

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208088Orig1s000

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 22, 2022
From: Hamid Shafiei, Ph.D.
Application Technical Lead, Branch IV
Division of New Drug Products 2
Office of New Drug Products

To: To Integrated Quality Assessment (IQA) # 4 of NDA 208088

Subject: Final Recommendation of Full Approval

In the IQA # 4 by the Application Technical Lead, Dr. Mark Seggel, dated August 24, 2020, this application was recommended for approval from the OPQ perspective. However, this application was tentatively approved on December 8, 2020, due to the period of patent protection and/or exclusivity of Jatenzo (testosterone undecanoate) oral capsules (NDA 206089). Since the exclusivity is to be expired on March 27, 2022, the applicant of this NDA resubmitted this application on January 28, 2022, requesting the full approval of this application.

This resubmission does not include any significant additional CMC information and the original recommendation of the approval of the application from the OPQ perspective which was captured in IQA # 4 dated August 24, 2020, remains unchanged. Therefore, from the OPQ perspective this application is recommended for full **approval**.

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

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/s/

HAMID R SHAFIEI
03/22/2022 03:36:37 PM

Memorandum

To: NDA 208088

From: Donna Christner, Ph.D.
DNDP/API II Branch Chief

Date: 31-May-2021

Re: Usage of Retested Drug Substance in Drug Product Manufacturing

Background

(b) (4)



(b) (4)

We recommend that you retest each batch of drug substance immediately prior to introducing it into the drug manufacturing process to confirm that it meets all appropriate specifications.

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/s/

DONNA F CHRISTNER
06/04/2021 11:32:43 AM

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 208088 TLANDO™ (testosterone undecanoate) capsules Assessment #4

Drug Product Name	Testosterone undecanoate capsules
Dosage Form	Capsule
Strength	112.5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Lipocine Inc., Salt Lake City, UT
US agent, if applicable	-
Application Type	505(b)(2)
NDA Classification Code*	Type 5, New applicant
Combination Product	na

* Previously referred to as the "Chemistry Classification Code."

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission after Complete Response (0066)	02/28/2020	Drug Substance, Drug Product, Labeling, OPMA, EA Team
Labeling (0068)	05/05/2020	Labeling
Quality Amendment (0070)	05/13/2020	Drug Product, OPMA
Quality Amendment (0071)	06/05/2020	OPMA
Labeling (Container Label) (0073)	07/22/2020	Drug Product, EA Team
Labeling (Container Label) (0074)	07/28/2020	Drug Product
Labeling (PI)	08/10/2020 (via email)	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeff Medwid	Donna Christner
Drug Product / Labeling	Mark Seggel (Hamid Shafiei)	Wendy Wilson (Moo-Jhong Rhee)
Manufacturing and Microbiology (OPMA)	James Norman (Juandria Williams [facilities])	Yubing Tang
Biopharmaceutics**	(Hansong Chen; Haritha Mandula)	(Vidula Kolhatkar)
RBPM	Marquita Burnett (Thao Vu)	
ATL	Mark Seggel	
Laboratory (OTR)	-	-
Environmental	Jim Laurenson	Scott Furness

* Review team from previous reviews cycles in ().

** Reviewer not assigned to 02/28/2020 resubmission.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

As resubmitted on February 28, 2020, Lipocine Inc.'s 505(b)(2) New Drug Application #208088 for TLANDO (testosterone undecanoate) capsules, 112.5 mg, is recommended for APPROVAL from the OPQ perspective.

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.

A 48-month expiration dating period for the drug product when stored at 20°C to 25°C has been granted.

As revised, product labeling complies with the requirements under 21 CFR 201.

The request for a categorical exclusion from an environmental assessment (EA), supplemented by information submitted by the applicant to aid in determining whether extraordinary circumstances exist, is accepted.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Testosterone undecanoate (TU) is a fatty acid ester of testosterone that is orally bioavailable. While attachment of the fatty acid side chain does not improve the aqueous solubility of testosterone, it facilitates absorption via the intestinal lymphatic system thus reducing first-pass metabolism in the liver. Once absorbed, the ester is cleaved by nonspecific esterases.

Testosterone undecanoate was first approved in the U.S. as AVEED, an injection for intramuscular administration, on March 5, 2014 (see NDA 022219). Note that the "Initial U.S. Approval" is considered 1953, the year in which Delatestryl (testosterone enanthate injection; NDA 009165), the first Orange Book-listed product with the active moiety 'testosterone,' was approved by the FDA.

Lipocine Inc. submitted NDA 208088 for testosterone undecanoate capsules, (b) (4) 112.5 mg, on August 28, 2015. (b) (4)

(b) (4) The drug product offers an alternative to the orally bioavailable but toxic alkylated testosterone derivative methyltestosterone, to the transdermal testosterone products and to other testosterone ester prodrugs formulated for subcutaneous or intramuscular administration (e.g., testosterone cypionate, testosterone enanthate, and testosterone undecanoate). The first oral testosterone undecanoate product, Clarus' JATENZO, was approved on under NDA 206089 on March 27, 2019.

Testosterone undecanoate is poorly soluble (less than 50 µg/mL) in water. TLANDO, an immediate-release drug product, is prepared as (b) (4) and the following excipients: (b) (4) (glyceryl monolinoleate; (b) (4)), polyoxyl 40 hydrogenated castor oil (b) (4) (b) (4) ascorbyl palmitate ((b) (4) and polyethylene glycol 8000 (b) (4) (b) (4)

Since the initial submission in 2015, NDA 208088 has received three Complete Response (CR) Letters due to clinical and clinical pharmacology deficiencies. While all deficiencies have been adequately resolved, the 3-year exclusivity granted to the recently approved JATENZO precludes full approval of NDA 208088. A tentative approval will therefore be issued.

A summary of submission and CMC review history is provided below.

Proposed Indication(s) including Intended Patient Population	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.
Duration of Treatment	As needed.
Maximum Daily Dose	225 mg testosterone undecanoate (2 x 112.5 mg capsules) taken twice daily with food.
Alternative Methods of Administration	Not applicable.

B. Quality Assessment Overview

Application and Review History

	Date	Comments
Original Submission	08/28/2015	• (b) (4) 112.5 mg capsules
IQA #1	06/02/2016	• 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. • 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. • The Biopharmaceutics review team has requested that Lipocine collect additional dissolution data using the revised methodology to confirm the interim acceptance criterion ($Q = 75\%$ at t_0 minutes).
CRL #1	06/28/2016	CR Issues: Clinical and clinical pharmacology Additional Comments: • Dissolution test – Generate and submit additional dissolution profile data using the FDA-recommended method on at least 6 production batches • Container and carton label revisions
Resubmission #1	08/08/2017	(b) (4) • Resubmission includes release dissolution data from 22 batches of the 112.5 mg strength (b) (4) that were manufactured in anticipation of product launch. Applicant agreed to perform previously requested dissolution testing.
Major Amendment	11/10/2017	Clock extended by 3 months
IQA #2	02/26/2018	• Labeling negotiations not completed; labeling does not comply with the requirements under 21 CFR 201 • Interim dissolution test acceptance criteria have been established. Lipocine agreed to provide additional dissolution profile data.
CRL #2	05/08/2018	CR Issues: Clinical and clinical pharmacology Additional Comments: • Applicant reminded of information request regarding dissolution testing dated November 30, 2017, and of their commitment dated December 8, 2017, to address the information request. • Comments regarding carton and container labeling
Resubmission #2	05/09/2019	
IQA #3	10/11/2019	• Labeling negotiations not completed • Sponsor has adopted recommended dissolution acceptance criteria • 48 months expiration dating period granted • EA cat. ex. supplemented to demonstrate no extraordinary circumstances
CRL #3	11/08/2019	Submit draft carton and container labeling based on your proposed revisions, dated September 16, 2019.
Resubmission #3	02/28/2020	
Amendment	05/13/2020	Request to (b) (4)

General Advice Ltr.	07/13/2020	Request to (b) (4) denied.
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Drug Substance: Adequate

No new drug substance information was provided in the February 28, 2020 NDA resubmission. The manufacture and control of testosterone undecanoate are documented in Type II DMF (b) (4) held by (b) (4). The DMF was last reviewed and found Adequate on September 24, 2019. That recommendation remains current. The NDA is recommended for APPROVAL from the drug substance CMC perspective. See the attached IQA Chapter 1.

Drug Product: Adequate

No new CMC information was included in the February 28, 2020 resubmission. The application continues to be recommended for APPROVAL from the Drug Product Perspective.

May 13, 2020 submission (SN 0070)

In anticipation of approval the original August 28, 2015 application and subsequent commercial launch, the Applicant manufactured 21 bulk capsule lots in May/June 2016. (b) (4) dissolution data for 22 batches were submitted in the August 8, 2017 resubmission (SN 0026) but no other information about these batches were provided. In the May 2020 submission, the Applicant requested that the Agency

(b) (4)

(b) (4)

Environmental Assessment: Adequate

The EA Team previously determined 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. Furthermore, a statement of no extraordinary circumstances was provided. The claim of categorical exclusion is accepted.” See IQA #1 for details.

Labeling: Adequate

Labeling negotiations were not completed during any of the 3 previous review cycles because clinical and clinical pharmacology deficiencies with the application precluded further action.

Nevertheless, the labeling (prescribing information and bottle) was reviewed from the CMC perspective. Deficiencies and recommendations were identified (see IQAs 1-3); comments were conveyed to the Applicant. During the current review cycle, and in collaboration with DMEPA and the DUOG labeling review team, revisions to sections 3, 11 and 16 of the prescribing information (PI) and to the bottle label were proposed. The EA Team provided language regarding product disposal to the bottle label, PI section 16 and Medication Guide.

The bottle label submitted July 28, 2020 (SN 0074) incorporates all Agency recommendations and conforms to the requirements of 21 CFR 201.

All recommended revisions to sections 3, 11 and 16 of the PI were incorporated in the draft version submitted by the Applicant via an August 10, 2020 email. As revised, the PI conforms to the requirements of 21 CFR 201.

See attached IQA Chapter IV, Labeling for final labeling.

Manufacturing: Adequate

The Status of the OPMA Review task for NDA-208088-ORIG-1-RESUB-67 was marked as ‘No Action Indicated’ in Panorama on April 1, 2020. The OPMA review team provided the following note for this task:

Review Recommendation: Adequate

Comments: There are no changes to the facilities and no new quality information in the 02/28/2020 resubmission.

The June 5, 2020 (SN 0071) amendment provides a corrected street address for the (b) (4) contract testing laboratory. This has no impact on the overall facilities status recommendation (below).

An 'Overall Manufacturing Inspection Recommendation' of APPROVE was issued on July 23, 2020 (see Attachment 1, Latest Submission Manufacturing Status).

Biopharmaceutics: Adequate

See IQAs #1, #2 and #3 for discussion of the development of the Sponsor's proposed method (including (b) (4)% Triton-X-100) and acceptance criteria ($Q = (b) (4)\%$ in (b) (4) minutes - considered too liberal).

Agreement on the following dissolution test method and acceptance criteria is documented in IQA #3.

USP Apparatus 2 (Paddle) at 100 rpm (b) (4)
Tier I medium: 1000 mL 1% Triton-X-100 in DI Water.
Tier II 1% Triton-X-100 medium plus Enzymes (<75,000 units/L pepsin)

Acceptance Criteria:

30 min: (b) (4) %

75 min: NLT (b) (4) %

The Status of the Biopharmaceutics Review task for NDA-208088-ORIG-1-RESUB-67 was marked as 'No Action Indicated' in Panorama on March 31, 2020.

Microbiology (if applicable): Adequate

The Status of the Microbiology Review task for NDA-208088-ORIG-1-RESUB-67 was marked as 'No Action Indicated' in Panorama on April 1, 2020. The OPMA review team provided the following note for this task:

Review Recommendation: Adequate

Comments: No new quality information in the 02/28/2020 resubmission

CDRH: (if applicable): Choose an item.

Not Applicable

C. Risk Assessment

From Initial Risk Identification			Review Assessment			
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments	
Appearance	• Process • Stability	L	(b) (4)	Acceptable	None.	
Identification	• CGMPs	L		Acceptable	None	
Assay	• Formulation • Raw materials • Process	L		Acceptable	None	
Related Substances Impurities/ Degradants	• Formulation • Raw materials • Process • Container Closure System	L		Acceptable	Potential impact of process conditions. (b) (4)	
				(b) (4)		
Uniformity of Dosage Units	• Formulation • Process	L		(b) (4)	Acceptable	Potential impact of process conditions.
Dissolution	• Raw materials • Formulation • Process	M			Acceptable	Potential impact of process conditions. (b) (4)
Microbial limits	• Raw materials • Process	L	Acceptable		None	

See Risk Assessment under IQA #2

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

na

2. Drug Substance Deficiencies

na

3. Drug Product Deficiencies

na

4. Labeling Deficiencies

na

5. Manufacturing Deficiencies

na

6. Biopharmaceutics Deficiencies

na

7. Microbiology Deficiencies

na

8. Other Deficiencies (Specify discipline, such as Environmental)

na

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Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D.
Application Technical Lead
OPQ/ONDP/DNDPII/Br4

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QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	J. Medwid 09/24/19	Assessment remains current

See IQA #2 for complete list of DMFs cited. Sufficient information has been submitted in the NDA and review of these DMFs is not needed.

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Application Number	Document(s)	Description
IND 106476	All	Lipocine IND for Oral TU

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Nonclinical	na			
CDRH-OPEQ	na			
Clinical	na			
Other	na			

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product (*see IQAs 1 - 3*)

CHAPTER III: Environmental Assessment (*see IQAs 1 - 3*)

CHAPTER IV: Labeling

CHAPTER V: Manufacturing Integrated Assessment (*see IQAs 1 - 3*)

CHAPTER VI: Biopharmaceutics (*see IQAs 1 - 3*)

CHAPTER VII: Microbiology (*see IQAs 1 - 3*)

CHAPTER VIII: Additional Quality Disciplines (*not applicable*)

Attachment 1. Latest Submission Manufacturing Status



Mark
Seggel

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CHAPTER IV: LABELING

Background: Refer to OPQ IQAs #1-3 for Hamid Shafiei's reviews of the CMC-related sections of the labeling (Prescribing Information and bottle). Labeling negotiations were not completed during the first three review cycles. However, some comments were conveyed to the Applicant. During the current review cycle, further revisions were made to the PI and to the bottle label to bring the labeling into conformance with the labeling requirements under 21 CFR 201.

The Applicant has agreed to the following Prescribing Information text and bottle label.

