

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203098Orig1s000

CHEMISTRY REVIEW(S)

NDA 203098

Testosterone Gel

25 mg (2.5 g gel), 50 mg (5.0 g gel) testosterone in packets

and

12.5 mg (1.25 g gel) testosterone (per actuation) in bottles with non-aerosol metered dose pumps

Perrigo Israel Pharmaceuticals Ltd.

Rajiv Agarwal, Ph.D

Review Chemist

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

**CMC REVIEW OF NDA 203098
For the Division of Reproductive and Urologic Drug Products
(HFD-580)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 203098
2. REVIEW #: 2
3. REVIEW DATE: 4-JAN-2013
4. REVIEWER: Rajiv Agarwal, Ph.D.
5. PREVIOUS DOCUMENTS:

Original Submission	05-JUL-2011
Amendment	21-NOV-2011
Amendment	22-NOV-2011
Amendment	01-DEC-2011
Amendment	19-JAN-2012
Amendment	01-FEB-2012
Amendment	06-FEB-2012
Amendment	21-FEB-2012
Amendment	29-FEB-2012
Amendment	22-MAR-2012
Amendment	26-MAR-2012
CMC review # 1	06-MAR-2012
Addendum	11-APR-2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission	01-AUG-2012
Amendment (labeling)	20-SEP-2012
E-mail	03-JAN-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Perrigo Israel Pharmaceuticals Ltd
Address: Industrial Zone, Yeruham, Israel 80500
Representative: Valerie Gallagher, Associate Director
502 Eastern Ave., Plant 6
Allegan, MI 49010

CMC Review Data Sheet

Telephone: 269-686-1590

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Testosterone Gel
b) Non-Proprietary Name: Testosterone
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Hormone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 12.5 mg testosterone per actuation (via pump) equal to 1.25 g of gel

and

25 mg and 50 mg testosterone per packet equal to 2.5g and 5g gel, respectively

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

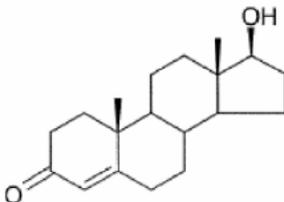
Not a SPOTS product

CMC Review Data Sheet

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

Chemical name: 1) Androst-4-en-3-one, 17-hydroxy-,
(17 β) -
2) 17 β -Hydroxyandrost-4-en-3-one

Structural formula:



Molecular formula: C₁₉H₂₈O₂

Molecular weight: 288.42

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE¹	STATUS²	DATE REVIEW COMPLETED	COMMENTS
II			(b) (4)	1	Adequate	06-SEP-2011	Dr. Joel Hathaway
III				4	Adequate	06-MAR-2012	Suitable
III				4	Adequate	06-MAR-2012	Suitable
III				4	Adequate	06-MAR-2012	Suitable

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
IND	107,130	Active

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	28-SEP-2012	Office of Compliance
Methods Validation	N/A, according to the current ONDQA policy	06-MAR-2012	Dr. Rajiv Agarwal
EA	Claim for the categorical exclusion is granted (see CMC review # 1)	06-MAR-2012	Dr. Rajiv Agarwal
BioPharmaceutics	Adequate	22-MAR-2012	Dr. Tapash Ghosh

Executive Summary Section

The CMC Review for NDA 203098

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The last CMC Addendum to CMC Review # 1 (11-APR-2012), has noted the following two pending issues:

- The finalized mock ups of the container/closures were not provided.
- PI labeling issues were not resolved.

Now the finalized mock up labels are submitted, and the labeling issues are also satisfactorily resolved in this resubmission (See the **Attachment-1**).

The final recommendation from the Office of Compliance has not been changed from the previous “Acceptable” (see the **Attachment-2**).

Therefore, from the ONDQA’s perspective, this NDA is now recommended for APPROVAL.

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

None

II. Summary of CMC Assessments

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

See the Review #1 (6-MAR-12) and its Addendum (11-APR-12)

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

See the Review #1 (6-MAR-12) and its Addendum (11-APR-12)

C. Basis for Approval Recommendation

All the labeling issues are satisfactorily resolved and the revised PI and labels for primary and secondary container closures are now submitted.

