

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206089Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: March 25, 2019

From: Mark R. Seggel, Ph.D.
Application Technical Lead
Office of New Drug Products
Branch V/DNDP II

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Office of New Drug Products
Branch V/DNDP II

To: OPQ IQA #3 for NDA 206089
Jatenzo (testosterone undecanoate) Capsules

Subject: Final Recommendation - APPROVAL

Summary:

The OPQ Integrated Quality Assessment (IQA) dated March 18, 2019, concluded that this 505(b)(2) NDA was Not Ready for Approval in its present form per 21 CFR 314.125(b)(8). Specifically, it was noted that labeling (prescribing information (PI), container/carton) negotiations had not been completed, and in its present form, the labeling did not comply with the requirements under 21 CFR 201. The NDA was otherwise complete and adequate from the OPQ perspective.

Recommended revisions to the prescribing information and to the bottle and carton labels have been conveyed to Clarus over the course of the review cycle. Revised PI were submitted by Clarus on March 13, 19, 20, 21 and 25, 2019 (via email). Final agreement on the PI was reached on March 25, 2019. Revised labels were submitted September 27, 2018, January 23, 2019, and March 19, 22, and 25, 2019 (via EDR).

The revised labeling (PI, bottle and carton) as of March 25, 2019 is complete and accurate from the OPQ perspective. See Dr. Hamid Shafiei's attached labeling review addendum for details.

Recommendation:

This NDA is now recommended for **Approval** from the OPQ perspective.

Application Technical Lead Signature:

Mark R. Seggel, Ph.D.,
CMC Lead (acting)

{see digital signature page}

MEMORANDUM

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

DATE: March 25, 2019

FROM: Hamid R. Shafiei, Ph.D.
Review Chemist (Branch V/DNDP II/ONDP)

Moo-Jhong Rhee, Ph.D.
Branch Chief (Branch V/DNDP II/ONDP)

TO: Package Insert (PI), Immediate Container,
and Carton Labeling/Label review # 1 for NDA 206089

SUBJECT: Final ONDP Recommendation from the Labeling/Label Review
Perspective

In the review # 1 of NDA 206089 originally submitted on January 3, 2014 and review # 2 of the NDA resubmission on June 22, 2017, this application was not recommended for approval in the form it was presented due to the CMC deficiencies noted in PI labeling as well as immediate container (bottles) and carton labels.

The CMC labeling-label deficiencies identified during the review # 1 and review # 2 of NDA 206089 were not addressed during first and second review cycles (see the **Attachment II**) because this application received CR letters both times from the clinical perspective.

This application was resubmitted again on September 27, 2018, and during this third review cycle, all CMC deficiencies for PI labeling as well as immediate container carton labels (**Attachment II**) were conveyed to the applicant. On March 25, the applicant has submitted the final PI labeling and immediate container and carton labels that have satisfactorily addressed all CMC labeling/labels deficiencies (**Attachment I**).

Recommendation: This application is now recommended for **approval** from the ONDP labeling-labels perspective.

Attachment I: Final PI and Labels

A. PI

a) Highlight Section

JATENZO™ (testosterone undecanoate) capsule, for oral use CIII

Initial U.S. Approval: 1953

JATENZO (testosterone undecanoate) capsules for oral use are available in the following strengths: 158 mg, 198 mg, 237 mg (3).

b) Full Prescribing Information

#3: Dosage Forms and Strengths

JATENZO capsules for oral use are available in three strengths:

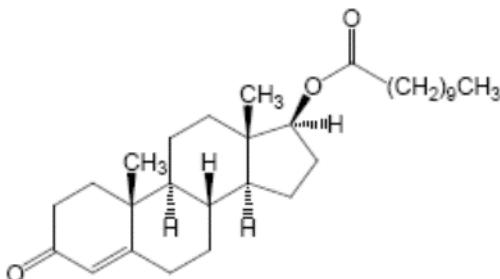
- The 158 mg testosterone undecanoate capsules are opaque red and imprinted with “158” in white ink.
- The 198 mg testosterone undecanoate capsules are opaque white and imprinted with “198” in red ink.
- The 237 mg testosterone undecanoate capsules are opaque orange and imprinted with “237” in white ink.

#11: Description

JATENZO for oral use is provided as a gelatin capsule containing testosterone undecanoate, a fatty-acid ester of testosterone. Testosterone undecanoate is a white to off-white yellow crystalline powder. Testosterone, an androgen, is formed by cleavage of the ester side chain of testosterone undecanoate.

Testosterone undecanoate is chemically described as 17β-hydroxyandrost-4-en-3-one undecanoate. It has the empirical formula of $C_{30}H_{48}O_3$ and the molecular weight of 456.7. The structural formula for testosterone undecanoate is presented in Figure 1.

Figure 1: Testosterone Undecanoate



JATENZO capsules are available in three strengths of 158 mg, 198 mg, and 237 mg.

The 158 mg strength is an opaque red capsule that contains 158 mg of testosterone undecanoate and is imprinted with “158” in white ink. The 198 mg strength is an opaque white capsule that contains 198 mg of testosterone undecanoate and is imprinted with “198” in red ink. The 237 mg strength is an opaque orange capsule that contains 237 mg of testosterone undecanoate and is imprinted with “237” in white ink. All capsule strengths also contain oleic acid, polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), borage seed oil, peppermint oil, and butylated hydroxytoluene as inactive ingredients.

Gelatin capsule shells are composed of the following inactive ingredients: Gelatin, sorbitol, glycerin, purified water, iron oxide red, FD&C Yellow #6, and titanium dioxide.

#16: HOW SUPPLIED/STORAGE AND HANDLING

JATENZO (testosterone undecanoate) capsules are available in three strengths of 158 mg, 198 mg, and 237 mg. Capsules are packaged as 120 units in wide-mouth, round, white HDPE bottles with white, polypropylene, child resistant caps and induction-sealed liner.

158 mg capsules are opaque red capsules imprinted with “158” in white ink and are supplied in bottles: NDC 69087-158-12.

198 mg capsules are opaque white capsules imprinted with “198” in red ink and are supplied in bottles: NDC 69087-198-12.

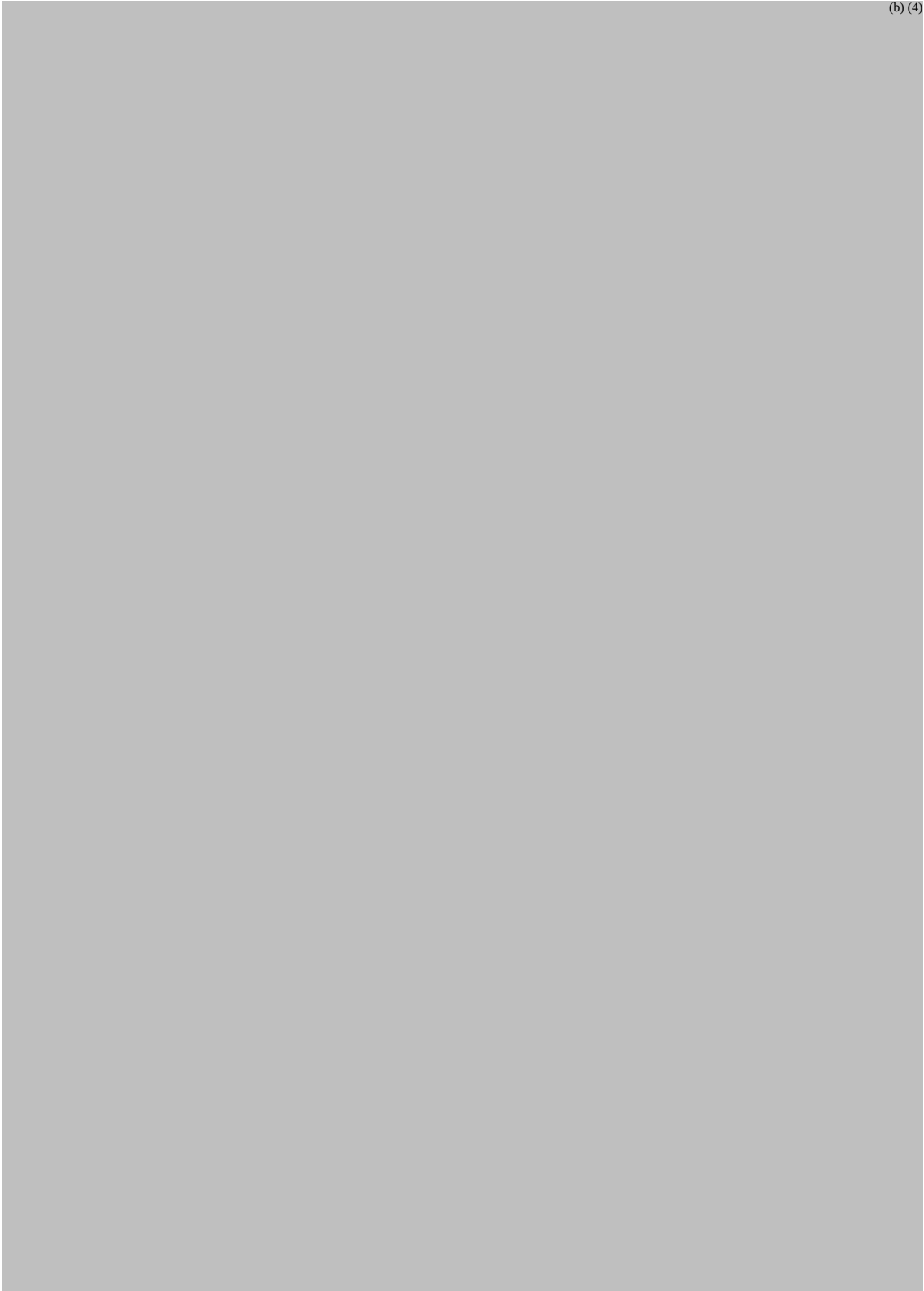
237 mg capsules are opaque orange capsules imprinted with “237” in white ink and are supplied in bottles: NDC 69087-237-12.

Keep JATENZO out of reach of children.

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Avoid exposing the capsules to moisture (store in a dry place).

B. Container/Carton Labels:

(b) (4)

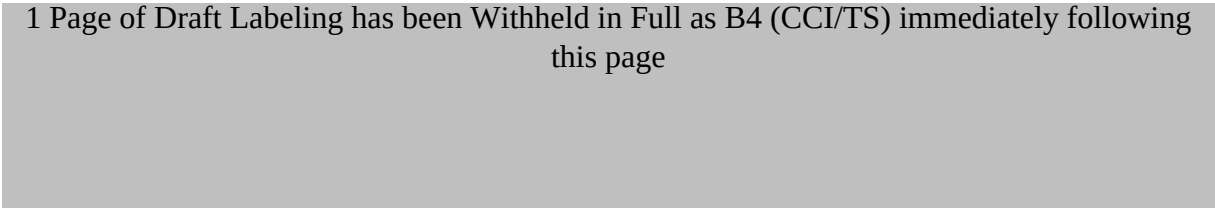


b. Carton Labels

(b) (4)



1 Page of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following
this page



Attachment II: PI labeling and container and carton labels deficiencies

The following CMC deficiencies for PI labeling as well as immediate container and carton labels were conveyed to the applicant during the review cycle #3, and they were resolved on March 25, 2019.

A. Regarding PI

a) Highlight Section

JATENZO (testosterone undecanoate) capsules for oral use are available in the following strengths:

- 158mg
- 198mg
- 237mg

b) Full Prescribing Information

#3: Dosage Forms and Strengths

The dosage form and strength must be revised to remove reference to (b) (4) and to include identifying characteristics for the capsules. The following revisions are recommended:

- 158 mg Testosterone Undecanoate (b) (4) capsules are opaque red capsules imprinted with “158” in white ink.
- 198 mg Testosterone Undecanoate (b) (4) capsules opaque white capsules imprinted with “198” in red ink.
- 237 mg Testosterone Undecanoate (b) (4) capsules are opaque orange capsules imprinted with “237” in white ink.

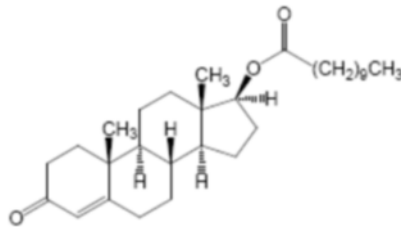
#11: Description

This section must be revised to include, route of administration, appropriate description of the drug product capsules, and pharmacological/therapeutic class. The following revisions is suggested:

JATENZO for oral use is provided as a gelatin capsule containing testosterone undecanoate, a fatty-acid ester of (b) (4) testosterone. (b) (4)

Testosterone undecanoate is chemically described as 17β-hydroxyandrost-4-en-3-one undecanoate. It has the empirical formula of C₃₀H₄₈O₃ and the molecular weight of 456.7. The structural formula for testosterone undecanoate is presented in Figure 1.

Figure 1: Testosterone Undecanoate



JATENZO capsules are available in three strengths of 158 mg, 198 mg, and 237 mg.

158 mg strength is an opaque red capsule that contains 158 mg of testosterone undecanoate (b) (4)

198 mg strength is an opaque white capsule that contains 198 mg of testosterone undecanoate (b) (4)

237 mg strength is an opaque orange capsule that contains 237 mg of testosterone undecanoate (b) (4)

Gelatin capsule shells are composed of the following inactive ingredients: Gelatin, sorbitol, glycerin, purified water, iron oxide red, FD&C Yellow #6, and titanium dioxide.

#16: How Supplied/Storage and Handling

This section must be revised to include the available units, packaging configuration, and an appropriate storage conditions. The following revision is recommended:

JATENZO (testosterone undecanoate) capsules are available in three strengths of 158 mg, 198 mg, and 237 mg. Capsules are packaged as 120 units in wide-mouth, round, white HDPE bottles with white, polypropylene, child resistant caps and induction-sealed liner.

158 mg capsules are opaque red capsules imprinted with “158” in white ink. (b) (4) are supplied in bottles (b) (4) NDC 69087-158-12.

198 mg capsules are opaque white capsules imprinted with “198” in red ink. (b) (4) are supplied in bottles (b) (4) NDC 69087-198-12.

237 mg capsules are opaque orange capsules imprinted with “237” in white ink. (b) (4) are supplied in bottles (b) (4) NDC 69087-237-12.

Keep JATENZO out of reach of children.

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).

Avoid exposing the capsules to moisture (store in a dry place).

B. Regarding of the Container/Carton Labels:

a) Immediate container labels: Bottles

None

b) Carton labels:

Revise the storage condition on the carton label from (b) (4) to “Store at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F)”.



Hamid
Shafiei

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Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 3/25/2019 04:56:37PM
GUID: 502d0913000029f9798ca689a802fa55



Mark
Seggel

Digitally signed by Mark Seggel

Date: 3/25/2019 05:23:08PM

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Recommendation: *As of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8).*

NDA 206089
Jatenzo
(testosterone undecanoate) Capsules
Review #3

Drug Name/Dosage Form	Testosterone Undecanoate Capsules (immediate release, soft gelatin capsules)
Strength	158 mg TU equivalent to 100 mg testosterone 198 mg TU equivalent to 125 mg testosterone 237 mg TU equivalent to 150 mg testosterone
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Clarus Therapeutics
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission, Class 2 (0060)	09/27/2018	Drug Substance; Drug Product (Labeling); Facilities
Labeling (Container-Carton)	01/23/2019	Drug Product (Labeling)

Quality Review Team (Current Review)

DISCIPLINE	REVIEWER	Office/Division/Branch
Drug Substance	Paresma Patel	OPQ/ONDP/DNDPAPI/NDBII
Drug Product / Labeling	Hamid Shafiei	OPQ/ONDP/DBRUP/NDBV
Facilities	Laurie Nelson	OPQ/OPF/DIA/IABIII
RBPM	Grafton Adams	OPQ/OPRO/RBPMBI
Application Technical Lead	Mark Seggel	OPQ/ONDP/DBRUP/NDBV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	P. Patel 01/29/2019	See DMF Review #4
	Type II			Adequate	J. Medwid 10/05/17	No new CMC info to date
	Type II			-		See DMF (b) (4) and associated reviews
	Type II			-		See Chemistry Review #1
	Type III			-		See Chemistry Review #1

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original IND, amendments, meet packages and associated reviews	IND 78104	Clarus' IND for oral testosterone undecanoate capsules as testosterone replacement therapy

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH	na			
Clinical	na			
Other	na			

Executive Summary

I. Recommendations and Conclusion on Approvability

In its present form, Clarus Therapeutics' second resubmission of their 505(b)(2) New Drug Application #206089, for Jatenzo (testosterone undecanoate) Capsules, 158 mg, 198 mg and 237 mg, is not ready for approval. Labeling (package insert) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	JATENZO is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired). • Hypogonadotropic hypogonadism (congenital or acquired).
Duration of Treatment	No limitations.
Maximum Daily Dose	396 mg twice daily.
Alternative Methods of Administration	Not applicable.

