CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204399Orig1s000

CHEMISTRY REVIEW(S)

Memorandum	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research
Date:	15-May-2014
To:	CMC Review #2 for NDA 204399
From:	Bogdan Kurtyka, Ph.D. CMC Reviewer, ONDQA Division II
Through:	Moo-Jhong Rhee, Ph.D. Chief, Branch IV ONDQA Division II
CC:	Donna Christner, Ph.D. CMC Lead, ONDQA Division II
Subject:	**Final CMC Recommendation**

Previous CMC Review #2 entered into DARRTS system on 01-May-2014 noted the following deficiency which resulted in the recommendation of "Non Approval" action:

> Because of time lapse between the original application and this resubmission, new inspection request was made and the Office of Compliance has ***not*** issued a new overall "Acceptable" recommendation for the facilities involved in this application.

Regarding this deficiency, on 14-May-2014 the Office of Compliance issued the overall "Acceptable" recommendation for establishment involved in this NDA (see the **Attachment 1**).

Recommendation:

Because the issue was resolved satisfactorily, from the ONDQA perspective, this NDA is now recommended for **Approval** with expiration dating periods of 36-month for tube and packet presentation, and 24-month for metered pump under the controlled room conditions.

Attachment 1: EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204399/000	**Sponsor:**	UPSHER SMITH
Org. Code:	580		6701 EVENSTAD DR
Priority:	5		MAPLE GROVE, MN 55369
Stamp Date:	18-OCT-2012	**Brand Name:**	TESTOSTERONE GEL 1%
PDUFA Date:	05-JUN-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	TESTOSTERONE GEL 1%
District Goal:	19-JUN-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		(b) (4)	
		003; GEL; TESTOSTERONE; 12.5MG/1.25GM	
		002; GEL; TESTOSTERONE; 50MG/5GM	

FDA Contacts:	B. KURTYKA	Prod Qual Reviewer		3017961431
	K. JENNINGS	Product Quality PM		3017962919
	J. ROULE	Regulatory Project Mgr	(HFD-580)	3017963993
	D. CHRISTNER	Team Leader		3017961341

Overall Recommendation:	ACCEPTABLE	on 14-MAY-2014	by C. CAPACCI-DANIEL	()	3017963532
	PENDING	on 05-DEC-2013	by EES_PROD		
	PENDING	on 05-DEC-2013	by EES_PROD		
	PENDING	on 05-DEC-2013	by EES_PROD		
	ACCEPTABLE	on 31-DEC-2012	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 27-DEC-2012	by EES_PROD		
	PENDING	on 26-NOV-2012	by EES_PROD		
	PENDING	on 26-NOV-2012	by EES_PROD		
	PENDING	on 26-NOV-2012	by EES_PROD		

Establishment:	**CFN:**		**FEI:**	(b) (4)	
				(b) (4)	
DMF No:			**AADA:**		
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER				
	FINISHED DOSAGE STABILITY TESTER				
Profile:	CONTROL TESTING LABORATORY		**OAI Status:**	NONE	
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	26-NOV-2012				
Decision:	ACCEPTABLE				
Reason:	BASED ON PROFILE				

Establishment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-MAY-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORIES "ALSO" (DRUGS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	10-MAR-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	05-DEC-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:**	**FEI:** 3004106442	
	UPSHER SMITH LABORATORIES INC MAPLE GROVE, , UNITED STATES 55369		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORIES "ALSO" (DRUGS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	05-DEC-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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/s/

BOGDAN KURTYKA
05/19/2014

MOO JHONG RHEE
05/20/2014
Chief, Branch IV

NDA 204399

Vogelxo (testosterone) gel
50 mg testosterone tube
50 mg testosterone packet
Metered pump 12.5 mg testosterone per actuation

Upsher-Smith Laboratories, Inc.

Bogdan Kurtyka, Ph.D.
Review Chemist

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

CMC REVIEW OF NDA 204399
For the Division of Reproductive and Urologic Products (HFD-580)

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CMC Review Data Sheet

1. NDA 204399

2. REVIEW #: 2

3. REVIEW DATE: 01-May-2013

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS:

Original Submission	18-Oct-2012
Labeling update	30-Jan-2013
Stability update	12-Mar-2013
Stability update	05-Apr-2013
Stability update	31-May-2013
Review #1	14-Jun-2013
Addendum	9-Aug-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	05-Dec-2013

7. NAME & ADDRESS OF SPONSOR:

Name:	Upsher-Smith Laboratories, Inc.
Address:	6701 Evenstad Drive Maple Grove, MN 55369
Telephone:	763-315-2000
Fax:	763-258-5578

8. DRUG PRODUCT NAME/CODE/TYPE:

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

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

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Anabolic steroid

11. DOSAGE FORM: Gel CODE: 066

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical CODE: 011

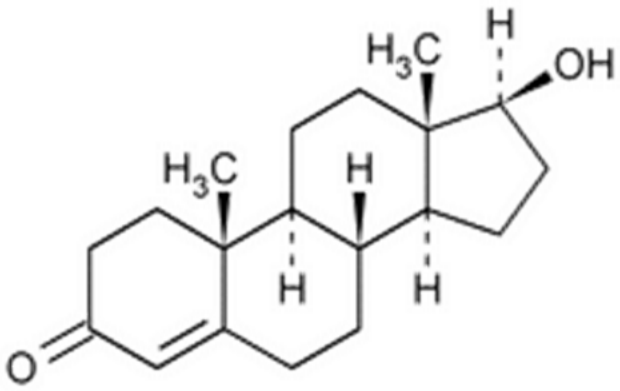
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Androst-4-en-3-one, 17-hydroxy-, (17β)-17β-Hydroxyandrost-4-en-3-one
USAN Name: Testosterone
CAS Number: 58-22-0
Structural Formula:



Molecular Formula: $C_{19}H_{28}O_2$
Molecular Weight: 288.42

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

CMC Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Testosterone	3	Adequate	20-Aug-2013	Reviewed by Gil Jong Kang, Ph.D.