Executive Summary Section

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

(See appended electronic signature page)

Rajiv Agarwal, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

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

C. CC Block: entered electronically in DARRTS

7 Pages have been Withheld in Full as B4 (CCI/TS)
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/s/

RAJIV AGARWAL
01/08/2013

MOO JHONG RHEE
01/08/2013
Chief, Branch IV

Memorandum

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

Date: April 10, 2012

From: Rajiv Agarwal, Ph.D; Ph.D
Review Chemist, Branch IV
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 203-098

Subject: Final Recommendation

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

1. The acceptance criterion for IVRT in the drug product specification (for both 2.5 and 5.0 g unit dose Aluminum foil packets and Non-Aerosol Metered dose Pumps) and the expiration dating period [REDACTED] (b) (4) were not acceptable.
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 March 22 and March 26, 2012, the applicant provided adequate information on the final "drug product specification" (for 2.5 and 5.0 g unit dose Aluminum foil packets and Non-Aerosol Metered dose Pumps) including the new agreed upon acceptance criterion for IVRT. Also provided is the stability data to justify the newly proposed 18 months of expiration dating period. Based on the provided information, 18 months of the expiration dating period can be granted.

All the CMC comments on labels are accepted by the applicant, although finalized mock up labels are pending. The labeling is still under review and not finalized.

Pending issues in "Description" and "How Supplied" sections are:

- Not acceptable expression of strength [REDACTED] (b) (4)
- Not acceptable storage temperature

Recommendation:

This NDA is **not** recommended for approval from the ONDQA perspective in its present form per 21 CFR 314.125(b)(6) until the labeling issues are satisfactorily resolved.

Attachments:

1. Final drug product specification for Aluminum Foil Packet

Specifications for Finished Product
Packaged in 2.5g and 5g Unit Dose Aluminum Foil Packets

Finished Product		
Tests	Specification	Method
(b) (4)		

Finished Product		
Tests	Specification	Method
(b) (4)		

Finished Product		
Tests	Specification	Method
(b) (4)		

2. Final drug product specification for Metered-Dose Pump

Specifications for Finished Product
Packaged in Bottles with Non-Aerosol Metered-Dose Pumps

Finished Product		
Tests	Specification	Method
(b) (4)		

Finished Product		
Tests	Specification	Method
(b) (4)		

Finished Product		
Tests	Specification	Method
(b) (4)		

*No further tests are needed. The calculated residual solvents in the drug product, derive from the excipients, meet the requirement of the ICH Guidance.

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

/s/

RAJIV AGARWAL
04/11/2012

MOO JHONG RHEE
04/11/2012
Chief, Branch IV

NDA 203-098

Testosterone Gel

**25 mg (2.5 g gel), 50 mg (5.0 g gel) testosterone in packets
and
12.5 mg (1.25 g gel) testosterone (per actuation) in bottles with non-aerosol metered
dose pumps**

Perrigo Israel Pharmaceuticals Ltd.

Rajiv Agarwal, Ph.D

Review Chemist

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

**CMC REVIEW OF NDA 203-098
For the Division of Reproductive and Urologic Drug Products
(HFD-580)**

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CMC Review Data Sheet

1. NDA 203-098
2. REVIEW #: 1
3. REVIEW DATE: 06-MAR-2012
4. REVIEWER: Rajiv Agarwal, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	05-JUL-2011
Amendment	21-NOV-2011
Amendment	22-NOV-2011
Amendment	01-DEC-2011
Amendment	19-JAN-2012
Amendment	01-FEB-2012
Amendment	06-FEB-2012
Amendment	21-FEB-2012
Amendment	29-FEB-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Perrigo Israel Pharmaceuticals Ltd
Address: Industrial Zone, Yeruham, Israel 80500
Representative: Valerie Gallagher, Associate Director
502 Eastern Ave., Plant 6
Allegan, MI 49010
Telephone: 269-686-1590

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Testosterone Gel
- b) Non-Proprietary Name: Testosterone
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5

CMC Review Data Sheet

- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Hormone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 12.5 mg testosterone per actuation (via pump) equal to 1.25 g of gel

and

25 mg and 50 mg testosterone per packet equal to 2.5g and 5g gel, respectively

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

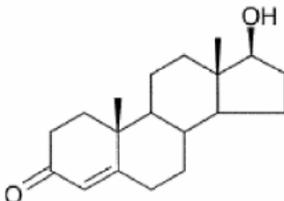
SPOTS product – Form Completed

Not a SPOTS product

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

Chemical name: 1) Androst-4-en-3-one, 17-hydroxy-, (17 β) -
2) 17 β -Hydroxyandrost-4-en-3-one

Structural formula:



CMC Review Data Sheet

Molecular formula: $C_{19}H_{28}O_2$

Molecular weight: 288.42

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
II			(b) (4)	1	Adequate	06-SEP-2011	Dr. Joel Hathaway
III				4	Adequate	06-MAR-2012	Suitable
III				4	Adequate	06-MAR-2012	Suitable
III				4	Adequate	06-MAR-2012	Suitable

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
IND	107,130	Active

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	24-AUG-2011	Office of Compliance
Methods Validation	N/A, according to the current ONDQA policy	06-MAR-2012	Rajiv Agarwal
EA	Claim for the categorical exclusion is granted (see review)	06-MAR-2012	Rajiv Agarwal
BioPharmaceutics	Pending		Dr. Tapash Ghosh

Executive Summary Section

The CMC Review for NDA 203-098

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

The Office of Compliance has made an overall “Acceptable” recommendation for the facilities involved in this application.

