

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205488Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: May 22, 2014

From: Hitesh Shroff
Senior CMC Reviewer
New Drug Quality Assessment Division II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
New Drug Quality Assessment Division II
ONDQA

To: CMC Review #1 of NDA 205488

Subject: Final Recommendation

The CMC review #1 has noted the following two pending issues:

1. Final "Acceptable" recommendation from the Office of Compliance was not issued.
2. Label/labeling issues were not resolved.

Because of these deficiencies, in the CMC Review #1, this NDA was not recommended for approval from the ONDQA perspective.

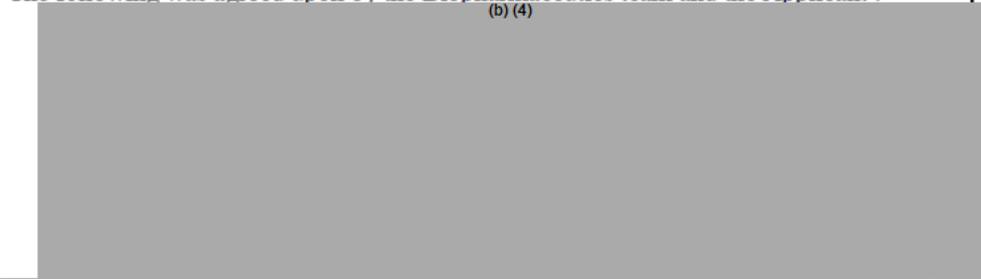
On May 21, 2014, the Office of Compliance issued the "Acceptable" recommendation for the facilities involved in the NDA (**Attachment 1**).

On May 11, 2014 and May 21, 2014 the label and labeling were submitted via email and they are revised satisfactorily from the ONDQA perspective (**Attachment 2**).

The Biopharmaceutics review was completed on April 2, 2014. The following is the recommendation from the Biopharmaceutics review.

RECOMMENDATION:

The following was agreed upon by the Biopharmaceutics team and the Applicant :
(b) (4)



Overall, the IVRT method and interim *in vitro* release acceptance criteria are acceptable for TBS-1 (testosterone nasal gel). From the Biopharmaceutics perspective, NDA 205488 for TBS-1 (testosterone nasal gel) is recommended for approval.

Signature
Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. RLostritto.

In the letter dated Jan 23, 2014 the applicant agreed to include IVRT specification criteria for both release and stability testing. The following revised drug product specification table was submitted on May, 21, 2014 via email. The drug product specification is adequate from ONDQA perspective (**Attachment 3**).

Recommendation:

This NDA is **now** recommended for approval from the ONDQA perspective.

ATTACHMENTS:

Attachment 1:

1. EES report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 205488/000	Sponsor:	TRIMEL BIOPHARMA SRL
Org. Code:	580		1001 G ST NORTHWEST STE 500
Priority:	5		WASHINGTON, DC 20001
Stamp Date:	29-APR-2013	Brand Name:	NATESTO
PDUFA Date:	28-MAY-2014	Estab. Name:	
Action Goal:		Generic Name:	TBD (TBS-1) NASAL GEL 4.5% TESTOSTERONE
District Goal:	30-DEC-2013	Product Number; Dosage Form; Ingredient; Strengths	001; GEL; TESTOSTERONE; 4.5% (5.5MG/ACTUATN)

FDA Contacts:	H. SHROFF	Prod Qual Reviewer	3017962116
	K. JENNINGS	Product Quality PM	3017962919
	J. ROULE	Regulatory Project Mgr	(HFD-580) 3017963993
	D. CHRISTNER	Team Leader	3017961341

Overall Recommendation:	ACCEPTABLE	on 21-MAY-2014	by C. CAPACCI-DANIEL ()	3017963532
	PENDING	on 09-SEP-2013	by EES_PROD	
	PENDING	on 03-JUN-2013	by EES_PROD	
	PENDING	on 03-JUN-2013	by EES_PROD	
	PENDING	on 03-JUN-2013	by EES_PROD	
	PENDING	on 03-JUN-2013	by EES_PROD	
	PENDING	on 03-JUN-2013	by EES_PROD	
	PENDING	on 03-JUN-2013	by EES_PROD	
	PENDING	on 03-JUN-2013	by EES_PROD	
	PENDING	on 03-JUN-2013	by EES_PROD	

Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	
DMF No:	(b) (4)	AADA:
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	02-AUG-2013	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE (b) (4)
DRUG SUBSTANCE OTHER TESTER

Profile: API NON-STERILE/INTERMEDIATE NEC **OAI Status:** NONE
INORGANIC/MINERAL

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JUN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JUN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-JUN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: OINTMENT, NONSTERILE (INCLUDES CREAM, JELLY, PASTE) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-JAN-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-DEC-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-JUN-2013
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
(b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-MAY-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3009146778
TRIMEL PHARMACEUTICALS CORPORATION
2488 DUNWIN DR.
MISSISSAUGA, ON, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Attachment 2:

1. Package Insert

(a) “Highlights” Section

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NATESTO safely and effectively. See full prescribing information for NATESTO.