[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	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Categorical exclusion granted (see Review #1)	11-Mar-2013	Bogdan Kurtyka, Ph.D.
Microbiology	N/A		

The CMC Review for NDA 204399

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

As previously indicated in the Review #1, the applicant of this NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The newly revised label/labeling including the generic product are acceptable.

Because of time lapse between the original application and this resubmission, new inspection request was made and the Office of Compliance has ***not*** issued a new overall "Acceptable" recommendation for the facilities involved in this application.

Therefore, from the ONDQA perspective, this NDA is ***not*** ready for approval per 21CFR 314.125(b)(13) in its present form until the "Acceptable" recommendation from the Office of Compliance is obtained.

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

N/A

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The sponsor references DMF (b) (4) (b) (4)) for details on the description, characterization, manufacture, packaging, specification for quality control testing, and stability of the drug substance, testosterone USP. A letter of authorization to cross reference the DMF is provided in the application. DMF (b) (4) has been reviewed previously by Dr. Gil Jong Kang and was deemed adequate to support ANDA 79178 (testosterone gel 1%).

(2) Drug Product

Testosterone gel 1% is indicated for deficiency or absence of endogenous testosterone as a testosterone replacement therapy. It is a clear, translucent gel. The inactive ingredients of the formulation are commonly used in topical drug products. All excipients are listed in the Inactive Ingredients Database and the proposed amounts do not exceed previously approved levels. The drug product is manufactured by (b) (4),

[redacted] (b) (4)

The drug product specification includes: description, identification, pH, assay, impurities, [redacted] (b) (4), uniformity of dosage unites (for tube and packet presentation), delivered dose uniformity (for pump presentation), in vitro release, assay of ethanol, pH, viscosity, minimum fill, and weight loss. The specification attributes and their analytical methods and acceptance criteria are deemed satisfactory except for *in-vitro* release test pending satisfactory recommendation from Biopharm Review.

Three container closure systems are proposed: single use 5 g tubes and packets, and 88 g multiple dose metered pump. The information included in the application demonstrates that the proposed container/closure systems meet all recommendations of relevant USP monographs and the Agency's guidance.

The sponsor provided the results of up to 36 months long-term stability studies, and proposed an 36-month expiration dating period for tube and packet presentation, and an 24-month expiration dating period for metered pump under the controlled room conditions. The requested expiration dating periods are granted.

The applicant claimed categorical exclusion from the Environmental Assessment based on 21CFR 25.31(a).

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

5 g of gel (one tube, one packet, or 4 pump actuations) containing 50 mg of testosterone should be applied once daily (preferably in the morning) to clean, dry intact skin of the shoulders and/or upper arms.

C. Basis for Not-Approval Recommendation

21CFR 314.125(b)(13)

- The Office of Compliance has not issued yet an overall "acceptable" recommendation for the manufacturing establishments.

III. Administrative

A. Reviewer's Signature: *(See appended electronic signature page)*
Bogdan Kurtyka, Ph.D.
CMC Reviewer, Branch IV/Division II/ONDQA

B. Endorsement Block: *(See appended electronic signature page)*
Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV/Division II/ONDQA

C. CC Block: Entered electronically in DARRTS

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/s/

BOGDAN KURTYKA
05/01/2014

MOO JHONG RHEE
05/01/2014
Chief, Branch IV

Memorandum	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research
Date:	09-Aug-2013
To:	CMC Review #1 for NDA 204399
From:	Bogdan Kurtyka, Ph.D. CMC Reviewer, ONDQA Division II
Through:	Moo-Jhong Rhee, Ph.D. Chief, Branch IV ONDQA Division II
CC:	Donna Christner, Ph.D. CMC Lead, ONDQA Division II
Subject:	**Final CMC Recommendation**

Previous CMC Review #1 dated 13-Jun-2013 and entered into DARRTS system on 14-Jun-2013 noted the following deficiencies which resulted in the recommendation of "Non Approval" action.

1. The specification of the drug product was not adequate due to unresolved *in-vitro* release rate test pending final Biopharm's Review.
2. Unresolved label/labeling issues

Regarding Item #1:

Biopharm's Review has been completed and entered in to DARRTS on 16-Jul-2013. The reviewer, Dr. Tapash Ghosh found the proposed *in-vitro* drug release method, its validation, and specification acceptance criteria acceptable for drug product release and for stability.

Regarding Item #2,

On 29-Jul-2013, the applicant submitted finalized label/labeling which are satisfactory from the ONDQA's perspective. The final version of Package Insert was placed in the eroom on 09-Aug-2013 (see the **Attachment 1**)

Recommendation:

Because these issues were resolved satisfactorily, from the ONDQA perspective, this NDA is now recommended for **Approval** with expiration dating periods of 36-month for tube and packet presentation, and 24-month for metered pump under the controlled room conditions.

