CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-260

CHEMISTRY REVIEW(S)

CMC BRANCH CHIEF MEMORANDUM

To:	NDA 22-260
From:	Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date:	10-Jun-2008
Drug:	Epoprostenol sodium
Route of administration:	Intravenous infusion
Strength:	1.5 mg/vial
Subject:	**"Approvable"** recommendation for NDA 22-260

Introduction: Epoprostenol sodium for Injection, is being developed for the treatment of primary pulmonary hypertension. The drug substance is currently approved for use in Flolan® for Injection (NDA 20-444); however, this formulation of Epoprostenol sodium is claimed to have an improved stability profile, is able to be reconstituted with commercially available IV fluids rather than a specially made diluent that is needed for dilution of Flolan. Moreover, this formulation is self-preserving which allows for extended shelf life after reconstitution. Several quality issues were identified during the review cycle and these issues were resolved with the applicant during the review.

Drug Substance: The drug substance is the sodium salt of Epoprostenol. The drug substance contains [redacted] b(4)
The drug substance is a metabolite of arachidonic acid and is the active ingredient in the marketed product Flolan® for Injection (NDA 20-444). This drug substance is a hygroscopic, white to off-white solid with a molecular formula $C_{20}H_{31}O_5Na$ and a molecular weight of 374.45. The drug substance is being manufactured and controlled by [redacted] b(4)
The DS synthesis is a [redacted] stage synthesis [redacted] The DMF holder has provided [redacted] and a [redacted] specification for the [redacted] that controls the quality of the starting material. The quality of the drug substance is assured through adequate controls on the materials used in the synthesis, intermediates generated, process controls and drug substance specification. The structure of the drug substance is confirmed by NMR (proton and carbon), mass spectroscopy, and FTIR. The impurities in the drug substance have been adequately characterized.

The applicant references DMF [redacted] for all relevant information pertaining to the drug substance including the manufacturer, final drug substance acceptance criteria, certificates of analyses and method of manufacture. DMF [redacted] was reviewed in conjunction with this application and was found to be "Adequate" as per DMF review #2. The drug substance has been assigned an expiration date of [redacted] months when stored at [redacted] packaged in [redacted]. b(4)

Drug product: Epoprostenol sodium is manufactured as a sterile, lyophilized powder for injection. The product is packaged in 10 ml [redacted] clear glass [redacted] vials with a 20 mm [redacted] rubber closure and a 20 mm flip-off [redacted] aluminum over seal. The drug b(4)
product is designed to be reconstituted with 5 mL of Sterile Water for Injection, 0.9% Sodium Chloride Injection [redacted] The drug product is composed of the drug substance epoprostenol sodium, arginine, mannitol and sodium hydroxide. Each vial contains 1.5 mg

of the active with a [redacted] overfill to insure that the complete dose is withdrawn. The quality of the drug product is assured through appropriate in-process manufacturing controls and adequate product specification. The product specification include tests and limits for appearance, reconstitution time, pH, moisture, uniformity of dosage form, specific identification, assay, impurities, particulate matter, bacterial endotoxins and sterility. An expiration period of 24 months has been assigned to the product when stored under controlled room temperature based on the 12 month stability data. The applicant had proposed an expiration period of 24 months. Additionally, an in-use period of 48 hours has been qualified for the reconstituted solution when stored at controlled room temperature. b(4)

The microbiological and sterility controls of the product were found to be acceptable by the microbiology reviewer and an "Approval" recommendation was made by the microbiology reviewer on 8-May-08.

Pending Issues: The Office of Compliance has not made an overall recommendation. Two sites pending are : [redacted] and [redacted] Additionally, the applicant will need to change the established name to "epoprostenol" from the current name [redacted] so that the name is in agreement with the labeled strength. b(4)

Recommended action: The application is recommended as **"Approvable"** from CMC perspective. The pending issues are an overall recommendation from the Office of Compliance for the facilities and acceptability of the labeling issue related to the established name. A final memorandum will be entered into DFS by the reviewer after these two issues have been resolved.

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/s/

Ramesh Sood
6/10/2008 03:54:59 PM
CHEMIST

NDA 22-260

Epoprostenol Sodium for Injection

GeneraMedix, Inc.