Natesto (testosterone) nasal gel CIII
Initial U.S. Approval: 1953

-----DOSAGE FORMS AND STRENGTHS-----

Natesto nasal gel is available as a metered-dose pump. One pump actuation delivers 5.5 mg of testosterone. (3)

(b) “Full Prescribing Information” Section

#3. Dosage Form and Strength

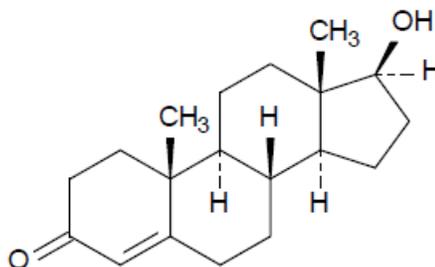
3. DOSAGE FORMS AND STRENGTHS

Natesto is a slightly yellow gel for intranasal use and is available in a dispenser with a metered dose pump. One pump actuation delivers 5.5 mg of testosterone.

#11. Description

11. DESCRIPTION

Natesto (testosterone) nasal gel is a slightly yellow gel containing 5.5 mg of testosterone in 122.5 mg of Natesto gel for nasal administration. The active pharmacologic ingredient in Natesto is testosterone, an androgen. Testosterone is a white to practically white crystalline powder chemically described as 17 β -Hydroxyandrost-4-en-3-one. The structural formula is:



MW: 288.4 MF: C₁₉H₂₈O₂

The inactive ingredients are castor oil, oleoyl polyoxyglycerides, and colloidal silicon dioxide.

#16 How Supplied/storage and Handling

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied

Natesto (testosterone) nasal gel is available as a metered dose pump containing 11 grams of gel dispensed as 60 metered pump actuations. One pump actuation delivers 5.5 mg of testosterone in 0.122 grams of gel.

NDC 42667-5511-1

16.2. Storage

Keep Natesto out of reach of children.

Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted to 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature.

16.3. Handling and Disposal

Used Natesto dispensers should be discarded in household trash in a manner that prevents accidental exposure of children or pets.

2. Labels

Immediate container label



(b) (4)

Container label



Attachment 3:

Revised Natesto specification

Test Parameter	Method/Reference	Acceptance Criteria Release	Acceptance Criteria Shelf-Life
Appearance	PV0591/ STM.GEN.001		(b) (4)
Identification A	PV0591/ STM.TBS1.001		
Identification B	PV0591/ STM.TBS1.001		
Assay	PV0591/ STM.TBS1.001		
Delivered Dose Uniformity	PV0591/ STM.TBS1.003		
In vitro Release Rate using Franz cell	PV0591/ STM.TBS1.004		
Related Compounds/Degradation Products	PV0591/ STM.TBS1.002		
Viscosity	PV0591/		

Test Parameter	Method/Reference	Acceptance Criteria Release	Acceptance Criteria Shelf-Life
Microbial Enumeration Test and Absence of Specified Organisms	STM.GEN.003 USP<61>&<62>		(b) (4)
(b) (4)			

(b) (4)
(b) (4)

LC- Label claim, 11.0mg per dose. One dose equals two actuations; each actuation =5.5mg

TAMC – Total aerobic microbial count

TYMC – Total combined yeasts/mould count

*Cumulative calculation based on the (b) (4) in the ingredients used to produce the drug product

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

/s/

HITESH N SHROFF
05/22/2014

MOO JHONG RHEE
05/22/2014
Chief, Branch IV

NDA 205488**Natesto (testosterone) nasal gel
4.5%****Primal BioPharma SRL****Hitesh Shroff, Ph.D.**
Review Chemist**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV****CMC Review of NDA 205488
For the Division of Reproductive and Urologic Products
(HFD-580)**

Table of Contents

Table of Contents	2
The Executive Summary	7
I. Recommendations..	7
A. Recommendation and Conclusion on Approvability.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product and Drug Substance.....	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block.....	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:	10
Body Of Data	10
S DRUG SUBSTANCE [testosterone]	10
P DRUG PRODUCT [(testosterone nasal gel)]	18
A APPENDICES	82
R REGIONAL INFORMATION	82
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	84
A. Labeling & Package Insert.....	84
B. Environmental Assessment Or Claim Of Categorical Exclusion.....	94
III. List of Deficiencies:.....	94
IV. Attachment.....	97