Attachment 1: Finalized labeling and labels

1. Package Insert

The final version of Package Insert was placed in the eroom by clinical Project Manager Jeannie Roule and was reviewed per email from PM:

Below is the link for the PI and Medguide for NDA 204399, T gel with Upsher Smith. http://eroom.fda.gov/eRoom/CDER10/CDERDivisionofReproductiveandUrologicProducts/0_a9d9. You should consider this the final agreed upon. There might be some further very minor formatting edits that SEALD will make at the very end.
Please review both of these one more time and make any final edits that you feel are necessary. If possible, please review this by COB today.
Then please enter any final memorandums into DARRTS that are needed to complete your NDA review.
Thanks,
Jeannie

(a) "Highlights" Section

VOGELXO ™ (testosterone) gel for topical use CIII
Initial U.S. Approval: 1953

Topical gel available as:

- 50 mg of testosterone in a unit-dose tube
- 50 mg of testosterone in a unit-dose packet
- 12.5 mg of testosterone per one pump actuation in a metered-dose pump

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths

Vogelxo (testosterone) gel is a clear to translucent hydroalcoholic topical gel for topical use available in unit-dose tubes, unit-dose packets, and multiple-dose metered pumps. Each tube or packet provides 50 mg testosterone in 5 g of gel. One pump actuation delivers 12.5 mg testosterone in 1.25 g of gel (4 actuations = 50 mg testosterone).

#11: Description

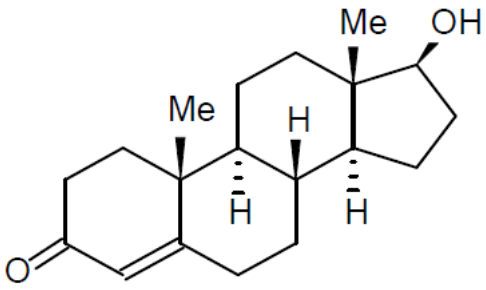
Vogelxo (testosterone) gel, for topical use is a clear translucent hydroalcoholic topical gel containing testosterone, an androgen. Vogelxo provides continuous transdermal delivery of testosterone for 24 hours, following a single application to intact, clean, dry skin of the shoulders and upper arms.

Vogelxo is available in unit-dose tubes, unit-dose packets, and a metered-dose pump. One 5-g or two 5-g tubes/packets of Vogelxo contains 50 mg or 100 mg of testosterone, respectively. One pump actuation dispenses 1.25 g of gel, which contains 12.5 mg of

testosterone. Four pump actuations or eight pump actuations contain 50 mg or 100 mg of testosterone, respectively. Each metered-dose pump container is capable of dispensing 60 pump actuations.

The active pharmacological ingredient in Vogelxo is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-β hydroxyandrost-4-en-3-one.

The structural formula is:



Testosterone ($C_{19}H_{28}O_2$) MW: 288.42

Inactive ingredients in Vogelxo are carbomer copolymer Type B, carbomer homopolymer Type C, diisopropyl adipate, ethyl alcohol, glycerin, methyl laurate, oleyl alcohol, polyethylene glycol, propylene glycol, purified water, and tromethamine.

#16: How Supplied/Storage and Handling

Vogelxo is supplied in unit-dose tubes in cartons of 30 and unit-dose packets in cartons of 30. Each tube or packet contains 50 mg testosterone in 5 g of gel.

Vogelxo is also supplied in a metered-dose pump that delivers 12.5 mg of testosterone per complete pump actuation. Each pump is capable of dispensing 60 metered pump actuations. Each pump actuation delivers 1.25 g of gel. The metered-dose pump is supplied in cartons of 2.

Vogelxo is available as follows:

