CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-260

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER

NAME OF APPLICANT / NDA HOLDER
GeneraMedix Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Epoprostenol Sodium for Injection

ACTIVE INGREDIENT(S)
Each vial contains Epoprostenol Sodium equivalent to 1.5 mg (1,500,000 ng) epoprostenol.

STRENGTH(S)
1.5 mg/vial

DOSAGE FORM
Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Robert J. D'Angelis	8/22/2007

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Robert J. D'Angelis	
Address 150 Allen Road	City/State Liberty Corner,NJ
ZIP Code 07938	Telephone Number 908-504-1357
FAX Number *(if available)* 908-504-1305	E-Mail Address *(if available)* rdangelis@generamedix.com

GeneraMedix 150 Allen Road, Liberty Corner, NJ 07938 (908) 504.1300

Epoprostenol Sodium for Injection
1.5 mg vial

Patent Certification

There are no relevant patents which claim the listed drug referred to in this application or that claim a use of the listed drug and for which information is required to be filed under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355 (b)(1)].

There are no relevant patents

Robert J. D'Angelis
Director, Regulatory Affairs
GeneraMedix Inc.

August 22, 2007
Date

GeneraMedix 150 Allen Road, Liberty Corner, NJ 07938 (908) 504.1300

Epoprostenol Sodium for Injection
1.5 mg vial

Exclusivity Statement

According to *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*), the listed drug, FLOLAN® (epoprostenol sodium) for Injection, received Orphan Drug Exclusivity which expired on April 14, 2007.

There is no unexpired exclusivity for this product.

Robert J. D'Angelis
Director, Regulatory Affairs
GeneraMedix Inc.

August 22, 2007
Date

EXCLUSIVITY SUMMARY

NDA # 22-260 SUPPL # n/a HFD # 110

Trade Name N/A

Generic Name epoprostenol for injection

Applicant Name GeneraMedix, Inc.

Approval Date, If Known 6/27/08

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-444 Flolan (epoprostenol) for Injection

NDA# N/A

NDA# N/A

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# N/A

NDA# N/A

NDA# N/A

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Russell Fortney
Title: Project Manager
Date: 6/19/08

Name of Office/Division Director signing form: Norman Stockbridge
Title: Director, Office of Drug Evaluation I

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Russell Fortney
7/1/2008 03:17:08 PM

Norman Stockbridge
7/1/2008 03:34:31 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-260 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: 8/27/07 **PDUFA Goal Date:** 6/27/08

HFD-110 **Trade and generic names/dosage form:** epoprostenol sodium for injection 1.5 mg vial

Applicant: GeneraMedix, Inc. **Therapeutic Class:** prostaglandins

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☐ Yes. Please proceed to the next question.
- X No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):**_____

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s):_____

Indication #1: _____

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- ☐ No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Daniel Brum
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Dan Brum
10/3/2007 11:39:16 AM

1.9

Per section 505B(a)(1) of the Federal Food, Drug and Cosmetic Act, a pediatric assessment is not required for this NDA because this NDA is not submitted for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

APPEARS THIS WAY ON ORIGINAL

GeneraMedix 150 ALLEN ROAD, LIBERTY CORNER, NJ 07938 (908) 504-1300

Dear Sir/Madam,

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act [21 U.S.C Section 335a(k) GeneraMedix Inc., hereby certifies that GeneraMedix Inc. did not and will not use, in any capacity, the services of any person debarred under sub section (a) and (b) [section 306 (a) or (b)] in connection with this ANDA.

Robert J. D'Angelis
Director, Regulatory Affairs
GeneraMedix Inc.

August 22, 2007
Date

APPEARS THIS WAY ON ORIGINAL

Memorandum to File

To: NDA 22-260
From: Kasturi Srinivasachar, Ph.D
Through: Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date: 25-Jun-2008
Drug: Epoprostenol sodium
Route of administration: Intravenous infusion
Strength: 1.5 mg/vial
Subject: CMC **"Approval"** recommendation for NDA 22-260

The Branch Chief Memorandum dated June 10, 2008 stated that this application was "approvable" pending an overall recommendation from the Office of Compliance on the cGMP status of manufacturing facilities. On June 23, 2008 an "Acceptable" overall recommendation was received and is attached on the following pages. The Applicant has revised the established name from [redacted] to "epoprostenol" to match the strength of the product. They have agreed to delete "ROOM TEMPERATURE" from the carton labels since that is not part of the name and they have a separate storage statement. The wording in the Dosage and Administration and How Supplied sections of the package insert will be revised so that storage conditions of the reconstituted and fully diluted solution for infusion will accurately reflect the conclusions from the in-use studies performed.

b(4)

There are no other pending CMC issues for this NDA and it may be APPROVED.

