

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205488Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 205488

SUPPL #

HFD #

Trade Name Natesto

Generic Name testosterone nasal gel

Applicant Name Trimel Biopharma, Inc.

Approval Date, If Known May 28, 2014

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

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

YES  NO

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

No

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA#

\*Please see attachment after the last page of this document

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

Study # TBS-1-2011-03

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study # TBS-1-2011-03

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # 070512 YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES   
Explain:

!  
! NO   
! Explain:

Investigation #2

YES   
Explain:

!  
!  
! NO   
! Explain:

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

YES  NO

If yes, explain:

---

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

Name of Office/Division Director signing form: Hylton V. Joffe, M.D.  
Title: Director, Division of Bone, Reproductive and Urologic Products

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

**Appl No**      **Proprietary Name**

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

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

/s/  
-----

JEANNIE M ROULE  
05/28/2014

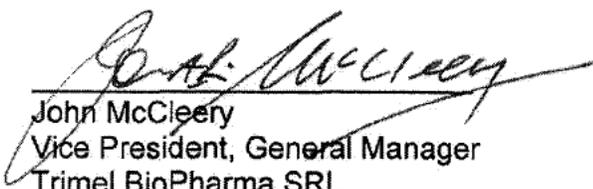
HYLTON V JOFFE  
05/29/2014



**Trimel BioPharma SRL.**  
Durants Business Centre, Suite B  
Durants, Christ Church, BB17097  
Barbados  
Phone 246-420-7548 Fax 246-420-7550

**Debarment Certification (FD&C Act 306 (k)(1))**

Trimel BioPharma SRL 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.

  
John McCleery  
Vice President, General Manager  
Trimel BioPharma SRL

April 12, 2013  
Date



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

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): \_\_\_\_\_

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

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

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

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

Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**This page was completed by:**

**Jeannie Roule**

*{See appended electronic signature page}*

**Regulatory Project Manager**

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

## **1. REQUEST FOR WAIVER OF PEDIATRIC STUDIES**

**Product name:**

TBS-1 Gel

**NDA number:**

NDA # 205,488

**Applicant:**

Trimel BioPharma SRL

**Indication(s):**

Primary and secondary hypogonadism

### **1.1. Age Groups Included in Waiver Request**

All pediatric age groups

### **1.2. Reasons for Requesting Waiver**

With regard to all pediatric age groups, this waiver is sought based on established criteria.

1. Studies would be highly impractical to conduct and,
2. The disease/condition does not exist in children and,
3. The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

### **1.3. Justification for Waiver**

Per the FDA's Draft Guidance for Industry - Recommendations for Complying with the Pediatric Rule [21 CFR 314.55a and 601.27a] (November 2000), and the Draft Guidance for Industry - How to Comply with the Pediatric Research Equity Act (September 2005), hypogonadism is a disease that is not applicable to pediatric patients. The signs and symptoms occur in the adult population and there are too few children with the disease/condition to study. Therefore, the requirement for pediatric studies should be waived.

### **1.4. Applicant Certification**

Pursuant to 21 CFR 314.55(c)(2)(ii), Trimel certifies that TBS-1 Gel is not likely to be used in the pediatric population.

## Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

**BACKGROUND**

Please check all that apply:  Full Waiver  Partial Waiver  Pediatric Assessment  Deferral/Pediatric Plan

BLA/NDA#: NDA (b) (4)

PRODUCT PROPRIETARY NAME: Natesto

ESTABLISHED/GENERIC NAME: testosterone nasal gel

APPLICANT/SPONSOR: Trimel Biopharma SRL

**PREVIOUSLY APPROVED INDICATION/S:**

- (1) \_\_\_\_\_ *N/A* \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

**PROPOSED INDICATION/S:**

- (1) Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

BLA/NDA STAMP DATE: April 28, 2013

PDUFA GOAL DATE: February 28, 2014

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

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

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

***Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)***

***Yes***  ***No***

***Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes***  ***No***

***If Yes, PMR # \_\_\_\_\_ NDA # \_\_\_\_\_***

***Does the division agree that this is a complete response to the PMR? Yes***  ***No***

***If Yes, to either question Please complete the Pediatric Assessment Template.***

***If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.***

## WAIVER REQUEST

*Please attach:*

**Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.**

**Note to PeRC Review Committee: The PI is attached along with the language that will be including in the approval letter (if the product is approved).**

**Pediatric Record**

1. Pediatric age group(s) to be waived. All pediatric age groups
2. Reason(s) for waiving pediatric assessment requirements (**Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.**)
  - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from adult-related conditions on the next page
  - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
  - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
  - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to

support this claim for review by the Division, and this data will be publicly posted. *(This reason is for Partial Waivers Only)*

3. *Provide justification for Waiver:*

With regard to all pediatric age groups, this waiver is sought based on established criteria.

1. Studies would be highly impractical to conduct and,
2. The disease/condition does not exist in children and,
3. The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.
4. The necessary studies would be impossible or highly impractical and there are too few children with the disease/condition to study.

In addition:

Per the FDA's Draft Guidance for Industry - Recommendations for Complying with the Pediatric Rule [21 CFR 314.55a and 601.27a] (November 2000), and the Draft Guidance for Industry - How to Comply with the Pediatric Research Equity Act (September 2005), hypogonadism is a disease that is not applicable to pediatric patients. The signs and symptoms occur in the adult population and there are too few children with the disease/condition to study. Therefore, the requirement for pediatric studies should be waived.

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*

### **8.4 Pediatric Use**

Safety and efficacy of Natesto has not been established in males less than 18 years of age. Improper use may result in acceleration of bone age and premature closure of epiphyses.



**Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver**

These conditions qualify for waiver because studies would be impossible or highly impractical

- |  |                               |
|--|-------------------------------|
| Age-related macular degeneration   | Cancer:                       |
| Alzheimer's disease  | Basal cell                    |
| Amyotrophic lateral sclerosis  | Bladder                       |
| Atherosclerotic cardiovascular disease   | Breast                        |
| Benign Prostatic Hyperplasia   | Cervical                      |
| Chronic Obstructive Pulmonary Disease  | Colorectal                    |
| Erectile Dysfunction   | Endometrial                   |
| Infertility  | Gastric                       |
| Menopausal and perimenopausal disorders  | Hairy cell leukemia           |
| Organic amnesic syndrome<br>(not caused by alcohol or other psychoactive substances) | Lung (small & non-small cell) |
| Osteoarthritis   | Multiple myeloma              |
| Parkinson's disease  | Oropharynx (squamous cell)    |
| Postmenopausal Osteoporosis  | Ovarian (non-germ cell)       |
| Vascular dementia/ Vascular cognitive disorder/impairment                            | Pancreatic                    |
| Actinic Keratosis  | Prostate                      |
|  | Renal cell                    |
|  | Uterine                       |

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 205488 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Natesto Established/Proper Name: testosterone nasal gel Dosage Form: gel		Applicant: Trimel Biopharma Agent for Applicant (if applicable): Keller and Heckman
RPM: Jeannie Roule		Division: DBRUP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: May 28, 2014</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>May 28, 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approval: May 28, 2014
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>Review(s) <i>(indicate date(s))</i></li> </ul>	5/7/14, 7/11/13
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None N/A DMEPA: <input checked="" type="checkbox"/> None 5/28/14 and 9/30/13 DMPP/PLT (DRISK): <input type="checkbox"/> None 5/14/14 OPDP: <input type="checkbox"/> None 5/22/14 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	June 13, 2013
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>This application is on the AIP               <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>11/30/2013</u> If PeRC review not necessary, explain: _____</li> </ul>	Entered into DARRTS 12/02/13
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	<input type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg <input type="checkbox"/> No mtg March 22, 2006 <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A March 14, 2001, January 11, 2013
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 28, 2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 27, 2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews <ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> No separate review See CDTL review May 27, 2014 May 20, 2014 and June 25, 2013 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See Clinical Review dated, 5/2014, pages 14-16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> N/A None. Class Labeling for CSS was used.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	N/A  <input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 4, 2014 and June 12, 2013
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 30, 2014 and June 18, 2013
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested March 14, 2014 and December 20, 2013
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/16/14 and 6/24/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None DPARP review: 8/3/2013
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None May 22, 2014, 12/16/13, 6/18/13
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed May 13, 2103
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None Biopharmaceutics, 4/02/14
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	September 10, 2013
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: May 21, 2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/  
-----

JEANNIE M ROULE  
06/09/2014



NDA 205488

**INFORMATION REQUEST**

Trimel Biopharma, Inc.  
c/o Keller and Heckman  
Attention: John Dubeck  
US Agent  
1001 G Street N.W., Suite 500  
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your New Drug Application (NDA) dated April 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone nasal gel.

During the course of our review of your NDA, we have detected a new potential safety signal. Morning serum cortisol concentrations were measured at baseline and on Day 90 in 273 subjects in Protocol TBS-1-2011-03. The mean (SD) cortisol concentrations at baseline and on Day 90 in that population were 12.3 (4.4) mcg/dL and 4.6 (4.1) mcg/dL, respectively. In the TID-only group (n=69 had values at baseline and on Day 90), the baseline and Day 90 mean (SD) cortisol concentrations were 12.0 (4.2) and 3.9 (3.4) mcg/dL. The minimal reported cortisol concentration in both populations was 0.3 mcg/dL. In Study TBS-1-2011-03, a total of 39% and 43% of subjects in the overall (n=306) and TID-only (n=76) populations, respectively, had serum cortisol concentrations below the lower limit of normal. Our assessment of clinical adverse events does not reveal a clinical correlation for this laboratory abnormality. We are unable to explain this significant decrease from baseline in serum cortisol concentration.

Provide your assessment of this laboratory test abnormality. In your response, clarify the methodology for analysis of cortisol, including the specific analytical methodology, the laboratory where testing was conducted, and whether the data reflect total a.m. cortisol. In addition, please comment on whether, in your opinion, the data reflect a drug-laboratory test interaction versus a true clinical finding of hypocortisolemia. Provide your assessment of potential clinical significance and your recommendations for action, if any.

We request a prompt written response to all these information requests in order to continue our evaluation of your NDA.

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

Sincerely,

*{See appended electronic signature page}*

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

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

/s/  
-----

JENNIFER L MERCIER  
04/07/2014



NDA 205488

**INFORMATION REQUEST**

Trimel Biopharma, Inc.  
c/o Keller and Heckman  
Attention: John Dubeck  
US Agent  
1001 G Street N.W., Suite 500  
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your New Drug Application (NDA) dated April 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone nasal gel.

We also refer to your amendment dated January 7, 2014, and received January 13, 2014.

We are continuing our review of your NDA and have the following information requests based on your submission dated January 7, 2014.

1. You report that a total of 37 men received one year of treatment with the proposed dose of 11 mg three times per day. Provide a justification that this long-term exposure is sufficient to support the three times per day dosing regimen. In your justification, you may include evidence from shorter term dosing of 11 mg TID (e.g., 6 months) or from other dose regimens, but if you do so, you should include an explanation of how those data are relevant.
2. Clarify which patients are included in the "TBS-1 BID" and "TBS-1 TID" groups in Table 2.
3. Clarify whether there are differences in duration of patient exposures between the groups in Table 2 that should be accounted for by analyses using patient-year exposures.
4. Clarify whether the existing datasets submitted in your NDA are amenable to conducting a new safety analysis focusing on three times per day dosing vs. twice daily dosing. If they are not amenable to such analyses, submit updated datasets.
5. The submission contains general safety and tolerability statements such as "There were no clinically meaningful changes in vital sign measurements for any of the treatment groups during the study." Include more detailed safety information on three times per day

dosing compared to twice daily dosing, including tables showing patient disposition, serious adverse events, withdrawal due to adverse events, laboratory and vital sign parameters. If this information is already included in the NDA, please direct us to their location.

In addition we have the following requests based on information that you submitted on April 29, 2013.

6. In Table 2 on Pages 52-53 of the clinical study report (CSR) for Study TBS-1-2011-03, you state that fasting serum total testosterone (T) concentrations were measured during the safety extension periods 1 and 2 (i.e., on Days 180, 270, and 360). However, we are unable to locate these data. Submit the individual fasting serum total T concentrations with descriptive statistics including the arithmetic mean, standard deviation, %CV, geometric mean, median, minimum, and maximum. If they were previously submitted, provide the location of these datasets.
7. In the summary of subject disposition (Table 4 on Page 67 and Table 5 on Page 69 of the CSR) for Study TBS-1-2011-03, you state that 274 subjects completed the 90-day treatment period and entered the extended safety period 1. However, in your primary efficacy results (Table 11 on Page 80 of the CSR) and pharmacokinetic analyses (Table 19 on Page 89 of the CSR) at Day 90, you only included (b) (4) subjects. Clarify this discrepancy.