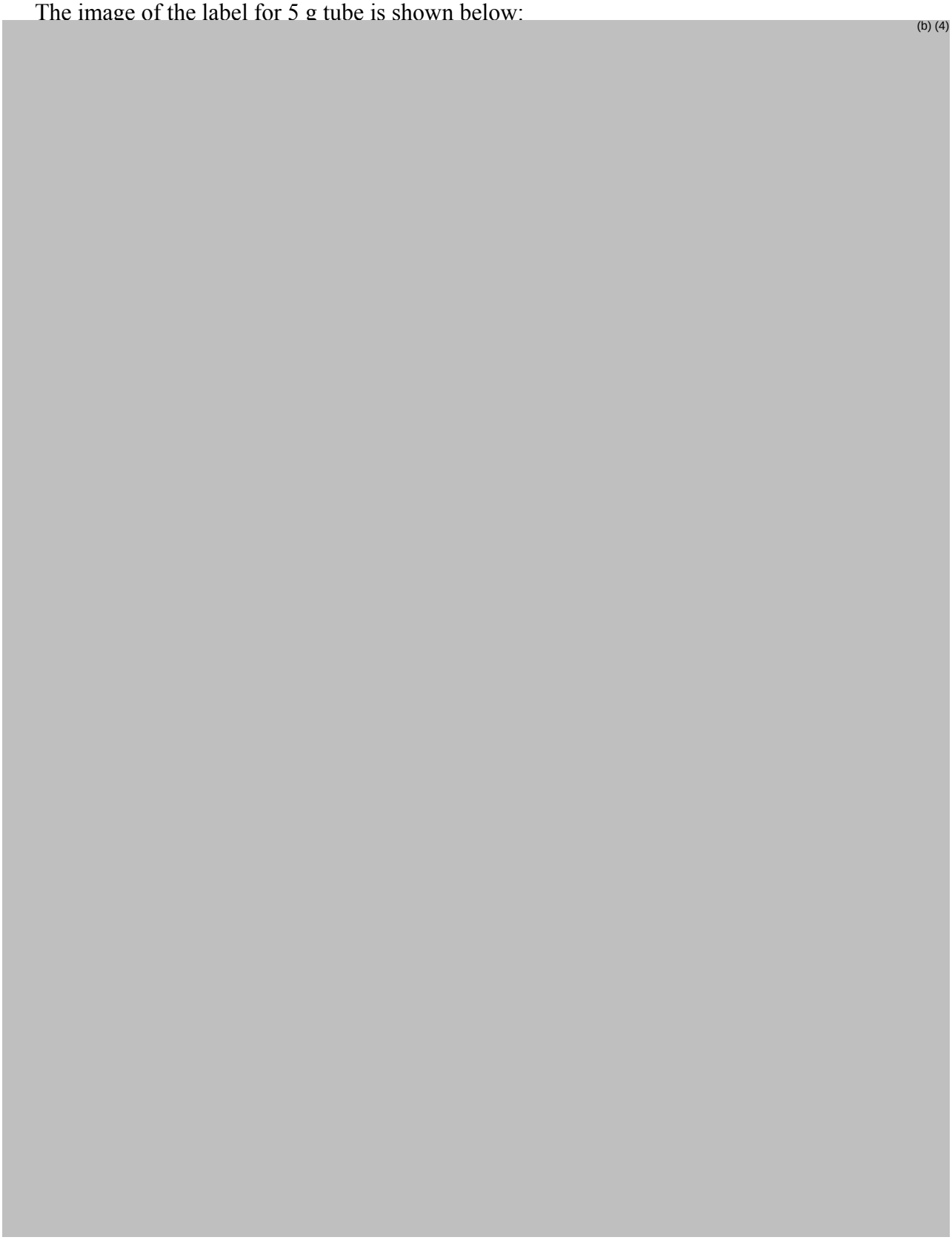
NDC Number	Strength	Package Size
0245-0871-05	50 mg of testosterone	30 tubes (5 g of gel per tube)
0245-0871-35	50 mg of testosterone	30 packets (5 g of gel per packet)
0245-0872-42	12.5 mg of testosterone per pump actuation	2 x 75 g pumps (each pump dispenses 60 metered 1.25 g of gel

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

2. Immediate container labels

The image of the label for 5 g tube is shown below:

(b) (4)



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

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/s/

BOGDAN KURTYKA
08/09/2013

MOO JHONG RHEE
08/09/2013
Chief, Branch IV

NDA 204399

TRADENAME (testosterone) gel
50 mg testosterone tube
50 mg testosterone packet
Metered pump 12.5 mg testosterone per actuation

Upsher-Smith Laboratories, Inc.

Bogdan Kurtyka, Ph.D.
Review Chemist

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

CMC REVIEW OF NDA 204399
For the Division of Reproductive and Urologic Products (HFD-580)

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CMC Review Data Sheet

1. NDA 204399

2. REVIEW #: 1

3. REVIEW DATE: 13-Jun-2013

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	18-Oct-2012
Labeling update	30-Jan-2013
Stability update	12-Mar-2013
Stability update	05-Apr-2013
Stability update	31-May-2013

7. NAME & ADDRESS OF SPONSOR:

Name:	Upsher-Smith Laboratories, Inc.
Address:	6701 Evenstad Drive Maple Grove, MN 55369
Telephone:	763-315-2000
Fax:	763-258-5578

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name: Testosterone
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anabolic steroid

11. DOSAGE FORM: Gel CODE: 066

CMC Review Data Sheet

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical CODE: 011

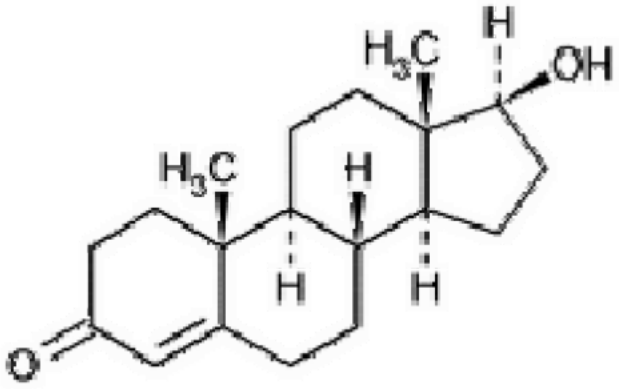
14. Rx/OTC DISPENSED: √ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Androst-4-en-3-one, 17-hydroxy-, (17β)-17β-Hydroxyandrost-4-en-3-one
USAN Name: Testosterone
CAS Number: 58-22-0
Structural Formula:



Molecular Formula: $C_{19}H_{28}O_2$
Molecular Weight: 288.42

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Testosterone	3	Adequate	11-May-2011	Reviewed by Ping Jin, Ph.D.
(b) (4)	III		(b) (4)	4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	

(b) (4)	III	(b) (4)	4	N/A	N/A	
	III		4	N/A	N/A	

[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	Acceptable	12-Mar-2013	Bogdan Kurtyka, Ph.D.
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Categorical exclusion granted (see review)	11-Mar-2013	Bogdan Kurtyka, Ph.D.
Microbiology	N/A		

The CMC Review for NDA 204399

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has ***not*** provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The office of Compliance has issued an overall recommendation of "Acceptable" for the facilities involved in this application (see the **Attachment**, p.73).

