CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202763Orig1s000

CHEMISTRY REVIEW(S)

NDA 202-763

Trade Name (testosterone) Gel 1%

Teva Pharmaceuticals USA

Zhengfang Ge, Ph.D.

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

For

Division of Reproductive and Urologic Drugs

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-763

2. REVIEW #: 1

3. REVIEW DATE: Dec 12, 2011

4. REVIEWER: Zhengfang Ge, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC team meeting minutes	May 12, 2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	Jan 13, 2011
Amendment 004	May 18, 2001
Amendment 006	June 10, 2011
Amendment 007	July 29, 2011
Amendment 008	Aug 15, 2011
Amendment 009	Sep 14, 2011
Amendment 011	Sep 28, 2011
Amendment 013	Dec 5, 2011

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA

Chemistry Review Data Sheet

Address:	400 Chestnut Ridge Rd Woodcliff Lake, NJ 07677
Representative:	Robert S. Vincent, Director, Regulatory Affairs
Telephone:	601-930-3610

8. DRUG PRODUCT NAME/CODE/TYPE:

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

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Androgen.

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 1% w/w gel

13. ROUTE OF ADMINISTRATION: Transdermal

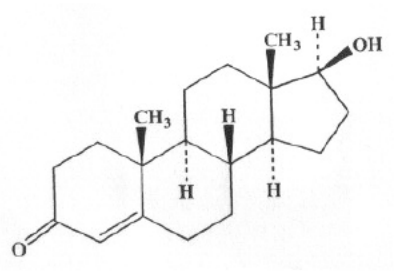
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

Chemical Name: 17β-Hydroxyandrost-4-en-3-one
Androst-4-en-3-one, 17-hydroxy-, (17β)-

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)	(b) (4)	1	Adequate	18-Aug-2011	Zhengfang Ge
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		Also subject of NDA 22-504, 22-309, (b) (4), (b) (4)
	III			3	Adequate	16-May-2007	Also subject of NDA (b) (4) (b) (4), 22-309, 22-504 DMF was reviewed for

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		
Pharm/Tox	N/A		
Biopharm	Unnecessary	9/11/2011	Tapash Ghosh, Ph.D.
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Acceptable		See review in section II/B
Microbiology	N/A		

The Chemistry Review for NDA 202-763

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

However, the Office of Compliance has ***not*** issued an overall "Acceptable" recommendation.

Labeling issues also have ***not*** been resolved as of this review.

Therefore, from the ONDQA perspective, this NDA is ***not*** recommended for "***Approval***" in its present form per 21CFR 314.125(b)(6),(13) until all the pending issues resolved.

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

None

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance, testosterone USP, is supplied by Cipla (DMF 21546). A Letter of Authorization is provided to reference the DMF for the CMC information. The DMF has been reviewed and is deemed adequate to support the approval of this NDA.

Drug Product

The drug product contains 1% w/w testosterone in a hydroalcoholic gel base for topical application. The drug product is indicated for hormone replacement for hypogonadal men. It is proposed to be supplied in 2.5g and 5g sachets, (b) (4)

(b) (4)

The other inactive ingredients include (b) (4) dehydroated alcohol, water and sodium hydroxyide. All the excipients comply to USP/NF.

Manufacturing process include [redacted] (b) (4)

Since isopropyl palmitate [redacted] (b) (4), it is important to maintain its concentration consistently in the product. [redacted] (b) (4)

The drug product specification includes [redacted] (b) (4)

Stability data provided in the NDA include 6 months under accelerated condition for all 6 batches of the product (3 batches each of 2.5g and 5g sachets), 12 months long term condition for 5 batches of the product and 36 months for one batch of the 5g sachet (Batch X028). All the stability data except the content of isopropyl palmitate are within the specification with no significant change throughout the storage. Decrease in isopropyl palmitate content was observed under accelerated and long term storage conditions with batch X028 showing most significant decrease. However, since batch X028 was manufactured [redacted] (b) (4) and packaged in a different batch of the sachets. It is reasonable to consider batch X028 an outlier and determined the expiration dating period based on the stability data of the 5 recent batches. Based on the extrapolation of 12 months stability data on the 5 batches of the product, the predicted content of isopropyl palmitate meets the acceptance criterion at 18th months. Therefore, the proposed 18 months expiration dating period is granted.

The final recommendation from the Office of Compliance for all the manufacturing and testing sites is pending as of this review.

