

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021463Orig1s000

CHEMISTRY REVIEW(S)

NDA 21-463

Fortesta (testosterone) gel

**10 mg of testosterone
per pump actuation**

Endo Pharmaceuticals, Inc.

Donna F. Christner, Ph.D.

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

For

**Division of Reproductive and Urologic Products
(HFD-580)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 21-463
2. REVIEW #: 4
3. REVIEW DATE: 10-DEC-2010
4. REVIEWER: Donna F. Christner, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	03-JUN-2002
Amendment	20-DEC-2002
Review # 1	21-JAN-2003
Amendment	31-Jan-2003
Amendment	13-Feb-2003
Amendment	18-Feb-2003
Amendment	26-Feb-2003
Amendment	03-Mar-2003
Complete Response/Correspondence (C)	17-Apr-2009
Amendment	18-May-2009
Amendment	28-Jul-2009
Amendment (NDA transfer of Ownership)	08-Sep-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Complete Response/Correspondence (C) SDN 61	30-Jun-2010
Amendment (Carton Labels) SDN 65	07-Sep-2010
Amendment (PI) SDN 66	09-Sep-2010
Amendment (PI) SDN 71	03-Dec-2010
Amendment (PI)	09-Dec-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Endo Pharmaceuticals, Inc.
Address: 100 Endo Blvd.
Chadds Ford, PA 19317
Representative: Colleen Murray, MS
Associate Director, Regulatory Affairs
Telephone: 610-459-7191

CMC Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Fortesta
b) Non-Proprietary Name: testosterone gel
c) Code Name/# (ONDQA only): CP601B
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Androgen

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 10 mg testosterone per pump actuation

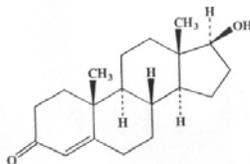
13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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



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

Molecular formula: C₁₉H₂₈O₂

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
(b) (4)	II	(b) (4)	Testosterone	3	Adequate	26-Jan-2010	Reviewed for NDA (b) (4) by M. Gautam-Basak
	II	(b) (4)	Testosterone	1	Adequate	23-Sep-2009	

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	76,634	

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	30-Sep-2009	E. Johnson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	Tradename:ACCEPTABLE	02-Nov-2010	Colleen Brennan
	PI: ACCEPTABLE	03-Dec-2010	Jibril Abdus-Samad
	Carton/Container: ACCEPTABLE	03-Dec-2010	Jibril Abdus-Samad
EA	ACCEPTABLE	22-Oct-2002	Donna F. Christner
Microbiology	APPROVAL	07-Nov-2002	Bryan S. Riley

Executive Summary Section

The CMC Review for NDA 21-463

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Review #3 made a recommendation of “Approval” from the CMC perspective based on the sufficient CMC information submitted to assure the identity, strength, purity, and quality of the drug product; adequate labels/labeling with required information; and “Acceptable” cGMP compliance of all facilities.

For this review cycle, the label and labeling were re-reviewed in the context of a new labeling approach for the testosterone drug products and have been revised satisfactorily, making the previous “Approval” recommendation from the CMC perspective still effective.

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

As proposed and committed to by the sponsor in the Complete Response submission dated 17-Apr-2009, it is acceptable to establish a specification for in vitro release within 12 months following product approval.

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance, testosterone USP is supplied by [REDACTED]^{(b) (4)} or [REDACTED]^{(b) (4)} and LOAs are supplied to reference the DMFs for CMC information. Both DMFs are adequate.

(2) Drug Product

Fortesta is a clear, colorless hydroalcoholic gel containing 2% w/w testosterone USP in a hydroalcoholic/propylene glycol gel base for topical application. It is supplied in a 60-g canister with a metered-dose pump that delivers 0.5 g/actuation which translates to 10 mg of testosterone. The initial daily dose is 40 mg testosterone which translates into 4 actuations of the pump mechanism. Depending on the clinical response, the dose can

Executive Summary Section

be titrated up or down. Fortesta is indicated for hormone replacement for hypogonadal men.