Labels are satisfactorily finalized, but final labeling is pending.

Therefore, from the ONDQA perspective, this NDA is *not* recommended for approval per 21 CFR 314.125(b)(1) and (6) in its present form until the issues delineated in the **List of Deficiencies** (p. 68) are satisfactorily resolved.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

(b) (4) DMF (b) (4) contains CMC information related to the testosterone drug substance. The CMC information related to the testosterone was previously reviewed on 06-SEP-2011 by Dr. Joel Hathaway and is deemed adequate.

The manufacturing/testing site for drug substance has been recommended as ACCEPTABLE based on profile. An OVERALL recommendation from the Office of Compliance is ACCEPTABLE (see **Attachment-1**).

(2) Drug Product

Testosterone Gel is a clear colorless hydroalcoholic gel packaged into two packaging configurations: 2.5g (or 25 mg testosterone) and 5g (or 50 mg testosterone) unit dose

Executive Summary Section

aluminum foil packets and in bottles with non-aerosol metered-dose pumps (delivers 1.25 g of gel or 12.5 mg of testosterone per actuation).

Information is provided on Testosterone Gel manufactured with Carbomer 940, NF (used in all clinical batches) and Testosterone Gel, manufactured with Carbopol 980 (using Carbomer homopolymer type C, NF) which will be used for commercial distribution. The amounts of both carbomers in the clinical (b) (4) and to-be-marketed (b) (4) formulations are (b) (4) and below the amounts listed in IIG for the same dosage form and route of administration. The applicant also changed the amount of alcohol from 67% to 69%. Using the scientific reasoning in the SUPAC-SS guidance, this change would qualify as a Level 2 excipient change, requiring updated stability data and comparative in vitro release data, but no bioequivalence studies. To qualify the change in excipients (carbomer grade) and the total excipient amount change (b) (4) the applicant performed the in-vitro studies to support the change from a (b) (4) Batch manufactured with carbomer 940, NF (used in clinical trial batches) to a (b) (4) Batch manufactured with Carbomer Homopolymer Type C, NF (Carbopol 980) which is the proposed commercial formulation. The results of the above studies demonstrate that no significant differences were found regarding the release of Testosterone Gel, (b) (4).

A very detailed manufacturing process of the gel product is provided in the submission. The manufacturing process is unique (b) (4)

(b) (4) The process appears to be robust, each process is monitored by reasonable critical steps and lower and higher limits of the processes (temp, speed, and pressure) are in place to ensure that a quality product can be manufactured. The manufacturing process is adequate.

All excipients, with the exception of isostearic acid, are USP/NF. During a meeting between the Perrigo and the Agency on 19-MAY-2010, a request was made by the Agency to include an assay for isostearic acid in the drug product specification with a proposed acceptance criterion along with method validation data. The applicant provided the information in the application. The applicant states that the content of isostearic acid in six batches of Testosterone Gel did not change much within the stability study at accelerated storage conditions. All the results were within the HPLC method precision. Based on the above results, the applicant believes it is not needed to include an assay test for isostearic acid in the drug product release and stability specifications.

Isostearic acid is (b) (4) in the literature but the applicant claims that this excipient (b) (4) and need not to be controlled and does not believe that it exhibits the aforementioned properties. (b) (4)

(b) (4) The Biopharmaceutical reviewer also recommended to add the specification of isostearic acid in the drug product specification and change its function (b) (4) in the drug product composition table. The applicant added the specification of isostearic acid in drug product specification and revised the function of isostearic acid in the composition table via amendment dated 01-FEB-2012. During the review of the amendment, it is noted that the acceptance criterion of isostearic acid is

Executive Summary Section

(b) (4) Since it is a functional excipient the acceptance criterion should be tightened to 90-110%. The request was communicated to the applicant. The applicant accepted the recommendation and provided the revised drug product specification (29-FEB-2012).

The specification for Testosterone Gel drug product packaged in bottles with non-aerosol metered-dose pump includes controls for universal attributes which are description, identity, assay, impurities, pH, viscosity, microbiology and Minimum Fill test. The uniformity of weight dosage and mean weight dosage tests are specifically for the metered- dose pump.

The applicant also included the specification for dissolution (b) (4). The Biopharmaceutics reviewer did not concur with the proposed dissolution methodology (b) (4) and requested (via IR letter dated 10-JAN-2012) the information "on why Franz cell is not used (b) (4) in dissolution testing". A t-con was held on 15-FEB-2012 and the applicant is advised by the Biopharmaceutics to adopt the Franz cell method or provide more information on the (b) (4) method to justify its use as a quality control method. The applicant submitted the responses on 29-FEB-2012 but it is determined to be deficient and use of "Franz Cell" was recommended and another information request was sent on 29-FEB-2012. The responses are pending.

