CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-387

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

23 March 2009

NDA: 22-387/N-000

Drug Product Name
Proprietary: Tyvaso.
Non-proprietary: treprostinil sodium.
Drug Product Priority Classification: S.

Review Number: 1.

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
27 JUN 2008	30 JUN 2008	08 JUL 2008	07 OCT 2008*
29 OCT 2008	29 OCT 2008	N/A	N/A
29 JAN 2009	29 JAN 2009	N/A	N/A
25 FEB 2009	25 FEB 2009	N/A	N/A

*Previously assigned to another microbiology reviewer.

Applicant/Sponsor
Name: United Therapeutics Corp.
Address: One Park Dr.
Suite 400
Research Triangle Park
NC 27709
Representative: Dean Bunce
Telephone: 919-485-8350

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA.

2. **SUBMISSION PROVIDES FOR:** A new drug product.

3. **MANUFACTURING SITE:**
Catalent Pharma Solutions (formerly Cardinal Health)
2200 Lake Shore Dr.
Woodstock, IL 60098

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
   - Solution for inhalation in ___ ampules to be administered via portable ultrasonic nebulizer.
   - 0.6 mg/mL.

5. **METHOD(S) OF STERILIZATION:** ___ b(4)

6. **PHARMACOLOGICAL CATEGORY:** The subject drug product is indicated for the treatment of pulmonary arterial hypertension.

B. **SUPPORTING/RELATED DOCUMENTS:** None.

C. **REMARKS:**
The application is submitted electronically in the CTD format.

An Initial Quality Assessment was performed by the ONDQA PAL on 23 July 2008. The IQA identified the lack of a test method and acceptance criterion for ___ in the drug product as a critical review issue and posed the questions as to whether this is acceptable. b(4)

Reviewer's Comment
Since the subject drug product is a solution for inhalation, a test method and acceptance criterion for ___ is not required.

The following information request was provided to the applicant regarding sterility assurance issues on 16 October 2008:

A sterility assurance review of NDA 22-387 is on-going. Please provide the following information, or reference to its location in the subject submission:

- Data sets from the container closure integrity studies.
- A narrative describing the environmental microbiological monitoring program which includes information regarding the sampling and testing methods, incubation conditions, alert and action limits and

routine production monitoring frequency.

- Data sets demonstrating the [redacted] ability to retain a microbial challenge from the subject drug product. b(4)
- Data sets supporting the holding periods listed in Module 3.2.P.3.5 of the subject submission.
- A narrative describing the [redacted] process simulation procedures, acceptance criteria and actions to be taken following a failed [redacted]. Include the frequency at which process simulations are performed, and data sets in support of the manufacture of the subject drug product at the Catalent Pharma Solutions manufacturing facility.

The applicant amended the NDA on 29 October 2008 with the container closure integrity and [redacted] validation studies. A second information request b(4) was forwarded to the applicant on 17 November 2008 reminding the applicant of the 3 bulleted items in the original information request which were not addressed in the applicant's 28 October 2008 amendment. The applicant amended the application with responses to the second microbiology information request on 29 January 2009 and on 25 February 2009. The applicant responses to these requests for information are summarized and reviewed in appropriate sections of this review.

File Name: N022387R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 22-387/N-000 is recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

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

b(4)

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.

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

III. Administrative

A. Reviewer's Signature _____
John W. Metcalfe, Ph.D.

B. Endorsement Block _____
Stephen Langille, Ph.D.

C. CC Block
N/A

10 Page(s) Withheld

6 Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Microbiology Review Section-_____

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

/s/

John Metcalfe
3/23/2009 10:00:56 AM
MICROBIOLOGIST

Stephen Langille
3/24/2009 10:26:39 AM
MICROBIOLOGIST