The majority of the CMC information was reviewed during the initial NDA submission in 2002. Updated CMC information submitted in the April 2009 Complete Response included addition of a new manufacturing site and the data to support the transfer, and updated methods and stability information. The application received a second Complete Response in September 2009, but there were no outstanding CMC issues. For the resubmission dated 30-Jun-2010, the only CMC issues were review of the carton/container labels and the Physician's insert. Information is adequate.

The final recommendation from the Office of Compliance is ACCEPTABLE.

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

Fortesta is packaged in [REDACTED] ^{(b) (4)} canister with a metered-dose pump. The initial dose is once daily application of 40 mg testosterone (4 pump actuations), with the option to change the dose to 10 mg or 70 mg/day depending on blood levels.

The sponsor has requested an expiration dating period of 24 months. Based on the stability data submitted to date, **24 months of expiration dating period is granted**. The recommended storage conditions are at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, adequate specifications, and container/closure for assuring consistent product quality of the drug substance and drug product. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period.. The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is ACCEPTABLE.

It should be noted that during the course of reviewing a similar testosterone drug product, some new review approaches to label/labeling of testosterone drug product has been established per DMEPA. The label/labeling have been revised to that effect, and from the CMC perspective, this NDA is recommended for "Approval".

Executive Summary Section

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

(See appended electronic signature page)

Donna F. Christner, 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

16 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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
12/10/2010

MOO JHONG RHEE
12/10/2010
Chief, Branch IV

NDA 21-463

**Fortesta
Testosterone gel
2%**

Endo Pharmaceuticals, Inc.

Donna F. Christner, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of Premarketing Assessment II
Branch III**

**CMC REVIEW OF NDA 21-463
For the Division of Reproductive and Urologic Products (HFD-580)**

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CMC Review Data Sheet

CMC Review Data Sheet

- 1. NDA 21-463
- 2. REVIEW #: 3
- 3. REVIEW DATE: 30-Sep-2009
- 4. REVIEWER: Donna F. Christner, Ph.D.
- 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	03-JUN-2002
Amendment	20-DEC-2002
Review # 1	21-JAN-2003
Amendment	31-Jan-2003
Amendment	13-Feb-2003
Amendment	18-Feb-2003
Amendment	26-Feb-2003
Amendment	03-Mar-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Complete Response/Correspondence (C)	17-Apr-2009
Amendment	18-May-2009
Amendment	28-Jul-2009
Amendment (NDA transfer of Ownership)	08-Sep-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Endo Pharmaceuticals, Inc.
Address: 100 Endo Blvd.
Chadds Ford, PA 19317
Representative: Colleen Murray, MS
Associate Director, Regulatory Affairs
Telephone: 610-459-7191

CMC Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Fortesta
b) Non-Proprietary Name: testosterone gel
c) Code Name/# (ONDQA only): CP601B
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Androgen

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 2% w/w

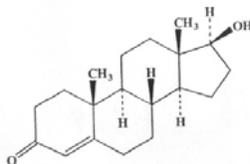
13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

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



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

Molecular formula: C₁₉H₂₈O₂

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
(b) (4)	II	(b) (4)	Testosterone	3	Adequate	29-Nov-2007	Reviewed for NDA (b) (4) by D. Klein
	II	(b) (4)	Testosterone	1	Adequate	23-Sep-2009	Reviewed by this reviewer

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	76,634	

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	30-Sep-2009	E. Johnson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	ACCEPTABLE	29-Jul-2009	Jibril Abdus-Samad
EA	ACCEPTABLE	22-Oct-2002	Donna F. Christner
Microbiology	APPROVAL	07-Nov-2002	Bryan S. Riley

Executive Summary Section

The CMC Review for NDA 21-463

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have required information. The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is ACCEPTABLE. .

Therefore, from the CMC standpoint, this NDA is recommended for APPROVAL.

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

As proposed and committed to by the sponsor in the Complete Response submission dated 17-Apr-2009, it is acceptable to establish a specification for in vitro release within 12 months following product approval.