Clarus Therapeutics submitted NDA 206089 for testosterone undecanoate capsules, 158 mg and 237 mg, on January 3, 2014. Testosterone undecanoate is an ester prodrug of testosterone that is orally bioavailable. It is absorbed via the intestinal lymphatic system thus reducing first-pass metabolism in the liver. Once absorbed, the ester is cleaved by non-specific esterases. The drug product offers a convenient alternative to the orally bioavailable but toxic alkylated testosterone derivative, methyltestosterone, and to the transdermal testosterone products. While there are other testosterone ester prodrugs on the market (e.g., testosterone cypionate, testosterone enanthate, and testosterone undecanoate), these products are formulated for subcutaneous or intramuscular administration.

A Complete Response Letter for NDA 206089 was issued on November 3, 2014 due to clinical, clinical pharmacology and nonclinical concerns. While the applicant had provided sufficient information to assure the identity, strength,

purity, and quality of the drug product, and all facilities had acceptable CGMP status, labeling had not been finalized.

The NDA was resubmitted on July 22, 2017 and included documentation for an intermediate strength drug product containing 198 mg testosterone undecanoate. A Complete Response Letter was issued on March 22, 2018 due to clinical and clinical pharmacology issues.

The NDA was again resubmitted on September 27, 2018.

B. Quality Assessment Overview

See Dr. Hamid Shafiei's Chemistry Review (#1) dated September 25, 2014, and subsequent addendum, for NDA 206089. See also Dr. Kelly Kitchens' Biopharmaceutics Review dated September 18, 2014.

Review of the July 22, 2017 resubmission is documented in OPQ IQA Review #2 dated February 26, 2018. At that time there were no chemistry, manufacturing and controls (CMC) deficiencies other than labeling.

Drug Substance

Testosterone undecanoate is an ester prodrug prepared by the acylation of testosterone with undecanoic acid, an 11-carbon straight chain fatty acid. The manufacture of testosterone undecanoate by (b) (4) and by (b) (4) is documented Type II Drug Master Files (b) (4) and (b) (4), respectively. Both DMFs were found **Adequate** to support the use of the active pharmaceutical ingredient in the manufacture of testosterone undecanoate capsules.

Drug Product

The September 27, 2018 resubmission includes a Certificate of Analysis (CoA) for bulk testosterone undecanoate 198 mg capsules manufactured by (b) (4) on October 3, 2017. Drug product batch 3166139 met all release testing requirements. No other drug product chemistry, manufacturing and controls changes or updates were reported.

A summary of drug product CMC based on OPQ IQA #2 is provided here for the convenience of the reader.

Jatenzo (testosterone undecanoate capsules) contains 158 mg, 198 mg and 237 mg of testosterone undecanoate, equivalent to 100 mg, 125 mg and 150 mg of testosterone, respectively. What Clarus refers to as a non-aqueous self-emulsifying drug delivery system (SEDDS) formulation was developed to maximize the amount of drug substance delivered. The product consists of a

liquid fill in a soft gelatin capsule. The capsule fill consists of oleic acid (b) (4), borage seed oil (b) (4), Polyoxyl 40 Hydrogenated Castor Oil NF (Cremophor RH40) (b) (4) and peppermint oil (b) (4). The latter reportedly serves as a (b) (4). The capsule fill also includes (b) (4) of the (b) (4) butylated hydroxyl toluene. The soft gelatin capsule shell is prepared from gelatin, a sorbitol (b) (4) glycerin (b) (4) titanium dioxide, and water. The same capsule fill is used in the preparation of all three product strengths.

The manufacturing process, in process controls, container/closure system, and drug product specification remain unchanged since reviewed by Dr. Shafiei in 2014. The product will be supplied in 120-count HDPE bottles with induction-sealed liners and child resistant caps. Stability data on all three product strengths have been provided. The data support the applicant's proposed expiration dating period of 30 months when stored at 20°C to 25°C.

Overall, sufficient information has been provided to assure the identity, strength, purity, and quality of the drug product. From the drug product review perspective, the application is recommended for **Approval**.

Biopharmaceutics

The dissolution test method and acceptance criteria were found acceptable during the first review cycle (see Dr. K. Kitchens review dated September 18, 2014). The July 22, 2017 resubmission included dissolution data of the intermediate strength capsule at release and on stability. Because the new strength is compositionally proportional to the lower and higher strengths already evaluated the test method and acceptance criterion are also applicable to the intermediate strength. The application is recommended for **Approval** from the biopharmaceutics review perspective (see OPQ IQA #2).

Product Quality Microbiology

Microbial limits testing is conducted in accordance with USP <61> and USP <62>. The acceptance criteria are consistent with USP <1111>. The NDA is recommended for **Approval** from the product quality microbiology perspective (see Dr. Bryan Riley's January 13, 2014 review and OPQ IQA #2). No changes have been made that would impact the previous assessment.

Facilities

The drug substance manufacturers, (b) (4) and (b) (4), and the drug product manufacturer, (b) (4) have acceptable CGMP status. Associated packaging and testing facilities also have acceptable CGMP status. An overall inspection recommendation of **Approve** was issued on February 28, 2019 (see Panorama and attached review).

Environmental Assessment

During the first review cycle, Dr. Jim Laurenson concluded that the applicant's claimed categorical exclusion was acceptable (see OPQ IQA #2). This assessment remains applicable.

Labeling

Carton labels, including the bulk shipping carton labels were reviewed in collaboration with DMEPA. Revisions to the format of the established name and storage conditions, among others, were made. The carton and bottles labels are now acceptable from the OPQ perspective. However, the prescribing information currently does not comply with the requirements under 21 CFR 201. Revised prescribing information was conveyed to the Applicant on March 8, 2019. A final assessment of the labeling is pending receipt of the updated labeling from the Applicant. (see Dr. Shafiei's Chemistry Review #1, OPQ IQA #2, and Dr. Shafiei's attached Labeling review(s)).

C. Special Product Quality Labeling Recommendations

Not Applicable.

D. Final Risk Assessment

See OPQ IQA #2 Attachment 1.

E. List of Deficiencies for Complete Response

Not Applicable.

Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D.
Acting CMC Lead for DBRUP
OPQ/ONDP/DNDPII/Branch V
March 18, 2019



Mark
Seggel

Digitally signed by Mark Seggel

Date: 3/18/2019 02:44:58PM

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LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

JATENZO (b) (4) (testosterone undecanoate) capsule, for oral use CIII
Initial U.S. Approval: 1953

2) DOSAGE FORMS AND STRENGTHS

JATENZO (b) (4) capsules for oral use are available (b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	JATENZOTM (testosterone undecanoate) capsules	Provided. Satisfactory
Dosage form, route of administration	capsule, for oral use	Provided. Satisfactory
Controlled drug substance symbol (if applicable)	CIII	Provided Satisfactory
Dosage Forms and Strengths (201.57(a)(8))	JATENZO (b) (4) capsules for oral use are available (b) (4) (b) (4) (b) (4)	Provided. However, it needs revision (see the recommended revision below). (b) (4) should be deleted. Unsatisfactory
Whether the drug product is scored	Not applicable	Not applicable

Revise the Dosage and Strengths in the Highlights to:

JATENZO (testosterone undecanoate) capsules for oral use are available in the following strengths:

- 158mg
- 198mg
- 237mg

2. “FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

JATENZO (b) (4) capsules for oral use only are available in three strengths:

- 158 mg Testosterone Undecanoate Capsule, (b) (4)
- 198 mg Testosterone Undecanoate Capsule, (b) (4)
- 237 mg Testosterone Undecanoate Capsule, (b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	JATENZO (b) (4) capsules for oral use only are available in three strengths:	Provided. However, dosage form should be revised from (b) (4) to "capsules". Unsatisfactory
Strengths: in metric system	158 mg Testosterone Undecanoate Capsule, (b) (4) 198 mg Testosterone Undecanoate Capsule, (b) (4) 237 mg Testosterone Undecanoate Capsule, (b) (4)	Provided. Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	158 mg Testosterone Undecanoate Capsule, (b) (4) 198 mg Testosterone Undecanoate Capsule, (b) (4) 237 mg Testosterone Undecanoate Capsule, (b) (4)	Provided. Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not provided	The 158 mg capsules are opaque red capsules imprinted with "158" in white ink 198 mg capsules are opaque white capsules imprinted with "198" in red ink 237 mg capsules are opaque orange capsules imprinted with "237" in white ink Unsatisfactory

The dosage form and strength must be revised to remove reference to (b) (4) and to include identifying characteristics for the capsules. The following revisions are recommended:

JATENZO capsules for oral use are available in three strengths:

- 158 mg Testosterone Undecanoate (b) (4) capsules are opaque red capsules imprinted with "158" in white ink.
- 198 mg Testosterone Undecanoate (b) (4) capsules opaque white capsules imprinted with "198" in red ink.
- 237 mg Testosterone Undecanoate (b) (4) capsules are opaque orange capsules imprinted with "237" in white ink.

2) #11: DESCRIPTION

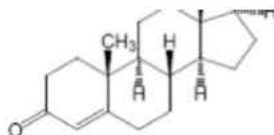
(b) (4)

Testosterone undecanoate, (b) (4) is a white to off-white yellow crystalline powder chemically described as 17 β -hydroxyandrost-4-en-3-one undecanoate.

Testosterone is formed by cleavage of the ester side chain of testosterone undecanoate. (b) (4)

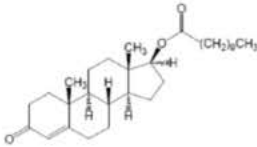
is presented in **Figure 1**.

Figure 1: Testosterone Undecanoate



(b) (4) oleic acid, polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), borage seed oil, peppermint oil, and butylated hydroxytoluene. (b) (4)

gelatin, sorbitol, glycerin, purified water, iron oxide red, FD&C Yellow #6, and titanium dioxide.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	JATENZO contains testosterone undecanoate	Provided. Satisfactory
Dosage form and route of administration	Not provided	Not provided. Unsatisfactory
Active moiety expression of strength with equivalence statement (if applicable)	Not provided	Not provided. Unsatisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	(b) (4) oleic acid, polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), borage seed oil, peppermint oil, and butylated hydroxytoluene. (b) (4) gelatin, sorbitol, glycerin, purified water, iron oxide red, FD&C Yellow #6, and titanium dioxide.	Provided. Satisfactory
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class	Not provided	Not provided. Unsatisfactory
Chemical name, structural formula, molecular weight	Testosterone undecanoate, (b) (4) (b) (4) is a white to off-white yellow crystalline powder chemically described as 17β-hydroxyandrost-4-en-3-one undecanoate. (b) (4) (b) (4) is presented in Figure 1 . Figure 1: Testosterone Undecanoate 	Provided. Since the API has been approved as testosterone undecanoate, the words (b) (4) should be removed. Unsatisfactory
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable

Other important chemical or physical properties (such as pKa or pH)

(b) (4) Reference to (b) (4) be removed.

Testosterone undecanoate, (b) (4)
(b) (4) is a white to off-white yellow crystalline powder.

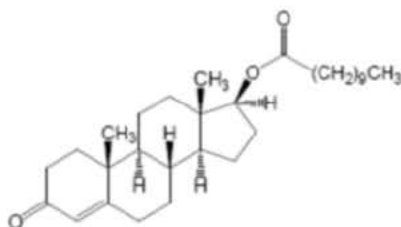
Unsatisfactory

This section must be revised to include, route of administration, appropriate description of the drug product capsules, and pharmacological/ therapeutic class. The following revisions is suggested:

JATENZO for oral use is provided as a gelatin capsule containing testosterone undecanoate, a fatty-acid ester (b) (4) testosterone. It is a white to off-white yellow crystalline powder. Testosterone is formed by cleavage of the ester side chain of testosterone undecanoate.

Testosterone undecanoate is chemically described as 17 β -hydroxyandrost-4-en-3-one undecanoate. It has the empirical formula of C₃₀H₄₈O₃ and the molecular weight of 456.7. The structural formula for testosterone undecanoate is presented in Figure 1.

Figure 1: Testosterone Undecanoate



JATENZO capsules are available in three strengths of 158 mg, 198 mg, and 237 mg.

158 mg strength is an opaque red capsule that contains 158 mg of testosterone undecanoate (b) (4) (b) (4)

198 mg strength is an opaque white capsule that contains 198 mg of testosterone undecanoate (b) (4)

237 mg strength is an opaque orange capsule that contains 237 mg of testosterone undecanoate (b) (4)

Gelatin capsule shells are composed of the following inactive ingredients: Gelatin, sorbitol, glycerin, purified water, iron oxide red, FD&C Yellow #6, and titanium dioxide.

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Keep JATENZO out of reach of children.

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	(b) (4)	Provided but needs revision. Unsatisfactory
Available units (e.g., bottles of 100 tablets)	Not provided	Not provided. Unsatisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	Provided. Satisfactory
Special handling (e.g., protect from light)	Not applicable	Not applicable
Storage conditions	(b) (4)	Provided but needs revision. Unsatisfactory
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Marketed by: Clarus Therapeutics, Inc. 555 Skokie Blvd., Suite 340 Northbrook, IL 60062, USA	Provided at the end of the PI. Satisfactory

This section must be revised to include the available units, packaging configuration, and an appropriate storage conditions. The following revision is recommended:

JATENZO (testosterone undecanoate) capsules are available in three strengths of 158 mg, 198 mg, and 237 mg. Capsules are packaged as 120 units in wide-mouth, round, white HDPE bottles with white, polypropylene, child resistant caps and induction-sealed liner.

158 mg capsules are opaque red capsules imprinted with "158" in white ink. 158 mg capsules are supplied in bottles containing 120 capsules with NDC number NDC 69087-158-12.

198 mg capsules are opaque white capsules imprinted with "198" in red ink. 198 mg capsules are supplied in bottles containing 120 capsules with NDC number NDC 69087-198-12.

237 mg capsules are opaque orange capsules imprinted with "237" in white ink. 237 mg capsules are supplied in bottles containing 120 capsules with NDC number NDC 69087-237-12.

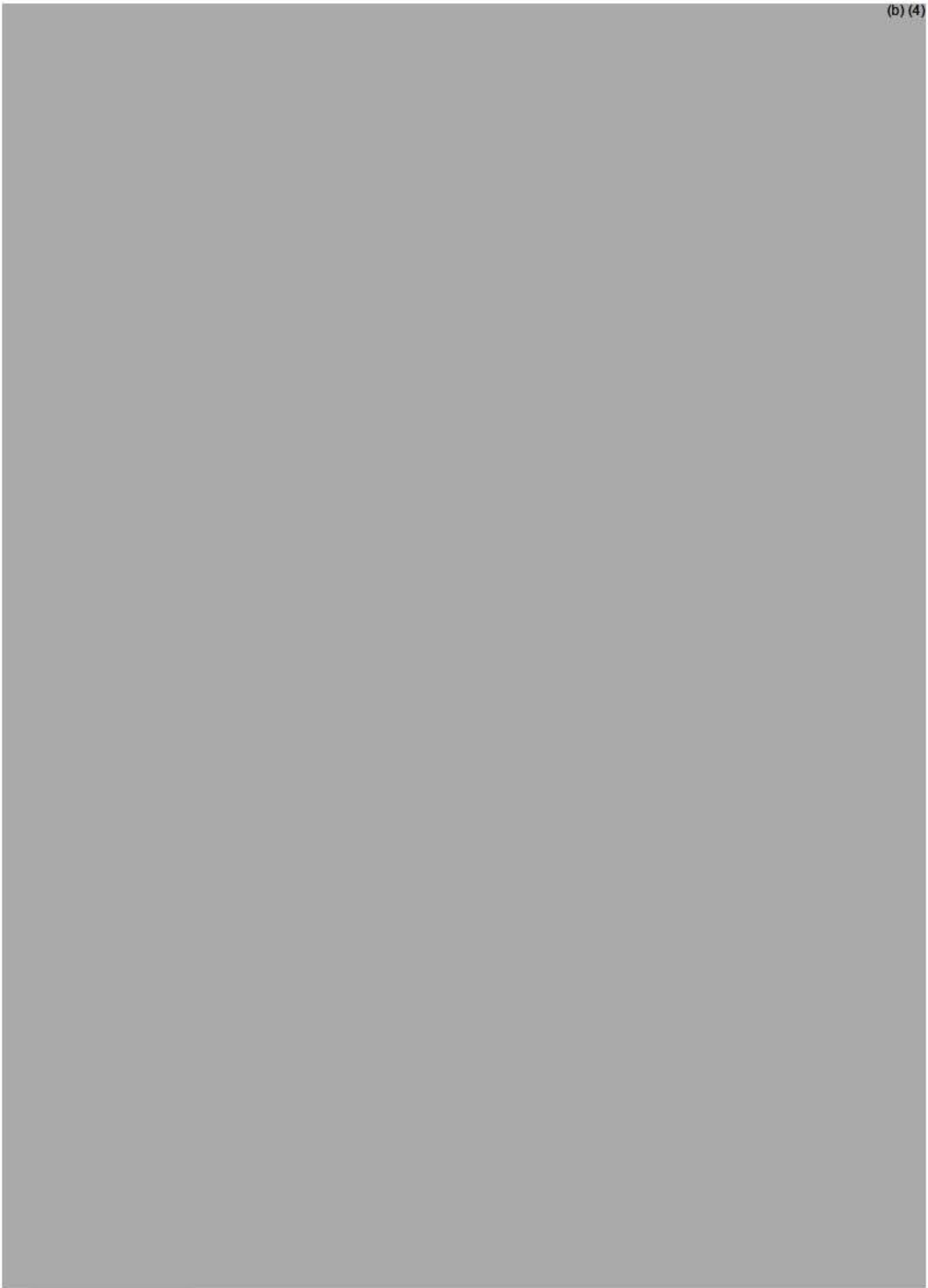
Keep JATENZO out of reach of children.

