CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022219Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: February 24, 2014

From: Yichun Sun, Ph.D.
Review Chemist, ONDQA
Division of New Drug Quality Assessment II
ONDQA

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

To: NDA 22219, CMC Review #3

Subject: Approval

The NDA was **NOT recommended for approval** due to lacking an overall "Acceptable" recommendation from the Office of Compliance at the time of Review #3 was written.

The overall **"Acceptable"** recommendation of **Establishment Evaluation** has been provided by the Office of Compliance (see Attachment 1).

As stated in Review #3, the two referred DMFs ((b) (4) and (b) (4)) are deemed adequate to support the NDA. The labels and labeling have been reviewed and found acceptable. **Thus, this application is now recommended for approval from the ONDQA's perspective.** An expiration dating period of 60 months is recommended for the drug product based on the available stability data.

Attachment - 1 (Summary Report of Establishment Evaluation)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22219/000	**Sponsor:**	ENDO PHARMS
Org. Code:	580		1400 ATWATER DR
Priority:	3		MALVERN, PA 19355
Stamp Date:	26-AUG-2007	**Brand Name:**	AVEED
PDUFA Date:	28-FEB-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	TESTOSTERONE UNDECANOATE
District Goal:	30-DEC-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; INJECTION; TESTOSTERONE UNDECANOATE; 250MG/1ML

FDA Contacts:	Y. SUN	Prod Qual Reviewer		3017961388
	V. PAWAR	Micro Reviewer	(HFD-805)	3017961587
	K. JENNINGS	Product Quality PM		3017962919
	J. ROULE	Regulatory Project Mgr	(HFD-580)	3017963993
	D. CHRISTNER	Team Leader		3017961341

Overall Recommendation:	ACCEPTABLE	on 24-FEB-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 17-SEP-2013	by EES_PROD		
	ACCEPTABLE	on 25-JAN-2013	by T. SHARP	()	3017963208
	PENDING	on 16-JAN-2013	by EES_PROD		
	PENDING	on 07-JAN-2013	by EES_PROD		
	PENDING	on 07-JAN-2013	by EES_PROD		
	ACCEPTABLE	on 26-MAR-2009	by FERGUSONS		
	ACCEPTABLE	on 26-JUN-2008	by FERGUSONS		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:	(b) (4)	**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
		(b) (4)	
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-FEB-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	**FEI:** (b) (4)	
		(b) (4)	
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

/s/

YICHUN SUN
02/25/2014

MOO JHONG RHEE
02/25/2014
Chief, Branch IV

NDA 22219

Aveed® (testosterone undecanoate) injection

Endo Pharmaceuticals, Inc.

Yichun Sun, Ph.D.

Review Chemist

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

CMC REVIEW OF NDA 22219
For the Division of Reproductive and Urologic Products (HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. NDA: #22219

2. REVIEW #: 3

3. REVIEW DATE: 3-February-2014

4. REVIEWER: Yichun Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-IND meeting minutes	November 30, 2005
IND 72,297	February 3, 2006
Original	August 24, 2007
Amendment	February 11, 2008
Amendment	February 22, 2008
Amendment	March 11, 2008
Amendment	April 30, 2008
Amendment	May 28, 2008
Amendment)	March 2, 2009
Amendment	March 27, 2009
Amendment	April 21, 2009
Amendment	June 8, 2009
Amendment	December 19, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	August 29, 2013
Amendment	September 20, 2013
Amendment	January 10, 2014

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Endo Pharmaceuticals Solutions, Inc.
Address:	1400 Atwater Drive Malvern, PA 19355
Representative:	Paula Clark
Telephone:	(484) 216-7397

8. DRUG PRODUCT NAME/CODE/TYPE:

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

- Chem. Type: 2
- Submission Priority: Standard Review

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Testosterone Replacement Therapy

11. DOSAGE FORM: Injection Solution

12. STRENGTH/POTENCY: 750 mg/vial (3 mL of 250 mg/mL of testosterone undecanoate solution)

13. ROUTE OF ADMINISTRATION: Intramuscular injection

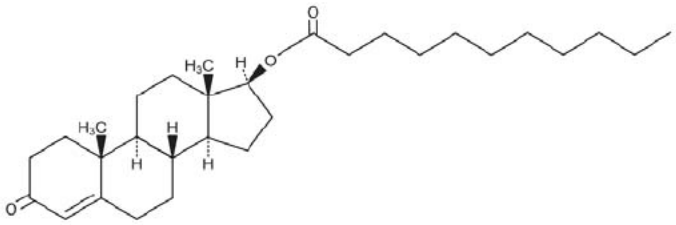
14. Rx/OTC DISPENSED: __X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

CAS: (17β)-17-[(1-Oxoundecyl)oxy]-androst-4-en-3-one
IUPAC: 17β-Undecanoyloxy-4-androsten-3-one or 3-Oxoandrost-4-en-17ß-yl-undecanoate



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

Molecular weight: 456.7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	April 5, 2013	Y. Sun
	II			3	Adequate	April 5, 2013	Y. Sun

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:
N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	pending	----	----
Pharm/Tox	N/A	----	----
Biopharm	N/A	----	----
LNC	N/A	----	----
Methods Validation	NA	----	----
DMET/DDMAC	N/A	----	----
EA	Categorical Exclusion Acceptable	See CMC Review #1, 7/7/2009	Y. Sun
Microbiology	DMF # (b) (4) is adequate.	4/21/2009	Vinayak Pawar

The Chemistry Review for NDA 22219

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA was recommended for approval from the ONDQA's perspective on August 14, 2009, after satisfactory resolution of labeling issues. But another Complete Response letter was sent on December 2, 2009 due to safety concerns.

The NDA was resubmitted on November 29, 2012. Although both DMF # (b) (4) referred for the drug substance and # (b) (4) referred for the drug product were adequate in supporting the NDA, this NDA was not approved on May 24, 2013 due to non-CMC issues.

The NDA was resubmitted on August 29, 2013. The two DMFs ((b) (4) and (b) (4)) were adequate as of April 5, 2013, and there have been no further amendments for the DMFs, and therefore, these two DMFs are still deemed adequate.

The submitted information on labels and labeling is satisfactory.

However, during the review, it is known that there had been some accident in the drug substance manufacturing facility rendering it not being able to be inspected. But now it is known to be ready for inspection and the facility has been scheduled for inspection.

Therefore, from the ONDQA's perspective, this NDA is not recommended for "Approval" until the Office of Compliance makes an overall "Acceptable" recommendation.

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

N/A

II. Summary of Chemistry Assessments

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

See Review #1 dated July 7, 2009

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

Aveed® (testosterone undecanoate) injection is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Three

milliliters of the injectable solution are to be injected at initiation, at 4 weeks, and every 10 weeks thereafter. Injections should be administered over at least one minute.

C. Basis for Not Approval Recommendation

The overall "Acceptable" recommendation of Establishment Evaluation has NOT been provided by the Office of Compliance for the drug substance manufacturer site (b) (4) as of this review.

Thus, this application is NOT recommended for approval from the ONDQA's perspective at the current state according to 21CFR 314.125(b)(13).

III. Administrative

A. Reviewer's Signature

/s/ Y. Sun, Ph.D.

B. Endorsement Block

Yichun Sun, Ph.D.
Reviewer _____ Date

Moo-Jhong Rhee, Ph.D.
Branch Chief _____ Date

C. CC Block

Donna Christner, Ph.D.
Pharmaceutical Assessment lead _____ Date

Kerri-Ann Jennings, M.S.
Project Manager _____ Date

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

The NDA was recommended for approval from the ONDQA's perspective pending satisfactory resolution of any issues on labels and labeling. However, another Complete Response letter issued on May 24, 2013 due to non-CMC issues.

The NDA was resubmitted on August 29, 2013. CMC information on the drug substance and drug product is referred to DMF # (b) (4) and # (b) (4), respectively. No amendments have been submitted to DMF # (b) (4) and DMF # (b) (4) since the last reviews dated April 5, 2013, which indicates that these DMFs are still adequate for supporting the use of testosterone undecanoate and its injection drug product for this NDA.

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

A. Labeling & Package Insert

The applicant provided the labeling and samples of mock-up container and carton labels as shown below.

1. CMC related information provided in the package insert:

(a) "Highlights" Section

AVEEDTM (testosterone undecanoate) injection, for intramuscular use CIII
Initial U.S. Approval: Year 1953

DOSAGE AND ADMINISTRATION

- For intramuscular use only (2.1).
- 3 mL (750 mg) is to be injected intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter (2.2).
- (b) (4)
- Inject AVEED deeply into the gluteal muscle following the usual precautions for intramuscular administration of oily solutions (2.3).

DOSAGE FORMS AND STRENGTHS

- 750 mg/3 mL (250 mg/mL) testosterone undecanoate sterile injectable solution is provided in an amber glass, single use vial with silver-colored crimp seal and gray plastic cap (3).

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

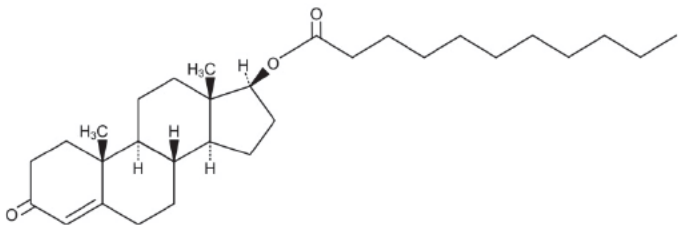
750 mg/3 mL (250 mg/mL) testosterone undecanoate sterile injectable solution is provided in an amber glass, single use vial with silver-colored crimp seal and gray plastic cap.

#11. Description

(b) (4)

The structural formula is:

FIGURE 2: Testosterone Undecanoate



$C_{30}H_{48}O_3$ MW: 456.7

Aveed is a clear, yellowish, sterile oily solution containing testosterone undecanoate, a testosterone ester, for intramuscular injection. Each single use vial contains 3 mL of 250 mg/mL testosterone undecanoate solution in a mixture of (b) (4) 1500 mg of benzyl benzoate and 885 mg of refined castor oil.

#16. How Supplied/Storage and Handling

How Supplied
AVEED, NDC 67979-511-43: 750 mg/3 mL (250 mg/mL) testosterone undecanoate sterile injectable solution is provided in an amber glass vial with silver-colored crimp seal and gray plastic cap. Each vial is individually packaged in a carton box.

Store at controlled room temperature 25 ºC (77 ºF); excursions permitted to 15 - 30 ºC (59 - 86 ºF) [See USP controlled room temperature] in its original carton until the date indicated.

Before use, each vial should be visually inspected. Only vials free from particles should be used.

Single Use Vial. Discard unused portion.

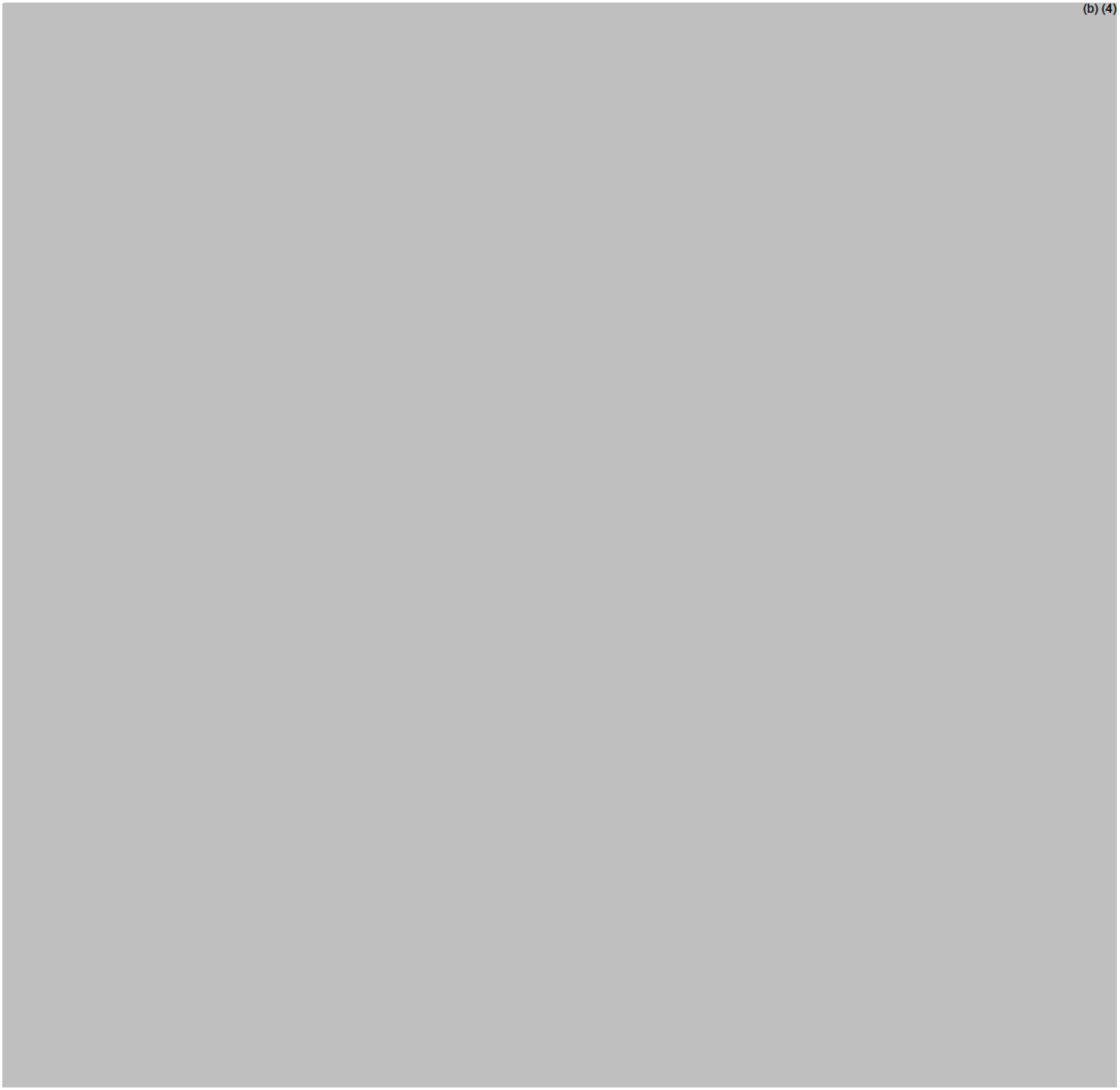
2. **CMC related information provided for the container and carton labels:**
The final mock up vial and carton labels are shown below:

Vial Label

(b) (4)

Carton Label

(b) (4)



Overall Evaluation:

The information on the labels and labeling is satisfactory.

B. Environmental Assessment Or Claim Of Categorical Exclusion

See CMC Review #1.

III. Establishment Evaluation Summary

The Office of Compliance has NOT given an overall "Acceptable" recommendation for the manufacturing facilities.

IV. List Of Deficiencies To Be Communicated

None.

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/s/

YICHUN SUN
02/03/2014

MOO JHONG RHEE
02/03/2014
Chief, Branch IV

Memorandum

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

Date: May 24, 2013

From: Yichun Sun, Ph.D.
Review Chemist, ONDQA
Division of New Drug Quality Assessment II
ONDQA

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

To: NDA 22219, CMC Review #2

Subject: Approval with pending reviewing of labels and labeling

The NDA was recommended for approval on August 27, 2009 from the ONDQA's perspective. However, a complete response letter was issued to the applicant due to safety concerns of the drug product on December 2, 2009.

The NDA was resubmitted on November 29, 2012. CMC information of the drug substance and drug product is referred to DMF # (b) (4) and # (b) (4) respectively. There were no amendments to DMF # (b) (4) since the last review dated June 25, 2008, which indicates that the DMF is adequate for supporting the use of testosterone undecanoate in NDA 22219. Since the last review dated August 27, 2009, amendments have been made to the DMF # (b) (4) referred for the CMC information of the drug product. The amendments of the DMF # (b) (4) have been reviewed and found adequate for supporting the use of the drug product, Aveed (testosterone undecanoate) injection in NDA 22219.

The **overall acceptable** recommendation of **Establishment Evaluation** has been provided by the Office of Compliance (see attachment I).

The labels and labeling have not been reviewed due to the action to be taken. Another Complete Response letter will be issued to the NDA applicant. **Thus, this application is now recommended for approval from the ONDQA's perspective pending satisfactory resolution of any issues on labels and labeling in the next review cycle.** An expiration dating period of 60 months is recommended for the drug product based on the available stability data.

Attachment - 1 (Summary Report of Establishment Evaluation)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22219/000	**Sponsor:**	ENDO PHARMS
Org. Code:	580		1400 ATWATER DR
Priority:	3		MALVERN, PA 19355
Stamp Date:	28-AUG-2007	**Brand Name:**	NEBIDO
PDUFA Date:	29-MAY-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	TESTOSTERONE UNDECANOATE
District Goal:	30-MAR-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; INJECTION; TESTOSTERONE UNDECANOATE; 250MG/1ML	

FDA Contacts:	Y. SUN	Prod Qual Reviewer		3017961388
	V. PAWAR	Micro Reviewer	(HFD-805)	3017961587
	K. JENNINGS	Product Quality PM		3017962919
	J. ROULE	Regulatory Project Mgr	(HFD-580)	3017963993
	D. CHRISTNER	Team Leader		3017961341

Overall Recommendation:	ACCEPTABLE	on 25-JAN-2013	by T. SHARP	()	3017963208
	PENDING	on 16-JAN-2013	by EES_PROD		
	PENDING	on 07-JAN-2013	by EES_PROD		
	PENDING	on 07-JAN-2013	by EES_PROD		
	ACCEPTABLE	on 26-MAR-2009	by FERGUSONS		
	ACCEPTABLE	on 26-JUN-2008	by FERGUSONS		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:	(b) (4)	**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:		**CFN:**	(b) (4)	**FEI:**	(b) (4)
					(b) (4)
DMF No:				**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER				
	DRUG SUBSTANCE RELEASE TESTER				
	DRUG SUBSTANCE STABILITY TESTER				
Profile:	(b) (4)			**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	07-JAN-2013				
Decision:	ACCEPTABLE				
Reason:	BASED ON PROFILE				

Establishment:		**CFN:**		**FEI:**	(b) (4)
					(b) (4)
DMF No:				**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER				
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS			**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	17-JAN-2013				
Decision:	ACCEPTABLE				
Reason:	BASED ON PROFILE				

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/s/

YICHUN SUN
05/24/2013

MOO JHONG RHEE
05/24/2013
Chief, Branch IV

Memorandum

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

Date: August 27, 2009

From: Yichun Sun, Ph.D.
Review Chemist, ONDQA
Premarketing Assessment Division II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Premarketing Assessment Division II
ONDQA

To: Previous Memorandum to CMC Review #2 for NDA 22-219

Subject: Update the Mock-up Carton Label

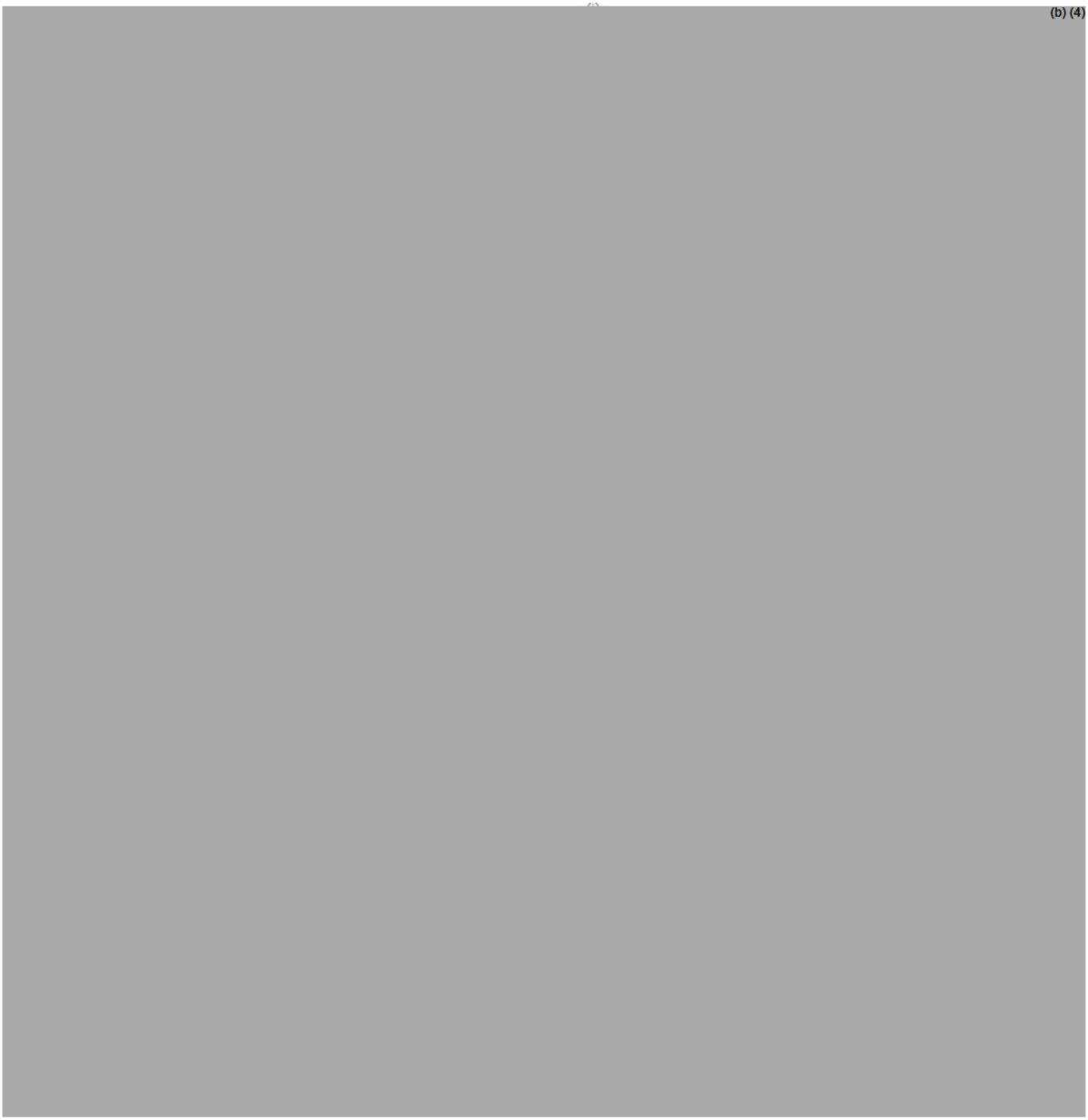
At the time of the memorandum to CMC Review #2 was written, the mock-up carton label was acceptable. However, per the request of DMEPA, the statements about storage requirement and package insert on the principal display panel of the carton label were deleted to make the Medication Guide statement more prominent. The deletion of these statements from the principal display panel would not affect the recommendation in the previous memorandum since these statements already appear on the carton side panel. The mock-up carton label was updated on August 24, 2009. This memorandum is to update the mock-up carton label in the previous memorandum to the CMC Review #2. **Thus, this application is still recommended for approval from the perspective of Chemistry, Manufacturing and Controls.**

Review Notes

Per the request of DMEPA, the statements about storage requirement and package insert on the principal display panel of the carton label were deleted to make the Medication Guide statement more prominent. The sponsor updated the mock-up carton label in the Labeling section on August 24, 2009 as shown below.

Final Carton Label

(b) (4)



As shown in the above mock-up carton label, the following items are provided:

- **Proprietary name, established name**
- **Controlled drug substance symbol**
- **Dosage strength**
- **Net quantity of dosage form**
- **“Rx only”**
- **Lot number and expiration date**
- **Storage conditions**
- **Bar code**
- **NDC number (requested but not required (21 CFR 207.35(b)(3)(i))**
- **Name of manufacturer/distributor**
- **Quantitative ingredient information (injectables)**
- **Statement of being sterile (if applicable)**
- **“See package insert for full prescribing information”**

Evaluation: Acceptable. The mock-up carton label provides all the required information as per 21 CFR 201.

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/s/

YICHUN SUN
08/27/2009

MOO JHONG RHEE
08/27/2009
Chief, Branch III

Memorandum

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

Date: August 14, 2009

From: Yichun Sun, Ph.D.
Review Chemist, ONDQA
Premarketing Assessment Division II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Premarketing Assessment Division II
ONDQA

To: NDA 22-219, CMC Review #2

Subject: Review of labeling, and mock-up labels for the container and carton

At the time of the CMC review was written, labeling review has not been completed. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling review is completed. On August 14, 2009, the review on labeling, and mock-up labels for container and carton was completed. The labeling, and mock-up labels for container and carton are acceptable. **Thus, this application is now recommended for approval from the perspective of Chemistry, Manufacturing and Controls.**

Review Notes

The sponsor provided the proposed labeling text and samples of mock-up labels for the container and carton in the Labeling section. CMC information is reviewed according to 21 CFR 201.