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance, testosterone USP is supplied by (b) (4) or (b) (4) and LOAs are supplied to reference the DMFs for CMC information. Both DMFs are adequate.

(2) Drug Product

Fortesta is a clear, colorless hydroalcoholic gel containing 2% w/w testosterone USP in a hydroalcoholic/propylene glycol gel base for topical application. It is supplied in a 60-g canister with a metered-dose pump that delivers 0.5 g/actuation which translates to 10 mg of testosterone. The initial daily dose is 40 mg testosterone which translates into 4 actuations of the pump mechanism. Depending on the clinical response, the dose can be titrated up or down. Fortesta is indicated for hormone replacement for hypogonadal men.

Executive Summary Section

The majority of the CMC information was reviewed during the initial NDA submission in 2002. Updated CMC information submitted in the Complete Response included addition of a new manufacturing site and the data to support the transfer, and updated methods and stability information.

The final recommendation from the Office of Compliance is still PENDING.

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

Fortesta is packaged in [REDACTED] ^{(b) (4)} canister with a metered-dose pump. The initial dose is once daily application of 40 mg testosterone (4 pump actuations), with the option to change the dose to 10 mg or 70 mg/day depending on blood levels.

The sponsor has requested an expiration dating period of 24 months. Based on the stability data submitted to date, **24 months of expiration dating period is granted.** The recommended storage conditions are at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, adequate specifications, and container/closure for assuring consistent product quality of the drug substance and drug product. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period. Labels have required information. The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is ACCEPTABLE.

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

(See appended electronic signature page)

Donna F. Christner, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

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

C. CC Block: entered electronically in DARRTS

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21463	ORIG-1	PROSTRAKAN LTD	FORTIGEL (TESTOSTERONE GEL) 2%
NDA-21463	ORIG-1	PROSTRAKAN LTD	FORTIGEL (TESTOSTERONE GEL) 2%
NDA-21463	ORIG-1	PROSTRAKAN LTD	FORTIGEL (TESTOSTERONE GEL) 2%
NDA-21463	ORIG-1	PROSTRAKAN LTD	FORTIGEL (TESTOSTERONE GEL) 2%

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/s/

DONNA F CHRISTNER
10/05/2009

MOO JHONG RHEE
10/05/2009
Chief, Branch III

Addendum to Review #2 of NDA 21-463

Drug Name: Fortigel

Sponsor: Cellegy Pharmaceuticals, Inc.
Address: 349 Oyster Point Boulevard
Suite 200
S. San Francisco, CA 94080

Indication: Testosterone Replacement for Hypogonadal Men

Reviewer: Donna F. Christner, Ph.D.
Date: 02-JUL-2003

Issue: Review of Labeling

PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	03-JUN-2002
Amendment	20-DEC-2002
Review # 1	21-JAN-2003
Amendment	31-JAN-2003
Amendment	13-FEB-2003
Amendment	18-FEB-2003
Amendment	26-FEB-2003
Amendment	03-MAR-2003
Review # 2	26-MAR-2003

SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	10-APR-2003
Amendment	13-MAY-2003

Comments: The following comments on the labeling were conveyed to the sponsor on 20-MAY-2003 via a teleconference. Dr. Azarnoff committed to the changes.

This NDA may be approved from a CMC viewpoint pending satisfactory resolution of the labeling issues.

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

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/s/

Donna Christner
7/2/03 03:48:33 PM
CHEMIST

The addendum for Review #2 concerning labeling

Moo-Jhong Rhee
7/2/03 03:54:44 PM
CHEMIST
I concur

NDA 21-463

**Fortigel
Testosterone Gel, 2%**

Cellegy Pharmaceutical, Inc.