We request a prompt written response to all these information requests in order to continue our evaluation of your NDA.

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

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, M.D., M.M.Sc.  
Director  
Division of Bone, Reproductive, and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

/s/  
-----

HYLTON V JOFFE  
02/06/2014



NDA 205488

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Trimel Biopharma, Inc.  
c/o Keller and Heckman  
Attention: John Dubeck  
US Agent  
1001 G Street N.W., Suite 500  
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your April 29, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for testosterone nasal gel.

On January 13, 2014, we received your January 7, 2014, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 28, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 28, 2014.

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

Sincerely yours,

*{See appended electronic signature page}*

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

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

/s/  
-----

JENNIFER L MERCIER  
01/16/2014

**MEMORANDUM**

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

**DATE:** January 15, 2014

**TO:** NDA 205488

**THROUGH:** Jeannie Roule

**SUBJECT:** Carton and Container comments

**APPLICATION NUMBER:** NDA 205488 (Natesto)

The DMEPA and CMC reviewers have comments regarding the Sponsor's carton and container for Natesto.

Please see attached email correspondences for all of the details.

**From:** Roule, Jeannie  
**Sent:** Wednesday, January 15, 2014 12:37 PM  
**To:** 'Wayne Kreppner'  
**Subject:** Carton and Container

**Attachments:** DMEPA and CMC carton container comments Jan 2014.doc  
Wayne,

Please see attached document regarding your carton and container labeling.

Regards,  
Jeannie



DMEPA and CMC  
carton container...

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

We have reviewed your revised container label and carton labeling that you submitted via email to Jeannie Roule on November 27, 2013, in response to our comments that you received via email on November 19, 2013. Some of your initial revisions are unacceptable and further revisions will be necessary.

The DMEPA and CMC reviewers have the following comments and recommendations:

1) The instructions on the container label are not identical to the instructions in the IFU and may cause confusion for the user.

2) [REDACTED] (b) (4)  
[REDACTED] These statements may cause the reader to misinterpret the instructions and contribute to a 'wrong route' error. As this is a nasal inhaler, references should be limited to how to use this product in the patient's nose and avoid referring to other parts of the face.

3) We recommend boxing the statement associated with priming the product so that this important step is not overlooked with its first use. If space permits, consider adding the word "IMPORTANT" in bold letters prior to the statement "For first time use of the pump see priming instructions *on previous page*".

4) Pursuant to an internal meeting with the Division, we determined that the diagrams which accompany the individual statements on the container label for using this product are inadequate. Specifically, there is no distinguishing detail between the outline of the nose and the product itself to assist the user in safely using the product. Consider adding more detail so that they better support the narratives associated with them.

5) Prominently display "Rx Only" statement on the immediate container label.

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

/s/  
-----

JEANNIE M ROULE  
01/16/2014

**PeRC PREA Subcommittee Meeting Minutes  
November 20, 2013**

**PeRC Members Attending:**

Lynne Yao  
Rosemary Addy  
Hari Cheryl Sachs  
George Greeley  
Jane Inglese  
Wiley Chambers  
Tom Smith  
Karen Davis-Bruno  
Colleen LoCicero  
Gregory Reaman  
Daiva Shetty  
Shrikant Pagay  
Ruthanna Davi  
Kevin Krudys  
Lily Mulugeta  
Maura O'Leary  
Robert Nelson  
Dianne Murphy  
William J. Rodriguez

**Agenda**

10:55	BLA	103948	(b) (4)	(b) (4)
11:10	NDA	21336/10		Emsame (selegiline) (b) (4)
	NDA	205437		Otezla (apremilast) Full Waiver
	NDA	205488		Natesto (testosterone nasal gel) Full Waiver
		(b) (4)		(b) (4)
	NDA	204886		Zonitivity (vorapaxar) Full Waiver
	NDA	22549		Adasuve (loxapine) Deferral Extension



**Emsame (selegiline) Assessment**

- NDA 21336 was approved on February 7, 2006, for Emsame (selegiline) for the treatment of major depressive disorder.
- Supplement 10 for NDA 21336 has a PDUFA goal date of February 43, 2014.



**Otezla (apremilast) Full Waiver**

- NDA 205437 seeks marketing approval for Otezla (apremilast) for the treatment of adult patients with active psoriatic arthritis.
- The application has a PDUFA goal date of March 21, 2014.
- The application triggers PREA as directed to a new active ingredient.

- *PeRC Recommendations:*
  - The PeRC agreed with a full waiver because studies are impossible or highly impractical. Full waivers have been previously granted for this indication.

#### **Natesto (testosterone nasal gel) Full Waiver**

- NDA 22508 seeks marketing approval for Natesto (testosterone nasal gel) as replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.
- The application has a PDUFA goal date of February 28, 2014.
- The application triggers PREA as directed to a new route of administration.
- *PeRC Recommendations:*
  - The PeRC agreed with a full waiver because studies are impossible or highly impractical because the disease/condition does not occur in children.
  - The Division should consider issuing a written request for this product if the Division believes that there would be a public health benefit in studying this product in children.

(b) (4)

#### **Zonitivity (vorapaxar) Full Waiver**

- NDA 204886 seeks marketing approval for Zonitivity (vorapaxar) for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI).
- The application has a PDUFA goal date of May 10, 2014.
- The application triggers PREA as directed to a new active ingredient.
- *PeRC Recommendations:*
  - The PeRC agreed with a full waiver because studies are impossible or highly impractical because the disease/condition does not occur in children.

#### **Adasuve (loxapine) Deferral Extension**

- NDA 22549 was approved on December 21, 2012, for Adasuve® (loxapine) inhalation powder for the treatment of agitation associated with schizophrenia or bipolar disorder.
- *PeRC Recommendations:*
  - The PeRC agreed with the Division to grant the deferral extension requires for both the PK study and the clinical study (b) (4)

(b) (4)

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

/s/  
-----

JANE E INGLESE  
12/02/2013

**MEMORANDUM**

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

**DATE:** November 19, 2013

**TO:** NDA 205488

**THROUGH:** Jeannie Roule

**SUBJECT:** Carton and Container comments

**APPLICATION NUMBER:** NDA 205488 (Natesto)

The DMEPA and CMC reviewers have comments regarding the Sponsor's carton and container for Natesto.

Please see attached email correspondences for all of the details.

**NDA 205488, Natesto**

The DMEPA and CMC reviewers have the following comments and recommendations regarding your carton, container and booklet for Natesto:

1. General Comments for Container Labels, Carton Labeling and booklet:

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 '( [REDACTED] <sup>(b) (4)</sup> )' to read '(testosterone) nasal 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, 'nasal 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. Prominently display "Rx Only" statement.

f. Add the following comment to the Storage description.

[See USP Controlled Room Temperature]

g. Delete the following statements: [REDACTED] <sup>(b) (4)</sup>

[REDACTED] See the recommendation below.

h. 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'.

i. Relocate the net quantity statement 'Total Contents = 11.0 g/dispenser' to appear at the bottom portion of the labeling.

- j. Increase the prominence of the route of administration ‘for intranasal use only’ by bolding and increasing the font size.
- k. Add the statement ‘This package is not child resistant’ to appear before the statement ‘Keep out of reach of children.’
- l. Relocate the NDC number to appear above the proprietary name and ensure that the font size does not compete with the name.
- m. Remove the Medication Guide statement, ‘(b) (4)’ since a Medication Guide is not being proposed for this product.

2. Following the revisions recommended in 1a through 1m 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) nasal 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.

Total Contents: 11 g/ dispenser

3. General Comments for 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.

4. General Comments for 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.

**From:** Roule, Jeannie  
**To:** ["Wayne Kreppner"](#)  
**Subject:** Natesto carton and container  
**Date:** Tuesday, November 19, 2013 11:07:00 AM  
**Attachments:** [Carton and Container comments DMEPA and CMC Nov 19 2013.doc](#)

---

Wayne,

Please confirm receipt of this email.

Once you have made the changes to your carton and container, please email the newer version to me. There is no need to submit a formal submission until we have 100% agreement with DMEPA, CMC and your company.

Regards,  
Jeannie

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

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

/s/  
-----

JEANNIE M ROULE  
11/20/2013



NDA 205488

**INFORMATION REQUEST**

Trimel BioPharma SRL  
c/o Keller and Heckman LLP  
Attention: John Dubeck, Authorized U.S. Agent  
1001 G Street NW, Suite 500 West  
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TBS-1 testosterone nasal gel.

We also refer to your October 9, 2013 submission, containing your response to our information request dated September 24, 2013.

We are reviewing the Biopharmaceutics section of your submission and have the following comments and information requests. We request a prompt written response by close of business November 1, 2013, in order to continue our evaluation of your NDA.

- We request that you commit to setting your proposed *in vitro* release acceptance criteria as interim specifications and not for information only.
- We recommend you conduct the *in vitro* release as per the methodology described in SUPAC-SS guidance, and report the specification as a range derived from the slope (in  $\mu\text{g}/\text{cm}^2/\text{hr}^{1/2}$ ) of the linear portion of the cumulative amount released versus  $\sqrt{t}$  curve (as opposed to what you proposed as the 3 time-point specifications). We do, however, agree with your proposal to revise the specification if necessary based on *in vitro* release data collected from 10 batches. You will have the opportunity to submit the information as a PAS following approval of your product.
- Please propose a revised specification along with all the raw data in an electronic format for the Agency to review with proper identification/description of the batches used to generate those data.

If you have any questions, call LCDR Kerri-Ann Jennings, Regulatory Project Manager, at (301) 796-2919.

Sincerely,

*{See appended electronic signature page}*

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

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

/s/  
-----

MOO JHONG RHEE  
10/25/2013  
Chief, Branch IV



NDA 205488

**INFORMATION REQUEST**

Trimel Biopharma, Inc.  
c/o Keller and Heckman  
Attention: John Dubeck  
US Agent  
1001 G Street N.W., Suite 500  
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your New Drug Application (NDA) dated April 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for testosterone nasal gel.

We also refer to your amendments dated August 1, 9 and 16, 2013.

We are continuing our review of your submissions and have the following comments and information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. The pre-defined, primary efficacy endpoint in your Phase 3 clinical study was the proportion of subjects with Cavg (0-24h) total testosterone (T) concentrations within the normal range on Day 90. It was further agreed that  $\geq 75\%$  of subjects would achieve the primary endpoint, with the lower bound of the 95% confidence interval  $> 65\%$ .

We have conducted an analysis of the primary efficacy data from TBS-1-2011-03 and [REDACTED] (b) (4) the to-be-marketed dose regimen. In the intent-to-treat (ITT) population, using last observation carried forward (LOCF) methodology for missing data, the point estimates and 95% confidence intervals that we determined for the various treatment groups (including BID, BID to TID, BID plus BID to TID, and TID) indicate that the agreed-upon level of success was achieved [REDACTED] (b) (4) in the TID group (n=73).

2. The primary efficacy analysis for TBS-1-2011-03 should be based on the dosing regimen and titration scheme shown in your proposed labeling [REDACTED] (b) (4). Alternatively, you might consider changing the dosing regimen to a fixed dose of 11 mg TID. If you choose to revise the labeled dosing regimen, the amount of data available to support efficacy and safety at the selected dose will be a review issue.

3. Our analysis generated discrepant results between the success rates for the BID-to-TID and the TID groups. The overall success rate in the BID-to-TID group ( (b) (4) ) lower than the success rate in the TID group (90.4%). In addition, we would expect that the success rate in the BID-to-TID group would be (b) (4) . Explain these discrepancies.
4. Your bioanalytical method validation reports entitled, “*The Validation of the determination of T and DHT in human serum using LC-MS/MS*” (Report (b) (4) 10364) issued on January 14, 2010 and “*The Validation of the determination of 17 $\beta$ -estradiol in human serum using LC-MS/MS*” (Report (b) (4) 10367) issued on February 22, 2011 by the bioanalytical laboratory (i.e., (b) (4) ) state that “*Long term stability in human serum was not performed in this validation study, because it will only cover a relatively short period of time. Long term stability experiments may be performed as a part of future studies.*”

We remind you that sample integrity is a critical review issue and the storage time in a long-term stability evaluation should equal or exceed the time between the date of first sample collection and the date of last sample analysis. Reference is made to the Agency’s Bioanalytical Method Validation Guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>).