APPEARS THIS WAY ON ORIGINAL

NDA 22-260
Epoprostenol for Injection

Safety Update: As no clinical trials were conducted to support this application, a Safety Update was not required.

Russell Fortney
6/27/08

APPEARS THIS WAY ON ORIGINAL

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

GeneraMedix INC
Robert Dangelis
150 ALLEN ROAD
LIBERTY CORNER NJ 07938
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

2. TELEPHONE NUMBER
908-5041357

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[ ] YES [X] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.
IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[ ] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
Epoprostenol Sodium for Injection

6. USER FEE I.D. NUMBER
PD3007540

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[X] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

OMB Statement:
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Robert D. Dangelis	Director, Regulatory Affairs	August 22, 2007

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$.00

Form FDA 3397 (03/07)

Close Print Cover sheet

1.3.4

Financial certification is not required because there are no covered clinical studies, as defined under 21 CFR 54.2 (e), submitted in this new drug application.

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-260

INFORMATION REQUEST LETTER

GeneraMedix Inc.
Attention: Robert J. D'Angelis
Director, Regulatory Affairs
150 Allen Road
Liberty Corner, NJ 07938

Dear Mr. D'Angelis:

Please refer to your August 27, 2007 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epoprostenol Injection.

We also refer to your submission dated April 2, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Regarding the change in appearance of the drug product from a white powder to translucent material on long-term storage, provide information related to any corresponding change in the product physical form (such as amorphous or crystalline), relationship between any product attribute and such change (e.g., residual moisture content) and the long-term impact of such change in the physical form on the performance of the drug product.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
5/27/2008 01:29:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-260

INFORMATION REQUEST LETTER

GeneraMedix Inc.
Attention: Robert J. D'Angelis
Director, Regulatory Affairs
150 Allen Road
Liberty Corner, NJ 07938

Dear Mr. D'Angelis:

Please refer to your August 27, 2007 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epoprostenol Injection.

We also refer to your submission dated April 2, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. You have proposed two sets of acceptance criteria for the release and shelf life for the drug product. Please be advised that the acceptance criteria that you propose for shelf-life are your regulatory specification. Please provide a consolidated specification table with release and stability limits.

2. Include an upper limit for the pH in the drug product specification.

3. The results for the Epoprostenol assay for batches 7141, 7143 and 7150 included in the batch analyses were ——— and —— respectively. The assay for the same batches at time 0 months in the stability studies were all —— Please explain this inconsistency. b(4)

4. The results of the compatibility studies show 2% to 3% loss in the assay; however, there was no increase in the impurity level. Please clarify.

5. The acceptance criterion for the —— impurity is NMT —— Please provide data to support that this impurity has been qualified at or revise the acceptance criteria based on the safety and available data. b(4)

6. Please update the post-approval stability commitment for the first three commercial lots to include storage under accelerated conditions.

7. You have proposed a 48 hour shelf life for the reconstituted drug product at room temperature. The data suggest that after 48 hours at 25°C, an increase of up to — of the —— impurity was observed. Should the drug product contain significant amount of the — impurity prior to reconstitution, it is likely the reconstituted drug product will be out of specification for the —— impurity if stored for 48 hours prior to use. Please explain what provisions have been made for this possibility. b(4)

8. The strength of the drug product is expressed as Epoprostenol; however, [redacted] is listed on the label. The established name will need to correspond to the strength used in the label. b(4)

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
4/21/2008 12:33:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-260

INFORMATION REQUEST LETTER

GeneraMedix Inc.
Attention: Robert J. D'Angelis
Director, Regulatory Affairs
150 Allen Road
Liberty Corner, NJ 07938

Dear Mr. D'Angelis:

Please refer to your August 27, 2007 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epoprostenol Injection.

We are reviewing the Microbiology section of your submission and have the following questions and requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the incubation conditions for all types of environmental monitoring (settle plates, ——— plates, etc.). b(4)

2. Provide validation data summaries for the sterilization of the lyophilizers used in the manufacture of epoprostenol sodium injection.

3. Please provide the following for each of the three most recent media fills (2007):
   a. The number of units filled.
   b. The number of units inspected.
   c. A summary of the growth promotion results.

4. Is there a provision to identify the contaminating microorganism found in a media fill?

5. Are samples pooled for the bacterial endotoxins test and is this taken into consideration so that the maximum valid dilution is not exceeded?

