CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-732

Microbiology Review(s)

MEMORANDUM

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

TO: NDA 21-732

DATE: 20 September 2004

SUBJECT: Addendum to Microbiologist's Review #2

FROM: James McVey
HFD-805
(301) 827-7504
FAX (301) 827-3084

Section I of Microbiology Review #2 for NDA 21-732 recommends approval and suggests language for a Phase IV commitment. This commitment was made in the amendment dated September 9, 2004. These data will resolve a low-risk concern that will confirm that the process is in a state of control. If the process is under control (which is likely), no additional action is needed. If it is not under control, a supplement should be submitted by the applicant. No follow up by the microbiology reviewer will be needed. For this reason, the commitment does not need to be discussed in the action letter.

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/s/

James McVey
9/21/04 07:05:17 AM
MICROBIOLOGIST

David Hussong
9/21/04 08:56:53 AM
MICROBIOLOGIST
addendum to microbiology review 2

Product Quality Microbiology Review
Review for HFD-580

September 14, 2004

NDA: 21732

Drug Product Name
Proprietary: Vantas
Non-proprietary: histrelin acetate implant
Drug Product Classification: GnRH Agonist

Review Number: 2

Subject of this Review
Submission Date: August 19, 2004 via Certified mail
September 9, 2004 via Fed Ex
Receipt Date: August 23, 2004 in e-mail attachment
September 9, 2004 Amendment
Consult Date: August 23, 2004. Response to first review.
Date Assigned for Review: August 23, 2004

Submission History (for amendments only)
Date(s) of Previous Submission(s):
December 12, 2003 and April 30, 2004.
Date(s) of Previous Micro Review(s): July 14, 2004

Applicant/Sponsor

Name:	Valera Pharmaceuticals, Inc.
Address:	8 Clarke Dr. Cranbury, NJ 08512-3617
Representative:	William Gray, Sr. Director Regulatory Affairs
Telephone:	(609) 409 9010

Name of Reviewer: James L. McVey

Conclusion: This application is recommended for approval from a product quality microbiology perspective.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N.A.

2. **SUPPLEMENT PROVIDES FOR:** N.A.

3. **MANUFACTURING SITE:** Valera Pharmaceuticals
8 Clarke Drive
Cranbury, New Jersey 08512

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** The subdermal implant contains 50 mg histrelin acetate per implant. The implant delivers a nominal rate of 50 – 60 micrograms histrelin acetate per day for one year. A sterile trochar device is provided for insertion of the implant after a minor incision is made to the inside of the upper arm.

5. **METHOD(S) OF STERILIZATION:** [ ] sterilization of the implant. [ ] vial is reviewed in the document. Sterilization of the trochar device is under CDRH review.

6. **PHARMACOLOGICAL CATEGORY:** GnRH agonist.

B. **SUPPORTING/RELATED DOCUMENTS:** N.A.

C. **REMARKS:** The assembled product is sent to — for sterilization. The validation study — Study No. 1999-GMP-0015) starts in Volume 12 on page 087 with an addendum starting on page 101 which is intended to clarify the original report with respect to the 1994 FDA Guideline for Submission of Documentation for Sterilization Process Validation. The original validation was apparently done in a device format. An e-mail from the review chemist indicates that she has been in contact with the applicant regarding the location of the sterility test provider in order to prevent an additional inspection request. She wants the contract sterilizer to do the sterility test. This change in testing facility included a request for the validated method at —

filename: 21372r1

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The application is recommended for approval from a product quality microbiology perspective. Phase IV commitments are provided.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –

Valera will complete a study of the potential sources of microbiological contamination on the first — production lots (P.5).

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Multiple steps of manual assembly make it possible to incorporate microorganisms inside the implant. Once placed into a 5 mL vials [ ] The trochar insertion device sterilization by [ ] will be reviewed by CDRH representatives.