**Donna F. Christner, Ph.D.
Division of Reproductive and Urologic Drug Products**

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Chemistry Review Data Sheet

1. NDA21-463
2. REVIEW #: 2
3. REVIEW DATE: 26-MAR-2003
4. REVIEWER: Donna F. Christner
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

Original	03-JUN-2002
Amendment	20-DEC-2002
Review # 1	21-JAN-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Amendment	31-JAN-2003
Amendment	13-FEB-2003
Amendment	18-FEB-2003
Amendment	26-FEB-2003
Amendment	03-MAR-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Cellegy Pharmaceuticals, Inc.
Address:	349 Oyster Point Blvd. Suite 200 South San Francisco, CA 94080 William L. Schary, Ph.D., RAC
Representative:	Vice President Regulatory Affairs and Quality
Telephone:	650-616-2200

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Fortigel 2%
- b) Non-Proprietary Name (USAN): Testosterone gel
- c) Code Name/# (ONDC only): CP601B
- d) Chem. Type/Submission Priority (ONDC 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: 2% w/w gel

13. ROUTE OF ADMINISTRATION: Topical

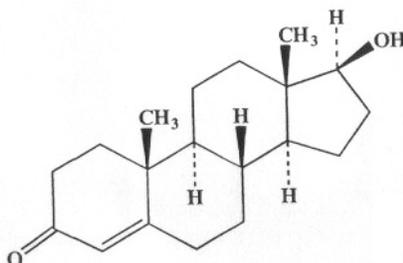
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)\[Note27\]](#):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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



Testosterone

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

Molecular formula: C₁₉H₂₈O₂

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	1	Adequate	11-OCT-2002	
	II		Testosterone	3	Adequate	19-SEP-2002	Reviewed by R. Agarwal for NDA 21-454
	III		Canisters	3	Adequate	07-NOV-2002	Reviewed by E. Pappas for NDA 20-934

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

Chemistry Review Data Sheet

- 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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	25-JUL-2002	
Pharm/Tox	Approval	05-AUG-2002	Krishan L. Raheja
Biopharm	See the review note on page 16	25-MAR-2003	
LNC	N/A		
Methods Validation	Will be sent to FDA labs		
DMETS	Tostrex/ Not recommended	26-OCT-2002	Kevin Dermanoski
	Tostran/Not recommended	04-FEB-2003	Alina Mahmud
	Fortigel/ Acceptable	18-MAR-2003	Tia Harper-Velazquez
EA	Acceptable	22-OCT-2002	Donna F. Christner
Microbiology	Approval	07-NOV-2002	Bryan S. Riley

The Chemistry Review for NDA 21-463

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from a Chemistry, Manufacturing and Controls point of view.

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

The sponsor commits to the following Phase IV commitments:



II. Summary of Chemistry Assessments

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

Fortigel (formerly Tostrex) is a clear, colorless hydroalcoholic gel containing 2% w/w Testosterone USP in a hydroalcoholic/propylene glycol gel base for topical application. It is supplied in a 60-g canister with a metered-dose pump that delivers 500 μL /actuation. The initial daily dose is (b) (4) Testosterone which translates into (b) (4) actuations of the pump mechanism. Fortigel is indicated for hormone replacement for hypogonadal men.

The drug substance, Testosterone USP, is supplied by (b) (4) or (b) (4) and LOAs are supplied to reference the DMFs for CMC information. Both DMFs have been recently reviewed and found adequate.

The formulation for Fortigel gel contains a (b) (4) composed of the following excipients: ethanol, isopropanol, propylene glycol, and oleic acid (b) (4). The other inactive ingredients include Carbomer 1382, trolamine, butylated hydroxytoluene, and water. Formulations containing 1% or 2% testosterone were used for PK studies, but the to-be-marketed formulation was used in the clinical trials.

Executive Summary Section

Tests for release of finished product include Appearance, Viscosity*, Density*, Metered-Dose Delivery*, pH, Testosterone Assay and Homogeneity, Testosterone Impurities*, Ethanol Content, Isopropanol Content*, Oleic Acid Content*, Propylene Glycol Content*, BHT Content and Homogeneity, *in vitro* Release testing*, and Microbial Tests. The revisions requested in Chemistry Review #1 concerning methods and acceptance criteria have been made and found acceptable. The effected tests are noted above with an asterisk.