The label/labeling issues are ***not*** fully resolved (see the **List of Deficiencies**, p.72).

Therefore, from the ONDQA perspective, this NDA is ***not*** ready for approval per 21CFR 314.125(b)(6) in its present form until the issues delineated in the "**List of Deficiencies**" (p.72) are satisfactorily resolved.

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

N/A

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The sponsor references DMF (b) (4) ((b) (4)) for details on the description, characterization, manufacture, packaging, specification for quality control testing, and stability of the drug substance, testosterone USP. A letter of authorization to cross reference the DMF is provided in the application. DMF (b) (4) has been reviewed previously by Dr. Ping Jin and was deemed adequate to support (b) (4) (testosterone gel).

(2) Drug Product

Testosterone gel 1% is indicated for deficiency or absence of endogenous testosterone as a testosterone replacement therapy. It is a clear, translucent gel. The inactive ingredients of the formulation are commonly used in topical drug products. All excipients are listed in the Inactive Ingredients Database and the proposed amounts do not exceed previously approved levels. The drug product is manufactured by

(b) (4)

The drug product specification includes: description, identification, pH, assay, impurities, (b) (4), uniformity of dosage unites (for tube and packet presentation), delivered dose uniformity (for pump presentation), in vitro release, assay of ethanol, pH, viscosity, minimum fill, and weight loss. The specification attributes and their analytical methods and acceptance criteria are deemed satisfactory except for *in-vitro* release test pending satisfactory recommendation from Biopharm Review.

Three container closure systems are proposed: single use 5 g tubes and packets, and 88 g multiple dose metered pump. The information included in the application demonstrates that the proposed container/closure systems meet all recommendations of relevant USP monographs and the Agency's guidance.

The sponsor provided the results of up to 36 months long-term stability studies, and proposed an 36-month expiration dating period for tube and packet presentation, and an 24-month expiration dating period for metered pump under the controlled room conditions. The requested expiration dating periods are granted.

The applicant claimed categorical exclusion from the Environmental Assessment based on 21CFR 25.31(a).

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

5 g of gel (one tube, one packet, or 4 pump actuations) containing 50 mg of testosterone should be applied once daily (preferably in the morning) to clean, dry intact skin of the shoulders and/or upper arms.

C. Basis for Not-Approval Recommendation

21 CFR 314.125(b)(1)

- Specification for the drug product is not deemed adequate until in-vitro release test is deemed adequate pending Biopharm's Review.

21CFR 314.125(b)(6)

- Prescribing Information lists incorrect established name and do not include all required information on product characteristics and inactive ingredients.
- Established name in all labels is incorrect.
- Labels do not display flammability warning.
- Some labels do not list lot number and expiration date, proper names for inactive ingredients, and dosage strength.

(see the **List of Deficiencies** on p.72).

III. Administrative

A. Reviewer's Signature: *(See appended electronic signature page)*
Bogdan Kurtyka, Ph.D.
CMC Reviewer, Branch IV/Division II/ONDQA

B. Endorsement Block: *(See appended electronic signature page)*

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV/Division II/ONDQA

C. CC Block: Entered electronically in DARRTS

65 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

BOGDAN KURTYKA
06/14/2013

MOO JHONG RHEE
06/14/2013
Chief, Branch IV

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

OND Division:	Division of Reproductive and Urologic Products
NDA:	204399
Applicant:	Upsher-Smith Laboratories, Inc
Stamp Date:	17-Oct-2012
PDUFA Date:	17-Aug02012
Trademark:	TBD
Established Name:	Testosterone
Dosage Form:	Gel
Route of Administration:	Topical
Indication:	Testosterone replacement therapy in adult males for the treatment of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).
CMC Lead:	Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	☐
Comments for 74-Day Letter	X	☐

Summary and Critical Issues:

A. Summary

The drug product is a clear, translucent, alcohol-based testosterone gel at 1% strength. The bulk gel is packaged into unit dose tubes of 50 mg of testosterone per 5 g of gel, sachets of 50 mg of testosterone per 5 g of gel, and metered dose pumps of 12.5 mg testosterone per pump actuation delivering 1.25 g of gel. Each metered dose pump contains 75 g of gel and can dispense 60 doses.

B. Critical issues for review

The DMF for testosterone was ADEQUATE on 11-May-2011. Updates have been submitted since that time. Therefore, the DMF amendments may require review.

Information on the manufacturing process is adequate to begin review. However, a master batch record cannot be located at this time. The CMC reviewer should double check the application, and if the MBR is not found, he can request it in line with requirements for a 505(b)(2) application.

Specifications appear in line with similar products. An in vitro release test has been developed and will require review by ONDQA BioPharm. Dr. Tapash Ghosh has been assigned.

The PI and carton/container labeling is provided and is adequate to allow review. However, the strength is presented as 1% which will need to be changed in line with current labeling practices for testosterone gels.

C. Comments for 74-Day Letter

Please submit a copy of the Master Batch Record.

D. Recommendation:

This NDA is fileable from a CMC perspective. Bogdan Kurtyka, Ph.D., has been assigned as the primary reviewer. Tapash Ghosh, Ph.D. is the assigned BioPharm reviewer.