6. The submitted USP <51> study provides microbiological data in support of storage of the reconstituted product solution at 2-8°C for 5 days. However, the study is insufficient to support storage of the diluted product solution at room temperature for 48 hours. Please provide microbiological data in support of these storage conditions for the diluted product. Reference is made to *Guidance for Industry ICH Q1A(R2) Stability Testing of New Drug Substances and Products* (Section II.B.7) and *ICH Q8 Pharmaceutical Development* (Section II.E).

   The microbiological study should be performed using a minimum countable inoculum to simulate potential microbial contamination that may occur during product constitution and dilution. It is generally accepted that growth is evident when the microbial population increases more than 0.5 Log10. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label-recommended fluids. Periodic

intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

If you have any questions, please call Russell Fortney, Regulatory Health Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
1/30/2008 07:07:44 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-260 Supplement # 000 Efficacy Suppl. Type: N/A

Proprietary Name: N/A
Established Name: epoprostenol sodium for injection
Strengths: 1.5 mg vial

Applicant: GeneraMedix
Agent for Applicant (if applicable): N/A

Date of Application: August 24, 2007
Date of Receipt: August 27, 2007
Date clock started after UN: N/A
Date of Filing Meeting: October 15, 2007
Filing Date: October 26, 2007
Action Goal Date (optional): N/A User Fee Goal Date: June 27, 2008

Indication requested: Long-term intravenous treatment of PPH and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy.

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☒ No fee (b)(2)

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?
   SAS Datasets and Draft Labeling (PLR format in SPL)

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,*

"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☐ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? orphan exemption YES ☐ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. YES ☒ NO ☐

- List referenced IND numbers: Pre-IND 77,269

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) August 17, 2007 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: PLR was submitted 10/5/07.

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☒

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☒
  No trade name proposed (essentially a generic of the RLD Flolan).

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? No changes to MG proposed.
  N/A ☐ YES ☐ NO ☒

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☐ NO ☒
  No changes to RiskMAP proposed.

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 15, 2007

NDA #: 22-260

DRUG NAMES: epoprostenol sodium for injection

APPLICANT: GeneraMedix, Inc.

BACKGROUND: This is a 505(b)(2) NDA for epoprostenol sodium that refers to the listed drug Flolan marketed under GlaxoSmithKline's NDA 20-444 and is for changes in the formulation of the listed drug. The changes in formulation include the omission of sodium chloride, substitution of arginine for glycine, and a higher pH. The sponsor believes these changes provide their drug with a better stability profile. Also, the sponsor states believes that their product can be reconstituted with either Sterile Water for Injection, USP, Sodium Chloride 0.9% Injection, USP, [redacted] whereas Flolan requires a special diluent for reconstitution. b(4)

ATTENDEES: Norman Stockbridge, Ellis Unger, Abraham Karkowsky, Kasturi Srinivasachar, Sherita McLamore, Anastasia Lolas, Janice Weiner, Edward Fromm, Russell Fortney, Dan Brum.

ASSIGNED REVIEWERS:

Discipline/Organization	Reviewer	Proposed Review Date
Medical:	Akinwole Williams, M.D.	May 1, 2008
Chemistry:	Sherita McLamore, Ph.D.	May 1, 2008
Microbiology:	Anastasia Lolas, Ph.D.	May 1, 2008
Other Consults:	N/A	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? (Consult in DFS) YES ☐ NO ☒
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

STATISTICS N/A ☒ FILE ☐ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☐ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☐

PHARMACOLOGY/TOX N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☒ NO ☐

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☒ No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Dan Brum, Pharm.D.
Regulatory Project Manager

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/s/

Dan Brum
10/19/2007 09:59:10 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-260

GeneraMedix, Inc.
Attention: Mr. Robert D'Angelis
150 Allen Rd.
Liberty Corner, NJ 07938

Dear Mr. D'Angelis:

Please refer to your new drug application (NDA) dated August 24, 2007, received August 27, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for epoprostenol sodium for injection, 1.5 mg vial.

We also refer to your submission dated October 5, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is June 27, 2008.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients.