The final recommendation from the Office of Compliance for all the manufacturing and testing sites is ACCEPTABLE.

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

Fortigel is packaged in (b) (4) canister with a metered-dose pump. The initial dose is once daily application of (b) (4) testosterone (b) (4) pump actuations), with the option to change the dose to (b) (4) depending on testosterone blood levels (b) (4). At the initial dosing regimen, the canister should hold enough drug product for (b) (4).

The sponsor has requested an expiry of 24 months. Based on the stability data submitted in the original application and additional real time data submitted up to 24 months, **24 months of expiry can be granted.** (b) (4)

(b) (4)
Because of the acceptable results from the second set of cycling studies, **the recommended storage conditions are to store at controlled room temperature with the cautionary statement “Do Not Freeze” included on the label.**

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has adequately addressed the 31 deficiencies outlined in Chemistry Review #1. They have developed methods for the quantitation of the components of the (b) (4) as requested. They have developed test methods for *in vitro* release. Metered-dose delivery has been revised to measure the total number of discharges from the canister and the dose uniformity over the entire contents. Limits have been set for impurities that correspond to levels found either in the drug substance (per ICH Q6A) or that reflect the actual manufacturing capability and stability characteristics of the product to date. The sponsor has committed to add the requested tests to the release and stability specifications.

Executive Summary Section

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Donna F. Christner/Date: 26-MAR-2003
Moo-Jhong Rhee/Date

C. CC Block

Org. NDA 21-463
HFD-580/Division File
HFD-580/MRhee/DChristner
HFD-580/EDeGuia

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this page is the manifestation of the electronic signature.**

/s/

Donna Christner
3/27/03 02:18:45 PM
CHEMIST

Moo-Jhong Rhee
3/27/03 04:13:58 PM
CHEMIST
I concur

NDA 21-463

Tostran (pending)

Cellegy Pharmaceutical, Inc.

Donna F. Christner, Ph.D.
Division of Reproductive and Urologic Drugs

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Chemistry Review Data Sheet

1. NDA 21-463
2. REVIEW #: 1
3. REVIEW DATE: 21-JAN-2003
4. REVIEWER: Donna F. Christner, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

03-JUN-2002

Amendment N000L

20-DEC-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Cellegy Pharmaceutical, Inc.
349 Oyster Point Boulevard
Address: Suite 200
S. San Francisco, CA 94080
Representative: William L. Schary, Ph.D., RAC
Telephone: 650-616-2200

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tostrex 2%
- b) Non-Proprietary Name (USAN): Testosterone gel
- c) Code Name/# (ONDC only): CP601B
- d) Chem. Type/Submission Priority (ONDC 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: 2% w/w gel

13. ROUTE OF ADMINISTRATION: Topical

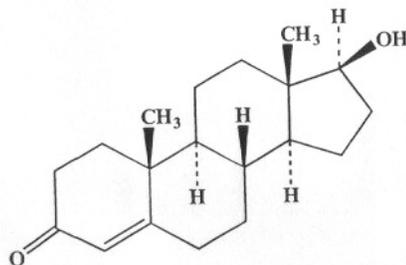
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)\[Note25\]](#):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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



Testosterone

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

Molecular formula: C₁₉H₂₈O₂

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	1	Adequate	11-OCT-2002	
(b) (4)	II	(b) (4)	Testosterone	3	Adequate	19-SEP-2002	Reviewed by Dr. Rajiv Agarwal for NDA 21-454
(b) (4)	III	(b) (4)	Canisters	5			LOA requested

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

Chemistry Review Data Sheet

- 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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	25-JUL-2002	
Pharm/Tox	Approval	05-AUG-2002	Krishan L. Raheja
Biopharm	N/A		
LNC	N/A		
Methods Validation	The methods validation package will be sent to and validated by FDA laboratories		
DMETS	Tostrex/ Not Recommended	26-OCT-2002	Kevin Dermanoski
	Tostran/Submitted 20-DEC-2002	31-DEC-2002	Sent for consult 31-DEC-2002
EA	Acceptable	22-OCT-2002	Donna F. Christner
Microbiology	Approval	07-NOV-2002	Bryan S. Riley

The Chemistry Review for NDA 21-463

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable from the chemistry, manufacturing, and controls point of view pending resolution of all the deficiencies listed in the Draft Deficiency Letter.