(b) (4)



(b) (4)

Assessment of Product Quality Related Aspects of Prescribing Information: {Adequate}

The original labeling included

(b) (4)

(b) (4) These statements are not relevant to this ester product and may be misleading by implying (b) (4). At the review team's request these statements were removed. The (b) (4) were re-introduced in the latest resubmission but have once again been removed as requested.

Minor changes were made to the content and format of Section 11, Description. Section 16 was revised to conform with the requirements of 21 CFR 201 and for consistency with the Agency's Labeling Review Tool.

Revised Prescribing Information was submitted via email on August 10, 2020. Formal submission of the PI is pending.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): {Adequate}

A Medication Guide is to be dispensed to each patient. OPQ recommended inclusion of the following:

- The inactive ingredients in TLANDO capsules are ascorbyl palmitate, glyceryl monolinoleate, polyethylene glycol 8000, and polyoxyl 40 hydrogenated castor oil. The capsule shell contains black iron oxide, gelatin, and titanium dioxide. The capsule is imprinted with black ink that contains ammonium hydroxide, black iron oxide, propylene glycol, and shellac. [This based on the revised text in Section 11, Description.]
- Store TLANDO at room temperature between 68°F to 77°F (20°C to 25°C). [The applicant proposed, (b) (4)]

The patient labeling review team independently made the same revisions to the Medication Guide.

The EA Team recommended the following language regarding disposal:

- How should I dispose of TLANDO?
 - Dispose of unused TLANDO via a take-back option.

- If a take-back option is unavailable, follow FDA instructions at www.fda.gov/drugdisposal for disposing of medicine (b) (4)

- (b) (4)

These disposal instructions have been added to the Agency's recommended revisions to Medication Guide.

It is anticipated that all recommended revisions to the Medication Guide will be adopted by the Applicant.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

Container Label (0074, 07/28/2020)

(b) (4)

3.2 Carton Labeling

Not applicable.

Assessment of Carton and Container Labeling: {Adequate}

The most recent modifications to the bottle label include revision of the storage statement to include the range 20°C to 25°C and other edits (replace (b) (4) with "to", each temperature followed by degree symbol and units) and inclusion of the statement, "Do NOT flush unused product," as requested by the EA Team.

As revised, the bottle label meets the labeling requirements under 21 CFR 201.

ITEMS FOR ADDITIONAL ASSESSMENT

Not Applicable

Overall Assessment and Recommendation:

As revised the, the prescribing information and bottle label are accurate and satisfy the requirements under 21 CFR 201. Although the final revised Medication Guide is pending, it is anticipated that all revisions recommended by the EA Team and the patient labeling review team will be adopted.

NDA 208088 is therefore recommended for APPROVAL from the product quality labeling perspective.

Mark R. Seggel, Ph.D.
Application Technical Lead
OPQ/ONDP/DNDPII/Br4

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Seggel

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/s/

MARK R SEGCEL
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RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 208088 TLANDO (testosterone undecanoate) capsules Assessment #3

Drug Product Name	Testosterone undecanoate capsules
Dosage Form	Capsules
Strength	112.5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Lipocine Inc., Salt Lake City, UT
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission (0050)	05/09/19	All
Amendment (0054)	08/02/19	DP (Labeling)
Amendment (0055)	08/20/19	Biopharm.
Amendment (0056)	08/27/19	DP (Labeling)
Amendment (0058)	09/03/19	DP (Labeling)
Amendment (0059)	09/16/19	Manufacturing
Amendment (0060)	09/16/19	DP (Labeling)
Amendment (0062)	10/10/19	DP, Biopharm.

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeff Medwid	Donna Christner
Drug Product	Hamid Shafiei	Moo-Jhong Rhee
Manufacturing and Microbiology	James Norman	Yubing Tang
Biopharmaceutics	Hansong Chen	Vidula Kolhatkar
Regulatory Business Process Manager	Marquita Burnett	
Application Technical Lead	Mark Seggel	
Laboratory (OTR)	-	-
Environmental	-	-

APPEARS THIS WAY ON ORIGINAL

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

In its present form, Lipocine Inc.'s resubmission of their 505(b)(2) New Drug Application #208088, for Tlando (testosterone undecanoate) capsules, 112.5 mg, is not ready for approval. Labeling negotiations have not been completed, and in its present form, the prescribing information 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.

A 48-month expiration dating period for the drug product has been granted.

The request for a categorical exclusion from an environmental assessment (EA), supplemented by information submitted by the applicant to aid in determining whether extraordinary circumstances exist, is accepted.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Proposed Indication(s) including Intended Patient Population	TLANDO 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	225 mg (two 112.5 mg capsules) twice daily, with food
Alternative Methods of Administration	Not applicable

First approved in 1953 for intramuscular injection, 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.

Lipocine Inc. submitted NDA 208088 for testosterone undecanoate capsules, (b) (4) 112.5 mg, on August 28, 2015. The drug product offers an alternative to the orally bioavailable but toxic alkylated testosterone derivative methyltestosterone, to the transdermal testosterone products and to other testosterone ester prodrugs formulated for subcutaneous or intramuscular administration (e.g., testosterone cypionate, testosterone enanthate, and testosterone undecanoate). The first *oral* testosterone undecanoate product, Clarus' Jatenzo, was approved on under NDA 206089 on March 27, 2019.

Since the initial submission in 2015, NDA 208088 has received two Complete Response (CR) Letters due to clinical and clinical pharmacology deficiencies. A third CR will be issued at the end of the current review cycle, again due to deficiencies with the clinical and clinical pharmacology.

B. Quality Assessment Overview

Regulatory History:

Initial NDA Submission	08/28/2015	(b) (4) 112.5 mg capsules
OPQ IQA #1	06/02/2016	OPQ Recommendation: Not Ready for Approval in its present form per 21 CFR 314.125(b)(8) (i.e., labeling). Interim dissolution test acceptance criteria established, and agreement reached on potential PMC to collect additional dissolution profile data using FDA recommended method.
Complete Response #1	06/28/2016	Clinical, nonclinical and clinical pharmacology deficiencies. Applicant reminded to generate dissolution profile data on at least 6 production batches using FDA-recommended dissolution method to confirm the acceptance criteria.
Resubmission	08/08/2017	(b) (4)
OPQ IQA #2	02/26/2018	OPQ Recommendation: Not Ready for

		Approval in its present form per 21 CFR 314.125(b)(8) (i.e., labeling).
Complete Response #2	05/08/2018	Clinical and clinical pharmacology deficiencies identified.
Resubmission	05/09/2019	Updated drug product stability data.

Drug Substance: Adequate

The manufacture and control of testosterone undecanoate are documented in Type II DMF (b) (4) held by (b) (4). The DMF, as updated March 22, 2019, remains adequate to support NDA 208088. The (b) (4) month retest period continues to be supported by stability test results. See DMF (b) (4) Chemistry Review #4, dated September 24, 2019 for details.

This NDA is recommended for **APPROVAL** from the drug substance CMC perspective. See Chapter I, Drug Substance, of this IQA. Also refer to IQA #1 and IQA #2.

Drug Product: Adequate

Additional long-term stability data from the three primary stability batches of 112.5 mg capsules was submitted in support of Lipocine's proposed extension of the expiration dating period from 24 months to (b) (4) months.

Although stability results show (b) (4), (b) (4) specification. An expiration dating period of (b) (4) months can therefore be granted from the drug product CMC perspective. See IQA Chapter II for details.

However, the (b) (4) month expiration dating period is not supported by the available dissolution data (see discussion below) and at this time only a 48-month expiration dating period can be granted. The applicant has acknowledged the 48-month expiry (see sn 0062, 10/10/19).

This NDA is recommended for **APPROVAL** from the drug product CMC perspective (see IQA Chapter II, Drug Product, for details). See also IQA #1 and IQA #2.

Labeling: Inadequate

Because the application continues to be deficient from the clinical perspective, negotiations on the content of the prescribing information (PI) were not initiated. However, the PI has been reviewed from the ONDP perspective (see IQA Chapter IV, Labeling) and draft revisions have been entered in DBRUP's SharePoint document. This document will not be conveyed to the applicant at this time. The attached labeling review is written from the perspective that the revisions to the PI have been or will be accepted as proposed, and therefore does not identify any deficiencies with the PI. However, as none of the requested changes have been made the PI (last draft version submitted September 3, 2019; sn 0058) is therefore deficient from the ONDP labeling perspective.

While Section 11, Description, should, ideally, include the proprietary name in association with the established name and dosage (i.e., Tlando (testosterone undecanoate) capsules), the proposed text for Section 11 as presented in Chapter IV is consistent with the approved PI for Jatenzo. This format appears to be preferred by the labeling review team as it is thought to minimize redundancy. This is acceptable if the running text of the PI conforms to 21 CFR 201.10(g)(1). Any future review of the PI should also consider the need to include mention of the silica gel desiccant in the bottle. A complete re-evaluation of the PI should be conducted following resubmission of the NDA.

DMEPA and CMC comments regarding the bottle label have been conveyed to the applicant. Revised labels were submitted September 3, 2019 (sn 0058) and September 16, 2019 (sn 0060). Deficiencies with the bottle label are identified in the attached CMC labeling review. Specifically, from the drug product reviewer's perspective the established name and dosage form should be presented on a single line beneath the proprietary name. In addition, the labeling review notes that the equivalency statement should be removed since the product is an ester and not a salt. Note, however, that the label, as revised September 3 was found adequate from the DMEPA perspective. And, the testosterone / testosterone undecanoate equivalency statement has already been removed as requested (see sn 0060).

Refer to FDA communications to Lipocine dated August 22, 2019 and September 11, 2019. Also refer to Denise Baugh's reviews of the label from the DMEPA perspective dated August 21, 2019 and September 9, 2019.

Manufacturing: Adequate

No changes to the product manufacturing process or to the manufacturing facilities have been made since the Complete Response Letter was issued on May 8, 2018.

Compliance of all manufacturing facilities with CGMPs was, however, re-evaluated to ensure that no issues had been identified since the last facilities assessment was completed (see IQA #2).

An Overall Manufacturing Inspection Recommendation of **APPROVE** was issued on June 11, 2019. The recommendation remains current (see IQA Attachment II: Submission Manufacturing Status Report, accessed October 9, 2019, for details).

Biopharmaceutics: Adequate

The establishment of appropriate dissolution test method and acceptance criteria is documented in IQA #1 and IQA #2. The dissolution test method employs a dissolution medium containing 1% Triton X-100. Because (b) (4) Tier II testing using the 1% medium containing pepsin may be required.

The present Biopharmaceutics review focused on the assessment of the dissolution test acceptance criteria (see IQA Chapter VI, Biopharmaceutics). Report RD-18-002 (sn 0045, April 20, 2018), was submitted to address FDA's recommended acceptance criteria (30 minutes: (b) (4) %; 75 minutes: NLT (b) (4) %). The report discusses the dissolution testing of batch 3315J13A. This batch, manufactured in October 2013, was used in pivotal efficacy study LPCN 1021-16-002 conducted December 2016 to February 2017. Based on their analyses of the dissolution profile data, Lipocine proposed alternative acceptance criteria (b) (4)

The May 9, 2019 stability update included dissolution profiles of the three registration batches of 112.5 mg capsules obtained at the 48, 53 and 65 months timepoints.

On August 12, 2019 the applicant was advised that, "[w]e continue to recommend the previously recommended acceptance criteria. These are supported by your stability data (b) (4) months' stability dissolution data of Batch 3314J13A and Batch 3315J13A show that they are able to meet the recommended criteria at Stage 1)." On August 20, 2019 (sn 0055), Lipocine revised the drug product specification to include the FDA-recommended dissolution test acceptance criteria. Note that the acceptance criteria are considered 'interim' as the applicant previously

agreed to submit data from at least six batches to finalize the acceptance criteria.

From the Biopharmaceutics perspective, NDA 208088, as amended, is recommended for **APPROVAL**.

As noted above, Lipocine has requested a (b) (4) month expiration dating based on the stability data through (b) (4) months. While this is acceptable from the drug product CMC perspective, the (b) (4) month expiry is not supported by the available dissolution data. At the (b) (4) month timepoint batch 3316K13A does not meet the dissolution test requirements when the revised acceptance criteria are applied. Although the batch may have met the requirements if Stage 2 and Stage 3 testing had been performed, as Lipocine claims (see sn 0062), the available dissolution data do not support a (b) (4) month expiry. Lipocine has acknowledged the 48-month expiration dating period, (b) (4)

Note: The Biopharmaceutics review refers to a PMC. However, because the NDA was not approved on either of the two previous review cycles, the PMC was not formalized.

Microbiology (if applicable): Adequate

No new information regarding product quality microbiology has been reported. See IQA #1 and IQA #2 for an assessment of product quality microbiology. Overall, the microbiology control for this product is adequate according to current quality standards.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Appearance	- Process - Stability	L	(b) (4)	Acceptable	None.
Identification	CGMPs	L		Acceptable	None
Assay	- Formulation - Raw materials - Process	L		Acceptable	None
Related Substances Impurities/Degradants	- Formulation - Raw materials - Process - Container Closure System	L		Acceptable	Potential impact of process conditions. (b) (4)

(b) (4)

Uniformity of Dosage Units	• Formulation • Process	L	(b) (4)	Acceptable	Potential impact of process conditions.
Dissolution	• Raw materials • Formulation • Process	M		Acceptable	Potential impact of process conditions.
Microbial limits	• Raw materials • Process	L		Acceptable	None

(b) (4)

See Risk Assessment under IQA #2

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

Not applicable

2. Drug Substance Deficiencies

Not applicable.

3. Drug Product Deficiencies

Not applicable

4. Labeling Deficiencies

Not applicable. Recommended revisions to the prescribing information will be conveyed to the applicant if and when the clinical and clinical pharmacology deficiencies have been adequately addressed.

5. Manufacturing Deficiencies

Not applicable

6. Biopharmaceutics Deficiencies

Not applicable

7. Microbiology Deficiencies

Not applicable

8. Other Deficiencies (Specify discipline, such as Environmental)

Not applicable

Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D.
CMC Lead
OPQ/ONDP/DNDPII/NDPBV
October 11, 2019

{see electronic signature page}

QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	J. Medwid 09/24/19	

See IQA #2 for complete list of DMFs cited. Sufficient information has been submitted in the NDA and review of these DMFs was not needed.