Provide long term stability data for T, DHT, and 17 $\beta$ -estradiol that supports the sample integrity in clinical studies involved in your NDA. In particular, provide a table summarizing the sample collection dates, storage temperature at the clinic, shipping dates to the bioanalytical laboratory, storage temperature at the bioanalytical facility prior to analysis, and the sample analysis date for each sample analyzed in Studies TBS-1-2011-03 and TBS-1-2011-04.

5. Serum total T concentrations at Day 90 in both the BID and TID groups show that approximately 20% of subjects had T concentrations below 300 ng/dL, approximately 33% had T concentrations between 300 and 500 ng/dL, and approximately 48% had T concentrations between 500 and 850 ng/dL. No subject had a T concentration above 850 ng/dL. These data raise concerns that in the majority of subjects, T concentrations remained closer to or below the lower limit of the eugonadal range rather than closer to the upper limit of the eugonadal range. In addition, these data suggest that a modest increase in the amount of testosterone in your current doses might improve the primary efficacy results, particularly in the BID group, while still maintaining T concentrations below 1050 ng/dL.

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

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, M.D., M.M.Sc.  
Director  
Division of Bone, Reproductive, and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

/s/  
-----

HYLTON V JOFFE  
10/09/2013

**MEMORANDUM**

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

**DATE:** September 23, 2013

**TO:** NDA 205488

**THROUGH:** Jeannie Roule

**SUBJECT:** Biopharmaceutics request

**APPLICATION NUMBER:** NDA 205488 (Natesto)

The Biopharmaceutical reviewer had a request for information regarding *in vitro* release acceptance criteria. The question was emailed to the Applicant.

Please see attached email correspondences for all of the details.

**From:** Roule, Jeannie  
**To:** ["Wayne Kreppner"](#)  
**Subject:** Another request concerning NDA 205488  
**Date:** Tuesday, September 24, 2013 1:05:00 PM

---

Wayne,

We are continuing our review of your submission for NDA 205488 and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

The question below is from the Biopharmaceutics reviewer:

The Agency acknowledged your responses on August 1, 2013, to the Biopharmaceutics comments communicated to you in the 74-day letter. In your response, you commented that you have implemented an *in vitro* release acceptance criteria (range) that is consistent with the SUPAC SS guidance based on data generated to date with the pivotal batches. Based on the data, it appears that the TBS-1 demonstrates “sameness” or no change over time.

However, it appears that still you did not propose an *in vitro* release acceptance criteria (range) for your product at release and during stability as a quality control parameter.

In light of the very tight *in vitro* release data you obtained from the pivotal batches, we recommend that you propose/implement the *in vitro* release acceptance criteria (range) for your systemic use product at release and during stability as a quality control parameter.

**Please respond to this information request no later than October 4, 2013.** If that is not possible, please let me know the date in which you plan to submit a response.

Please confirm receipt.

Regards,

Jeannie Roule

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

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

/s/  
-----

JEANNIE M ROULE  
09/24/2013

**MEMORANDUM**

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

**DATE:** September 23, 2013

**TO:** NDA 205488

**THROUGH:** Jeannie Roule

**SUBJECT:** Statistical and Mid-Cycle meeting

**APPLICATION NUMBER:** NDA 205488 (Natesto)

The Statistical reviewer had a request for information regarding subjects in each treatment group. The question was emailed to the Applicant.

Please see attached email correspondences for all of the details.

**From:** Roule, Jeannie  
**Sent:** Monday, September 23, 2013 3:11 PM  
**To:** 'Wayne Kreppner'  
**Subject:** Question concerning NDA 205488

Wayne,

We are continuing our review of your submission for NDA 205488 and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

Kindly reply no later than September 30, 2013. If that is not possible, please let me know and provide a date that you believe we will receive the requested information.

Provide the number of subjects in each treatment group who meet the compliance ranges in the following table based on your ITT population. This definition of compliance is stated in section 10.5 on page 75 of Clinical Study Report TBS-1-2011-03.

	< 80% compliance	80% ≤ compliance ≤ 120%	> 120% compliance
Subjects who stayed on BID for entire study			
Subjects who titrated from BID to TID			
Subjects who stayed on TID for entire study			

Regards,  
Jeannie

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

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

/s/  
-----

JEANNIE M ROULE  
09/24/2013



IND 070512  
NDA 205488

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Trimel BioPharma SRL  
c/o Keller and Heckman LLP  
1001 G Street N.W., Suite 500 West  
Washington, DC 20001

ATTENTION: John B. Dubeck  
U.S. Agent for Trimel BioPharma

Dear Mr. Dubeck:

Please refer to your Investigational New Drug Application (IND) dated August 2, 2004, and received August 5, 2004, submitted under section 505(i) and your New Drug Application (NDA) dated and received April 29, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Testosterone Intranasal Gel, 5.5 mg per actuation.

We also refer to your IND correspondence, dated April 3, 2013, and received April 4, 2013 and your NDA correspondence dated and received May 15, 2013, requesting review of your proposed proprietary name, Natesto. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Natesto, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 15, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application contact Jeannie Roule, Regulatory Project Manager in the Division of Bone, Reproductive and Urologic Products (DBRUP), at (301) 796-3993.

Sincerely,

*{See appended electronic signature page}*

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

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

/s/  
-----

CAROL A HOLQUIST  
07/23/2013



NDA 205488

**NDA ACKNOWLEDGMENT**

Trimal Biopharma, Inc.  
c/o Keller and Heckman  
Attention: John Dubeck  
US Agent  
1001 G Street N.W., Suite 500  
Washington, D.C. 20001

Dear Mr. Dubeck:

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

Name of Drug Product: testosterone nasal gel

Date of Application: April 29, 2013

Date of Receipt: April 29, 2013

Our Reference Number: NDA 205488

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 28, 2013, in accordance with 21 CFR 314.101(a).

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

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

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

*{See appended electronic signature page}*

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

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

/s/  
-----

JEANNIE M ROULE  
05/07/2013



IND 070512

**ADVICE/INFORMATION REQUEST**

Trimal Biopharma, Inc.  
c/o Keller and Heckman  
Attention: John Dubeck  
US Agent  
1001 G Street N.W., Suite 500  
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for testosterone nasal gel.

We are sending this letter in response your January 11, 2013, meeting package that was submitted in response to your December 7, 2012, correspondence requesting a meeting to discuss the content of your NDA submission and confirm the acceptability of your CMC, preclinical and clinical programs to support the filing of your NDA.

The meeting originally scheduled for February 13, 2013, was cancelled. We have enclosed responses to your questions posed in your meeting package (see attachments). We encourage you to request another meeting between Trimal Biopharma, Inc. and the FDA if there are items that need to be further clarified. We will try to schedule another meeting, if needed, as soon as possible when all parties involved are available.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]. If your IND is in eCTD format, submit 7-day reports electronically in eCTD format. If your IND is not in eCTD format, you may submit 7-day reports by telephone or fax;
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this

Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

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

Sincerely,

*{See appended electronic signature page}*

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

## CMC Questions

### **Question 1 (3.2.1.1): Viscosity**

At the EOP2 Meeting on March 14, 2011, the Agency requested that viscosity be performed on the drug product packaged in the dispenser at release and on stability. Trimel is currently

(b) (4)  
Trimel proposes a viscosity specification of NLT  
(b) (4) based on this data. For routine commercial batches,  
Trimel will (b) (4)

Is the Agency in agreement with this approach?

**FDA Response to Question 1:** No, we do not agree with your proposal to test the viscosity (b) (4)  
The stability protocol should include viscosity of the gel packaged in the dispenser. In addition, although you report that the increases in viscosity observed do not affect the dose delivery, the viscosity specification should include an upper bound as well to control the quality of the drug product. You will also need to justify the lower bound in your NDA application.

In regard to Microbiology issues, we have the following additional comments and requests:

1. The proposed microbial limits specification for the drug product should comply with USP recommendations.
2. As discussed at the end of phase 2 meeting on 14 March 2011, the following information should be provided in the New Drug Application:
  - a. The results of in-use stability studies conducted to evaluate microbial contamination of the formulation and container closure system during product use.
  - b. The results of studies investigating air and/or microbial ingress into the airless delivery system.

### **Question 2 (3.2.1.2): Diffusion Rate/Franz Cell**

At the EOP2 Meeting on March 14, 2011, the Agency requested an *in vitro* release method for drug release and stability during development and clinical/pivotal manufacturing. According to the Guidance for Industry: Non-sterile Semisolid Dosage Forms, Scale Up and Post-approval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Release Testing and *in vivo* Bioequivalence Documentation (May 2007), the *in vitro* release method, based on the diffusion cell system (Franz cell system) should be used to characterize the performance of the gel. Trimel has developed a method and is currently gathering data for the diffusion rate of the gel from initial time point as well as during stability time points for shelf life monitoring and intends to provide this data in the NDA. TBS-1 exhibits sameness as per the FDA guidance, based on the ratio of the median release rate between the batches at

**time 0 and 18 months. When process changes are made to the commercial batches, Trimel will follow SUPAC guidelines for batch to batch comparisons using the diffusion cell method.**

**Is the Agency in agreement with this approach?**

***FDA Response to Question 2:*** Your approach to develop the *in-vitro* release test (IVRT) as a quality control tool at release as well as during stability is acceptable. We would like to remind you that you need to submit the details of the development and validation of your IVRT method (apart from the analytical method development and validation) in the NDA. The SUPAC SS clearly mentions that the *in vitro* release methodology should be appropriately validated. The IVRT method development and validation report should contain (but not limited to) the following information:

1. Choice of *in-vitro* diffusion apparatus and condition
2. Linearity and Range
3. Accuracy/Precision and Reproducibility
4. Recovery, Mass Balance & Dose Depletion
5. Sensitivity
6. Specificity
7. Selectivity
8. Robustness
9. Membrane Inertness
10. Receptor Solution Solubility/Stability

The IVRT method's sensitivity, specificity, selectivity and robustness need to be performed with altered product lots that contain 50% and 150% of the label claim of API in the reference product, with the test evaluating a minimum of one run of 6 diffusion cells each per product concentration, including the reference. You may consult ONDQA for specific guidelines in this respect.

### **Clinical Questions**

#### ***Question 3 (3.2.2): Efficacy and Safety***

**The sponsor has completed the efficacy portion of its Phase III study evaluating the efficacy and safety of 4.5% TBS-1 when administered BID and TID. As per the agreed protocol, patients in the BID arm that did not meet the titration model criteria based on PK blood draw on Day 30, were switched to the TID administration regimen on Day 45. Primary and secondary endpoints are being analyzed as agreed to with the Agency at the EOP2 meeting on March 14, 2011, and the recommendation from the Agency of October 31, 2011. The primary efficacy endpoint was the proportion of subjects with an average serum concentration of testosterone at Day 90 within the normal range. A total of 274 men completed the efficacy portion of the study and the results have met the primary efficacy endpoint.**

**The sponsor is conducting a long term safety and tolerability study on the product to meet**

**the safety requirements agreed with the Agency at the Pre IND meeting of March 14, 2011. As agreed the NDA submission will include 6 months of safety data from > 200 patients and 1 year of safety data from 50 patients. Preliminary data is available for over 200 subjects with 6 months data and 25 patients with 1 year data in the briefing document for review. The sponsor intends to submit this efficacy and safety study (TBS-1-2011-03), as the pivotal study in the NDA submission.**

**Is this acceptable for filing to the Agency?**

**FDA Response to Question 3:** The decision to file an NDA is made only after preliminary review of the submission. An NDA for TBS-1 testosterone nasal gel based upon the single Phase 3 Study TBS-1-2011-03, along with Phase 2 Study TBS-1-2010-01, and Phase 1 Study TBS-1-2011-04, may be adequate for filing. Complete clinical study reports (CSRs) for these three studies should be submitted in the NDA.