B. Brief Description of Microbiology Deficiencies – None.

C. Assessment of Risk Due to Microbiology Deficiencies – Not Applicable.

III. Administrative

A. Reviewer's Signature _'_____

B. Endorsement Block
Review Microbiologist, James L. McVey
Microbiology Supervisor, David Hussong

C. CC Block
DFS

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✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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/s/

James McVey
9/14/04 02:37:02 PM
MICROBIOLOGIST

David Hussong
9/14/04 03:21:58 PM
MICROBIOLOGIST
Microbiology Review

Product Quality Microbiology Review
Review for HFD-580

July 14, 2004

NDA: 21732

Drug Product Name
Proprietary: Vantas
Non-proprietary: histrelin acetate implant
Drug Product Classification: GnRH Agonist

Review Number: 1

Subject of this Review
Submission Date: December 12, 2003 and April 30, 2004 Amendment
Receipt Date:
Consult Date: February 11, 2004 and May 4, 2004
Date Assigned for Review: February 19, 2004

Submission History (for amendments only)
Date(s) of Previous Submission(s):
Date(s) of Previous Micro Review(s):

Applicant/Sponsor

Name:	Valera Pharmaceuticals, Inc.
Address:	8 Clarke Dr. Cranbury, NJ 08512-3617
Representative:	William Gray, Sr. Director Regulatory Affairs
Telephone:	(609) 409 9010

Name of Reviewer: James L. McVey

Conclusion: Approvable.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N.A.

2. **SUPPLEMENT PROVIDES FOR:** N.A.

3. **MANUFACTURING SITE:** Valera Pharmaceuticals
8 Clarke Drive
Cranbury, New Jersey 08512

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** The subdermal implant contains 50 mg histrelin acetate per implant. The implant delivers a nominal rate of 50 – 60 micrograms histrelin acetate per day for one year. A sterile trochar device is provided for insertion of the implant after a minor incision is made to the inside of the upper arm.

5. **METHOD(S) OF STERILIZATION:** [ ] sterilization of implant in [ ] vial. Sterilization of the trochar device is under CDRH review.

6. **PHARMACOLOGICAL CATEGORY:** GnRH agonist.

B. **SUPPORTING/RELATED DOCUMENTS:** N.A.

C. **REMARKS:** The April 30, 2004 amendment is in response to a phone call request for additional information by the review chemist. The assembled product is sent to [ ] for sterilization. The validation study [ ] Study No. 1999-GMP-0015) starts in Volume 12 on page 087 with an addendum starting on page 101 which is intended to clarify the original report with respect to the 1994 FDA Guideline for Submission of Documentation for Sterilization Process Validation. The original validation was apparently done in a device format.

filename: 21372r1

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The application is approvable pending resolution of the product quality microbiology concerns listed below.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Multiple steps of manual assembly make it possible to incorporate microorganisms inside the implant. Once placed into a 5 mL vials [redacted] The trochar insertion device sterilization by [redacted] will be reviewed by CDRH representatives.

B. Brief Description of Microbiology Deficiencies – Clarification is needed regarding release testing, container closure integrity and the contractors role in sterility testing.

C. Assessment of Risk Due to Microbiology Deficiencies – Significant risk exists if these issues are not clarified.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Review Microbiologist, James L. McVey
Microbiology Supervisor, Peter H. Cooney

C. CC Block
DFS

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___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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/s/

James McVey
7/19/04 01:26:27 PM
MICROBIOLOGIST

Peter Cooney
7/19/04 03:10:27 PM
MICROBIOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office): Peter Cooney, Ph.D.
Director, Office of Microbiology (HFD-805)
Room 18B-08

FROM: Nenita Crisostomo, Project Manager
Division of Reproductive and Urologic Drug Products
Phone: 301-827-7260

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 4, 2004		21-732	Response to Chemistry Info Request	April 30, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vantas (histrelin acetate implant)	Standard	GnRH agonist	June 11, 2004

NAME OF FIRM: Valera Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- X PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Dear Dr. Cooney:

This submission is an amendment to the existing new NDA submitted in December 12, 2003. Please include this document with your existing review materials for this submission as requested by Dr. Suong Tran, Chemist. Please call me if you have any questions.

Thank you,
Nita Crisostomo

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Nenita Crisostomo
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