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

None

II. Summary of Chemistry Assessments

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

Tostrex is a clear, colorless hydroalcoholic gel containing 2% w/w Testosterone USP in a hydroalcoholic/propylene glycol gel base for topical application. It is supplied in a 60-g canister with a metered-dose pump that delivers 500 µL/actuation. The initial daily dose is (b) (4) Testosterone which translates into (b) (4) actuations of the pump mechanism. Tostrex is indicated for hormone replacement for hypogonadal men.

The drug substance, Testosterone USP is supplied by (b) (4) and LOAs are supplied to reference the DMFs for CMC information. Both DMFs have been recently reviewed and found adequate.

The formulation for Tostrex gel contains a (b) (4) composed of the excipients ethanol, isopropanol, propylene glycol and oleic acid. (b) (4) The other inactive ingredients include Carbomer 1382, trolamine, butylated hydroxytoluene and water. Formulations containing 1% or 2% testosterone were used for PK studies, but the to-be-marketed formulation was used in the clinical trials.

Tests for release of finished product include Appearance, Viscosity, Density, Metered-Dose Delivery, pH, Testosterone Assay and Homogeneity, Testosterone Impurities, Ethanol Content, BHT Content and Homogeneity, and Microbial Tests. **Revisions of Acceptance Criteria for Viscosity, Density, and Testosterone Impurities, and the development of additional tests for Metered-Dose Delivery, *in vitro* release testing, and the components of the (b) (4) are requested.**

Executive Summary Section

The final recommendation from the Office of Compliance for all the manufacturing and testing sites is ACCEPTABLE.

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

Tostrex is packaged in (b) (4) canister with a metered-dose pump. The initial dose is once daily application of (b) (4) testosterone (b) (4) pump actuations), with the option to change the dose to (b) (4) depending on blood levels. At the initial dosing regimen, the canister should hold enough drug product for (b) (4)

The sponsor has requested an expiry of 24 months. Based on the stability data submitted to date, **18 months of expiry can be granted**. The recommended storage conditions are at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

The NDA is approvable pending satisfactory response to the Deficiencies listed at the end of this review. Acceptance criteria need to be set for Viscosity and Density. Metered-Dose Delivery should be revised to measure the total number of discharges from the canister and the dose uniformity over the entire contents. Limits should be set for individual testosterone impurities and the limits for total impurities should be tightened to reflect the actual manufacturing capability and stability characteristics of the product. Additional tests should be developed and implemented to measure *in vitro* release of testosterone from the gel and to quantitate all the components of the (b) (4)

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Donna F. Christner/Date: 21-JAN-2003
Moo-Jhong Rhee/Date

C. CC Block

Org. NDA 21-463
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HFD-580/EDeGuia

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/s/

Donna Christner
1/22/03 08:11:21 AM
CHEMIST

CMC review for Tostrex/Tostran

Moo-Jhong Rhee
1/22/03 11:13:40 AM
CHEMIST
I concur

NDA FILEABILITY CHECKLIST

NDA Number: 21-463

Applicant: Cellegy Pharmaceutical, Inc
349 Oyster Point Boulevard
Suite 200
S. San Francisco, CA 94080

Stamp Date: 03-Jun-2002

Drug Name: Tostrex

Container Closure: A metered dose pump comprised of (b) (4) canister and a fixed volume pumping mechanism. The 60-g canister dispenses 500 µL of testosterone gel/pump depression. The initial dose is (b) (4) of gel, corresponding to (b) (4) of testosterone.

Strength: 2% Testosterone gel.