Chemistry Review Data Sheet

1. NDA 205488

2. REVIEW:#1

3. REVIEW DATE: 15-Oct-2013

4. REVIEWER: Hitesh Shroff, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	29-Apr-2013
Labeling Amendment	3-Jul-2013

7. NAME & ADDRESS OF APPLICANT

Name: Trimel BioPharma SRL.
Address: Durants Business Center, Suite B
Durants, Christ Church, Barbados, BB17097

Representative: John Dubeck
Keller and Heckman LLP
1001 G Street N.W.
Washington DC 20001

Telephone: 202-434-4125
Email: dubeck@khlaw.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Natesto
- b) Non-Proprietary Name (USAN): Testosterone
- b) Code Name/# (ONDQA only): None
- c) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3, 5
 - Submission Priority: S

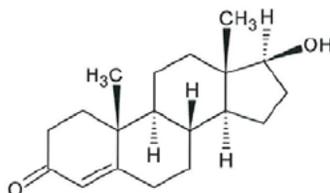
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Androgen

11. DOSAGE FORM: Gel

Chemistry Review Data Sheet

12. STRENGTH/POTENCY: Testosterone gel 4.5 % , 5.5 mg testosterone per actuation
13. ROUTE OF ADMINISTRATION: Nasal
14. Rx/OTC DISPENSED: X Rx ___ OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___ SPOTS product – Form Completed
X Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Testosterone

Name: Testosterone
Chemical name: 17 β -hydroxyandrost-4-en-3-one
CAS numbers: 58-22-0
Molecular Formula: C₁₉H₂₈O₂
Molecular Weight: 288.4^(b)₍₄₎ g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	[REDACTED]	(b) (4)		Adequate	Dec 11, 2013	
	II			3	Adequate		ADEQUATE on 10-Oct-2012. No updates.
	III			4	Adequate		
	III			4	Adequate		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Pending		Kelly Kitchens
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Claim for categorical exclusion granted	04-Sep-2013	Raanan Bloom
Microbiology	Adequate	13-May-2013	Bryan Riley

The Chemistry Review for NDA 204708

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.

However, labeling issues are still *not* satisfactorily resolved.

Also, an overall “Acceptable” recommendation for the facilities involved in this application from the Office of Compliance has *not* been made as of this review.

Therefore, from the ONDQA perspective, this NDA is *not* ready to recommend for approval in its present form per 21 CFR 314.125(b)(6), and (13) until the pending issues are satisfactorily resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendations at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

(1) Drug Substance

Natesto nasal gel contains testosterone as an active ingredient. Testosterone is a white to practically white crystalline powder. It is manufactured by (b) (4) (DMF (b) (4)) and (b) (4) (DMF (b) (4)). The detailed CMC information for the drug substance is provided in the respective DMFs. The applicant provided letters of authorization to reference both DMFs. The DMF (b) (4) was reviewed in October 2010 and deemed adequate. Since then there have been no changes in the manufacturing process and controls in the DMF. The DMF (b) (4) was reviewed in December 2013 and was found to be adequate. The proposed specification of the drug substance, testosterone, includes identification, assay, related substances, melting point and particle sizes, and it is deemed adequate to assure the identity, strength, purity and quality of the drug substance.

(2) Drug Product

Natesto (testosterone) nasal gel is a slightly yellow gel containing 4.5 % testosterone. Natesto is available as a metered-dose pump containing 11 g of gel dispensed as 60 metered pump actuations. One pump actuation delivers 5.5 mg of testosterone in 122.5 mg of gel. The pump is capable of performing 60 actuations after 10 priming actuations. The inactive ingredients are castor oil, Oleoyl polyoxylglycerides and colloidal silicon dioxide.

The manufacturing of Natesto is performed using conventional gel manufacturing methods such as (b) (4). Three primary stability batches containing approximately (u) (4) of gel were manufactured at (b) (4).

The proposed release specification of the finished product includes appearance, identification, assay of the active ingredient, impurities, delivered dose uniformity, viscosity and microbial limits. The proposed specification is deemed adequate to assure the identity, strength, purity, and quality of the drug product.

Based on the stability data from three production scale batches of drug product at long term (18 months) and accelerated (6 months) conditions, the proposed 24 months expiration dating period, when stored at room temperature, is granted.

B. Description of How the Drug Product is Intended to be Used

Natesto (testosterone) nasal gel is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Natesto is available as a metered-dose pump consisting 11 g of gel dispensed as 60 metered pump actuation. One pump actuation delivers 5.5 mg of testosterone in 122.5 mg of gel. The starting dose of Natesto is 11 mg of testosterone (2 pump actuations) applied intranasally twice daily.

