CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-868

MICROBIOLOGY REVIEW

Product Quality Microbiology Review
Review for HFD-510
28 NOVEMBER 2005

NDA: 21-868/N 000

Drug Product Name
Proprietary: Exubera
Non-proprietary: Insulin [rDNA origin] Inhalation Powder 1mg/3mg
Drug Product Classification: Insulin, Inhaled

Review Number: 2

Subject of this Review
Submission Date: 21 SEP 2005 and 9 NOV 2005
Receipt Date: 21 SEP 2005 and 9 NOV 2005
Consult Date: 21 SEP 2005 and 9 NOV 2005
Date Assigned for Review: 21 SEP 2005 and 9 NOV 2005

Submission History (for amendments only).
Submission Date: 27 DEC 2004 – Original Submission.
Receipt Date: 27 DEC 2004
Consult Date: 01 JAN 2005
Review Date: 26 AUG 2005

Applicant/Sponsor
Name: Pfizer, Inc.
Address: MS 6025 – B6275
50 Pequot Avenue
New London, CT 06320
Representative: Brian A. Green
Telephone: (860) 732-0959

Name of Reviewer: James L. McVey

Conclusion: Approval is recommended from a product quality microbiology perspective.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Amendment to an original submission in electronic CTD format.

2. **SUBMISSION PROVIDES FOR:** Manufacture and distribution of Insulin inhalation powder.

3. **MANUFACTURING SITE:** For the spray dried powder:
Nectar Therapeutics
150 Industrial Road
San Carlos, CA 94070

For the blister filling (primary and secondary packaging):
Pfizer Inc.
100 Pfizer Drive
Terra Haute, IN 47802
CFN 1819598

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Special dry powder aerosol system. 1 mg and 3 mg blisters for application with provided inhalation device as needed.

5. **METHOD(S) OF STERILIZATION:** N.A. (non – sterile)

6. **PHARMACOLOGICAL CATEGORY:** Insulin (hormone)

B. **SUPPORTING/RELATED DOCUMENTS:** Letter to IND — dated Feb., 2000 concerning Microbial Limits and Yeasts and Molds Testing: we agreed with Pfizer that harmonized microbial limits in Pharmacopeal Forum 28(3) were appropriate and that no yeast and mold testing was needed for Phase I studies. Subsequent USP <1111> rewrites have removed all recommended microbiological levels, referring to the individual monographs where appropriate. The USP chapter on human insulin has microbial limits of 300 cfu/g, "the test being performed on a portion of about — accurately weighed" and absence of the compendial indicator organisms. The bacterial endotoxin limit is stated to be NMT —. Insulin injection is required to be sterile and has a bacterial endotoxin limit of NMT —.

C. **REMARKS:** The concern over microbial contamination is primarily because this drug delivery system bypasses the standard defense mechanisms and delivers the drug deep into the lung. The bulk drug product should have very low to no bioburden when dispensed into the blisters. The product is —

[redacted]

[redacted] . The applicant has requested that the endotoxin and microbial limits tests for the drug product release be put into a skip lot sampling procedure. A history of successful testing is provided but it is not clear how many lots are a production scale and under production Quality Systems control. Final conclusion of the endotoxin skip lot testing plan is provided in the 11/9/05 electronic submission and updated specifications are provided in that submission (See last page).

filename: N21868R2.doc

APPEARS THIS WAY ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approve.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – None.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product

B. Brief Description of Microbiology Deficiencies. None.

C. Assessment of Risk Due to Microbiology Deficiencies. N.A.

III. Administrative

A. Reviewer's Signature _____

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

C. CC Block DFS N21868r2.doc

5 Page(s) Withheld

6 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology-_____

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

/s/

James McVey
11/28/2005 02:23:33 PM
MICROBIOLOGIST

David Hussong
11/30/2005 03:09:39 PM
MICROBIOLOGIST

MEMO

DATE: 2/14/2005

TO: OLUCHI ELEKWACHI; JANICE BROWN

COPY: DAVID HUSSONG

FROM: JAMES L. MCVEY

RE: N21-868 FILING MEETING COMMENTS

Skip lot testing, as indicated for Bacterial Endotoxin Testing and Microbial Limits with freedom from *E. coli*, *P. aeruginosa*, *Salmonella* sp. and *S. aureus*, will not be acceptable without sufficient history of process control. This is not usually available for a new application.

JLM