CMC related information provided in the package insert:

"Highlights" Section

- **Proprietary name and established name:** AVEED™ (testosterone undecanoate) injection.
- **Dosage and Administration:** 3 mL is to be injected intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter.
- **Controlled drug substance symbol:** CIII
- **Dosage Forms and Strengths:** 3 mL of 250 mg/mL (750 mg) of testosterone undecanoate sterile injectable solution is provided in an amber glass, single use vial with silver-colored crimp seal and grey plastic cap.

Evaluation: Acceptable.

"Full Prescribing Information" Section

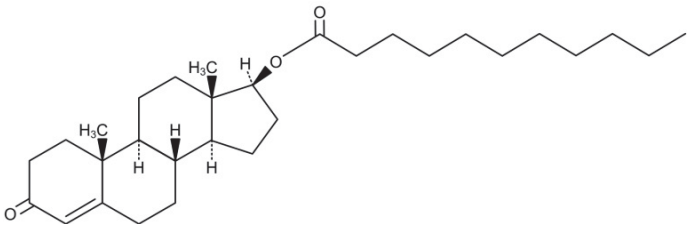
3: Dosage Forms and Strengths

- **Available dosage forms:** Injectable solution.
- **Strengths (in metric system):** 3 mL of 250 mg/mL (750 mg) testosterone undecanoate sterile injectable solution.
- **A description of the identifying characteristics of the dosage forms:** An amber glass, single use vial with silver-colored crimp seal and grey plastic cap.

Evaluation: Acceptable.

#11: Description

- **Proprietary name and established name:** AVEED (testosterone undecanoate) injection.
- **Dosage form and route of administration:** Intramuscular injection.
- **Inactive ingredient information:** Each 3 mL vial contains 1500 mg of benzyl benzoate and 885 mg of refined castor oil.
- **Statement of being sterile:** Sterile.
- **Pharmacological/therapeutic class:** Testosterone replacement therapy.
- **Chemical name, structural formula, molecular weight:** 17 β-undecanoyloxy-4-androsten-3-one. It has the empirical formula $C_{30}H_{48}O_3$ with a molecular weight of 456.7, and the following structural formula:



- **Other important chemical or physical properties (such as pKa or pH):** AVEED is a clear, yellowish, sterile oily solution for intramuscular injection. Testosterone undecanoate is a white to off-white crystalline substance. The active form, testosterone, is formed by cleavage of the side chain.

Evaluation: Acceptable.

#16: How Supplied/Storage and Handling

- **Strength of dosage form:** 3 mL of 250 mg/mL (750 mg) testosterone undecanoate injectable solution.
- **Available units:** Single Use Vial.
- **Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting:** An amber glass vial with silver-colored crimp seal and plastic cap.
- **NDC number:** NDC 67979-511-43.
- **Special handling (e.g., protect from light):** Visually inspected before use.
- **Storage conditions:** Store at room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP controlled room temperature].

Evaluation: Acceptable.

CMC related information provided for the container and carton labels:
The vial and carton labels have been modified in the complete response to the Approvable Letter dated June 27, 2008. CMC related information provided for the vial and carton labels are shown below:

Proposed Vial Label

(b) (4)

As shown in the above mock-up vial label, the following items are provided:

- **Proprietary name, established name**
- **Controlled drug substance symbol**
- **Dosage strength**
- **Net contents**
- **"Rx only"**
- **Storage conditions**
- **NDC number (requested but not required (21 CFR 207.35(b)(3)(i))**
- **Name of manufacturer/distributor**

Evaluation: Lot number and expiration date are missing from the vial label.

Information Request:
An IR letter dated May 19, 2009 was sent to request the applicant to add lot number and expiration date to the vial label.

An amendment dated June 8, 2009 was received. The vial label has been updated as shown below:

Updated Vial Label

(b) (4)

As shown in the above updated mock-up vial label, the following items are provided:

- **Proprietary name, established name**
- **Controlled drug substance symbol**
- **Dosage strength**
- **Net contents**
- **Lot number and expiration date**
- **"Rx only"**
- **Storage conditions**
- **NDC number (requested but not required (21 CFR 207.35(b)(3)(i))**
- **Name of manufacturer/distributor**

Note: The (b) (4) has been replaced with Aveed because (b) (4) was rejected by the FDA. The requirement of linear bar code on the label is exempted because of limited space of the label. See CMC review #1 for details.

The mock-up vial label was updated again on July 23, 2009 to correct a typographical spelling error in the generic name, testosterone undecanoate. However, the lot number and expiration date were missing from the updated mock-up vial label. The applicant was asked to add lot number and expiration date to the vial label, and to make editorial changes to the strength expression on the vial label. The final mock-up vial label was received on August 14, 2009 and is shown below.

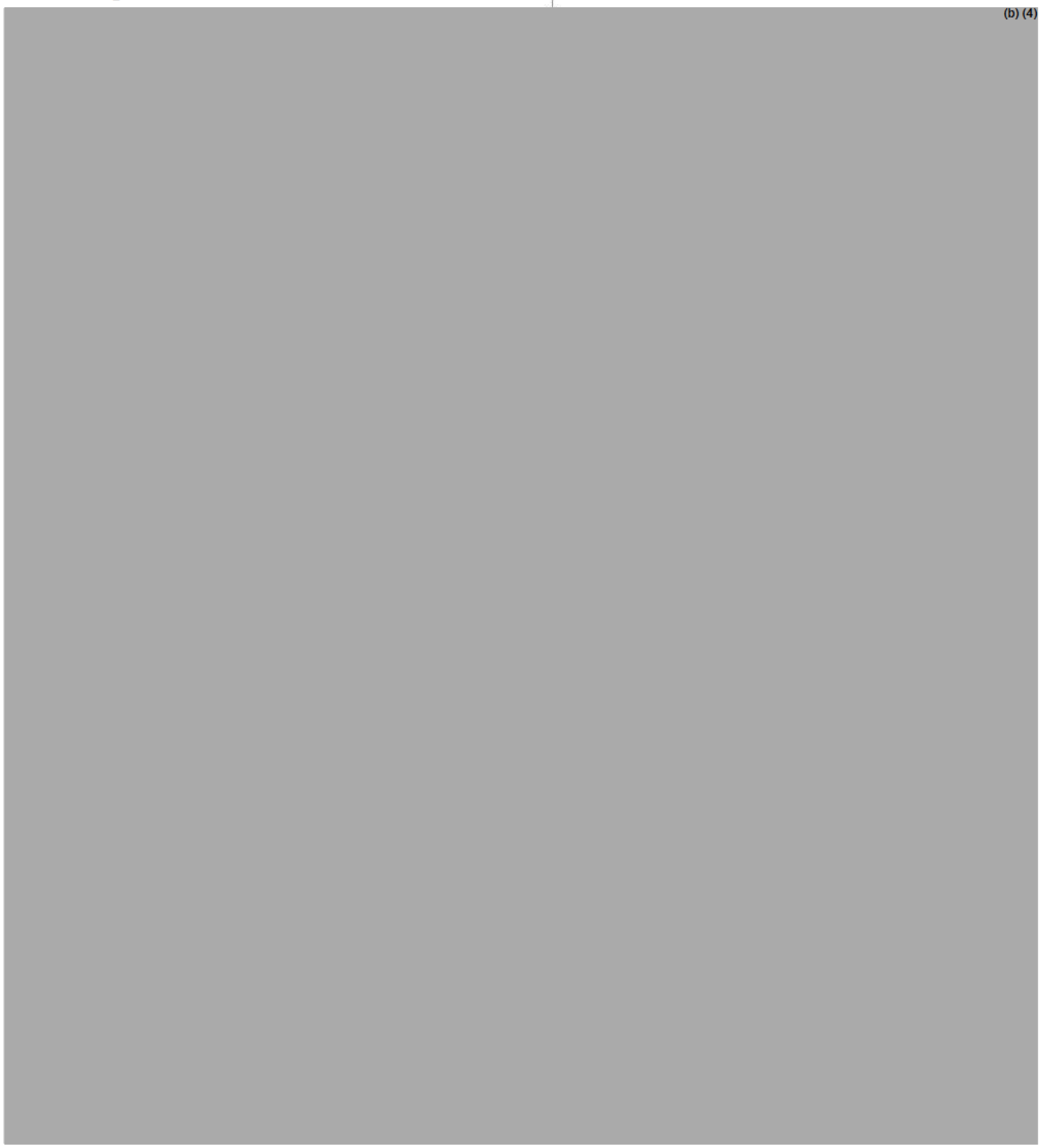
Final Vial Label

As shown in the above mock-up vial label, the following items are provided:

- **Proprietary name, established name**
- **Controlled drug substance symbol**
- **Dosage strength**
- **Net contents**
- **Lot number and expiration date**
- **"Rx only"**
- **Storage conditions**
- **NDC number (requested but not required (21 CFR 207.35(b)(3)(i))**
- **Name of manufacturer/distributor**

Evaluation: Acceptable. The mock-up vial label provides all the required information as per 21 CFR 201.

Proposed Carton Label



As shown in the above mock-up carton label, the following items are provided:

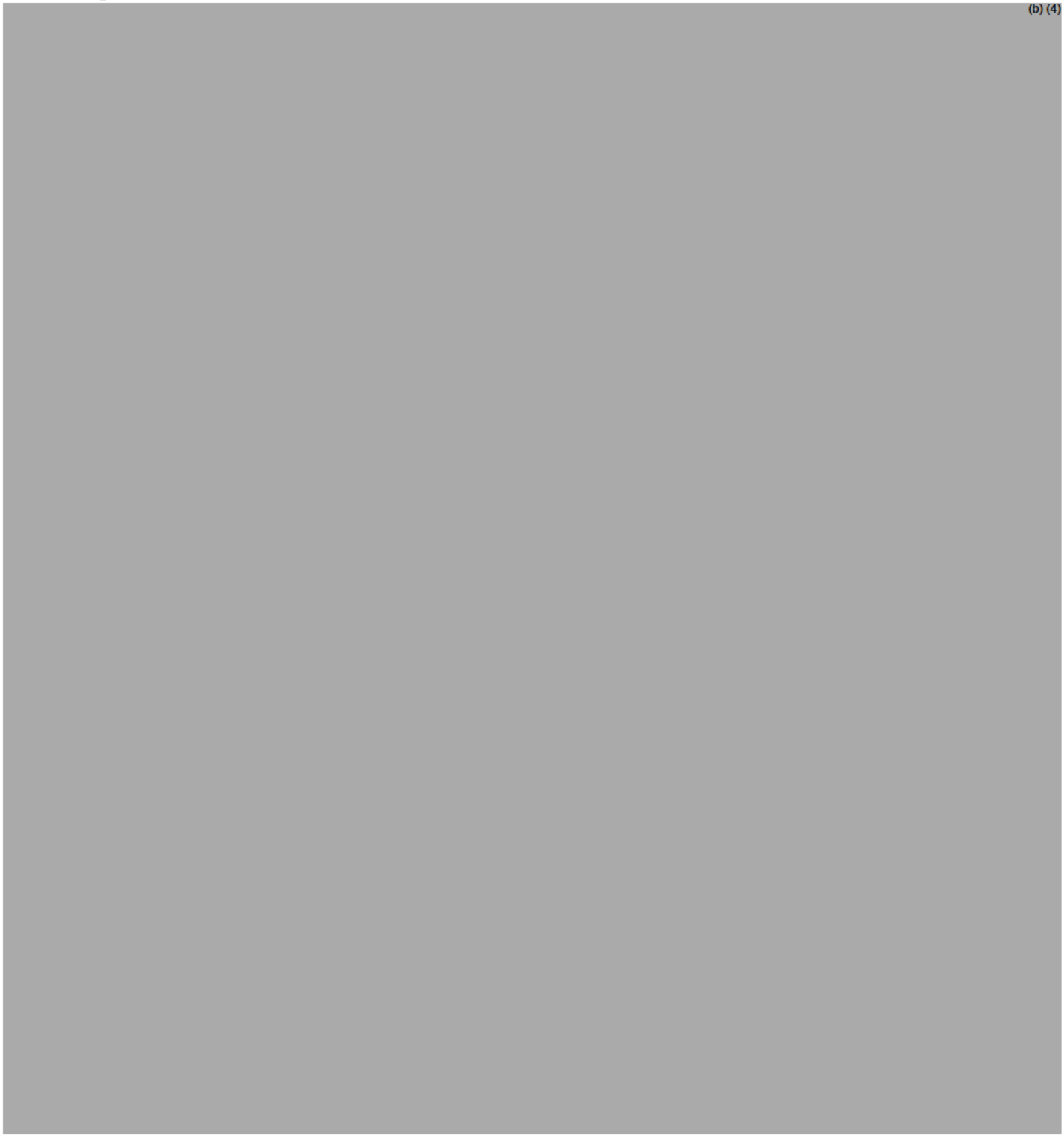
- **Proprietary name, established name**
- **Controlled drug substance symbol**
- **Dosage strength**
- **Net quantity of dosage form**
- **"Rx only"**
- **Storage conditions**
- **Bar code**
- **NDC number (requested but not required (21 CFR 207.35(b)(3)(i))**
- **Name of manufacturer/distributor**
- **Quantitative ingredient information (injectables)**
- **Statement of being sterile (if applicable)**
- **"See package insert for full prescribing information"**

Evaluation: Lot number and expiration date are missing from the carton label.