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Avoid exposing the capsules to moisture (store in a dry place).

II. Labels

1. IMMEDIATE CONTAINER

(b) (4)



Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The trade name and established name are displayed.	Provided with appropriate prominence. Satisfactory
Dosage strength	Capsules: 158 mg 198mg 237mg	Provided. Satisfactory
Net contents	120 Soft Gelatin Capsules	Provided. Satisfactory
"Rx only" displayed prominently on the main panel	Displayed.	Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	Displayed.	Satisfactory
Lot number and expiration date (21 CFR 201.17)	The location for lot number and expiration is displayed.	Provided. Satisfactory
Storage conditions	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F).	Provided. Satisfactory
Bar code (21CFR 201.25)	Displayed.	Satisfactory
Name of manufacturer/distributor	Displayed.	Satisfactory
And others, if space is available	Keep this and all medicines out of reach of children. Contains FD&C Yellow # 6. (b) (4)	Satisfactory.

2. CARTON LABELS:

(b) (4)



(b) (4)



Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Displayed.	Provided with appropriate prominence. Satisfactory
Dosage strength	158 mg 198 mg 237 mg	Provided. Satisfactory
Net contents	120 capsules per bottle 12 bottles	Provided. Satisfactory
"Rx only" displayed prominently on the main panel	Displayed	Displayed. Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	Displayed. Satisfactory
Lot number and expiration date (21 CFR 201.17)	The location on the carton where the lot number and expiration will be placed has been designated.	Provided. Satisfactory
Storage conditions	(b) (4)	Provided. It should be revised to "Store at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F)". Unsatisfactory
Bar code (21CFR 201.25)	Displayed	Displayed. Satisfactory
Name of manufacturer/distributor	Clarus Therapeutics, Inc. Northbrook, IL	Displayed. Satisfactory
And others, if space is available	Contains FD&C Yellow #6 (b) (4)	Provided Satisfactory

Revise the storage condition on the carton label from (b) (4) to "Store at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F)".

III. LIST OF DEFICIENCIES:

A. Regarding PI

Highlights

Revise the Dosage and Strengths in the Highlights to:

JATENZO (testosterone undecanoate) capsules for oral use are available in the following strengths:

- 158mg
- 198mg
- 237mg

Full Prescribing Information

#3: Dosage Forms and Strengths

The dosage form and strength must be revised to remove reference to (b) (4) and to include identifying characteristics for the capsules. The following revisions are recommended:

JATENZO capsules for oral use are available in three strengths:

- 158 mg Testosterone Undecanoate (b) (4) capsules are opaque red capsules imprinted with “158” in white ink.
- 198 mg Testosterone Undecanoate (b) (4) capsules opaque white capsules imprinted with “198” in red ink.
- 237 mg Testosterone Undecanoate (b) (4) capsules are opaque orange capsules imprinted with “237” in white ink.

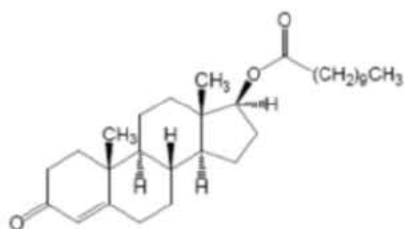
#11: Description

This section must be revised to include, route of administration, appropriate description of the drug product capsules, and pharmacological/ therapeutic class. The following revisions is suggested:

JATENZO for oral use is provided as a gelatin capsule containing testosterone undecanoate, a fatty-acid ester of (b) (4) testosterone. It is a white to off-white yellow crystalline powder. Testosterone is formed by cleavage of the ester side chain of testosterone undecanoate.

Testosterone undecanoate is chemically described as 17 β -hydroxyandrost-4-en-3-one undecanoate. It has the empirical formula of C₃₀H₄₈O₃ and the molecular weight of 456.7. The structural formula for testosterone undecanoate is presented in Figure 1.

Figure 1: Testosterone Undecanoate



JATENZO capsules are available in three strengths of 158 mg, 198 mg, and 237 mg.

158 mg strength is an opaque red capsule that contains 158 mg of testosterone undecanoate (b) (4)

[REDACTED]

198 mg strength is an opaque white capsule that contains 198 mg of testosterone undecanoate (b) (4)

[REDACTED]

237 mg strength is an opaque orange capsule that contains 237 mg of testosterone undecanoate (b) (4)

Gelatin capsule shells are composed of the following inactive ingredients: Gelatin, sorbitol, glycerin, purified water, iron oxide red, FD&C Yellow #6, and titanium dioxide.

#16: How Supplied/Storage and Handling

This section must be revised to include the available units, packaging configuration, and an appropriate storage conditions. The following revision is recommended:

JATENZO (testosterone undecanoate) capsules are available in three strengths of 158 mg, 198 mg, and 237 mg. Capsules are packaged as 120 units in wide-mouth, round, white HDPE bottles with white, polypropylene, child resistant caps and induction-sealed liner.

158 mg capsules are opaque red capsules imprinted with “158” in white ink. 158 mg capsules are supplied in bottles containing 120 capsules with NDC number NDC 69087-158-12.

198 mg capsules are opaque white capsules imprinted with “198” in red ink. 198 mg capsules are supplied in bottles containing 120 capsules with NDC number NDC 69087-198-12.

237 mg capsules are opaque orange capsules imprinted with “237” in white ink. 237 mg capsules are supplied in bottles containing 120 capsules with NDC number NDC 69087-237-12.

Keep JATENZO out of reach of children.

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).

Avoid exposing the capsules to moisture (store in a dry place).

B. Regarding of the Container/Carton Labels:

a) Immediate container labels:

None

b) Carton labels:

Revise the storage condition on the carton label from (b) (4) to “Store at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F)”.

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

- Multiple PI labeling deficiencies have been noted.
- The carton labels require revisions.

Recommendation:

From the ONDP perspective, this application is *not* recommended for approval per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name:

Hamid Shafiei, Ph.D.
Reviewer, Branch V
DNDP II/ONDP/OPQ

Secondary Reviewer Name:

I concur with Dr. Shafiei’s assessment and his recommendation that the labels and labeling are *not* ready for approval in its present form per 21 CFR 314.125 (b)(6) from the ONDP perspective.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP/OPQ



Hamid
Shafiei

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Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee

Date: 1/11/2019 09:59:34AM

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Mark
Seggel

Digitally signed by Mark Seggel

Date: 3/18/2019 02:55:41PM

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Recommendation: *As of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8).*

NDA 206089
Jatenzo
(testosterone undecanoate capsules)
Review #2

Drug Name/Dosage Form	Testosterone Undecanoate Capsules (immediate release, soft gelatin capsules)
Strength	158 mg TU equivalent to 100 mg testosterone 198 mg TU equivalent to 125 mg testosterone * 237 mg TU equivalent to 150 mg testosterone
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Clarus Therapeutics
US agent, if applicable	-

*new strength added in re submission

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission (0030)	06/22/17	Team
Labeling (0041)	10/03/17	Product
Labeling (0044)	11/09/17	Product

Quality Review Team

DISCIPLINE	REVIEWER	Office/Division/Branch
Drug Substance	Jeff Medwid	OPQ/ONDP/DNDPAPI/NDBII
Drug Product	Hamid Shafiei	OPQ/ONDP/DBRUP/NDBV
Facilities	Laurie Nelson	OPQ/OPF/DIA/IABIII
Biopharmaceutics	Mei Ou	OPQ/ONDP/DB/BBII
Microbiology	Bryan Riley	OPQ/OPF/DMA/MABII
RBPM	Thao Vu	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Mark Seggel	OPQ/ONDP/DBRUP/NDBV
Environmental	Jim Laurenson	OPQ/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	H. Shafiei 02/09/18	
	Type II			Adequate	J. Medwid 10/05/17	
	Type II			-		See DMF (b) (4) and associated reviews
	Type II			-		See Chemistry Review #1
	Type III			-		See Chemistry Review #1

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original IND, amendments, meet packages and associated reviews	IND 78104	Clarus' IND for oral testosterone undecanoate capsules as testosterone replacement therapy

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH	na			
Clinical	na			
Other	na			

Executive Summary

I. Recommendations and Conclusion on Approvability

In its present form, Clarus Therapeutics' resubmission of their 505(b)(2) New Drug Application #206089, for Jatenzo (testosterone undecanoate capsules) 158 mg, 198 mg and 237 mg, is not ready for approval. Labeling (package insert, container/carton) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	JATENZO is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired). • Hypogonadotropic hypogonadism (congenital or acquired).
Duration of Treatment	No limitations.
Maximum Daily Dose	396 mg twice daily.
Alternative Methods of Administration	Not applicable.

Clarus Therapeutics submitted NDA 206089 for testosterone undecanoate capsules, 158 mg and 237 mg, on January 3, 2014. Testosterone undecanoate is an ester prodrug of testosterone that is orally bioavailable. It is absorbed via the intestinal lymphatic system thus reducing first-pass metabolism in the liver. Once absorbed, the ester is cleaved by non-specific esterases. The drug product offers a convenient alternative to the orally bioavailable but toxic alkylated testosterone derivative methyltestosterone and to the transdermal testosterone products. While there are other testosterone ester prodrugs on the market (e.g., testosterone cypionate, testosterone enanthate, and testosterone undecanoate), these products are formulated for subcutaneous or intramuscular administration.

A Complete Response Letter for NDA 206089 was issued on November 3, 2014 due to clinical, clinical pharmacology and nonclinical concerns. While the applicant had provided sufficient information to assure the identity, strength,

purity, and quality of the drug product, and all facilities had acceptable CGMP status, labeling had not been finalized.

The July 22, 2017 resubmission includes documentation for an intermediate strength drug product containing 198 mg testosterone undecanoate.

The resubmission review timeline was extended by three months on October 4, 2017 following submission of a major amendment.

B. Quality Assessment Overview

See Dr. Hamid Shafiei's Chemistry Review (#1) dated September 25, 2014, and subsequent addendum, for NDA 206089. See also Dr. Kelly Kitchens' Biopharmaceutics Review dated September 18, 2014.

Drug Substance

Testosterone undecanoate is an ester prodrug prepared by the acylation of testosterone with undecanoic acid, an 11-carbon straight chain fatty acid. The manufacture of testosterone undecanoate by (b) (4) and by (b) (4) is documented Type II Drug Master Files (b) (4) and (b) (4) respectively. Both DMFs were found Adequate to support the use of the active pharmaceutical ingredient in the manufacture of testosterone undecanoate capsules.

Drug Product

Jatenzo (testosterone undecanoate capsules) contains 158 mg, 198 mg and 237 mg of testosterone undecanoate, equivalent to 100 mg, 125 mg and 150 mg of testosterone, respectively. To maximize the amount of drug substance delivered, a non-aqueous self-emulsifying drug delivery system (SEDDS) formulation was developed. The product consists of a liquid fill in a soft gelatin capsule. The capsule fill consists of oleic acid (b) (4), borage seed oil (b) (4), Polyoxyl 40 Hydrogenated Castor Oil NF (Cremophor RH40) (b) (4) and peppermint oil (b) (4). The latter serves as a (b) (4). The capsule fill also includes (b) (4) of the (b) (4) butylated hydroxyl toluene. The soft gelatin capsule shell is prepared from gelatin, a sorbitol (b) (4) glycerin (b) (4), titanium dioxide, and water. The same capsule fill is used in the preparation of all three product strengths.

The manufacturing process, in process controls, container/closure system, and drug product specification remain unchanged since last reviewed by Dr. Shafiei in 2014.

The product will be supplied in 120-count HDPE bottles with induction-sealed liners and child resistant caps.

Stability data on all three product strengths have been provided. The data support the applicant's proposed expiration dating period of 30 months when stored at

(b) (4)

Overall, sufficient information has been provided to assure the identity, strength, purity, and quality of the drug product. From the drug product review perspective the application is recommended for **Approval** (see attached review).

Biopharmaceutics

The dissolution test method and acceptance criteria were found acceptable during the first review cycle (see Dr. K. Kitchens review dated September 18, 2014). The resubmission includes dissolution data of the new, intermediate strength capsule at release and on stability. Because the new strength is compositionally proportional to the lower and higher strengths already evaluated. The test method and acceptance criterion are also applicable to the intermediate strength. The application is recommended for **Approval** from the biopharmaceutics review perspective (see attached review).

Product Quality Microbiology

Microbial limits testing is conducted in accordance with USP <61> and USP <62>. The acceptance criteria are consistent with USP <1111>. The NDA is recommended for **Approval** from the product quality microbiology perspective (see Dr. Bryan Riley's January 13, 2014 review (attached)). No changes have been made that would impact the previous assessment.

Facilities

The drug substance manufacturers, (b) (4) and (b) (4) and the drug product manufacturer, (b) (4) have acceptable CGMP status. Associated packaging and testing facilities also have acceptable CGMP status. An overall inspection recommend of **Approve** was issued on February 1, 2018 (see attached review).

Environmental Assessment

During the first review cycle, Dr. Jim Laurenson concluded that the applicant's claimed categorical exclusion was acceptable (see attached EA review). This assessment remains applicable.

Labeling

In collaboration with DMEPA, preliminary comments were conveyed to the applicant. Because the application will once again receive a Complete Response,

labeling negotiations with the applicant have not been initiated. In its present form, the labeling does not comply with the requirements under 21 CFR 201. A full review of the package insert and container labels will be completed upon resubmission of the NDA.

C. Special Product Quality Labeling Recommendations

Not Applicable.

D. Final Risk Assessment

See Attachment 1.

E. List of Deficiencies for Complete Response

Not Applicable.

Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D.
Acting CMC Lead for DBRUP
OPQ/ONDP/DNDPII/Branch V
February 23, 2018



Mark
Seggel

Digitally signed by Mark Seggel

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BIOPHARMACEUTICS

Product Background:

NDA:206089-ORIG-1-RESUB-31, [505(b)(2)]

Drug Product Name / Strength: Jatenzo (Testosterone Undecanoate) Soft Gelatin Capsule, 158 mg, 198 mg and 237 mg

Route of Administration: Oral

Applicant Name: Clarus Therapeutics, Inc.

The proposed indication: Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).

Review Summary:

NDA 206089 was originally submitted on 01/03/2014 as a 505(b)(2) application for the proposed drug product, Oral Testosterone Undecanoate (TU), Soft Gelatin Capsule, 158 mg and 237 mg, equivalent to 100 mg and 150 mg testosterone (T), respectively. On 11/03/2014, a Complete Response (CR) was issued to the application (*see CR letter in DARRTS dated 11/03/2014*).

The Applicant re-submitted this NDA on 06/22/2017 as a 505(b)(1) application in seeking approval for the proposed Jatenzo (Testosterone Undecanoate) Soft Gelatin Capsule, 158 mg and 237 mg, with an additional intermediate strength, 198 mg (equivalent to 125 mg testosterone).