REGULATORY BRIEFING RECOMMENDATION: Branch-level

_____
Donna F. Christner, Ph.D.

NDA Number: 204399	**Type: 5**	**Established/Proper Name: testosterone gel**
Applicant: Upsher-Smith	**Letter Date: 17-Oct-2012**	**Stamp Date: 17-Oct-2012**

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		

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 26-Nov-2012 by Kerri-Ann Jennings.
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.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • 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.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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.	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: • 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		Request for a categorical exclusion as per 21 CFR 25.31(a)

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 DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Cross-reference to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to DMF (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		
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		36 months for tube and packet 24 months for metered dose pump
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	N/A

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)	Testosterone	07-Dec-2011	ADEQUATE on 11-May-2011. Updates since that time. May require review.
	IV		(b) (4)	02-Aug-2012	Excipients normally do not require review
	IV			10-Jul-2012	Excipients normally do not require review
	IV			19-Jun-2012	Excipients normally do not require review
	IV			19-Jun-2012	Excipients normally do not require review
	III			26-Jun-2012	See ONDC Policies on (b) (4)
	III			09-May-2012	
	III			25-Jan-2012	
	III			13-Jun-2012	
	III			04-Jul-2012	
	III			04-Jul-2012	
	III			25-Jun-2012	

(b) (4)	MAF		(b) (4) 14-May-2012	
	III		23-May-2012	
	III		06-Jul-2012	
	III		15-Jun-2012	
	III		15-Jun-2012	
	III		18-Jun-2012	

(b) (4)

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		Strength is presented as 1% which will need to be changed in line with current labeling practices for testosterone gels

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. Date
CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

{See appended electronic signature page}

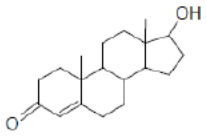
Moo-Jhong Rhee, Ph.D. Date
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: _____Yes; ___x____No Review date: 26-Nov-2012_
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, supplied by (b) (4). Full information is provided in DMF (b) (4) The following information is provided in the NDA.



Testosterone

Manufacturing

The applicant has provided the following flow chart for the synthesis of testosterone. Full information is provided in the cross-referenced DMF.

(b) (4)

The following sites have manufacturing responsibilities for the drug substance:

Table 4: Manufacturer of Testosterone, USP

Facility Establishment No.	Contact Information	Responsibility
(b) (4)		
Upsher-Smith Laboratories, Inc. 6701 Evenstad Drive Maple Grove, MN 55369 Establishment No.: 3004106442	Nancy Van Gieson Vice President, Quality and Corporate Compliance/Chief Compliance Officer Phone: (763) 315-2000 Fax: (763) 315-2195 e-mail: Nancy.VanGieson@Upsher-Smith.com	Alternate laboratory for drug substance release testing
[1]DMF Letter of Authorization is provided in Module 1, Section 1.4.1.		

Comment: *EES was submitted on 26-Nov-2012 by Kerri-Ann Jennings. As of 27-Nov-2012, all sits are ACCEPTABLE based on profile.*

Specifications

The quality of the drug substance is assured by adherence to the following specification. Full information is in the cross-referenced DMF.

Table 6: Testosterone, USP Specifications

Test	Analytical Method	Acceptance Criteria		
		USL	USP	(b) (4)
Description	TM-00001	White to off white crystalline powder	Not applicable	White to practically white powder (b) (4)
Identification A (IR)	USP <197K>	Exhibits spectra similar to that of the Reference Standard	Exhibits maxima only at the same wavelengths as that of a similar preparation of the corresponding USP Reference Standard	(b) (4)
Identification B (UV)	USP <197U>	Exhibits spectra similar to that of the Reference Standard	Exhibit maxima and minima at the same wavelengths and absorptivities and/or absorbance ratios are within specified limits	
Melting Range	USP <741>	153°C – 157°C	Between 153°C and 157°C	
Specific Rotation	USP <781S>	Between +101° and +105°	Between +101° and +105°	
(b) (4)				
Assay (HPLC)	TM-00172	97.0% - 103.0% of $C_{19}H_{28}O_2$	97.0% - 103.0% of $C_{19}H_{28}O_2$	
Related Substances (HPLC)	TM-00172			
Any Unspecified		NMT (b) (4)%	Not applicable	
Total		NMT	Not applicable	
Residual Solvents (GC)				
All Classes	USP <467>	Meets the requirements	Meets the requirements	
(b) (4)				

The applicant reports that a retest interval of (b) (4) is applied to the drug substance.

Comment: *Information in the application and the cross-referenced DMF are adequate to allow review.*

DRUG PRODUCT

The drug product is a clear, translucent, alcohol-based testosterone gel at 1% strength. The bulk gel is packaged into unit dose tubes of 50 mg of testosterone per 5 g of gel, sachets of 50 mg of testosterone per 5 g of gel, and metered dose pumps of 12.5 mg testosterone per pump actuation delivering 1.25 g of gel. Each metered dose pump contains 75 g of gel and can dispense 60 doses. The formulation is as follows:

Table 2: Qualitative/Quantitative Composition of USL's Testosterone Gel 1%

Component (Proprietary Name)	Grade	Function	1% Bulk Gel Formulation		Unit Dose Tube or Unit Dose Packet	Multiple Dose Metered Pump	
			% (w/w)	mg/g	Amount per 50 mg Dose (5 g gel) (mg)	Amount per 1.25 g Actuation (mg)	Amount per 75 g Pump (mg)
Testosterone	USP	Drug substance (API)	1.00	(b) (4)	50.00	12.50	(b) (4)
Alcohol (Ethyl Alcohol, (b) (4)	USP						(b) (4)
Glycerin (b) (4)	USP						
Diisopropyl Adipate (b) (4)	House Standard						
Methyl Laurate (b) (4)	House Standard						
Oleyl Alcohol (b) (4)	NF						
Carbomer Homopolymer Type C (b) (4) (b) (4)	NF						
Carbomer Copolymer Type B (b) (4)	NF						
Propylene Glycol	USP						

