y
	TL:	Lynnda Reid	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (for BLAs/BLA efficacy supplements)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	N
	TL:	Donna Christner	Y
Quality Microbiology (for sterile products)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	James Tolliver	N
	TL:	Silvia Calderon	N
Other reviewers	DPARP: Sofia Chaudhry		Y
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input 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
<p><b>CLINICAL</b></p> <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>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input 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 NME NDA or original BLA , 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 checked="" 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> <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

<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</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>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<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 style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <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 type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<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? (NDAs/NDA supplements only)</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><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 OMPQ?</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 type="checkbox"/> NO</p>

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</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>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:**

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V):  
September 23, 2013

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<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 checked="" 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"/>	
<input type="checkbox"/>	<p>If priority review:</p> <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 OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>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 in the CST eRoom at:  <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<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.