Information Request:
An IR letter dated May 19, 2009 was sent to request the applicant to add lot number and expiration date to the carton label.

An updated carton label was received on June 8, 2009. The updated carton label is shown below:

Updated Carton Label

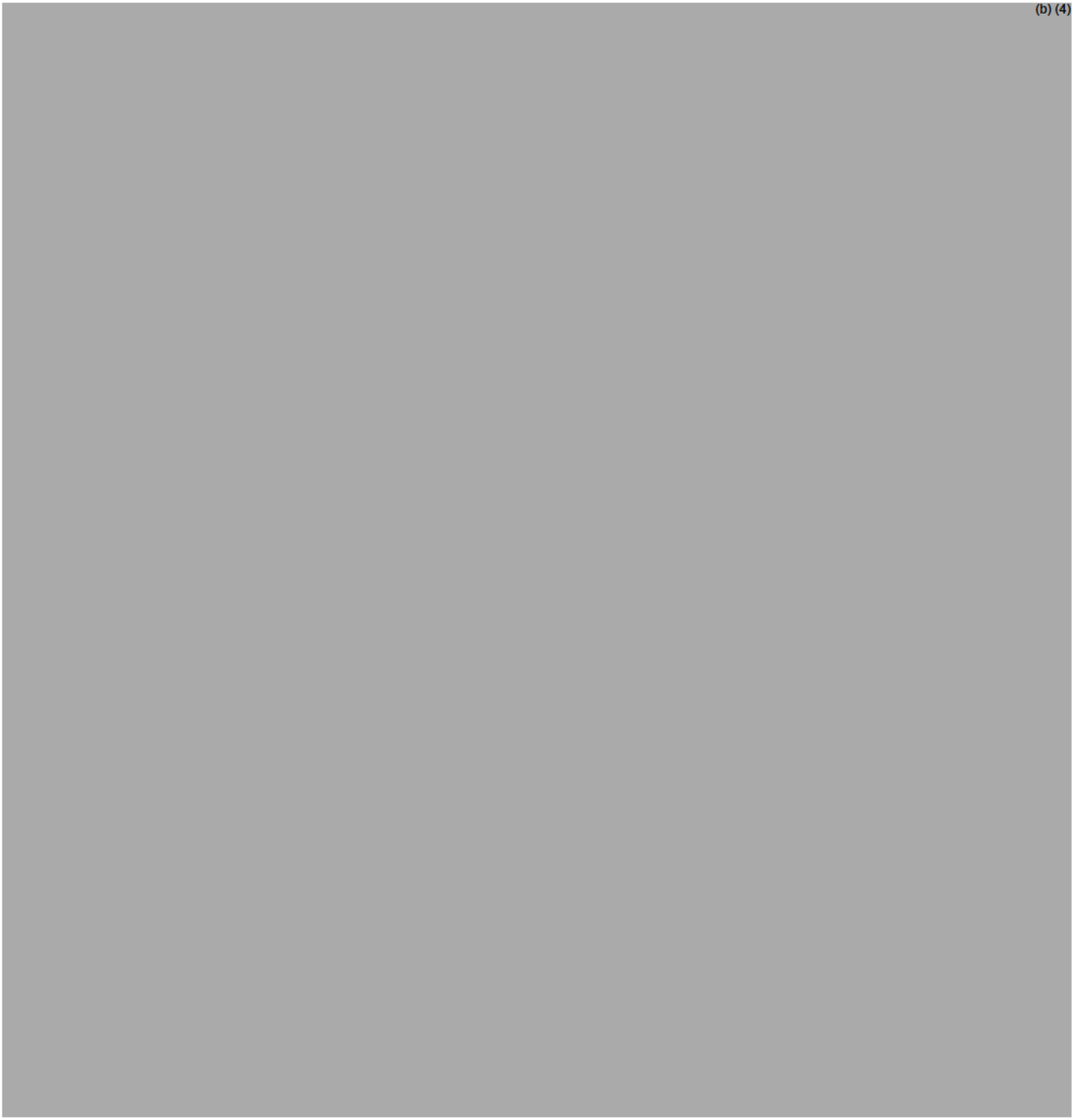


As shown in the above updated mock-up carton label, the following items are provided:

- **Proprietary name, established name**
- **Controlled drug substance symbol**
- **Dosage strength**
- **Net quantity of dosage form**
- **"Rx only"**
- **Lot number and expiration date**
- **Storage conditions**
- **Bar code**
- **NDC number (requested but not required (21 CFR 207.35(b)(3)(i))**
- **Name of manufacturer/distributor**
- **Quantitative ingredient information (injectables)**
- **Statement of being sterile (if applicable)**
- **"See package insert for full prescribing information"**

The mock-up carton label was updated again on July 23, 2009 to correct a typographical spelling error in the generic name, testosterone undecanoate. However, the lot number, expiration date and Medication Guide requirement were missing from the updated mock-up vial label. The applicant was asked to add lot number, expiration date and "Dispense the enclosed Medication Guide to each patient" to the carton label, and to make editorial changes to the strength expression. The final mock-up carton label was received on August 14, 2009 and is shown below.

Final Carton Label



As shown in the above mock-up carton label, the following items are provided:

- **Proprietary name, established name**
- **Controlled drug substance symbol**
- **Dosage strength**
- **Net quantity of dosage form**
- **"Rx only"**
- **Lot number and expiration date**
- **Storage conditions**
- **Bar code**
- **NDC number (requested but not required (21 CFR 207.35(b)(3)(i))**
- **Name of manufacturer/distributor**
- **Quantitative ingredient information (injectables)**
- **Statement of being sterile (if applicable)**
- **"See package insert for full prescribing information"**

Evaluation: Acceptable. The mock-up carton label provides all the required information as per 21 CFR 201.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22219	ORIG 1		NEBIDO
NDA 22219	ORIG 1		NEBIDO
NDA 22219	ORIG 1		NEBIDO

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

/s/

YICHUN SUN
08/14/2009

MOO JHONG RHEE
08/14/2009
Chief, Branch III

NDA 22-219

Aveed® (testosterone undecanoate) injection

Endo Pharmaceuticals, Inc.

Yichun Sun, Ph.D.

Review Chemist

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

CMC REVIEW OF NDA 22-219
For the Division of Reproductive and Urologic Products (HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. NDA: #22-219

2. REVIEW #: 2

3. REVIEW DATE: 7-July-2009

4. REVIEWER: Yichun Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-IND meeting minutes	November 30, 2005
IND 72,297	February 3, 2006
Original	August 24, 2007
Amendment (BL)	February 11, 2008
Amendment (BZ)	February 22, 2008
Amendment (C)	March 11, 2008
Amendment (C)	April 30, 2008
Amendment (BC)	May 28, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (RP)	March 2, 2009
Amendment (XA)	March 27, 2009
Amendment (BC)	April 21, 2009
Amendment (BL)	June 8, 2009
Amendment (BL)	June 22, 2009

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Endo Pharmaceuticals, Inc.
Address:	100 Endo Boulevard Chadds Ford, PA 19317
Representative:	Mark Roessel
Telephone:	(610) 558-9800

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Aveed® (It was Nebido® in the original submission)
b) Non-Proprietary Name (USAN): Testosterone undecanoate
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 2
- Submission Priority: Standard Review

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Testosterone Replacement Therapy

11. DOSAGE FORM: Injection Solution

12. STRENGTH/POTENCY: 750 mg/vial (3 mL of 250 mg/mL of testosterone undecanoate solution)

13. ROUTE OF ADMINISTRATION: Intramuscular

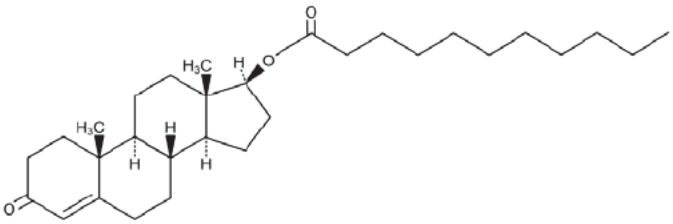
14. Rx/OTC DISPENSED: __X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

CAS: (17β)-17-[(1-Oxoundecyl)oxy]-androst-4-en-3-one
IUPAC: 17β-Undecanoyloxy-4-androsten-3-one, or 3-Oxoandrost-4-en-17ß-yl-undecanoate



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

Molecular weight: 456.7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	June 25, 2008	Y. Sun
	II			1	Adequate	July 2, 2009	Y. Sun

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:
N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Acceptable	03/26/2009	S. Ferguson
Pharm/Tox	N/A	----	----
Biopharm	N/A	----	----
LNC	N/A	----	----
Methods Validation	To be validated per ONDQA Policy	----	----
DMET/DDMAC	N/A	----	----
EA	Categorical Exclusion Acceptable	See review #1	Y. Sun
Microbiology	DMF # (b) (4) is adequate.	4/21/2009	Vinayak Pawar

The Chemistry Review for NDA 22-219

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling review is not complete yet as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling review is completed.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance used in the drug products of this NDA is testosterone undecanoate, which is an ester of the naturally-occurring androgen, testosterone. The active moiety, testosterone, is formed by cleavage of the undecanoic acid side chain. Testosterone undecanoate is a white to off-white crystalline substance. Detailed CMC information was referred to DMF # (b) (4) which is reviewed and found adequate for supporting the use of Testosterone undecanoate in NDA 22-219.

Drug Product

Aveed® is the drug product that contains 3 mL of 250 mg/mL of Testosterone undecanoate oily solution in each (b) (4) amber glass vial with a (b) (4) grey, stopper. Aveed® is a clear, yellowish, sterile oil solution for intramuscular injection. Testosterone undecanoate oily solution is consisted of testosterone undecanoate (750 mg/vial), refined castor oil (885 mg/vial) and benzyl benzoate (1500 mg/vial). Each mL of 250 mg/mL testosterone undecanoate solution provides 157.9 mg testosterone. Detailed CMC information was referred to DMF # (b) (4) which is reviewed and found adequate for supporting the use of Testosterone undecanoate oily solution in NDA 22-219.

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

Aveed® (testosterone undecanoate) injection is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Three milliliters of the injectable solution are to be injected at initiation, at 4 weeks, and every 10 weeks thereafter. Injections should be administered over at least one minute.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. All facilities have acceptable site recommendations. However, labeling review is not completed as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling review is completed.

III. Administrative

A. Reviewer's Signature

/s/ Y. Sun, Ph.D.

B. Endorsement Block

Yichun Sun, Ph.D.
Reviewer _____ Date

Moo-Jhong Rhee, Ph.D.
Branch Chief _____ Date

C. CC Block

Donna Christner, Ph.D.
Pharmaceutical Assessment lead _____ Date

Jeannie C. David M.S.
Project Manager _____ Date

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

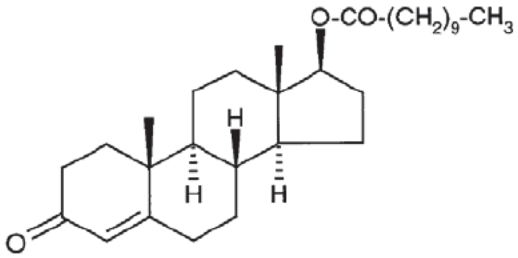
S DRUG SUBSTANCE [Testosterone undecanoate (b) (4)]

S.1 General Information [Testosterone undecanoate (b) (4)]

S.1.1 Nomenclature

INN Name: Testosterone undecanoate
CAS: (17β)-17-[(1-Oxoundecyl)oxy]-androst-4-en-3-one
IUPAC: 17β-Undecanoyloxy-4-androsten-3-one, or 3-Oxoandrost-4-en-17ß-yl-undecanoate

S.1.2 Structure



S 1.3 General Properties

The drug substance used in the drug product, Aveed®, is testosterone undecanoate, which is an ester of the naturally-occurring androgen, testosterone. The active form, testosterone, is formed by cleavage of the undecanoic acid side chain. Testosterone undecanoate is a white to off-white crystalline substance. It is practically insoluble in water, soluble in ethanol and methanol.