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
All	IND 106476	Original IND for Oral TU

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH-ODE / OC	na			
Clinical	na			
Other	-			

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Analysis (*See IQA #1 and IQA #2*)

CHAPTER IV: Labeling

CHAPTER V: Manufacturing (Process and Facilities) (*See IQA #1 and IQA #2*)

CHAPTER VI: Biopharmaceutics

CHAPTER VII: Microbiology (*See IQA #1 and IQA #2*)

CHAPTER VIII: Additional Quality Discipline (*Not Applicable*)

Attachment I: Revised Drug Product Specification

Attachment II: Submission Manufacturing Status Report

CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:



Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TLANDO	Satisfactory
Established name(s)	(testosterone undecanoate) capsules	Satisfactory
Route(s) of administration	for oral use	Satisfactory
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Capsules: 112.5mg testosterone undecanoate	Satisfactory
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	CIII	Satisfactory
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include	N/A	N/A

pharmacy bulk package and imaging bulk package.		
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1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	N/A

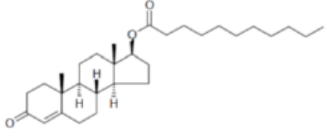
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Capsules, 112.5 mg testosterone undecanoate.

Capsules have white opaque body and grey opaque cap, and are imprinted with "112" in black ink.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	capsules	Satisfactory
Strength(s) in metric system	112.5mg	Satisfactory
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	capsules are white opaque body, grey opaque cap capsules, imprinted with "112" in black.	Satisfactory
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TLANDO for oral use is provided as a gelatin capsule containing testosterone undecanoate	Provided. Satisfactory
Dosage form(s) and route(s) of administration	Capsule for oral use	Provided Satisfactory
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Each capsule contains 112.5 mg of testosterone undecanoate as the active ingredient and the following inactive ingredients: (b) (4) (b) (4) polyoxyl 40 hydrogenated castor oil, polyethylene glycol, ascorbyl palmitate, gelatin, titanium dioxide, black iron oxide, and imprint ink	Provided. Satisfactory
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A

Pharmacological/therapeutic class	an androgen	Provided. Satisfactory
Chemical name, structural formula, molecular weight	Testosterone undecanoate is chemically described as (b) (4) 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: 	Provided. Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Testosterone undecanoate is a white to off-white crystalline substance	Provided. Satisfactory

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Capsules	Satisfactory
Strength(s) in metric system	112.5 mg	Satisfactory
Available units (e.g., bottles of 100 tablets)	120 capsules packaged in HDPE bottles	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	capsules are composed of white opaque body with a grey opaque cap, imprinted with "112" in black ink	Satisfactory
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP controlled room temperature.]	Satisfactory
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging	(b) (4)	Satisfactory

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Provided with adequate font size and prominence	Satisfactory
Dosage strength	112.5 mg	Satisfactory
Route of administration	Not displayed	Not required. Satisfactory
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Provided but not applicable to this API.	(b) (4) should be removed. Unsatisfactory
Net contents (e.g. tablet count)	120 capsules	Satisfactory
"Rx only" displayed on the principal display	Displayed	Satisfactory
NDC number	Displayed	Satisfactory
Lot number and expiration date	Location to display the actual lot # and expiration date is displayed	Satisfactory
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Displayed	Satisfactory
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A

Bar code	Displayed	Satisfactory
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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Displayed	Satisfactory
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	(b) (4)	Satisfactory

Assessment of Carton and Container Labeling: Inadequate

- Since the active ingredient is not a salt, the equivalency statement in the label for the active ingredient should be removed.
- The established name should be expressed per 21 CFR 201.10(g)(2) (see the list of deficiencies below)

ITEMS FOR ADDITIONAL ASSESSMENT

A. Regarding the container label

1. Since the active ingredient is not a salt, it is not subject to the USP salt policy and therefore, the equivalency statement should be removed.

2. The established name needs to be expressed as follows with the same font and sizes to be in line with 21 CFR 201.10 (g)(2) in terms of typography and layout:

TLANDO (testosterone undecanoate) capsules
112.5mg

Or

TLANDO
(testosterone undecanoate) capsules
112.5mg

Overall Assessment and Recommendation:

From the ONDP perspective, this application is not deemed ready for approval in its present as per 314.125(b)(6) until the container label deficiencies delineated above are satisfactorily addressed.

Primary Labeling Assessor:

Hamid R. Shafiei, Ph.D.
Reviewer, Brach V / DNDPII / ONDP / OPQ

Secondary Assessor Name:

I concur with Dr. Shafiei's assessment and his recommendation that the container label of this application must be revised as delineated above to meet the statutory requirement.

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



Hamid
Shafiei

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Moo Jhong
Rhee

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BIOPHARMACEUTICS**Product Background:**

NDA/ANDA: NDA 208088 resubmission

Drug Product Name / Strength: Tlando (testosterone undecanoate) Capsules, 112.5 mg

Route of Administration: Oral

Applicant Name: Lipocine Inc.

Review Summary: Adequate

Lipocine Inc. developed Tlando (testosterone undecanoate) Capsules 112.5 mg (b) (4) and submitted the original submission, NDA 208088, to the Agency on 8/28/2015 to seek approval through a 505 b (2) pathway. It is indicated for testosterone replacement therapy in adults, 18 years or older, males for conditions associated with a deficiency of absence of endogenous testosterone – primary hypogonadism (congenital or acquired) or secondary hypogonadism (congenital or acquired).

On 6/28/2016, the FDA issued a CR letter to NDA 208088 original submission. The Biopharmaceutics team concluded that NDA 208088 original submission was acceptable for approval with a PMC (see Dr. Haritha Mandula's Biopharmaceutics review for NDA 208088 Overall Quality Assessment dated June 02, 2016 for details).

On 8/8/2017, the Applicant resubmitted this NDA to the Agency. In this resubmission, the Applicant stopped (b) (4). The Biopharmaceutics team again concluded that NDA 208088 resubmission was acceptable for approval with a PMC, which is listed in "Key Outstanding Issues from Last Cycle" section below of this review for details.

On 5/8/2018, another CR was issued to this NDA resubmission. On 5/9/2019, the Applicant resubmitted NDA 208088 for the second to the Agency.

In this NDA resubmission, the Biopharmaceutics review focuses on the Applicant's response to the Biopharmaceutics PMC, and the dissolution acceptance criteria.

In the previous review, the two-tier dissolution testing method has been approved for routine quality control and stability testing. However, the applicant's proposed dissolution acceptance criterion in the current resubmission was liberal, the following acceptance criteria were recommended by the Agency and accepted by the Applicant:

30 minutes: (b) (4) %
75 minutes: NLT (b) (4) %

Overall, the following dissolution method and acceptance criteria have been approved:

	Tier I	Tier II
Apparatus	Apparatus 2 (Paddle)	Apparatus 2 (Paddle)
Medium	1% Triton-X-100 in DI Water	1% Triton-X-100 in DI Water + Enzyme (<75,000 units/L Pepsin)
Medium volume	1000 mL	1000 mL
Rotation Speed	100 rpm	100 rpm
Temperature	37 °C	37 °C
Sampling points	15, 30, 45, and 60 minutes	15, 30, 45, and 60 minutes
Acceptance criteria	30 minutes: (b) (4) % 75 minutes: NLT (b) (4) %	30 minutes: (b) (4) % 75 minutes: NLT (b) (4) %

From a Biopharmaceutics perspective, this Reviewer recommends that NDA 208088 Tlando (testosterone undecanoate) Capsules, 112.5 mg is **adequate for approval**.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0045	4/20/2018
0050	5/9/2019
0055	8/27/2019

Highlights of Key Outstanding Issues from Last Cycle:

In the 5/5/2018 CR letter, the following Biopharmaceutics PMC was included:

Employ the following dissolution specifications for both release and stability on an interim basis for one-year post-approval:

30 minutes: (b) (4) %

75 minutes: NLT (b) (4) %

In the meantime, generate and evaluate the dissolution data profile (n=12 tablets/batch, mean, SD, RSD, profiles) using the currently approved dissolution method for release and stability testing for at least 6 production batches. Additionally, submit dissolution data for 112.5 mg clinical batches if unexpired batches are available. Collect dissolution samples at 15, 30, 45, 60, 75, 90, and 120 minutes. Submit the generated dissolution data profiles at your earliest convenience, but by the first Annual Report at the latest, in order to finalize the dissolution acceptance criteria for your drug product.

Concise Description Outstanding Issues Remaining: none

Dissolution Method and Acceptance Criteria**Reviewer's Assessment:****1. The Newly proposed dissolution acceptance criteria**

In Document Titled "RD-18-002" submitted on April 19, 2018, the Applicant rejected the Agency recommended interim dissolution acceptance criteria (i.e. 30 min: (b) (4)%; 75 min: NLT (b) (4)%). Instead, they proposed the following acceptance criteria:

(b) (4)

The recommended acceptance criteria	The Applicant's newly proposed acceptance criteria
30 minutes: (b) (4) % 75 minutes: NLT (b) (4) %	(b) (4)

In this resubmission, the Applicant used one old clinical batch (i.e. 3315J13A) to conduct two new clinical studies (efficacy: LPCN 1021-18-001 and safety: LPCN 1021-18-003). The Applicant believed that the dissolution from this lot can be further utilized to establish a new specification for dissolution stability testing.

The Applicant summarized the stability dissolution data (up to 48 months) at 30 minutes of Lots 3314J13A, 3315J13A, and 3316K13A, which were generated in (b) (4) Triton-X in DI Water, and found that many units are out of the recommended range (i.e. (b) (4) %). Therefore, they concluded that the recommended criteria for 30 minutes are tight.

(b) (4)

(b) (4)

Based on the above data analysis, the Applicant concluded that the recommended acceptance criteria are tight for their proposed drug product. They will gather dissolution data for these dissolution timepoints over the following year to evaluate whether the following dissolution acceptance criteria should be adopted for drug product. In the interim, they will evaluate dissolution data based on the previous dissolution specification and acceptance criterion ($Q = \frac{(b)(4)}{(4)}\%$ at $(b)(4)$ minutes).

(b) (4)

Reviewer's assessment

The Applicant's newly proposed acceptance criteria are not acceptable due to the following reasons:

- The newly proposed criteria are liberal. Testosterone undecanoate is a BCS Class II drug, which has low solubility. Drug dissolution is the rate limiting step for drug absorption. Appropriate dissolution acceptance criteria are crucial from a product quality perspective.*
- The Applicant do not have any data to support their criterion for $(b)(4)$ minutes.*
- The Applicant used dissolution data from 36 months old of stability samples to conduct data analysis. However, these data were generated in $\frac{(b)(4)}{(4)}\%$ Triton X-100 in DI Water. The currently approved dissolution medium is 1% Triton X-100 in DI Water.*
- To support the proposed criterion for 75 minutes time point, the Applicant $(b)(4)$ $(b)(4)$ The proposed acceptance criteria should be supported by the actual data, and $(b)(4)$ is not acceptable.*

The dissolution acceptance criteria should be set based on the release data of the fresh clinical lots. The stability data are generally not considered for criteria setting. This is a special case as the Applicant do not have any release dissolution data of the clinical batches using the currently approved dissolution method.

Batch 3315J13A was manufactured on 10/08/2013. When the new clinical studies were conducted on 9/5/2018 (LPCN 1021-18-001) and 11/8/2018 (LPCN 1021-18-003), respectively, this batch was about 5 years old. It is valid to use the stability dissolution data of Batch 3315J13A for criteria justification because of the new clinical studies conducted.

Based on the available data, the recommended acceptance criteria are appropriate and supported by the dissolution data of the aged clinical batches. 53 months' stability dissolution

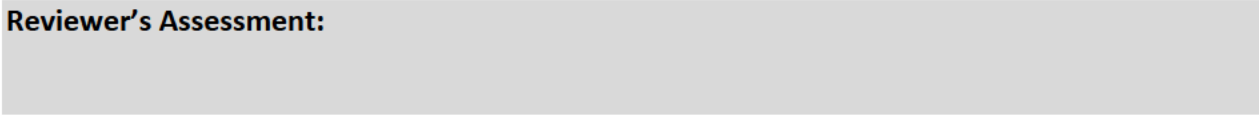
data (with and without pepsin) of Lot 3314J13A and Lot 3315J13A show that they are able to meet the recommended criteria at Stage 1. Lot 3316K13A could not meet them at any stage at (b) (4) months' time point (in the presence of pepsin) because of some slow release units. But 48 months' data in absence of pepsin show that it likely meets the criteria at Stage 2.

It should be noted that the proposed shelf life for the proposed product is (b) (4) months, which is being reviewed by the Drug Product Reviewer.

2. Information Request

On 8/12/2019, the FDA sent a two-item Biopharmaceutics Information Request (IR) to the Applicant. On 8/27/2019, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this Reviewer's assessment of the Applicant's response.

(b) (4)

Bridging of Formulations**Reviewer's Assessment:** N/A
***Biowaiver Request*****Reviewer's Assessment:**
**R Regional Information*****Comparability Protocols*****Reviewer's Assessment:**


Post-Approval Commitments**Reviewer's Assessment:*****Lifecycle Management Considerations******List of Deficiencies:***

None.

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, PharmD., Ph.D.

Biopharmaceutics reviewer

OPQ/ONDP/Division of Biopharmaceutics

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

Vidula Kolhatkar, Ph.D.

Acting Biopharm. Secondary Reviewer

DB/ONDP/OPQ/CDER/FDA



Hansong
Chen

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Vidula
Kolhatkar

Digitally signed by Vidula Kolhatkar

Date: 9/20/2019 03:05:04PM

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ATTACHMENT 1. DRUG PRODUCT SPECIFICATION

As submitted August 20, 2019 (sn 0055) to incorporate revised dissolution test acceptance criteria. Table 1 was resubmitted on October 10, 2019 (sn 0062).

