

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-556Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

28 DEC 2012

NDA: 22-556

Drug Product Name

Proprietary: Karbinal ER (proposed)

Non-proprietary: Carbinoxamine ER Oral Suspension

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
04 OCT 2012	05 OCT 2012	07 OCT 2012	07 OCT 2012
06 DEC 2012	07 DEC 2012	N/A	N/A

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
7 DEC 2010	1	31 AUG 2011
10 JUN 2011	1	31 AUG 2011
24 JUN 2011	1	31 AUG 2011
12 AUG 2011	1	31 AUG 2011

Applicant/Sponsor

Name: Tris Pharma, Inc.

Address: 2033 Route 130
Monmouth Junction, NJ 08852

Representative: W. Scott Groner

Telephone: 732-940-0358

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Class 2 resubmission of a 505(b)(2) NDA
 2. **SUBMISSION PROVIDES FOR:** New drug product
 3. **MANUFACTURING SITE:** Tris Pharma, Inc.
2033 Route 130
Monmouth Junction, NJ 08852
Registration Number: 3004712471
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Oral suspension
 - 4 mg carbinoxamine maleate per 5 mL
 5. **METHOD(S) OF STERILIZATION:** Non-sterile drug product
 6. **PHARMACOLOGICAL CATEGORY:** Treatment of allergic rhinitis
- B. **SUPPORTING/RELATED DOCUMENTS:** Microbiology review #1 dated 31 August 2011.
- C. **REMARKS:** This submission is the eCTD format. The following information request was sent to the applicant on 15 November 2012 and a response was received on 07 December 2012. The response has been incorporated into the relevant section of this review.

Microbiology Comment:

We refer you to deficiency 5 in the 07 October 2011 complete response letter for NDA 22-556. In the 04 October 2012 Class 2 resubmission Tris Pharma (b) (4) for *Burkholderia cepacia* complex (BCC) species. In advance of the release of a compendial test for these organisms it is current agency policy to require high-risk new drug products to be free of these organisms. You may demonstrate the absence of BCC with a release test or you may utilize in process controls to insure that the final drug product does not contain BCC. If you choose to utilize in process controls in place of release testing provide a summary of the risk assessment that identified likely sources of BCC in the final product and the testing schedule and methods for components identified as likely sources of contamination. If you choose to utilize release testing please submit a revised specification and provide the proposed test method.

filename: N022556R2.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – This application is recommended for approval on the basis 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** – This is a non-sterile, preserved, extended release oral suspension with a complex manufacturing process. The microbiological quality of the precursors is adequately controlled.
- B. Brief Description of Microbiology Deficiencies** – Not applicable.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

III. Administrative

- A. Reviewer's Signature** _____
Jessica G. Cole, PhD
- B. Endorsement Block** _____
Bryan Riley, PhD
Microbiology Team Leader
- C. CC Block**
N/A

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/s/

JESSICA COLE
12/31/2012

BRYAN S RILEY
12/31/2012
I concur.

Product Quality Microbiology Review

30 AUG 2011

NDA: 22-556

Drug Product Name

Proprietary: Karbinal ER (proposed)

Non-proprietary: Carbinoxamine ER Oral Suspension, eq. to 4 mg carbinoxamine maleate per 5 mL

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
7 DEC 2010	7 DEC 2010	7 JUL 2011	8 JUL 2011
10 JUN 2011	10 JUN 2011	N/A	N/A
24 JUN 2011	24 JUN 2011	N/A	N/A
12 AUG 2011	15 AUG 2011	N/A	N/A

Applicant/Sponsor

Name: TrisPharma, Inc.

Address: 2033 Route 130
Monmouth Junction, NJ 08852

Representative: W. Scott Groner

Telephone: 732-940-0358

Name of Reviewer: Jessica G. Cole, Ph.D.

Conclusion: Approvable pending revision of the deficiencies on page 9.

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** New 505(b)2 NDA
 - 2. SUBMISSION PROVIDES FOR:** New extended release oral formulation
 - 3. MANUFACTURING SITE:** Tris Pharma, Inc.
2033 Route 130
Monmouth Junction, NJ 08852
Registration Number: 3004712471
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Extended release oral suspension
 - 4 mg/5 mL
 - 5. METHOD(S) OF STERILIZATION:** Non-sterile drug product
 - 6. PHARMACOLOGICAL CATEGORY:** Treatment of multiple allergic conditions.
- B. SUPPORTING/RELATED DOCUMENTS:** None.
- C. REMARKS:** The following information request was sent to the applicant on 15 July 2011.

Microbiology Comment:

Provide the following information or a reference to its location in the subject submission.

1. Provide the methods and results from preservative effectiveness testing. Include the results from Batch No. 0132-157.
2. Provide the microbial limits test method or clearly define the sample used for testing. We note that your patient dose is 4 mg/5 mL, yet the limits for microbes are expressed in CFU/g. Provide a justification for the microbial limit expressed in grams rather than milliliters for this liquid drug product.
3. Provide a copy of the study mentioned in the 24 June 2011 response to Question 3. This study should have evaluated the microbiological burden prior to [REDACTED] (b) (4) [REDACTED].
4. Provide test methods and acceptance criteria to demonstrate the drug product is free of the objectionable microorganism *Burkholderia cepacia*. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

Please identify potential sources for introduction of *B. cepacia* during the manufacturing process and describe the steps to minimize the risk of *B. cepacia* complex organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A

risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

There are currently no compendial methods for detection of *B. cepacia* complex (Bcc). At this point in time it would be sufficient to precondition representative strain(s) of *B. cepacia* in water and/or your drug product without preservatives and demonstrate that your proposed method is capable of detecting small numbers of Bcc. Your validation studies should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning (minimum 48 hours) of the organisms occurs during these method validation studies.

We refer you to *Envir. Microbiol.* 13(1):1-12, 2011 for more information on the *B. cepacia* complex of organisms. We refer you to *J. Appl. Microbiol.* 1997 Sep;83(3):322-6 for more information on the recovery of *B. cepacia* organisms from pharmaceutical environments.

Several requests for feedback on the *B. cepacia* test were received prior to the 12 August 2011 submission. For a summary of those unofficial communications see files N022556memo2.doc and N022556memo3.doc.

filename: N022556R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – This application is approvable pending revision of the deficiencies on page 9.
- 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** – This is a non-sterile, extended release oral suspension with a complex manufacturing process. The microbiological quality of the precursors is adequately controlled.
- B. Brief Description of Microbiology Deficiencies** – Only a single lot of drug product underwent AET testing and the specifications should be revised to include the absence of *Burkholderia cepacia* complex organisms.
- C. Assessment of Risk Due to Microbiology Deficiencies** – There is a moderate risk of release of product with unacceptable microbiological contamination levels.

III. Administrative

- A. Reviewer's Signature** _____
Jessica G. Cole, Ph.D.
- B. Endorsement Block** _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

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/s/

JESSICA COLE
08/31/2011

STEPHEN E LANGILLE
08/31/2011