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RESEARCH**

APPLICATION NUMBER:
202245Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

02 MAY 2011

NDA: 202-245

Drug Product Name

Non-proprietary: Codeine Sulfate Oral Solution (30 mg/5 mL)

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
27 SEPT 2010	27 SEP 2010	1 FEB 2011	3 FEB 2011
23 FEB 2011	23 FEB 2011	3 MAR 2011	N/A
10 MAR 2011	10 MAR 2011	N/A	N/A
12 APR 2011	12 APR 2011	N/A	N/A
27 APR 2011	27 APR 2011	N/A	N/A

Applicant/Sponsor

Name: Roxane Laboratories, Inc.

Address: 1809 Wilson Road
Columbus, OH 43228

Representative: Elizabeth Ernst

Telephone: 614-272-4785

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

Conclusion: Recommended for approval.

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Original 505(b)(2) NDA
 - 2. SUBMISSION PROVIDES FOR:** New drug product
 - 3. MANUFACTURING SITE:** Boehringer Ingelheim Roxane, Inc (BIRI)
1809 Wilson Road
Columbus, OH 43228
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - (b)(4) oral solution
 - 30 mg/mL
 - 500 mL multi-dose bottle
 - 5. METHOD(S) OF STERILIZATION:** Non-sterile drug product
 - 6. PHARMACOLOGICAL CATEGORY:** Pain reliever
- B. SUPPORTING/RELATED DOCUMENTS:** None.
- C. REMARKS:** This submission was in the eCTD format. This application references Roxane Laboratories NDA 22-402 (Codeine Sulfate Tablets) for findings of safety and efficacy. The following information request was sent to the ONDQA PM on 28 February 2011 and a response was received on 10 March 2011.
1. Provide a justification for the total yeast and mold limit of (b)(4) We refer you to USP<1111> which recommends a limit of 10 CFU/mL for oral solutions.
 2. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. 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. Your test method should be validated and a discussion of those methods should be provided. Test methods 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.
- The following information request was sent to the ONDQA PM on 11 March 2011 and a response was received on 12 April 2011 and 25 April 2011.
- Your amendment dated 10 March 2011 is inadequate to demonstrate that your product is free of the objectionable microorganism *Burkholderia cepacia*. While *B. cepacia* used to be classified as a *Pseudomonad*, it is not a member of this genus and as such the USP<62> test for the absence of *Pseudomonas* is not adequate. We refer you to *Envir. Microbiol.* 13(1):1-12, 2011 for more information on the *B. cepacia* complex of organisms. If your internal work instruction 046-(b)(4)2005 Isolation, Characterization, and Identification of Microorganisms contains a validated screen specific for *B. cepacia*, provide this work instruction and the method validation studies.
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USP<62> does not describe validated studies which demonstrate the absence of this objectionable organism.

Your risk assessment is inadequate to determine the likelihood of *B. cepacia* contamination of your final drug product. Your reliance on the (b) (4) system and the capacity of a test for *Pseudomonas* to provide assurance of absence of this objectionable organism is insufficient. *B. cepacia* complex are highly adaptable organisms which are capable of growth in (b) (4) drug products and water used in industrial applications. Additionally, organisms isolated in pharmaceutical plants have been shown to be more resistant to (b) (4) than strains grown under traditional laboratory conditions. We refer you to *J. Appl. Microbiol.* 1997 Sep;83(3):322-6 for more information. 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.

As there are currently no compendial methods for detection of *B. cepacia* complex we have provided a suggestion for a potential validation scheme. However, any validated method capable of detecting *B. cepacia* complex organisms would be adequate. 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 the proposed method in USP<62> is capable of detecting small numbers of this microorganism. 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.

The responses to all information requests are incorporated into the relevant sections of this review.

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – 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, (b) (4) aqueous solution for oral use. The drug product components are controlled to minimize the presence of microbes and the (b) (4) is present throughout the manufacturing process.
- 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, Ph.D.
- B. Endorsement Block** _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

6 pages has been withheld in full as B(4) CCI/TS immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA COLE
05/04/2011

STEPHEN E LANGILLE
05/04/2011