Nonetheless, we would like to apprise you of the following current potential Clinical review issues:

1. Based on wide peak-to-trough fluctuations in serum testosterone concentrations observed with BID or TID dosing of TBS-1 testosterone nasal gel, the Division had previously recommended that, in addition to standard pharmacokinetic endpoints, that you assess clinical efficacy endpoints in a placebo-controlled, Phase 3 trial. Study TBS-1-2010-01 lacks a placebo control. Thus, the clinical endpoints in TBS-1-2010-1 may be difficult, or impossible, to interpret. In lieu of clinical evidence from a placebo-controlled study, your NDA should contain a justification for clinical relevance of the pharmacokinetic profile of TBS-1 testosterone nasal gel.
2. Your proposed label states mean average testosterone concentrations of (b) (4) and (b) (4) for the 11 mg BID fixed dose (b) (4). These average concentrations, which reflect the to-be-marketed regimen, could be interpreted as being low in the normal range. Your NDA should include justification that TBS-1 testosterone gel provides clinically beneficial testosterone concentrations that are within the normal range.
3. Subjects in Study TBS-1-2010-01 were randomized in a 3:1 ratio to 11 mg BID (low dose) or 11 mg TID (high dose). Only those subjects in low dose arm underwent dose titration. Similarly, your to-be-marketed dose regimen is a starting dose of 11 mg BID (b) (4). Therefore, should the data from the high dose arm be included in the primary assessment of efficacy in TBS-1-2010-01? Your NDA should address this concern.
4. Your meeting package appears to demonstrate an approximate 21% reduction in average serum testosterone concentrations in patients with allergic rhinitis compared to asymptomatic patients. Your NDA should address the clinical importance of this finding

and propose specific measures to handle it (e.g. specific labeling, including recommendations for holding or stopping therapy).

5. You propose to revise the per-protocol, (b) (4) for product labeling. Your NDA should include substantial evidence to justify that change (see response to Question 4).

**Question 4 (3.2.2):**

(b) (4)

(b) (4)

**Is this acceptable?**

**EDA Response to Question 4:** It is premature to agree to labeling language with regard to the (b) (4) without a complete review of the Phase 3 study. In your NDA, provide the rationale for your proposed dosing regimen (b) (4).

**Labeling Questions**

**Question 5 (3.2.3.1): Warnings and Precautions**

**Trimel has completed a Drug-Drug Interaction study as agreed to with the Agency at the EOP2 Meeting on March 14, 2011. This study assessed the relative bioavailability, safety and tolerability of TBS-1 when administered to patients with symptomatic untreated and treated (oxymetazoline) seasonal allergic rhinitis as well as asymptomatic subjects using an environmental challenge chamber (ECC) model.**

**Administration of TBS-1 under asymptomatic, symptomatic and symptomatic but treated conditions of allergic rhinitis demonstrated a reliable increase in testosterone serum concentrations under all three treatment conditions. TBS-1 bioavailability during the symptomatic state of allergic rhinitis was 21% lower compared the asymptomatic state, based on AUC<sub>0-24</sub> values. The relative decrease in bioavailability of TBS-1 under symptomatic seasonal rhinitis was neither ameliorated nor aggravated by the administration of oxymetazoline.**

We plan on describing the specifics of the study result in the product label (b) (4) Section 12 “Clinical Pharmacology” but will not include any restrictions for the use of TBS-1 in patients with allergic rhinitis.

Does the Agency agree with this approach?

***FDA Response to Question 5:*** It is premature to agree to labeling language without a complete review of the drug-drug interaction study. In Section 7.4 of your proposed Full Prescribing Information label, you recommend (b) (4)

Provide your rationale for the new recommendation.

Other measures to address the reduction of serum testosterone concentrations in patients with allergic rhinitis might include restricted use, closer monitoring of testosterone levels, or switch to alternative formulations of testosterone. This will be a review issue. Your proposal to address this issue should encompass not only patients with allergic rhinitis, but also patients with other chronic nasal conditions or alternations in nasal anatomy.

In addition, we have the following comments and requests concerning nasal safety of TBS-1 testosterone nasal gel:

1. We had previously recommended a patient diary in the Phase 3 study for collection of nasal symptoms. It is not clear that a nasal symptom diary was kept in TBS-1-2010-01
2. Currently, there are 100 fewer patients in the Day 180 safety database compared to Day 90. Your NDA should address the reason for this difference (e.g. were these discontinuations and if so, for what reason).
3. It is unclear how the adverse events in the AE tables provided in the meeting package were tabulated. Your NDA should clarify the duration of exposure reflected in the AE tables and whether patients or events were counted more than once.
4. Your NDA should include an exposure-adjusted analysis of nasal AEs and a tabulation of the ENT symptoms and examination findings by dose group to assist in our review.
5. We note a trend towards increased nasal “Other” AEs categorized over time. Your NDA should clarify the nature and severity of these AEs.

We also have the following preliminary comments on your proposed labeling:

1. (b) (4)
2. As we have previously stated, without a placebo control group, all reported nasal AEs should be included in labeling, not just those deemed “possibly, probably or definitely related”.
3. As noted previously, if you propose (b) (4), your NDA should contain justification and supporting evidence.
4. The NDA should contain specific data regarding the absorption and clearance of testosterone rather than terms such as “rapidly absorbed”, “rapidly cleared”, “reliable increases in testosterone serum concentrations” and “restores testosterone levels”.

5. The NDA should contain specific data regarding effects on nasal mucosa, rather than the term (b) (4)

**Question 6 (3.2.3.2): Class Labeling**

The applicant intends to (b) (4) The application will make reference to previously reviewed and approved testosterone labels. Based on this approach the label will be consistent with the other products in this class, modified to include the clinical information specific to this product and specific instructions for use.

**Does the Agency agree with this approach?**

**FDA Response to Question 6:** In response to your statement that you intend to (b) (4) the answer is no.

We note that you intend to rely upon data from published literature to support nonclinical safety. If you intend to rely, in part, on information required for approval that comes from studies not conducted by or for you or for which you do not have a right of reference, then your marketing application will be a 505(b)(2) application. We recommend that you submit literature references to support the nonclinical sections of the labeling, i.e., Sections 8.1 and 13.

Your label will be, for the most part, consistent with the other products in its class, and will be modified to include the clinical information specific to your product and specific instructions for use.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on published literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. You should include a copy of such published literature reports and identify any listed drug(s) described in the published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or

published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which an applicant relies.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

#### **PREAA Question**

##### **Question 7 (3.2.4): Pediatric Waiver**

**Trimel intends to submit a pediatric waiver for TBS-1 as there is an extremely small population of pediatric patients in need of testosterone therapy for primary hypogonadism and clinical studies to establish the efficacy and safety are highly impractical. The label will state that the product is NOT to be used in patients under the age of 18.**

**Does the FDA agree the TBS-1 meets the requirements of exclusion from the pediatric study requirements for new drugs?**

**FDA Response to Question 7:** Your request for a pediatric waiver must be brought before the Pediatric Review Committee for their advice and recommendation. The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov)

#### **ADDITIONAL INFORMATION:**

##### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and

Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**OTHER INSPECTION REQUESTS (Non-Manufacturing)**

**Office of Scientific Investigations (OSI)**

Clinical investigative sites may undergo inspection by OSI. The attached request is relevant to the clinical sites and should be included in your NDA.

If you have additional questions concerning the Office of Scientific Investigations (OSI) requests, please direct them to Roy Blay (Roy.Blay@fda.hhs.gov, 301-796-3332).

**Clinical Pharmacology**

Your NDA should include the bioanalytical method(s) used in your clinical studies and name(s) of the bioanalytical sponsor and the location(s).

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

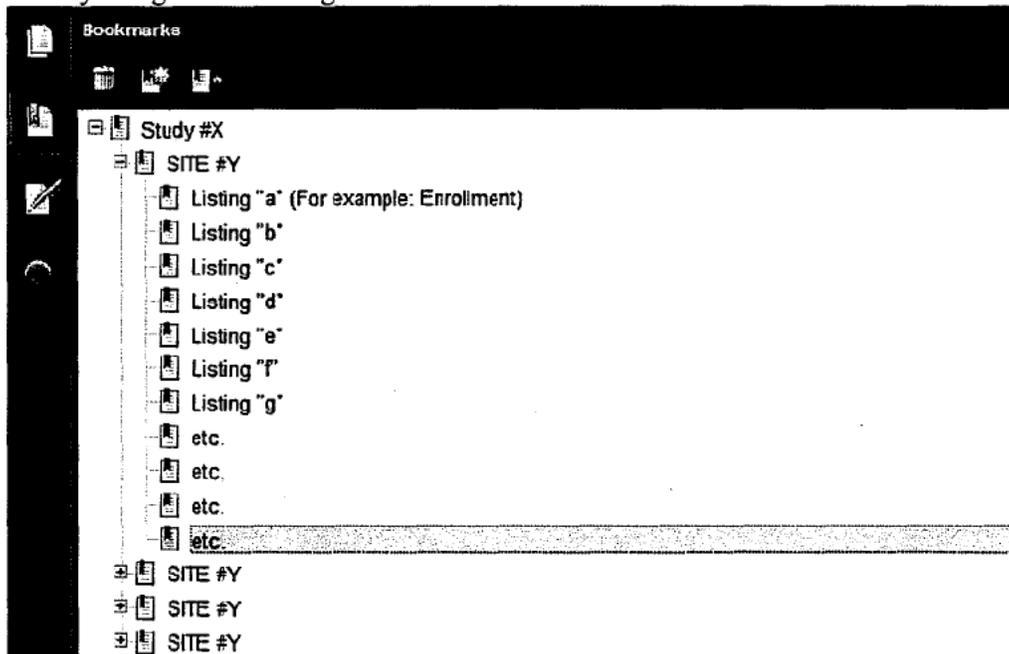
**I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
    - a. Site number
    - b. Principal investigator
    - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
    - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  
  2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
    - a. Number of subjects screened for each site by site
    - b. Number of subjects randomized for each site by site
    - c. Number of subjects treated who prematurely discontinued for each site by site
  
  3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
    - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
    - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
    - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
    - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
  
  4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
-

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

## II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



**III. Request for Site Level Dataset:**

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

## **Attachment 1**

### **1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions**

#### **1.1 Introduction**

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

#### **1.2 Description of the Summary level clinical site dataset**

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

#### **Site-Specific Efficacy Results**

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

**Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)**

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

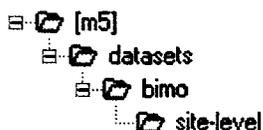
## Attachment 2

### Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

---

<sup>1</sup> Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page  
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

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

*/s/*

-----  
**AUDREY L GASSMAN**  
**03/05/2013**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 070512

MEETING MINUTES

Keller and Heckman LLP  
U.S. Agent for Trimel BioPharma SRL  
Attention: John Dubeck  
1001 G Street, N.W., Suite 500 West  
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TBS-1 testosterone nasal gel.

We also refer to the teleconference between representatives of your firm and the FDA on March 14, 2011. The purpose of the meeting was to discuss the phase 2 results, specifically the acceptability of the CMC and Preclinical programs to support a NDA filing and also the phase 3 study design.

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

If you have any questions, call Jeannie Roule, Regulatory Project Manager at (301) 797-3993.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** End-of-Phase 2

**Meeting Date and Time:** March 14, 2011 @ 1-2 PM  
**Meeting Location:** Teleconference

**Application Number:** IND 070512  
**Product Name:** TBS-1 testosterone nasal gel  
**Indication:** Testosterone replacement therapy in males  
**Sponsor/Applicant Name:** Trimel BioPharma SRL

**Meeting Chair:** Mark Hirsch  
**Meeting Recorder:** Jeannie Roule

**FDA ATTENDEES**

George Benson, M.D.	Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D.	Medical Team Leader, DRUP
Harry Handelsman, D.O.	Medical Officer, DRUP
Lynnda Reid, Ph.D.	Pharmacology Supervisor, DRUP
Jeffrey Bray, Ph.D.	Pharmacology Reviewer, DRUP
Myong Jin Kim, Pharm.D.	Clinical Pharmacology Team Leader, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology (DCP) III
Hyunjin Kim, Pharm D.	Clinical Pharmacology Reviewer, OTS, OCP,DCP III
Mahboob Sobhan, Ph.D.	Statistical Team Leader, Division of Biometrics (DB) III, OTS
Xin Fang, Ph.D.	Statistical Reviewer, DB III, OTS
Donna Christner, Ph.D.	Pharmaceutical Assessment Lead, Office of Pharmaceutical Sciences (OPS), Office of New Drug Quality Assessment (ONDQA), Division of Pre-Marketing Assessment (DPA) II
Steven Langille, Ph.D.	Microbiology Product Quality Reviewer, New Drug Microbiology Staff, OPS
Jennifer Mercier	Chief, Project Management Staff, DRUP
Jeannie Roule	Regulatory Health Project Manager, DRUP

**SPONSOR ATTENDEES**

Bruce Brydon	CEO, Trimel BioPharma Inc.
Wayne Kreppner MSc	VP Regulatory, Technical Operations, Trimel BioPharma Inc.
Jodi Dickstein Ph.D.	Director, Regulatory Affairs, Trimel BioPharma Inc.
(b) (4)	(b) (4)
Houri Simonian, Ph.D.	Director, Analytical Chemistry, Trimel BioPharma Inc.
Natalia Tkachenko, M.D.	Director, Clinical Nasal Products, Trimel BioPharma Inc.