Table 1. Testosterone Undecanoate Capsules Drug Product Specifications, 112.5 mg

Test	Test Method	Specification
Description Appearance (112.5 mg)	Visual SOP-QUA-0684	Capsule, white opaque body and grey opaque cap with "112" printed in black ink on the body with a (b) (4) colourless band.
Identification* Testosterone undecanoate	HPLC EAM0227	The retention time of the major peak in the chromatogram of the assay preparation is within (b) (4) % of that in the chromatogram of the standard preparation.
Identification* Testosterone undecanoate	IR EAM0225	The IR spectrum of the sample exhibits maxima at approximately (b) (4) cm^{-1} , (b) (4) cm^{-1} and (b) (4) cm^{-1} which confirms the presence of testosterone undecanoate.
Assay Testosterone undecanoate	HPLC EAM0227	Release and shelf-life: (b) (4) % of label claim
Uniformity of Dosage Units* Testosterone undecanoate	HPLC EAM0228	USP <905>
Impurities (b) (4)	HPLC EAM0227	NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % Individual unspecified impurities NMT (b) (4) % Total unspecified impurities NMT (b) (4) % Total impurities NMT (b) (4) %
Dissolution: App II, HPLC	USP <711> EAM0289	30 minutes: (b) (4) % 75 minutes: NLT (b) (4) % Level 1, 2 and 3 **
(b) (4)		
Microbial Limit Total aerobic count Total yeast and moulds Absence of E. coli	USP <61,62>	NMT (b) (4) cfu/g NMT (b) (4) cfu/g Absent in (b) (4) g
HPLC: high performance liquid chromatography IR: infrared spectroscopy NMT: Not More Than		
RRT : relative retention time cfu: colony forming unit NLT: Not Less Than		

* Performed at release testing only.

** If results do not comply with Level 1 criteria, continue testing through three levels unless the results conform to Level 2 criteria established in USP <711>. If results do not comply through Level 3 testing, repeat Level 1 with pepsin as directed in Section 3.2.P.5.2. Continue testing with pepsin through three levels unless the results conform to Level 1 or Level 2 criteria established in USP <711>.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARK R SEGCEL
10/11/2019 01:00:19 PM

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 208088

Tlando (testosterone undecanoate) Capsules

Review #2

Drug Name/Dosage Form	Tlando (testosterone undecanoate) Capsules
Strength	112.5 mg TU (b) (4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Lipocine Inc., Salt Lake City, UT
US agent, if applicable	not applicable

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission (0026)	08/08/17	All
Amendment (0029)	09/28/17	Biopharmaceutics
Amendment (0031)	10/27/17	Biopharmaceutics
Labeling/Package Insert (0032)	10/31/17	Drug Product
Amendment (0038)	12/08/17	Biopharmaceutics
Amendment (0039)	12/12/17	Drug Substance/Facilities

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION / BRANCH
Drug Substance	Jeffrey Medwid	OPQ/ONDP/DNDPAPI/NDBII
Drug Product	Hamid Shafiei	OPQ/ONDP/DBRUP/NDBV
Process	James Norman	OPQ/OPF/DPAII/PABV
Microbiology	James Norman	OPQ/OPF/DPAII/PABV
Facility	Juandria Williams	OPQ/OPF/DIA/IABIII
Biopharmaceutics	Hansong Chen	OPQ/ONDP/DB/BBII
Regulatory Business Process Manager	Thao Vu	OPQ/ONDP/DBRUP/NDBV
Application Technical Lead	Mark Seggel	OPQ/ONDP/DBRUP/NDBV
Environmental Assessment (EA)	James Laurenson	OPQ/ONDPEA Team

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	J. Medwid; 10/05/17	
	Type III			N/A		
	Type III			N/A		
	Type IV			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

APPLICATION NUMBER	DOCUMENT	DESCRIPTION
IND 106476	All	Original IND for TU

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	na			
Pharmacology/Toxicology	na			
DMEPA	complete	Labeling revisions proposed.	02/16/18	D. Baugh
CDRH	na			



QUALITY ASSESSMENT



Clinical	na			
Other	na			

na: not applicable

APPEARS THIS WAY ON ORIGINAL

Executive Summary

I. Recommendations and Conclusion on Approvability

In its present form, Lipocine Inc.'s resubmission of their 505(b)(2) New Drug Application #208088, for Tlando (testosterone undecanoate) Capsules, 112.5 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.

Interim dissolution test acceptance criteria have been established. Lipocine has agreed to provide additional dissolution profile data from production batches.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	TLANDO 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	225 mg twice daily, with food
Alternative Methods of Administration	Not applicable.

Lipocine Inc. submitted NDA 208088 for testosterone undecanoate capsules, (b) (4) 112.5 mg, on August 28, 2015. 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 208088 was issued on June 28, 2016 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, additional dissolution data were requested when the application was resubmitted. Although labeling revisions were recommended, labeling had not been finalized.

The August 8, 2017 resubmission includes updated chemistry, manufacturing and controls information. (b) (4) (b) (4)

The resubmission review timeline was extended by three months on November 14, 2017, following submission of a major amendment.

B. Quality Assessment Overview

See OPQ IQA #1 dated June 2, 2016 for the first integrated quality review of NDA 208088.

Drug Substance

Testosterone undecanoate is an ester prodrug prepared by the (b) (4) (b) (4) The manufacture of testosterone undecanoate by (b) (4) is documented Type II Drug Master File (DMF) (b) (4) The DMF continues to be adequate to support the use of the active pharmaceutical ingredient in the manufacture of testosterone undecanoate capsules. See also OPQ IQA #1 and the attached Drug Substance review chapter.

Note that Lipocine included a Letter of Authorization (LoA) to cross-reference (b) (4) Type II DMF (b) (4) without any other supporting information. The LoA was withdrawn at the Agency's request.

Drug Product

Tlando (testosterone undecanoate) Capsules contain 112.5 mg testosterone undecanoate, (b) (4) (b) (4) (b) (4) (b) (4) Testosterone undecanoate is (b) (4) (b) (4) (glyceryl monolinoleate; (b) (4) polyoxyl 40 hydrogenated castor oil (b) (4) ascorbyl palmitate (b) (4) and polyethylene glycol 8000 (b) (4)

(b) (4)

The resubmission includes several minor changes to the drug product and the product specification. The capsule shell color was changed from (b) (4) (b) (4) to opaque white body and opaque grey cap, with "112" printed in black ink.

The product specification was revised to include an acceptance criterion (not more than (b) (4) %) for an unidentified, specified degradant at (b) (4). The (b) (4)

Addition of a new unidentified specified impurity with a qualified acceptance limit is considered acceptable as long as no changes to the acceptance limits for other impurities and the total impurities are proposed. In this case the limits for Total Unspecified Impurities and Total Impurities remain unchanged at NMT (b) (4) % and NMT (b) (4) %, respectively. Re-analysis of the test article used in the 90-day dog repeated dose toxicology study confirms that it was present and therefore qualified at the proposed level of NMT (b) (4) %.

The analytical procedure for identification, assay and related substance by HPLC has been modified to provide improved resolution of impurities. The HPLC procedure has been adequately validated and is suitable for the intended use.

The resubmission includes 42 month long term data from the primary stability batches. While the data support an expiration dating period longer than 24 months, Lipocine intends to extend the shelf-life based on long-term data obtained on the validation batches.

From the drug product review perspective, this new drug application is recommended for **Approval** with a drug product expiration dating period of 24 months at 25°C (see OPQ IQA #1 and attached review chapter).

Biopharmaceutics

During the first review cycle, the biopharmaceutics review team determined that the NDA was approvable, although a post-marketing commitment (PMC) to generate dissolution data to confirm the acceptance criterion ($Q = \frac{(b) (4)}{(4)}\%$ in (b) (4) minutes) was proposed. While Lipocine had agreed to the PMC, because a Complete Response was issued, the following "Additional Comment" was included in the Letter instead of the PMC:

We have the following additional comments and recommendations. You should adequately address these comments in your resubmission.

1. Generate and submit additional dissolution profile data (individual, average, standard deviation, profiles) using the following FDA-recommended dissolution method for release and stability testing of at least 6 production batches (n=12 tablets/batch):

Apparatus: 2 (Paddles) with helix sinkers
Paddle Speed: 100 rpm
Medium: Tier I: 1% Triton-X in DI Water
Tier II: Tier I + Enzyme (<75,000 units/L Pepsin)
Volume: 1000 mL
Temperature: 37°C ± 0.5°C

Note that pepsin is added to Tier II medium because

(b) (4)

(b) (4)

Additional dissolution data were provided in the resubmission, however these consisted of results from a single time point. Profile data from 3 batches of each strength were once again requested. Data for three batches of 112.5 mg capsules were provided.

(b) (4)

(b) (4)

Based on the available albeit limited profile data (see sn 0031, 10/27/17), the biopharmaceutics review team requested (IR #2, 11/30/17) that Lipocine adopt the following interim acceptance criteria and to continue to collect dissolution profiles at release and on stability:

30 minutes: (b) (4) %

75 minutes: NLT (b) (4) %

Lipocine has agreed to implement the interim acceptance criteria and to generate the requested data post-approval (see sn 0038, 12/08/17).

Dr. Hansong Chen concludes that from the Biopharmaceutics perspective, NDA 208088 for Tlando (testosterone undecanoate) Capsules, 112.5 mg is adequate for **Approval** with the commitment outlined above.

Product Manufacturing Process and Product Quality Microbiology

The resubmission included one minor process change. The applicant proposes to

(b) (4)

(b) (4)

This change is adequate from the process perspective.

Overall, the resubmission remains **Adequate** from the process perspective (see OPQ IQA #1 and attached review chapter).

Facilities

All drug substance and drug product manufacturing facilities were found to be operating in compliance with CGMPs. Packaging and testing facilities including those that are operating under new names or with an expanded role also have acceptable CGMP status. An overall inspection recommendation of **Approve** was issued on September 5, 2017.

Environmental Assessment

The claimed categorical exclusion from the Environmental Assessment requirements was previously found **Acceptable** (see OPQ IQA #1 dated May 31, 2016).

Labeling

In collaboration with DMEPA, labeling recommendations were previously 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

Other than unresolved labeling issues, there are no specific deficiencies for the Complete Response letter.

The following comment from the Biopharmaceutics review team should be included as an Additional Comment in the action letter. (This comment was previously conveyed to the applicant in Information Request #2 dated November 30, 2017. Lipocine committed to generate the requested dissolution profiles for at least 6 production batches (see amendment 0038 dated December 8, 2017.)

Employ the following dissolution specifications for both release and stability on an interim basis for one year post-approval:

30 minutes: (b) (4) %

75 minutes: *NLT* (b) (4) %

In the meantime, generate and evaluate the dissolution data profile (n=12 tablets/batch, mean, SD, RSD, profiles) using the currently approved dissolution method for release and stability testing for at least 6 production batches. Additionally, submit dissolution data for 112.5 mg clinical batches if unexpired batches are available. Collect dissolution samples at 15, 30, 45, 60, 75, 90, and 120 minutes. Submit the generated dissolution data profiles at your earliest convenience, but by the first Annual Report at the latest, in order to finalize the dissolution acceptance criteria for your drug product.

Alternatively, the following comment may be included in the CR Letter:

We remind you of our information request regarding dissolution testing dated November 30, 2017 and your commitment dated December 8, 2017 to address the information request.

Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D.
Acting CMC Lead for DBRUP
OPQ/ONDP/DNDPII/Branch V
February 25, 2018



Mark
Seggel

Digitally signed by Mark Seggel

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ASSESSMENT OF MICROBIOLOGY

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Pharmaceutical Development - Microbiological Attributes: [3.2.P.2.5](#)

The manufacturing process for testosterone undecanoate capsules consists of (b) (4)
(b) (4)

In addition, batches will be tested by USP <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests and <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms as detailed in USP <1111> Microbiological Attributes of Nonsterile Pharmaceutical Products.

(b) (4)

Relevant Specifications: [3.2.P.5.1](#)

(b) (4)

Microbial Limit		
Total aerobic count	USP <61,62>	NMT (b) (4) cfu/g
Total yeast and moulds		NMT (b) (4) cfu/g
Absence of E. coli		Absent in (b) (4)

Reviewer's Note: Each bottle contains a desiccant pouch (b) (4)

(b) (4)

(b) (4)

Microbial testing results for both lots at t=6 months met the proposed specifications of NMT (b) (4) cfu/g for total aerobic count, NMT (b) (4) cfu/g for total yeasts and moulds, and Absent in (b) (4)g for absence of *E. coli*. No microbial testing was required at t=3 months.

Stability Data – 3.2.P.8.1 and 3.2.P.8.3

Reviewer's Note: Microbial limits were tested at t=0 and 6 months under accelerated conditions and t=0 and 12 months under long-term conditions. The applicant did not provide any stability data at t = 24 mo.

(b) (4)

Results from Testosterone Undecanoate 112.5 mg Capsules Primary Stability Batches

(b) (4)

Microbial Limit	The total aerobic count was < (b) (4) cfu/g at all timepoints. The total yeasts and molds was < (b) (4) fu/g at all timepoints. <i>E. coli</i> was absent at all timepoints.
-----------------	--

Reviewer's Assessment: Adequate

The applicant proposes to test microbial limits at release according to USP <1111> (NMT (b) (4) TAMC, NMT (b) (4) TYMC, absence of *E. Coli*) and test according to the ICH Q1A schedule during stability testing.

The product exhibited no microbial growth over 6 mo ACC and 12 mo LT stability testing. Capsules are packed with desiccant in (b) (4) bottles and tested to contain NMT (b) (4) % w/w by (b) (4). In addition, the raw materials are low bioburden.

2.3.P.7 Container/Closure System

Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Reviewer's Assessment: N/A for solid oral dosage forms

The product is packaged in induction-sealed HDPE bottles. Refer to the drug product assessment for an evaluation of the container/closure system.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Section 3.2.P.4.5 Excipients of Human or Animal Origin

(b) (4) capsules: [TSE Statements and Certifications](#)

(b) (4) for banding: [BSE-TSE Statement](#)

Reviewer's Assessment: Adequate

The applicant provided TSE/BSE certification for the only two excipients of animal origin.

If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Reviewer's Assessment: N/A

N/A for solid oral dosage forms

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate

The microbial controls are adequate for this gelatin product. The applicant proposed to test every lot at release according to USP <61,62> with limits in line with USP <1111>. Every stability batch is proposed to be tested according to the ICH Q1A schedule.

This alone would be sufficient. The applicant also controls the (b) (4) in the finished product and ensures that the raw materials will comply with the USP <1111> limits. The product is also packaged with desiccant, which should limit microbial growth. Overall, the microbiology control, as amended, for this product is adequate according to current quality standards.

James Norman, Ph.D., OPF/DPAII/BV, 05/06/2016

Update 10/18/2017: As mentioned in the process review, the 08/08/2017 resubmission includes a (b) (4) and the applicant has adequate microbial controls for the finished products. Adequate.

James J. Norman, Ph.D., Chemical Engineer, OPF/DPAII/BV, 10/18/2017

Secondary Review Comments and Concurrence:

I concur with Dr. James Norman's assessment and conclusion.