Table 2: Qualitative/Quantitative Composition of USL's Testosterone Gel 1% (Continued)

Component (Proprietary Name)	Grade	Function	1% Bulk Gel Formulation		Unit Dose Tube or Unit Dose Packet	Multiple Dose Metered Pump	
			% (w/w)	mg/g	Amount per 50 mg Dose (5 g gel) (mg)	Amount per 1.25 g Actuation (mg)	Amount per 75 g Pump (mg)
Polyethylene Glycol (b) (4) (b) (4)	NF	Viscosity building agent					(b) (4)
Purified Water	USP	Co-Solvent					
Tromethamine (b) (4)	USP	Neutralizer					
TOTAL							
				Nominal fill	(b) (4)	not applicable	(b) (4)
				Overfill		not applicable	
				Total fill	5.2 g	not applicable	88.0 g

Manufacturing

The following facilities have manufacturing responsibilities for the drug product.

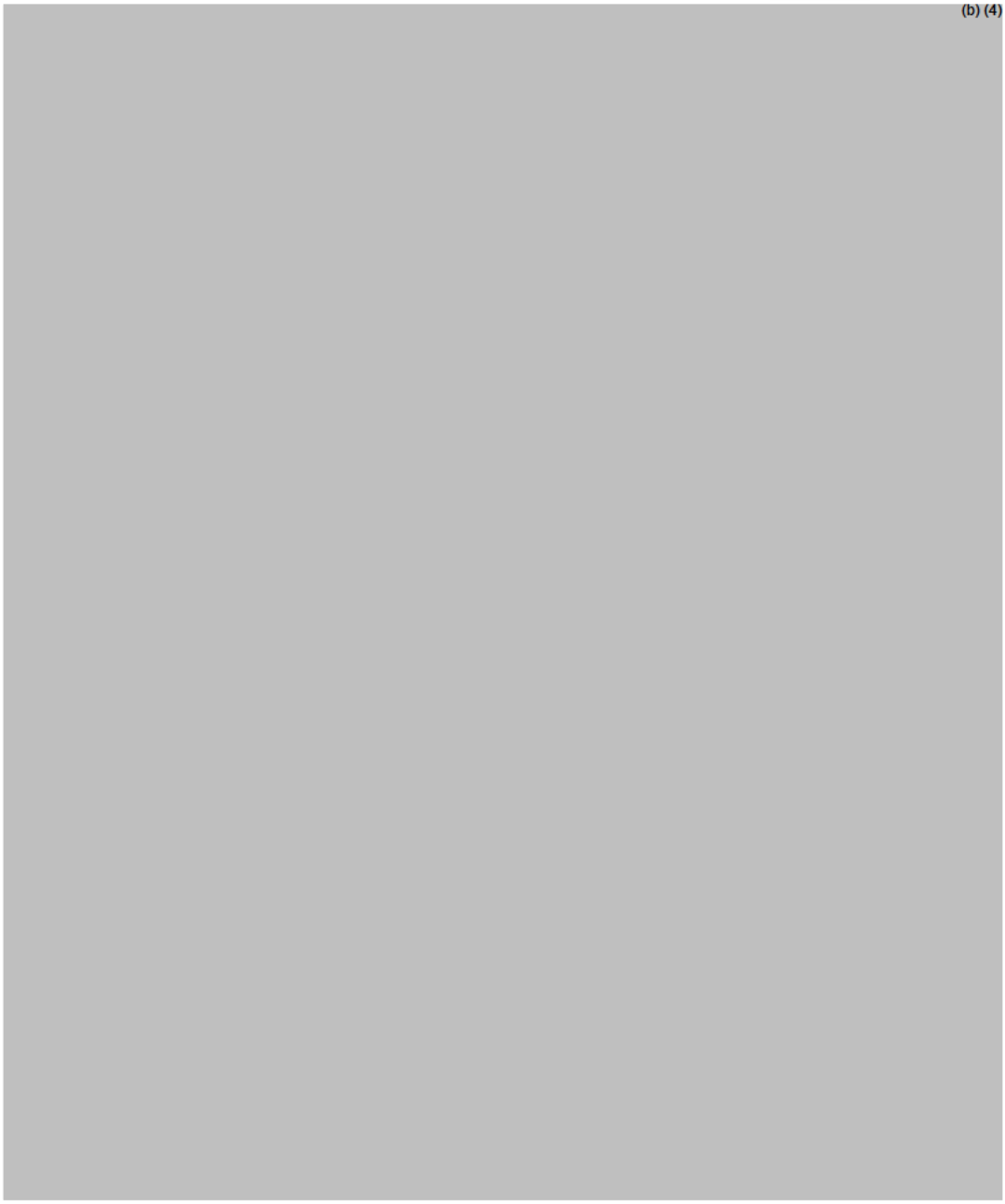
Table 1: Facilities and Responsibilities for the Drug Product

Facility	Contact Information	Responsibility
Upsher-Smith Laboratories, Inc. 6701 Evenstad Drive Maple Grove, MN 55369 Establishment No.: 3004106442	Nancy Van Gieson Vice President, Quality and Corporate Compliance/Chief Compliance Officer Phone: (763) 315-2000 Fax: (763) 315-2195 e-mail: Nancy.VanGieson@Upsher-Smith.com	NDA holder; Alternate laboratory for excipient, drug substance, and packaging component testing and drug product release/stability testing
[redacted] (b) (4)		