**BACKGROUND:** To date, Trimel has completed three clinical trials in hypogonadal men; one Phase I, and two Phase II studies. A third Phase II study is ongoing. A summary of the completed and ongoing studies were presented in the briefing document.

The most recently completed study, Nasabol-01-2009, examined the efficacy and tolerability of 3.2% TBS-1 testosterone nasal gel. In this study, the results for the 11 mg twice daily dose did **not meet the FDA's principle acceptance criterion for standard testosterone therapies; that at least 75% of subjects should achieve an average total testosterone concentration within the normal range.** In addition, a linear increase in testosterone concentrations with escalating doses was not achieved. The Sponsor stated that the lack of a linear increase suggested that testosterone absorption was limited by inability of the nasal cavity to hold the tested volumes of TBS-1.

Based on the results of Nasabol-01-2009, Trimel is currently conducting an additional Phase II dose finding study, TBS-1-2010-01, evaluating higher concentrations of TBS-1 (4.0% and 4.5%) in reduced volumes. In addition, Trimel is evaluating two and three times daily dosing regimens.

For the TBS-1 NDA, in addition to the three completed trials and one ongoing study, Trimel proposes to conduct a single Phase III study. In addition to the Phase III study, Trimel proposes to perform a drug-drug interaction study to assess the relative bioavailability, safety and tolerance of TBS-1 when administered to patients with seasonal allergic rhinitis in the symptomatic, symptomatic but treated, and asymptomatic states.

**DISCUSSION:**

The following preliminary draft responses were provided to the Sponsor on March 10, 2011, in response to the questions posed in the Sponsor's **meeting package update provided to the Division on February 9, 2011.** The Sponsor's **questions are presented below in bolded text, followed by the Division's responses in normal text.** Additional discussion held during the meeting is summarized below in *italics*.

**Chemistry, Manufacturing, and Controls Questions:**

**1. Per the March 22nd 2006 meeting minutes, the Agency informed the applicant to develop a test for in vitro release. According to the Guidance for Industry: Nonsterile Semisolid Dosage Forms, Scale Up and Postapproval Changes: Chemistry, Manufacturing and Controls, the recommended *in vitro* release method for topical dosage forms that meets the requirement of drug release testing is based on an open chamber diffusion cell system, such as a Franz cell system, fitted with a synthetic membrane. Trimel intends to develop and validate a Franz cell assay for drug release during development and clinical/pivotal manufacturing** (b) (4).

**Does the Agency agree with this approach?**

Response: We agree with your use of a Franz cell assay and use for drug release during development and clinical/pivotal manufacturing. The test should also be included on stability during development. However, it is premature to agree to final tests and specifications for the commercial product at this time.

*Additional Discussion: The Sponsor stated that they [REDACTED] (b) (4) and they will submit an update to the Division in April, 2011.*

*Post-meeting comment: We acknowledge your proposal at the meeting to conduct IVRT at [REDACTED] (b) (4) during the stability studies. However, we have considered your proposal and recommend that you perform IVRT at all stability time points during development so that adequate data are available for review at the NDA stage.*

**2. As noted in the briefing document, Table 3.2.5-1 Specifications of COMPLEO Bulk Gel and Final Product, the finished drug product is tested to the listed test parameters and specifications at the time of release and stability testing. Does the Agency agree with the test parameters and specifications for COMPLEO?**

Response: Viscosity should be performed on drug product packaged in the dispenser both for release and on stability. The microbial limit testing has been consulted to OPS Microbiology to determine if the tests and acceptance criteria are adequate for a multi-use container for a preservative-free formulation, or if other tests are recommended. Please refer to the **Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation (July 2002)** (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm>) for a comprehensive list of tests that should be included for this dosage form and other issues that should be addressed during development of your product.

*Additional Discussion: The Sponsor stated that they did monitor viscosity but did not observe any changes. They plan to collect additional viscosity data and submit them to the Division.*

*The Sponsor acknowledged the FDA Guidance for gels and sprays but believes that their product does not fall into either category. The Sponsor stated their plan to do all testing that they deem appropriate for the product.*

*The Sponsor described the airless system of the delivery mechanism of their product. They explained that outside air does not enter the system but, nevertheless, they intend on testing for microbes as per the USP Guidance. The Division stated that the Sponsor's current microbe specifications appear to be acceptable but the Division is concerned about nasal contamination that will enter back into the device after the device has been used. The Sponsor reiterated that the outside air is always external to the device. The Division asked whether the Sponsor had data to resolve the Division concerns. The Sponsor responded that microbial studies had been performed on the expelled gel. The Division stated that because the content of the device is unpreserved, there is a continued concern about the shelf life of the drug product. The Division requested that in-use stability studies be conducted to evaluate microbial contamination of the formulation and container closure system during product use. The Division also asked the Sponsor to provide the results of studies investigating air and/or microbial ingress into the airless delivery system.*

**3. Trimel has completed an extractables study on its proposed container and will perform leachables in line with Product Quality Research Institute's guideline on Leachables and Extractables Management in Orally and Inhaled and Nasal Drug Products (OINDP). Does the Agency agree with this approach?**

**Response:** In addition to the PQRI guidelines, you should also refer to the following Guidances for Industry: **Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products- Chemistry, Manufacturing, and Controls Documentation (July 2002)** and **Container Closure Systems for Packaging Human Drugs and Biologics- Chemistry, Manufacturing, and Controls Documentation (May 1999)**

(<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm>.) for information on what is needed for extractable and leachable testing.

*Additional Discussion: There was no further discussion.*

**4. For the Phase III clinical study, we intend to use a multiple dose dispenser for gel deposition into the nasal cavity as shown in the figure below. The dispenser is a finger actuated dispensing system designed to dispense 5.5 mg of 4.5% w/w COMPLEO gel per actuation from a non-pressurized container into the nasal cavity. The dispenser is designed to deliver 45 doses (90 actuations) of COMPLEO. The key components of the multiple dose dispense include a barrel, base, pump and actuator composed of (b) (4) and a piston composed of (b) (4)**

**As the bioadhesive gel is responsible for delivering the testosterone at the site of administration and not the multiple dose dispenser, (b) (4) for release testing and stability purposes. Does the Agency agree with this approach?**

**Response:** No. The formulation and container closure system collectively constitute the drug product. Therefore, tests should be included for pump delivery, spray content uniformity, etc. Refer to *the* Guidance for Industry: **Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation (July 2002)** (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm>) for a comprehensive list of tests that should be included for this dosage form. Results of the performance tests for the pump may be important to show that the gel will be deposited in the same area of the nasal cavity as for deposition using the syringe.

*Additional Discussion: The Sponsor stated that the container closure system is designed to dispense a droplet of the drug into the nasal cavity. Neither a spray nor a plume is expected.*

*The Division commented that it would be beneficial if the Sponsor submitted the device containing a placebo sample so that it could be further evaluated and the Sponsor agreed. The Division inquired that if indeed it is a drop, how does the Sponsor intend to instruct the patient to spread the drop within their nasal cavity? The Sponsor explained that when the drop is dispensed into the nasal cavity there is no need to manipulate it.*

**5. According to the Guidance for Industry: Nonsterile Semisolid Dosage Forms, Scale Up and Postapproval Changes: Chemistry, Manufacturing and Controls, the proposed pivotal clinical trial batch size is (b) (4) kg. From the bulk, we intend to fill (b) (4) multiple dose dispensers containing (b) (4) g of gel which would represent 100,000 doses. Samples from these pivotal clinical trial batches will be put on stability (according to ICH) and serve as primary stability data for the NDA application. Updates on the stability of COMPLEO in the multiple dose dispenser will be provided to the Agency as it becomes available. The applicant currently has supportive stability data on testosterone intranasal gel at various concentrations in various container closure systems including bulk (stored in (b) (4) containers within (b) (4) bags), (b) (4) containers and a (b) (4) syringe. Does the Agency concur with this approach?**

**Response:** Because you are changing the packaging from a single-use syringe to a multi-dose spray bottle, you should submit some preliminary stability data on your Phase 3 clinical supplies prior to initiation of the trial. We recommend that you submit stability data under both long-term and accelerated stability conditions. Also, since your formulation does not contain a preservative, you will need to address how contamination of the remaining drug product is minimized once the product is in-use. The adequacy of your microbial limits specification has been consulted to OPS Microbiology and additional guidance will be provided.

In general, your primary stability studies should be performed on three batches of drug product in your commercial container closure system. Data gathered on the formulation in other container closure systems can be used as supportive data. Please ensure that your stability samples are stored both in the upright and inverted orientations. Changes in batch size above a factor of ten between the pivotal clinical batches and the proposed commercial batches would need to be bridged by comparative in vitro release testing.

*Additional Discussion: The Sponsor stated that they will submit 2-3 months real time and accelerated stability information. They further commented that they have redesigned the cap so it is rounded and the product can only be stored standing on its base or on its side.*

*The Division asked how the batch size compares to the proposed commercial plan. The Sponsor stated (b) (4)*

*The Division reiterated its concern about the lack of no preservative. The Sponsor believes that once the Division sees the actual device the Division will understand that there is no backflow potential and, therefore, a preservative is not necessary. They further stated that there is a DMF on file and they are planning to submit an updated LOA in the NDA. Trimel informed the Division that there is a commercially available device similar to the one that the Sponsor is proposing. The Division stated that they will need to see the device and will likely request a consult from CDRH.*

**Nonclinical Question:**

**6. The applicant has performed local tolerance studies (HET-CAM, acute dose and repeated dose) and a 3-month repeat dose toxicity study in male rabbits to support the**

safety of nasally applied testosterone. At our proposed maximum dose and dosing regimen (33 mg t.i.d dosing) the daily exposure margin will be 4-fold to the clinical exposure. At our proposed minimum dose and dosing regimen (22 mg b.i.d. dosing) the daily exposure margin will be 6-fold to the clinical exposure. We feel that the combination of literature data and the studies completed by the applicant constitutes a complete pre-clinical and toxicology section as prescribed in the ICH guidance M3(R2) and is sufficient for NDA submission. Is the Agency in agreement with this approach?

Response: Yes, if the rabbit repeat dose toxicity study included the novel excipient oleoyl polyoxyglycerides (which is not in any FDA-approved drug product). If not, then an additional rabbit toxicology study using the clinical formulation containing oleoyl polyoxyglycerides is recommended.

*Additional Discussion: The Sponsor confirmed that the study was done with the polyoxyglycerides for male rabbits.*

**Clinical Question:**

7. To date, Trimel has completed four Phase II clinical trials in hypogonadal men: TBS-1-2010-01, Nasobol-01-2009, MAT/05 and MAT/04. The most recently completed Phase II study (TBS-1-2010-01) evaluated the PK profile of a higher concentration of COMPLEO (4.5%) with a reduced dose weight for equivalent doses to those studied in Nasobol-01-2009.

For the COMPLEO NDA, in addition to the four completed trials, Trimel proposes to conduct a single Phase III study to demonstrate that 4.5% COMPLEO restores testosterone to normal physiological levels in hypogonadal men (Cavg 0-24h  $\geq$  300 ng/dl and  $\leq$  1050ng/dl). The study synopsis is provided in Appendix A.

In the Phase III study, we intend to investigate 4.5% COMPLEO at the lowest efficacious dose. Two hundred (200) patients will initially receive 5.5 mg of a 4.5% w/w COMPLEO gel per nostril b.i.d. at 2100 and 0700 hours; total daily dose 22 mg/day. A testosterone serum PK profile will be performed on Day 30. Patients that do not achieve a testosterone serum Cavg of 300 ng/dL on Day 30 will be switched to the t.i.d. administration regimen at 2100, 0700 and 1300 hours for total daily dose of 33 mg/day on Day 45. The final testosterone serum PK profile will be performed on Day 90. Secondary endpoints will include subjective assessments of the subjects overall sexual desire/libido, vigor/vitality, erection parameters and mood assessment at baseline, Day 45 and Day 90.