The strength of the drug product was expressed as [redacted] (b) (4) however, in order to be consistent with the marketed testosterone product, the applicant agreed to change it to "XX mg of testosterone per packet*, each packet contains XX g of gel" as requested by the Agency.

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

Testosterone gel 1% is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary Hypogonadism (Congenital or Acquired)
- Hypogonadotropic Hypogonadism (Congenital or Acquired)

Recommended starting dose: 5 g for adult males, applied topically once daily. Apply to clean, dry, intact skin of shoulders and upper arms and/or abdomen. Do NOT apply testosterone gel to the genitals. Dose adjustment for adult males: if serum testosterone level is below the normal

range, adjust dose from 5 g to 7.5 g and from 7.5 g to 10 g.

C. Basis for Not-Approval Recommendation

21CFR314.125 (13)

- The overall "Acceptable" recommendation has ***not*** been issued from the Office of Compliance.

21CFR 314.125 (6)

- Labeling issues are ***not*** resolved (see the List of Deficiencies on p. 59)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Zhengfang Ge, Ph.D.
Reviewer/ONDQA

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

C. CC Block

Donna Christner

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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/

ZHENGFANG GE
12/14/2011

MOO JHONG RHEE
12/14/2011
Chief, Branch IV

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

OND Division:	Division of Reproductive and Urologic Products
NDA:	202763
Applicant:	TEVA
Stamp Date:	14-Jan-2011
PDUFA Date:	14-Nov-2011
Trademark:	None submitted
Established Name:	Testosterone
Dosage Form:	Gel. 1%
Route of Administration:	Transdermal
Indication:	Testosterone replacement in adult males
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 sponsor has provided the following information on the composition of the drug product. The drug product is a 1% testosterone gel that is available in (b) (4) presentations: a 2.5 g sachet, a 5.0 g sachet (b) (4) each 2.5 g sachet provides 25 mg of testosterone and each 5 g sachet provides 50 mg of testosterone.

The sponsor originally sought to submit an ANDA, which was the subject of two Refuse to Review letters (See REVIEW NOTES). They were subsequently advised that they would need to submit the application under the 505(b) pathway.

B. Critical issues for review

The drug substance DMF will require review.

The specification for isopropyl palmitate may need to be tightened since it is used (b) (4)

C. Comments for 74-Day Letter

Please provide additional stability data by month 5 of the review clock.

D. Recommendation:

This NDA is fileable from a CMC perspective. Zhengfang Ge, Ph.D. is assigned as the primary reviewer. It is recommended that this be designated for a Branch-level Regulatory Briefing because the drug substance has been approved before in a gel formulation.

_____
Donna F. Christner, Ph.D.

NDA Numbe202763r: **Type: 5** **Established/Proper Name: testosterone**

Applicant: TEVA **Letter Date: 14-Jan-2011** **Stamp Date: 14-Jan-2011**

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		356h Inspections requested on 09-Feb-2011 by R. McKnight
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		356h Inspections requested on 09-Feb-2011 by R. McKnight
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		356h Inspections requested on 09-Feb-2011 by R. McKnight

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	No contract facilities used as per 356h
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		356h

* 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 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		Information cross-referenced to (b) (4) LOA provided.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Information cross-referenced to (b) (4) LOA provided.
14.	Does the section contain information regarding the characterization of the DS?	X		Information cross-referenced to (b) (4) LOA provided.
15.	Does the section contain controls for the DS?	X		Information cross-referenced to (b) (4) LOA provided.
16.	Has stability data and analysis been provided for the drug substance?	X		Information cross-referenced to (b) (4) LOA provided.
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		Organized as for an ANDA submission
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		Organized as for an ANDA submission
21.	Is there a batch production record and a proposed master batch record?	X		Organized as for an ANDA submission
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Organized as for an ANDA submission
23.	Have any biowaivers been requested?		X	BE study performed
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		Organized as for an ANDA submission
25.	Does the section contain controls of the final drug product?	X		Organized as for an ANDA submission
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Proposed (b) (4) of expiration dating period based on three lots of drug product packaged in each container closure system. At least 6 months of data are provided for 2.5g sachet (b) (4). 3 months of accelerated and 24 months of long term data are provided for one lot of the 5g sachet presentation, with 6 months for two 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		Validation packages provided for both drug substance and drug product

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	Information provided in DP section. Limits set in line with USP guidelines