Sherita D. McLamore, Ph.D.
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA: 22-260

2. REVIEW: #1

3. REVIEW DATE: March 21, 2008

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	August 24, 2007
Amendment	May 30, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	GeneraMedix
Address:	150 Allen Road Liberty Corner, NJ 07938
Representative:	Robert J. D'Angelis
Telephone:	908-504-1357

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: n/a
b) Non-Proprietary Name (USAN): Epoprostenol Sodium
c) Code Name/# (ONDC only): EP, EPP
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of primary pulmonary hypertension

11. DOSAGE FORM: IV

12. STRENGTH/POTENCY: 1.5 mg/vial

13. ROUTE OF ADMINISTRATION: Infusion

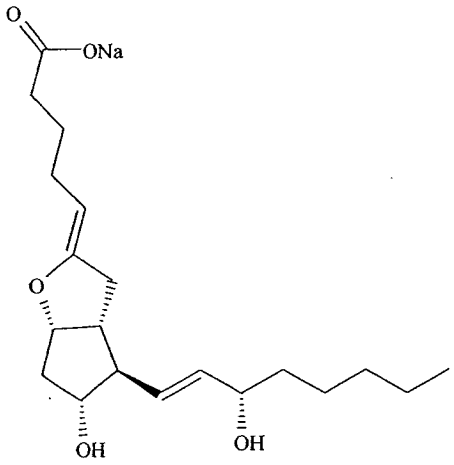
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: (5*Z*, 9α, 11α, 13*E*, 15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-diene-1-oic acid sodium salt
Molecular Weights: 374.45
Molecular Formula: $C_{20}H_{31}NaO_5$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
	II		Epoprostenol Sodium	1	Adequate	5/25/08	
	III			4	n/a	n/a	
	III			4	n/a	n/a	

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Biometrics	N/A	N/A	N/A
EES	Pending	Pending	Sherita McLamore, Ph.D.
Pharm/Tox	Pending	Pending	Charles Resnick, Ph.D.
Biopharm	Pending	Pending	Robert Kumi, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Acceptable	6/5/08	Sherita McLamore, Ph.D.
DMETS	Pending	Pending	
EA	Categorical Exclusion 21 CFR 25 31(b) *Acceptable*	6/5/08	Sherita McLamore, Ph.D.
Microbiology	Approval	5/7/08	Anastasia Lolas, Ph.D.

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 22-260

The Executive Summary

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 22-260 is approvable. The approval from a CMC standpoint is contingent on an acceptable recommendation from the Office of Compliance and an adequate response to the CMC deficiencies outlined below:

1. *Please provide updated labeling which displays the established name of the drug product as Epoprostenol.*

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

The drug substance is the sodium salt of Epoprostenol. The drug substance contains [redacted] b(4)

[redacted] The drug substance is a metabolite of arachidonic acid and is the active ingredient in the marketed product Flolan® for Injection (NDA 20-444). This drug substance is a hygroscopic, white to off-white solid with a molecular formula $C_{20}H_{31}O_5Na$ and a molecular weight of 374.45. The drug substance is being manufactured and controlled by [redacted] The applicant references DMF [redacted] for all relevant information pertaining to the drug substances including the manufactures, acceptance criteria, certificates of analyses and method of manufacture. DMF [redacted] was reviewed in conjunction with this application and was deemed deficient. A deficiency letter was sent to the holder on March 3, 2008. The holder provided an adequate response to each of the deficiencies outlined in the March 3rd letter on May 7, 2008. The DMF was considered adequate to support this application. b(4)

The drug product, Epoprostenol sodium for Injection, is being developed for treatment of primary pulmonary hypertension. The free acid of the drug product is a metabolite of arachidonic acid and is a naturally occurring prostaglandin. The drug product is manufactured as a sterile, lyophilized powder for reconstitution. The drug product is packaged in a 10 mL vial with a 20 mm rubber closure. The drug product is designed to be reconstituted with 5 mL of Sterile Water for Injection, 0.9% Sodium Chloride Injection [redacted]. The drug product is composed of the drug substance, Epoprostenol sodium, arginine, mannitol and sodium hydroxide. Each vial contains 1.5 mg of the active with a [redacted] overfill to insure that the complete dose is withdrawn. The drug product formulation has been compared to the marketed product, Flolan® for Injection. While the drug product formulation is not identical to the Flolan® formulation, the phamacokinetics were shown to be identical. b(4)