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) YES

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?	x		
6	Has an environmental assessment report or categorical exclusion been provided?	x		
7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		Minimal information on filling procedure.
9	Has stability data and analysis been provided to support the requested expiration date?	x		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?	x		
14	Is there a Methods Validation package?	x		
15	Is a separate microbiological section included?		x	Information was collected and sent for microbiology consult 9-JUL-02

This application **meets the filing requirement** from the CMC point of view. This application is adequate to review from the CMC standpoint.

Review Chemist: Donna F. Christner, Ph.D.
Team Leader: Moo-Jhong Rhee, Ph.D.

Date: 31-JUL-2002
Date:

cc:
Original NDA 21-463
HFD-580/NDA 21-463/Division File
HFD-580/Chem/DChristner/MRhee
HFD-580/PM/EDeGuia
HFD-580/DivDir/DShames

NDA Number: 21-463 Applicant: Cellegy Pharmaceutical Drug Name: Tostrex 2%

Have all DMF References been Identified?

DMF Number	Holder	Description	LOA Included	Status
	(b) (4)	Testosterone Drug substance	Included	
		Testosterone Drug substance	Included	

Comments:

In a t-con on 28-JUN-02, (b) (4) of Cellegy agreed to forward DMF authorization letters from the manufacturers of the to-be-marketed closed container system. He stated that the manufacturer of the container (b) (4) had a current DMF and that the manufacturer of the pump system (b) (4) was in the process of preparing the DMF.

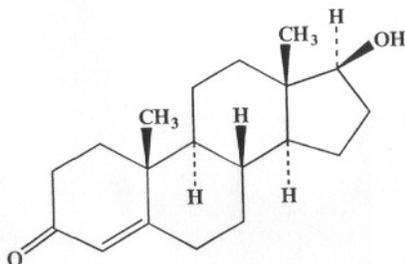
SUMMARY

DRUG SUBSTANCE:

The active ingredient in Tostrex 2% is Testosterone. Two sites manufacture the drug substance: (b) (4) and (b) (4) (USA). Detailed information on the synthesis and characterization of Testosterone is provided in the Drug Master Files ((b) (4)) and letters of authorization to cross-reference the DMFs are provided in the submission.

The following information is included in the submission:

CAS number: 58-22-0
Molecular Weight: 288.42
Molecular Formula: C₁₉H₂₈O₂
Structural Formula:



Testosterone

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

DRUG PRODUCT:

Dosage form: Transdermal gel
Strength: 2% Testosterone
Route of Administration: Transdermal

Components and composition:

COMPONENTS	AMOUNTS (mg/g)	% W/W	FUNCTION	REFERENCE TO STANDARD
Testosterone	20.0	2.0	Active Ingredient	USP
Propylene Glycol	(b) (4)	(b) (4)	(b) (4)	USP
Ethyl Alcohol, (b) (4)				House Standard
Isopropyl Alcohol				USP
Oleic Acid				NF
Carbomer 1382				House Standard
Trolamine				NF
Butylated Hydroxytoluene				NF
Purified Water				USP
(b) (4)				NF

Manufacturers:

Drug Substance:

Testosterone USP is manufactured and quality controlled at the following manufacturing sites, covered under DMFs:



Drug Product:

The company below is responsible for the manufacture and quality control of the drug product and quality control operations of the drug substance, excipients, packaging components and packaged drug product. It also fills the bulk gel into the metered dose canister and assembles the canister and package insert into the secondary packaging:



The following company is responsible for the alcohol assay method development, validation and alcohol sample testing.  subcontracts this responsibility to:



Drug Product Manufacturing and Testing:

(b) (4)

Release tests for the bulk drug product include Appearance, pH, density, viscosity, Testosterone identity, Ethanol Homogeneity, Ethanol Content, Testosterone Homogeneity and Testosterone Assay. (b) (4) The packaged product release specifications include the above tests, plus metered-dose delivery, determination of net contents, microbial limits and anti-microbial effectiveness testing.