This reviewer agrees with the Biopharmaceutics reviewer's recommendation that a Franz cell should be used to provide confidence in the testosterone release analysis in vitro. The applicant needs to revise the drug product specification sheet (release and stability) as requested.

The HPLC stability-indicating test for assay and impurities profile has been validated for accuracy, precision, specificity, and linearity as per ICH Q2(R1) and Analytical Procedures and Methods Validation Chemistry, Manufacturing, and Controls Documentation draft guidance recommendations. A GC method is used to assay ethanol and the method has been validated.

(b) (4) is a related substance and, in the formulation, its concentration did not increase during stress and stability studies, therefore, it is not monitored in the drug product, but only in the drug substance. The increase of the specified (b) (4) degradation impurity was observed under stress conditions and is monitored during the stability studies.

The product is packaged in two packaging configurations: 2.5g and 5g unit dose aluminum foil packets and bottles with non-aerosol metered-dose pumps (1.25 g gel per actuation). (b) (4)

In the (b) (4) non-aerosol metered-dose pump, the drug product is filled in (b) (4). The inner layer of the pouch, which comes in contact with the drug product, is identical to the inner layer of the unit dose Aluminum foil packets. The packaging is suitable to package the hydroalcoholic drug product. The pump can dispense 75 g of gel or 60 metered 1.25 g doses (net quantity of the gel is 88 gm). Before using the pump for the first time, the patient is advised to prime the pump

Executive Summary Section

by fully depressing the pump three times and discarding the gel. (b) (4)

The amount of isostearic acid, (b) (4) remained constant over 6 months under the accelerated stability condition in both the packaging configurations, suggesting that these packaging configurations do not absorb this functional excipient at least over the 6 months at the accelerated storage temperature.

However, there is a significant change (b) (4) in the amount of isostearic acid over 12 months, and limited supporting data for the fate of this functional excipient on stability, the expiration dating period should not be extended beyond the real time data. Once more data are available, the expiration dating period could be extended post-approval.

Therefore, based upon the totality of stability data, a one year(12 month) expiration dating period for the drug product stored under the recommended room temperature storage conditions may be recommended.

The manufacturing/testing site for drug product has been recommended as ACCEPTABLE based on profile. An OVERALL recommendation from the Office of Compliance is ACCEPTABLE (See Attachment-1).

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

For Pump: Patients should be instructed to prime the pump before using it for the first time by fully depressing the pump mechanism (actuation) 3 times and discard this portion of the product to assure precise dose delivery. After the priming procedure, patients should completely depress the pump one time (actuation) for every 1.25 g (Testosterone Gel, (b) (4) Pump) of product required to achieve the daily prescribed dosage.

For Packets: The entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. Alternately, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until entire contents have been applied.

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(1)

- The specification of the drug product is not deemed adequate to assure the *quality* of the drug product because the validity of the dissolution (in vitro release) method and its acceptance criterion are not satisfactorily resolved.
- There is a significant change (b) (4) in the amount of isostearic acid over 12 months, the expiration dating period should not be extended beyond the real time data. Therefore, requested (b) (4) expiration dating period can not be granted.

Executive Summary Section

21 CFR 314.125 (b)(6)

- The labeling is still under revision and is subject to agreement with the applicant.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Rajiv Agarwal, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

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

C. CC Block: entered electronically in DARRTS

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/s/

RAJIV AGARWAL
03/06/2012

MOO JHONG RHEE
03/06/2012
Chief, Branch IV

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

OND Division: Division of Reproductive and Urologic Products
NDA: 203-098
Applicant: Perrigo
Stamp Date: 05-Jul-2011
PDUFA Date: 05-May-2012
Trademark: None submitted
Established Name: Testosterone
Dosage Form: Gel
Route of Administration: Topical/transdermal
Indication: Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

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

Testosterone gel ^(b)₍₄₎ is a clear colorless hydroalcoholic gel packaged in two packaging configurations. Each gram of gel contains 10 mg of testosterone.

- Unit dose aluminum foil packets of 2.5 g (25 mg testosterone) and 5 g (50 mg testosterone)
- Bottles with non-aerosol metered-dose pumps. Each pump actuation delivers 1.25 g of gel, which corresponds to 12.5 mg of testosterone

B. Critical issues for review

Drug substance information provided in the application and the cross-referenced DMF is adequate to allow review. PharmTox should be made aware of the study report supporting the levels of ^(b)₍₄₎ and evaluate if the applicant's justification is adequate.

