CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-538

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

02 JAN 2008

NDA: 21-538/N-000 (AC)

Drug Product Name
Proprietary: Accretropin™
Non-proprietary: Somatropin (rDNA origin)
Drug Product Priority Classification: S

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
20 JULY 2007	23 JULY 2007	07 DEC 2007	30 JULY 20007

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
09 MAY 2006	1	02 MAR 2006

Applicant/Sponsor

Name: Cangene Corporation
Address: 155 Innovation Drive
Winnipeg, Manitoba
R3T 5Y3 Canada
Representative: Jonathan Kirkwood,
Manager, Regulatory Affairs
(905) 405-2914
(Authorized Agent) Minerva Devera
Director QA/RA
Chesapeake Biological Laboratories, Inc.
1111 South Paca Street
Baltimore, MD 21230-2591
Telephone: (410) 843-5005 x2147

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

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

2. **SUBMISSION PROVIDES FOR:** Marketing of a new drug product

3. **MANUFACTURING SITE:**

Bulk Drug Substance	Finished Drug Product:
Cangene Corporation	Cangene Corporation
Biotechnology Manufacturing Facility	155 Innovation Drive
26 Henlow Bay	Winnipeg, Manitoba
Winnipeg, Manitoba	R3T 5Y3 Canada
R3Y 1G4	

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile Liquid for Injection; multidose, phenol preserved solution. Subcutaneous, 5mg/mL (15 IU/ml), (1 ml in a — — vial).

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

6. **PHARMACOLOGICAL CATEGORY:** Growth hormone

B. **SUPPORTING/RELATED DOCUMENTS:**
- Microbiology Review #1, R. Mello, 02 MAR 2007

C. **REMARKS:**
- The submission is a paper desk copy (3 volumes) not in CTD format.
- The submission is a complete response to the Agency's Approvable Action Letter of 08 March 2007.
- The applicant states, several times in the current submission, that the relevant information had been submitted previously. During the initial microbiology review of the 09 MAY 2006 submission, several appendices containing that relevant information were not provided for review. It is noted here that the previous submission documentation had difficulties in clearing Canadian/US Customs, and that some of the volumes were delayed (or possibly lost) during their transit through Customs.

Filename: N021538N000R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - None

II. Summary of Microbiology Assessments

A.

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 _____
Robert J. Mello, Ph.D.

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

C. CC Block
In DFS

12 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Microbiology-_____

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/s/

Robert Mello
1/2/2008 09:35:32 AM
MICROBIOLOGIST

Recommend Approval

Stephen Langille
1/2/2008 09:39:29 AM
MICROBIOLOGIST

Product Quality Microbiology Review

02 MAR 2007

NDA: 21-538/N-000

Drug Product Name
Proprietary: Accretropin™
Non-proprietary: Somatropin (rDNA origin)
Drug Product Priority Classification: S

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
09 MAY 2006	10 MAY 2006	25MAY 2006	25MAY 2006

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Cangene Corporation
Address: 155 Innovation Drive
Winnipeg, Manitoba
R3T 5Y3 Canada
Representative: Minerva Devera
(Authorized Agent) Director QA/RA
Chesapeake Biological Laboratories, Inc.
1111 South Paca Street
Baltimore, MD 21230-2591
Telephone: (410) 843-5005 x2147

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is approvable from microbiology product quality standpoint pending receipt of additional information.

Product Quality Microbiology Data Sheet

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

2. **SUBMISSION PROVIDES FOR:** Marketing of a new drug product

3. **MANUFACTURING SITE:**

Bulk Drug Substance	Finished Drug Product:
Cangene Corporation	Cangene Corporation
Biotechnology Manufacturing Facility	155 Innovation Drive
26 Henlow Bay	Winnipeg, Manitoba
Winnipeg, Manitoba	R3T 5Y3 Canada
R3Y 1G4	

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile Liquid for Injection; multidose, phenol preserved solution. Subcutaneous, 5mg/mL (15 IU/ml), (1 ml in a vial). b(4)

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

6. **PHARMACOLOGICAL CATEGORY:** Growth hormone

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

C. **REMARKS:**

- The ONDQA Initial Quality Assessment was submitted (X. Ysern) on 12 JUNE 2006, and states the following for the microbiology consult:
  - [redacted] b(4)
  - [redacted]
  - [redacted]
- The entire submission was submitted primarily as a paper format, technical submission, in CTD format (51 total volumes). The package insert, clinical safety/efficacy summaries, case report forms, and SAS transport files were submitted electronically.