The dissolution method and acceptance criterion for the proposed drug product (158 mg and 237 mg) have been reviewed and found acceptable in the Biopharmaceutics review for the original NDA submission. The original NDA was recommended for approval from the Biopharmaceutics perspective (*see Biopharmaceutics review in DARRTS dated 09/18/2014*). The implemented dissolution specification for the proposed drug product (158 mg and 237 mg) is summarized in the following table:

USP Apparatus	Rotation Speed	Dissolution Medium	Temperature	Acceptance Criterion
II (Paddle)	75 rpm	900 mL of phosphate buffer pH 6.8 with 1.0% Triton X-100	37°C	Q ^(b) ₍₄₎ % in 30 minutes

For the resubmission, Biopharmaceutics review will focus on the evaluation of comparative dissolution data between the newly proposed intermediate strength product (198 mg) and the previous two strengths product (158 mg and 237 mg).

Submission:

06/22/2017

eCTD 0030/Resubmission

Review:

In the resubmission, the implemented dissolution method and acceptance criterion are the same as the dissolution specification approved in the original submission for the 158 mg and 237 mg strengths products. The approved dissolution method and acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 30 minutes for the proposed intermediate strength (198 mg) is appropriate considering the three strengths products have compositionally proportional formulation. The dissolution data of the proposed intermediate strength product met the approved dissolution acceptance criterion. The comparative dissolution profile data demonstrated that the proposed intermediate strength product has similar dissolution behavior compared to the original two strengths products. Therefore, the implemented dissolution method and acceptance criterion are acceptable for all three strengths products. Note that the acceptance of the pharmacokinetic (PK) data and the *in vivo* dose titration results among these three strengths products from the pivotal clinical study (CLAR-15012) will be assessed by the Office of Clinical Pharmacology (OCP).

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 206089 for Jatenzo (Testosterone Undecanoate) Soft Gelatin Capsule, 158 mg, 198 mg and 237 mg, is recommended for APPROVAL.

The implemented dissolution specification for the proposed Jatenzo (Testosterone Undecanoate) Soft Gelatin Capsule, 158 mg, 198 mg and 237 mg, is summarized in the following table:

USP Apparatus	Rotation Speed	Dissolution Medium	Temperature	Acceptance Criterion
II (Paddle)	75 rpm	900 mL of phosphate buffer pH 6.8 with 1.0% Triton X-100	37°C	$Q = \frac{(b)}{(4)}\%$ in 30 minutes

BCS Designation**Reviewer's Assessment:**

The Applicant did not submit a formal request for BCS Class 1 or Class 3 designation or relevant information/data for the drug substance or drug product.

Solubility: The solubility of drug substance, testosterone undecanoate, was submitted in the original application. From the data, the drug substance has low solubility in water but high solubility in organic solvents, as presented in Table 1.

Table 1: Physicochemical properties of testosterone undecanoate
(from M.3.2.S.1.3 of 01/03/2014 submission)

Table 3.2.S.1.3 Pfizer-1 Physicochemical Properties of Testosterone Undecanoate *	
Appearance	White crystals or crystalline powder to off-white yellow powder
Solubility	
Chloroform	Very soluble
Methanol	Soluble
Isopropanol	Soluble
Acetone	Freely Soluble
Benzene	Freely Soluble
Ethanol	Sparingly soluble
Vegetable Oil	Slightly soluble
Water	Insoluble
Specific Optical Rotation	+68° to +72°
Melting Range	60°C to 63°C
Hygroscopicity	Not hygroscopic
Solid State Form	(b) (4)
*Source of data is from the DMF information supplied by the two drug substance manufacturers	

Permeability: No data is submitted in this application.

Dissolution: The proposed drug product is immediate-release soft gelatin capsules. The dissolution method and acceptance criterion have been reviewed and accepted in the Biopharmaceutics review for the original submission. The dissolution profile data of additional intermediate strength is reviewed in the following section.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

1. Composition of the drug product

The dose-proportional composition of the proposed three strengths product is presented in Table 2. According to the Applicant, (b) (4)

The batch size, manufacturing equipment and manufacturing process used for production of registration batches are identical to the intended commercial scale, equipment and process. Therefore, no additional *in vitro* formulation bridging studies are needed to support commercialization.

Table 2: Unit composition of Testosterone Undecanoate 158 mg, 198 mg and 237 mg capsules (from M.2.7.1 of 06/22/2017 resubmission addendum)

Ingredient	Amount (mg) 158 mg capsule	Amount (mg) 198 mg capsule	Amount (mg) 237 mg capsule	Function
Formulation				
Testosterone Undecanoate	158.30 ¹	197.88 ²	237.46 ³	Active Ingredient (b) (4)
Oleic Acid NF, EP				(b) (4)
Borage Seed Oil ⁴				
Butylated Hydroxytoluene NF, EP (BHT)				
Peppermint Oil NF, FCC				
Polyoxyl 40 Hydrogenated Castor Oil NF (Cremophor RH40)				
Total Fill Weight				(b) (4) (u) (4)

2. Dissolution method

The dissolution method and acceptance criterion have been approved in the original NDA submission. According to the Applicant, the tests and the acceptance criteria (i.e. appearance, identification, assay, degradation products, dissolution, uniformity, and microbial limits) to release commercial 198 mg capsules are identical to the 158 mg and 237 mg capsules. Because of the dose-proportional of three strengths product, and the (b) (4) fill materials, and manufacturing process, it is acceptable to implement the same dissolution method and acceptance criterion for the newly proposed intermediate strength product. The dissolution method and acceptance criterion for all three strengths product are summarized in Table 3.

Table 3: Dissolution specification for Testosterone Undecanoate soft gelatin capsules, 158 mg, 198 mg and 237 mg

USP Apparatus	Rotation Speed	Dissolution Medium	Temperature	Acceptance Criterion
II (Paddle)	75 rpm	900 mL of phosphate buffer pH 6.8 with 1.0% Triton X-100	37°C	Q (b) (4) % in 30 minutes

The approved dissolution analytical method (ATM-CMB-J0006) for 158 mg and 237 mg capsules was provided in M.3.2.P.5.2 in both original submission and the resubmission. The dissolution analytical method (ATM-CMB-J0009) for 198 mg capsules was provided in M.3.2.P.5.2 in the resubmission. The analytical procedure and validation reports are under purview by a CMC chemist. According to the Applicant, the two dissolution methods are identical, as presented in Table 4. From the Biopharmaceutics perspective, the two dissolution analytical methods for all three strengths products are the same; therefore, the dissolution analytical method (ATM-CMB-J0009) for 198 mg capsules is acceptable.

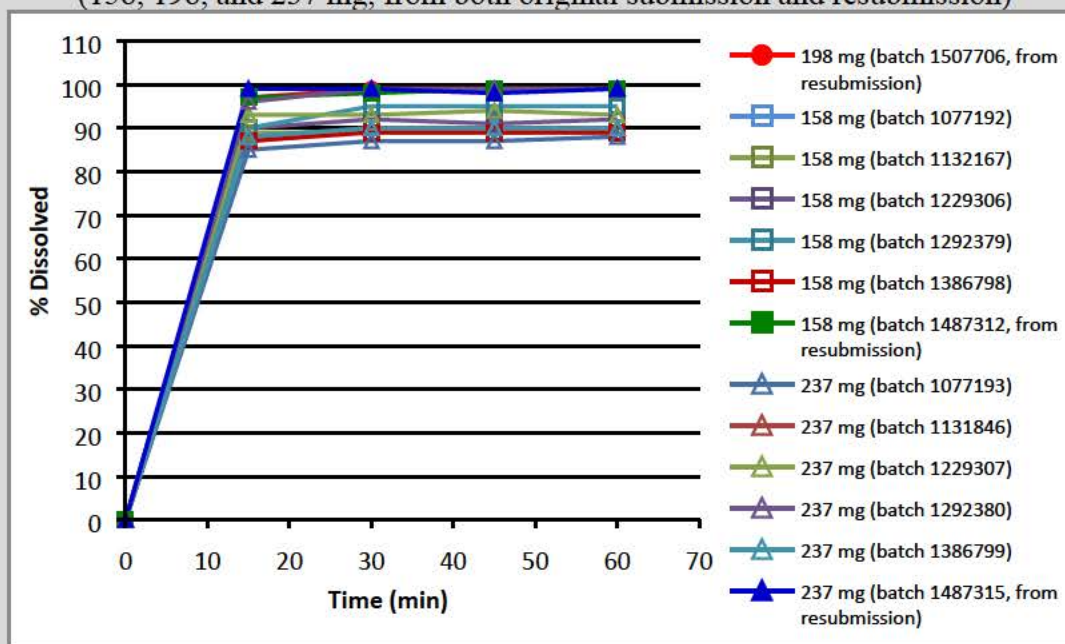
Table 4: Comparison of commercial dissolution methods for 158 mg, 198 mg, and 237 mg capsules (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Table 3.2.P.8.3 Catalent-12 Comparison of Commercial Dissolution Methods for 158 mg, 237 mg and 198 mg Capsules			
	Method Number	Media	Paddle speed
Commercial Dissolution Method for 158 mg and 237 mg Capsules	ATM-CMB-J0006	1.0%Triton X-100 in 900 mL pH 6.8 phosphate buffer	75 rpm
Commercial Dissolution Method for 198 mg Capsules	ATM-CMB-J0009	1.0%Triton X-100 in 900 mL pH 6.8 phosphate buffer	75 rpm

3. Dissolution data

One registration batch of 198 mg capsules (batch 1507706) was manufactured in November 2014, which was used in clinical study (CLAR-15012) and stability studies. The batch information and dissolution data of all three strengths product which have been used for dissolution test, clinical and stability studies are given in Appendix 1. The comparative dissolution profiles of all three strengths product are plotted in Figure 1.

Figure 1: Mean dissolution profiles of Testosterone Undecanoate soft gelatin capsules (158, 198, and 237 mg, from both original submission and resubmission)



As illustrated in Figure 1, more than (b) (4)% of the label claim of drug product dissolved in (b) (4) minutes for all the three strengths products generated by the same dissolution method suggesting all three strengths products having similar dissolution profiles so that the similarity factor (f_2) calculation is not applicable per the *FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Form*. The dissolution data

of all three strengths product have met the approved dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 30 minutes.

4. Dissolution data in stability tests

The dissolution data collected under long-term stability condition (25°C/60% RH in HDPE bottles) for eight (8) batches of 158 mg capsules, eight (8) batches of 237 mg capsules, and one (1) batch of 198 mg capsules was submitted in M.3.2.P.8.3. The data are given in Appendix 2.

All batches of three strengths product passed the dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 30 minutes at stability intervals of 0, 2, 3, 6, 9, 12, 15, 18, 24, 30, 36, 42 and 48 months, except for one batch of 158 mg capsules (Lot 1077192) and one batch of 237 mg capsules (Lot 1077193). The 158 mg batch (Lot 1077192) passed dissolution test at 0, 9, 12, 15, 18, 24, and 36 months, but failed at 30, 42 and 48 months, as presented in Table 5. The 237 mg batch (Lot 1077193) passed dissolution test from 0 to 36 months, but failed at 42 and 48 months, as presented in Table 6. According to the Applicant, the reason for the dissolution failure above is not known.

According to the Applicant, no trends (e.g. decrease in dissolution rate with time) were observed for any other batches of three strengths product under long-term stability storage conditions. The failure of Lot 1077192 (158 mg at 30 and 36 months, presented in Table 7) would indicate that the dissolution methodology used, combined with the dissolution specification of $Q = \frac{(b)}{(4)}\%$ at 30 minutes, is stringent enough to be able to serve as a good quality control test.

The dissolution data of 158 mg product (Lot 1077192) at 30 months has been communicated with the drug product reviewer for their evaluating the proposed expiry period of 30 months. The acceptance of this specific batch at 30 months is pending on the acceptance of the recommended expiry from the CMC perspective.

Table 5: Dissolution data of Testosterone Undecanoate 158 mg Capsules
Lot Number 1077192 at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 submission)

Table 3.2.P.8.3 Catalent-19 Stability Data for Testosterone Undecanoate 158 mg Capsules Lot Number 1077192 at 25°C/60 % RH								
		Related Substances/ Degradation Products			Dissolution ⁵ : Mean Percent Dissolved (Range)			
Months	Assay (TU %)	T (%)	TO (%)	Total RS (%)	15 Min	30 Min	45 Min	60 Min
0	101.0 ¹	0.31	0.0	0.38	87	90	90	90 (b) (4)
9 ²	97.9	1.48	0.35	1.90	86	89	89	89 (b) (4)
12	96.4	1.77	0.51	2.41	89	86	86	86 (b) (4)
15.5	95.5	2.14	0.80	3.26	88	91	91	91 (b) (4)
18	96.6	2.39	1.01	3.71	81	88	89	89 (b) (4)
24	94.0	2.89	1.61	4.98	60	89	91	92 (b) (4)
30	92.9	3.26	2.24	6.29	13	74	86	87 (b) (4)
36	90.0	3.60	2.87	7.45	79	86	92	89 (b) (4)
42 ³	88.6	4.04	3.66	8.94	42	58	76	82 (b) (4)
48 ⁴	86.0	4.29	4.24	10.16	71	60	74	85 (b) (4)

Table 6: Dissolution data of Testosterone Undecanoate 237 mg Capsules
Lot Number 1077193 at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 submission)

Table 3.2.P.8.3 Catalent-27 Stability Data for Testosterone Undecanoate 237 mg Capsules Lot Number 1077193 at 25°C/60 % RH								
		Related Substances/ Degradation Products			Dissolution ⁴ : Mean Percent Dissolved (Range)			
Months	Assay (TU %)	T (%)	TO (%)	Total RS (%)	15 Min	30 Min	45 Min	60 Min
0	101.0 ¹	0.28	0.0	0.35	85	87	87	88 (b) (4)
9 ²	97.5	1.38	0.34	1.85	84	84	84	84 (b) (4)
12	96.2	1.79	0.52	2.38	83	84	84	84 (b) (4)
15.5	96.3	2.01	0.77	2.98	88	91	91	91 (b) (4)
18	96.6	2.23	0.96	3.41	86	87	87	87 (b) (4)
24	94.6	2.69	1.56	4.69	90	91	91	91 (b) (4)
30	92.7	3.10	2.18	5.99	85	87	87	87 (b) (4)
36	90.5	3.37	2.71	6.98	76	88	89	89 (b) (4)
42 ³	89.1	3.67	3.34	8.07	63	80	87	87 (b) (4)
48	87.1	4.05	4.09	9.49	51	75	82	83 (b) (4)

Table 7: Dissolution data at 0, 12, 24, 30 and 36 months, $Q = \frac{(b)}{(4)}\%$ in 30 minutes
(from M.3.2.P.8.3 of 06/22/2017 submission)

Table 3.2.P.8.3 Catalent-39 Application of USP Acceptance Criteria for Q Value of $\frac{(b)}{(4)}\%$ at 30 Minutes to Dissolution Data at 0, 12, 24, 30 and 36 Months								
Capsule Strength (mg)	Batch #	Location of Dissolution Data (Report #)	Dissolution Method	Results at T=0 Months	Results at T=12 Months	Results at T=24 Months	Results at T=30 Months	Results at T=36 Months
158 mg Capsules								
158	1077192	CLAR-PD-17-004	J0002	Pass	Pass	Pass	Fail	Fail
158	1132167	CLAR-PD-17-005	J0002	Pass	Pass	Pass	Pass	Pass
158	1229306	CLAR-PD-17-006	J0002	Pass	Pass	Pass	Pass	Pass
158	1292379	CLAR-PD-17-007	J0002	Pass	Pass	Pass	Pass	Pass
158	1386798	CLAR-PD-17-008	J0006	Pass	Pass	Pass ¹	Pass	Pass
158	1487311	CLAR-PD-17-009	J0006	Pass	Pass	Pass	(---) ¹	(---)
158	1487312	CLAR-PD-17-010	J0006	Pass	Pass	Pass	(---)	(---)
158	1487313	CLAR-PD-17-011	J0006	Pass	Pass	Pass	(---)	(---)
237 mg Capsules								
237	1077193	CLAR-PD-17-012	J0002	Pass	Pass	Pass	Pass	Pass
237	1131846	CLAR-PD-17-013	J0002	Pass	Pass	Pass	Pass	Pass
237	1229307	CLAR-PD-17-014	J0002	Pass	Pass	Pass	Pass	Pass
237	1292380	CLAR-PD-17-015	J0002	Pass	Pass	Pass	Pass	Pass
237	1386799	CLAR-PD-17-016	J0006	Pass	Pass	Pass ¹	Pass	Pass
237	1487314	CLAR-PD-17-017	J0006	Pass	Pass	Pass	(---)	(---)
237	1487315	CLAR-PD-17-018	J0006	Pass	Pass	Pass	(---)	(---)
237	1487316	CLAR-PD-17-019	J0006	Pass	Pass	Pass	(---)	(---)
198 mg Capsules								
198	1507706	CLAR-PD-17-020	J0009	Pass	Pass	Pass	(---)	(---)

(b) (4)

Bridging of Formulations

Reviewer's Assessment:

The acceptance of the PK data and *in vivo* dose titration results among the three strengths products generated from the pivotal clinical study (CLAR-15012) is under purview by the OCP. The batch information and the comparative dissolution data of the three strengths product used in this clinical study are presented in Table 8 below. The batch analysis data including comparative dissolution data of the three strengths product are presented in the following Table 9.