The applicant indicates that the drug product is manufactured, stability tested and released by [redacted] The drug product will be packaged in 10 mL/ 20mm [redacted] clear glass [redacted] vial with a 20 mm [redacted] stopper and a 20 mm flip-off [redacted] aluminum overseal. The applicant includes a complete description of each of the packaging component including manufacturers, certificates of analyses, drawings, diagrams and specifications for each of the packaging components. b(4)

As indicated in the stability section of this review, the applicant includes 12 months stability data for three pilot scale batches of the drug product. These batches were manufactured at the commercial site according to the commercial process and were packaged in the to-be marketed container closure system. The samples were stored under long-term and accelerated conditions, inverted and upright. The applicant tested the following attributes on stability: visual appearance, lyophilized product, constituted solution, reconstituted time, pH, moisture, assay, related substances, particulate matter, sterility, endotoxins and reconstituted stability. After 12 months of storage under long term and 6 months under accelerated conditions, there were no stability trends observed. All stability results were acceptable and within the proposed specification limits. The applicant has requested a 24 month shelf life for the drug product and included statistical analyses on six months of stability data. The data were analyzed in accordance with the ICH Q1E guidance. The applicant has provided adequate information to support the requested 24-month expiry.

B. Description of How the Drug Product is Intended to be Used

The drug product, Epoprostenol sodium for Injection, is being developed for treatment of primary pulmonary hypertension. The drug product is manufactured as a sterile lyophilized powder. The active is currently approved for use in Flolan® for Injection (NDA 20-444); however, this formulation of Epoprostenol sodium has an improved stability profile, is able to be reconstituted with commercially IV fluids rather than a specially made diluent. Moreover, when reconstituted with Water for Injection or Sodium Chloride, 0.9% for Injection, this formulation is self-preserving which allows for extended shelf life after reconstitution.

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-260 is **Approvable** from a Chemistry standpoint. Approval from a CMC perspective is contingent on an acceptable recommendation from the Office of Compliance. All sites were submitted to the Office of Compliance in September of 2007. At this time OC recommendation for the [redacted] and the [redacted] sites are pending. Accordingly, an overall recommendation has not been issued for this application. b(4)

III. Administrative

Executive Summary Section

A. Reviewer's Signature

B. Endorsement Block
SMcLamore/Date
RSood

C. CC Block
Orig. NDA 22-260

81 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

Sherita McLamore
6/10/2008 10:05:54 AM
CHEMIST

Ramesh Sood
6/10/2008 11:49:09 AM
CHEMIST

23-JUN-2008 FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application	: NDA 22260/000	Sponsor:	GENERAMEDIX
Org Code	: 110		150 ALLEN RD STE 110
Priority	: 5S		LIBERTY CORNER, NJ 07938
Stamp Date	: 27-AUG-2007	Brand Name	: EPOPROSTENOL SODIUM
PDUFA Date	: 27-JUN-2008	Estab. Name:	
Action Goal	:	Generic Name:	EPOPROSTENOL SODIUM
District Goal:	28-APR-2008	Dosage Form:	(INJECTION)
		Strength	: 1.5 MG/VIAL

FDA Contacts:	S. GOLDIE	Project Manager	301-796-2055
	S. MCLAMORE	Review Chemist	301-796-1710
	K. SRINIVASACHAR	Team Leader	301-796-1760

Overall Recommendation: ACCEPTABLE on 23-JUN-2008
by S. FERGUSON(HFD-322) 301-796-3247

Establishment : CFN : [redacted] FEI : [redacted]

[redacted] b(4)

DMF No: AADA:

Responsibilities: [redacted] b(4)

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-SEP-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : [redacted]

[redacted] b(4)

DMF No: AADA:

Responsibilities: [redacted] b(4)

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JUN-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

b(4)

DMF No: AADA:

Responsibilities: [redacted]

b(4)

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-APR-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : [redacted]

b(4)

DMF No: AADA:

Responsibilities: [redacted]

b(4)

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date:		23-JUN-08
Decision	:	ACCEPTABLE
Reason	:	DISTRICT RECOMMENDATION

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/s/

Kasturi Srinivasachar
6/25/2008 03:34:24 PM
CHEMIST

Ramesh Sood
6/25/2008 07:58:23 PM
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