The following six (6) Microbiology sections (white binders) were provided for this review:

- Module 1 (Volume 1/51)
- Module 2 (Volumes 2/51 & 3/51)
- Module 3 (Volumes 13/51, 14/51, 15/51)

Filename: N021538N000R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - The application is approvable from microbiology product quality standpoint pending receipt of additional information.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not Applicable

II. Summary of Microbiology Assessments

A.

b(4)

B. Brief Description of Microbiology Deficiencies –

- Lack of data and details of methods for
  - three referenced container closure studies
  - preservative effectiveness testing
- Lack of information on facility monitoring
- Lack of information on production hold times
- No microbial validation
- Lack of information and studies on component and equipment
- Insufficient information on the validation process

b(4)

C. Assessment of Risk Due to Microbiology Deficiencies – Due to a lack of microbiological data for review, the maintenance of sterility assurance of the final packaged drug product cannot be adequately assessed.

III. Administrative

A. Reviewer's Signature _____
Robert J. Mello, Ph.D.

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

C. CC Block
In DFS

16 Page(s) Withheld

8 Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Microbiology-_____

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/s/

Robert Mello
3/3/2007 10:42:09 AM
MICROBIOLOGIST

AZZpprovaable pending additional information

David Hussong
3/3/2007 11:01:43 AM
MICROBIOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCES
NEW DRUG MICROBIOLOGY STAFF

MEMORANDUM

Date: 19 JUNE 2006

TO: Kati Johnson

FROM: Robert J. Mello, Ph.D., Reviewer, New Drug Microbiology Staff

Cc: David Hussong, Ph.D., Associate Director, New Drug Microbiology Staff
James L. McVey, Team Leader, New Drug Microbiology Staff

SUBJECT: Fileability memo: NDA 21-538, Accretropin™ (Somatropin, [rDNA] Origin) for Injection

I have reviewed the following volumes of NDA 21-538, Accretropin™ (Somatropin, [rDNA] Origin) for Injection, submitted in CTD format by Cangene Corporation from a microbiology product quality standpoint for the purpose of fileability of the application:

- Module 1, Volume 1 of 1 (Submission volume 1 of 51)
- Module 3, Volume 10 of 19 (Submission volume 13 of 51)
- Module 3, Volume 12 of 19 (Submission volume 15 of 51).

I find, based on the summary information provided, that the application is fileable. However, the applicant should be advised that the following data and reports could not be found and will be required for review. It is recommended that they be submitted as an amendment to the application.

1) The antimicrobial preservative effectiveness test reports and data (to include actual methods used) for the final formulated drug product containing 0.34% phenol preservative.
2) The study reports and data (to include actual methods used) for the container closure studies used to assure maintenance of the microbial integrity of the final drug product, to include

b(4)

3)

4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCES
NEW DRUG MICROBIOLOGY STAFF

MEMORANDUM

5) Validation study reports and data for components used in the manufacture of the drug product. Information provided should also include:

b(4)

6) Endotoxin test method validation to include
   a. type of assay used for assessing the final drug product
   b. Endotoxin limit determination
   c. Maximum valid dilution (MVD) determination
   d. Enhancement/Inhibition results

END

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/s/

Robert Mello
6/22/2006 11:06:33 AM
MICROBIOLOGIST

Fileable, with comments

James McVey
6/22/2006 11:41:09 AM
MICROBIOLOGIST