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)	01-Dec-2010	eCTD DMF. Will require review
(b) (4)	III	(b) (4)	(b) (4)	13-Dec-2010	No review found. **May require review unless information is in the NDA.**
	III			02-Dec-2010	(b) (4)
	III			01-Dec-2010	No review found. **May require review unless information is in the NDA.**
					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		Contains SPL table. Labeling will need to be modified in line with other recent testosterone labels.
33.	Have the immediate container and carton labels been provided?	X		Labeling will need to be modified in line with other recent testosterone label. No tradename has been submitted

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.		X	N/A
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

{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

REVIEW NOTES

The sponsor has provided the following information in their cover letter:

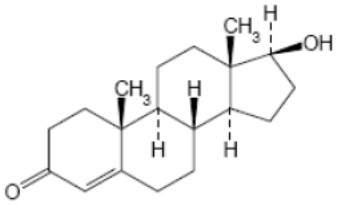
Teva Pharmaceuticals USA herewith submits a New Drug Application for the drug product Testosterone Gel 1% in accord with Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act. Reference is made to our Original ANDA (b) (4) for Testosterone Gel, 1% submitted on December 29, 2008 and the Agency's Refuse to Receive Letter dated April 7, 2009. The basis for the letter was that Teva's formulation contained different ingredients than those contained in the RLD.

(b) (4)

DRUG SUBSTANCE

The drug substance is testosterone. The majority of the information is provided in the cross-referenced (b) (4). The sponsor provides the following information. The application is in the Question/Answer format preferred by Office of Generic Drugs. While this does not make the application a RTF, it is different from what is normally submitted and reviewed in ONDQA.

Molecular Structure



Nomenclature:

- Systematic Chemical Name (IUPAC Nomenclature)
  Androst-4-en-3-one, 17- hydroxy-, (17β) - 17β –Hydroxyandrost-4-en-3-one
- USAN : Testosterone
- BAN : Testosterone

Manufacturing

The drug substance is manufactured at the following facility:

DRUG SUBSTANCE:

Manufacturer of the Active Drug Substance (Testosterone, USP)	
Name	Cipla Ltd.
Address	(b) (4)
Telephone	
Drug Master File No.	021546
FEI #	3004545699
DUNS #	677602447
Authorized US Agent	
Name	(b) (4)
Address	
Telephone	
Fax	
Contact Person	
Email	

Comment: *Inspection requests were submitted on 09-Feb-2011 by Rebecca McKnight.*

The sponsor has provided the following information on specifications and impurities in the drug substance:

Table No.5: API Specifications (Batch No. L100135)

Test	Specifications	Results
AS PER USP 30 STANDARDS		
Description	White or slightly creamy white crystals or crystalline powder. It is odorless and is stable in air.	Meets the requirement
Solubility	Practically insoluble in water, freely soluble in dehydrated alcohol and in chloroform, soluble in dioxane and slightly soluble in ether.	Meets the requirement
Identification A) By Infrared absorption spectrophotometry B) By Ultraviolet and Visible absorption spectrophotometry	 The infrared absorption spectrum of the sample in potassium bromide dispersion is concordant with the spectrum obtained from the similar preparation of USP Testosterone RS. The light absorbance of the sample solution in the range from 200 nm to 400 nm exhibits maxima at about same wavelength as that of standard solution	Meets the requirement
Melting range (°C)	(b) (4)	(b) (4)
Specific Rotation (Degree)	(b) (4)	
(b) (4)		
Assay (By HPLC – on dried basis) (% w/w)		
(b) (4)		
Heavy Metals		Meets the requirement
Related Substances (By HPLC) (%)		Meets the requirement
(b) (4)		(b) (4)
Impurity (b) (4)		
Impurity		
Any other impurity		
Total impurities		

Test	Specifications	Results
Residual Solvents (By Gas chromatography) (ppm)		Meets the requirement
(b) (4)		

The sponsor has provided the following information on the potential impurities in the drug substance:

Table No.2

Impurity	Source	Control
(b) (4)		

Comment: *Full information is provided in the cross-referenced DMF which will require review.*

DRUG PRODUCT

The sponsor has provided the following information on the composition of the drug product. The drug product is a 1% testosterone gel that is available in (b) (4) presentations: a 2.5 g sachet, a 5.0 g sachet (b) (4) each 2.5 g sachet provides 25 mg of testosterone and each 5 g sachet provides 50 mg of testosterone.

