CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200740Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

20 August 2012

NDA: 200-740

Drug Product Name
Proprietary: Cystaran
Non-proprietary: Cysteamine Hydrochloride Ophthalmic Solution

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
30 March 2012	2 April 2012	2 April 2012	4 April 2012
3 August 2012	3 August 2012	N/A	N/A

Submission History (for amendments only):

Submit Date(s)	Microbiology Review #	Review Date(s)
4 March 2010	1	29 July 2010
28 July 2010	1	29 July 2010

Applicant/Sponsor
Name: Sigma-Tau Pharmaceuticals, Inc.
Address: 9841 Washington, Blvd., Suite 500
Gaithersburg, MD 20878

Representative: Gianfranco Fornasini, Ph.D.
Telephone: 301-670-2192

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505b(2) application resubmission

2. SUBMISSION PROVIDES FOR: New topical ophthalmic drug product

3. MANUFACTURING SITE: Hi-Tech Pharmacal Co. Inc.
26 Edison St.
Amityville, NY 11701

Sigma-Tau PharmaSource, Inc.
6925 Guion Road
Indianapolis, IN 46268
FDA FEI 1835063

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Sterile ophthalmic solution in [redacted] (b) (4) multiple dose droptainers
- 0.65%
- Topical

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

6. PHARMACOLOGICAL CATEGORY: Treatment of corneal cystine crystal accumulation in cyctinosis patients.

B. SUPPORTING/RELATED DOCUMENTS: The first product quality microbiology review of NDA 200-740 completed on 29 July 2010.

C. REMARKS: The NDA was submitted in eCTD format. Although the first product quality microbiology review of NDA 200-740 recommended approval, a Complete Response Letter was issued for the original submission due to issues with the drug product and drug substance manufacturing sites. The applicant will retain the drug product manufacturing site recommended for approval in the first product quality microbiology review and add a second drug product manufacturing site, Sigma-Tau PharmaSource, Inc. The following information request was sent to the applicant on 23 July 2012:

1. Provide the results of minimum and maximum equipment load validation studies conducted in the [redacted] (b) (4)

(b) (4)

3. Provide the (b) (4) *bioburden limit for Cystaran.*

4. Provide the type(s) of microbiological media and the post-sampling incubation conditions used for (b) (4) *bioburden testing.*

Responses to these requests were provided by the applicant in an amendment dated 3 August 2012.

filename: N200740R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 200-740 is recommended for approval from the standpoint of product quality microbiology

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

The drug product is (b) (4)

B. Brief Description of Microbiology Deficiencies -

No product quality microbiology deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies -

Not applicable

III. Administrative

A. Reviewer's Signature _____

Stephen E. Langille, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block

John Metcalfe, Ph.D. – Senior Microbiology Reviewer

C. CC Block

N/A

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/s/

STEPHEN E LANGILLE
08/20/2012

JOHN W METCALFE
08/20/2012
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 200740 **Applicant:** Sigma Tau Pharmaceuticals **Letter Date:** 3/30/2012

Drug Name: Cystaran® **NDA Type:** Resubmission **Stamp Date:** 4/2/2012

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		Section 3.3 and 3.5
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Section 3.3
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Section 3.5
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		Section 2.5
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Sections 5.1 and 5.2
7	Has the applicant submitted the results of analytical method verification studies?	X		Section 5.3
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	X		No such studies or data were requested from the NDMS.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The original submission of NDA 200740 was recommended for approval by the NDMS in July of 2010. A CR letter was issued because the drug substance and drug product manufacturing facilities were not cGMP compliant. The 3/30/2012 resubmission of NDA 200740 provides for additional drug substance and drug product manufacturing sites. The drug product manufacturing site proposed in the original submission, Hi-Tech Pharmacal Co. Inc., will also be used to manufacture the drug product. The applicant did not provide updated information to support the use of Hi-Tech Pharmacal Co. Inc. for the manufacture of Cystaran® but did provide additional information to support the use of the alternate facility, Sigma-Tau PharmaSource Inc. Because the product quality microbiology information associated with Hi-Tech Pharmacal Co. Inc. was

recommended for approval by the NDMS less than two years ago, this submission approach is acceptable.

Stephen E, Langille Ph.D.	4/10/2012
Reviewing Microbiologist	Date
John Metcalfe, Ph.D.	4/10/12
Microbiology Secondary Reviewer	Date

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/s/

STEPHEN E LANGILLE
04/11/2012

JOHN W METCALFE
04/11/2012
I concur.

Product Quality Microbiology Review

29 July 2010

NDA: 200-740

Drug Product Name
Proprietary: Cystoran
Non-proprietary: Cysteamine Hydrochloride Ophthalmic Solution

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
4 March 2010	4 March 2010	9 March 2010	10 March 2010
28 July 2010	28 July 2010	N/A	N/A

Submission History (for amendments only): Not applicable

Applicant/Sponsor
Name: Sigma-Tau Pharmaceuticals, Inc.
Address: 9841 Washington, Blvd., Suite 500
Gaithersburg, MD 20878

Representative: Gianfranco Fornasini, Ph.D.
Telephone: 301-670-2192

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505b(2) application

2. SUBMISSION PROVIDES FOR: New topical ophthalmic drug product

3. MANUFACTURING SITE: Hi-Tech Pharmacal Co. Inc.
26 Edison St.
Amityville, NY 11701

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Sterile ophthalmic solution
- 0.65%
- Topical

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

6. PHARMACOLOGICAL CATEGORY: Treatment of corneal cystine crystal accumulation in cyctinosis patients.

B. SUPPORTING/RELATED DOCUMENTS: Not applicable

C. REMARKS: The NDA was submitted in eCTD format.

filename: N200740R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 200-740 is recommended for approval from the standpoint of product quality microbiology

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

The drug product is (b) (4)

B. Brief Description of Microbiology Deficiencies -

No product quality microbiology deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies -

Not applicable

III. Administrative

A. Reviewer's Signature _____

Stephen E. Langille, Ph.D.

B. Endorsement Block

James McVey – Team Leader

C. CC Block

N/A

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

STEPHEN E LANGILLE
08/03/2010

JAMES L MCVEY
08/03/2010
I concur.