A formulation change was made late in development, changing from Carbomer 940 NF to Carbomer 980 NF to mimic the same change made in the RLD, Androgel 1%. It was agreed during the preIND meeting that the remaining clinical studies could be performed with the

original formulation, and that data would need to be provided to bridge to the to-be-marketed formulation. According to the Pharmaceutical Development Section, (Att. 3.2.P.2-3), the applicant performed three in vitro release studies to support the formulation change, comparing the two formulations to each other and each of the formulations to the RLD, AndroGel 1%. The report states that the 90% confidence intervals fell between 75-113% for all tests and demonstrate similarity. Information is also provided in the Attachment 3.2.P.3.3-2 and 3.2.P.3.3-3 on the in vitro method. The ONDQA BioPharm reviewer should evaluate if the information is adequate.

In-vitro release studies were performed to support both the formulation change and scale-up. The ONDQA BioPharm reviewer should evaluate the in vitro release studies to determine the adequacy.

The applicant was advised to include a specification for the isostearic acid used [REDACTED] (b) (4), or provide justification why this was not necessary. In Section 3.2.P.5.6, the applicant states that they developed and validated a method for isostearic acid and monitored it on stability in both container closure systems. Since there was no change in the amount when held at up to 6 months at accelerated conditions, the applicant has not included a test in the specification. In addition, in the cover letter, the applicant provides information on a PK study that compared gels containing 0.3% and 0.45% isostearic acid which demonstrated that there was no difference in the blood levels with a 50% decrease in isostearic acid concentration. However, the applicant has also provided data showing that in screening formulations, different levels of isostearic acid gave different in vitro release profiles. The data will require careful review.

The applicant has performed extractable/leachable studies on the product contact surfaces of the container closure systems. PharmTox may need to evaluate the levels of extractables/leachables found in the study.

C. Comments for 74-Day Letter

There are ONDQA BioPharm comments to be conveyed (see Attachment 1) in the 74-day letter.

D. Recommendation:

This NDA is fileable from a CMC perspective. Rajiv Agarwal, Ph.D, Ph.D is the assigned primary reviewer. Tapash Ghosh, Ph.D. has been assigned from ONDQA BioPharm to evaluate the in vitro release data provided in support of the formulation change and scale-up. In an email dated 02-Sep-2011, he included comments to be conveyed to the applicant. In order to expedite the request, they were included in the 74-day letter (See Attachment 1 for comments).

REGULATORY BRIEFING RECOMMENDATION: Branch-level.

Donna F. Christner, Ph.D.

NDA Number: 203-098

Type: 5

Established/Proper Name:

testosterone

Applicant: Perrigo

Letter Date: 04-Jul-2011

Stamp Date: 05-Jul-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		Applicant was advised to include a specification (b) (4). Applicant has provided justification for not including a specification. Information will require review.

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		See 356h
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		<p style="text-align: center;">See 356h</p> <p><i>Sites were submitted to EES on 13-Jul-2011 by Becky McKnight. OC ACCEPTABLE recommendation for drug substance manufacturing site made on 13-Jul-2011. OVERALL ACCEPTABLE recommendation made for application on 18-Jul-2011 with a re-evaluation date of 28-Jan-2012.</i></p>
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		<p style="text-align: center;">See 356h</p> <p><i>Sites were submitted to EES on 13-Jul-2011 by Becky McKnight. OC ACCEPTABLE recommendation for drug product manufacturing site made on 18-Jul-2011. OVERALL ACCEPTABLE recommendation made for application on 18-Jul-2011 with a re-evaluation date of 28-Jan-2012.</i></p>

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	No additional facilities in application
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		See 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		Claim for a categorical exclusion as per 21 CFR 25.31(a) provided in Mod 1.12.14

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		See DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		See DMF
14.	Does the section contain information regarding the characterization of the DS?	X		See DMF
15.	Does the section contain controls for the DS?	X		See DMF
16.	Has stability data and analysis been provided for the drug substance?	X		See DMF
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		Link provided in Section 3.2.P.3.3
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	BE studies performed
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		
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		As per IQP 5105, a Methods Validation Request does not appear to be required for this application. The primary reviewer should reevaluate this during the review cycle.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	

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	Pharmacia & Upjohn	(b) (4)	06-May-2011	ADEQUATE on 23-Sep-2009 by D. Christner. Updates since last review. May require review.
	III	Constantia Teich		16-May-2007	No review found.
	III	Rexam		27-Aug-2010	No review found.
	III	Rexam		09-Nov-2010	No review found.

**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		(b) (4) Applicant will need to express strength in terms of mg of testosterone delivered per gel measure.
33.	Have the immediate container and carton labels been provided?	X		Applicant has not submitted a tradename. However, it is not required.

