

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202317Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

REV-QUALITYMICRO-02 (Review Noted (NAI))
NDA-202317
ORIG-1
Supporting Document 36
Resubmission/Class 2
Submit Date: 02/27/2013 - FDA Received Date: 02/27/2013

The product quality microbiology review on NDA 202317 was completed on 3/26/12. NDA 202317 was recommended for approval from a product quality microbiology perspective but received a complete response letter for CMC, clinical and non-clinical issues. The resubmission of 2/17/13 did not provide for any changes to the approved product quality microbiology test methods or specifications.

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/s/

STEPHEN E LANGILLE
08/14/2013

Product Quality Microbiology Review

26 March 2012

NDA: 202-317/N-000

Drug Product Name

Proprietary: Nitrogen Mustard

Non-proprietary: Mechlorethamine Hydrochloride Gel 0.02%

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
27 July 2011	27 July 2011	22 August 2012	25 August 2012
6 March 2012	6 March 2012	N/A	N/A

Submission History (for amendments only) N/A

Applicant/Sponsor

Name: Ceptaris Therapeutics Inc.
Address: 101 Lindenwood Dr. Suite 400
Malvern, PA 19355

Representative: Lisa Wittmer, Ph.D.
Telephone: 610-975-9290

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

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Original NDA
 - 2. SUBMISSION PROVIDES FOR:** Manufacturing and microbiological testing information
 - 3. MANUFACTURING SITE:** University of Iowa
Pharmaceuticals
Iowa City, IA
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - 60 mg of (b) (4) gel packaged in (b) (4) tubes
 - Topical - applied to the skin
 - 0.02%
 - 5. METHOD(S) OF STERILIZATION:** non-sterile
 - 6. PHARMACOLOGICAL CATEGORY:** Treatment of mycosis fungoides (cutaneous T-cell lymphoma) (b) (4)
- B. SUPPORTING/RELATED DOCUMENTS:** Not applicable
- C. REMARKS:**
The submission was provided in eCTD format. A product quality microbiology information request was sent to the applicant on 4 January 2012.

filename: N202317r1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 202-317 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 formulated into a (b) (4) gel containing (b) (4) isopropanol. The drug product is manufactured under GMP conditions and is unlikely to support microbial growth.

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

Bryan Riley, Ph.D. – Team Leader

C. CC Block

N/A

Product Quality Microbiology Assessment

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA**

S DRUG SUBSTANCE

Not applicable

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product –
The drug product is a translucent gel for topical administration packaged in a multiple dose re-sealable (b)(4) tube.
- Drug product composition –
The drug product composition was provided in table 3.2.P.1.2 of the application and is reproduced in table 1 below.

Table 1: Drug product composition

Component	Quality Standard	Function ¹	Percentage (% w/w)	Amount (g/tube)			
Mechlorethamine Hydrochloride (MCH, NM)	USP	Active Pharmaceutical Ingredient	0.02	0.012			
Diethylene Glycol Monoethyl Ether (diEGEE; (b)(4) ²)	NF	(b)(4)		(b)(4)			
Propylene Glycol (PG)	USP						
Isopropyl Alcohol ² (IPA)	USP						
Glycerin	USP						
Lactic Acid (b)(4) (LA)	USP						
Hydroxypropylcellulose, (HPC) (b)(4)	NF						
Sodium Chloride (NaCl)	USP						
(b)(4) Menthol	USP						
Edetate Disodium (b)(4)	USP						
Butylated Hydroxytoluene (BHT)	NF						
TOTAL						100%	60g

¹Kibbe, AH, editor. Handbook of Pharmaceutical Excipients. 3rd ed. London: Pharmaceutical Press; 2000.

(b)(4)

The drug product consists of a number of organic components (b) (4). The risk of microbial proliferation in this product is minimal. However, the applicant (b) (4) has agreed to conduct microbial limits testing at release and on stability batches. Additional (b) (4) testing is not required based upon the chemical composition of the drug product.

- Description of container closure system –
The drug product is supplied in multiple dose (b) (4) tubes (b) (4).

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity –
Not applicable.
- (b) (4)
The results of (b) (4) testing were provided in Report STL10-156 and tables (3.2.P.2.5)1 and (3.2.P.2.5)2. Testing was conducted according to (b) (4) methodology and the results of the testing conducted on three batches each of the (b) (4) tubes and the 60 g tubes. Each of the lots passed (b) (4) testing (b) (4).
- Justification for not having a microbial limit specification for a non-sterile drug product -
Not applicable.