S.2 Manufacture [Testosterone undecanoate (b) (4)]

S.2.1 Manufacturers

(b) (4)

The site is used for (b) (4) Testosterone undecanoate.

Evaluation: Acceptable. The Office of Compliance has given an overall acceptable recommendation for the manufacturing facility.

S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

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S.4.2 Analytical Procedures

Detailed information regarding the analytical techniques used to identify, qualify and quantify testosterone undecanoate drug substance and its impurities was refereed to DMF # (b) (4)

Evaluation: Acceptable.

S.4.3 Validation of Analytical Procedures

Validation of the analytical procedures for the drug substance was referred to DMF # (b) (4)

Evaluation: Acceptable.

S.4.4 Batch Analyses

Results of batch analyses for the drug substance were referred to DMF # (b) (4)

Evaluation: Acceptable.

S.4.5 Justification of Specification

Justification of specifications for the drug substance was referred to DMF # (b) (4).

Evaluation: Acceptable.

S.5 Reference Standards or Materials [Testosterone undecanoate (b) (4)]

Reference standards for the drug substance and its impurities were referred to DMF # (b) (4)

Evaluation: Acceptable.

S.6 Container Closure System [Testosterone undecanoate (b) (4)]

The container closure system used for the drug substance was referred to DMF # (b) (4)

Evaluation: Acceptable.

S.7 Stability [Testosterone undecanoate (b) (4)]

S.7.1 Stability Summary and Conclusions

The stability summary and conclusions for the drug substance were referred to DMF # (b) (4)

Evaluation: Acceptable.

S.7.2 Postapproval Stability Protocol and Stability Commitment

N/A

S 7.3 Stability Data

The stability data of the drug substance were referred to DMF # (b) (4)

Evaluation: Acceptable.

P DRUG PRODUCT [Aveed® (testosterone undecanoate) injection]

P.1 Description and Composition of the Drug Product [Aveed® (testosterone undecanoate) injection]

The drug product, Aveed® (Testosterone undecanoate) injection is an oily injectable solution packaged in (b) (4) amber glass vials with (b) (4) grey, stoppers. Each vial contains 3 mL of 250 mg/mL of Testosterone undecanoate oily solution. Aveed® is a clear, yellowish and sterile oily solution for intramuscular injection. Testosterone undecanoate oily solution is consisted of testosterone undecanoate (750 mg/vial), refined castor oil (885 mg/vial) and benzyl benzoate (1500 mg/vial). Each mL of 250 mg/mL testosterone undecanoate solution provides 157.9 mg testosterone.
Detailed information regarding the composition of Aveed® was referred to DMF # (b) (4)
The composition of the Aveed® (Testosterone undecanoate) injection is shown in the following Table.

Composition of Aveed® Injection

Ingredient	Amount per vial (mg)	Function	Reference to standards
Testosterone undecanoate	750	Active ingredient	DMF (b) (4)
Benzyl benzoate	1500	(b) (4)	USP/Ph. Eur.*
Castor oil refined for parenteral use	885		USP/Ph. Eur.*
(b) (4)			

*:Microbiological test according to EP and USP (limit: not more than (b) (4) cfu/g)
(b) (4)

Evaluation: Acceptable. All the excipients are of compendial grades.

P.2 Pharmaceutical Development [Aveed® (testosterone undecanoate) injection]

P.2.1 Components of the Drug Product

The components used in the drug products are referred to DMF # (b) (4)

Evaluation: Acceptable.

P.2.1.1 Drug Substance

The drug substance, testosterone undecanoate, is referred to DMF (b) (4) The drug substance used in the drug product, Aveed®, is testosterone undecanoate, which is an ester of the naturally-occurring androgen, testosterone. The active moiety, testosterone, is formed by cleavage of the undecanoic acid side chain. Testosterone undecanoate is a white to off-white crystalline substance. It is practically insoluble in water, soluble in ethanol and methanol.

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Evaluation: Acceptable. All 6 batches including 2 registration batches (two lots of 750 mg/vial Aveed®) met the acceptance criteria set for the drug product.

P.5.5 Characterization of Impurities

Characterization of impurities present in the drug product was referred to DMF # (b) (4)

Evaluation: Acceptable.

P.5.6 Justification of Specification(s)

Justification of drug product specification was referred to DMF # (b) (4)

Evaluation: Acceptable.

P.6 Reference Standards or Materials [Aveed® (testosterone undecanoate) injection]

Information on the reference standards was referred to DMF # (b) (4)

Evaluation: Acceptable.

P.7 Container Closure System [Aveed® (testosterone undecanoate) injection]

Information on the packaging components used for Aveed® was referred to DMF # (b) (4)

Evaluation: Acceptable.

P.8 Stability [Aveed® (testosterone undecanoate) injection]

P.8.1 Stability Summary and Conclusion

Stability studies are being conducted on two validation batches of Aveed® drug product (750 mg/3 mL vials), which were manufactured at (b) (4) All vials were stored (b) (4) The stability testing conditions were: 25°C/60% RH, 30°C/65% RH and 40°C/75% RH. The samples are scheduled to be stored at 25°C/60% RH and 30°C/65% RH over a period of 60 months, and at 40°C/75% RH over a period of 6 months. After stored at 25°C/60% RH and 30°C/65% RH for 18 months, and 40°C/75% RH for 6 months, no significant degradation was observed from the drug product tested. No significant time dependency could be observed for all other investigated parameters during the aforementioned period of the stability studies.

(b) (4)

Note: (b) (4)

Stability studies were also conducted on 3 pilot batches of Aveed® drug product (750 mg/3 mL vials), which were manufactured (b) (4)

An expiration dating period of (b) (4) months for the 3 mL vial (750 mg testosterone undecanoate) drug product was proposed based upon the current 30 months of long-term stability data obtained from pilot-scale batches of the drug product.

Detailed information regarding the stability studies and reports are referred to DMF # (b) (4)

Evaluation: Acceptable. An expiration dating period of (b) (4) months is recommended for the drug product based on the available stability data provided in DMF # (b) (4)

P.8.2 Postapproval Stability Protocol and Stability Commitment
See CMC review #1.

Evaluation: Acceptable.

P.8.3 Stability Data
Detailed information on stability data was referred to DMF # (b) (4)

Evaluation: Acceptable.

A APPENDICES

A.1 Facilities and Equipment (biotech only)
N/A

A.2 Adventitious Agents Safety Evaluation
N/A

A.3 Novel Excipients
N/A

R REGIONAL INFORMATION

R1 Executed Batch Records

Executed batch records were referred to DMF # (b) (4)

Evaluation: Acceptable.

R2 Comparability Protocols

N/A

R3 Methods Validation Package

Information on method validation package was referred to DMF # (b) (4)

Evaluation: Acceptable.

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

A. Labeling & Package Insert

The sponsor provided the proposed labeling text and samples of mock-up container and carton labels in the Labeling section.

Labeling review has not been completed as of the date of this review.

B. Environmental Assessment Or Claim Of Categorical Exclusion

See CMC review #1.

Evaluation: Acceptable.

III. Establishment Evaluation Summary

The Office of Compliance has given an overall acceptable recommendation for the manufacturing facilities. The summary report of Establishment Evaluation is attached below:

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22219/000	**Sponsor:**	ENDO PHARMS
Org. Code:	580		100 ENDO BLVD
Priority:			CHADDS FORD, PA 19317
Stamp Date:	28-AUG-2007	**Brand Name:**	NEBIDO
PDUFA Date:	02-SEP-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	TESTOSTERONE UNDECANOATE
District Goal:	04-JUL-2009	**Dosage Form:**	(INJECTION)
		Strength:	250 MG/ML

FDA Contacts:	ID = 132902	Project Manager	
	Y. SUN	Review Chemist	301-796-1388
	D. CHRISTNER	Team Leader	301-796-1341

Overall Recommendation:	ACCEPTABLE	on 26-MAR-2009	by S. FERGUSON	(HFD-322)	301-796-3247
	ACCEPTABLE	on 26-JUN-2008	by S. FERGUSON	(HFD-322)	301-796-3247

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:	(b) (4)	**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
	FINISHED DOSAGE STERILIZER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-MAR-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:	(b) (4)	**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-MAR-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	20-MAR-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

IV. List Of Deficiencies To Be Communicated

None, except for possible labeling issues.

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/s/

Yichun Sun
7/7/2009 02:18:19 PM
CHEMIST

Moo-Jhong Rhee
7/7/2009 02:22:33 PM
CHEMIST
Chief, Branch III

NDA 22-219

NEBIDO® (testosterone undecanoate) injection

Indevus Pharmaceuticals, Inc.

Yichun Sun, Ph.D.

Review Chemist

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

CMC REVIEW OF NDA 22-219
For the Division of Reproductive and Urologic Products (HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. NDA: #22-219

2. REVIEW #: 1

3. REVIEW DATE: 26-June-2008

4. REVIEWER: Yichun Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-IND meeting minutes	November 30, 2005
IND 72,297	February 3, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	August 24, 2007
Amendment (BL)	February 11, 2008
Amendment (BZ)	February 22, 2008
Amendment (C)	March 11, 2008
Amendment (C)	April 30, 2008
Amendment (BC)	May 28, 2008

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Indevus Pharmaceuticals, Inc.
Address:	33 Hayden Avenue Lexington, MA 02421
Representative:	John Berryman
Telephone:	(781) 402-3451

8. DRUG PRODUCT NAME/CODE/TYPE:

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

- Chem. Type: 2
- Submission Priority: Standard Review

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Testosterone Replacement Therapy

11. DOSAGE FORM: Injection Solution

12. STRENGTH/POTENCY: 750 mg/vial (3 mL of 250 mg/mL of testosterone undecanoate solution)

13. ROUTE OF ADMINISTRATION: Intramuscular injection

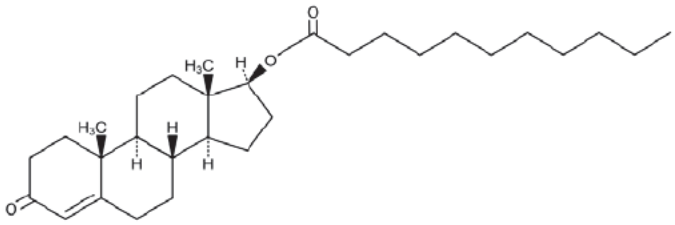
14. Rx/OTC DISPENSED: __X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

CAS: (17β)-17-[(1-Oxoundecyl)oxy]-androst-4-en-3-one
IUPAC: 17β-Undecanoyloxy-4-androsten-3-one 3-Oxoandrost-4-en-17ß-yl-undecanoate



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

Molecular weight: 456.7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	June 25, 2008	Y. Sun
	II			1	Inadequate	June 25, 2008	Y. Sun

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:
N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Acceptable	6/26/2008	S. Ferguson
Pharm/Tox	N/A	----	----
Biopharm	N/A	----	----
LNC	N/A	----	----
Methods Validation	To be validated per ONDQA Policy	----	----
DMET/DDMAC	"Injection" instead of (b) (4) was recommended for the dosage form and administration route following the established name on the labels and labeling.	5/13/2008	Walter Fava
EA	Categorical Exclusion Acceptable	See Review Date Above	Y. Sun
Microbiology	The application is approvable pending resolution of items listed as deficiencies in DMF # (b) (4)	6/25/2008	Vinayak Pawar

The Chemistry Review for NDA 22-219

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has not provided sufficient CMC information to assure the purity of the drug product. Therefore, from a CMC perspective, this NDA is recommended for "Approvable" pending resolution of the issues delineated in the deficiency letter issued on June 25 for DMF # (b) (4)

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance used in the drug products of this NDA is testosterone undecanoate, which is an ester of the naturally-occurring androgen, testosterone. The active form, testosterone, is formed by cleavage of the undecanoic acid side chain. Testosterone undecanoate is a white to off-white crystalline substance. Detailed CMC information was referred to DMF # (b) (4) which is reviewed and found adequate for supporting the use of Testosterone Undecanoate in NDA 22-219.

