CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-066

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

07 MAY 2008

NDA: 22-260 BI

Drug Product Name
Proprietary: N/A
Non-proprietary: Epoprostenol Sodium for Injection
Drug Product Priority Classification: 5S

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
02-APR-2008	02-APR-2008	07-APR-2008	07-APR-2008

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
24-AUG-2007	1	28-JAN-2008

Applicant/Sponsor
Name: GeneraMedix Inc.
Address: 150 Allen Road
Liberty Corner, NJ 07938

Representative: Robert J. D'Angelis
Director, Regulatory Affairs
Telephone: 908-504-1357

Name of Reviewer: Anastasia G. Lolas

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** BI amendment to new drug application

2. **SUBMISSION PROVIDES FOR:** Responses to microbiology questions identified in Microbiology Review #1

3. **MANUFACTURING SITE:**

Drug Substance	*Drug Product*
[redacted]	[redacted]

b(4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
   - Sterile lyophilized powder in a 10 mL glass vial
   - Intravenous injection
   - 1.5 mg epoprostenol in a vial

5. **METHOD(S) OF STERILIZATION:** [redacted]

b(4)

6. **PHARMACOLOGICAL CATEGORY:** GI prostaglandins

B. **SUPPORTING/RELATED DOCUMENTS:**
   - Microbiology Review #1 of NDA 22-260 dated 28-JAN-2008

C. **REMARKS:** This amendment is an electronic submission and is in response to 6 microbiology questions communicated to the applicant on 30-JAN-2008 (see DFS).

The applicant was contacted on 23-APR-2008 regarding media fills and the F_0 values for the validation studies of lyophilizer sterilization. An electronic response was received on 07-MAY-2008 and has been incorporated in the relevant sections of the review.

file name: N022260R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 22-260 is recommended for approval based on product quality microbiology

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

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is ——— and ——— filled prior to lyophilization and packaging. Sterile filtration consists of ——— filter in series. Six deficiencies were identified in the first review. The applicant's responses are assessed in this review. b(4)

B. Brief Description of Microbiology Deficiencies – None

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

III. Administrative

A. Reviewer's Signature _____
Anastasia G. Lolas

B. Endorsement Block
Bryan S. Riley, Ph.D.

C. CC Block
N/A

4 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Microbiology-1

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/s/

Anastasia Lolas
5/8/2008 10:22:09 AM
MICROBIOLOGIST

Bryan Riley
5/8/2008 12:23:29 PM
MICROBIOLOGIST
I concur.

Product Quality Microbiology Review

28 JAN 2008

NDA: 22-260

Drug Product Name
Proprietary: N/A
Non-proprietary: Epoprostenol Sodium for Injection
Drug Product Priority Classification: 5S

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
24-AUG-2007	27-AUG-2007	13-SEP-2007	28-SEP-2007

Submission History (for amendments only) – N/A

Applicant/Sponsor
Name: GeneraMedix Inc.
Address: 150 Allen Road
Liberty Corner, NJ 07938

Representative: Robert J. D'Angelis
Director, Regulatory Affairs
Telephone: 908-504-1357

Name of Reviewer: Anastasia G. Lolas

Conclusion: Approvable pending the resolution of product quality microbiology deficiencies (see Section 3 of review)

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** New drug application

2. **SUBMISSION PROVIDES FOR:** New drug product (improved formulation and usage compared to reference listed drug)

3. **MANUFACTURING SITE:**

Drug Substance	*Drug Product*
[redacted]	[redacted]

b(4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
   - Sterile lyophilized powder in a 10 mL glass vial
   - Intravenous injection
   - 1.5 mg epoprostenol in a vial

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

6. **PHARMACOLOGICAL CATEGORY:** GI prostaglandins

B. **SUPPORTING/RELATED DOCUMENTS:**
   - IND 77,269
   - NDA 20-444

C. **REMARKS:** This is an electronic submission in CTD format. It is a 505(b)(2) application that refers to the listed drug Flolan® for Injection (NDA 20-444). The proposed formulation differs from that of the approved drug and due to this, it is stated that the product is more stable.

