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RESEARCH**

APPLICATION NUMBER:

022219Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

April 21, 2009

NDA: 22-219/N-000/AZ

Drug Product Name

Proprietary: Nebido®

Non-proprietary: testosterone undecanoate for injection

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
March 02, 2009	March 02, 2009	March 25, 2009	March 26, 2009

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
August 24, 2007	1	June 20, 2008

Applicant/Sponsor

Name: Indevus Pharmaceuticals Inc.

Address: 33 Hayden Avenue, Lexington, MA 02421- 7971

Representative: Mark C. Roessel, Vice President, Reg. Affairs

Telephone: 781-402-3468 (phone)

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: The application is recommended for approval from microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Amended Original NDA
 2. **SUBMISSION PROVIDES FOR:** A long-acting therapeutic agent for deficiency or absence of endogenous testosterone.
 3. **MANUFACTURING SITE:** [REDACTED] (b) (4)
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 250 mg/mL of the active ingredient in an oily solution, in a 3mL vial for intramuscular injection.
 5. **METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** For treatment of deficiency or absence of endogenous testosterone.
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF [REDACTED] (b) (4)
- C. **REMARKS:** The original NDA 22-219 received an approvable status pending resolution of items listed as deficiencies in DMF [REDACTED] (b) (4). The sponsor submitted an amendment (amendment 19) informing FDA that it contains a complete response to the deficiencies cited in the approvable letter dated June 27, 2008. The amendment is in an electronic format in EDR. As a result the chemistry, manufacturing and controls information for the drug product has been updated on August 14, 2008 in the revised Drug Master File [REDACTED] (b) (4) (7th amendment, in sections 1, 2, & 3).

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – The application is recommended for approval based on the data provided in DMF (b) (4)
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - NA**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – (b) (4)
- B. Brief Description of Microbiology Deficiencies** – None.
- C. Assessment of Risk Due to Microbiology Deficiencies** – None.

III. Administrative

- A. Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D.
Review Microbiologist, CDER/OPS/NDMS
- B. Endorsement Block** _____
David Hussong, Ph.D.
Assoc. Director., CDER/OPS/NDMS
- C. CC Block**
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT- QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE - N/A

P DRUG PRODUCT
No change

P.3 Manufacture

(b) (4) - N/A

(b) (4) -N/A

(b) (4) -N/A

(b) (4) MANUFACTURING PROCESS

The revised chemistry, manufacturing and controls information for the drug product is contained in Drug Master File (b) (4) (7th amendment, in sections 1, 2, & 3) dated August 14, 2008. The revised information is acceptable.

P.3.5 Process Validation and/or Evaluation

(b) (4) - N/A

(b) (4) - N/A

(b) (4) - N/A

MANUFACTURING PROCESS

The revised chemistry, manufacturing and controls information for the drug product is contained in Drug Master File (b) (4) (7th amendment, in sections 1, 2, & 3) dated August 14, 2008. The revised information is acceptable.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None

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

/s/

Vinayak Pawar
4/23/2009 04:29:19 PM
MICROBIOLOGIST

Recommended for approval from microbiology product quality standpoint.

David Hussong
4/23/2009 10:24:22 PM
MICROBIOLOGIST

I concur with the reviewer's assessment that the DMF holder has resolved remaining questions about the manufacturing controls for this product, and the microbiology aspects of this application are acceptable for approval.

Product Quality Microbiology Review

20 June 2008

NDA: 22-219

Drug Product Name

Proprietary: Nebido®

Non-proprietary: testosterone undecanoate for injection

Drug Product Priority Classification: S1

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
August 24, 2007	August 28, 2007	October 29, 2007	November 05, 2007

Submission History (for amendments only) - N/A

Applicant/Sponsor

Name: Indevus Pharmaceuticals Inc.

Address: 33 Hayden Avenue, Lexington, MA 02421- 7971

Representative: John Berryman, Vice President, Reg. Affairs

Telephone: 781-402-3451 (phone)

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: The application is approvable pending resolution of items listed as deficiencies in the DMF (b) (4)

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original NDA
2. **SUBMISSION PROVIDES FOR:** long-acting therapeutic agent for deficiency or absence of endogenous testosterone.
3. **MANUFACTURING SITE:** (b) (4)
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 250 mg/mL of the active ingredient in an oily solution, in a 3mL vial for intramuscular injection.
5. **METHOD(S) OF STERILIZATION:** (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** For treatment of deficiency or absence of endogenous testosterone.
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF (b) (4)
- C. **REMARKS:** The consult requests review of an original NDA 22-219 for an intramuscular injection of therapeutic agent for deficiency or absence of endogenous testosterone. The submission is in electronic form in EDR. The chemistry, manufacturing and controls information for the drug product is contained in Drug Master File (b) (4) originally submitted by (b) (4) Indevus Pharmaceuticals amended this NDA on February 22, 2008 to inform FDA that the 3mL, 750 mg dose should be the basis of labeling and review (b) (4) Initial Quality Assessment has been filed by Donna F. Christner.