Drug Product

Nebido® is the drug product that contains 3 mL of 250 mg/mL of Testosterone undecanoate oily solution in each (b) (4) amber glass vial with a (b) (4) grey, stopper. Nebido® is a clear, yellowish, sterile oil solution for intramuscular injection. Testosterone undecanoate oily solution is consisted of testosterone undecanoate (750 mg/vial), refined castor oil (885 mg/vial) and benzyl benzoate (1500 mg/vial). Each mL of 250 mg/mL testosterone undecanoate solution provides 157.9 mg testosterone. Detailed CMC information was referred to DMF # (b) (4) which is reviewed and found inadequate pending resolution of the issues delineated in the deficiency letter issued on June 25 for DMF # (b) (4)

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

Nebido® (testosterone undecanoate) injection is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Three milliliters of the injectable solution are to be injected at initiation, at 4 weeks, and every 10 weeks thereafter. Injections should be administered over at least one minute.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has not provided sufficient CMC information to assure the purity of the drug product. Therefore, from a CMC perspective, this NDA is recommended for "Approvable" pending resolution of the issues delineated in the deficiency letter issued on June 25 for DMF # (b) (4)

III. Administrative

A. Reviewer's Signature

/s/ Y. Sun, Ph.D.

B. Endorsement Block

Yichun Sun, Ph.D.
Reviewer _____ Date

Moo-Jhong Rhee, Ph.D.
Branch Chief _____ Date

C. CC Block

Donna Christner, Ph.D.
Pharmaceutical Assessment lead _____ Date

Scott Goldie
Project Manager _____ Date

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE [Testosterone undecanoate (b) (4)]

S.1 General Information [Testosterone undecanoate (b) (4)]

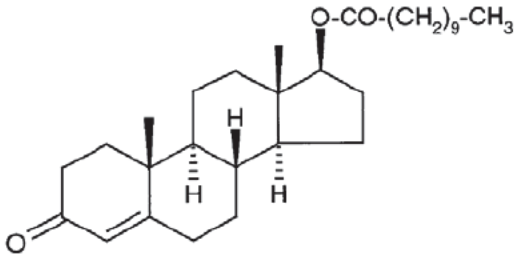
S.1.1 Nomenclature

INN Name: Testosterone undecanoate

CAS: (17β)-17-[(1-Oxoundecyl)oxy]-androst-4-en-3-one

IUPAC: 17β-Undecanoyloxy-4-androsten-3-one 3-Oxoandrost-4-en-17ß-yl-undecanoate

S.1.2 Structure



S 1.3 General Properties

The drug substance used in the drug product Nebido® is testosterone undecanoate, which is an ester of the naturally-occurring androgen, testosterone. The active form, testosterone, is formed by cleavage of the undecanoic acid side chain. Testosterone undecanoate is a white to off-white crystalline substance. It is practically insoluble in water, soluble in ethanol and methanol.

S.2 Manufacture [Testosterone undecanoate (b) (4)]

S.2.1 Manufacturers

(b) (4)

The site is used for (b) (4) Testosterone undecanoate.

(b) (4)

This site is used for (b) (4) Testosterone undecanoate.

3 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

S.4.2 Analytical Procedures

Detailed information regarding the analytical techniques used to identify, qualify and quantify testosterone undecanoate drug substance and its impurities was refereed to DMF # (b) (4)

Evaluation: Acceptable.

S.4.3 Validation of Analytical Procedures

Validation of the analytical procedures for the drug substance was referred to DMF # (b) (4)

Evaluation: Acceptable.

S.4.4 Batch Analyses

Results of batch analyses for the drug substance were referred to DMF # (b) (4)

Evaluation: Acceptable.

S.4.5 Justification of Specification

Justification of specifications for the drug substance was referred to DMF # (b) (4)

Evaluation: Acceptable.

S.5 Reference Standards or Materials [Testosterone undecanoate (b) (4)]

Reference standards for the drug substance and its impurities were referred to DMF # (b) (4)

Evaluation: Acceptable.

S.6 Container Closure System [Testosterone undecanoate (b) (4)]

The container closure system used for the drug substance was referred to DMF # (b) (4)

Evaluation: Acceptable.

S.7 Stability [Testosterone undecanoate (b) (4)]

S.7.1 Stability Summary and Conclusions

The stability summary and conclusions for the drug substance were referred to DMF (b) (4)

Evaluation: Acceptable.

S.7.2 Postapproval Stability Protocol and Stability Commitment

N/A

S 7.3 Stability Data

The stability data of the drug substance were referred to DMF # (b) (4)

Evaluation: Acceptable.

P DRUG PRODUCT [Nebido® (testosterone undecanoate) injection]

P.1 Description and Composition of the Drug Product [Nebido® (testosterone undecanoate) injection]

The drug product, Nebido® (Testosterone undecanoate) injection is an oily injectable solution packaged in (b) (4) amber glass vials with (b) (4) grey, stoppers. Each vial contains 3 mL of 250 mg/mL of Testosterone undecanoate oily solution. Nebido® is a clear, yellowish and sterile oil solution for intramuscular injection. Testosterone undecanoate oily solution is consisted of testosterone undecanoate (750 mg/vial), refined castor oil (885 mg/vial) and benzyl benzoate (1500 mg/vial). Each mL of 250 mg/mL testosterone undecanoate solution provides 157.9 mg testosterone.

Detailed information regarding the composition of Nebido® was referred to DMF # (b) (4)

The composition of the Nebido® (Testosterone undecanoate) injection is shown in the following Table.

Composition of Nebido® Injection

Ingredient	Amount per vial (mg)	Function	Reference to standards
	(b) (4) 750 mg/vial		
Testosterone undecanoate	750	Active ingredient	DMF (b) (4)
Benzyl benzoate	1500	(b) (4)	USP/Ph. Eur.*
Castor oil refined for parenteral use	885		USP/Ph. Eur.*
(b) (4)			

*:Microbiological test according to EP and USP (limit: not more than (b) (4) cfu/g)

(b) (4)

Evaluation: Acceptable. All the excipients are of compendial grades.

P.2 Pharmaceutical Development [Nebido® (testosterone undecanoate) injection]

P.2.1 Components of the Drug Product

The components used in the drug products are referred to DMF # (b) (4)

Evaluation: Acceptable.

9 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Evaluation: Acceptable.

A APPENDICES
A.1 Facilities and Equipment (biotech only)
N/A

A.2 Adventitious Agents Safety Evaluation
N/A

A.3 Novel Excipients
N/A

R REGIONAL INFORMATION
R1 Executed Batch Records
Executed batch records were referred to DMF # (b) (4)

Evaluation: Acceptable.

R2 Comparability Protocols
N/A

R3 Methods Validation Package
Information on method validation package was referred to DMF # (b) (4)

Evaluation: Acceptable.

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

A. Labeling & Package Insert

The sponsor provided the proposed labeling text and samples of carton and container labels in the Labeling section. However, the proposed labeling text in the Labeling section has not been reviewed according to 21 CFR 201 because of the approvable status of the NDA.

CMC related information provided in the vial and carton labels:

The vial and carton labels have been modified multiple times with or without FDA's request. CMC related information provided in the final and vial and carton labels are shown below:

Vial Label

(b) (4)

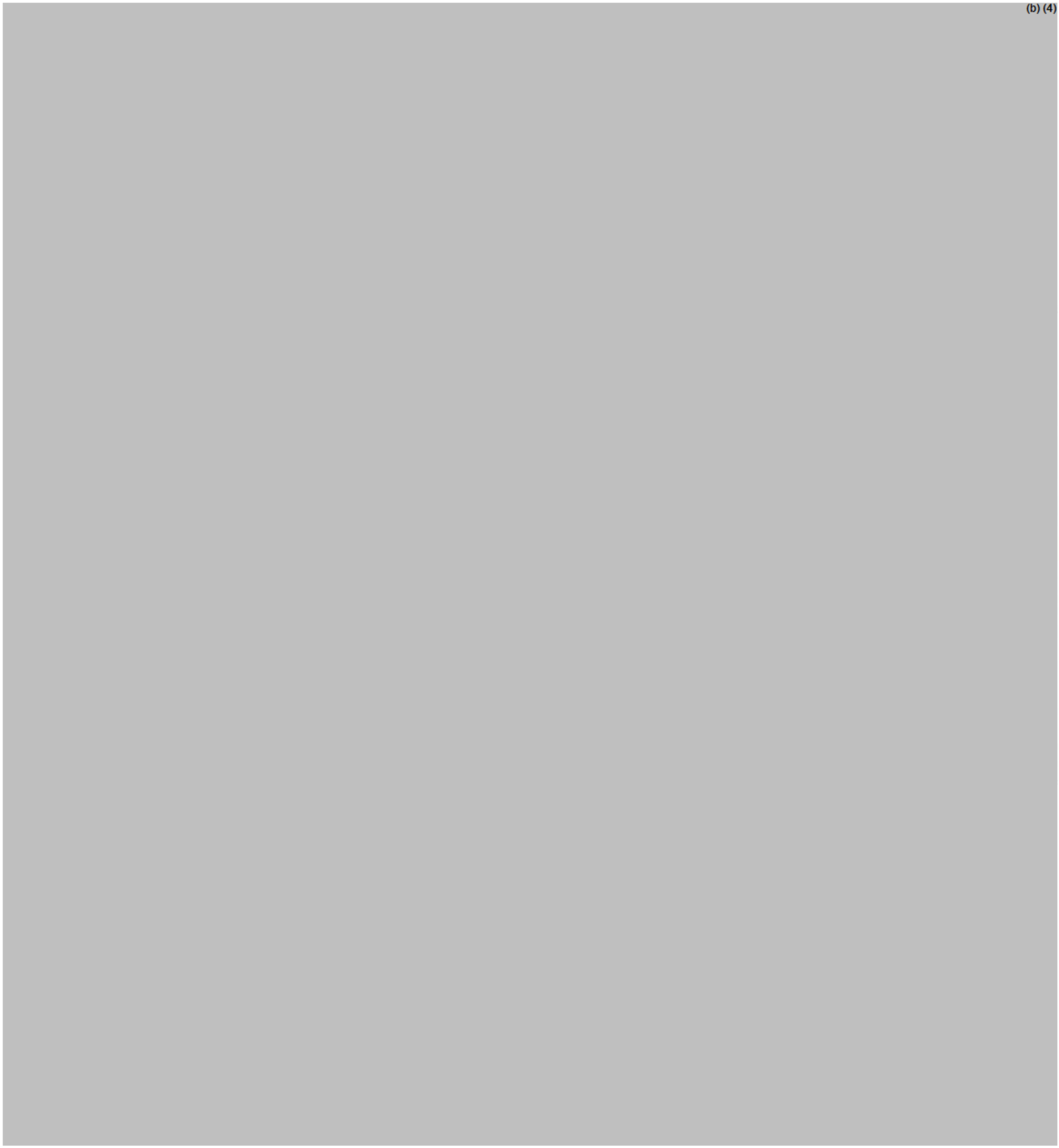
As shown in the above sample label, the following items are provided:

- **Proprietary name, established name**
- **Dosage strength**
- **Net contents**
- **Lot number and expiration date**
- **"Rx only"**
- **Storage conditions**
- **NDC number (requested but not required (21 CFR 207.35(b)(3)(i))**
- **Name of manufacturer/distributor**

Evaluation: Acceptable. According to 21CFR201.25, the bar code requirement on the label can be exempted if compliance is not technically feasible. The requirement of linear bar code on the label is exempted because of limited space of the label. An amendment dated April 30, 2008 was received from the sponsor to request exemption from the barcode labeling requirement for the vial label (b) (4) If printed along the horizontal axis, would be too curved for consistent barcode resolution. Alternatively, the barcode if printed along the vertical axis, is too long to fit on this small vial label (and if compressed, again loses scanning resolution). Linear bar code is printed on the carton label and only one vial is to be stored in its original carton.