All patients enrolled into the 3-month efficacy portion will be requested to participate in the extended open label (b) (4)-month safety study. Patients will receive the same dose in the safety extension as they were receiving at the end of the efficacy phase of the clinical study. This will provide (b) (4) months of safety data, confirming the tolerability of 4.5% COMPLEO to the nasal mucosa in approximately 200 subjects. Safety parameters will include a daily diary, monthly ENT examinations, vital signs, adverse events, CBC and serum testosterone, DHT and estradiol. A complete CBC, clinical chemistry profile, urinalysis, serum PSA and digital rectal prostate exam will be performed at the close out visit.

**In addition to the pivotal Phase III study, Trimel intends to perform a Drug-Drug Interaction study as requested by the Agency in the pre IND meeting on October 18, 2004. This study will assess the relative bioavailability, safety and tolerability of COMPLEO when administered to patients with symptomatic untreated and treated (oxymetazoline) seasonal allergic rhinitis as well as symptomatic asymptomatic subjects using an environmental exposure chamber model. The synopsis for this study is provided in Appendix B.**

**Will the clinical study plan described above be sufficient for an NDA filing?**

Response: The clinical plan is not yet sufficient for an NDA filing. We have the following efficacy, safety and study design concerns and proposals for their resolution:

Efficacy concern: PK-based efficacy endpoints alone are not sufficient for Compleo due to wide peak to trough fluctuations in serum testosterone (T) resulting in considerable time outside the normal physiological range and multiple testosterone peaks.

- In addition to Cavg and Cmax, time within the normal range (TWRN) should be incorporated as an additional PK-based efficacy endpoint.
- Several clinical (pharmacodynamic) efficacy endpoints should be incorporated into the Phase 3 study in order to provide support for a clinical androgenic effect of Compleo. You might consider parameters likely to be affected by testosterone replacement, such as bone mineral density, lean and fat body composition, libido, erectile function, and mood. The best possible assessment tools and questionnaires should be selected for these endpoints. Please be aware that the results from these pharmacodynamic assessments, while useful as supportive clinical evidence to the PK-based efficacy parameters, are unlikely to result in labeling claims. Additional discussion would be needed in regard to endpoint validation and study design (e.g., need for a placebo control) if such labeling claims are desired.

*Additional discussion. The Sponsor stated that despite the PK profile of the twice or thrice daily nasal instillations, the product is capable of meeting the FDA's PK-based efficacy criteria for testosterone replacement. The Sponsor also remarked that observed increases in serum DHT and estradiol concentrations themselves ought to be viewed as clinically meaningful evidence of efficacy. In response, the Division reiterated its position that clinical endpoints will be needed for TBS-1 to confirm the relevance of the PK endpoints.*

*The Sponsor inquired about particular clinical endpoints. The Division stated that it does not have any definite guidelines in place at this time for selection of clinical endpoints for studies in the treatment of male hypogonadism; however, the Sponsor can consider the following: bone mineral density, body composition, mood and psychosexual questionnaires, and measures of erectile function. The Sponsor agreed to submit a proposal for clinical assessments.*

*The Division acknowledged the Sponsor's inclusion of SF36 and the UCLA 7-Day Psychosexual Survey, but stated that these were not sufficient. The Division stated that the SF 36 was too general and there are many problems with the UCLA survey.*

*The Sponsor asked that DRUP to clarify the request concerning "time within normal range." DRUP responded that the Sponsor should count the hours that the patient maintains a total testosterone concentration within the normal range. The Sponsor agreed to calculate this and provide this specific information.*

**Safety concern:** The total duration of treatment (b) (4) is not sufficient to assess long-term nasal safety nor to define potential risks associated with wide peak to trough fluctuations (e.g., negative effects on mood, prostate health, and blood pressure).

As previously agreed at the October 18, 2004, Pre-IND meeting, the safety extension should be 9 months, for a total treatment duration of 12 months. At least 50 patients should be exposed for  $\geq 1$  year and approximately 200 patients for  $\geq 6$  months. In addition, we recommend incorporating an active control arm (e.g., an approved testosterone product) in order to compare the major safety parameters (e.g., PSA, CBC, serum lipids, etc).

*Additional Discussion: The (b) (4) (b) (4) (b) (4) The Division stated that the NDA should be complete upon filing, including the full 12 months of safety data. The Sponsor questioned whether additional valuable information would be generated from a full year of exposure compared to just (b) (4) months, but, nonetheless, Sponsor agreed to conduct a 9-month safety extension to achieve the safety objectives laid out by the Division.*

**Study design concern:** (b) (4) (b) (4)

(b) (4) (b) (4) scheme cannot be determined for Compleo, then we recommend incorporating two, fixed-dose arms in the Phase 3 study (11 mg BID and 11 mg TID).

*Additional Discussion: The Sponsor stated a plan to conduct the study as proposed in the protocol synopsis despite the Division's concerns; that is, they will use (b) (4) (b) (4)*

*The Division disagreed with the Sponsor's plan, stating that (b) (4) (b) (4) The Division remarked that the Sponsor's approach seemed risky since there is the distinct possibility that it will be difficult, perhaps impossible, to demonstrate the appropriateness and functionality of a (b) (4)*

(b) (4) The Division cannot recommend that the Sponsor continue their plans with the currently proposed (b) (4). The Division recommended that the Sponsor propose an alternate plan. The Division further noted that if the Sponsor's paradigm cannot be translated into (b) (4) based upon feasible clinical practice, then that that would constitute a major concern and review issue.

Instead, the Division recommended that the Sponsor evaluate the PK of fixed doses, then review the data for twice daily and thrice daily dosing separately. The Division recommended a fixed-dose, parallel arm study design.

Despite this advice, the Sponsor continued to express a desire to study a (b) (4). The Division again cautioned the Sponsor concerning their plan of doing a (b) (4). If the Sponsor did not wish to study fixed doses, then the Division recommended that the Sponsor prospectively develop a reliable titration method to titrate patients from BID to TID dosing and incorporate it into the Phase III study. The Division stated that (b) (4). Based on the product profile, this could be a challenge.

#### Additional Clinical comments

1. For enrollment, biochemical hypogonadism (a.m. serum T  $\leq$  300 ng/dL) should be confirmed by repeat a.m. serum T  $\leq$  300 ng/dL.
2. Detailed procedures and specific assessments for the monthly ENT examinations should be provided. These will be evaluated by our Division of Pulmonary Allergy and Rheumatology Products (DPARP).
3. Comments from DPARP regarding the design and procedures in the Drug-Drug Interaction study (TBS-1-2011-02) are forthcoming.

#### Additional Clinical Pharmacology comments

1. Any subjects taking dietary supplements affecting testosterone concentration such as androstenedione should be excluded from the proposed phase 3 study.
2. Explain the reason for the significant difference in responder rates (51.9% vs. 100%) between studies Nasobol-01-2009 and TBS-1-2010-01 when total daily doses were similar in the two studies (28 mg/day vs. 27 mg/day).
3. Subjects in the decongestion arm should receive the maximum single dose of oxymetazoline in your proposed drug-drug interaction study.

*Additional Discussion: Regarding Additional Clinical Pharmacology comment #2, DRUP asked whether the Sponsor was assuming that a decreased volume would serve to increase efficacy. The Sponsor stated that they noticed better patient compliance when using the lower volume,*

*with less gel dripping from the nose. The Sponsor contended that the major issues in Nasobol-01-2009 were non-compliant patients and large gel volume.*

**Additional Biometrics comment**

The final protocol should pre-specify the sample size adjustment for anticipated drop-outs and number of completers required at endpoint.

*Additional Discussion: There was no further discussion.*

**Post-meeting comments from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP):**

**1) Regarding ENT exams in the Phase III study**

- a. *The Sponsor's plan to conduct monthly ENT examinations appears reasonable. Assessment for nasal adverse events is generally based on direct examination of the nasal nose and nasal mucosa. The safety concerns of local irritation, nasal ulceration, and the rare occurrence of nasal septal perforation are adverse events that are diagnosed on direct examination. In addition to the monthly ENT direct examinations, patients will be asked to complete a daily diary. These procedures are adequate to assess for local nasal toxicity and we do not have additional recommendations for nasal safety assessments.*
- b. *Typically, for products containing novel excipients that are going to be used on a chronic basis, we would generally require safety data out to 1 year (minimum 100 patients), with at least 300 patients also exposed for at least 6 months. Therefore, the Sponsor should collect data out to one year in a subset of patients. The Division's previous recommendation of at least 50 patients for 1 year seems quite small; however, if there are no safety signals seen with shorter term exposure, then this number may be adequate.*

**2) Regarding the design and procedures in the Drug-Drug Interaction Study**

- a. *The Sponsor should provide specific details in the protocol about where this study will be conducted.*
- b. *Oxymetazoline (Afrin nasal spray) is sold over the counter and is used (short term – not recommended for use more than 3 days) for nasal congestion. It does not have an effect on the other symptoms of allergic rhinitis and it is not the most commonly used medication for allergic rhinitis (these are usually antihistamines or nasal steroid sprays). However, the potential for reducing systemic absorption of testosterone is probably greatest with the use of oxymetazoline because of its vasoconstrictor effect. Therefore, given the objective of the study, oxymetazoline is probably the best choice to use in this situation.*

- c. The patient population selected and the exclusion criteria seem appropriate.*
- d. The Sponsor proposes a 7 day wash out period. Since this is a cross over study, it is important to ensure that the wash out period is sufficient.*

**ACTION ITEMS**

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

**ATTACHMENTS AND HANDOUTS**

None

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

/s/  
-----

MARK S HIRSCH  
05/04/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 70,512

Mattern Pharmaceuticals AG  
Attention: Susanne Wilhelm, M.S., RAC  
Application Specialists International, Inc.  
109 Shore Drive  
Garner, NC 27529

Dear Ms. Wilhelm:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Nasobol® (testosterone nasal gel).

We also refer to the Type C meeting between representatives of your firm and the FDA on March 22, 2006. The purpose of the meeting was to provide guidance regarding your Phase 2 data and pre-Phase 3 development plans.

We further refer to your correspondence dated March 21, 2006, containing your responses to our March 17, 2006 preliminary draft comments and answers.

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

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** March 22, 2006      **TIME:** 1 pm – 2:30 pm

**LOCATION:** Food and Drug Administration  
White Oak Building 22, Conference Room 1421  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**APPLICATION:** IND 70,512

**DRUG NAME:** Nasobol® (testosterone nasal gel)

**TYPE OF MEETING:** Type C, Guidance

**MEETING CHAIR:** Mark Hirsch, M.D.

**MEETING RECORDER:** John Kim, R.Ph., J.D.

**FDA ATTENDEES:**

Mark Hirsch, M.D. – Medical Team Leader, DRUP  
Anthony Orenca, M.D., Ph.D. – Medical Officer, DRUP  
Harry Handelsman, O.D. – Medical Officer, DRUP  
Roger Wiederhorn, M.D. – Medical Officer, DRUP  
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology (OCP)  
Stephan Ortiz, R.Ph., Ph.D. – Clinical Pharmacology Reviewer, OCP  
Donna Christner, Ph.D. – Pharmaceutical Assessment Lead, Pre-Marketing Assessment Division II (PMAD II), Office of New Drug Quality Assessment (ONDQA)  
Wafa Harrouk, Ph.D. – Pharmacology/Toxicology Reviewer, DRUP  
John Kim, R.Ph., J.D. – Regulatory Health Project Manager, DRUP

**MATTERN ATTENDEES:**

Claudia Mattern, Ph.D. – Chief Technical Officer, Mattern Pharmaceuticals AG  
Eric Wiechert, Ph.D. – President, Applications Specialists International, Inc. (ASI, Inc.),  
CMC/Regulatory Consultant and US Representative  
Susanne Wilhelm, M.S., RAC – Regulatory Affairs Manager, ASI Inc.

(b) (4)

(b) (4)

(b) (4)

**BACKGROUND:**

Nasobol® is an intranasal gel intended for testosterone replacement in men with primary or secondary hypogonadism. A Pre-IND meeting was held on October 18, 2004. The original IND was submitted on June 28, 2005, and contained a protocol for a 14-day study in 21

hypogonadal men (Clinical Study TST-DF-02-MAT/05). The Sponsor requested this meeting to discuss: the Phase 2 study results, a protocol for a Phase 3 study, a protocol for a drug-drug interaction study, additional CMC requirements for Phase 3, and a waiver/deferral of pediatric studies. Draft responses to the meeting questions were provided to the Sponsor on March 17, 2006. The Sponsor submitted a response on March 21, 2006.