From the results, the three strengths products (1) have dose proportional formulation, (2) were manufactured from the same site, (3)

(b) (4)

(b) (4) (4) have less than (b) (4) batch size difference, and (5) showed comparable dissolution profile data. Therefore, no additional *in vitro* formulation bridging is needed from the Biopharmaceutics perspective.

Table 8: Batch information for Testosterone Undecanoate 158, 198 and 237 mg capsules used in clinical study CLAR-15012 (from M.2.7.1 of 06/22/2017 submission)

Capsule Strength (Batch Type)	Batch #	Drug Substance Supplier and Batch #	Theoretical Drug Product Batch Size (# of Capsules)	Month of Manufacture	Container – Closure	Capsule Use
158 mg (Validation batch)	1487312	(b) (4)	(b) (4)	August 2014	HDPE 250 cc bottle with child resistant cap	CLAR-15012 CLAR-15013 Stability
198 mg (Registration batch)	1507706			November 2014	HDPE 300 cc bottle with child resistant cap	CLAR-15012 Stability
237 mg (Validation batch)	1487315			August 2014	HDPE 400 cc bottle with child resistant cap	CLAR-15012 CLAR-16015 Stability

Table 9: Batch analysis data for Testosterone Undecanoate 158, 198 and 237 mg capsules used for studies CLAR-15012 and CLAR-16015 (from M.2.7.1 of 06/22/2017 submission)

Test	Acceptance Criteria (Per the CoA)	Batch 1487312 CoA	Batch 1507706 CoA	Batch 1487315 CoA
		158 mg	198 mg	237 mg
Appearance	1	Pass	Pass	Pass
Identification by HPLC	2	Pass	Pass	Pass
Identification by Scan	3	Pass	Pass	Pass
Assay	(b) (4) % of label claim	(b) (4)		
Testosterone	NMT (b) (4) %			
Testosterone Oleate	NMT (b) (4) %			
Individual Unknowns	Each NMT (b) (4) %			
Total Impurities	NMT (b) (4) %			
Content Uniformity	Conforms to USP	Avg= (b) (4) % Conforms	Avg= (b) (4) % Conforms	Avg= (b) (4) % Conforms
Dissolution	15, 30, 45, 60 min report results: Average % release (range) Q= (b) (4) % at 30 min	15 avg=97%	15 avg=97%	15 avg=99%
		30 avg=98%	30 avg=99%	30 avg=99%
		45 avg=99%	45 avg=99%	45 avg=98%
		60 avg=99%	60 avg=99%	60 avg=99%
		(b) (4) cfu/g	(b) (4) cfu/g	(b) (4) cfu/g
Total Aerobic Microbial ⁴	NMT (b) (4) cfu/g	(b) (4) cfu/g	(b) (4) cfu/g	(b) (4) cfu/g
Total Yeast and Mold ⁵	NMT (b) (4) cfu/g	(b) (4) cfu/g	(b) (4) cfu/g	(b) (4) cfu/g
<i>Escherichia coli</i>	Absent in (b) (4) g	Absent in (b) (4) g	Absent in (b) (4) g	Absent in (b) (4) g

¹Appearance: 158 mg: Opaque red oblong soft gelatin capsule with "158" printed on one side with white ink
198 mg: Opaque white oblong soft gelatin capsule with "198" printed on one side with red ink
237 mg: Opaque orange oblong soft gelatin capsule with "237" printed on one side with white ink
²Identification by HPLC Retention Time: Retention time of the major peak corresponds to the testosterone undecanoate reference standard
³Identification by Wavelength Scan (HPLC diode array UV detector): Wavelength Scan (b) (4) corresponds to that of the reference standard
⁴Total Aerobic Microbial Count
⁵Total Combined Yeast and Mold Count
NMT = Not More Than; LOD = Limit of Detection; RRT = Relative Retention Time

Biowaiver Request

Reviewer's Assessment:

Because PK data for all three strengths product has been generated in clinical study CLAR-15012, biowaiver request for the lower strength (158 mg) and the intermediate strength (198 mg) product are not needed.

List of Deficiencies: None

APPENDIX 1

The batch information and the dissolution data of the proposed Jatenzo (Testosterone Undecanoate) soft gelatin capsules, 158 mg, 198 mg and 237 mg, from both the original submission and the resubmission, generated by the approved dissolution method, are presented in the following Table 10-17. Note that there are two commercial manufacturers have been identified in this NDA as suppliers of the drug substance,

(b) (4) (referred to in this NDA as (b) (4) located in (b) (4) and (b) (4) (referred to in this NDA as (b) (4) located in (b) (4)). The 198 mg strength product was manufactured by (b) (4).

Table 10: Batch information for Testosterone Undecanoate **158 mg** capsules in long-term stability studies in HDPE bottles (from M.2.3.P of 06/22/2017 resubmission)

Table 2.3.P.8-7 Batch Information for Testosterone Undecanoate 158 mg Capsules For Long Term Stability Studies in HDPE Bottles					
Capsule Strength (Batch Type)	Batch #	Drug Substance Supplier and Batch #	Month of Manufacture	Months of Data ¹ Available and (Study Status)	Capsule Use
158 mg (Registration batch)	1077192	(b) (4)	June 2010	48 months (complete)	CLAR-09007 Stability
158 mg (Registration batch)	1132167		December 2010	48 months (complete)	CLAR-09007 Stability
158 mg (Registration batch)	1229306		November 2011	48 months (complete)	CLAR-09007 CLAR-12010 CLAR-12011 Stability
158 mg (Registration batch)	1292379		June 2012	42 months (complete)	CLAR-12010 CLAR-12011 Stability
158 mg (Registration batch)	1386798		June 2013	42 months (ongoing)	Stability
158 mg (Validation batch)	1487311		August 2014	24 months (ongoing)	Stability
158 mg (Validation batch)	1487312		August 2014	24 months (ongoing)	CLAR-15012 CLAR-15013 Stability
158 mg (Validation batch)	1487313		August 2014	24 months (ongoing)	Stability
¹ Data at 25°C/60% RH					

Table 11: Batch information for Testosterone Undecanoate **198 mg** capsules in Long-term stability studies in HDPE bottles (from M.2.3.P of 06/22/2017 resubmission)

Table 2.3.P.8-9 Batch Information for Testosterone Undecanoate 198 mg Capsules For Long Term Stability Studies in HDPE Bottles					
Capsule Strength (Batch Type)	Batch #	Drug Substance Supplier and Batch #	Month of Manufacture	Months of Data ¹ Available and (Study Status)	Capsule Use
198 mg (Registration batch)	1507706	(b) (4)	November 2014	24 months (ongoing)	CLAR-15012 Stability
¹ Data at 25°C/60% RH					

Table 12: Batch information for Testosterone Undecanoate **237 mg** capsules in long-term stability studies in HDPE bottles (from M.2.3.P of 06/22/2017 resubmission)

Table 2.3.P.8-8 Batch Information for Testosterone Undecanoate 237 mg Capsules For Long Term Stability Studies in HDPE Bottles					
Capsule Strength (Batch Type)	Batch #	Drug Substance Supplier and Batch #	Month of Manufacture	Months of Data ¹ Available and (Study Status)	Capsule Use
237 mg (Registration batch)	1077193	(b) (4)	June 2010	48 months (complete)	CLAR-09007 Stability
237 mg (Registration batch)	1131846		December 2010	48 months (complete)	CLAR-09007 Stability
237 mg (Registration batch)	1229307		November 2011	48 months (complete)	CLAR-09007 CLAR-12010 CLAR-12011 Stability
237 mg (Registration batch)	1292380		June 2012	42 months (complete)	CLAR-12010 Stability
237 mg (Registration batch)	1386799		June 2013	42 months (ongoing)	CLAR-12010 Stability
237 mg (Validation batch)	1487314		August 2014	24 months (ongoing)	Stability
237 mg (Validation batch)	1487315		August 2014	24 months (ongoing)	CLAR-15012 CLAR-16015 Stability
237 mg (Validation batch)	1487316		August 2014	24 months (ongoing)	Stability
¹ Data at 25°C/60% RH					

Table 13: Dissolution data of **198 mg** Testosterone Undecanoate soft gelatin capsules (batch 1507706, n=6) (from M.3.2.P.5.4 of 06/22/2017 resubmission)

Test	Acceptance Criteria Per Catalent's Certificate of Analysis ²	Results For 198 mg Capsule Batch 1507706
Dissolution	Q= (b) (4) % at 30 min Report results at 15, 30, 45, 60 min (average and range)	15 min avg=97% 30 min avg=99% 45 min avg=99% 60 min avg=99% (b) (4)

Table 14: Original dissolution data of **158 mg** Testosterone Undecanoate soft gelatin capsules (from M.2.3.P of 01/03/2014 submission)

Test	Acceptance Criteria	Batch 1077192	Batch 1132167	Batch 1229306	Batch 1292379	Batch 1386798
		DS Batch Xianju X1-091202 X1-091203	DS Batch Xianju X1-100301 X1-091205	DS Batch Pfizer TTUM11001K	DS Batch Pfizer TTUM11004K	DS Batch Pfizer G86810
Dissolution	15, 30, 45 min report results % release (average & range) Q= (b) (4) at 60 min	15 avg=87%	15 avg=89%	15 avg=90%	15 avg=90%	15 avg=87% (b) (4)
		30 avg=90%	30 avg=89%	30 avg=92%	30 avg=95%	30 avg=89% (b) (4)
		45 avg=90%	45 avg=89%	45 avg=91%	45 avg=95%	45 avg=89% (b) (4)
		60 avg=90%	60 avg=89%	60 avg=92%	60 avg=95%	60 avg=89% (b) (4)

Note: the approved dissolution acceptance criterion is Q= (b) (4) % in 30 minutes.

Table 15: Additional dissolution data of **158 mg** Testosterone Undecanoate soft gelatin capsules (batch 1487312, n=6)
(from certificate of analysis in M.3.2.P.5.4 of 06/22/2017 resubmission)

Test	Method	Specification	Results				Notebook Reference Test Date	
Dissolution	ATM-CMB-J0006.01	Meets USP <711> criteria Q= (b) (4) % at 30 minutes	Vessel #	% Release				BK 05, LDR 99 29Sep2014
			15 Min	30 Min	45 Min	60 Min		
			1	(b) (4)				
			2					
			3					
			4					
			5					
			6					
			Avg (n=6)	97	98	99	99	
%RSD	1.8	0.3	0.2	0.3				

Table 16: Original dissolution data of **237 mg** Testosterone Undecanoate soft gelatin capsules (from M.2.3.P of 01/03/2014 submission)

Test	Acceptance Criteria	Batch 1077193	Batch 1131846	Batch 1229307	Batch 1292380	Batch 1386799
		DS Batch	DS Batch	DS Batch	DS Batch	DS Batch (b) (4)
Dissolution	15, 30, 45 min report results % release (average & range) Q= (b) (4) % at 60 min	15 avg=85%	15 avg=88%	15 avg=93%	15 avg=96%	15 avg=88% (b) (4)
		30 avg=87%	30 avg=90%	30 avg=93%	30 avg=99%	30 avg=90% (b) (4)
		45 avg=87%	45 avg=90%	45 avg=94%	45 avg=99%	45 avg=90% (b) (4)
		60 avg=88%	60 avg=90%	60 avg=93%	60 avg=99%	60 avg=90% (b) (4)

Note: the approved dissolution acceptance criterion is Q= (b) (4) % in 30 minutes.

Table 17: Additional dissolution data of **237 mg** Testosterone Undecanoate soft gelatin capsules (batch 1487315, n=6)
(from certificate of analysis in M.3.2.P.5.4 of 06/22/2017 resubmission)

Test	Method	Specification	Results					Notebook Reference Test Date
Dissolution	ATM-CMB-J0006.01	Meets USP <711> criteria Q= (b) (4) % at 30 minutes	Vessel #	% Release				BK 12, LDR 134 13Oct2014
			15 Min	30 Min	45 Min	60 Min (b) (4)		
			1					
			2					
			3					
			4					
			5					
			6					
			Avg (n=6)	99	99	98	99	
%RSD	0.3	0.4	0.5	0.3				

APPENDIX 2

The batch information and the dissolution data of the proposed Jatenzo (Testosterone Undecanoate) soft gelatin capsules, 158 mg, 198 mg and 237 mg, generated under long-term stability condition (25°C/60% RH), are presented in the following Table 18-37.

Table 18: Batch information of eight (8) batches of **158 mg** capsules
(from M.3.2.P.8.3 of 06/22/2017 resubmission)

Table 3.2.P.8.3 Catalent-16 Location of Data for the Long Term Stability Studies in HDPE Bottles for Testosterone Undecanoate 158 mg Capsules			
Capsule Strength (Batch Type)	Batch #	Months of Data ¹ Available and (Study Status)	Stability Report Number
158 mg (Registration batch)	1077192	48 months (complete)	CLAR-PD-17-004
158 mg (Registration batch)	1132167	48 months (complete)	CLAR-PD-17-005
158 mg (Registration batch)	1229306	48 months (complete)	CLAR-PD-17-006
158 mg (Registration batch)	1292379	42 months (complete)	CLAR-PD-17-007
158 mg (Registration batch)	1386798	42 months (ongoing)	CLAR-PD-17-008
158 mg (Validation batch)	1487311	24 months (ongoing)	CLAR-PD-17-009
158 mg (Validation batch)	1487312	24 months (ongoing)	CLAR-PD-17-010
158 mg (Validation batch)	1487313	24 months (ongoing)	CLAR-PD-17-011
¹ Data at 25°C/60% RH			

Table 19: Batch information of one (1) batches of **198 mg** capsules
(from M.3.2.P.8.3 of 06/22/2017 resubmission)

Table 3.2.P.8.3 Catalent-18 Location of Data for the Long Term Stability Study in HDPE Bottles for Testosterone Undecanoate 198 mg Capsules			
Capsule Strength (Batch Type)	Batch #	Months of Data ¹ Available and (Study Status)	Stability Report Number
198 mg (Registration batch)	1507706	24 months (ongoing)	CLAR-PD-17-020
¹ Data at 25°C/60% RH			

Table 20: Batch information of eight (8) batches of **237 mg** capsules
(from M.3.2.P.8.3 of 06/22/2017 resubmission)

Table 3.2.P.8.3 Catalent-17 Location of Data for the Long Term Stability Studies in HDPE Bottles for Testosterone Undecanoate 237 mg Capsules			
Capsule Strength (Batch Type)	Batch #	Months of Data ¹ Available and (Study Status)	Stability Report Number
237 mg (Registration batch)	1077193	48 months (complete)	CLAR-PD-17-012
237 mg (Registration batch)	1131846	48 months (complete)	CLAR-PD-17-013
237 mg (Registration batch)	1229307	48 months (complete)	CLAR-PD-17-014
237 mg (Registration batch)	1292380	42 months (complete)	CLAR-PD-17-015
237 mg (Registration batch)	1386799	42 months (ongoing)	CLAR-PD-17-016
237 mg (Validation batch)	1487314	24 months (ongoing)	CLAR-PD-17-017
237 mg (Validation batch)	1487315	24 months (ongoing)	CLAR-PD-17-018
237 mg (Validation batch)	1487316	24 months (ongoing)	CLAR-PD-17-019
¹ Data at 25°C/60% RH			