Acceptable

P.3 Manufacture

P.3.1 Manufacturers

The drug product will be manufactured at the

University of Iowa Pharmaceuticals (UIP)
College of Pharmacy
115 S. Grand Avenue, Suite G20
Iowa City, IA

P.3.3 Description of the Manufacturing Process and Process Controls

A detailed description and flowchart of the manufacturing process was provided in section 3.2.P.3.3. (b) (4)

The drug product is then dispensed into tubes.

Acceptable

P.3.5 Process Validation and/or Evaluation

Not applicable

P.5 Control of Drug Product

P.5.1 Specifications

Section 3.2.P.3.5 of the original submission states that when tested, the product would conform to microbial testing requirements. Neither the requirements nor the test method were provided. The following information request was sent to the applicant on 4 January 2012:

Microbial limits testing should be conducted at the initial time point (at a minimum) on stability batches according to USP <61>/<62> methodology or equivalent. The microbial limits specification should be consistent with USP <1111> recommendations for cutaneous use. Once a satisfactory product history has been established, a post-approval supplement may be submitted to the FDA requesting a waiver of microbial limits testing of stability batches.

In response to this information request, the applicant agreed to conduct microbial limits testing according to USP <61/62> methodology on stability batches and as part of the drug product's release specification. The microbial limits specifications are as follows:

Acceptable

P.5.2 Analytical Procedures

- Endotoxin –
Not applicable

- Sterility –
Not applicable

- Microbial Limits –
The microbial limits specifications for the drug product were provided in section 3.2.P.5.1.

-
- Total aerobic microbial count: (b) (4)
 - Total yeast and mold count: (b) (4)
 - Absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Acceptable

P.7 Container Closure System

See section P.1 of this review.

P.8 Stability

P.8.1 Stability Summary and Conclusion

Specifications and testing schedule for the post-approval stability program.

- Container Closure Integrity –
Not applicable
- Endotoxin –
Not applicable
- Microbial Limits -
On 6 March 2012, Ceptaris Therapeutics Inc. submitted an amendment to the NDA in response to the 4 January 2012 information request. Ceptaris agreed to microbial limits testing at the initial time point on drug stability batches according to USP <61>/<62> using the microbial limits suggested in <1111>.

P.8.3 Stability Data

A limited amount of stability data supporting (b) (4) testing was provided in section 3.2.P.2.5 and is summarized in section 2.5 of this review.

Acceptable

A APPENDICES

Not applicable

R REGIONAL INFORMATION

Not applicable

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-
QUALITY (CTD-Q)
MODULE 1**

A. PACKAGE INSERT

The package insert states that the drug product is for topical application to dry skin and should be stored, refrigerated between 35°F-46°F.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

Not applicable

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/s/

STEPHEN E LANGILLE
03/26/2012

BRYAN S RILEY
03/26/2012
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 202-317

Applicant: Yaupon
Therapeutics Inc.

Letter Date: 27 July 2011

Drug Name: Mechlorethamine
Hydrochloride Gel 0.02%

NDA Type: 505b2

Stamp Date: 27 July 2011

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		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		The applicant submitted the results of microbial recovery studies that may be suitable for microbial limits testing.
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	(b) (4)
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?		X	
7	Has the applicant submitted the results of analytical method verification studies?		X	The results of (b) (4) studies were not provided.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	X		No such studies/data were requested from the product quality microbiology group.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: Mechlorethamine Hydrochloride Gel 0.02% is a non-sterile topical gel packaged in (b) (4) tubes. The drug product (b) (4) does contain (b) (4) isopropyl alcohol. The results of (b) (4) studies were not provided. With regard to microbial limits, section 3.2.P.5.1 states that "When tested, the product will

conform to requirements.” The test methodology and acceptance criteria were not provided. The following comments should be conveyed to the sponsor:

Microbiology Comments:

1. Provide the results of (b) (4) testing on three lots of drug product using (b) (4) methodology or equivalent.
 2. Provide the microbial limits specification and test method for the finished drug product in section 3.2.P.5.1 of the application. The acceptance criteria for cutaneous use drug products provided in USP <1111> are recommended.
-

Stephen E. Langille, Ph.D.
Microbiology Reviewer

Date

James McVey
Microbiology Team Leader

Date

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/s/

STEPHEN E LANGILLE
09/07/2011

JAMES L MCVEY
09/08/2011
I concur.