# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204200Orig1s000
# 204200Orig2s000

# MICROBIOLOGY REVIEW(S)

# Product Quality Microbiology Review

**August 7, 2012**

**NDA: 204-200**

**Drug Product Name**
**Proprietary:** Adrenalin® Injection
**Non-proprietary:** Epinephrine Injection, USP

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

| Submit | Received | Review Request | Assigned to Reviewer |
|---|---|---|---|
| 07 MAR 2012 | 07 MAR 2012 | 15 MAR 2012 | 16 MAR 2012 |
| 14 MAY 2012 | 16 MAY 2012 | N/A | N/A |
| 4 JUN 2012 | 4 JUN 2012 | N/A | N/A |

**Applicant/Sponsor**
**Name:** JHP Pharmaceuticals, LLC
**Address:** Morris Corporate Centre 2
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054
**Representative:** Steve Richardson, VP Scientific and Regulatory Affairs
**Telephone:** 973-658-3561

**Name of Reviewer:** Erika Pfeiler, Ph.D.

**Conclusion:** Recommend Approval

# Product Quality Microbiology Data Sheet

**A. 1. TYPE OF SUBMISSION:** 505(b)(2)

**2. SUBMISSION PROVIDES FOR:** Marketing of a sterile drug

**3. MANUFACTURING SITE:** JHP Pharmaceuticals LLC
870 Parkdale Road
Rochester, MI 48307

**4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**

- Sterile aqueous solution, 1 ml (b) (4)
- Intramuscular, subcutaneous, (b) (4) or intraocular injection; ophthalmic wash
- 1 mg/ml

**5. METHOD(S) OF STERILIZATION:** (b) (4)

**6. PHARMACOLOGICAL CATEGORY:** Treatment for severe anaphylactic reaction and maintenance of mydraisis in cataract surgery

**B. SUPPORTING/RELATED DOCUMENTS:** Microbiology Review 20 of DMF (b) (4) (16 March 2012)

**C. REMARKS:**

This application was submitted in the eCTD format.

Two information requests were submitted via the RPM on May 4, 2012 and May 24, 2012. Responses were received on May 16 and June 4, and were incorporated into the relevant sections of the review.

May 4 IR

- Clarify whether stoppers are supplied endotoxin-free. If stoppers are not supplied endotoxin free, provide a protocol and validation studies for the depyrogenation of stoppers (b) (4) of the drug product.
- Provide personnel monitoring protocols and schedules.
- For container closure studies, describe how stoppers for both vial sizes are processed prior to insertion in test vials. Are sterilization parameters the same as or different from stoppers used in production?
- Provide endotoxin and bioburden alert/action levels for WFI (b) (4) used in manufacturing.
- Clarify whether (b) (4) is used in manufacturing the drug product. If so, provide media fill and sterilization/endotoxin validation studies for this line.
- Provide the most recent requalification reports (b) (4)

- Provide data from inhibition/enhancement studies used to determine the (b) (4) dilution used in endotoxin testing of the drug product.
- State the number of articles that will be tested for sterility and endotoxin levels in each production batch of drug product.

May 24 IR

- Please describe the sterilization (b) (4)
- Confirm (b) (4)
- The table 'Location of Operations' (3.2.P.3.3, Description of Manufacturing Process and Process Controls, Page 10) states (b) (4) Please clarify.

**filename:** N204200R1.doc

# Executive Summary

**I. Recommendations**

**A. Recommendation on Approvability –** Recommend for approval on the basis of product quality microbiology.

**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 –** Product is sterilized (b) (4) .

**B. Brief Description of Microbiology Deficiencies –** N/A

**C. Assessment of Risk Due to Microbiology Deficiencies –** N/A

**III. Administrative**

**A. Reviewer's Signature _____**
Erika Pfeiler, Ph.D.

**B. Endorsement Block_____**
Bryan Riley, Ph.D.
Microbiology Team Leader

**C. CC Block**
N/A

10 Page(s) has been Withheld in Full as b4 (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/

---

ERIKA A PFEILER
08/07/2012

BRYAN S RILEY
08/08/2012
I concur.

# PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number: 204-200** **Applicant: JHP Pharmaceuticals** **Letter Date: 3/7/12**

**Drug Name: Adrenalin® Injection** **NDA Type: 505(b)(2)** **Stamp Date: 3/7/12**

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 | | |
| 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) [redacted] |
| 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 | | |
| 8 | Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions? | | | N/A |
| 9 | Is this NDA fileable? If not, then describe why. | X | | |

**Additional Comments:**
This NDA is for a sterile aqueous solution to be injected or used as an ophthalmic wash in cataract surgery.

**Request for the 74-day letter:**

- Clarify whether stoppers are supplied endotoxin-free. If stoppers are not supplied endotoxin free, provide a protocol and validation studies for the depyrogenation of stoppers (b) (4) [redacted] of the drug product.

- Provide personnel monitoring protocols and schedules.

- For container closure studies, describe how stoppers for both vial sizes are processed prior to insertion in test vials. Are sterilization parameters the same as or different from stoppers used in production?

- Provide endotoxin and bioburden alert/action levels for WFI and (b) (4) used in manufacturing.

- Clarify whether (b) (4) is used in manufacturing the drug product. If so, provide media fill and sterilization/endotoxin validation studies for this line.

- Provide the most recent requalification reports (b) (4)

- Provide data from inhibition/enhancement studies used to determine the (b) (4) dilution used in endotoxin testing of the drug product.

- State the number of articles that will be tested for sterility and endotoxin levels in each production batch of drug product.

Erika Pfeiler, Ph.D.
Reviewing Microbiologist Date

Bryan Riley, Ph.D.
Microbiology Team Leader Date

---

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

---

/s/

---

ERIKA A PFEILER
04/12/2012

BRYAN S RILEY
04/12/2012
I concur.