Table 21: Dissolution Data for Testosterone Undecanoate **158 mg** Capsules
Lot Number **1077192** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ⁵ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	87	90	90	90 (b) (4)
9 ²	86	89	89	89 (b) (4)
12	89	86	86	86 (b) (4)
15.5	88	91	91	91 (b) (4)
18	81	88	89	89 (b) (4)
24	60	89	91	92 (b) (4)
30	13	74	86	87 (b) (4)
36	29	86	92	89 (b) (4)
42 ³	42	58	76	82 (b) (4)
48 ⁴	21	60	74	85 (b) (4)

Table 22: Dissolution Data for Testosterone Undecanoate **158 mg** Capsules
Lot Number **1132167** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ³ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	89	89	89	89 (b) (4)
3 ²	87	87	87	87 (b) (4)
6	87	87	87	87 (b) (4)
9	87	88	88	88 (b) (4)
12	86	88	88	88 (b) (4)
18	84	86	86	86 (b) (4)
24	83	84	84	85 (b) (4)
30	86	88	88	88 (b) (4)
36	87	88	88	88 (b) (4)
42	84	87	87	87 (b) (4)
48	71	87	87	87 (b) (4)

Table 23: Dissolution Data for Testosterone Undecanoate **158 mg** Capsules
Lot Number **1229306** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	90	92	91	92 (b) (4)
2	89	92	92	92 (b) (4)
3	87	91	91	91 (b) (4)
6	84	86	86	86 (b) (4)
9	90	92	92	92 (b) (4)
12	89	89	89	89 (b) (4)
18	90	90	90	91 (b) (4)
24	90	91	91	91 (b) (4)
30	87	88	88	88 (b) (4)
36	81	87	88	88 (b) (4)
42	83	84	85	86 (b) (4)
48	58	83	84	86 (b) (4)

Table 24: Dissolution Data for Testosterone Undecanoate **158 mg** Capsules
Lot Number **1292379** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	90	95	95	95 (b) (4)
2	98	98	98	99 (b) (4)
3	98	97	97	97 (b) (4)
6	93	93	91	93 (b) (4)
9	95	95	95	95 (b) (4)
12	94	94	95	94 (b) (4)
18	91	91	91	92 (b) (4)
24	88	89	89	89 (b) (4)
30	88	89	89	89 (b) (4)
33	89	89	90	90 (b) (4)
36	85	87	87	87 (b) (4)
42 ¹	87	89	89	89 (b) (4)

Table 25: Dissolution Data for Testosterone Undecanoate **158 mg** Capsules
Lot Number **1386798** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	87	89	89	89 (b) (4)
2	87	90	90	90 (b) (4)
3	87	88	89	89 (b) (4)
6	88	90	90	91 (b) (4)
9	86	88	88	88 (b) (4)
12	83	88	88	88 (b) (4)
18	85	85	85	85 (b) (4)
24	72	77	77	77 (b) (4)
30	75	85	87	87 (b) (4)
36	74	83	83	84 (b) (4)
42	81	85	86	86 (b) (4)

Table 26: Dissolution Data for Testosterone Undecanoate **158 mg** Capsules
Lot Number **1487311** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	94	95	95	95 (b) (4)
2	92	93	95	96 (b) (4)
3	97	93	95	96 (b) (4)
6	95	96	96	96 (b) (4)
9	94	94	94	94 (b) (4)
12	90	95	96	96 (b) (4)
18	91	96	96	96 (b) (4)
24	91	91	91	91 (b) (4)

Table 27: Dissolution Data for Testosterone Undecanoate **158 mg** Capsules
Lot Number **1487312** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	94	97	97	96 (b) (4)
2	94	97	96	97 (b) (4)
3	95	97	97	98 (b) (4)
6	96	97	98	98 (b) (4)
9	93	94	95	96 (b) (4)
12	89	98	98	98 (b) (4)
18	87	94	95	95 (b) (4)
24	90	91	91	91 (b) (4)

Table 28: Dissolution Data for Testosterone Undecanoate **158 mg** Capsules
Lot Number **1487313** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	93	94	94	95 (b) (4)
2	95	97	97	97 (b) (4)
3	97	98	97	94 (b) (4)
6	97	98	98	98 (b) (4)
9	92	94	95	96 (b) (4)
12	96	97	97	98 (b) (4)
18	92	96	95	94 (b) (4)
24	87	90	90	91 (b) (4)

Table 29: Dissolution Data for Testosterone Undecanoate **237 mg** Capsules
Lot Number **1077193** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ⁴ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	85	87	87	88 (b) (4)
9 ²	84	84	84	84 (b) (4)
12	83	84	84	84 (b) (4)
15.5	88	91	91	91 (b) (4)
18	86	87	87	87 (b) (4)
24	90	91	91	91 (b) (4)
30	85	87	87	87 (b) (4)
36	76	88	89	89 (b) (4)
42 ³	63	80	87	87 (b) (4)
48	51	75	82	83 (b) (4)

Table 30: Dissolution Data for Testosterone Undecanoate **237 mg** Capsules
Lot Number **1131846** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ³ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	88	90	90	90 (b) (4)
3 ²	87	87	87	87 (b) (4)
6	85	86	86	86 (b) (4)
9	89	89	90	90 (b) (4)
12	89	87	87	87 (b) (4)
18	84	86	86	86 (b) (4)
24	84	85	84	83 (b) (4)
30	88	87	87	87 (b) (4)
36	87	88	88	88 (b) (4)
42	87	87	87	87 (b) (4)
48	87	88	88	88 (b) (4)

Table 31: Dissolution Data for Testosterone Undecanoate **237 mg** Capsules
Lot Number **1229307** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	93	93	94	93 (b) (4)
2	91	92	92	92 (b) (4)
3	84	86	87	87 (b) (4)
6	88	88	89	89 (b) (4)
9	84	85	85	85 (b) (4)
12	87	87	88	88 (b) (4)
18	89	88	89	89 (b) (4)
24	90	90	90	90 (b) (4)
30	85	86	86	86 (b) (4)
36	87	88	88	88 (b) (4)
42	82	81	82	81 (b) (4)
48	75	81	81	82 (b) (4)

Table 32: Dissolution Data for Testosterone Undecanoate **237 mg** Capsules
Lot Number **1292380** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	15 Min	30 Min	45 Min	60 Min
0	96	99	99	99 (b) (4)
2	97	98	97	97 (b) (4)
3	97	97	97	97 (b) (4)
6	97	97	97	97 (b) (4)
9	96	96	96	96 (b) (4)
12	95	95	96	96 (b) (4)
18	94	93	94	94 (b) (4)
24	89	90	91	91 (b) (4)
30	88	90	90	90 (b) (4)
33	88	90	91	91 (b) (4)
36	87	87	88	88 (b) (4)
42	88	90	90	90 (b) (4)

Table 33: Dissolution Data for Testosterone Undecanoate **237 mg** Capsules
Lot Number **1386799** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	88	90	90	90 (b) (4)
2	87	89	89	89 (b) (4)
3	89	91	92	92 (b) (4)
6	89	88	89	89 (b) (4)
9	86	87	87	87 (b) (4)
12	80	88	89	88 (b) (4)
18	77	82	84	85 (b) (4)
24	75	78	78	78 (b) (4)
30	75	85	87	87 (b) (4)
36	81	83	83	83 (b) (4)
42	84	86	86	86 (b) (4)

Table 34: Dissolution Data for Testosterone Undecanoate **237 mg** Capsules
Lot Number **1487314** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	97	96	95	97 (b) (4)
2	91	91	92	92 (b) (4)
3	97	97	97	97 (b) (4)
6	96	95	95	96 (b) (4)
9	97	97	97	96 (b) (4)
12	95	96	96	97 (b) (4)
18	85	94	94	94 (b) (4)
24	84	90	90	90 (b) (4)

Table 35: Dissolution Data for Testosterone Undecanoate **237 mg** Capsules
Lot Number **1487315** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	97	97	97	97 (b) (4)
2	94	95	95	95 (b) (4)
3	93	94	95	95 (b) (4)
6	94	93	94	96 (b) (4)
9	93	95	94	94 (b) (4)
12	94	95	95	95 (b) (4)
18	91	94	94	94 (b) (4)
24	91	89	91	90 (b) (4)

Table 36: Dissolution Data for Testosterone Undecanoate **237 mg** Capsules
Lot Number **1487316** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	99	98	99	99 (b) (4)
2	91	93	93	93 (b) (4)
3	91	92	93	93 (b) (4)
6	89	91	92	93 (b) (4)
9	91	96	96	96 (b) (4)
12	96	98	97	98 (b) (4)
18	90	94	94	94 (b) (4)
24	83	89	90	90 (b) (4)

Table 37: Dissolution Data for Testosterone Undecanoate **198 mg** Capsules
Lot Number **1507706** at 25°C/60 % RH (from M.3.2.P.8.3 of 06/22/2017 resubmission)

Months	Dissolution ¹ : Mean Percent Dissolved (Range)			
	15 Min	30 Min	45 Min	60 Min
0	97	99	99	99 (b) (4)
2	93	95	94	95 (b) (4)
3	98	99	100	100 (b) (4)
6	91	95	95	97 (b) (4)
9	93	95	95	95 (b) (4)
12	93	95	95	95 (b) (4)
18	93	94	96	96 (b) (4)
24	87	92	93	93 (b) (4)

Primary Biopharmaceutics Reviewer Name and Date:

10/04/2017

Mei Ou, Ph.D.

Biopharmaceutics Reviewer

Division of Biopharmaceutics (DB), Branch III

Office of New Drug Products (ONDP)

Office of Pharmaceutical Quality (OPQ)

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

10/24/2017

Min Li, Ph.D.

Acting Biopharmaceutics Lead

Division of Biopharmaceutics (DB), Branch III

Office of New Drug Products (ONDP)

Office of Pharmaceutical Quality (OPQ)

Tertiary Reviewer Name and Date (and Tertiary Summary, as needed):

Kimberly W. Raines, Ph.D.

Acting Branch Chief

Division of Biopharmaceutics (DB), Branch III

Office of New Drug Products (ONDP)

Office of Pharmaceutical Quality (OPQ)



Kimberly
Raines

Digitally signed by Kimberly Raines

Date: 12/13/2017 10:30:09PM

GUID: 508da6fd000284a73fdbbe11d01b3132f



Mei
Ou

Digitally signed by Mei Ou

Date: 12/13/2017 02:37:53PM

GUID: 54ca9d7000073c57d2eb7cc6e42c05bb



Min
Li

Digitally signed by Min Li

Date: 12/21/2017 08:59:19AM

GUID: 5390b860000014ac1413f0693cdb1440



Juandria
Williams

Digitally signed by Juandria Williams

Date: 2/06/2018 09:01:09AM

GUID: 513b65ab0005b7cb48614cd3d341d717



Laurie
Nelson

Digitally signed by Laurie Nelson

Date: 2/01/2018 08:34:36AM

GUID: 5922f76e00c40bfb158ba986788152c0

MEMORANDUM

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

DATE: Oct 28, 2014

TO: NDA 206089/CMC Review #1
FROM: Hamid Shafiei, Ph.D., CMC Reviewer
(ONDQA Division II/Branch IV)

THROUGH: Moo-Jhong Rhee, Ph.D., Chief, Branch IV
(ONDQA Division II)

SUBJECT: **Final Recommendation**

The previous CMC Review #1, dated 9/25/2014, made a recommendation of not approval of this NDA because of the following unresolved issues:

1. The Office of Compliance has not made a final recommendation of “Acceptable” for all facilities involved in this application.
2. Label/labeling issues identified in the application have not been resolved satisfactorily.

On 10/28/2014, the Office of Compliance has issued an overall “Acceptable” recommendation (see the **Attachment**).

However, the resolution of label/labeling issues has been deferred to the next review cycle.

Recommendation:

From the ONDQA perspective, this NDA is **not** recommended for approval in its present form, per 21 CFR 314.125(b)(6).

Attachment:

Last Milestone	Com pian ce statu s	Milestone Date	OAI Alert Status	EER Re- eval Date	Overall Recommen dation	Decision Date	Overall Re-eval Date
OC RECOMMENDATION	AC	1/30/2014	**NONE* *	6/20/2016	Acceptable	10/28/2014	12/30/2015
OC RECOMMENDATION	AC	2/3/2014	**NONE* *	12/30/2015	Acceptable	10/28/2014	12/30/2015
OC RECOMMENDATION	AC	1/31/2014	**NONE* *	2/14/2016	Acceptable	10/28/2014	12/30/2015
OC RECOMMENDATION	AC	4/7/2014	**NONE* *	4/3/2017	Acceptable	10/28/2014	12/30/2015
OC RECOMMENDATION	AC	2/3/2014	**NONE* *	1/15/2018	Acceptable	10/28/2014	12/30/2015
OC RECOMMENDATION	AC	1/31/2014	**NONE* *	11/25/2017	Acceptable	10/28/2014	12/30/2015
OC RECOMMENDATION	AC	10/28/2014	**NONE* *	8/1/2017	Acceptable	10/28/2014	12/30/2015

Hamid Shafiei -A

Digitally signed by Hamid Shafiei -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Hamid Shafiei -A, 0.9.2342.19200300.100.1.1=2000350820
Date: 2014.10.28 16:32:31 -04'00'

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Moojhong Rhee -S,
0.9.2342.19200300.100.1.1=1300041261
Date: 2014.10.28 16:45:23 -04'00'

NDA 206089

Rextoro[®] (testosterone undecanoate) Capsule

Clarus Therapeutics, Inc.

Hamid R. Shafiei, Ph.D.

Review Chemist

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

**CMC REVIEW
For the Division of Reproductive, Urology, and Bone Product**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 206089
2. REVIEW #: 1
3. REVIEW DATE: 25-Sep-2014
4. REVIEWER: Hamid R. Shafiei, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	01/03/2014
Correspondence (C)	
Amendment (BC)	02/04/2014
Amendment (BC)	04/21/2014

7. NAME & ADDRESS OF APPLICANT:

Name: Clarus Therapeutics, Inc.
Address: 555 Skokie Blvd, Suite 340
Northbrook, Illinois 60062

Representative: Robert E. Dudley, Ph.D., President and CEO
Telephone: (847) 562-4300
rdudley@clarustherapeutics.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Rextoro Soft Gelatin Capsule, 158mg and 237mg
- b) Non-Proprietary Name: Testosterone Undecanoate
- c) Code Name/# (ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 2
 - Submission Priority: S

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

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Testosterone Replacement in Male

11. DOSAGE FORM: Capsule (soft gelatin)

12. STRENGTH/POTENCY: 158mg and 237mg

13. ROUTE OF ADMINISTRATION: Oral

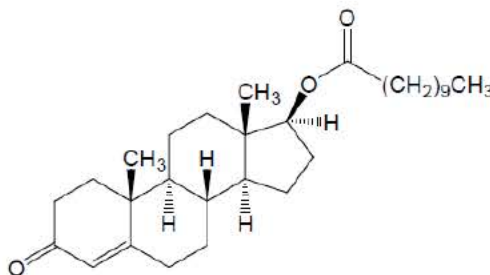
14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

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

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

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



Testosterone Undecanoate

Empirical Formula: $C_{30}H_{48}O_3$

Molecular Weight: 456.70

CAS Number: 5949-44-0

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)	(b) (4)	3	Adequate	12/16/2013	Reviewed by Hitesh Shroff, Ph.D.
	II			1	Adequate	09/05/2014	Reviewed by Hamid Shafiei, Ph.D.
	II			1	Adequate	09/05/2014	Reviewed by Hamid Shafiei, Ph.D.
	II			4			
	III			4			

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		
NDA		

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Approval	9/18/14	Kelly Kitchens, Ph.D.
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	N/A		
EA	Categorical exclusion (see review)		
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 206089

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product, Rextoro® (testosterone undecanoate) soft gelatin capsules 158mg, 237mg.

However, the Office of Compliance has *not* made an overall “Acceptable” recommendation regarding the facilities involved in this NDA.

Also label/labeling issues identified have *not* been satisfactorily resolved.

Therefore, from the ONDQA perspective, this NDA is *not* ready for approval in its present form, per 21 CFR 314.125(b)(6) & (13).

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

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance, testosterone undecanoate (TU) is the undecanoic ester of testosterone. This drug substance has been developed to facilitate the formulation of an oral dosage form for the treatment patients needing testosterone replacement therapy. This drug substance is a non-hygroscopic white crystalline powder. It has 6 chiral centers and its configuration is confirmed by specific optical rotation of +68° to +72°. It has a melting range of 60°C to 63°C (b) (4)

This active ingredient is very soluble in chloroform, freely soluble in benzene and acetone, soluble in methanol and isopropanol, sparingly soluble in ethanol, slightly soluble in vegetable oil, and insoluble in water.