Yubing Tang, Ph.D., Acting Branch Chief, OPF/DPAII/BV, 05/06/2016



James
Norman

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Yubing
Tang

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BIOPHARMACEUTICS**Product Background:**

NDA/ANDA: NDA 208088 resubmission

Drug Product Name / Strength: Tlando (testosterone undecanoate) Capsules, 112.5 mg

Route of Administration: Oral

Applicant Name: Lipocine Inc.

Review Summary:

Lipocine Inc. developed Tlando (testosterone undecanoate) Capsules 112.5 mg (b) (4) and submitted the original submission, NDA 208088, to the Agency on 8/28/2015 to seek approval through a 505 b (2) pathway. It is indicated for testosterone replacement therapy in adults, 18 years or older, males for conditions associated with a deficiency of absence of endogenous testosterone – primary hypogonadism (congenital or acquired) or secondary hypogonadism (congenital or acquired).

On 6/28/2016, the FDA issued a CR letter to NDA 208088 original submission. The Biopharmaceutics team concluded that NDA 208088 original submission was acceptable for approval with a PMC, which is listed in “Key Outstanding Issues from Last Cycle” section below of this review for details. (b) (4)

In this NDA resubmission, the Biopharmaceutics review is focusing on the Applicant’s response to the Biopharmaceutics PMC, and the dissolution acceptance criteria.

The following two-tier dissolution testing method has been recommended for routine quality control and stability testing, which was accepted by the Applicant:

	Tier I	Tier II
Apparatus	Apparatus 2 (Paddle)	Apparatus 2 (Paddle)
Medium	1% Triton-X in DI Water	1% Triton-X in DI Water + Enzyme (<75,000 units/L Pepsin)
Medium volume	1000 mL	1000 mL
Rotation Speed	100 rpm	100 rpm
Temperature	37 °C	37 °C
Sampling points	15, 30, 45, and 60 minutes	15, 30, 45, and 60 minutes

The Applicant originally proposed the following dissolution specification:

NLT $\frac{(b)(4)}{(4)}\%$ in $\frac{(b)(4)}{(4)}$ minutes

Based on the data provided, this specification was not set appropriately. We requested the Applicant to use the following specifications on an interim basis:

30 minutes: $\frac{(b)(4)}{(4)}\%$

75 minutes: NLT $\frac{(b)(4)}{(4)}\%$

The Specifications will be reevaluated after more dissolution data are submitted.

The Applicant committed to submit more dissolution data to reevaluate the specifications.

From a Biopharmaceutics perspective, this Reviewer recommends that NDA 208088 Tlando (testosterone undecanoate) Capsules, 112.5 mg is **adequate** for approval with the following commitment.

Employ the following dissolution specifications for both release and stability on an interim basis for one year post-approval:

30 minutes: $\frac{(b)(4)}{(4)}\%$

75 minutes: NLT $\frac{(b)(4)}{(4)}\%$

In the meantime, generate and evaluate the dissolution data profile (n=12 tablets/batch, mean, SD, RSD, profiles) using the currently approved dissolution for release and stability testing for at least 6 production batches. Submit the generated dissolution data profiles at your earliest convenience, but by the first Annual Report at the latest, in order to finalize the dissolution acceptance criteria for your drug product.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED NDA 208399 resubmission	DOCUMENT DATE
0026	8/8/2017
0029	9/28/2017
0031	10/27/2017
0038	12/8/2017

Highlight Key Outstanding Issues from Last Cycle:

In the 6/28/2016 CR letter, the following Biopharmaceutics PMC was included:

Your proposed dissolution acceptance criterion of NLT $\frac{(b)(4)}{(4)}\%$ (Q) in $\frac{(b)(4)}{(4)}$ minutes for both release and stability is approved on an interim basis for one year post-approval.

In the meantime, generate and evaluate the dissolution data profile (n=12 tablets/batch) using the FDA recommended dissolution method for release and stability testing for at least 6 production batches. Submit the generated dissolution data profiles (using the FDA approved dissolution

method) at your earliest convenience, but by the first Annual Report at the latest, in order to finalize the dissolution acceptance criterion for your drug product.

Concise Description Outstanding Issues Remaining: none

BCS Designation

Reviewer's Assessment: The Applicant did not report testosterone undecanoate's BCS classification; however, the literature reported that it is a BCS II drug, which has poor solubility and high permeability.

Solubility: not reported

Permeability: Not reported.

Dissolution: See the Biopharmaceutics review.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

1. Information Request 1

(b) (4)

(b) (4)

2. The Approved dissolution method

During the review process of the original submission, (b) (4) was observed in stability batches as early as 6 months. However, (b) (4) was observed during dissolution testing of fresh production lots. A two-tier dissolution testing method has been recommended for routine quality control and stability testing, which was accepted by the Applicant.

Table 2. The dissolution method finalized in the original submission

	Tier I	Tier II
Apparatus	Apparatus 2 (Paddle)	Apparatus 2 (Paddle)
Medium	1% Triton-X in DI Water	1% Triton-X in DI Water + Enzyme (<75,000 units/L Pepsin)
Medium volume	1000 mL	1000 mL
Rotation Speed	100 rpm	100 rpm
Temperature	37 °C	37 °C
Sampling points	15, 30, 45, and 60 minutes	15, 30, 45, and 60 minutes

In the original submission, the Applicant collected dissolution samples at 15, 30, 45, and 60 minutes. In Biopharmaceutics Information Request 1, we requested the Applicant to collect the dissolution samples at 100 rpm (rotation speed in the finalized dissolution method) at additional time points (such as 75 minutes and 90 minutes). The newly submitted dissolution data show that the Applicant collected dissolution samples at 75, 90, and 120 minutes as well.

3. In vitro release data and specification

In the response to Biopharmaceutics IR 1, the Applicant provided the complete dissolution data (individual n=12/batch, mean, SD, RSD, and profiles) for the following three batches of Strength 112.5 mg:

Batch 3703D16

Batch 3718D16

Batch 3719D16

Table 3. Batch information for the clinical and stability batches in the original submission

Batch number	Strength	Batch size	Manufacturing date	Batch use
3314J13A	112.5 mg	(b) (4)	10/06/2013	Clinical and stability 1021-13-001 1021-14-001 1111-15-001

3316K13A	112.5 mg	(b) (4)	10/03/2013	Clinical and stability 1021-13-001
3315J13A	112.5 mg		10/08/2013	Clinical and Stability 1021-16-002

(b) (4)

Table 4. Mean dissolution data of clinical and launch batches

Batch/Time (min)	15	30	45	60	75	90	120
3314J13A 112.5 mg	19.7	46.5	66.2	80.3	n.d.	n.d.	n.d.
3316K13A 112.5 mg	20.3	49.3	69.8	84.7	n.d.	n.d.	n.d.
3315J13A 112.5 mg	14.5	39.9	60.9	76.2	n.d.	n.d.	n.d.

(b) (4)

Batch 3703D16 112.5 mg	26.3	54.4	74.1	86.9	92.7	93.5	93.3
Batch 3718D16 112.5 mg	29.3	57.5	75.1	86.6	90.9	92.7	93.0
Batch 3719D16 112.5 mg	26.4	54.3	72.7	84.4	90.6	92.9	92.2

n.d.= not determined

The Applicant proposed the following specifications for the proposed products in the original submission:

(b) (4)

Per the PMC in the CR letter, this proposed specification was used on an interim basis. According to our current practice, the selection of the final specification time point should be where $Q = \frac{(b) (4)}{(4)}\%$ dissolution occurs. In Biopharmaceutics IR 1, we requested the Applicant to reconduct dissolution tests by collecting dissolution samples at additional time points (such as 75 minutes and 90 minutes). As recommended, the Applicant collected dissolution samples at 75, 90, and 120 minutes. The newly generated dissolution data listed in Table 4 show that all three batches have a mean dissolution >90% at 75 minutes.

The proposed drug product is a (b) (4) dissolving product. Per our current practice, it is necessary to set dissolution acceptance criteria at two or more sampling time points. The first-time point should include a dissolution range and the second-time point should be where $Q = \frac{(b) (4)}{(4)}\%$ dissolution occurs.

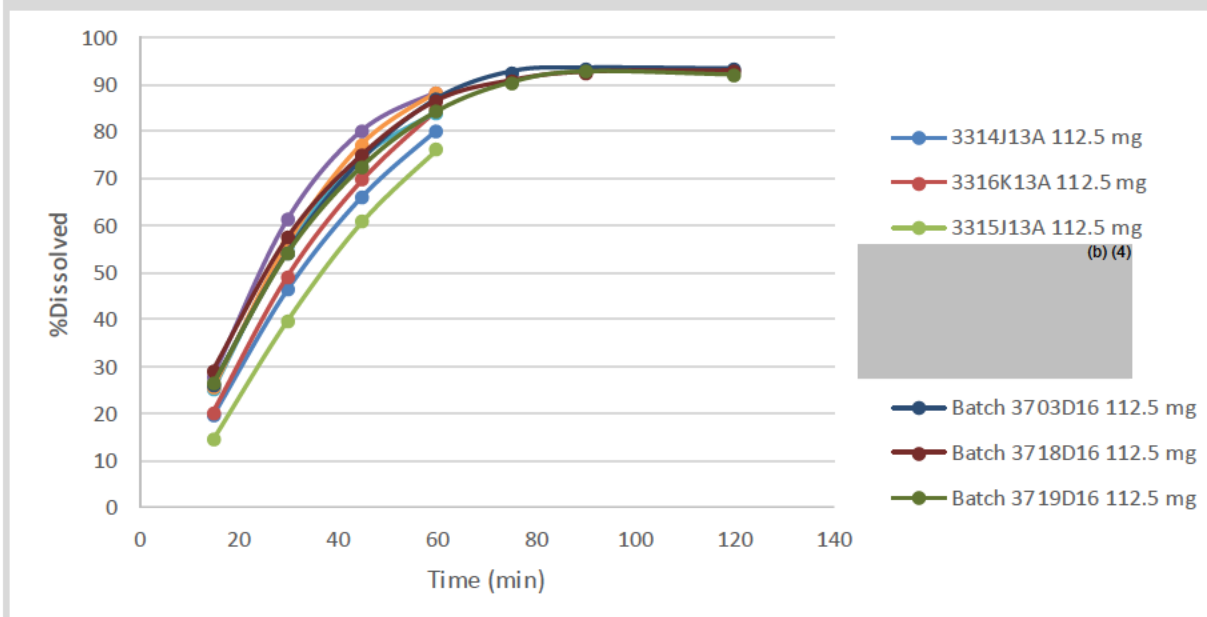
Based on the available data, the following acceptance criteria are appropriate for the proposed drug products:

30 minutes: (b) (4) %
75 minutes: NLT (b) (4) %

The dissolution data show that all clinical, stability, and commercial batches are able to meet the above specification at 30 minutes. However, all clinical batches of 112.5 mg strength are expired and do not have the dissolution data at 75 minutes.

Therefore, we requested the Applicant to utilize the above dissolution acceptance criteria for both release and stability on an interim basis for one year post-approval. After the Applicant submits more data, we will re-evaluate the dissolution specification.

Figure 1. mean dissolution profiles of clinical batches and clinical and launch batches



4. Information Request 2

On 11/30/2017, the FDA sent another Biopharmaceutics Information Request (IR) to the Applicant. On 12/8/2017, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this Reviewer's assessment of the Applicant's response.

Individual Dissolution Data for Batch 3703D16

Pot	% Release						
	Sampling Time (min)						
	15	30	45	60	75	90	120
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	26.3	54.4	74.1	86.9	92.7	93.5	93.3
%RSD	8.7	7.3	5.6	3.6	2.3	1.2	1.1

Individual Dissolution Data for Batch 3718D16

Pot	% Release						
	Sampling Time (min)						
	15	30	45	60	75	90	120
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	29.3	57.5	75.1	86.6	90.9	92.7	93.0
%RSD	5.9	6.4	5.7	3.7	2.8	1.7	0.7

Individual Dissolution Data for Batch 3719D16

Pot	% Release						
	Sampling Time (min)						
	15	30	45	60	75	90	120
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	26.4	54.3	72.7	84.4	90.6	92.9	92.2
%RSD	13.7	9.7	7.1	4.0	3.3	2.8	1.9

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: N/A

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: N/A

Bridging of Formulations

Reviewer's Assessment: N/A

Biowaiver Request

Reviewer's Assessment:

R Regional Information

Comparability Protocols**Reviewer's Assessment:****Post-Approval Commitments****Reviewer's Assessment:**

Employ the following dissolution specifications for both release and stability on an interim basis for one year post-approval:

30 minutes: (b) (4) %

75 minutes: NLT (b) (4) %

In the meantime, generate and evaluate the dissolution data profile (n=12 tablets/batch, mean, SD, RSD, profiles) using the currently approved dissolution method for release and stability testing for at least 6 production batches. Additionally, submit dissolution data for 112.5 mg clinical batches if unexpired batches are available. Collect dissolution samples at 15, 30, 45, 60, 75, 90, and 120 minutes. Submit the generated dissolution data profiles at your earliest convenience, but by the first Annual Report at the latest, in order to finalize the dissolution acceptance criteria for your drug product.

Lifecycle Management Considerations**List of Deficiencies:**

None.

The applicant has committed to generate and submit dissolution data by the time of first annual report at the latest. Accordingly, the following comments should be included in the Action Letter:

Employ the following dissolution specifications for both release and stability on an interim basis for one year post-approval:

30 minutes: (b) (4) %

75 minutes: NLT (b) (4) %

In the meantime, generate and evaluate the dissolution data profile (n=12 tablets/batch, mean, SD, RSD, profiles) using the currently approved dissolution method for release and stability testing for at least 6 production batches. Additionally, submit dissolution data for 112.5 mg

clinical batches if unexpired batches are available. Collect dissolution samples at 15, 30, 45, 60, 75, 90, and 120 minutes. Submit the generated dissolution data profiles at your earliest convenience, but by the first Annual Report at the latest, in order to finalize the dissolution acceptance criteria for your drug product.