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(6)

- The label/labeling issues are not finalized

21 CFR 314.125 (b)(13)

- No overall "ACCEPTABLE" site recommendation has been made from the Office of Compliance for this application.

(see the **List of Deficiencies**, p. 94)

III. Administrative**A. Reviewer's Signature**

Hitesh Shroff, Ph.D./ 16-Dec-2013

B. Endorsement Block

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, Division 2

C. CC Block

Donna Christner, Ph.D.

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/s/

HITESH N SHROFF
12/16/2013

MOO JHONG RHEE
12/16/2013
Chief, Branch IV

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division: Division of Reproductive and Urologic Products
NDA: 205488
Applicant: Trimel BioPharma SRL
Stamp Date: 29-Apr-2013
PDUFA Date: 28-Feb-2014
Trademark: TBD
Established Name: Testosterone
Dosage Form: Gel
Route of Administration: Nasal
Indication: Primary hypogonadism (congenital or acquired) in men. Hypogonadotropic hypogonadism (congenital or acquired) in men.

CMC Lead: Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	x	<input type="checkbox"/>
Comments for 74-Day Letter	x	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

The drug product is a testosterone gel for intranasal application. The airless pump delivery system is designed to deliver (b) (4) (122.5 mg) of gel per pump actuation, which translates to 5.5 mg of testosterone per actuation. Each clinical dose translates to one actuation per nostril, for a total of two actuations, or 11 mg testosterone. The gel is designed to be bioadhesive for retention in the nasal cavity.

B. Critical issues for review

Specifications will require careful review, especially the viscosity test since this is an important parameter for this dosage form via this route of administration.

C. Comments for 74-Day Letter

There are no CMC comments to be conveyed at this time. The following ONDQA BioPharm request should be conveyed:

You proposed to apply IVRT when process changes are made during manufacturing, following SUPAC guidelines for batch to batch monitoring. However, the in vitro release rate test method

will not be proposed as a release and stability test for commercial use. You proposed to continue to test this parameter for the current on-going stability studies.

We recommend that you propose an in-vitro release acceptance criteria (range) based on your developed IVRT methodology for your product at release and during stability as a quality control parameter. Your proposed specification will be based on generated data on the final to be marketed batches. Submit all the generated data in electronic format (excel). Also, along with proposed in-vitro release specification, include IVRT method development and validation report.

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/Binding
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.

D. Recommendation:

This NDA is fileable from a CMC perspective.

Hitesh Shroff, Ph.D. has been assigned as the primary CMC reviewer. Tapash Ghosh, Ph.D. has been assigned as the ONDQA BioPharm reviewer. As per an email dated 03-May-2013, no OPS Microbiology reviewer will be assigned.

REGULATORY BRIEFING RECOMMENDATION: Branch-level

Donna F. Christner, Ph.D.

NDA Number: 205488 Type: 5 (New Formulation or New Manufacturer, Same or New Indication)

Established/Proper Name: testosterone

Applicant: Trimel BioPharma SRL

Letter Date: 29-Apr-2013

Stamp Date: 29-Apr-2013

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		IND 70512

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		EES submitted on 03-Jun-2013
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.		X	N/A

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical Exclusion requested. Forwarded to Ron Bloom on 29-Apr-2013 for evaluation. As per email, categorical exclusion is acceptable.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to the following DMFs: DMF (b) (4) (b) (4) DMF (b) (4) (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to the following DMFs: DMF (b) (4) (b) (4) DMF (b) (4) (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to the following DMFs: DMF (b) (4) (b) (4) DMF (b) (4) (b) (4)
15.	Does the section contain controls for the DS?	X		Cross-reference to the following DMFs: DMF (b) (4) (b) (4) DMF (b) (4) (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to the following DMFs: DMF (b) (4) (b) (4) DMF (b) (4) (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		Executed batch record provided.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		24 months expiry requested based on 18 months long term data for 3 lots
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		OPS Microbiology review submitted to DARRTS on 13-May-2013. Adequate.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	07-Mar-2012	ADEQUATE on 06-Sep-2011. Updates since that time. May require review.
	II			06-Mar-2011	ADEQUATE on 10-Oct-2012. No updates.
	III			28-Feb-2013	May require review
	III			28-Feb-2013	May require review
					See ONDC Policies on Bottles and Blisters*

**Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001
Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002*

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		Numerous labeling comments to be conveyed during the review cycle
33.	Have the immediate container and carton labels been provided?	X		Numerous labeling comments to be conveyed during the review cycle

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	No comments to be conveyed at this time

