CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-779

Microbiology Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Microbiology (HFD-805) for Microbiology Consult
Attn: Dr. Peter Cooney

FROM:
Monica Cooper, Ph.D. (HFD-110)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 12, 2004		**21-779**	**NDA**	**June 30, 2004**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ventavis (iloprost) Inhalation Solution	**Standard**	**Treatment of Pulmonary Arterial Hypertension**	**February 15, 2005**

NAME OF FIRM: **CoTherix, Inc.**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Ventavis is a sterile, aqueous solution formulated for inhalation via a nebulizer. Please review the microbiology. This NDA was submitted as an electronic document and is available through the Electronic Document Room (EDR).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Monica Cooper, Ph.D.	☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Monica Cooper
8/12/04 10:50:32 AM

Product Quality Microbiology Review
Review for HFD-110
16 December 2004

NDA: 21-779 Response Amendment

Drug Product Name
Proprietary: Ventavis Inhalation Solution
Non-proprietary: iloprost
Drug Product Classification: Treatment of pulmonary arterial hypertension.

Review Number: 2

Subject of this Review
Submission Date: 15 December 2004
Receipt Date: 15 December 2004 (e-mail)
Consult Date: 15 December 2004
Date Assigned for Review: 15 December 2004

Submission History (for amendments only)

Applicant/Sponsor

Name:	CoTherix, Inc.
Address:	5000 Shoreline Court, Suite 101 South San Francisco, CA 94080
Representative:	Ms Klara Dickinson Director, Regulatory Affairs Email: kdickinson@cotherix.com

Telephone: (650) 808-6518
Fax: (650) 808-6899

Name of Reviewer: James L. McVey

Conclusion: The information provided supports the sterility claim from a product quality microbiology perspective.

Product Quality Microbiology Data Sheet

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

2. **SUPPLEMENT PROVIDES FOR:** Manufacture and distribution for sale of a sterile inhalation solution.

3. **MANUFACTURING SITE:** Iloprost inhalation solution is manufactured for CoTherix by [ ]
The [ ] manufacturing facility address is:

[ ]

The contact person at [ ] for preapproval inspection related activities is:

[ ]

The U.S. Agent for [ ] Schering AG is:

[ ]

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Iloprost Inhalation Solution is packaged in mL clear, type I glass ampules. Each ampule has a net content of mL of µg/mL Iloprost.

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

6. **PHARMACOLOGICAL CATEGORY:** Treatment of pulmonary hypertension.

B. **SUPPORTING/RELATED DOCUMENTS:** N.A.

C. **REMARKS:** See Section 3 for reviewers comments.

filename: N21779r2

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approve.

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 product is formulated and

[redacted]

B. Brief Description of Microbiology Deficiencies – N.A.

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

III. Administrative

A. Reviewer's Signature /S/

B. Endorsement Block

Microbiologist: James L. McVey
Microbiology Supervisor: David Hussong

C. CC Block

cc: DFS

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page(s) of trade secret and/or confidential commercial information (b4)

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/s/

James McVey
12/20/04 11:09:25 AM
MICROBIOLOGIST

David Hussong
12/21/04 09:42:20 AM
MICROBIOLOGIST

Product Quality Microbiology Review
Review for HFD-110
9 December 2004

NDA: 21779 N000

Drug Product Name
Proprietary: Ventavis Inhalation Solution
Non-proprietary: iloprost
Drug Product Classification: Treatment of pulmonary arterial hypertension.

Review Number: 1

Subject of this Review
Submission Date: 30 Jun 2004
Receipt Date:
Consult Date: 12 Aug 2004
Date Assigned for Review: 19 Aug 2004

Submission History (for amendments only)
Date(s) of Previous Submission(s):
Date(s) of Previous Micro Review(s):

Applicant/Sponsor
Name: CoTherix, Inc.
Address: 5000 Shoreline Court, Suite 101
South San Francisco, CA 94080
Representative: Ms Klara Dickinson
Director, Regulatory Affairs
Email: kdickinson@cotherix.com

Telephone: (650) 808-6518
Fax: (650) 808-6899

Name of Reviewer: James L. McVey

Conclusion: Approvable pending the resolution of product quality microbiology issues.

Product Quality Microbiology Data Sheet

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

2. **SUPPLEMENT PROVIDES FOR:** Manufacture and distribution for sale of a sterile inhalation solution.

3. **MANUFACTURING SITE:** Iloprost inhalation solution is manufactured for CoTherix by [redacted]
The [redacted] manufacturing facility address is:

[redacted]

The contact person at [redacted] for preapproval inspection related activities is:

[redacted]

The U.S. Agent for [redacted] Schering AG is:

[redacted]

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Iloprost Inhalation Solution is packaged in – mL clear, type I glass ampules. Each ampule has a net content of – mL of – µg/mL Iloprost.

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

6. **PHARMACOLOGICAL CATEGORY:** Treatment of pulmonary hypertension.

B. **SUPPORTING/RELATED DOCUMENTS:** N.A.

C. **REMARKS:** See Section 3 for reviewers comments.

filename: N21779r1

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable.

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 – Product is formulation [ ]

B. Brief Description of Microbiology Deficiencies – [ ] The impact of the drug product on the potential contaminant should be assessed in order to assure adequate lethality is administered.

C. Assessment of Risk Due to Microbiology Deficiencies – The risk to human health cannot be assessed until the data requested is provided.

III. Administrative

/S/

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist: James L. mcVey
Microbiology Supervisor: David Hussong

C. CC Block
cc: DFS

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/s/

James McVey
12/9/04 03:36:02 PM
MICROBIOLOGIST

David Hussong
12/9/04 03:55:24 PM
MICROBIOLOGIST
microbiology review with moderate risk deficiencies noted - APPROVABLE