Qualitative/Quantitative Composition

Ingredients	Function	Amount (gm) / 2.5 gm sachet	Amount (gm) / 5 gm sachet	Amount (gm) / (b) (4)	Amount (% w/w)
Testosterone, USP	Active	0.025	0.05		1.00
Dehydrated Alcohol, USP	(b) (4)		(b) (4)		(b) (4)
Carbomer Homopolymer Type C (b) (4) NF)					
Isopropyl Palmitate, NF	(b) (4)				
Sodium Hydroxide, NF	(b) (4)				
Purified Water, USP					
Total:	-	2.5	5.0		

Excipients are compendial and are controlled by compendial methods.

(b) (4)

Manufacturing

The drug product is manufactured at the following facilities:

DRUG PRODUCT:

Site of Drug Product Manufacturing, Processing, Packaging, Labeling and Testing	
Name	Cipla Ltd.
Address	(b) (4) Goa - 403722 India
FEI #	3004081307
DUNS #	650072015
Telephone	91- 832-2782581
Fax	91-832-2782805
Contact Person	Mr.Tapas Datta, Site Manager
Email	tapasdatta@cipla.com

Comment: *Inspection requests were submitted on 09-Feb-2011 by Rebecca McKnight.*

The sponsor has provided the following flow chart for manufacturing. A narrative is also provided.

Schematic Diagram of Manufacturing Process

Comment: *Information is adequate for review.*

SPECIFICATIONS

The quality of the drug product is assured by the following specifications. Different specifications are provided for drug product packaged in sachets (b) (4)

Table No.32: Summary of the specification for Testosterone gel 1%w/w (sachet pack)

Test Items	Release criteria	Stability (or shelf life criteria)
Description	Clear Colourless gel	
Identification (HPLC)	The retention time of the principal peak in the chromatogram of sample solution corresponds to that in the chromatograms of the standard solution as obtained with the test for assay.	NA
Identification (TLC)	A positive identification for Testosterone is indicated if the Rf value for the sample preparation is ±10% of that obtained for the standard solution	NA
Fill Weight	(b) (4)	NA
Apparent pH		NA
Spreadability		(b) (4)
Viscosity		
Assay: Content of Testosterone		
Content of Dehydrated alcohol		
Content of Isopropyl palmitate		
Related Substances Single maximum impurity Total impurity		
(b) (4		

Table No.32: Summary of the specification for Testosterone gel 1%w/w (sachet pack) (Continued)

Test Items	Release criteria	Stability (or shelf life criteria)
Microbial Examination of Non Sterile Products:		
(1.□ Microbial Enumeration Test	NMT 100 cfu per g	NMT 100 cfu per g
Total aerobic microbial count	NMT 10 cfu per g	NMT 10 cfu per g
Total combined yeasts & mold count.		
2) Test for specified organisms		
Escherichia coli	Absent per g	Absent per g
Salmonellae	Absent per 10g	Absent per 10g
Staphylococcus aureus	Absent per g	Absent per g
Pseudomonas aeruginosa	Absent per g	Absent per g
Bile tolerant gram negative bacteria	NMT 10 per g	NMT 10 per g

(b) (4)

(b) (4)

Comment: *Information is adequate to allow review. The specification for isopropyl palmitate may need to be tightened* (b) (4)

CONTAINER CLOSURE

The following presentations are provided for in the application:

Table No. 36: Proposed packing for Testosterone Gel

(b) (4)

The sponsor proposes a (b) (4) for drug product packaged in 2.5 g and 5 g sachets and (b) (4) The following stability package is provided:

Presentation	Number of batches	Data available	Year Manufactured
2.5 g sachets	3 batches	6 months accelerated 6 months long term	(b) (4)
5.0 g sachets	1 batch **Lot X028**	3 months accelerated 24 months long term	
	2 batches **Lot X145 and X146**	6 months accelerated 6 months long term	
(b) (4)			

Comment: *Adequate information is provided in order to set an expiry. However, the data package may not be sufficient to gran* (b) (4) *A request will be made to the sponsor to submit additional stability data by month 5 of the review cycle.*

LABELING

The sponsor has provided a copy of the carton/container labels and the PI. The sponsor has not designated a Tradename at this time, so the labeling has only the established name on the mock-ups.