{See appended electronic signature page}

Donna F. Christner, Ph.D.
 CMC Lead
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

{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

Date

Attachment A: Nanotechnology product evaluating questions:

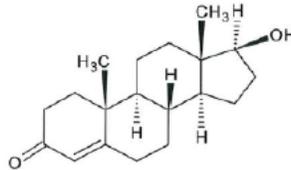
1, This review contains new information added to the table below: _____ Yes; ___ x ___ No Review date: <u>12-Jun-2013</u>
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No _____; Maybe (please specify) _____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____
3 b) What is the source of the nanomaterial? _____
4) Is the nanomaterial a reformulation of a previously approved product? Yes _____ No _____
5) What is the nanomaterial functionality? Carrier _____; Excipient _____; Packaging _____ API _____; Other _____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble _____
7) Was particle size or size range of the nanomaterial included in the application? Yes _____ (Complete 8); No _____ (go to 9).
8) What is the reported particle size? Mean particle size _____; Size range distribution _____; Other _____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial? _____ _____

DRUG SUBSTANCE

The drug substance is testosterone. Information is provided in the cross-referenced DMFs. It is provided by two alternate suppliers: (b) (4) (DMF (b) (4)) and (b) (4) (DMF (b) (4)). The following general information is provided in the application.

Approved Name	Testosterone
Chemical Name IUPAC CAS	17 β -Hydroxyandrost-4-en-3-one 17 β -Hydroxy-4-androsten-3-on
Compendial Name (USP, Ph. Eur.)	Testosterone
Chemical Abstract Service Number (CAS)	58-22-0

Structural Formula



Molecular Formula

$C_{19}H_{28}O_2$

Molecular Mass

288.4 (b) (4)

(b) (4)

Manufacturing:

The (b) (4) drug substance is manufactured via the following synthetic pathway:

Figure 1: Synthetic Route



The following facilities have responsibilities for production of the testosterone API:

Table 1: Manufacturing Unit Operations and Associated Sites

Site	Unit Operation			
	Drug Substance Mfg	(b) (4)	Release Testing	Stability Testing
(b) (4)	X		X ¹	X
		X	X ²	X
			X ³	
			X ⁴	

¹ release testing on (b) (4) drug substance

² particle size determination

³ quality control testing (except for particle size determination and microbiological purity) and final QC release

⁴ quality control testing of microbial purity

Comment: Inspection requests were submitted on 03-Jun-2013. As of that time, the (b) (4) facilities have been submitted to the District Office. The (b) (4) facility is ASSIGNED INSPECTION TO IB.

The applicant reports the following impurities:

Table 1: Potential Impurities of Testosterone – (b) (4)

According to Ph. Eur. (Trimer Code)	Impurity			Limits	
	Chemical Name	Structure	Origin	Ph. Eur./ (b) (4)	In-house
(b) (4)					

Table 1: Proposed Specifications for Testosterone

Test Parameter	Method	Specification
Appearance	STM.GEN.001/PV0576	White or slightly creamy white crystals or crystalline powder
Identification A	USP<197K>	IR spectrum corresponds to that of the Testosterone standard
Identification B	USP<197U>	UV spectrum corresponds to that of the Testosterone standard
Melting Range	USP<741>	Between 153° and 157°
Specific Rotation	USP<781S>	Between +101° and +105°
Loss on Drying	USP<731>	NMT 1.0%
Assay	USP UV/TLC	97.0% - 103.0% (on dried basis)
Assay	HPLC/STM.TBS1.006	(b) (4) % (on dried basis)
Related Compounds	HPLC (Ph. Eur.)	(b) (4) NMT (b) (4) % (b) (4) NMT (b) (4) % (b) (4) NMT (b) (4) % (b) (4) NMT (b) (4) % Single Unknown: NMT (b) (4) % Total Impurities: NMT (b) (4) %
Related Compounds	TLC (Ph. Eur.)	(b) (4) NMT (b) (4) % (b) (4) NMT (b) (4) %
Residual Solvents/OVI	USP<467>	(b) (4) NMT (b) (4) ppm (b) (4) NMT (b) (4) ppm (b) (4) NMT (b) (4) ppm
Particle Size	Laser Diffraction USP<429> (b) (4)	Report Results: d ₅₀ : NMT (b) (4) μm d ₉₀ : NMT (b) (4) μm

The applicant reports that the stability data support a (b) (4) month retest period when stored in double bagged (b) (4) bags in a (b) (4) drum stored at controlled room temperature. Information is provided in the cross-referenced DMF.

Comment: Information in the NDA and the cross-referenced DMF is adequate to allow review.