APPEARS THIS WAY ON ORIGINAL



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	BioPharmaceutics comments included in the 74-day letter in order to expedite the request. (See Attachment 1 for comments).

{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; <u> x </u> No Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No <u> x </u> ; 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? _____ _____

REVIEW NOTES

Clinical studies were performed under IND 107130. The applicant originally sought to submit an ANDA. However, due to differences in formulation compared to the RLD, Perrigo was advised that body transfer clinical safety studies would be required. The following information on the regulatory history is available in DARRTS. A brief overview follows. DARRTS should be consulted for full information.

The IND was opened on 17-Dec-2009. Danuta Gromek-Woods was the primary CMC reviewer. No comments were conveyed to the sponsor.

Type C Guidance meeting was held on 19-May-2010. The following CMC-related issues were discussed:

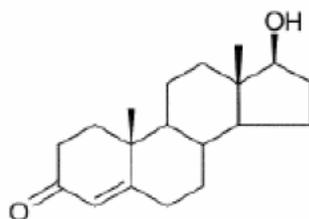
- The formulation was modified from one using Carbomer 940 NF to Carbomer 980 NF and the sponsor requested to perform any additional studies with the original formulation. This was acceptable from a CMC standpoint.
- The sponsor requested to make the change wither during the NDA review period or as a post-approval change. The sponsor was advised that it was not acceptable to make the change during the review cycle. They were referred to the SUPAC-SS guidance for information on studies needed to bridge the two formulations.
- The sponsor was advised to include a specification for isosteric acid or provide justification to not include a specification for this (b) (4).
- The sponsor was advised to develop a routine in vitro release test.
- The sponsor was advised by the Office of Regulatory Policy that the sachets and pumps were two different dosage forms. ***This recommendation was reversed at a later date.***

CMC Amendment submitted 19-Jul-2010. The sponsor submitted a CMC amendment to include a dissolution test (as opposed to in-vitro release testing). This was reviewed by Tapash Ghosh, Ph.D. The recommendation was as follows:

The sponsor's proposed dissolution methodology for the proposed Testosterone Gel, (b) (4) is not acceptable by the Agency. Routine release/dissolution specification is not required (but optional) for release and stability of semisolid products. However, the Agency recommends adherence to the SUPAC-SS guidance and the use of a Franz cell to measure and compare release rates between test and reference semisolid products to qualify formulation and/or site changes.

DRUG SUBSTANCE

The drug substance is testosterone, USP. Full information is provided in DMF (b) (4). The following information is provided in the application for ease of review.



Testosterone

1. Name and Full Address of the Facility

Manufacturer:

Manufacturing Site:



Comment: Sites were submitted to EES on 13-Jul-2011 by Becky McKnight. OC ACCEPTABLE recommendation for drug substance manufacturing site made on 13-Jul-2011. OVERALL ACCEPTABLE recommendation made for application on 18-Jul-2011 with a re-evaluation date of 28-Jan-2012.

The following synthetic scheme is provided in the application. A brief narrative is also provided. See cross-referenced DMF for full information.

Reaction scheme for the preparation of Testosterone, USP



The NDA applicant has provided the following information on the drug substance specifications.

TEST	SPECIFICATIONS
(b) (4)	

The specifications are based on the USP monograph. In addition, residual solvents that were used in the manufacturing process of Testosterone, USP are tested to verify their removal. The Assay and impurities profile are tested according to manufacturer's method to control the quality and safety of the Testosterone USP drug substance.

The impurities specifications are:

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

Comment: Information provided in the application and the cross-referenced DMF is adequate to allow review. PharmTox should be made aware of the study report (b) (4) and evaluate if the applicant's justification is adequate.

DRUG PRODUCT

Testosterone gel (b) (4) is a clear colorless hydroalcoholic gel packaged in two packaging configurations. Each gram of gel contains 10 mg of testosterone.

- Unit dose aluminum foil packets of 2.5 g (25 mg testosterone) and 5 g (50 mg testosterone)
- Bottles with non-aerosol metered-dose pumps. Each pump actuation delivers 1.25 g of gel, which corresponds to 12.5 mg of testosterone

The to-be-marketed formulation is as follows:

INGREDIENTS	GRADE	FUNCTION	QUANTITY		
			mg/g	% w/w	Batch Size (b) (4)
ACTIVE:					
Testosterone, USP	USP	Active Ingredient	10.00		(b) (4)
INACTIVE:					
Sodium Hydroxide NF	NF				(b) (4)
Dehydrated Alcohol, USP	USP				
Carbomer homopolymer type C, NF	NF				
Isostearic Acid	-				
Purified Water, USP	USP				
Total					

Clinical trials were performed with a slightly different formulation that contained Carbomer 940, NF. This change also required a change in the amount of alcohol. The changes were in response to the innovator’s corresponding formulation change.