**DISCUSSION POINTS:**

The discussions that follow were generated from the Sponsor's specific questions, the Division's preliminary responses, and the Sponsor's additional comments received prior to the meeting. The Sponsor provided two handouts that are attached.

**QUESTION #1:** *Does the Agency concur with the revised protocol for the pivotal phase III study?*

**DRUP Response:** No. The Division does not concur with the Phase 3 protocol. Based upon the results from your Phase 2 study, we consider it premature to provide comments for a Phase 3 protocol for Nasobol. Pharmacokinetic profiles achieved in the Phase 2 study using twice or thrice daily Nasobol 7.6mg regimens were not physiological. Nasobol shows rapid absorption and rapid elimination following each dose. The exposure characteristics of Nasobol with sharp peaks and rapid declines are not comparable to the exposure of normal physiologic serum testosterone (T) levels. We, therefore, have concerns that pharmacokinetics cannot be used to determine adequate physiologic T replacement with Nasobol. Our main concerns are these:

- Demonstrating efficacy is problematic as Nasobol does not mimic physiologic levels of serum T. It is not known whether the expected downstream clinical effects of T replacement in hypogonadal men will manifest at the current Nasobol dose and regimen. We note that most subjects administered 7.6mg three times daily experienced periods where T concentrations fell below the lower limit of normal (300ng/dL). And, statistically significant mean reductions (not increases) in serum hemoglobin, RBCs, and hematocrit levels were observed at the follow-up visit compared to screening.
- "Bursts" in serum T concentration observed soon after each dose of Nasobol 7.6mg TID could mediate safety problems; such as, adverse effects on mood (e.g. anger), on the prostate (e.g. stimulation of latent cancer), and perhaps on blood pressure (e.g. increases in BP).

**Additional Discussion:** Discussion ensued regarding the Division's response to Question #1. The Sponsor stated that the concentration-time profile for testosterone in healthy men shows a circadian rhythm with a significant peak in the morning and increasing concentrations after 8 PM. The Sponsor stated that fluctuations in testosterone levels seen with Nasobol should be viewed as beneficial; while continuously stable hormone concentrations may be viewed as detrimental via suppression of endogenous T. The Division reiterated its primary concern: that the serum T concentration-time profile observed for Nasobol, with wide peak to trough fluctuations, is quite different than the normal physiologic profile, may not be adequate for serum T replacement therapy in hypogonadal men, and may be associated with additional risks

compared with the normal physiologic T profile. Therefore, serum T cannot be used as the primary endpoint for registration for Nasobol.

The Sponsor inquired as to the sort of data that would, therefore, be required for registration of Nasobol. The Division stated that a controlled clinical trial (or trials) would be necessary, using clinical endpoints as the primary evidence for effectiveness. Discussion ensued as to the best clinical endpoint and design for such a study and no agreement was reached. While no agreement was reached on the amount of safety information required, the Division indicated that years of data would be necessary to support safety of Nasobol.

In terms of a path forward, DRUP suggested the following:

- Reformulate the product to achieve more physiological T replacement.
- Provide a proposal to conduct controlled clinical studies to support the *clinical* efficacy and safety of Nasobol 7.6mg twice or thrice daily.
- Propose some other means to resolve our concerns.

**QUESTION #2:** *Is the protocol for the proposed drug-drug interaction study acceptable and sufficient to support an NDA?*

**DRUP Response:** The proposed drug-drug interaction study is adequate to determine the effect of nasally administered products on the PK of Nasobol. We request assessments of blood pressure and heart rate prior to the dose of Nasobol and at the time of each blood sampling.

The Sponsor should be aware that other clinical pharmacology studies are required in support of an NDA. For example, if the clinical and to-be-marketed formulations are not identical, appropriate bridging studies are required.

**QUESTION #3:** *We assume that according to the minutes of our telephone conference of 18 October 2004 both the results of the pivotal phase III study (after 12 weeks) and the drug-drug interaction study serve as the basis for deciding on the NDA approval. Does the Agency agree?*

**DRUP Response:** No. See our responses to Questions #1 and #2, regarding the Phase 3 trial and other studies that may be required, respectively. Please be aware that an NDA must be complete upon filing, with all efficacy and safety information necessary for approval, including long-term safety data.

**QUESTION #4:** *We feel the CMC information provided with the IND is also sufficient for the NDA with the exception of updating the stability data available at the time of filing. Does the Agency agree with this statement?*

**DRUP Response:** No, the Division does not agree with this statement. During the 30-day safety review of the IND, the chemist evaluates whether there are concerns that would affect the safety of the subjects in a clinical trial. This review is in no way exhaustive, and it should not be

construed that the submitted data is adequate for NDA filing. We have the following recommendations for the CMC section of an NDA application for Nasobol:

- Please refer to the following Guidances for information on submission of information to an NDA:
  - 1) M4: Common Technical Document for the Registration of Pharmaceuticals for Human Use M4: The CTD -- Quality [HTML] or [PDF]
  - 2) Nasal Spray and Inhalation Solution, Suspension, and Drug Products [HTML] or [PDF] (Issued 7/2002; Posted 7/3/2002)
  - 3) SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (Issued 5/1997; Posted 6/16/1997)
- Develop a test for in vitro release. This should be added to the release and stability specifications.
- Outline any formulation changes. Additional Discussion: Sponsor indicated that no changes have been made and none are planned.
- Outline any manufacturing changes that may have occurred. Additional Discussion: Sponsor stated that manufactured changes were outlined in Volume 4.
- Include a specification for delivered dose. Additional Discussion: Sponsor stated that a specification for delivered dose was included in Volume 4.
- Demonstrate the need for (b) (4).

A more exhaustive review of the IND submission will be performed, and any other CMC recommendations will be conveyed prior to the start of Phase 3 trials.

#### Additional Clinical Comments

- Results from otorhinolaryngological exams were not provided in the Phase 2 study report. Please provide these results.

Additional Discussion: The Sponsor provided these results on March 21, 2006. In future trials, the Division recommends a more systematic procedure for conducting otorhinolaryngological exams.

- The available clinical experience with Nasobol is quite limited (n=8 single-dose subjects, and n=21 subjects for 14 consecutive days; all from the same center in Romania). It may be beneficial to meet with the Division again after additional Phase 1 and Phase 2 studies have been conducted.
- Provide an explanation for the protocol-defined food restrictions during 24-hour blood sampling in the Phase I and II studies. Is there any reason to believe that food or eating may result in testosterone exposure differences?

Additional Discussion: Sponsor anticipated no exposure differences based upon food or eating. The feeding schedule was intended simply for site convenience.

- Justify that data from these 29 non-U.S. patients is applicable to the U.S. population. We have concerns that weight differences in potentially heavier U.S. patients may result in testosterone exposure differences.

Additional Discussion: The Sponsor indicated that no differences were found in the pharmacokinetics of testosterone in subjects with normal body weight (BMI  $\leq 25$ ) versus subjects who were overweight. In subsequent trials, the Sponsor would enroll heavier subjects.

- We note that screening serum T was  $<50\text{ng/dL}$  in 20 of 21 subjects, and serum LH was also quite low in many Phase 2 study subjects. Please provide specific medical diagnoses for these 21 subjects, many of whom appear to have severe hypogonadotropic hypogonadism.

Additional Discussion: Specific medical diagnoses were provided on March 21, 2006. The Sponsor stated that severely hypogonadal subjects were specifically enrolled in this Phase 2 study to demonstrate the effectiveness of Nasobol. The Sponsor indicated an intention to enroll a range of hypogonadal patients in subsequent studies, including less severe degrees of hypogonadism.

- Labeling for all testosterone products in the U.S. is currently under intense review and will be evolving.
- No claims for the treatment of aging males ("andropause") will be allowed in labeling.
- Nasobol would ultimately qualify for a waiver of pediatric studies for all females and for males up to age 10. For males aged 11-16, studies would be required. The Sponsor was encouraged to communicate with the Division of Metabolism and Endocrinology Products (DMEP) regarding pediatric studies for Nasobol.
- At some point in during drug development, the PK of Nasobol in patients with allergic rhinitis should be assessed, because of potential for differences in testosterone exposure.
- The Division considers the AMS questionnaire to be an exploratory instrument for purposes of assessing clinical efficacy in hypogonadal men. The Sponsor clarified that the lower the AMS score, the higher the improvement.

#### Pharmacology/Toxicology Comments

- In the event that the formulation of Nasobol is changed, be advised that additional bridging toxicity studies might be requested.

Additional Discussion: When the Sponsor inquired whether certain changes in formulation (e.g. (b) (4)) would require additional bridging studies, the Sponsor was informed to submit such a proposal in writing for review.

**ACTION ITEMS:**

- The Project Manager will provide meeting minutes within 30 days of the meeting date.

**Signature: Meeting Chair**

*{See Appended Electronic Signature}*

**Mark Hirsch, M.D.  
Medical Team Leader**

**ATTACHMENTS: Handouts**

Handout #1

Formulation	Study	N	Treatment (g)	EMM	Mean T (months)	ABC (months) <sup>a</sup>	C <sub>0</sub> (months)	C <sub>100</sub> (months)	C <sub>200</sub> (months)
Nasal	b.i.d. (0 AMZ2PM)	7	14	25.8 ± 4.4 (19.5-31.0)	1.9 ± 1.9	202 (201; 241)	16.9 (8.2; 14.5)	29.8 (21.9; 40.5)	3.5 (1.9; 4.6)
	b.i.d. (0 AMZ8PM)	7	14		1.3 ± 2.1	272 (100; 410)	11.5 (7.3; 17.6)	29.6 (16.1; 54.4)	5.45 (3.4; 8.7)
	t.i.d.	7	14		0.5 ± 0.5	305 (277; 337)	16.4 (11.2; 23.9)	39.4 (31; 58.1)	7.6 (4; 14.5)
Androgel <sup>b</sup>		34	7	27	< 6.74	304 ± 134	-	26.60	5.76
		76	30	-	6.8	150 ± 18	14.80	19.96	8.15
		102	30	29.9	8.5	-	12.7	18.8	6.2
Striant <sup>c</sup>		39	7	27.4	< 6.7	451	-	31.50	11.1
	30	94	30	30	8.1	-	12.7	18.8	15.2
Testim <sup>d</sup>	30	100	30	29.9	8.1	-	21.5	31.5	13.6
	100	73	30	-	6.46	300 ± 20	19.40	30.97	12.32
AndroGel <sup>e</sup>	30	78	30	-	6.46	446 ± 39	27.46	41.6	17.51
	100	78	30	-	6.46	446 ± 39	27.46	41.6	17.51

<sup>a</sup> Karkhane et al. JCEM 49: 2036, 2004  
<sup>b</sup> Smith et al. JCEM 48: 2673, 2003  
<sup>c</sup> Swindle et al. JCEM 43: 4206, 2000

Handout #2

	Group A b.i.d. 0AMZ2PM	Group B b.i.d. 0AMZ8PM	Group C t.i.d. 0AMZ2PMZ8PM
Total (no. of samples)			(b) (4)
300 - 1,000 ng/dL (%)			
< 100 ng/dL (%)			
< 200 ng/dL (%)			
< 300 ng/dL (%)			
200 - 250 ng/dL (%)			
251 - 299 ng/dL (%)			
> 1,000 ng/dL (%)			

<sup>a</sup> 1,000 ng/dL - upper limit of the adopted laboratory (b) (4)

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

/s/

-----  
Mark S. Hirsch  
4/20/2006 04:24:33 PM

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** October 18, 2004      **TIME:** 1 pm – 2:30 pm  
**LOCATION:** Teleconference  
**APPLICATION:** PIND 70,512  
**DRUG NAME:** Nasobol™ (testosterone nasal gel)  
**TYPE OF MEETING:** Type B, Pre-IND  
**MEETING CHAIR:** Mark Hirsch, M.D.  
**MEETING RECORDER:** John Kim, R.Ph., J.D.