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Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – The application is recommended for approvable pending resolution of items listed as deficiencies in the DMF (b) (4)
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - NA**

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – (b) (4)

- B. **Brief Description of Microbiology Deficiencies** – None.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – None.

III. Administrative

- A. **Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D.
- B. **Endorsement Block** _____
David Hussong, Ph.D.
- C. **CC Block**
N/A

Product Quality Microbiology Assessment

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA**

S DRUG SUBSTANCE - N/A

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – (b) (4)
(b) (4) Testosterone undecanoate 750 mg in oily solution is presented in a 3 ml vial presentation.
- Drug product composition – The quantitative composition for (b) (4) (b) (4) the 750 mg formula is shown in Table 1.

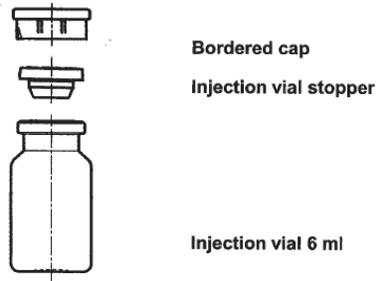
Table 1. Drug Product Composition (reproduced from Drug Product section 2.3.P)

Ingredients	Unit and/or percentage formula	Function	Reference to Standards
	(b) (4) 750 mg vial		
<i>Active Ingredient</i> 1. Testosterone undecanoate	750 mg	Active substance	8217 h, US-DMF (b) (4)
<i>Excipients</i> 2. benzyl benzoate 3. castor oil (b) (4)	1500 mg (b) (4)	(b) (4)	USP/Ph.Eur (b) (4)

Indevus Pharmaceuticals amended this NDA on February 22, 2008 to inform FDA that the 3mL, 750 mg dose should be the basis of labeling and review (b) (4)

- Description of container closure system – The primary container closure system consists of (b) (4) amber class 1 glass vial (Ph. Eur.) with (b) (4) rubber stopper and (b) (4) crimp with (b) (4) plastic cap (see Figure 1).

Figure 1. Primary Container Closure



P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity – Referenced in DMF (b) (4).
- (b) (4)
- Justification for not having a microbial limit specification for a non-sterile drug product – N/A

P.3 Manufacture

P.3.1 Manufacturers – The manufacturer of Testosterone is (b) (4)

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4) - N/A

(b) (4) -N/A

(b) (4) -N/A

(b) (4) **MANUFACTURING PROCESS**

The chemistry, manufacturing and controls information for the drug product is contained in Drug Master File (b) (4)

P.3.5 Process Validation and/or Evaluation

(b) (4) – N/A

(b) (4) – N/A

(b) (4) – N/A

MANUFACTURING PROCESS

The chemistry, manufacturing and controls information for the drug product is contained in Drug Master File (b) (4)

P.5 Control of Drug Product

P.5.1 Specifications**P.5.2 Analytical Procedures**

The chemistry, manufacturing and controls information for the drug product is contained in Drug Master File (b) (4)

- Endotoxin – DMF (b) (4)
- Sterility – DMF (b) (4)
- Microbial Limits – DMF (b) (4)

P.7 Container Closure System– See section P.1.

P.8 Stability**P.8.1 Stability Summary and Conclusion****MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS**

The chemistry, manufacturing and controls information for the drug product is contained in Drug Master File (b) (4)

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The chemistry, manufacturing and controls information for the drug product is contained in Drug Master File (b) (4)

P.8.3 Stability Data

Stability data and supportive stability data was provided in section 3.2.P.8.3.

A APPENDICES - N/A

R REGIONAL INFORMATION -N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1**A. PACKAGE INSERT**

Labeling information will be revised as stated in the sponsor's amendment to this NDA dated February 22, 2008.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

Indevus Pharmaceuticals amended this NDA on February 22, 2008 to inform FDA that the 3mL, 750 mg dose should be the basis of labeling and review (b) (4)

The application is approvable pending resolution of items listed as deficiencies in DMF (b) (4). A letter conveying the DMF deficiencies will be provided to the DMF holder.

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/s/

Vinayak Pawar
6/20/2008 04:30:23 PM
MICROBIOLOGIST

The application is approvable pending resolution of items listed
as deficiencies in DMF (b) (4)

David Hussong
6/20/2008 04:45:14 PM
MICROBIOLOGIST

I concur with the microbiology reviewer's recommendation that this
application is APPROVABLE pending resolution of CMC deficiencies
in the DMF.