Comment: *EES was submitted on 26-Nov-2012 by Kerri-Ann Jennings. As of 27-Nov-2012, all sites except the* [redacted] (b) (4) *drug product manufacturing site in* [redacted] (b) (4) [redacted] *were ACCEPTABLE based on profile. On 07-Dec-2012, the District office updated the status of this site as ACCEPTABLE; the recommendation from the Office of Compliance is outstanding.*

The applicant has provided the following flow chart for manufacture of the bulk gel. Flow charts for packaging into the three different container closure configurations are also provided. Narratives are provided as well. Executed batch records are submitted as well, however, a master batch record cannot be located at this time. The CMC reviewer should double check the application, and if the MBR is not found, he can request it in line with requirements for a 505(b)(2) application.

Figure 1: Manufacturing Process Flow Diagram; Testosterone Gel 1% - (b) (4) batch



Comment: *Information is adequate to begin review. However, a master batch record cannot be located at this time. The CMC reviewer should double check the application, and if the MBR is not found, he can request it in line with requirements for a 505(b)(2) application.*

Specifications

The quality of the drug product is assured by adherence to the following specification:

Table 14: Testosterone Gel 1% Specifications

Test R (Release), S (Stability)	Test Method	Acceptance Criteria (Release and Stability -where applicable)
Description (R,S)	1034-104	Clear translucent gel (b) (4)
Identification A [TLC] (R)	TM-00354	The sample spot has retention factor (R_f) within (b) (4) % to a similarly made reference standard.
Identification B [HPLC] (R)	TM-00351	The retention of the major peak in the sample is within (b) (4) of the retention time of the major peak in the standard.
Assay [HPLC] (R,S)	TM-00351	(b) (4) LC[1]
Degradation Products [HPLC] (R,S)	TM-00351	Specified: (b) (4) NMT (b) (4) % NMT % NMT % NMT % Any Unspecified NMT % Total Unspecified NMT Total NMT
Residual Solvents (R)	USP <467> (b) (4)	Meets Requirements
Uniformity of Dosage Units – Content Uniformity[2] [HPLC] (R)	TM-00352	(b) (4)

Table 14: Testosterone Gel 1% Specifications (Continued)

Test R (Release), S (Stability)	Test Method	Acceptance Criteria (Release and Stability -where applicable)
Delivered Dose Uniformity[3] [HPLC] (R,S)	1034-076	(b) (4)
In-Vitro Release [HPLC] (R)	KABS-1811-LC	
(b) (4)	TM-00353	
Apparent pH (R,S)	USP <791>	
Viscosity (R,S)	TM-00355	

Test R (Release), S (Stability)	Test Method	Acceptance Criteria (Release and Stability -where applicable)
Minimum Fill (R)	USP <755>	(b) (4)
Weight Loss (S)	IQC.022	

[1]LC = Label Claim
[2]Specific to the tube and packet package presentation
[3]Specific to the multiple dose metered pump package presentation

Comment: *Specification appears in line with similar products. An in vitro release test has been developed and will require review by ONDQA BioPharm. Dr. Tapash Ghosh has been assigned.*

Container Closure Systems

The drug product is packaged in the following container closure systems:

7.1. Tube

The tube package presentation is a printed 3.0" x 0.5" (b) (4) tube with a removable orifice seal and a white ribbed screw cap. The tube is filled with 5 g of drug product (b) (4) A description of the unit dose 5 g tube is located in Table 33. Full tube details are provided in Section 3.2.P.7.

7.2. Packet

The packet container closure system consists of printed (b) (4)
(b) (4)

7.3. Pump

(b) (4)

Comment: *Information is adequate to allow review.*

Stability

Based on the following stability package, the applicant is requesting the following expiration dating periods when stored at controlled room temperature:

- Unit dose tube and unit dose packet: 36 months
- Metered dose pump: 24 months

Table 40: Primary and Supportive Stability Studies for Testosterone Gel 1%

Presentation	Packaged Batch Number - Purpose	Available Data (months)	
		25 °C/60% RH	40°C/75% RH
Laminate Tube (5 g)	42956 - Primary	Through 36 months	Through 3 months[1]
	46322 - Primary	Through 36 months	Through 3 months[1]
	50287 - Primary	Through 36 months	Through 6 months
	64540A - Primary	Through 24 months	Through 6 months
	71766C - Supportive	Through 9 months	Through 6 months
Packet (5 g)	42956A - Primary	Through 36 months	Through 3 months[1]
	46322A - Primary	Through 36 months	Through 3 months[1]
	50287A - Primary	Through 36 months	Through 6 months
Metered Dose Pump (88 g)	71766B - Primary	Through 9 months	Through 6 months
	73886A/C/E - Primary	Through 6 months	Through 6 months
	75828A - Primary	Through 3 months	Through 3 months
Metered Dose Pump (b) (4)	60336A - Supportive	Through 24 months	Through 3 months

[1] The duration of the accelerated stability studies conducted in support of ANDA 79-178

Comment: *The provided information is adequate to determine an expiration dating period.*

Labeling

The PI and carton/container labeling is provided and is adequate to allow review.

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
12/10/2012

MOO JHONG RHEE
12/10/2012
Chief, Branch IV