**FDA ATTENDEES:**

Mark Hirsch, M.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580  
Harry Handelsman, M.D. – Medical Officer, DRUDP (HFD-580)  
John Kim, R.Ph., J.D. – Regulatory Project Manager, DRUDP (HFD-580)  
Wafa Harrouk, Ph.D. – Pharmacologist, DRUDP (HFD-580)  
Jean Salemm, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)  
Dhruba J. Chatterjee, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)  
Julie Bullock, Pharm.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)  
David Hussong, Ph.D. – Associate Director for Microbiology, Office of Pharmaceutical Science (OPS), New Drug Microbiology (HFD-805)

**EXTERNAL CONSTITUENT ATTENDEES:**

Udo Mattern – Mattern Pharmaceuticals AG/ Mattern Research, Inc.  
Claudia Mattern, Ph.D. – Mattern Pharmaceuticals AG/ Mattern Research, Inc.  
Christian Sigd, M.D. – Mattern Pharmaceuticals AG/ Mattern Research, Inc.

(b) (4)

**BACKGROUND:**

The Sponsor, Mattern Pharmaceuticals, seeks a Pre-IND meeting with the Division regarding Nasobol™ (testosterone nasal gel). Nasobol is a novel intranasal product intended for hormone replacement in males with primary or secondary hypogonadism. The Sponsor would like to

**BACKGROUND (cont'd):**

discuss its development plans and requirements for a New Drug Application under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FD&C Act).

The Sponsor submitted the meeting package with the meeting request. The meeting package contained a number of questions for the Division to address. Preliminary draft responses were sent to the Sponsor prior to the meeting date. The meeting was subsequently changed to a teleconference in lieu of a face-to-face meeting. The Sponsor also submitted additional comments for the Division to consider in preparation for the teleconference.

**DISCUSSION POINTS:**

The discussions that follow were generated from the Sponsor's specific questions, the Division's preliminary responses, and the Sponsor's additional comments prior to the teleconference.

**QUESTION #1 – Preclinical studies:**

*Does the Division agree with the proposal* (b) (4) ?

**DIVISION RESPONSE:**

The studies conducted to date are sufficient to support the proposed initial clinical study. However, based on the new route of administration, a 3-month toxicity study using the formulation intended to be used in clinical trials should be conducted in either the rat or the rabbit via the intranasal route to support clinical trials longer than 2 weeks duration. A recommended study design would include nontreated (sham control), vehicle control and 3 drug treatment groups. The highest dose used should be based on the maximum feasible dose. This may be accomplished by increasing the concentration of testosterone in the clinical formulation or by administering multiple daily dosing. At least one of the dosing groups should mimic the proposed clinical dosing protocol, i.e., once, twice or three times daily administration. Safety endpoints should include in-life clinical assessment, clinical pathology, plasma testosterone and dihydrotestosterone levels, complete necropsy, major organ weights and histopathological evaluation of the respiratory tract including multiple samples from the nasal cavity (n=3-5), reproductive organs and brain as well as any gross lesions. We recommend submission of the nonclinical protocol for review prior to initiation of the study.

**Additional comments:**

- Sponsor indicated that it is willing to conduct a 3 month study in rats or rabbits via intranasal route to support clinical trials longer than 2 weeks duration. However, the Sponsor inquired as to the Division's rationale and requirement for a longer duration preclinical study given that the intranasal dosage is expected to be lower than other that applied to the skin or ingested in other dosage forms. The Sponsor believed that (b) (4) study should be sufficient to characterize potential nasal toxicity.
- The Division explained that because the Sponsor's product is a novel route of administration for testosterone replacement therapy, and because none of the excipients have been used intranasally, a 3 month study is the minimum preclinical requirement.

Because the general toxicity of testosterone is well known, The Division is only requesting the Sponsor to conduct a 3 month toxicity study instead of a full toxicology program.

**QUESTION #2 – PK Studies:**

- a) *Does the FDA concur with Mattern's proposal for pK studies?*
- b) *Will such studies "likely" satisfy FDA requirements for approval of NDA?*

**DIVISION RESPONSE:**

- a) The Division concurs with the studies proposed in the outline of your drug development plan. For this indication, an NDA may consist of a single, 12-week, Phase 3 study (with safety extension) and "supportive evidence", such as your single and multiple-dose studies. One comment: Gather both total serum testosterone and serum dihydrotestosterone (DHT) in all pharmacokinetic (PK) studies.
- b) The NDA approval decision will be based on a review of data from these studies.

**Additional comments:**

- The Sponsor agreed to report data for both total serum testosterone and serum DHT in all PK studies.
- The Sponsor acknowledged the clinical requirements for NDA submission.

**QUESTION #3 – Safety study:**

- a) *Does the Division concur with the proposed safety/tolerability study; (b) (4) [redacted] ?*
- b) *Will such a study likely satisfy FDA requirements for approval of an NDA pursuant to section 505(b)(2)?*
- c) *Will such a study likely qualify for 3 years of market exclusivity?*

**DIVISION RESPONSE:**

- a) The Division can not concur with Sponsor's proposal to continue the safety and tolerability aspects of the Phase 3 study for (b) (4) [redacted]. Revise the pivotal study to include a 9-month safety extension period, so that at least 50 patients will be treated for ≥1 year and at least 200 patients for ≥6 months. Include periodic detailed nasal examinations by an ENT physician.

At an appropriate time in development, submit a complete protocol for the single Phase 3 trial (and safety extension) including such details as design and procedures, number of subjects involved, endpoints, analysis plan, study duration, and eligibility criteria. The Division cannot provide concurrence for the Phase 3 study until we've reviewed this protocol.

- b) This NDA would be a 505(b)(1) application – not a 505(b)(2).
- c) The sponsor of an approved NDA under 505(b)(1) is granted 3 years of market exclusivity for the product.

**Additional comments:**

- The Sponsor agreed to revise the pivotal study to include a 9 month safety extension so that at least 50 subjects will be treated for  $\geq 1$  year and at least 200 subjects for  $\geq 6$  months, as recommended by the Division. Also, the Sponsor agreed to include periodic detailed nasal examinations by an ENT physician.

**QUESTION #4 – Chemistry, Manufacturing, and Controls (CMC):**

*Do the proposed chemistry, manufacturing, and control procedures appear to be acceptable to the Division?*

**DIVISION RESPONSE:**

The CMC information as presented appears to be acceptable. Additionally, the following should be submitted with the IND:

- A letter of authorization from (b) (4), the drug substance manufacturer that will authorize the Agency to review the Drug Master File (DMF) for the drug substance.
- Drug product stability data to support the use of the drug product during clinical studies.
- Information on the (b) (4) material used for the unit container. Provide a statement that the (b) (4) is acceptable for use according to 21 CFR regulations. If the (b) (4) has not been approved for use, then results from toxicity studies according to the USP <87>, in-vitro toxicity testing, should be provided.

**SPONSOR RESPONSE:**

- The Sponsor indicated that a letter of authorization is available and that (b) (4) has already submitted the DMF authorization letter to the Agency.
- The Sponsor indicated that drug stability data are available for 3 months storage at 25°C and 40° C, temperature cycling (-20° C/+ 40° C changing every 12 hours for 4 weeks), and from photostability studies.
- The Sponsor will provide appropriate DMF references, specifications and tests that support the use of (b) (4) for the container system, and is conducting the toxicity study according to USP <87>.

**ADDITIONAL CMC COMMENTS:**

- The Division recommended that a test be developed to be included in the drug product specification that will control the amount delivered from the unit dose container. The Sponsor indicated that a test method has been developed to control the amount delivered from the container.
- The Division inquired if the excipient, (b) (4), is a (b) (4). The Sponsor explained that (b) (4) is not a (b) (4). The Sponsor further explained that a (b) (4) would not be desirable in this

formulation. (b) (4) "is added for its (b) (4)  
"

- The Division recommended the addition of a microbiological test for bioburden to the drug product specification, and that the Sponsor develops a protocol to demonstrate the adequacy of the formulation to prevent growth of bioburden in the absence of antimicrobial preservatives. Due to the low water activity of this formulation, emphasis on bacterial spores and fungi would be anticipated. The Sponsor indicated that a test for bioburden is done and will be part of the specification in conformance with USP <61>.

**ADDITIONAL CLINICAL COMMENTS:**

- The Division requested that the Sponsor provide a justification for the starting dose of 7.5mg in the first IND study. The Sponsor indicated that the dose was selected based on previous experience with an aqueous formulation and from data in literature which will be included in the IND. The Sponsor remarked that if the dose is too low or too high, it will repeat the first study.
- The Sponsor was advised to carefully choose a formulation, a dose, and a dose regimen so as to avoid serum testosterone concentrations above the normal physiological range.
- The proposed future label states that the (b) (4)  
Current labels for the proposed indication advise that (b) (4)  
The Sponsor understood that (b) (4)
- Future submissions will provide serum testosterone concentrations using the units "ng/dL," not "nmol/L."
- In the trials, biochemical hypogonadism will be defined as total serum testosterone concentration <300ng/dL.
- The Division requested the Sponsor to address differences in absorption with intercurrent illness, such as upper respiratory infections (URI) or allergic rhinitis. The Sponsor proposed to label the product to exclude subjects suffering from such illnesses or to conduct such studies under a Phase 4 commitment. The Division disagreed with a Phase 4 commitment proposal, and indicated that such labeling restrictions may not be realistic. But the Division agreed that these subjects can be excluded in the Phase 1 and Phase 2 trials. However, in Phase 3 trials, the Sponsor needs to further discuss with the Division on which subjects to exclude.
- Consistent with labeling for all other approved testosterone products, no claims for the "treatment of aging" or "andropause" will be allowed in labeling. The Sponsor agreed that these will not be claimed.

- Because the proposed "future" label states that testosterone is contraindicated in those patients with known prostate cancer, the Sponsor agreed that future labeling will state that testosterone is contraindicated in patients with known or suspected prostate cancer.
- The Division inquired as to the potential consequences of inhaling or snorting this nasal testosterone product. The Sponsor explained that this product is highly viscous and is not expected to spread very much; the formulation is designed to adhere to the nasal mucosa. However, if the product does move up the nasal cavity or if it is swallowed, the Sponsor believes that it is not likely to have adverse consequences. The Division expressed concern that this product may pass through the cribriform plate into the cerebrospinal fluid. Several methods were discussed to address this issue, such as, radio-labeled study, assessment of cerebrospinal fluid in animals, and animal brain pathology. It was agreed that additional discussion will be needed to address this concern.

**ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS:**

- The Sponsor clarified that the fill size is 100 microliters in each nostril in the first study for 14 days using 3.5 mg of testosterone in a 120 mg formulation.
- The Division indicated that drug-drug interaction studies with other nasal drugs (e.g. steroids, OTC products) will need to be performed because this is a pre-approval issue. The Division disagreed with the Sponsor's proposal to either conduct Phase 4 studies or to contraindicate.
- The Sponsor will submit the full study report for the human study that was described in the pre-IND meeting package to the IND.

**DECISIONS (AGREEMENTS) REACHED:**

- A 3 month toxicology study in rats or rabbits via intranasal route to support clinical trials longer than (b) (4) duration will be conducted.
- Data for both total serum testosterone and serum DHT in all PK studies will be reported.
- The pivotal study will be revised to include a 9 month safety extension as recommended by the Division to treat at least 50 subjects for >1 year and 200 subjects for > 6 months, and also, to include periodic detailed nasal examinations by an ENT physician.
- This NDA would be a 505(b)(1) application, and 505(b)(1) applications are granted 3 years exclusivity.
- Appropriate DMF references, specifications and tests that support the use of (b) (4) for the container system will be provided.
- Serum testosterone concentrations will be expressed as "ng/dL."

- Biochemical hypogonadism will be defined as total serum testosterone concentration <300ng/dL.
- The Division will agree to exclude subjects with intercurrent illness, such as URI, allergic rhinitis, etc., in Phase 1 & 2 studies. Additional discussion will be held prior to Phase 3 trial(s).
- The labeling will not make any claims for the "treatment of aging" or "andropause," and will state that testosterone is contraindicated in patients with known or suspected prostate cancer.
- Full study report for the human study that was described in the pre-IND meeting package will be submitted in the IND.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

- The Sponsor will discuss further with the Division regarding CMC issues of release specification and establishing limits during the course of the IND.
- Specific protocols for drug-drug interaction studies with other nasal drugs will require future discussion.
- Means of addressing potential absorption into cerebrospinal fluid will require further discussion.

**ACTION ITEMS:**

- The Project Manager will provide meeting minutes within 30 days of the meeting date.

Signature: Meeting Chair

*{See Appended Electronic Signature}*

Mark Hirsch, M.D.