If you have any questions, please call Dan Brum, Pharm.D., Regulatory Health Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
10/19/2007 09:19:46 AM

Meeting Minutes

Date:	**August 17, 2007**
Application:	**Pre-IND 77,269**
Drug:	**epoprostenol sodium for injection**
Sponsor:	**GeneraMedix**
Purpose:	**Pre-NDA Meeting**
Meeting Type:	**B**

FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer
Charles Resnick, Ph.D.	Team Leader, Phamacology/Toxicology
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead, Pre-Marketing, ONDQA
Angelica Dorantes, Ph.D.	Clinical Pharmacologist
Janice Weiner, J.D., MPH	Regulatory Counsel, Office of Regulatory Policy
Donald Hare	Office of Pharmaceutical Science, Office of Generic Drugs
Dan Brum	Regulatory Health Project Manager
Russell Fortney	Regulatory Health Project Manager

GeneraMedix Attendees:

Leonore C. Witchey-Lakshmanan, Ph.D.	Sr. Director, Development
Martin A. Joyce, Ph.D.	Vice-President, Research and Development
Robert J. D'Angelis, RAC	Director, Regulatory Affairs
Vincent P. Andolina	Vice-President, Regulatory Affairs
Robyn J. Barst, MD	Medical Consultant: Director, Pulmonary Hypertension Center, Columbia University Medical Center

Background:

The sponsor requested a teleconference to discuss their development strategy including stability studies performed to date with regard to their ability to support a 505(b)(2) NDA submission. We have assigned the sponsor a Pre-IND number for tracking purposes and this meeting request is the sponsor's first submission with regards to this product. The Agency has determined that this drug product cannot be submitted under 505(j) because the proposed parenteral formulation contains modifications that do not fall within the scope of the 'exception excipient' provisions defined in the regulations (e.g. preservatives, buffers, and antioxidants [21 CFR 314.94(a)(9)(iii)]).

Meeting:

The sponsor requested responses to the following questions listed in the meeting briefing package. The questions are repeated below, and the Division's preliminary responses are in bold. Italicized text reflects further discussion during the meeting.

1) Because our formulation is a solution at the time of delivery and is administered by continuous intravenous infusion, in our opinion our product should receive a therapeutic equivalence rating of

AP against the RLD Flolan, and eligible for a waiver of in vivo bioequivalence studies. Does the Agency concur?

FDA Response: While we agree that an *in vivo* bioequivalence study is not required, a therapeutic equivalence determination cannot be made until after approval.

2) We acknowledge that the pH of this product is higher than typical products; however, we also understand that this pH is in fact similar to several marketed products that are delivered in much higher quantities at dosing time. These products include:
   Flolan: pH ~10.5 (the original formulation/at time of delivery of epoprostenol)
   Zovirax: pH ~10-11 (at time of delivery)
   Aloprim: pH ~11 (at the time of delivery)
   Dilantan: pH ~12 (at time of delivery)

   Except for epoprostenol, these medicines are dosed in much higher quantities over much shorter periods of time. Epoprostenol is dosed in very small quantities, allowing for much more dilution in the blood, with much less potential for irritation. Therefore, we propose that no other biocompatibility testing be required for this product in the final diluted state (see Section 11.B.3. below for brief summary of biocompatibility study performed during development). Does the Agency concur?

   FDA Response: We recommend that you conduct a relatively small safety study in which subjects are administered the drug peripherally to examine the potential for adverse events (i.e. pain, thrombophlebitis) due to an alternative site of administration. Also, with regard to sterility, we recommend that you create a post-marketing patient registry powered to exclude an increase in adverse effects compared to the listed drug relied upon, Flolan.

   The sponsor plans to submit an IND to include a proposal for a phase I study comparing peripheral infusion-related adverse events (e.g. pain, phlebitis) between Flolan and GeneraMedix' epoprostenol. The Agency is willing provide feedback on a draft proposal in advance of a full study protocol submission. With regard to the protocol, the following considerations were discussed:

   1. *The administration of relatively high doses of epoprostenol should be given to patients rather than healthy volunteers.*
   2. *Developing a plan to handle additional fluid load due to carrier co-administration if indicated.*
   3. *The study is being conducted to evaluate the safety of peripheral administration of the study drug; the efficacy of epoprostenol for the proposed indications previously has been established. Such information may be conveyed to patients in the informed consent form.*

   Depending on the timing and quantity of submission of the study results, the Agency will decide if a review clock extension to the PDUFA goal date is warranted.

   The Agency expects the sponsor to conduct post-marketing surveillance (e.g. a patient registry) to determine if their new formulation of epoprostenol is associated with an increase in the rate of infection (e.g. compared to Flolan).

3) As per ICH Q1C, we propose to submit 6 months' data at the accelerated condition of 40° C along with 6 months' data at the intended storage condition of 25° C. Long-term data beyond six months are available from the development work. We believe these data are sufficient for an