# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022534Orig1s000**

# MICROBIOLOGY REVIEW(S)

# Product Quality Microbiology Review

**01 March 2011**

**NDA:** 22-534/Supporting Document-021

**Drug Product Name**
**Proprietary:** Docefrez™.
**Non-proprietary:** Docetaxel.

**Review Number:** 1.

**Dates of Submission(s) Covered by this Review**

| Submit | Received | Review Request | Assigned to Reviewer |
|---|---|---|---|
| 03 NOV 2010 | 03 NOV 2010 | 16 NOV 2010 | 17 NOV 2010 |
| 21 DEC 2010 | 21 DEC 2010 | N/A | N/A |

**Applicant/Sponsor**
**Name:** Sun Pharma Global FZE
**Address:** Executive Suite
P.O. Box 122304
Sharjah, United Arab Emirates

**U.S. Agent for the Applicant**
**Name:** Salamandra, LLC.
**Address:** 4800 Hampden Lane,
Suite 900
Bethesda, MD. 20814

**Representative:** Karin A. Kook, Ph.D.
**Telephone:** 301-652-6110

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

**Conclusion:** Recommend approval.

# Product Quality Microbiology Data Sheet

**A. 1. TYPE OF SUBMISSION:** Class 2 Resubmission.

**2. SUBMISSION PROVIDES FOR:** The following changes to the manufacturing process equipment:

- Replacement of (b) (4).
- Replacement of (b) (4).
- Addition of an (b) (4).
- Replacement of a capping machine for both product and diluent.
- Addition of a vial leak testing machine.

**3. MANUFACTURING SITE:**
Sun Pharmaceutical Industries Limited
Halol-Baroda Highway
Halol-389350
Gujarat-India

**4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**

- Lyophilized powder in glass vial and diluent in glass vial.
- Intravenous injection.
- 20 mg/vial & 80 mg/vial.

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

**6. PHARMACOLOGICAL CATEGORY:** Anti-cancer agent.

**B. SUPPORTING/RELATED DOCUMENTS:** Microbiology Review of NDA 22-534/N-000; dated 13 November 2009.

**C. REMARKS:**
This reviewer recommended approval of the original NDA in a review dated 13 November 2009 on the basis of product quality microbiology. The Review Division issued tentative approval of the NDA on 23 February 2010. The applicant submitted a Class 2 resubmission on 03 November 2010 which provided changes to the manufacturing process. Finally, the applicant submitted an amendment on 21 December 2010 withdrawing some of the major changes which were provided in the 03 November 2010 submission. The changes which were withdrawn include the following: (b) (4) (21 December 2010 Cover Letter; Page 2).

**File Name:** N022534ResubR1.doc

# Executive Summary

## I. Recommendations

**A. Recommendation on Approvability –** NDA 22-534/Supporting Document-021 is recommended for approval from the standpoint 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 -** (b) (4)

(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**_____
Bryan S. Riley, Ph.D.

**C. CC Block**
N/A

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/s/

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JOHN W METCALFE
03/01/2011

BRYAN S RILEY
03/01/2011
I concur.

# Product Quality Microbiology Review

**13 November 2009**

**NDA:** 22-534/N-000

**Drug Product Name**
**Proprietary:** Docefrez™.
**Non-proprietary:** Docetaxel.

**Review Number:** 1.

**Dates of Submission(s) Covered by this Review**

| Letter | Stamp | Review Request | Assigned to Reviewer |
|---|---|---|---|
| 23 APR 2009 | 23 APR 2009 | 04 JUN 2009 | 11 JUN 2009 |
| 03 SEP 2009 | 03 SEP 2009 | N/A | N/A |

**Applicant/Sponsor**
**Name:** Sun Pharma Global FZE
**Address:** Executive Suite
P.O. Box 122304
Sharjah, United Arab Emirates

**U.S. Agent for the Applicant**
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**Address:** 4800 hampden Lane,
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Bethesda, MD. 20814

**Representative:** Karin A. Kook, Ph.D.
**Telephone:** 301-652-6110

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

**Conclusion:** Recommend approval.

# Product Quality Microbiology Data Sheet

**A. 1. TYPE OF SUBMISSION:** Original New Drug Application.

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

**3. MANUFACTURING SITE:**
Sun Pharmaceutical Industries Limited
Halol-Baroda Highway
Halol-389350
Gujarat-India

**4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Lyophilized powder in glass vial and diluent in glass vial.
- Intravenous injection.
- 20 mg/vial & 80 mg/vial.

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

**6. PHARMACOLOGICAL CATEGORY:** Anti-cancer agent.

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

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

An Initial Quality Assessment has been completed by ONDQA (dated 17 June 2009). There are no critical review items pertaining to microbiology identified in the IQA.

A Microbiology Information Request was forwarded to the applicant by the OND Project Manager on 27 August 2009. Following is the information request:

> A microbiology review of NDA 22-534/N-000 is in progress. Reference is made to the *1994 Guidance for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, and to the *2004 Guidance for Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practices*.
>
> Please provide the following information or reference to its location in the subject submission:
>
> - A narrative which includes the following information regarding

the environmental microbiological monitoring program:
- The sampling and testing methods.
- The sample incubation conditions.
- The routine production monitoring frequency.
- The alert and action limits.

- The maximum time allowed for the manufacture of the drug product from the beginning of compounding until the end of lyophilization.

- A narrative which includes the following information regarding the performance of media fill process simulations:
  - The number of simulations conducted per year in support of a given manufacturing process.
  - The acceptance criteria for media fill process simulations.
  - The actions to be taken following a failed media fill.
  - The manner in which a lyophilization process is simulated. Did media fills JK6025, JK6026, JK6027 and JK6033 include simulations of the lyophilization process?

- The subject submission contains Bacterial Endotoxins Testing verification data on only one batch of product and one batch of diluent. Reference is made to the *1987 Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices* which states, "at least three production batches of each finished product should be tested for inhibition and enhancement".
  - Provide BET verification data sets representative of 2 additional batches of product and 2 additional batches of diluent.

- The "Report for Sterility Test Validation" (Module 3.2.P.3.5) states that the method of sterility analysis is (b) (4) . In contrast, the directions provided in the Analytical Test Procedure (Module 3.2.P.5.2) state on Page 22 of 24 (b) (4)
  - Clarify whether the sterility test method is by (b) (4) .
  - How many product units are used per sterility test?
  - How are the lyophilized units (b) (4) ?
  - Provide a narrative that describes each step of how the sterility test verification was performed (e.g. how did "Test" samples differ from "Positive Controls")?

- Lower the diluent endotoxin limit to 0.5 EU/mL. This limit will be equivalent to the USP monograph endotoxin limits for the infusion fluids (0.9% saline or 5% dextrose) that the constituted product will be administered in.

The NDA was amended with a response to this Information Request on 03 September 2009. Applicant responses are summarized and reviewed in appropriate sections of this review.

**File Name:** N022534R1.doc

APPEARS THIS WAY ON ORIGINAL

# Executive Summary

## I. Recommendations

**A. Recommendation on Approvability –** NDA 22-534/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 -** (b) (4)

(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

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| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22534 | ORIG-1 | SUN PHARMA GLOBAL FZE | DOCEFREZ INJECTION (20/80 MG/VIAL) |

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/s/

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JOHN W METCALFE
11/13/2009

STEPHEN E LANGILLE
11/13/2009