Comments on Drug Product Manufacture, Packaging and Testing:

- A description of all packaging operations (primary, secondary and tertiary) and relevant in-process controls needs to be supplied (*Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application*), along with sampling plans and copies of any relevant SOPs.
- Steps taken to (b) (4) should be addressed. Refer to batch records for Lot 0D068A for (b) (4) canister.
- Information on storage conditions and tests for bulk gel returned to inventory should be provided. (*Guidance of Industry: Container Closure System for Packaging Human Drugs and Biologics*).
- Metered-dose delivery should be revised to determine the total number of discharges from the container and the dose uniformity over the entire contents.
- Detailed information on the sampling plan, including methods for sampling within canisters, for analytical tests should be supplied.
- Analytical tests should be developed for oleic acid, isopropanol, and propylene glycol (b) (4) (b) (4) Refer to US Patent (b) (4)

Stability:

Eight batches have been placed on stability, and the sponsor is requesting a 24-month expiration date. The three registration batches (b) (4) batch size) in (b) (4) canisters currently have stability data for 18 months. Two supporting lots (b) (4) batch size) in (b) (4) canisters have 24 month stability data. Three additional supporting batches ((b) (4) batch size) in (b) (4) canisters have been on stability for 12 to 18 months. Scale-up to a commercial batch size of (b) (4) is planned. The registration batches should have 24 month stability available during the review cycle.

Time points and batch information for stability testing are as follows:

	BATCH	BATCH SIZE	PACKAGING	25°C/60% RH		40°C/75% RH		
				FINISHED (Months)	PLANNED (Months)	FINISHED (Months)		
REGISTRATION BATCHES	0D067A	(b) (4)	60-g (b) (4) metered dose canister	0, 3, 6, 9, 12, and 18	(b) (4)	0, 1, 2, 3, and 6		
	0D068A		60-g (b) (4)* metered dose canister	0, 3, 6, 9, 12, and 18		0, 1, 2, 3, and 6		
	0D090A		60-g (b) (4)* metered dose canister	0, 3, 6, 9, 12, and 18		0, 1, 2, 3, and 6		
SUPPORTING BATCHES	8H044A (2% GEL)		(b) (4)	(b) (4)		0, 3, 6, 9, 12, 18, and 24	(b) (4)	0, 1, 2, 3, and 6
	8H045B (b) (4)					0, 3, 6, 9, 12, 18 and 24		0, 1, 2, 3, and 6
	0C046A					60-g (b) (4)* metered dose canister		0, 3, 6, 9, 12, and 18
	0J057A	60-g (b) (4)* metered dose canister			0, 3, 6, 9, and 12	0, 1, 2, 3, and 6		
	0J058A	60-g (b) (4) metered dose canister			0, 3, 6, 9, and 12	0, 1, 2, 3, and 6		

(b) (4)

Stability testing includes the following: Appearance, pH, viscosity, density, weight loss, metered-dose delivery, BHT homogeneity, BHT content, Testosterone homogeneity, Testosterone assay, ethanol content, impurities, microbial limits, and AET. Metered-dose delivery was not performed on the accelerated stability samples. Microbial limits and AET were not tested under accelerated conditions, and under the long-term studies were tested at 0, 6, and 12 months and are

(b) (4)

The sponsor has proposed an expiration date of 24 months. **Based on the available real time stability data, only 18 months may be granted.** The sponsor commits to the continuation of current stability studies described in the application, and also commits to monitor stability in the first three production batches and one batch per year at a minimum throughout the expiration dating period, per 21 CFR 314.81 (b)(2).

Comment on stability testing:

- Freeze and thaw studies should be performed to determine the effects of high and low temperature variations on drug product quality and performance (for example, phase separation).
- Stability data for 24 months in the registration batches should be provided during the review cycle for a 24 month expiry.

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this page is the manifestation of the electronic signature.**

/s/

Donna Christner
8/27/02 07:37:12 AM
CHEMIST

This is the fileability form for the Tostrx NDA
that we discussed yesterday

Moo-Jhong Rhee
8/27/02 09:22:10 AM
CHEMIST
I concur