Comment: *Recently, during review of the carton/container labels and PI for a number of similar testosterone drug products, DMEPA expressed concern about identifying the strength of the dosage form* (b) (4) *and also listing both the mg of testosterone and the mg of gel in the Dosage and Administration section of the PI. Although from the CMC perspective, it was acceptable* (b) (4) *as a way of*

expressing strength, since DMEPA felt strongly about this issue, ONDQA deferred the issue to DMEPA and negotiated labeling that was acceptable to both ONDQA and DMEPA.

(b) (4)

[redacted]

For the sachet, final wording will need to be negotiated with DMEPA. However, the following is suggested:

For 2.5 g sachet:

TRADENAME
(testosterone gel)
25 mg of testosterone per sachet*

*Each sachet contains 2.5 g of gel

For 5.0 g sachet:

TRADENAME
(testosterone gel)
50 mg of testosterone per sachet*

*Each sachet contains 5 g of gel

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
03/09/2011

MOO JHONG RHEE
03/09/2011
Chief, Branch IV

Memorandum

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

Date: **February 9, 2012**

From: **Zhengfang Ge, Ph. D.**

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

To: **CMC Review #1 of NDA 202-763**

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.

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

On January 13, 2012, the Office of Compliance issued the "Acceptable" recommendation for the facilities involved in the NDA (see the **Attachment 1**).

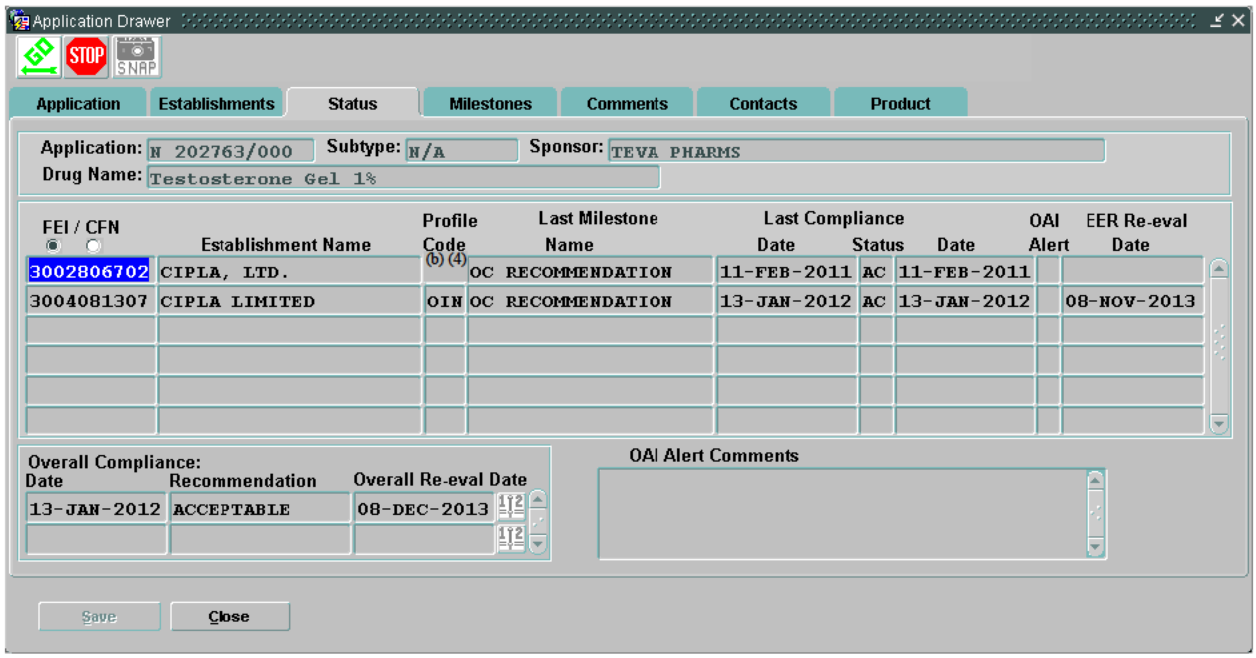
On February 8, 2012, the applicant provided the revised label and labeling via e-mail and they are revised satisfactorily from the ONDQA perspective (see the **Attachment 2**).

Recommendation:

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

Attachment:

1. EES report



2. Copies of final labels

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ZHENGFANG GE
02/09/2012

MOO JHONG RHEE
02/09/2012
Chief, Branch IV