Executive Summary Section

There are two proposed drug substance manufacturers in this application, (b) (4) and (b) (4) manufacturing process is provided in DMF (b) (4) and (b) (4) manufacturing process is provided in DMF (b) (4)

Both manufactures' drug substance release specification for testosterone undecanoate includes testing and acceptance criteria for appearance, identity, specific rotation, melting range, assay, related substances (related impurities), residual solvents, loss on drying (water content), and residue on ignition. In addition, (b) (4) drug substance release specification includes testing and acceptance criteria for heavy metals, (b) (4) acidity, and microbial limits. The drug product manufacturer, (b) (4) also tests and accepts each batch of drug substance according to the manufacturers' specifications prior to release for use in product manufacturing. The drug substance specifications proposed by both manufacturers adhere to ICH Q3A and Q3C guidelines. Therefore, the proposed drug substance specification is considered adequate.

Based on the supporting stability data, (b) (4) has assigned a re-test period of (b) (4) months for testosterone undecanoate manufactured at (b) (4) manufacturing site. However, due to limited available stability data, (b) (4) has assigned a re-test period of (b) (4) months for testosterone undecanoate manufactured at (b) (4) manufacturing site. Both proposed re-test dates are adequately supported by the stability data provided.

In general the drug substance, testosterone undecanoate produced by both manufacturers, (b) (4) and (b) (4) is adequate for use in the manufacture of the drug product Rextoro (testosterone undecanoate) soft gelatin capsules.

(2) Drug Product

The drug product Rextoro[®] (testosterone undecanoate) is formulated as soft gelatin capsules at two strengths of 158mg (100mg testosterone equivalent) and 237mg (150mg testosterone equivalent) for oral administration. This drug product is intended for the treatment of patients requiring testosterone replacement therapy. Both capsules are manufactured from a (b) (4) formulation. Testosterone undecanoate 158mg capsules are red with the capsule fill weight of (b) (4) mg, and 237mg capsules are orange with capsule fill weight of (b) (4) mg. These soft gelatin capsules are imprinted with 158mg or 237mg in white ink on the opaque capsules. (b) (4) capsules are packaged into an appropriately sized wide mouth round white HDPE bottle with a child resistant closure and induction seal (250CC HDPE bottles for 158mg soft gelatin capsules and 400CC HDPE bottles for 237mg soft gelatin capsules).

Executive Summary Section

Capsule (b) (4) formulation contains (b) (4)% testosterone undecanoate as the active ingredient and (b) (4)% oleic acid, NF, EP, (b) (4)% borage seed oil, (b) (4)% pepper mint oil, NF, FCC, (b) (4)% polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), NF, and (b) (4)% butylated hydroxytoluene (BHT), NF, EP.

The soft gelatin capsule shells are manufactured from Gelatin (b) (4). The capsule shells also contain sorbitol (b) (4), glycerin (b) (4), and purified water, appropriate colorant, and imprinting ink. All excipients used in the manufacture of the drug product are compendial with exception of borage seed oil. Although borage seed oil is considered a non compendial excipient, it is used in currently marketed dietary supplements. Furthermore, borage seed oil is tested and accepted according to a well-established specification. Therefore, the use of borage seed oil in the formulation of this drug product is deemed acceptable.

The proposed drug product specification includes testing and acceptance criteria for appearance, identity, assay, related substances (degradation impurities), dissolution, uniformity of dosage unit (content uniformity), and microbial limits. The proposed drug product specification including dissolution (Biopharm's Review dated 9/18/14) is considered adequate to assure identity, strength, purity, and quality of the drug product.

Based on the long-term stability results from the registration batches of drug product and its statistical analysis per ICH guideline, an expiration dating period of 30 months has been assigned to Rextoro[®] (testosterone undecanoate) soft gelatin capsules of 158mg and 237mg. The proposed expiration dating period is considered acceptable.

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

The drug product Rextoro[®] (testosterone undecanoate) soft gelatin capsules 158mg and 237mg are formulated for oral administration in patients requiring testosterone replacement therapy. The recommended starting dose is 200mg of testosterone taken orally as two 158mg testosterone undecanoate soft gelatin capsules twice daily. 158mg soft gelatin capsules are red and imprinted with 158 using a white ink on the opaque capsules. (b) (4) soft gelatin capsules (158mg strength), are packaged in 250CC wide-mouth round white HDPE bottles with a child-resistant cap and induction liner. 237mg soft gelatin capsules are orange and imprinted with 237 using a white ink on the opaque capsules. (b) (4) soft gelatin capsules (237mg strength) are packaged in 400CC wide-mouth round white HDPE bottles with a child-resistant cap and induction liner.

C. Basis for Approvability or Not-Approval Recommendation

21 CFR 314.125 (b)(6)

- Label/labeling issues have not been resolved.

Executive Summary Section

21 CFR 314.125 (b)(13)

- The final “Acceptable” recommendation from the Office of Compliance is still “Pending”.

(see the **List of Deficiencies** on p. 81)

III. Administrative

A. Reviewer’s Signature:

(See appended electronic signature page)

Hamid R. Shafiei, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

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

C. CC Block: entered electronically in DFS

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

CMC Assessment Section

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section

(b) (4) (testosterone undecanoate) (b) (4) capsules (b) (4)

Evaluation:

Item	Comments on the Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	The proprietary name, (b) (4) is provided but the established name, testosterone undecanoate is missing. Unsatisfactory
Dosage form, route of administration	Dosage form, soft gelatin capsule is missing but the route of administration, for oral use is provided. Unsatisfactory
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (201.57(a)(8))	
	(b) (4)
	Not a standard language for declaring the strength. Unsatisfactory
Whether the drug product is scored	N/A

The following comments should be conveyed to the applicant.

- Correct the product name to (b) (4)
- Revise dosage form and strengths to (b) (4)

CMC Assessment Section

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths

(b) (4)

Evaluation:

Item	Comments on the Information Provided in NDA
Available dosage forms	(b) (4) capsules Satisfactory
Strengths: in metric system	158mg and 237mg Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	(b) (4) Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not provided in this section Unsatisfactory

The following comments should be conveyed to the applicant.

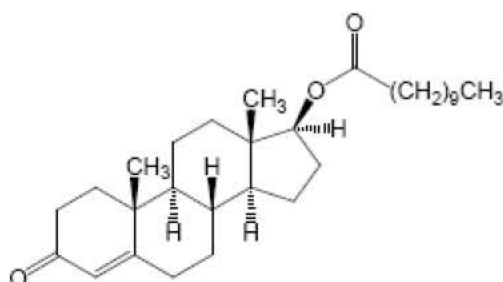
- Include the description of the drug product.
 - 158mg capsules are red imprinted with 158 in white ink
 - 237mg capsules are orange imprinted with 237 in white ink

CMC Assessment Section

#11: Description

(b) (4)

(b) (4)
 Testosterone undecanoate is a white to off-white yellow crystalline powder (b) (4)



[Drug Substance, Section 3.2.S.1.2]

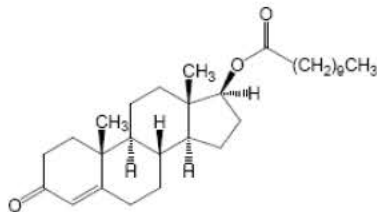
(b) (4) oleic acid, polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), borage seed oil, peppermint oil, and butylated hydroxytoluene.

(b) (4) gelatin, sorbitol, glycerin, purified water, iron oxide red, FD&C Yellow #6, and titanium dioxide. [Drug Product, Section 3.2.P.2]

Evaluation:

Item	Comment on the Information Provided in NDA
Proprietary name and established name	(b) (4) contains testosterone undecanoate Satisfactory
Dosage form and route of administration	Not provided in this section Unsatisfactory
Active moiety expression of strength with equivalence statement (if applicable)	Not provided in this section Unsatisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	➤ (b) (4) oleic acid, polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), borage seed oil, peppermint oil, and butylated hydroxytoluene. ➤ (b) (4)

CMC Assessment Section

	(b) (4) gelatin, sorbitol, glycerin, purified water, iron oxide red, FD&C Yellow #6, and titanium dioxide. Satisfactory
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Not provided in this section. Unsatisfactory
Chemical name, structural formula, molecular weight	Testosterone undecanoate is a white to off-white yellow crystalline powder (b) (4)  Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	(b) (4) Testosterone undecanoate is a white to off-white yellow crystalline powder. Satisfactory

The following comments should be conveyed to the applicant.

- Provide dosage form and route of administration.
- Provide active moiety expression of strength with equivalence statement.
- Provide pharmacological/ therapeutic class for the drug product.

#16: How Supplied/Storage and Handling

(b) (4)

Keep (b) (4) out of reach of children.

(b) (4). [Drug Product, Section 3.2.P.8.1]

CMC Assessment Section

Evaluation:

Item	Comments on the Information Provided in NDA
Strength of dosage form	Strengths are given as (b) (4). This is incorrect. The actual capsule strengths are 158mg and 237mg. Unsatisfactory
Available units (e.g., bottles of 100 tablets)	Not provided.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Capsule imprinting is incorrect. NDC number is provided. Unsatisfactory
Special handling (e.g., protect from light)	N/A
Storage conditions	(b) (4) Unsatisfactory
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Marketed by: Clarus Therapeutics, Inc. 555 Skokie Blvd., Suite 340 Northbrook, IL 60062, USA Manufacturer is not provided. Unsatisfactory

The following comments should be conveyed to the applicant.

- Correct the capsule strengths from (b) (4) to 158mg and 237mg.
- Provide number capsules per bottles, bottles sizes, and number of bottles packaged per shipping cartons.
- Correct the capsule imprinting to 158 and 237.
- Correct the storage condition to “Store at 20° to 25°C (68° to 77°F) with excursions permitted to 15° to 30°C (59° to 86°F)”.
- Provide the manufacturer’s information.

CMC Assessment Section

2. Immediate container labelsEvaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)))	Provided. Satisfactory
Dosage strength	Provided. But need to provide active moiety expression of strength with equivalence statement. Unsatisfactory
Net contents	Provided. Satisfactory
“Rx only” displayed prominently on the main panel	Displayed. Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	Displayed Satisfactory
Lot number and expiration date (21 CFR 201.17)	Displayed on the flap. Satisfactory
Storage conditions	Correctly displayed. Satisfactory
Bar code (21CFR 201.25)	Displayed. Satisfactory
Name of manufacturer/distributor	Provided. Satisfactory
And others, if space is available	N/A

The following comments should be conveyed to the applicant.

- Provide active moiety expression of strength with equivalence statement.

CMC Assessment Section

- Add parenthesis on the established name.
Add the statement of presence of FD&C Yellow #6 on the label [per
CFR 201.20(a)

3. Shipping carton labeling

CMC Assessment Section



Item	Information Provided in NDA
Proprietary name, established name (font size, prominence)	Provided. Satisfactory
Dosage strength	Provided Satisfactory
Net quantity of dosage form	Provided. Satisfactory
"Rx only" displayed prominently on the main panel	Not applicable to the shipping carton.
Lot number and expiration date	Expiration date is provided. Lot number does not apply to shipping carton. Satisfactory
Storage conditions	Provided. Satisfactory
Bar code (21CFR 201.25)	Provided. Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	Provided. Satisfactory
Manufacturer/distributor's name	Not provided. Unsatisfactory
Quantitative ingredient information (injectables)	Not applicable.
Statement of being sterile (if applicable)	Not applicable.
"See package insert for dosage information"	Not applicable to the shipping carton.
"Keep out of reach of children" (Required for OTC)	Not applicable to the shipping carton.

CMC Assessment Section

in CFR. Optional for Rx drugs)	
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The following comments should be conveyed to the applicant.

- Add manufacturer/distributor's name to the shipping carton label.
- Add parenthesis on the established name.
- Add the statement of presence of FD&C Yellow #6 on the label [per CFR 201.20(a)]
- Provide active moiety expression of strength with equivalence statement.
- Storage temperature should be consistent with that of the container label

B. Environmental Assessment Or Claim Of Categorical Exclusion

Clarus Therapeutics, Inc. has requested for Categorical Exclusion from the environmental assessment analysis under 21.CFR.25.31(b). For detailed evaluation of categorical exclusion requested by Clarus, a consult request has been submitted to the ONDQA environmental assessment team. The supporting information regarding the request for the categorical exclusion was reviewed by Dr. James P. Laurenson. On July 10, 2014, Dr. Laurenson recommended that the categorical exclusion from the environmental assessment analysis be granted.

III. List Of Deficiencies**A. Regarding Labels and labeling:**

1) Package insert:

“Highlights” Section:

- Correct the product name to “(b) (4) (testosterone undecanoate) (b) (4) capsules for oral use.
- Revise dosage form and strengths to “(b) (4) is provided as 158mg and 237mg testosterone undecanoate soft gelatin capsules.

“Dosage Form and Strength” Section:

- Include the description of the drug product.
 - 158mg capsules are red imprinted with 158 in white ink
 - 237mg capsules are orange imprinted with 237 in white ink

“Description” Section:

- Provide dosage form and route of administration.

CMC Assessment Section

- Correct the product name to (b) (4) (testosterone undecanoate)”
- Provide active moiety expression of strength with equivalence statement.
- Revise and list the active ingredient in alphabetical order.
- Provide pharmacological/ therapeutic class for the drug product.

“How Supplied/Storage and Handling” Section:

- Correct the capsule strengths from (b) (4) to 158mg and 237mg.
- Provide number capsules per bottles, bottles sizes, and number of bottles packaged per shipping cartons.
- Correct the capsule imprinting to 158 and 237.
- Correct the storage condition to “Store at 20° to 25°C (68° to 77°F) with excursions permitted to 15° to 30°C (59° to 86°F)”.
- Provide the manufacturer’s information.

2) Container label:

- Add manufacturer/distributor's name to the shipping carton label.
- Add parenthesis on the established name.
- Add the statement of presence of FD&C Yellow #6 on the label [per CFR 201.20(a)]
- Provide active moiety expression of strength with equivalence statement.

3) Shipping carton label

- Add manufacturer/distributor's name to the shipping carton label.
- Add parenthesis on the established name.
- Add the statement of presence of FD&C Yellow #6 on the label [per CFR 201.20(a)]
- Provide active moiety expression of strength with equivalence statement.

B. Regarding GMP compliance:

- The Office of Compliance has not made a final recommendation on the facilities involved in this application.