(b) (4)

The (b) (4) drug substance is manufactured via the following synthetic pathway:

Figure 1: Synthetic Route for Process B



The following facility has manufacturing responsibilities for the (b) (4) substance:

Table 1: Manufacturing Unit Operations and Associated Sites

Site	Unit Operation		
	Drug Substance Mfg	Release Testing	Stability Testing
(b) (4)	X	X	X

Comment: Inspection requests were submitted on 03-Jun-2013. As of that date, the facility was ACCEPTABLE based on profile.

The applicant reports the following impurities:

Table 1: Potential Impurities of Testosterone (b) (4)

Impurity				Limits	
According to Ph. Eur. (Trinel Code)	Chemical Name	Structure	Origin	Ph. Eur. / (b) (4)	In-house
(b) (4)					

Table 2: Additional Potential Impurities from (b) (4) and Comparison to Trinel Impurity Profile

Impurity				Limits	
According to Ph. Eur.	Chemical Name	Structure	Origin	(b) (4)	In-house
(b) (4)					

Impurity	Limits
(b) (4)	

Table 1: Proposed Specifications for Testosterone

Test Parameter	Method	Specification
Appearance	STM.GEN.001/PV0576	White powder
Identification A	USP<197K>	IR spectrum corresponds to that of the Testosterone standard
Identification B	USP<197U>	UV spectrum corresponds to that of the Testosterone standard
Melting Range	USP<741>	Between 153° and 157°
Specific Rotation	USP<781S>	Between +101° and +105°
Loss on Drying	USP<731>	NMT 1.0%
Assay	USP UV/TLC	97.0% - 103.0% (on dried basis)
Assay	HPLC/STM.TBS1.006	(b) (4) % (on dried basis)
Related Compounds	HPLC (Ph. Eur.)	(b) (4) NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % Single Unknown: NMT (b) (4) % Total Impurities: NMT (b) (4) %
Related Compounds	TLC (Ph. Eur.)	(b) (4) NMT (b) (4) % NMT (b) (4) %
Residual Solvents/OVI	USP<467>	(b) (4) NMT (b) (4) ppm NMT (b) (4) ppm
Particle Size	Laser Diffraction USP<479> (b) (4)	Report Results: d ₅₀ : NMT (b) (4) μm d ₉₀ : NMT (b) (4) μm

The applicant reports that the stability data support a (b) (4) month retest period when stored in bagged (b) (4) bags in a (b) (4) drum stored at controlled room temperature. Information is provided in the cross-referenced DMF.

Comment: Information in the NDA and the cross-referenced DMF is adequate to allow review.

DRUG PRODUCT

The drug product, TBS-1, is a viscous bioadhesive oil-based formulation containing solubilized testosterone intended for intranasal application for the treatment of hypogonadism in men.

TBS-1 Bulk Gel is formulated with the following compendial inactive ingredients: castor oil, oleoyl polyoxyglycerides and colloidal silicon dioxide. TBS-1 Bulk Gel is packaged in labeled clear multiple dose dispensers, referred to as TBS-1 Finished Product.

Each dose consists of two actuations, one actuation per nostril. Each actuation contains 5.5 mg of testosterone in TBS-1 Finished Product for a total testosterone dose of 11.0 mg/dose.

Table 1: Components, Quantity, Quality Standards and Function - TBS-1 Finished Product

Component	Amount (% w/w)	Amount Delivered per Actuation (mg)	Amount Delivered per Dose (mg)	Quantity per Unit ^a (mg)	Function	Quality Standard
Testosterone	4.5%	5.5	11.0	(b) (4)	Active ingredient	USP
Castor oil	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP
Oleoyl polyoxyglycerides					Ph. Eur./NF	
Colloidal silicon dioxide					NF	
Total					(b) (4)	N/A

^a Unit is the multiple dose dispenser

TBS-1 Finished Product is supplied in a (b) (4) multiple dose pump container. The container closure relies on (b) (4).



The patient is instructed to place his finger or thumb on the pump of the actuator and to advance the tip of the actuator until the finger on the pump reaches the base of the nose. The patient depresses the pump and the gel is expelled onto the nasal mucosa.

Each actuation delivers 122.5 mg which translates to a volume of (b) (4) µl. (The specific gravity of the gel is reported to be (b) (4)).

Specification

The applicant has provided the following specification for both the bulk gel and the packaged product:

5.1. Specification(s)

The proposed quality control specifications for TBS-1 Bulk Gel for batch release are summarized in Table 1.