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, PharmD., Ph.D., 10/31/2017, 1/22/2018

Biopharmaceutics reviewer

OPQ/ONDP/Division of Biopharmaceutics

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

Vidula Kolhatkar, Ph.D.; February 01, 2018

Acting Biopharm. Secondary Reviewer

DB/ONDP/OPQ/CDER/FDA



Hansong
Chen

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Vidula
Kolhatkar

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Juandria
Williams

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I. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

Initial Risk Assessment for NDA 208088 Testosterone Undecanoate Capsules, (b) (4) 112.5 mg, as indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Product Attribute / CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Appearance	- Process - Stability	1	3	1	3	
Identification	CGMPs	1	5	1	5	
Assay	- Formulation - Raw materials - Process	2	3	3	18	Drug Load: (b) (4) % in Capsule Fill Not a narrow therapeutic index drug.
Related Substances Impurities / Degradants	- Formulation - Raw materials - Process - Container Closure System	2	3	3	18	Degradation profile adequately characterized; no particularly hazardous degradants identified. Appropriate storage conditions established. (b) (4)
Uniformity of Dosage Units	Formulation	2	3	4	24	Drug Load: (b) (4) % in Capsule Fill
Dissolution	- Raw materials - Formulation	3	3	3	27	(b) (4) Two-tier dissolution test with pepsin.
Microbial Limits	Raw materials	1	4	4	16	(b) (4) Product stored in tight bottle, with desiccant.

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Appearance	• Process • Stability	L	(b) (4)	Acceptable	None.
Identification	• CGMPs	L		Acceptable	None
Assay	• Formulation • Raw materials • Process	L		Acceptable	None
Related Substances Impurities/Degradants	• Formulation • Raw materials • Process • Container Closure System	L		Acceptable	Potential impact of process conditions.
			(b) (4)	(b) (4)	
Uniformity of Dosage Units	• Formulation • Process	L	(b) (4)	Acceptable	Potential impact of process conditions.
Dissolution	• Raw materials • Formulation • Process	M		Acceptable	Potential impact of process conditions.
Microbial limits	• Raw materials • Process	L		Acceptable	None

#####



Mark
Seggel

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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 208088 Review #1

Drug Name/Dosage Form	Tlando (testosterone undecanoate) Capsules
Strength	(b) (4) (b) (4) 112.5mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Lipocine Inc., Salt Lake City, UT
US agent, if applicable	not applicable

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA (0000)	08/28/2015	All
Labeling (0002)	10/14/2015	Product
Quality / Response to IR (0009)	02/17/2016	Biopharmaceutics; Process; Microbiology
Quality / Response to IR (0011)	03/08/2016	Facilities; Product; Process
Quality / Response to IR (0013)	03/25/2016	Process; Product; Biopharmaceutics
Quality / Response to IR (0014)	03/29/2016	Biopharmaceutics
Quality / Response to IR (0015)	04/18/2016	Process; Product; Biopharmaceutics
Quality / Response to IR (0016)	04/29/2016	Product
Quality / Response to IR (0017)	05/03/2016	Biopharmaceutics
PMR/PMC/Quality – Other (0018)	05/24/2016	Biopharmaceutics

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION / BRANCH
Drug Substance	Jeffrey Medwid	ONDP/DNDAP I
Drug Product	Hamid Shafiei	OPQ/ONDP/DNDP II/Branch V
Process	James Norman	OPF/DPAII/BV
Microbiology	James Norman	OPF/DPAII/BV
Facility	Juandria Williams	OPF/DIA/Branch III
Biopharmaceutics	Haritha Mandula	ONDP/DB/Branch II
Regulatory Business Process Manager	Thao Vu	OPRO
Application Technical Lead	Mark Seggel	DNDP II/Branch V
Environmental Assessment (EA)	James Laurenson	ONDP EA Team

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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	J. Medwid; 03/09/16	
	Type III			N/A		
	Type III			N/A		
	Type IV			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		

Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

APPLICATION NUMBER	DOCUMENT	DESCRIPTION
IND 106476	All	Original IND for TU

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	na			
Pharmacology/Toxicology	complete	See attachment to this review.		
DMEPA	complete	Labeling revisions proposed.	05/04/16	W. Fava



QUALITY ASSESSMENT



CDRH	na			
Clinical	na			
Other	na			

na: not applicable

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

In its present form, Lipocine Inc.'s 505(b)(2) New Drug Application #208088, for Testosterone Undecanoate Capsules, 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.

While there are no other outstanding chemistry, manufacturing and controls deficiencies, the Biopharmaceutics review team has requested that Lipocine collect additional dissolution data using the revised methodology to confirm the acceptance criterion (see PMC described below).

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

PMC: Lipocine commits to generate and evaluate the dissolution data profile (n=12 capsules/batch) based on initial (release) testing for at least six production batches (at least 3 batches for each strength). Dissolution testing will be performed using the FDA recommended dissolution method for release and stability testing. The dissolution data profiles will be submitted via a CBE-30 supplement by May 27, 2017.

II. Summary of Quality Assessments

Tlando capsules for oral administration contain testosterone undecanoate (TU), a prodrug of the androgen testosterone (T). Tlando is indicated for testosterone replacement therapy (TRT). Testosterone undecanoate is currently available as Aveed (testosterone undecanoate injection), an oily solution for intramuscular injection (see NDA 22219, AP March 5, 2014). Clarus Therapeutics submitted NDA 206089 for testosterone undecanoate soft gelatin capsules for oral administration in January 2014. A Complete Response letter was issued.

Other approved ester prodrugs of testosterone for TRT include testosterone cypionate and testosterone enanthate. Both are supplied in oily solutions for intramuscular injection.

A. Drug Substance [testosterone undecanoate] Quality Summary

Testosterone undecanoate (TU) is the undecanoic acid ester of testosterone (i.e., 17 β -undecanoyloxy-4-androsten-3-one). Non-specific esterases in the blood, and liver, and intestinal wall, hydrolyze testosterone undecanoate testosterone. While attachment of the medium-chain fatty acid to testosterone does not improve aqueous solubility, it allows for oral drug delivery, targeting absorption via the intestinal lymphatics and reducing the first-pass effect.

Testosterone undecanoate has the empirical formula of C₃₀H₄₈O₃ and a molecular weight of 456.7. (The molecular weight of testosterone is 288.42.) (b) (4). It is insoluble in water (<0.1 μ g/mL), soluble in methanol and isopropanol, and freely soluble in acetone. Only one solid state form of TU has been described.

The manufacture of testosterone undecanoate used in the manufacture of Tlando is documented in (b) (4). (b) (4) Drug Master File (DMF) (b) (4). The DMF was previously reviewed in support of Clarus Therapeutics' unapproved NDA 206089 (testosterone undecanoate soft gelatin capsules). Updates to the DMF were recently reviewed by Dr. Jeff Medwid, and found adequate.

TU is synthesized by the (b) (4). [see review history in darrts; not reviewed in conjunction with NDA 208088]].

The specification necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug product made from the substance (21 CFR 314.50(d)(1)(i)), includes tests for identity, assay ((b) (4) %), optical rotation, residual solvents (complies with ICH Q1C), (b) (4), heavy metals (not more than (nmt) (b) (4) ppm), residue on ignition, and impurities. Specified impurities included (b) (4). Individual unspecified impurities are limited to nmt (b) (4) % and total impurities to nmt (b) (4) %. Overall, the drug substance is of suitable quality for use in Tlando (testosterone undecanoate) Capsules.

A (b) (4) month retest period for drug substance stored at (b) (4) has been established.

Note that Phase I and nonclinical studies were conducted with TU supplied by (b) (4) and (b) (4). These materials were of comparable quality to the (b) (4) API.

This NDA is recommended for approval from the CMC drug substance perspective. All CMC issues concerning the drug substance have been satisfactorily resolved.

B. Drug Product [testosterone undecanoate capsules] Quality Summary

Testosterone undecanoate capsules were developed as an immediate release, (b) (4) oral dosage form for testosterone replacement therapy. The formulation provides for a (b) (4) system after administration. (b) (4) (b) (4) testosterone undecanoate capsules will be available in (b) (4) (b) (4) 112.5 mg strengths (equivalent (b) (4) 71.2 mg testosterone, respectively, assuming complete hydrolysis of the ester linkage). (b) (4)

The proposed labeled doses of testosterone undecanoate are (b) (4) 225 mg (b) (4) 2 x 112.5 mg (b) (4) (b) (4) administered twice daily.

The drug products are prepared from (b) (4) the following excipients: (b) (4) (glyceryl monolinoleate; (b) (4) polyoxyl 40 hydrogenated castor oil (b) (4) (b) (4) ascorbyl palmitate (b) (4) and (b) (4) polyethylene glycol 8000 (b) (4) (b) (4)

Typically, capsule shells are imprinted with a (b) (4) code number (b) (4) (b) (4) Given the similarity of the capsules (b) (4) and (b) (4) Ideally, the capsules also would have been imprinted with the strength.

All excipients are compendial and are commonly used in other approved oral products. The gelatin capsules are manufactured by (b) (4) meet all USP/NF and Ph. Eur. requirements, and comply with TSE/BSE regulations.

Note that the to-be-marketed formulation was used in Phase III clinical trials; a Phase I formulation (b) (4)

Testosterone undecanoate capsules, (b) (4) 112.5 mg, are packaged in 120-count, (b) (4) HDPE bottles, respectively. Bottles are provided with a (b) (4), and a silica gel desiccant pack to absorb moisture. The bottles induction sealed with a child-resistant closure. The 120 capsule count bottles provide a 30 day supply of the (b) (4) twice daily 2 x 112.5 mg dose.

The regulatory specification necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product at release and on stability includes tests for capsule appearance, identity, assay (b) (4) (%), uniformity of dosage units (by capsule weight), (b) (4) microbial limits, and impurities. The specified impurities consist of the (b) (4)

(b) (4) Dr. Laurie McCleod-Flynn, DBRUP Pharm./Tox. reviewer was consulted regarding potential toxicology issues with the (b) (4) Based on an in-silico QSAR evaluation of the mutagenicity of this (b) (4) impurity, Dr. McLeod-Flynn concluded that the limit of (b) (4) % previously approved by the Division is acceptable. Unspecified impurities are limited to nmt (b) (4) % each and nmt (b) (4) % in total. A limit of nmt (b) (4) % total specified and unspecified impurities has been established.

Based on the available stability data, an expiration dating period of 24-months when the drug product is stored at 25°C/60% RH has been granted

Dr. Hamid Shafiei recommends approval of the application from the ONDP drug product CMC perspective.

Product Manufacturing Process

(b) (4)

(b) (4)

Dr. James Norman, OPF reviewer, concluded that, “for this stage of the product lifecycle, the applicant has provided adequate information to show that the process is reliable and robust. The process is adequate, as amended, for NDA approval.”

Product Quality Microbiology

Dr. Norman concluded that, “the microbial controls are adequate for this gelatin product. The applicant proposed to test every lot at release according to USP <61,62> with limits in line with USP <1111>. Every stability batch is proposed to be tested according to the ICH Q1A schedule...The applicant also controls the (b) (4) in the finished product and ensures that the raw materials will comply with the USP <1111> limits. The product is also packaged with desiccant, which should limit microbial growth. Overall, the microbiology control, as amended, for this product is adequate according to current quality standards.”

Biopharmaceutics

In order to assure quality control and consistent bioavailability, an in-vitro dissolution test was proposed by the applicant. The method employed (b) (4)

(b) (4) However, from the Biopharmaceutics perspective, the proposed (b) (4)

(b) (4). At the request of Dr. Haritha Mandula, ONDP Division of Biopharmaceutics, the method has been revised to use a 1% Triton X-100 dissolution medium. However, most dissolution data for drug product at release and on stability was obtained using the older test conditions. Only limited data are available using the revised conditions on older samples. Until additional data from newly manufactured product batches becomes available, an acceptance criterion of $Q = \frac{(b)(4)}{(4)}\%$ in $\frac{(b)(4)}{(4)}$ minutes is approved on an interim basis. Lipocine has agreed to a post-marketing commitment (PMC) to submit a CBE-30 supplement proposing a final acceptance criterion within 11 months of approval. Data from three newly manufactured production batches of each capsule strength at release and on stability will be submitted. It is anticipated that these data will confirm the acceptance criterion of $Q = \frac{(b)(4)}{(4)}\%$ in $\frac{(b)(4)}{(4)}$ minutes.

(b) (4)

(b) (4)
a two-tier dissolution test is appropriate. If drug product fails Stage 1 testing (n = 6; 1% Triton X-100 [i.e., Tier I]), testing will be repeated using the Tier I medium plus enzyme, pH 2.0 ($\leq 75,000$ units Pepsin / L).

In-vitro alcohol dose-dumping was observed in medium containing 20% and 40% alcohol. This observation has been conveyed to the clinical pharmacology review team for assessment of potential clinical impact.

As amended, this NDA is recommended for approval from the Biopharmaceutics perspective.

C. Manufacturing Facilities

Testosterone undecanoate drug substance is manufactured at (b) (4),
(b) (4) Drug substance testing is performed at (b) (4). These three API-related facilities have acceptable CGMP status.

The drug product is manufactured and tested by (b) (4).
(b) (4) Drug product is packaged by (b) (4). Additional product testing is conducted by (b) (4).
(b) (4) All facilities have acceptable CGMP status.

Dr. Juandria Williams, in OPQ's Office of Process and Facilities, has concluded that, "there appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval to support approval of NDA 208088."

D. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Tlando
Non Proprietary Name of the Drug Product	testosterone undecanoate capsules
Non Proprietary Name of the Drug Substance	testosterone undecanoate
Proposed Indication(s) including Intended Patient Population	The drug product is indicated for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.
Duration of Treatment	Duration not specified, but could be long-term
Dosage Strengths	(b) (4) 112.5mg testosterone undecanoate (TU), (b) (4)
Dosing Regimen	(b) (4) (b) (4) 225 mg (b) (4) oral with food, twice daily (b) (4)

Maximum Daily Dose	(b) (4) mg TU / day
Alternative Methods of Administration	None.

E. Biopharmaceutics Considerations

1. BCS Classification: Not provided

- Drug Substance: Aqueous < (b) (4) µg/mL. Soluble in methanol, isopropanol and freely soluble in acetone. . Laboratory solubility analysis suggests the Biopharmaceutical Classification System (BCS) classification of testosterone undecanoate as a poorly soluble compound. (The measured solubility is well below the required solubility of the (b) (4).)
- Drug Product: Not provided

2. Biowaivers/Biostudies

- Biowaiver Requests: None
- PK studies: Yes, these will be reviewed by Division of Clinical Pharmacology.
- IVIVC: None

F. Novel Approaches

Not applicable.

G. Any Special Product Quality Labeling Recommendations

The labeling will indicate that the drug product should be dispensed in the original container.

H. Life Cycle Knowledge Information (see Attachment A)

I. Environmental Analysis

While there clearly is some potential for hormonal activity from this product, which raised concern per recent draft FDA guidance on hormonally active drugs in the environment, 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)). Thus, the request for a categorical exclusion from an environmental assessment (EA), supplemented by information submitted by the applicant 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.

