

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204485Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 03 December 2013

TO: Quynh Nguyen
Regulatory Health Project Manager
CDER/OND/ODEI/DCRP

FROM: Erika Pfeiler, Ph.D.
Microbiologist
CDER/OPS/New Drug Microbiology Staff
(301) 796-0642

THROUGH: John Metcalfe, Ph.D.
Senior Review Microbiologist
CDER/OPS/New Drug Microbiology Staff

SUBJECT: Product Quality Microbiology Assessment of NDA 204485 Post-Dilution Hold in Various Diluents

Post-dilution hold data for NDA 204485 in 5% Dextrose Injection USP, Lactated Ringer's USP, Plasma-Lyate A Injection USP, and Ringer's Injection USP, is adequate to support an 18 hour hold at room temperature and a 24 hour hold under refrigeration.

NDA 204485 was submitted on 26 September 2012 and proposed a 24-hour post-dilution hold time for the drug product in 0.9% saline at room temperature or under refrigeration. After an information request, data from microbiological post-dilution hold studies were submitted, and the product quality microbiology review was finalized in DARRTS (08 April 2013) in which these studies were found to be adequate to support a post-dilution hold time of 18 hours at room temperature and 24 hours under refrigeration. The applicant subsequently submitted an amendment to the NDA (21 June 2013) supporting an extended post-dilution hold time for the drug product in 5% Dextrose Injection, USP. This information was not reviewed, as it had been determined by this time that a complete response letter would be issued. A complete response letter for this application was issued on 19 July 2013.

The applicant submitted a complete response and proposed drug product labeling on 18 October 2013. As part of the complete response, the applicant responded to a clinical pharmacology comment asking for in-use stability data in alternative fluids. As part of this response, the applicant provided microbiological hold study data with the drug product diluted in Lactated

MEMORANDUM

Ringer's USP, Plasma-Lyate A Injection USP, and Ringer's Injection USP, although the proposed labeling does not discuss use of these fluids in drug product dilution.

The applicant performed all post-dilution hold studies using the maximum dilution of the drug product (and therefore the maximum dilution of antimicrobial preservative) in these solutions. Five species of microorganism (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus epidermis*, *Candida albicans*, and *Aspergillus brasiliensis*) were inoculated to achieve a concentration of approximately 10^4 - 10^5 CFU/ml. Inoculated drug product solution was held either under refrigeration (2-8°C) or at room temperature. Samples held under refrigeration were sampled at 12, 24, and 48 hours after inoculation, and samples held at room temperature were sampled at 6, 12, 24, and 36 hours. No increases of $\geq 0.5 \log_{10}$ CFU/ml were noted with any storage condition or diluting solution.

Reviewer's Note: The applicant submitted microbiological data to support post-dilution hold times in various diluents for 24 hours at room temperature or under refrigeration. Studies were performed using a higher concentration of microorganisms than what was previously recommended in a 20 November 2012 information request (10^5 CFU/ml instead of <100 CFU/ml.) Although the inoculum used was high, data from the studies do not indicate growth of the tested microorganisms under the hold periods. This high inoculum is not likely to mask any growth promoting effects of the drug product. However, studies were carried out for 36 hours at room temperature and 48 hours under refrigeration, and as a result, support a maximum hold time of 18 hours at room temperature and 24 hours under refrigeration, which is the same post-dilution hold time that was determined to be adequate for dilution in 0.9% saline.

END

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
12/03/2013

JOHN W METCALFE
12/03/2013
I concur.

Product Quality Microbiology Review

05 April 2013

NDA: 204485

Drug Product Name

Proprietary: Pitressin® Injection

Non-proprietary: vasopressin injection, USP

Review Number: 1

Dates of Submission(s) Covered by this Review

| Submit | Received | Review Request | Assigned to Reviewer |
|---------------|-----------------|-----------------------|-----------------------------|
| 25 SEP 2012 | 26 SEP 2012 | 28 SEP 2012 | 05 OCT 2012 |
| 13 NOV 2012 | 13 NOV 2012 | N/A | N/A |
| 06 DEC 2012 | 06 DEC 2012 | N/A | N/A |
| 01 FEB 2013 | 01 FEB 2013 | N/A | N/A |
| 01 APR 2013 | 02 APR 2013 | 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: Gerald Vasquez

Telephone: 973-658-3551

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:** Application for a marketed but unapproved drug
 - 3. MANUFACTURING SITE:**
JHP Pharmaceuticals LLC
870 Parkdale Road,
Rochester, MI 48307, USA
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
Sterile injection for intravenous infusion, 1 ml vial containing 20 pressor units
 - 5. METHOD(S) OF STERILIZATION:** (b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** Treatment of vasodilatory (post-cardiotomy and septic) shock
- B. SUPPORTING/RELATED DOCUMENTS:** Microbiology Review 20 of DMF (b) (4) (16 March 2012)
- C. REMARKS:** N/A

filename: N204485R1.doc

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** – N/A

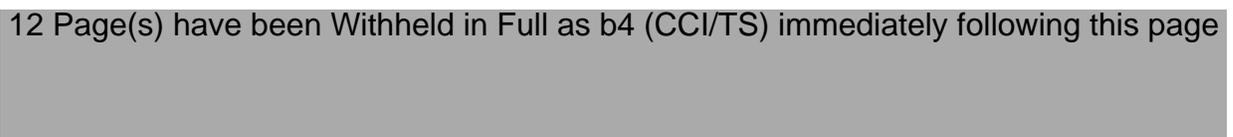
II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – N/A
- 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** _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

12 Page(s) have 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
04/05/2013

STEPHEN E LANGILLE
04/08/2013

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 204485

Applicant: JHP
Pharmaceuticals LLP

Letter Date: 9/25/2012

Drug Name: Pitressin Injection **NDA Type:** 505(b)(2)

Stamp Date: 9/26/2012

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 | The submission is in English |
| 5 | Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies? | X | | |
| 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 | If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data? | | X | There is no microbiological data to support a post-dilution hold; however, the label does not call for extended hold times. The applicant will be notified that hold time will be limited to 4 hours at room temperature and 24 hours under refrigeration and that supporting data may be submitted if a longer period is desired. |
| 10 | Is this NDA fileable? If not, then describe why. | X | | |

Additional Comments: Please include the following comment in the 74-day letter.

Your application does not contain microbiological data to support an extended post-dilution hold period. Without this data, drug product labeling should recommend that the post-dilution storage period is not more than 4 hours at room temperature or 24 hours under refrigeration. If you desire a longer hold period, microbiological data should be provided to demonstrate that the diluted product solution will not support microbial growth during the proposed storage period. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Generally, "no growth" is interpreted as not more than a 0.5 log₁₀ increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3 times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers (≤ 100 CFU/mL) of challenge microbes. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

Erika Pfeiler, Ph.D.

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
11/08/2012

BRYAN S RILEY
11/08/2012
I concur.