

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207926Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

12 DEC 2014

NDA: 207926

Drug Product Name

Proprietary: (None)

Non-proprietary: Phenylephrine Hydrochloride Ophthalmic Solution, USP

Review Number: 1

Dates of Submission(s) Covered by this Review

<u>Submit</u>	<u>Received</u>	<u>Review Request</u>	<u>Assigned to Reviewer</u>
11 JUL 2014	11 JUL 2014	15 JUL 2014	18 JUL 2014
12 Sep 2014	12 Sep 2014	N/A	N/A

Applicant/Sponsor

Name: Akorn, Inc.

Address: 1925 West Field Court
Suite 300
Lake Forest, IL 60045

Representative: Sam Boddapati, Ph.D.

Telephone: 847-353-4909

Name of Reviewer: Neal J. Sweeney, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** 505 (b) (1) Original NDA
2. **SUBMISSION PROVIDES FOR:** Marketing of new drug product
3. **MANUFACTURING SITE:**
- Akorn, Inc.
1222 W. Grand Avenue
Decatur, IL 62522
- Drug Establishment Registration #: 1450114
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Phenylephrine hydrochloride solution 25mg/mL and 100 mg/mL (2.5% and 10%) in LDPE dropper bottles for topical ophthalmic administration.
5. **METHOD(S) OF STERILIZATION:**
[REDACTED] (b) (4) processing/filling.
6. **PHARMACOLOGICAL CATEGORY:** Alpha-1 adrenergic receptor agonist indicated for the dilation of the pupil.

B. **SUPPORTING/RELATED DOCUMENTS:**
(none)

C. **REMARKS:**

The applicant has been marketing Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10% under "Grandfather" status since August 18, 1993, and has filed the subject NDA (207926) for Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10% according to Compliance Policy Guide (CPG), Section 440.100. DSS has requested DTOP to expedite the review of NDA 207926 to avoid a possible drug shortage. Although the application is classified as "standard" review (May 11, 2015 PDUFA date) the Division will expedite the review of the application to complete the reviews in six months. The internal goal date is January 11, 2015.

A Microbiology information request was issued on August 28, 2014, and a corresponding IR response was received by the Agency on September 12, 2014. The Microbiology IR requested process validation information for the [REDACTED] (b) (4) process used for sterilization of the container/closure components.

File name: N207926R1.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** - Recommended for Approval.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

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** – Based upon the information provided, no microbiology deficiencies were identified.
- C. **Contains Potential Precedent Decision(s)**- Yes No
(If yes, provide a brief description and a reference to the page where the precedent is discussed in depth)

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O ^(3, 4, 5)	Severity of Effect (S)	Detect. (D)	Risk Priority Number ⁶ (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b)(4)					(b)(4)	Simulations and interventions conducted during media fills, Environmental monitoring



Reviewer's Note: As the drug product formulation contains a preservative, a (b) (4) . Additionally, since the drug product is indicated for topical administration the sterility "S" value was (b) (4) . The drug product is formulated with WFI and indicated for topical ophthalmic use, and not indicated to be used in conjunction with surgery. Therefore the endotoxin risk for the drug product and the corresponding route of administration is inherently very low.

B. Final Risk Assessment -

In-process controls include bioburden testing of drug substance, excipients, and bulk solution, bioburden and endotoxin testing (b) (4), established maximum hold times, and (b) (4) testing. Media fills include simulations, interventions and environmental monitoring. Formulation containing (b) (4) % of the labeled benzalkonium chloride preservative concentration meets USP <51> Antimicrobial Effectiveness Testing acceptance criteria for Category 1 products. Sterilization of filling equipment and container/closure components utilize validated processes, and the (b) (4) process was validated by microbial retention validation studies for the two product concentrations. Container/closure integrity was demonstrated for each of the three product configurations. Therefore the applicant has mitigated the risk for drug product non-sterility.

IV. Administrative

A. Reviewer's Signature _____
Neal J. Sweeney, Ph.D.

B. Endorsement Block _____
John W. Metcalfe, Ph.D.

C. CC Block
N/A

22 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Signature Neal J. Sweeney -A
Neal J. Sweeney, Ph.D.

Digitally signed by Neal J. Sweeney -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13001095
87, cn=Neal J. Sweeney -A
Date: 2014.12.21 19:54:47 -05'00'

Endorsement Block John W. Metcalfe -A
John W. Metcalfe, Ph.D.

Digitally signed by John W. Metcalfe -A
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ou=People, 0.9.2342.19200300.100.1.1=1300198103,
cn=John W. Metcalfe -A
Date: 2014.12.22 09:50:15 -05'00'

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 207926

Applicant: Akorn, Inc.

Letter Date: 11 July 2014

Drug Name: Phenylephrine
HCl ophthalmic solution 2.5%
& 10%

NDA Type: 505(b)(2) Standard

Stamp Date: 11 July 2014

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		eCTD
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		3.2.P.3.3. (b) (4) of C/C components, (b) (4) bioburden testing, sterile filtration bulk solution, (b) (4) filling of bottles.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		3.2.P.3.5. Sterilization of equipment, microbial retention, hold time, and media fills. (b) (4) process validation or DMF authorization letter was not included.
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		3.2.P.3.5. C/C integrity 3.2.P.3.5AET
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		3.2.P.5.1. sterility and C/C (release and stability),
7	Has the applicant submitted the results of analytical method verification studies?	X		3.2.P.3.5 (sterility and c/c testing)
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	X		In an April 3, 2014 t-con with the applicant the Agency requested (as a response to the proposed CMC data plan for the NDA) sterilization process validation to be submitted in the NDA.
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?	N/A	N/A	Not designed for reconstitution or dilution.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments:

The following Information Request should be forwarded to the applicant via 74-Day Letter:

The application indicates that the drug product container/closure components are (b) (4) [redacted], and that received container/closure components are accompanied by a (b) (4) [redacted] Processing. Please provide container/closure sterilization process validation reports for these components. Alternatively you may reference a Drug Master File containing this information, and provide the corresponding Letter of Authorization citing the DMF submission date of the aforementioned validation data.

19 Aug 2014

Neal J. Sweeney, Ph.D., (Primary Reviewer)

Date

John W. Metcalfe, Ph.D., (Secondary Reviewer)

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

/s/

NEAL J SWEENEY
08/20/2014

JOHN W METCALFE
08/20/2014
I concur.