Furthermore, an adequate statement of no extraordinary circumstances was provided. The claim of categorical exclusion is accepted.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Recommendation and Signature:

I concur with the OPQ review team recommendations that this 505(b)(2) NDA be approved pending finalization of the labeling, as required under 21 CFR 314.125(b)(8).

Mark R. Seggel
CMC Lead (acting)
ONDP Div. II / Branch V
May 31, 2016

Mark R.
Seggel -
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facilities are determined acceptable to support approval of ANDA 208088.

Juandria Williams, PhD; DIA/B3
May 7, 2016

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Secondary Review Comments and Concurrence:

I concur

Grace E. McNally, Acting Branch Chief, OPQ/OPF/DIA
May 10, 2016

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ASSESSMENT OF THE BIOPHARMACUETICS

28. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

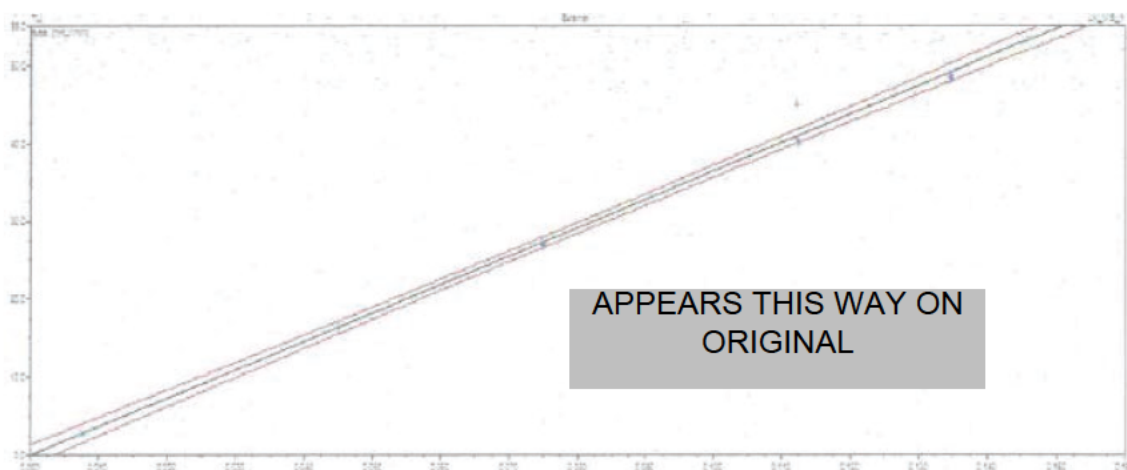
Applicant's Response:

Dissolution Method Validation:

The dissolution method validation was proposed for the analysis of Testosterone undecanoate capsules to support release of product for Phase III clinical trials and stability studies. The method was developed by (b) (4) based on a method supplied by the client and validated in accordance with protocol MWEPROT0620 v01. The method has been validated for specificity, linearity, precision, accuracy, solution stability, robustness, sink condition evaluation and filter compatibility.

The applicant proposed Addendum 01 to MWEPRQT0620 v01, which details the supplemental validation required to support the use of pepsin in the dissolution media. This dissolution media has been proposed for clinical, commercial release and stability batches which require stage 2 testing as a result of (b) (4). The supplemental validation parameters assessed were accuracy, solution stability and comparison of reference standard response.

Linearity:



Robustness:

Name	Peak Area	% Recovery	RT	Asymmetry	Column Efficiency
Nominal Sample	6251.495	100.4	6.692	1.248	4237
Sample 1 – Column temperature 27°C	6271.376	100.7	7.213	1.262	4028
Sample 2 – Column Temperature 33°C	6247.173	100.5	6.214	1.222	3808
Sample 3 – Flow rate 0.9ml/min	6962.625	100.6	7.451	1.246	3822
Sample 4 – Flow rate 1.1ml/min	5694.317	100.5	6.070	1.236	3979
Sample 5 – MP composition 88:12 MeOH:H ₂ O	6264.934	100.6	10.821	1.262	3806
Sample 6 – MP composition 92:8 MeOH:H ₂ O	6271.175	100.8	5.242	1.257	3811
Sample 7 – Wavelength 240nm	6228.909	100.6	6.695	1.253	3466
Sample 8 – wavelength 244nm	6176.034	100.6	6.693	1.246	3438
Sample 9 – injection volume 38µl	5953.809	100.6	6.695	1.256	3411
Sample 10 – injection volume 42µl	6579.271	100.6	6.698	1.256	3212

Parameter	Status (Pass/Fail)	Acceptance Criteria	Result Reference
Sink condition confirmation (Solubility)	N/A	For information only	Section 4.1 Table 1
Filter compatibility	Pass	(b) (4) % recovery compared with control	Section 4.2 Table 2
Specificity	Pass	There must be no significant interference (b) (4) % area) of the Testosterone Undecanoate (TU) peak from the excipients, dissolution medium or diluent solutions.	Section 4.3 Figure 1
Precision (Repeatability of Determination)	Pass	Response (peak area) $RSD\% \leq \frac{(b)(4)}{(4)}$ n=6 Retention time $RSD\% \leq \frac{(b)(4)}{(4)}$ n=6	Section 4.4 Table 3-4
Precision (Repeatability of Preparation)	Pass*	<u>Standards:</u> Response factor (area response/concentration $RSD\% \leq \frac{(b)(4)}{(4)}$ n=6) Retention time $RSD\% \leq \frac{(b)(4)}{(4)}$ n=6) <u>Samples:</u> At 60 minutes: $RSD\% \leq \frac{(b)(4)}{(4)}^{**}$ (n=6)	Section 4.5 Table 5-8
Intermediate Precision	Pass	$RSD\% \leq \frac{(b)(4)}{(4)}$ (n=12)	Section 4.6 Table 9-12
Linearity	Pass	The R^2 obtained for the slope of recovery vs concentration must be $\geq \frac{(b)(4)}{(4)}$ The %RSD of the response factor (Area response/concentration) must be $\leq \frac{(b)(4)}{(4)}\%$. The y-intercept must be within $\pm \frac{(b)(4)}{(4)}\%$ of the area response obtained from the equation of the line for a theoretical 100% solution.	Section 4.7 Table 13 Figure 2
Accuracy	Pass*	(b) (4) % theoretical	Section 4.8 Table 14-15
Solution Stability	Pass	(b) (4) % difference from initial.	Section 4.9 Table 16-23
Reference Standard Response	Pass	(b) (4) %	Section 4.10 Table 24

* refer to section 5 for discussion

** criteria updated refer to section 5 for discussion

Dissolution Method Development:

(b) (4)

Justification of specifications:

A dissolution acceptance criterion of Q greater than (b) (4)% label claim was originally established for testosterone undecanoate capsules based on release and stability testing of the registration batches using the (b) (4)% Triton X-100 dissolution method. Subsequently, the Office of Pharmaceutical Quality (OPQ) recommended that the applicant use a dissolution method including 1% Triton X-100 as the dissolution medium. A 1% Triton X-100 dissolution method was developed by the drug product manufacturer, and the 30 month stability samples of the registration batches were tested. When the dissolution medium was changed to 1% Triton X-100, the release rates observed were about (b) (4)% lower than those observed using (b) (4)% Triton X-100. Therefore, the dissolution results from the 30 month samples were used to develop a new dissolution acceptance criterion, as summarized below.

(b) (4)

Based on dissolution stability data from registration lots for the 112.5 mg capsule:

- The minimum individual value observed after 1 hour dissolution was (b) (4)% at the 30 month timepoint for lot 3316K13A.
- The minimum mean value (n=6) observed after 1 hour dissolution was (b) (4)% at the 30 month timepoint for lot 3315J13A.

Given the dissolution stability data gathered to date, a dissolution acceptance criterion of Q greater than (b) (4)% label claim at (b) (4) (b) (4) is proposed by the applicant.

Reviewer's Assessment:

- The dissolution method is adequately validated for specificity, linearity, precision, accuracy, solution stability, robustness, sink condition evaluation and filter compatibility. As requested the applicant also provided additional method validation for the revised final dissolution method using 1% Triton X-100 as the dissolution medium. The method validation is adequate.
- The applicant submitted a detailed method development report which explored the impact of surfactant, apparatus, volume, speed and addition of enzyme. The applicant's dissolution method development report and the final accepted method are adequate.
- Effect of (b) (4) was observed in stability batches as early as 6 months. (b) (4) effect was observed during dissolution testing of fresh production lots.
- A two tier dissolution testing method has been recommended for routine quality

control and stability testing, which the applicant accepted.

The two-tier dissolution method is recommended if the gelatin capsule product fails the initial dissolution testing.

- Tier I: USP Type II, RPM: 100 ± 2 ; 1000 mL of 1% Triton-X in DI Water
- Tier II: Tier I + Enzyme ($<75,000$ units/L Pepsin)
- The applicant submitted alcohol dose dumping data as requested during the pre-IND meetings. There was an effect of dose dumping observed with increasing concentrations of alcohol. The Office of Clinical Pharmacology was requested to interpret this finding in light of the need for any in vivo alcohol dose dumping study with this drug product.
- The proposed dissolution specification of NLT (b) (4) % (Q) in (b) (4) minutes is approved on an interim basis for one year based on the data submitted. In the meantime, the applicant will be requested to generate and evaluate the dissolution data using the FDA recommended dissolution method for release and stability testing for batches manufactured for one year post-approval. After one-year post-approval, the applicant should submit the generated dissolution data and justification of the proposed dissolution specification for review in order to finalize the dissolution specification for both release and stability testing for the drug product.

29. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Applicant's Response: n/a

Reviewer's Assessment: There were no changes in the formulation, manufacturing process, manufacturing sites during the development to the commercial product.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

A two tier dissolution testing method has been recommended for routine quality control and stability testing, which the applicant accepted and updated their methods section.

The two-tier dissolution method is recommended if the gelatin capsule product fails the initial dissolution testing.

- Tier I: USP Type II, RPM: 100 ± 2 ; 1000 mL of 1% Triton-X in DI Water
- Tier II: Tier I + Enzyme (<75,000 units/L Pepsin)

The following comments should be conveyed to the applicant in the action letter:

Your proposed dissolution acceptance criterion of NLT $\frac{(b)}{(4)}\%$ (Q) in $\frac{(b)}{(4)}$ minutes for both release and stability is approved on an interim basis for one year post-approval.

In the meantime, generate and evaluate the dissolution data profile (n=12 tablets/batch) using the FDA recommended dissolution method for release and stability testing for at least 6 production batches. Submit the generated dissolution data profiles (using the FDA recommended dissolution method) at your earliest convenience, but by the first Annual Report at the latest, in order to finalize the dissolution acceptance criterion for your drug product.

Haritha Mandula, Ph.D.
Biopharmaceutics Reviewer,
Office of New Drug Products,
05/13/2016

Haritha
Mandula -A

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ou=People,
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cn=Haritha Mandula -A
Date: 2016.06.01 18:32:08 -04'00'

Secondary Review Comments and Concurrence:

I concur with the Biopharmaceutics assessment.

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Quality Assessment Lead (Acting)
Division of Biopharmaceutics, Branch II
May 16, 2016

Kelly M.
Kitchens -S

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ASSESSMENT OF MICROBIOLOGY

30. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:Pharmaceutical Development - Microbiological Attributes: 3.2.P.2.5

The manufacturing process for testosterone undecanoate capsules consists of

(b) (4)

(b) (4)

In addition, batches will be tested by USP <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests and <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms as detailed in USP <1111> Microbiological Attributes of Nonsterile Pharmaceutical Products.

Raw Material Controls: 3.2.P.4

(b) (4)

Relevant Specifications: 3.2.P.5.1

(b) (4)

Microbial Limit		
Total aerobic count		(b) (4) cfu/g
Total yeast and moulds	USP <61,62>	NMT (b) (4) cfu/g
Absence of E. coli		Absent in (b) (4)

Reviewer's Note: Each bottle contains a desiccant pouch

(b) (4)

(b) (4)

(b) (4)

Microbial testing results for both lots at t=6 months met the proposed specifications of NMT (b) (4) cfu/g for total aerobic count, NMT (b) (4) cfu/g for total yeasts and moulds, and Absent in (b) (4) g for absence of *E. coli*. No microbial testing was required at t=3 months.

Stability Data – 3.2.P.8.1 and 3.2.P.8.3

Reviewer's Note: Microbial limits were tested at t=0 and 6 months under accelerated conditions and t=0 and 12 months under long-term conditions. The applicant did not provide any stability data at t = 24 mo.

(b) (4)

Results from Testosterone Undecanoate 112.5 mg Capsules Primary Stability Batches

(b) (4)

Microbial Limit	The total aerobic count was < (b) (4) cfu/g at all timepoints. The total yeasts and molds was < (b) (4) cfu/g at all timepoints. <i>E. coli</i> was absent at all timepoints.
-----------------	---

Reviewer's Assessment: Adequate

The applicant proposes to test microbial limits at release according to USP <1111> (NMT 10³ TAMC, NMT 10² TYMC, absence of *E. Coli*) and test according to the ICH Q1A schedule during stability testing.

The product exhibited no microbial growth over 6 mo. ACC and 12 mo. LT stability testing. Capsules are packed with desiccant in induction-sealed bottles and tested to contain NMT (b) (4) % w/w by (b) (4). In addition, the raw materials are low bioburden.

2.3.P.7 Container/Closure System

31. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Reviewer's Assessment: N/A for solid oral dosage forms

The product is packaged in induction-sealed HDPE bottles. Refer to the drug product assessment for an evaluation of the container/closure system.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

32. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Section 3.2.P.4.5 Excipients of Human or Animal Origin

(b) (4) capsules: [TSE Statements and Certifications](#)

(b) (4) for banding: [BSE-TSE Statement](#)

Reviewer's Assessment: Adequate

The applicant provided TSE/BSE certification for the only two excipients of animal origin.

33. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Reviewer's Assessment: N/A

N/A for solid oral dosage forms

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY**Reviewer's Assessment and Signature:**

The microbial controls are adequate for this gelatin product. The applicant proposed to test every lot at release according to USP <61,62> with limits in line with USP <1111>. Every stability batch is proposed to be tested according to the ICH Q1A schedule.

This alone would be sufficient. The applicant also controls the (b) (4) in the finished product and ensures that the raw materials will comply with the USP <1111> limits. The product is also packaged with desiccant, which should limit microbial growth. Overall, the microbiology control, as amended, for this product is adequate according to current quality standards.