The ONDQA PAL Assessment in DFS identifies the following critical issues for review:
- Lack of bioburden testing for the drug substance.
- Sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life.
- The claim that the reconstituted product solution is self-preserving.

file name: N022260R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 22-260 is approvable pending the resolution of product quality microbiology deficiencies (see Section 3)

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

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is [redacted] and [redacted] filled prior to lyophilization and packaging. Sterile filtration consists of [redacted] filter in series. The sterilization processes and microbiological specifications are reviewed. b(4)

B. Brief Description of Microbiology Deficiencies – The applicant should perform a microbial growth study to demonstrate that the product does not support growth following dilution of the reconstituted solution at room temperature for at least 48 hours. The applicant did not submit validation summaries regarding the sterilization of the lyophilizers used in the manufacture of the product.

C. Assessment of Risk Due to Microbiology Deficiencies – Moderate to high risk to the patient.

III. Administrative

A. Reviewer's Signature _____
Anastasia G. Lolas

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

C. CC Block
N/A

14 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Microbiology- 2

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/s/

Anastasia Lolas
1/28/2008 10:21:58 AM
MICROBIOLOGIST

Stephen Langille
1/28/2008 11:41:37 AM
MICROBIOLOGIST

MEMORANDUM

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

DATE: October 9, 2007

TO: File

FROM: Anastasia G. Lolas, Microbiology Reviewer, NDMS/OPS

THROUGH: Bryan S. Riley, Ph.D., Senior Microbiology Reviewer, NDMS/OPS

cc: Daniel Brum, Regulatory Project Manager, DCRP/ODEI/OND

SUBJECT: NDA 22-260 filing – Product Quality Microbiology

NDA 22-260 was submitted on 24-AUG-2007 by GeneraMedix, Inc. (Liberty Corner, NJ). A consult was sent by ONDQA on 13-SEP-2007 and an assignment made on 28-SEP-2007. The application is a 505(b)(2) electronic submission in the CTD format. An Initial Quality Assessment has been entered in DFS highlighting sterility assurance and maintenance of sterility over the shelf-life of the product. In addition, there are some labeling proposals that require attention during the review.

Epoprostenol Sodium for Injection is a sterile, lyophilized product supplied as 1.5 mg in a 10 mL —— glass vial —— sealed with a 20 mm rubber stopper —— and a flip-off cap —— It is stated that the product can be prepared up to – days in advance when stored at refrigerated temperatures and allows for delivery over 48 hours at 25°C. It is formulated at a high pH (NLT —— The lyophilized product is reconstituted with 5 mL sterile water for injection, sodium chloride for injection, 0.9% ——————————. The reconstituted solution is further diluted with the same diluent prior to administration via intravenous infusion. b(4)

The product is manufactured by —— processing. The bulk solution is —— sterilized through —— filters in series, filled into vials and lyophilized. b(4)

The Sterility Assurance Validation information is located in Section 3.2.P.3.5. The submission contains the following:

- Description and composition — Section 3.2.P.1
- Container-closure integrity studies — Section 3.2.P.2.5.1
- Microbial growth studies (to support the labeling claims) — Section 3.2.P.2.5.2

MEMORANDUM

➢ Description of the manufacturing process & controls	Section 3.2.P.3.3
➢ Floor plans, materials and personnel flow	Section 3.2.P.3.3.2
➢ Filter retention studies	Section 3.2.P.3.5.1
➢ [redacted]	Section 3.2.P.3.5.3
➢ Stopper and equipment sterilization	Section 3.2.P.3.5.4
➢ [redacted]	Section 3.2.P.3.5.5
➢ Media fills	Section 3.2.P.3.5.6
➢ Environmental monitoring	Section 3.2.P.3.3.5
➢ Microbiological specifications	Section 3.2.P.5.1
➢ Sterility and bacterial endotoxins method qualification	Section 3.2.P.5.3.2
➢ Stability protocol	Section 3.2.P.8.1
➢ Labeling	Module 1

b(4)

Based on this information, there are no filing issues from the product quality microbiology perspective.

END

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/s/

Anastasia Lolas
10/10/2007 09:55:30 AM
MICROBIOLOGIST