

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206323Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

14 April 2015

NDA: 206-323/N000

Drug Product Name

Proprietary: NA

Non-proprietary: Codeine Phosphate and Chlorpheniramine Maleate

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
22 August 2014	22 August 2014	26 August 2014	28 August 2014
5 February 2015	5 February 2015	NA	NA

Submission History (for 2nd Reviews or higher) - NA

Applicant/Sponsor

Name: Spriaso, LLC

Address: The Parc at Gateway, #911
5 South 500 West
Salt Lake City, UT 84101

Representative: Lara Noah
Director of Regulatory Affairs
Nexgen Pharma, Inc.
46 Corporate Park, Suite 100
Irvine CA 92606

Telephone: (719) 579-9650

Name of Reviewer: Denise A. Miller

Conclusion: Recommended for approval from a quality microbiology perspective.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original New Drug Application
2. **SUBMISSION PROVIDES FOR:** The manufacture and marketing of the subject drug product.
3. **MANUFACTURING SITE:**
Nexgen Pharma Inc.
1835 E. Cheyenne Road
Colorado Springs CO 80905
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Dosage Form: Extended release tablet
 - Route of Administration: Oral
 - Strength/Potency: 40mg/8mg per tablet
5. **METHOD(S) OF STERILIZATION:** Non-sterile
6. **PHARMACOLOGICAL CATEGORY:** Temporary relief of cough ^(b)
₍₄₎
-
- B. **SUPPORTING/RELATED DOCUMENTS:**
- C. **REMARKS:** NA

filename: N206323N000R1.docx

Executive Summary**I. Recommendations**

- A. Recommendation on Approvability** - Recommended for Approval from a quality microbiology perspective.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** - NA

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The manufacturing process uses ^{(b) (4)}

- B. Brief Description of Microbiology Deficiencies** – there were no deficiencies identified in the submitted information.
- C. Assessment of Risk Due to Microbiology Deficiencies** – NA
- D. Contains Potential Precedent Decision(s)**- Yes No

III. Administrative

- A. Reviewer's Signature** _____
Denise A. Miller
Microbiologist, OPF/DMA/Branch II
- B. Endorsement Block** _____
Neal J. Sweeney, Ph.D.
Senior Microbiologist, OPF/DMA/Branch II
- C. CC Block**
N/A

Product Quality Microbiology Assessment

This is a non-sterile oral tablet. The tableting process starts with [REDACTED] (b) (4)

[REDACTED] The tablets are not coated.

The release specifications and the stability program do not include testing for microbial quality and the exclusion of these tests was justified based on the decision tree #8 of ICH Guidance Q6(R2). The justification states that the three submission batches were tested, but the results were not provided. The sponsor also stated in section 3.2.P.2.5 that the drug product was capable of supporting microbial growth.

The 74-day letter included the following information request:

1. We note that microbial limits testing is not included in either the drug product specification or the post approval stability protocol. If you propose to waive microbial limits release and stability testing for your drug product, this proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points.
 - a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
 - i. Define the maximum processing time [REDACTED] (b) (4).
 - ii. Define the maximum holding time [REDACTED] (b) (4).
 - b. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
 - c. Describe activities taken when microbiological acceptance criteria are not met at control points.
2. If you elect to perform microbial limits testing for drug product release and stability, please submit revised a drug product specification and stability protocol indicating microbial limits testing and corresponding acceptance criteria, as well as methods suitability verification data for the microbiological methods used to demonstrate the microbiological quality of the drug product.

Response received 05 February 2015:

- 1) The microbiological tests of the three submission lots support that [all are zero CFUs] and are attached in the submission in section 3.2.P.2.
- 2) The microbiological suitability tests demonstrate the presence of the drug substantially reduces the number of microorganisms and the microbial tests of the three submission lots support that [all are zero CFUs]. So there is no need to have a microbial attribute for the product's release specification.

Review of Response: The sponsor updated section 3.2.P.2.5. The update included a correction to the statement that the product supports microbial growth corrected to state that the product does not support microbial growth. This correction was supported by the bioburden method suitability testing following USP <61> results demonstrating a suppression of microbial growth by the drug product. The sponsor further states that manufacturing process (b) (4) and the tablets are not coated. They also state that the incoming raw materials are controlled for burden. Of note, the sponsor did not mention the (b) (4)

-ADEQUATE-

Reviewer Comment: The response is adequate. The bioburden of the drug product is controlled through testing of the raw materials, an (b) (4) manufacturing process, and the inability of the drug product to support microbial growth.

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None

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/s/

DENISE A MILLER
04/22/2015

NEAL J SWEENEY
04/22/2015
I concur.

PRODUCT QUALITY MICROBIOLOGY NON-STERILE

DRUG PRODUCT FILING CHECKLIST

NDA Number: 206-323 **Applicant:** Spriaso LLC **Letter Date:** 22 August 2014
Drug Name: Codeine **NDA Type:** 505(b)(2) **Stamp Date:** 22 August 2014
 Phosphate and
 Cholrpheniramine Maleate
 Extended Release Tablets
Dosage Form: Tablet **Reviewer:** Denise Miller

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?	√		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?		√	No microbiological controls were submitted.
3	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?		√	
4	Has the applicant submitted the results of analytical method verification studies?	NA		
5	Has the applicant submitted preservative effectiveness studies (if applicable)?	NA		
6	Is this NDA fileable? If not, then describe why.	√		

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Denise Miller
CDER/OPS/NDMS

Date

Neal Sweeney, Ph.D.
CDER/OPS/NDMS

Date

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

/s/

DENISE A MILLER
10/24/2014

NEAL J SWEENEY
10/24/2014
I concur.