James Norman, Ph.D., OPF/DPAII/BV, 05/06/2016

James J. Norman
-S (Affiliate)

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(Affiliate)
DN: c=US, o=U.S. Government, ou=HHS,
ou=CDER, ou=People,
o=973421920030010011-1001560894,
cn=James J. Norman S (Affiliate)
Date: 2016.06.01 14:41:58 -0400

Secondary Review Comments and Concurrence:

I concur with Dr. James Norman's assessment and conclusion.

Yubing
Tang -A

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o=973421920030010011-1300085
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Date: 2016.06.01 22:38:17 -0400

Yubing Tang, Ph.D., Acting Branch Chief, OPF/DPAII/BV, 05/06/2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

34. Is the applicant's claim for categorical exclusion acceptable?

35. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

As part of IND 106476, the applicant stated their expectation that the NDA would qualify for exclusion from environmental assessment requirements under 21 CFR 25.31(b) and (c), and asked whether FDA agreed. FDA replied with concerns regarding both exclusions. Also, a statement regarding extraordinary circumstances, per 21 CFR 25.15(a), was absent, and such a statement must accompany a claim for categorical exclusion.

Regarding 21 CFR 25.31(b), while the product appeared to qualify for a categorical exclusion under this exclusion, based on the less than 1 ppb expected introduction concentration (EIC) calculated in Appendix 14 of the applicant's Type B, Pre-NDA Meeting Briefing Package, the published literature indicated that this product has the

potential for harm to the environment at EICs less than 1 ppb.² Testosterone also is androgenic and thus subject to the 2015 draft FDA guidance, *Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity*, which notes that this product could constitute an "extraordinary circumstance" if available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment (21 CFR 25.21(a)). Nevertheless, the calculated EIC appeared to be significantly lower than relevant predicted no effects concentrations (PNECs) in the literature.³ Therefore, FDA requested a brief review of the relevant literature or other data to substantiate the claim for a categorical exclusion under 21 CFR 25.31(b).

Regarding 21 CFR 25.31(c), the product did not appear to qualify for the exclusion due to the lack of data to substantiate the claim that the substance occurred naturally in the environment and the action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Supporting data was requested.

Reviewer's Assessment:

As part of NDA 208088, the applicant provided the requested data to support the exclusions under 21 CFR 25.31(b) and (c). Specifically, they noted that:

1. A model-based estimated surface water concentration of testosterone from anthropogenic activity is (b) (4)
2. There is rapid degradation of testosterone in the environment via aerobic biodegradation.
3. The predicted no-effect concentration (PNEC) value for testosterone is (b) (4) ng/L ((b) (4) ppb), which exceeds the EIC of (b) (4)
4. Animal feeding operations are a major source of testosterone in the environment resulting in surface water levels as high as of (b) (4) ng/L ((b) (4) ppb), which is (b) (4) times the EIC estimated for sponsor's drug ((b) (4))

The applicant argued that the EIC of (b) (4) ppb is far lower than concentrations resulting from other factors such as animal feeding operations. Furthermore, they stated, rapid degradation of testosterone in the environment indicates that any environmental burden due to the applicant's drug will have negligible environmental impact. The applicant also

² For example, see Section II.C (pp. 7-13) of USFDA, 2013, "Response to Citizen Petition to the FDA Commissioner under the National Environmental Policy Act and Administrative Procedure Act Requesting an Amendment to an FDA Rule Regarding Human Drugs and Biologics," Docket No. FDA-2010-P-0377.

³ For example, see Khan, U. and Nicell, J. (2010), "Assessment of the Aquatic Release and Relevance of Selected Endogenous Chemicals: Androgens, Thyroids and Their in Vivo Metabolites," *Contaminants of Emerging Concern in the Environment: Ecological and Human Health Considerations*, R. U. Halden. Washington, DC, American Chemical Society: 437-468.

noted that the active moiety, testosterone, is found naturally in the environment. The applicant concluded that the available data establish that, at the expected level of exposure, there is no potential for serious harm to the environment.

The calculations used by the applicant to estimate an EIC of (b) (4) ppb, and thus an EIC < 1 ppb, appear to be correct, which satisfies the categorical exclusion of 21 CFR 25.31(b). The applicant also noted that testosterone is naturally found in the environment, but does not provide any argument that the action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products. Such an argument would be needed under 21 CFR 25.31(c). The applicant did highlight the much higher amounts of testosterone potentially occurring near animal feeding operations, but these are not naturally occurring levels and thus are not relevant for this exclusion.

Given that the exclusion under 21 CFR 25.31(b) appears valid, the question then is whether approval of the application would constitute extraordinary circumstances by significantly affecting the quality of the human environment. The applicant provided a detailed review of the literature focusing on predicted environmental concentrations (PECs) of testosterone in surface water; calculation of risk quotients, RQs (PECs/PNECs), of less than 1; a review of the metabolism/excretion of testosterone in humans; and an estimate of the EIC RQ, also less than 1. Using the results for three different eco-toxicity assays that assessed chronic exposure, and involved three different taxa, the applicant estimated a PNEC for testosterone to be (b) (4) ppb. The RQ data in particular show that the resulting estimated RQs due to this product would range up to approximately (b) (4) even with several worst-case assumptions associated with the EIC. 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)).

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

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. Furthermore, a statement of no extraordinary circumstances was provided. The claim of categorical exclusion is accepted.

James P. Laurenson, Environmental Officer, CDER/OPQ/ONDP EA Team, 5/4/2016

Digitally signed by James P. Laurenson -S

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Secondary Review Comments and Concurrence:

Concur

M. Scott Furness, Deputy Director, ONDP 5/6/2016

Michael S.
Furness -S

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I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert



(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	TRADE NAME (testosterone undecanoate)	Proprietary name Tlando has been accepted by the Agency and will be displayed when labeling is resubmitted. Established name is provided. Satisfactory
Dosage form, route of administration	Capsules for oral use	Dosage form and route of administration are provided. Satisfactory
Controlled drug substance symbol (if applicable)	CIII	Provided Satisfactory
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	TRADE NAME is available as (b) (4) 112.5mg capsules	The dosage forms and strengths are described correctly. Satisfactory

Conclusion:

The Highlights Section of the PI is Adequate.

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Oral capsules	Provided Satisfactory
Strengths: in metric system	112.5mg (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	Not provided Unsatisfactory

Conclusion:

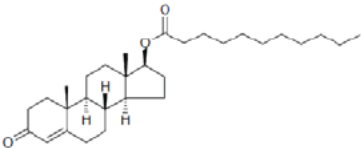
Not adequate. Provide the description of the identifying characteristics of the dosage forms.

#11: Description (21CFR 201.57(c)(12))

(b) (4)



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	TRADE NAME and testosterone undecanoate are provided but not appropriately.	Need revising. Unsatisfactory
Dosage form and route of administration	(b) (4) 112.5mg capsules. Route of administration is not provided.	Rout of administration is not provided. Unsatisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	(b) (4) and 112.5mg testosterone undecanoate (b) (4) (b) (4)	Provided Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Inactive ingredient information is provided.	Provided. Satisfactory
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class	Not clearly stated	Not clear. Unsatisfactory

Chemical name, structural formula, molecular weight	Chemical Name: 17β-undecanoyloxy-4-androsten-3-one Structural formula:  Molecular weight: 456.7 Empirical formula: C₃₀H₄₈O₃	All necessary information provided. Satisfactory
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)	Testosterone undecanoate is a white to off-white crystalline substance.	Provided. Satisfactory

Conclusion:

Not adequate. Revise the description section and include the following changes:

- 1) The drug product name should include established name, i.e., TRADE NAME (testosterone undecanoate)
- 2) Add route of administration
- 3) Provide pharmacological/therapeutic class

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	{TRADE NAME} is a capsule product containing 112.5 mg testosterone undecanoate (b) (4) (b) (4)	Strength provided Satisfactory
Available units (e.g., bottles of 100 tablets)	{TRADE NAME} is supplied in HDPE bottles with a foil liner and a child resistant cap. Units are not provided (b) (4)	Not provided Unsatisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	NDC numbers not provided. Unsatisfactory
Special handling (e.g., protect from light, do not freeze)	Not applicable	Not applicable
Storage conditions	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP controlled room temperature.]	Provided. Satisfactory

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: (b) (4)	Provided. Satisfactory

Conclusion:

Not adequate. Revise this section to include the following information:

- 1) Available units per each strength
- 2) NDC number for each available units per strength

2. Container and Carton Labeling

1) Immediate Container Label

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	LPCN 1021 (testosterone undecanoate)	LPNC 1021 will change to approved Trade Name, Tlando. Font size and prominence of the trade name and established name is acceptable Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(b) (4) 112.5mg	Provided Satisfactory
Route of administration (21.CFR 201.100(b)(3))	Not provided	Not provided Unsatisfactory
Net contents* (21 CFR 201.51(a))	120 capsules	Provided Satisfactory
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	(b) (4)	Provided. Satisfactory
Lot number per 21 CFR 201.18	The location on the immediate container label where the lot number will be displayed is provided. Satisfies 21 CFR 201.18.	Provided Satisfactory
Expiration date per 21 CFR 201.17	The location on the immediate container label where the expiration date will be displayed is provided. Satisfies 21 CFR 201.17.	Provided Satisfactory
“Rx only” statement per 21 CFR 201.100(b)(1)	“Rx only” is displayed. Satisfies 21 CFR 201.100(b)(1).	Displayed
Storage (not required)	Storage condition displayed.	Provided Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Displayed	Provided Satisfactory
Bar Code per 21 CFR	Bar Code is displayed.	Provided

201.25(c)(2)***		Satisfactory
Name of manufacturer/distributor (21 CFR 201.1)	Name of manufacturer/distributor is appropriately displayed.	Provided Satisfactory
Others	Not applicable	Not applicable

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

Not adequate. The container label should be revised to include the approved trade name and route of administration.

2) Carton Labeling

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		(b) (4)
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables) [201.10(a), 21CFR201.100(d)(2)]		
Sterility Information (if applicable)		
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		
Storage Conditions		

NDC number
(per 21 CFR 201.2)
(requested, but not required
for all labels or labeling), also
see 21 CFR 207.35(b)(3)

Bar Code per 21 CFR
201.25(c)(2)**

Name of
manufacturer/distributor

“See package insert for dosag
information” (21 CFR 201.55

“Keep out of reach of
children” (optional for Rx,
required for OTC)

Route of Administration (not
required for oral, 21 CFR
201.100(d)(1) and (d)(2))

Conclusion:

Not adequate.

(b) (4) ,,

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer’s Assessment and Signature:

The following CMC label/labeling deficiencies need to be addressed before the approval of this application:

A. Package Insert:

1) #3 Dosage Forms and Strengths:

- Provide the description of the identifying characteristics of the capsules

2) #11 Description:

- Revise the drug product name to include established name, i.e.,

TRADE NAME (testosterone undecanoate)

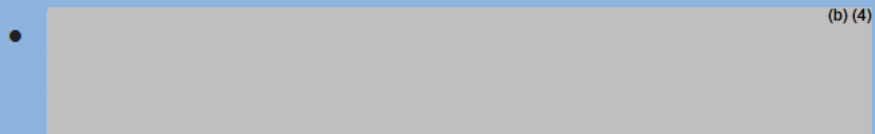
- Add route of administration
- Provide pharmacological/therapeutic class

3) #16: How Supplied/Storage and Handling:

- Provide available units in commercial packaging for each strength
- Provide NDC number for each packaging configuration

B. Immediate Container and Carton Labels:

- Revised the immediate container label to include the approved trade name and route of administration.



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

**Hamid
Shafiei -S**

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cn=Hamid Shafiei -S,
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Secondary Review Comments and Concurrence:

I concur with Dr. Shafiei's assessment on the labeling and labels.

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

Moojhong Rhee -S

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II. List of Deficiencies To Be Communicated

A. Biopharmaceutics

The following comment was communicated to the applicant as a post-marketing commitment (PMC):

Your proposed dissolution acceptance criterion of NLT (b) (4) % (Q) in (b) (4) minutes for both release and stability is approved on an interim basis for one year post-approval.

In the meantime, generate and evaluate the dissolution data profile (n=12 tablets/batch) using the FDA recommended dissolution method for release and stability testing for at least 6 production batches. Submit the generated dissolution data profiles (using the FDA recommended dissolution method) at your earliest convenience, but by the first Annual Report at the latest, in order to finalize the dissolution acceptance criterion for your drug product.

B. Label/Labeling

1. Package Insert:

1) #3 Dosage Forms and Strengths:

- Provide the description of the identifying characteristics of the capsules

2) #11 Description:

- Revise the drug product name to include established name, i.e., *TRADE NAME (testosterone undecanoate)*
- Add route of administration
- Provide pharmacological/therapeutic class

3) #16: How Supplied/Storage and Handling:

- Provide available units in commercial packaging for each strength
- Provide NDC number for each packaging configuration

2. Immediate Container and Carton Labels:

- Revised the immediate container label to include the approved trade name and route of administration.

- (b) (4)

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

Initial Risk Assessment for NDA 208088 Testosterone Undecanoate Capsules, (b) (4)
112.5 mg, as indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Product Attribute / CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Appearance	• Process • Stability	1	3	1	3	
Identification	• CGMPs	1	5	1	5	
Assay	• Formulation • Raw materials • Process	2	3	3	18	Drug Load: (b) (4) % in Capsule Fill Not a narrow therapeutic index drug.
Related Substances Impurities / Degradants	• Formulation • Raw materials • Process • Container Closure System	2	3	3	18	Degradation profile adequately characterized; no particularly hazardous degradants identified. Appropriate storage conditions established. (b) (4)
Uniformity of Dosage Units	• Formulation (b) (4)	2	3	4	24	Drug Load: (b) (4) % in Capsule Fill
Dissolution	• Raw materials • Formulation (b) (4)	3	3	3	27	(b) (4)
Microbial Limits	• Raw materials (b) (4)	1	4	4	16	(b) (4) (u) (4) Product stored in tight bottle, with desiccant.

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Appearance	• Process • Stability	L	(b) (4)	Acceptable	None.
Identification	• CGMPs	L		Acceptable	None
Assay	• Formulation • Raw materials • Process	L		Acceptable	None
Related Substances Impurities/Degradants	• Formulation • Raw materials • Process • Container Closure System	L		Acceptable	Potential impact of process conditions.
(b) (4)					
Uniformity of Dosage Units	• Formulation • Process	L	(b) (4)	Acceptable	Potential impact of process conditions.
Dissolution	• Raw materials • Formulation • Process	M		Acceptable	Potential impact of process conditions.
Microbial limits	• Raw materials • Process	L		Acceptable	None

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