Carton Label

(b) (4)



As shown in the above mock-up carton label, the following items are provided:

- **Proprietary name, established name**
- **Dosage strength**
- **Net quantity of dosage form**
- **"Rx only"**
- **Lot number and expiration date**
- **Storage conditions**
- **NDC number (requested but not required (21 CFR 207.35(b)(3)(i))**
- **Name of manufacturer/distributor**
- **Statement of being sterile (if applicable)**
- **"See package insert for dosage information"**

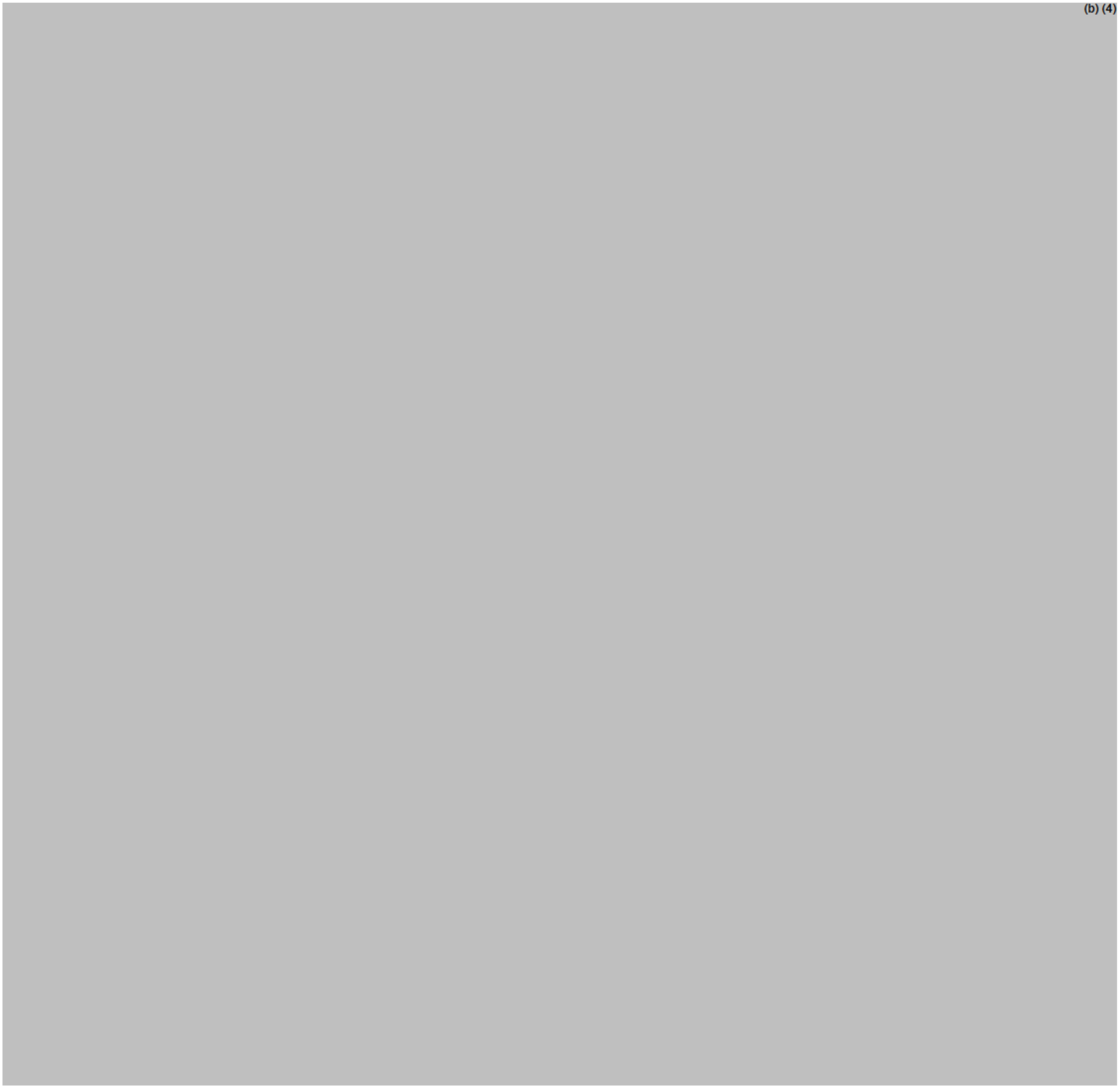
Evaluation: Quantitative ingredient information and Bar code need to be on the carton label.

Information Request
An IR letter dated February 29, 2008 was sent to the sponsor to request the sponsor to add Quantitative ingredient information and Bar code to the carton label.

An updated carton label was received on May 19, 2008. The updated carton label is shown below.

Updated Carton Label

(b) (4)



Conclusion: Acceptable. Quantitative ingredient information and Bar code are added to the carton label.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The sponsor, Indevus Pharmaceuticals Inc., requested categorical exclusion from the preparation of an environmental assessment in accordance with 21 CFR 25.31(b). The total fifth year drug substance production estimates for testosterone undecanoate for the dosage form and strengths included in this application are lower than (b) (4) kg per year. Use is assumed to be evenly distributed throughout the U.S. Therefore the expected point of entry concentration in any of the next five years of production is markedly lower than the 1 ppb limit. Further, Indevus Pharmaceuticals Inc. stated that, to the best of their knowledge, no extraordinary circumstances exist.

Conclusion: Acceptable. The applicant would qualify for categorical exclusion from the preparation of an environmental assessment as the concentration of testosterone undecanoate will be less than 1 ppb, based on estimation.

III. Establishment Evaluation Summary

The Office of Compliance has given an overall acceptable recommendation for the manufacturing facilities. The summary report of Establishment Evaluation is attached below:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 22219/000 Sponsor: INDEVUS PHARMS
Org Code: 580 33 HAYDEN AVE
Priority: LEXINGTON, MA 02421
Stamp Date: 28-AUG-2007 Brand Name: NEBIDO
PDUFA Date: 28-JUN-2008 Estab. Name:
Action Goal: Generic Name: TESTESTERONE UNDECANOATE
District Goal: 29-APR-2008 Dosage Form: (INJECTION)
Strength: 250 MG/ML
FDA Contacts: ID = 132902 Project Manager
Y. SUN Review Chemist 301-796-1388
D. CHRISTNER Team Leader 301-796-1341

Overall Recommendation: ACCEPTABLE on 26-JUN-2008 by S. FERGUSON
(HFD-322) 301-796-3247

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

DMF No: (b) (4) AADA:
Responsibilities:
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER \

FINISHED DOSAGE STABILITY TESTER
FINISHED DOSAGE STERILIZER
Profile: SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-SEP-07
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

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

DMF No: (b) (4) AADA:
Responsibilities:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: (b) (4) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-JUN-08
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

IV. List Of Deficiencies To Be Communicated

None.

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

/s/

Yichun Sun
6/26/2008 05:01:15 PM
CHEMIST

Moo-Jhong Rhee
6/26/2008 05:06:24 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Reproductive and Urologic Products
NDA:	22-219
Applicant:	Indevus Pharmaceuticals
Stamp Date:	28-Aug-2007 (Posted 29-Aug-2007)
PDUFA Date:	27-Jun-2008
Trademark:	Nebido
Established Name:	Testosterone undecanoate
Dosage Form:	Injection
Route of Administration:	Injection
Indication:	Testosterone replacement therapy in hypogonadal males
PAL:	Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	x	☐
Comments for 74-Day Letter	x	☐

Summary and Critical Issues:

A. Summary

Drug product is Nebido (testosterone undecanoate) intramuscular injection intended as a long-acting therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Nebido is approved throughout Europe with Schering AG as the sponsor. Indevus Pharmacueticals has obtained exclusive rights from Bayer Schering AG (formerly Schering AG) to (b) (4) seek marketing authorization for Nebido in the US.

Nebido drug product contains 250 mg/ml Testosterone undecanoate as the active ingredient in an oily solution for intramuscular injection. It is provided (b) (4) in a (b) (4) amber glass vial with a (b) (4) grey stopper, contianing a fill volume of (b) (4) 3 ml (750 mg) (b) (4) Testosterone undeacanoate (250 mg/ml).

Clinical trials have been conducted under IND 72,297. Complete drug substance and drug product information are provided in the referenced DMFs. No information is provided in Module 3, although an overview of the information is provided in Module 2.

B. Critical issues for review

Both DMFs were reviewed in conjuction with the IND, but were reviewed only in the context of safety to initiate the clinical trials. Both DMFs will require full review for this NDA.

DRUG SUBSTANCE:

Testosterone undecanoate drug substance has been manufactured at the [redacted] site for all clinical trial materials and initial commerical supplies. Sponsor has submitted a second site in [redacted] as an alternate API manufacturing site. Sponsor states that the process was transferred without process changed and the comparability of the drug substance from the [redacted] and [redacted] sites has been confirmed and documented in DMF [redacted] While the sponsor states that the drug substance manufactured at the [redacted] and [redacted] sites are comparable, this is a review issue. The comparability data should include structural elucidation data, impurity profile, particle sizes, polymorphs and stability data from the [redacted] site. In addition, release data and at least three months of long term and accelerated stability data from three batches is expected, along with the standard stability commitment. If the DMF does not contain this information it should be requested from the DMF holder.

DRUG PRODUCT:

Drug product is sterile and is manufactured using [redacted] A microbiological consult will be sent for review of the manufacturing process.

Sponsor has identified a number of different manufacturing and stability sites where data was generated. Expiration dating will need to be carefully evaluated because different sites are involved and the equivalency of the drug products will need to be determined.

C. Comments for 74-Day Letter

Please state what expiration dating you are requesting for the product.

Color mock-ups for the carton and immediate container labels, including any logos, should be provided in order to allow full review of these labels.

Clarify which drug product will be commercially available ([redacted] 3 [redacted] ml in vials) and update the Physician's Insert accordingly.

D. Recommendation:

This NDA is fileable from a CMC perspective. There are several critical issues which need to be evaluated during the review as outlined above. Three comments should be included in the 74-day letter. A single reviewer, Yichun Sun, Ph.D. has been assigned.

_____

Donna F. Christner, Ph.D.

Filing Checklists

A. Administrative Checklists;

YES	NO		Comments
X		On its face, is the section organized adequately?	
X		Is the section indexed and paginated adequately?	
X		On its face, is the section legible?	
X		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	DMF (b) (4) DMF (b) (4)
X		Has an environmental assessment report or categorical exclusion been provided?	CE as per 21 CFR 25.31(b)

B. Technical Checklists;

1. Drug Substance

X		Does the section contain synthetic scheme with in-process parameters?	DMF (b) (4)
X		Does the section contain structural elucidation data?	DMF (b) (4)
X		Does the section contain specifications?	DMF (b) (4)
X		Does the section contain information on impurities?	DMF (b) (4)
X		Does the section contain validation data for analytical methods?	DMF (b) (4)
X		Does the section contain container and closure information?	DMF (b) (4)
X		Does the section contain stability data?	DMF (b) (4)

2. Drug Product

X		Does the section contain manufacturing process with in-process controls?	DMF (b) (4)
X		Does the section contain quality controls of excipients?	DMF (b) (4)
X		Does the section contain information on composition?	DMF (b) (4)
X		Does the section contain specifications?	DMF (b) (4)
X		Does the section contain information on degradation products?	DMF (b) (4)
X		Does the section contain validation data for analytical methods?	DMF (b) (4)
X		Does the section contain information on container and closure systems?	DMF (b) (4)
X		Does the section contain stability data with a proposed expiration date?	DMF (b) (4)
X		Does the section contain information on labels of container and cartons?	
X		Does the section contain tradename and established name?	

C. Review Issues

X		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	X	Is a team review recommended?	
X		Are DMFs adequately referenced?	

DMF No.	Holder	Description	LOA	Status
(b) (4)			Yes	Reviewed on 03-May-2006 by Zhengfang Ge, Ph.D. for IND 72297 and found acceptable to initiate trials. **Will Require Review for NDA**
			Yes	Reviewed on 03-May-2006 by Zhengfang Ge, Ph.D. for IND 72297 and found acceptable to initiate trials. **Will Require Review for NDA**
			Yes DMF (b) (4)	
			Yes DMF (b) (4)	Reference information concerns Bacterial Endotoxin Reduction (BER) Validation data. **Will be consulted to microbiology.**
			Yes DMF (b) (4)	Reviewed on 03-Jul-2007 by Norman Gregory for NDA (b) (4) and found adequate for use as an intermediate.

Assessment Notes

Drug product is Nebido (testosterone undecanoate) intramuscular injection intended as a long-acting therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Nebido is approved throughout Europe with Schering AG as the sponsor. Indevus Pharmacueticals has obtained exclusive rights from Bayer Schering AG (formerly Schering AG) to (b) (4) seek marketing authorization for Nebido in the US.

Clinical trials have been conducted under IND 72,297. Complete drug substance and drug product information are provided in the referenced DMFs. No information is provided in Module 3, although an overview of the information is provided in Module 2. There have been a number of CMC-related meetings/correspondences, outlined below:

- **PreIND meeting held 30-Nov-2005:** Rajiv Agarwal, Ph.D., Ph.D., was the assigned chemist. There was one question, refering to a presubmission request for review of the DMFs for both the drug substance and drug product DMFs to determine if the DMFs were sufficient for filing. Sponsor was informed that each section of the CTD format had been addressed in the drug product DMF, but evlauation of this information would be made upon submission of the IND/NDA. The following comments/information requests were made:

    1. Provide information on the drug substance (structure, physico-chemical propoerties, specifications, acceptance testing performed by drug product manufacturer) and drug product (unit and batch composition, specifications and stability testing) in the NDA for ease of review
    2. Provide a LOA for the DMFs for the drug substance and container closure system
    3. Establish acceptance criteria for benzyl benzoate in the drug product to be tested at both release and stability
    4. Confirm that testing of the drug product conforms to USP guidelines

In addition, PharmTox made the comment that the drug product would be considered as a New Molecular Entitiy (NME) because the moiety had not been previously approved in the US. Sponsor did not agree, but stated that it was a prodrug. Although it is an ester of an approved moiety (testosterone) and as such would not be considered an NME, CMC defered the discussion until such time as data could be reviewed to determine the molecule's regulatory status.