Clinical Trial Formulation:

INGREDIENTS	GRADE	FUNCTION	QUANTITY		
			mg/g	% w/w	Batch Size (b) (4)
ACTIVE:					
Testosterone, USP	USP	Active Ingredient	10.00	(b) (4)	(b) (4)
INACTIVE:					
Sodium Hydroxide NF	NF				(b) (4)
Dehydrated Alcohol, USP	USP				
Carbomer 940, NF	NF				
Isostearic Acid	-				
Purified Water, USP	USP				
(b) (4)					

The applicant has provided the following information on the formulation change:

Please note that two formulations are supporting this NDA:

- Testosterone Gel, (b) (4) manufactured with Carbomer 940, NF (used in all clinical batches)
- Testosterone Gel, (b) (4) manufactured with Carbopol 980 (using Carbomer homopolymer type C, NF) which will be used for commercial distribution.

As discussed in details in module 1 section 1.6.3 Correspondence Regarding Meetings, and module 3 section 3.2.P.2 Pharmaceutical Development, the RLD manufacturer switched to Carbopol 980 (Carbomer homopolymer type C, NF) and changed the alcohol concentration from 69% to 67%. Perrigo adopted both changes. During the Pre-IND meeting, it was agreed that all studies will continue to be conducted with the Carbomer 940 formulation, and that three batches for the Carbopol 980 (Carbomer homopolymer type C, NF) formulation will be manufactured and submitted in this NDA to support commercial distribution.

Comment: According to the Pharmaceutical Development Section, (Att. 3.2.P.2-3), the applicant performed three in vitro release studies to support the formulation change, comparing the two formulations to each other and each of the formulations to the RLD, Androgel 1%. The report states that the 90% confidence intervals fell between 75-113% for all tests and demonstrate similarity. Information is also provided in the Attachment 3.2.P.3.3-2 and 3.2.P.3.3-3 on the in vitro method. The ONDQA BioPharm reviewer should evaluate if the information is adequate.

MANUFACTURING

The applicant has provided the following information on the manufacturing site for the drug product:

MANUFACTURING, PACKAGING AND CONTROL SITES FOR DRUG PRODUCT

Address:
Perrigo Israel Pharmaceuticals Ltd.
Industrial Zone
Yeruham 80500
Israel

Contact Person:
Dalit Fuchs
Director Regulatory Affairs
Perrigo Israel Pharmaceuticals Ltd
Tel: 269-686-1590
Fax: 269-673-7655

Comment: Sites were submitted to EES on 13-Jul-2011 by Becky McKnight. OC ACCEPTABLE recommendation for drug product manufacturing site made on 18-Jul-2011. OVERALL ACCEPTABLE recommendation made for application on 18-Jul-2011 with a re-evaluation date of 28-Jan-2012.

The applicant has provided narratives and flow charts for the (b) (4) batches manufactured with Carbomer 940, NF and the (b) (4) batch manufactured with Carbomer homopolymer Type C, NF (Carbopol 980). They have also provided in-vitro release comparisons to support the formulation change and the scale up. (See 3.2.P.3, attachments 3-1, 3-2, and 3-3).

Comment: The ONDQA BioPharm reviewer should evaluate the in vitro release studies to determine the adequacy. Tapash Ghosh has been assigned. In an email dated 02-Sep-2011, he included comments to be conveyed to the applicant. In order to expedite the request, they were included in the 74-day letter (See Attachment 1 for comments).

SPECIFICATIONS

The applicant has provided the following specifications for the drug product package in sachets and in the metered dose pump. The uniformity of dosage test is specific for the sachets and the uniformity of dosage and mean dosage weight is specific for the metered dose pump.

Specifications for Finished Product
Packaged in 2.5g and 5g Unit Dose Aluminum Foil Packets

Finished Product		
Tests	Specification	Method
(b) (4)		

Finished Product		
Tests	Specification	Method
(b) (4)		

Finished Product		
Tests	Specification	Method
(b) (4)		

Specifications for Finished Product
Packaged in Bottles with Non-Aerosol Metered-Dose Pumps

Finished Product		
Tests	Specification	Method
(b) (4)		

Finished Product		
Tests	Specification	Method
(b) (4)		

Finished Product		
Tests	Specification	Method
(b) (4)		

Comment: The applicant was advised to include a specification for the isostearic acid used (b) (4), or provide justification why this was not necessary. In Section 3.2.P.5.6, the applicant states that they developed and validated a method for isostearic acid and monitored it on stability in both container closure systems. Since there was no change in the amount when held at up to 6 months at accelerated conditions, the applicant has not included a test in the

specification. In addition, in the cover letter, the applicant provides information on a PK study that compared gels containing 0.3% and 0.45% isostearic acid which demonstrated that there was no difference in the blood levels with a 50% decrease in isostearic acid concentration. However, the applicant has also provided data showing that in screening formulations, different levels of isostearic acid gave different in vitro release profiles (see below).