Table 1: Quality Control Specifications for TBS-1 Bulk Gel

Test Parameter	Method Haupt/Trimel	Acceptance Criteria
Appearance	PV0591/ STM.GEN.001	Slightly yellow gel
Identification A	PV0591 / STM.TBS1.001	(b) (4)
Identification B	PV0591/ STM.TBS1.001	(b) (4)
Assay	PV0591/ STM.TBS1.001	(b) (4)%
Related Compounds/Degradation Products	PV0591/ STM.TBS1.002	(b) (4) % Single unknown impurity Total impurities
Viscosity	PV0591/ STM.GEN.003	(b) (4)
(b) (4)		
(b) (4)		

NET = not less than

* Cumulative calculation based on the (b) (4) in the ingredients used to produce the drug product

Table 2: Quality Control Specification for TBS-1 Finished Product

Test Parameter	Method Haupt/Trimel	Acceptance Criteria Release	Acceptance Criteria Shelf-Life
Appearance	PV0591/ STM.GEN.001	(b) (4)	
Identification A	PV0591 / STM.TBS1.001	(b) (4)	
Identification B	PV0591/ STM.TBS1.001		
Assay	PV0591/ STM.TBS1.001		
Delivered Dose Uniformity	PV0591/ STM.TBS1.003	(b) (4)	
Related Compounds/ Degradation Products	PV0591/ STM.TBS1.002	(b) (4) ≤ (b) (4) % Single unknown impurity ≤ (b) (4) % Total impurities ≤ (b) (4) %	(b) (4) ≤ (b) (4) % Single unknown impurity ≤ (b) (4) % Total impurities ≤ (b) (4) %
Viscosity	PV0591/ STM.GEN.003	(b) (4)	(b) (4)
Microbial Enumeration Test and Absence of Specified Organisms	USP<61>&<62>	(b) (4)	

LC - Label claim, 11.0mg per dose. One dose equals two actuations; each actuation =5.5mg

TAMC - Total aerobic microbial count

TYMC - Total combined yeasts/mould count

* Cumulative calculation based on the (b) (4) in the ingredients used to produce the drug product

Comment: As per the Microbiology review submitted to DARRTS on 13-May-2013, the microbiology specification is acceptable.

The applicant has developed an IVRT test for changes. ONDQA BioPharm has requested that the IVRT be performed routinely. See Attachment 1 for the email. This request will be conveyed in the 74-day letter.

Manufacture

The drug product is manufactured and tested at the following facilities:

Table 1: Manufacturing of TBS-1

Name and Address	Responsibility
(b) (4)	Analytical testing of the starting materials Manufacture of the bulk gel Filling of the multiple dose dispensers Analytical testing of bulk and finished product for release and stability testing Secondary packaging and labeling site
(b) (4)	Analytical testing for stability program
(b) (4)	Microbial enumeration test and absence of specified organisms for stability program

Comment: The facilities were submitted to EES on 03-Jun-2013. (b) (4) is Assigned Inspection. The (b) (4) facilities are Submitted to the DO.

The applicant has provided the following flow chart. A narrative is also provided as are details such as mixing time and speeds:

Figure 1: Manufacturing Process Flow Chart for Manufacture of TBS-1 Bulk Gel

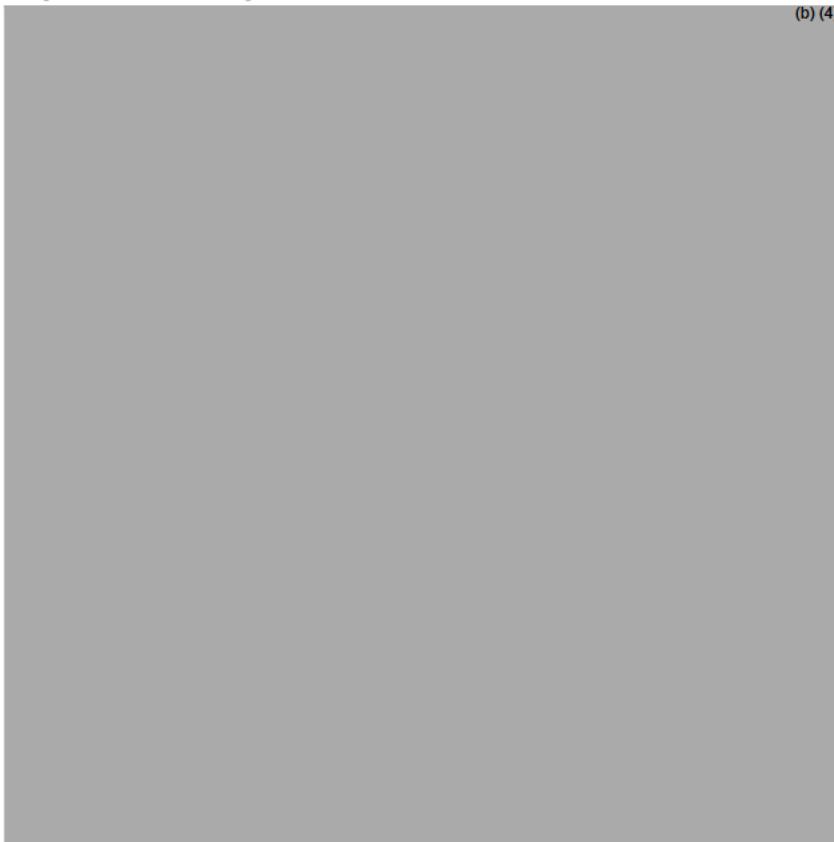


Figure 2: Manufacturing Process Flow for TBS-1 Finished Product



The applicant has provided batch release data on 5 lots of drug product. Three lots are the primary stability lots manufactured in 2011 using Testosterone supplied by (b) (4). The other two lots were manufactured in February 2013 and are slated to be used for stability studies. One lot uses testosterone supplied by (b) (4) and the second lot uses testosterone supplied by (b) (4). Release data alone is provided for these two lots.

Comment: In the past, we have requested that drug substance from an additional supplier be qualified for use by manufacturing multiple batches of drug product and placing them on stability. The applicant has provided one batch with the new drug substance supplier. Although this is atypical, in this instance and as discussed with Dr. Moo-Jhong Rhee, it should be adequate for the following reasons:

- *Testosterone is a well-known drug substance with a USP monograph for which the degradation products are known. As such, it is not anticipated that a different impurity profile will emerge on drug product stability*
- *The alternate supplier, (b) (4), has a long history of manufacturing testosterone drug substance for use in many approved products.*

Container closure

(b) (4)

(b) (4) have been qualified according to UDP<661> and USP<87>. The (b) (4) component was tested according to USP<87>.

Full information is provided in the cross-referenced DMFs (b) (4) and (b) (4)

Comment: Information is adequate to allow review.

Stability

The applicant proposes a 24 month expiration dating period based on the following stability data package:

Table 3: Stability Data for TBS-1 Finished Product

Lot Number (Trimel Code)	Purpose	Data Provided in Module 3.2.P.8.3
2372 (TBS-107)	Primary stability	25°C /60%RH; 18 months
		40°C /75%RH ; 6 months

Lot Number (Trimel Code)	Purpose	Data Provided in Module 3.2.P.8.3
2373 (TBS-108)	Primary stability	25°C /60%RH; 18 months
		40°C /75%RH ; 6 months
2374 (TBS-109)	Primary stability	25°C /60%RH; 18 months
		40°C /75%RH ; 6 months
1969 (TBS-059)	Orientation study	Upright 25°C /60%RH; 18 months
		Upright 40°C /75%RH; 6 months
		Inverted 25°C /60%RH; 18 months
		Inverted 40°C /75%RH; 6 months
		Horizontal 25°C /60%RH; 18 months
		Horizontal 40°C /75%RH; 6 months
3B35950 (CSL-024)	Photostability	Light 1.2 Lux hrs, UV 2000 Watt H/m ²
2372 (TBS-107)	Freeze/Thaw	Cycle 1: 3 Days at -20C /2 Days at 25°C/60%RH Cycle 2: Duplicate 3 Days at -20°C/2 Days at 25C/60%RH

Comment: The amount of data in the stability package is adequate to determine an expiration dating period.

ATTACHMENT 1

-----Original Message-----

From: Ghosh, Tapash
Sent: Friday, May 24, 2013 5:11 PM
To: Jennings, Kerri-Ann; Roule, Jeannie
Cc: Dorantes, Angelica; Christner, Donna; Ghosh, Tapash
Subject: RE: Biopharmaceutics Assignment: ORIGINAL NDA SUBMISSION: nda205488

Hi Kerri/Jeannie:

The following is a Biopharm IR. I don't know whether we need/should wait until filing meeting or go ahead and send now. Thanks,

Tapash

You proposed to apply IVRT when process changes are made during manufacturing, following SUPAC guidelines for batch to batch monitoring. However, the in vitro release rate test method will not be proposed as a release and stability test for commercial use. You proposed to continue to test this parameter for the current on-going stability studies.

We recommend that you propose an in-vitro release acceptance criteria (range) based on your developed IVRT methodology for your product at release and during stability as a quality control parameter. Your proposed specification will be based on generated data on the final to be marketed batches. Submit all the generated data in electronic format (excel). Also, along with proposed in-vitro release specification, include IVRT method development and validation report.

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/Binding
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.

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

/s/

DONNA F CHRISTNER
06/18/2013

MOO JHONG RHEE
06/18/2013
Chief, Branch IV