- **IND review dated 20-Apr-2006:** Zhengfang Ge was the assigned reviewer. Information was provided in the referenced DMFs for which the DMFs were examined and found to be adequate to support the initiation of the IND. In the DMF (b) (4) review, the question concerning a test for benzyl benzoate was addressed (see PIND meeting comment above). Because the benzyl benzoate is used at a concentration of (b) (4) % as (b) (4) addition of such a test was deemed unnecessary, and was confirmed by both Dr. Agarwal and Dr. John Metcalf, microbiology reviewer. The sponsor was asked to provide COAs for the batches used in the preclinical and clinical studies for further PharmTox assessment.

Drug Substance

General information is provided in Module 2 (Quality Overall Summary) of the NDA. Complete information is provided in DMF (b) (4) which will require review. The following drug substacne information is provided in the NDA:

INN Name: Testosterone undecanoate

Compendial Name: Testosterone undecanoate

Chemical Names:

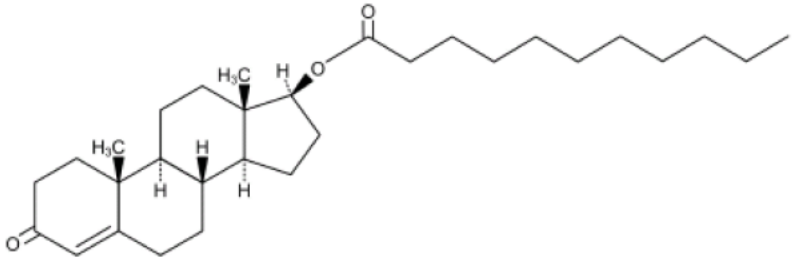
CAS: (17β)-17-[(1-Oxoundecyl)oxy]-androst-4-en-3-one

IUPAC: 17β-Undecanoyloxy-4-androsten-3-one 3-Oxoandrost-4-en-17ß-yl-undecanoate

Company or laboratory code: (b) (4) ZK 5448

Structural Formula

Testosterone undecanoate is a white to off-white crystalline substance with the following molecular structure:



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

Molecular Weight: 456.7

Administrative information for the DMF is as follows:

Holder name:	(b) (4)
Holder Address:	
Holder phone:	
Holder contact person:	
Contact person´s email address:	

The following Manufacturing sites are involved in production of the drug substance. All sites will be submitted to EES.

Synthesis and purification: (b) (4)

Address:

Contact person:

Phone:

Email address:

Alternatively: (b) (4)

Address:

Contact person at site:

Phone:

Email address:

Sponsor states that all drug substance batches used in the clinical supplies and for initial commercial supplies have been manufactured in the (b) (4) site in (b) (4) An alternate manufacturing site may also be used. Sponsor states that the process was transferred without process changed and the comparability of the drug substance from the (b) (4) and (b) (4) sites has been confirmed and documented in DMF (b) (4)

Comment: *While the sponsor states that the drug substance manufactured at the* (b) (4) *and* (b) (4) *sites are comparable, this is a review issue. The comparability data should include structural elucidation data, impurity profile, particle sizes, polymorphs and stability data from the* (b) (4) *site. In addition, release data and at least three months of long term and accelerated stability data from three batches is expected, along with the standard stability commitment. If the DMF does not contain this information it should be requested from the DMF holder.*

It was unclear from a quick scan of the DMF where stability studies were performed. This information was requested from the DMF holder via email and a reply received on 18-Sep-2007. The DMF holder stated that stability studies are performed at the site of manufacture. Local contact information for the (b) (4) *site was not included in the DMF. This information was provided by the DMF holder on 24-Sep-2007. Sites were submitted to EES on 24-Sep-2007.*

A flow chart for the (b) (4) pathway has been provided:

(b) (4)

The specifications for the drug substance are as follows:

Table 1: Drug Substance Tests and Specifications

Test	Specification
Description	White or nearly white, crystalline substance
IR Spectrum	Matches reference spectrum
Identification (HPLC/PDA)	Corresponds
Specific optical rotation	(b) (4)
Water content (KF)	
Heavy metals	
(b) (4)	
Related substances (HPLC) testosterone	
Related substances (HPLC)	
(b) (4)	
Related substances (HPLC)	
(b) (4)	
Related substances (HPLC) Sum of impurities non-specified	
Related substances (HPLC) Each impurity non-specified	
Related substances (HPLC) Total of impurities (specified + non-specified)	

Test	Specification
(b) (4)	(b) (4)
Residual solvent GC	
Residual solvent GC	
Residual solvent GC	
Assay UV (b) (4)	
Microbial contamination	
Endotoxins (LAL)	

Information on Characterization, Reference Standards, Container Closure System, and Stability are provided in the referenced DMF.

Comment: *The DMF will require review.*

Drug Product

Complete information on the drug product is provided in DMF [redacted] An overview of the information is provided in Module 2 of the NDA and is outlined below.

Nebido drug product contains 250 mg/ml Testosterone undecanoate as the active ingredient in an oily solution for intramuscular injection. It is provided [redacted] in a [redacted] amber glass vial with a [redacted] grey stopper, contianing a fill volume of [redacted] 3 ml (750 mg) [redacted] Testosterone undeacanoate (250 mg/ml). The formulation is shown below:

Names of ingredients	Unit and/or percentage formula	Function	Reference to standards
[redacted]	750 mg i.m. (vial)		
Active ingredient: 1.testosterone undecanoate	750.0 mg	active substance	[redacted]
Excipients: 2. benzyl benzoate	1500.0 mg	[redacted]	USP / Ph. Eur *
3. castor oil refined for parenteral use	885.0 mg		USP / Ph. Eur *
[redacted]			

*Microbiological test according to EP and USP (limit: not more than [redacted] cfu/1g)

The drug product is manufactured [redacted] and complete information is provided in the referenced DMF. Administrative data is as follows:

3.1. Administrative Data

Holder name:	[redacted]
Holder Address:	
Holder phone:	
Holder contact person:	
Contact person´s email address:	

Drug product is manufactured at the following facility:

3.2. Manufacturing Site

Manufacturing of the bulk solution: (b) (4)

Filing into (b) (4) Vials

Primary Packaging

Release Testing

Secondary Packaging

Batch Release

Address: (b) (4)

Contact person at site:

Phone:

Email address:

Comment: *The DMF has been recently updated showing that the* (b) (4) *site in the only site for manufacture. The DMF holder was contacted to clarify where stability studies were conducted and stated in an email dated 18-Sep-2007 that stability studies are performed at the site of manufacture. The site was submitted to EES on 24-Sep-2007.*

The sponsor uses the following manufacturing scheme for the drug product:

Flow Chart of the Process

(b) (4)

Sponsor states that castor oil and benzyl benzoate [redacted] In the cover letter, sponsor states that an assay test for benzyl beonzoate (as requested at the PreIND meeting) was not delevoped because [redacted] This question was also addressed in the IND review where it was felt that an assay test was unnecessary because the benzyl benzoate was [redacted]% of the formulation (See ASSESSMENT NOTES). Benzyl benzoate is an FDA approved excipient used at up to 46% concentration for intramuscular injection. Castor oil is an FDA approved excipient without a listed percentage for injection in pure form [redacted] It is also a food substance generally recognized as safe.

Sponsor states [redacted] In addition, the oily formulation [redacted]

Sponsor states that the manufacture of Nebido [redacted]

Sponsor states that the manufacturing [redacted] process for the vials is in progress.

Comment: *A microbiological consult was requested on 21-Sep-2007 for review of the manufacturing process through the OND PM, John Kim..*

Excipients are tested according to the USP and Ph.Eur. monographs. Microbiological testing is also tested as per USP and Ph.Eur.

Excipient	Pharmacopoeia	Additional Testing
Benzyl benzoate	Ph. Eur./USP	Microbiological test according to EP and USP (limit: not more than [redacted]cfu/1g)
Castor oil, refined	Ph. Eur./USP	Microbiological test according to EP and USP (limit: not more than [redacted]cfu/1g)

[redacted]

Drug product specifications for release and stability are as follows:

Table 1: Drug Product Tests and Specifications

Test	Specification
Appearance/visible particles	Clear, free of particles
Clarity	Clear or not more opalescent than reference (b) (4)
Color	Not more intense in color than reference solution (b) (4)
Identification of testosterone undecanoate (HPLC, HPLTC)	A) HPLC The main peaks of sample and reference correspond to each other regarding the retention time B) HPLC/UV Spectrum The UV spectra of the main peaks of sample and reference correspond to each other regarding absorption maxima C) HPTLC The principle spot of sample and reference correspond to each other regarding Rf value Perform A and B or A and C
Extractable Volume	individual volume ≥ nominal volume
Particulate contamination – sub visible particles (automatic particle count)	(b) (4)
Acid value	
Related substances and degradation products of testosterone undecanoate: (HPLC)	
Assay of testosterone undecanoate (HPLC)	
Bacterial Endotoxins (LAL)	
Sterility	Sterile; no viable microorganisms detectable

Sponsor states that tests are either USP/Ph.Eur. or are validated. Full information is provided in the DMF.

Test results are provided for two lots used in the US Phase 3 trials and the current validation lots manufactured in 3 ml (b) (4) vials. The formulation used in the clinical trials is identical to that for the to-be-marketed product. The container closure system has been modified from a (b) (4)

(b) (4) to a Type I amber glass vials (b) (4) Lot, the use, and the release data are shown below:

Lot	Use	Packaging
(b) (4)		
N372001	Validation	Type I glass 3 mL vial
N372002	Validation	Type I glass 3 mL vial
(b) (4)		

Test Results for Clinical and Validation Lots

Test	Lot N372001	Lot N372002
(b) (4)		(b) (4)
Appearance	Passes test	Passes test
Clarity	Passes test	Passes test
Color	(b) (4)	(b) (4)
Identification (TU)	Passes test	Passes test
Extractable Volume	Passes test	Passes test
(b) (4)		
Particulate contamination > (b) (4) µm > µm		
Acid value		
Related substances and degradation products of testosterone undecanoate: (b) (4)		
Unspecified, individual		
Unspecified, sum		
Total		
Assay (TU)		
Bacterial Endotoxins		
Sterility	Passes test	Passes test

Full information on the Reference Standard is provided in DMF (b) (4) as is information on the container closure system. Sponsor states that extensive stability studies (up to 60 months) exists on the product in (b) (4) and that compatibility studies have been conducted with the stoppers and are included in the DMF.

Sponsor states that the following stability data are contained in the DMF. They state that a shelf life of 60 months for climatic zones (b) (4) has been established for this product. The narrative in the NDA provides the following information (tabluated for each of use).

Container closure system	Manufacturing site	Stability site	Scale	25ºC/60%RH	30ºC/70%RH	40ºC/75%RH
(b) (4)						

Sponsor also states that photostability studies in (b) (4) vials have been confirmed in studies per ICH gidance. Sponsor does not explicitly state what expiry they are requesting.

Comment: *The DMF holder was contacted on 17-Sep-2007 and stated that stability studies are performed at the manufacturing facilities. Sponsor should state what expiration dating they are requesting.*

Draft carton and container labels are provided, but they are text only and contain the note that the format, color and layout of the printing are subject to change. Color mock-ups for the carton and immediate container labels, including any logos, should be provided in order to allow full review of these labels. Labels should also include the volume of drug product that is contained in each container.

Comment: *Color mock-ups for the carton and immediate container labels, including any logos, should be provided in order to allow full review of these labels. Labels should also include the volume of drug product that is contained in each container.*

The PI is submitted. In the HOW SUPPLIED section, it lists (b) (4) The application states that (b) (4) vials containing 3 ml (b) (4) of product are avaialable. Sponsor should clarify what drug product will be commercially available.

Comment: *Clarify which drug product will be commercially available ((b) (4) 3 (b) (4) ml in vials) and update the Physician's Insert accordingly.*

A categorical exclusion for preparation of an environmental assessment as per 21 CFR 25.31(b) is requested in Module 1.

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/s/

Donna Christner
10/30/2007 07:41:59 AM
CHEMIST

Hard copy reviewed. Changes made as per your review

Moo-Jhong Rhee
10/30/2007 01:30:25 PM
CHEMIST
Chief, Branch III