The table below summarizes the different formulations used in the screening

Components	T06P027 [%w/w]	T06P033 [%w/w]
Testosterone	(b) (4)	
Ethyl Alcohol		
Carbopol 940		
Isostearic acid		
Sodium Hydroxide		
Purified Water		

Chart for formulation T06P027 versus the RLD



This is a review issue which will require careful evaluation.

CONTAINER CLOSURE

The drug product is available in both sachets and a metered dose pump. Applicant has provided DMF references and the results of USP<661> and USP<87> for all product contact surfaces. Applicant notes that the variation of aluminum foil for the sachets was changed (b) (4). USP testing is provided for both variations. Applicant also states that extractable/leachable studies were also conducted on all product contact surfaces.

Comment: Information is adequate to allow review. PharmTox may need to evaluate the levels of extractables/leachables found in the study.

STABILITY

The applicant has provided the following stability package in support of their requested (b) (4) expiry. Stability data are provided on both the Carbomer 940 formulation and the Carbomer 980 formulation in all three container closure systems. Thermal cycling studies were also performed on both formulations in sachets and pumps.

Formulation	Presentation	Batches	Data available	Manufactured/Scale
Carbomer 940 NF (clinical trial material)	2.5 g sachets	T4001	3 months accelerated 24 months long term	2005 (b) (4)
	5.0 g sachets	T4001	3 months accelerated 24 months long term	2005
		T06P033	3 months accelerated 24 months long term	2003
		006262	36 months long term	2007
		28508	3 months accelerated 12 months long term	2009
	pump	004832*	3 months accelerated 12 months long term	2007
Carbomer 980, NF formulation (to-be-marketed)	2.5 g sachets	034418	6 months accelerated 6 months long term	Aug 2010/ (b) (4)
		034419*	6 months accelerated 6 months long term	Aug 2010/
		034421	6 months accelerated 6 months long term	Aug 2010/
	5.0 g sachets	034412	6 months accelerated 6 months long term	Aug 2010/
		034413*	6 months accelerated 6 months long term	Aug 2010/
		034414	6 months accelerated 6 months long term	Aug 2010/
	pump	034422	6 months accelerated 6 months long term	Aug 2010/
		034423*	6 months accelerated 6 months long term	Aug 2010/
		034424	6 months accelerated 6 months long term	Aug 2010/

*thermal cycling studies

Comment: Information is adequate to allow review.

LABELING

Copies of the package labels and PI are provided. Labeling follows approved testosterone gel products, although there has been a change in the designation of strength, (b) (4) to mg of testosterone delivered per dose. The applicant will need to be advised that these changes will need to be made.

Comment: Information is adequate to allow review.

ATTACHMENT 1:

BIOPHARMACEUTICS COMMENTS INCLUDED IN THE 74-DAY LETTER

IR for NDA 203-098 (Testosterone Gel by Perrigo)

Biopharmaceutics Comments:

In-Vitro Release Test (IVRT)

- Please describe (preferably in a tabular format) the number of times that the *in-vitro* release test (IVRT) was performed to support this submission, including each time the rationale for performing this test.
- The SUPAC SS guidance clearly mentions that the *IVRT* methodology should be appropriately validated. In reviewing the information you provided, the development and validation report for the *IVRT* study could not be found. Please submit the complete development and validation report for the *IVRT* method, including the criteria for membrane selection (membrane binding, membrane resistance, membrane stability), membrane equilibrium, medium solubility, method precision, method sensitivity, method reproducibility, selection of time points, etc. Also, provide the details of analytical validation parameters including linearity, range, detection limit, specificity, precision, sensitivity, robustness, etc. If you have already provided this information in your NDA submission, please specify where it is located (proper section, page/link, etc.).
- For the submitted *IVRT* results, provide the computation of ordering the 36 individual T/R ratios from lowest to highest to identify the 8th and the 29th ordered individual ratios.

Dissolution

- In reviewing the information provided by you, the development and validation report for the dissolution method (# 30701304-06) could not be found. Please submit full development and validation report for the dissolution method including the criteria for apparatus selection, medium selection, rotational speed, temperature, sampling time point, method precision, method sensitivity, method reproducibility, selection of time points, etc.. Also, provide the details of analytical validation parameters including linearity, range, detection limit, specificity, precision, sensitivity, robustness, etc. If you have provided these information already, please direct us to the proper section/link.
- Submit full release profiles (with data) at different time points instead of release at 60 min.

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
09/14/2011

MOO JHONG RHEE
09/14/2011
Chief, Branch IV