CMC Assessment Section

IV. Attachments: EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 206089/000	Action Goal:	
Stamp Date:	03-JAN-2014	District Goal:	04-MAY-2014
Regulatory:	03-NOV-2014		
Applicant:	CLARUS 555 SKOKIE BLVD STE 340 NORTHBROOK, IL 60062	Brand Name:	TESTOSTERONE UNDECANOATE
Priority:		Estab. Name:	
Org. Code:	580	Generic Name:	
Application Comment:		Product Number; Dosage Form; Ingredient; Strengths	002; CAPSULE, SOFT GELATIN; TESTOSTERONE UNDECANOATE; 150MG 001; CAPSULE, SOFT GELATIN; TESTOSTERONE UNDECANOATE; 100MG
FDA Contacts:	H. SHAFIEI K. JENNINGS J. ROULE D. CHRISTNER	Prod Qual Reviewer Product Quality PM Regulatory Project Mgr Team Leader	3017962326 3017962919 3017963993 (HFD-580) 3017961341
Overall Recommendation:	PENDING PENDING PENDING	on 07-APR-2014 on 11-MAR-2014 on 30-JAN-2014	by EES_PROD by EES_PROD by EES_PROD



CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
Establishment Comment: (b) (4)
Profile: CAPSULES, SOFT GELATIN OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	30-JAN-2014				JENNINGSK
SUBMITTED TO DO INITIAL STATUS, CSG DP MANUFACTURER	31-JAN-2014	10-Day Letter			CAPACCIDANIC
DO RECOMMENDATION BASED ON THE INSPECTION THAT I CONDUCTED FROM SOFTGEL CAPSULES.	03-FEB-2014	(b) (4)		ACCEPTABLE	MTOLLON
OC RECOMMENDATION	03-FEB-2014			ACCEPTABLE	CAPACCIDANIC



CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE OTHER TESTER

Establishment Comment: THE RESPONSIBILITY AT THIS SITE IS DRUG SUBSTANCE TESTING FOR DRUG PRODUCT MANUFACTURING. (on (b) (4) by K. JENNINGS () 3017062019)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	30-JAN-2014				JENNINGSK
OC RECOMMENDATION	31-JAN-2014			ACCEPTABLE	CAPACCIDANIC



CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTEREstablishment Comment: THE RESPONSIBILITIES AT THIS SITE ARE RELEASE TESTING (EXCEPT FOR MICROBIAL TESTING) OF DRUG PRODUCT (BULK); STABILITY TESTING OF PACKAGED DRUG PRODUCT. (on 27-JAN-2014 by K. JENNINGS ())
3017962919)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	30-JAN-2014				JENNINGSK
SUBMITTED TO DO LAST INSPECTION CSG; WERE LABS SUFFICIENTLY COVERED TO SUPPORT CTL EER?	30-JAN-2014	10-Day Letter			DOBBINE
ASSIGNED INSPECTION TO IB PLEASE CONDUCT PRE-APPROVAL INSPECTION FOR THIS NDA, 206089 AND NDAS 206352 AND 205718.	10-FEB-2014	Product Specific and GMP Inspection			KDORAZIO
DO RECOMMENDATION THE INSPECTION OF THE FACILITY AND APPLICATION WAS CONDUCTED INSPECTION IS CLASSIFIED AS NAI FOR GMP AND NAI FOR PAI.	04-APR-2014	(b) (4)		ACCEPTABLE AND FOUND TO BE ACCEPTABLE. THE	MKLAPAL
OC RECOMMENDATION	07-APR-2014			ACCEPTABLE	SAFAAJAZIR



CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment Comment: THE RESPONSIBILITY AT THIS SITE IS PRIMARY CONTAINER PACKAGING.
ADDITIONAL CONTACT AT SITE: (b) (4) (on 29-JAN-2014 by K. JENNINGS ())
3017962919)

Profile: CAPSULES, SOFT GELATIN OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	30-JAN-2014				JENNINGSK
OC RECOMMENDATION	31-JAN-2014			ACCEPTABLE	CAPACCIDANIC

CMC Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

DMF No: (b) (4) AADA:

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

Establishment Comment: THE RESPONSIBILITIES OF THIS SITE ARE PRODUCTION OF DRUG SUBSTANCE, QUALITY RELEASE TESTING OF DRUG SUBSTANCE, AND STABILITY OF DRUG SUBSTANCE. (on 24-JAN-2014 by K. JENNINGS () 3017962919)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	30-JAN-2014				JENNINGSK
OC RECOMMENDATION	30-JAN-2014			ACCEPTABLE	IYERS

CMC Assessment Section

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

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

DMF No: AADA:

Responsibilities: (b) (4)

Establishment Comment: THE RESPONSIBILITY AT THIS SITE IS PRIMARY CONTAINER PACKAGING.
ADDITIONAL SITE CONTACT: (b) (4)
by K. JENNINGS () 3017962919

Profile: CAPSULES, SOFT GELATIN OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	30-JAN-2014				JENNINGSK
SUBMITTED TO DO INITIAL PROFILE, PACKAGING ONLY	31-JAN-2014	10-Day Letter			CAPACCIDANIC
DO RECOMMENDATION THE PAI/GMP INSPECTION OF THIS FIRM CONDUCTED (b) (4) IS BEING CLASSIFIED VAI AND THE INITIAL STATUS OF THE CSG PROFILE IS LISTED AS ACCEPTABLE. THE PROFILE WILL BE FINALIZED ONCE THE FACTS REPORT IS SET TO COMPLETE. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.	31-JAN-2014			ACCEPTABLE	VMATUSOV
OC RECOMMENDATION	03-FEB-2014			ACCEPTABLE	CAPACCIDANIC

CMC Assessment Section

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

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

DMF No: (b) (4) AADA:

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

Establishment Comment: THE RESPONSIBILITIES AT THIS SITE ARE: PRODUCTION OF DRUG SUBSTANCE, QUALITY RELEASE TESTING OF DRUG SUBSTANCE AND STABILITY OF DRUG SUBSTANCE. (on 29-JAN-2014 by K. JENNINGS () 3017962919)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	30-JAN-2014				JENNINGSK
OC RECOMMENDATION	30-JAN-2014			ACCEPTABLE	CAPACCIDANIC
SUBMITTED TO DO	11-MAR-2014	GMP Inspection			WILLIAMSJU
GMP EXPIRES 21-JUL-2014; PDUFA IS 03-NOV-2014.					
DO RECOMMENDATION	11-MAR-2014			ACCEPTABLE	TUNGL
INSPECTION CONDUCTED (b) (4) AND CLASSIFIED AS VAL. TESTOSTERONE UNDECANOATE AND CSN WAS COVERED.					
OC RECOMMENDATION	20-MAR-2014			ACCEPTABLE	WILSONT
SUBMITTED TO DO	07-APR-2014	Extension Request			SAFAAIJAZIR
PDUFA GOAL DATE: 03-NOV-2014.					
21-JUL-2011 + 3YRS FOR CSN = 21-JUL-2014 WHICH FALLS BEFORE THE GOAL DATE IN NOVEMBER.					
21-JUL-2015					
The DO is requested to clear the extension request unless the DO finds that the methods used in, or the facilities and controls used for the manufacture, processing and packing of the drug are inadequate to preserve its identity, strength, quality or purity.					
PDUFA GOAL DATE					
ASSIGNED INSPECTION TO IB	14-APR-2014	GMP Inspection			TUNGL
PDUFA 03-NOV-2014. WILL BE OVER 3 YEARS SINCE LAST INSPECTION. ASSIGN A GMP INSPECTION.					
INSPECTION SCHEDULED	23-MAY-2014		01-AUG-2014		MCHASEY

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

/s/

HAMID R SHAFIEI
09/25/2014

MOO JHONG RHEE
09/25/2014
Chief, Branch IV



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science**

Memorandum

Date: July 10, 2014

From: James P. Laurenson, OPS/ONDQA EA Staff

To: Hamid Shafiei, ONDQA Primary CMC Reviewer
Kerri-Ann Jennings, ONDQA PM
Donna Christner, ONDQA CMC Lead

Subject: NDA 206-089, Oral Testosterone Undecanoate (TU): Review of Claim for Categorical Exclusion

Sponsor: Clarus Therapeutics, Inc.
555 Skokie Blvd, Suite 340
Northbrook, IL 60062

A. Summary

Clarus Therapeutics, Inc. (Clarus) has submitted a new drug application (NDA) for oral testosterone undecanoate (TU). This product uses soft gelatin capsules for oral administration. Each capsule contains TU equivalent to either 100 mg or 150 mg testosterone per capsule. Oral TU is a pro-drug and is formulated to deliver pharmacological dosages of testosterone to hypogonadal men. The sponsor submitted a claim for categorical exclusion from an environmental assessment (EA) under 21 CFR 25.31(b). FDA responded by noting that while the estimated introductory concentration (EIC-aquatic) is less than the 1 ppb categorical exclusion level, published literature indicated that this product has the potential for harm to the environment at the expected level of exposure. The sponsor subsequently submitted an update of their claim for a categorical exclusion. FDA reviewed this information and has concluded that the categorical exclusion request, supplemented by information submitted to aid in determining whether extraordinary circumstances exist, is adequate. There is no information available indicating that additional environmental information is warranted for this application. The claim of categorical exclusion is accepted.

B. Background

Clarus has submitted NDA 206-089 for oral TU in soft gelatin capsules for oral administration. Each capsule contains TU equivalent to either 100 mg or 150 mg of testosterone per capsule. Oral TU is a pro-drug and is formulated to deliver pharmacological dosages of testosterone to hypogonadal men. In Environmental Impact for Testosterone

Undecanoate: Request for Categorical Exclusion (IND 78104; dated August 19, 2013), the sponsor submitted documentation regarding (1) a claim for categorical exclusion for this product under 21 CFR 25.31(b), which is for actions that increase the use of the active moiety but for which the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb); (2) that the action will not result in additional incidental exposure to testosterone in the human environment, and indeed may decrease the opportunity for incidental or unintended exposure of sensitive populations (e.g., women and children) to testosterone; (3) that the active ingredient is naturally found in the environment, and this formulation will not result in a biologically significant increased amount in the environment; and (4) that there are no known extraordinary circumstances, and that an environmental assessment (EA) would not be required.

FDA responded at the pre-NDA meeting (IND 78104; meeting letter date Nov 4, 2013) by noting that while the estimated introductory concentration (EIC-aquatic) is less than the 1 ppb categorical exclusion level, published literature indicated that this product has the potential for harm to the environment at the expected level of exposure (Thomas et al. 2002, Leon et al. 2007, Deksis 2008, Khan and Nicell 2010, Bellet et al. 2012, Hoffmann and Kloas 2012, USEPA 2012) and thus that the product might constitute an "extraordinary circumstance" under 21 CFR 25.21. While FDA agreed that the orally delivered formulation might decrease incidental or unintended human exposure, this could not necessarily be said of exposure to aquatic organisms, given the apparent increase in total use of the active moiety. Additional information thus was requested to demonstrate that this product will displace currently marketed testosterone products without significantly increasing environmental introductions of testosterone or metabolites. Furthermore, FDA noted that as described in Section II of the EA guidance (USFDA 1998) and in the preamble to 62 FR 40570 (July 29, 1997), information such as this, including the ratio of the predicted environmental concentration to the predicted no-effects concentrations (PEC/PNEC), could aid in determining whether extraordinary circumstances exist and thus whether the criteria for a categorical exclusion have been met.

In response to the pre-NDA meeting, the sponsor acknowledged that despite the fact that the EIC-aquatic for testosterone released as result of their product was calculated to be less than 1 ppb, the fact that testosterone is a potent hormone suggests that its impact on the aquatic environment needs to be considered in greater detail. The sponsor subsequently submitted an update of Environmental Impact for Testosterone Undecanoate: Request for Categorical Exclusion for an Environmental Assessment (Module 1.12.14; submission date 1/03/2014; report dated December 9, 2013). Therefore, the main goals of this review are to determine whether the claim for categorical exclusion and the statement regarding the lack of extraordinary circumstances is acceptable based on this update.

C. Review of Claim for Categorical Exclusion

Clarus states that the formulation of TU qualifies for a categorical exclusion for several reasons. Below are summaries of these reasons, with each reason followed by FDA responses in italics:

1. The EIC-Aquatic for testosterone is less than 1 ppb (calculated to be (b) (4) ppb). A more realistic, yet still very conservative EIC, would be (b) (4) ppb, which assumes that about (b) (4) % of the administered testosterone dose is excreted into the environment without metabolic conversion or in a metabolic form that is easily converted back to testosterone. The sponsor also notes that displacement of currently approved testosterone products by the sponsor's oral TU product would likely reduce the amount of testosterone released into the environment across all testosterone replacement products. *FDA: The calculations used by the sponsor appear to be correct. The value of (b) (4) ppb, however, should be used for the categorical exclusion, not the reduced value of (b) (4) ppb, because while metabolism is indeed expected to occur, no data are provided about the aquatic toxicity of the metabolic products. Thus, at least equivalent toxicity of these metabolic products with testosterone would need to be assumed. The claim that displacement of currently approved testosterone products by oral TU product would likely reduce the amount of testosterone released into the environment across all testosterone replacement products is unsubstantiated quantitatively. Nevertheless, the EIC of (b) (4) ppb is indeed less than 1 ppb, which satisfies the categorical exclusion of 21 CFR 25.31(b). The question then is whether this action—approval of NDA 206-089—constitutes extraordinary circumstances that indicate that this action may significantly affect the quality of the human environment.*
2. The active ingredient formed by TU (i.e., testosterone), is naturally found in the environment, and this formulation will not result in a biologically significant increase of testosterone in the environment. The various formulations of testosterone (in various drug delivery formats) are already on the market for hormone replacement therapy. Because an oral replacement formulation will likely have better patient acceptance, it is reasonable to expect that this product would replace, at least in part, the use of topically applied testosterone preparations. The sponsor also estimates that by the year 2019 (5 years after introduction of the product), (b) (4) of TU per year will be used as a result of this product's distribution, which is equivalent to about (b) (4) of testosterone. *FDA: The sponsor provides several compelling arguments and literature sources supporting their conclusion that testosterone is naturally found in the environment, and this formulation will not result in a biologically [emphasis added] significant increase of testosterone in the environment. This information, however, is not used to claim a categorical exclusion specifically under 21 CFR 25.31(c), which is for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products. This exclusion appears to be relevant only regarding the fact that testosterone occurs naturally in the environment. That is, while this product might not result in a biologically significant increase, the real question for this categorical exclusion, as noted also by the sponsor, is whether this product will alter significantly the concentration or distribution of testosterone or its metabolites or degradation products. In this case, (b) (4) of testosterone noted above is (b) (4) the current use of approximately (b) (4) (IMS 2014). Furthermore, the sponsor estimates a worst case PEC increase of (b) (4) %. This latter estimate appears to be based on a speculative "worst*

case” increase of testosterone use of (b) (4). Nevertheless, while some of the current testosterone use may be replaced by this product, even if all of it is replaced there would be an increased use and thus likely increased concentration of testosterone. Furthermore, any increased concentrations would occur downstream of sewage treatment plants (STPs) and thus would not be distributed evenly across surface waters. On the other hand, oral formulations, compared to topical formulations, would be expected to (a) undergo significantly more metabolism and (b) reduce wash-off introductions from topical formulations. Therefore, at this point it is not clear whether this product would “alter significantly the concentration or distribution of the substance, its metabolites, or degradation products” and thus would satisfy the 21 CFR 25.31(c) categorical exclusion.

3. The product will not result in additional incidental exposure to testosterone in the human environment, and that in fact the sealed soft gelatin capsule oral delivery system will decrease the opportunity for incidental or unintended exposure of sensitive populations. *FDA: While this claim may be true—and the sponsor provides several compelling arguments and literature sources supporting this claim—lower incidental exposure to humans does not mean that less testosterone will be used or that less will enter the aquatic environment.*

Clarus also provides several arguments supporting their statement that to the best of their knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment per 21CFR 25.15. In particular, Clarus provides a detailed review of the literature focusing on estimation of testosterone in surface water; calculation of risk quotient (PEC/PNEC) using projected annual production five year after introduction of the product; a review of the metabolism/excretion of TU in humans; agricultural contributions due to runoff from fields; and total androgen load in surface waters. Using the results for three different eco-toxicity assays that assessed chronic exposure, and involved three different taxa, the applicant estimated a Predicted No Effect Concentration (PNEC) for testosterone to be (b) (4) µg/L. The risk quotient data in particular show that the resulting estimated quotient due to this product would range up to approximately (b) (4) (b) (4) even with several worst-case assumptions. As a result, FDA would agree that testosterone introductions into the environment from approval of this application do not appear to pose a significant risk. Thus, while there clearly is some potential for hormonal activity from testosterone, there is little available data to establish that, at the expected level of exposure, there is the potential for serious harm to the environment from this action (21 CFR 25.21(a)).

D. Conclusions

FDA concludes that the categorical exclusion request, supplemented by information submitted to aid in determining whether extraordinary circumstances exist, is adequate. There is no information available indicating that additional environmental information is warranted in order to evaluate the claim of categorical exclusion. The claim of categorical exclusion is accepted.

E. References

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/s/

JAMES P LAURENSEN
07/10/2014

MEMORANDUM



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

DATE: 10 January 2014

TO: NDA 206089

FROM: Bryan S. Riley, Ph.D.
Team Leader (Acting)
OPS/New Drug Microbiology Staff

THROUGH: Stephen E. Langille, Ph.D.
Master Review Microbiologist
OPS/New Drug Microbiology Staff

cc: Jeannie Roule
Regulatory Project Manager
OND/DBRUP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for
REXTORO (Testosterone Undecanoate) Capsules [Submission Date:
3 January 2014]

The Microbial Limits specification for Rextoro (Testosterone Undecanoate) Capsules is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

REXTORO is a Soft Gelatin Capsule for oral administration.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

MEMORANDUM

Table 1 – Microbial Limits Specifications

Test	Acceptance Criteria
Total Aerobic Microbial Count (USP <61>)	NMT (b) (4) CFU/g
Total Yeast and Mold Count (USP <61>)	NMT (b) (4) CFU/g
<i>E. coli</i> (USP <62>)	Absent in (b) (4)

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will also be tested for Microbial Limits at 12, 18, 24, 30, 36 and 42 months as part of the post-approval stability protocol.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol.

END

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/s/

BRYAN S RILEY
01/13/2014

STEPHEN E LANGILLE
01/13/2014