CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201444Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

07 September 2010

NDA: **201-444/N-000**

Drug Product Name
Proprietary: (b) (4)
Non-proprietary: Sodium Nitrite Injection; Sodium Thiosulfate Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
21 MAY 2010	21 MAY 2010	21 August 2010	25 MAY 2010
02 JULY 2010	02 JULY 2010	n/a	n/a
10 AUGUST 2010	10 AUGUST 2010	n/a	n/a
18 AUGUST 2010	18 AUGUST 2010	n/a	n/a
03 SEPTEMBER 2010	03 SEPTEMBER 2010	n/a	n/a

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Hope Pharmaceuticals
Address: 16416 N. 92nd Street #125
Scottsdale, AZ 85260
Representative: Craig Sherman, M.D., President
Telephone: 480-607-1970

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA, 505(b)(2)

2. SUBMISSION PROVIDES FOR: Marketing Authority

3. MANUFACTURING SITE: Cangene bioPharma, Inc. (a.k.a. CBL, Inc.)
1111 S. Paca Street
Baltimore, MD 21230

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Injection, solutions, Intravenous,

- 30mg/ml (sodium nitrite), 10ml in a 10ml/20mm (b) (4) glass vial sealed with a (b) (4) stopper and a (b) (4) flip-off (b) (4) aluminum overseal.
- 250mg/ml (sodium thiosulfate), 50ml in a 50ml/20mm (b) (4) glass tubing vial sealed with a (b) (4) stopper and a (b) (4) flip-off (b) (4) aluminum overseal.

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

6. PHARMACOLOGICAL CATEGORY: Antidote for cyanide poisoning

B. SUPPORTING/RELATED DOCUMENTS:

- (b) (4) Letter of Authorization dated 16 March 2010 for (b) (4) for the (b) (4) for the Bacterial endotoxin reduction (BER) validation study (page 54 of 19 April 2005 submission) and the following BER tables:
  - Family Bracketed Validation Data - BER Validation Table: (Table 1), Page 10 (6 OCT 2008 Submission)
  - Supporting Validation Data - Photographs of Family Configurations: (Table 1A), Page 11, (6 OCT 2008 Submission)
  - Supporting Validation Data - BER Validation History: (Table 1B) Pages 12-13 (6 OCT 2008 Submission)
- Microbiology review #11 of (b) (4) dated 15 December 2008 (DARRTS 05 January 2009, S. Donald , (b) (4))

C. REMARKS:

- An ONDQA Initial Quality Assessment was entered into DARRTS on 17 JUNE 2010 (D. Christodoulou). The Microbiology Product Quality staff was requested to review the microbiological process validation studies related to (b) (4) sterilization, in-process controls and container/closure integrity.
- The submission is electronic in CTD format. It is accessible through EDR.
- The drug product manufacturing facility filling suite used to manufacture the initial stability batches is being renovated. Upon completion, the drug products (b) (4). Since the two drug products are (b) (4) sterilized, the impact of the room change is minimized. There is no change to

the (b) (4) sterilization (b) (4) or process as a result of the renovation. However, the Applicant was advised that a change supplement may be required prior to initiating commercial production. The current review relates to the facility and controls used to produce the initial stability batches.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend 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 – There are two separate drug products that will be co-packaged as the cyanide antidote kit – sodium nitrite (10mls in a 10ml vial) and sodium thiosulfate (50mls in a 50ml vial). Although there is no formal claim of (b) (4) there are many in-process controls which provide for a greatly reduced bioburden of the formulation prior to (b) (4) sterilization. Following formulation each solution may be held for NMT (b) (4)
(b) (4)

B. Brief Description of Microbiology Deficiencies – None. There is one COMMENT which stipulates that pre-sterilization bioburden testing must be continued until sufficient evidence of microbial control of the manufacturing process has been provided.

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

III. Administrative

A. Reviewer's Signature: _____

Robert J. Mello, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block: _____

John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer

C. CC Block

NDA 210-444

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201444	ORIG-1	HOPE PHARMACEUTICALS	SODIUM NITRITE INJECTION

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/s/

ROBERT J MELLO
09/07/2010

JOHN W METCALFE
09/07/2010
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 201-444 **Applicant: Hope Pharmaceuticals** **Submit Date: 21 MAY 2010**

Drug Name: (b) (4) (sodium nitrite injection: sodium thiosulfate injection) **NDA Type: 505(b)(2)** **Received Date: 21 MAY 2010**

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?	Yes		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	Yes		Section 3.2.P for each product.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	Yes		Summary narratives and tabulated data tables were provided.
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?		No	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	Yes		Container closure studies were submitted. Products are not preserved.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	Yes		Section 3.2.P.5.1
7	Has the applicant submitted the results of analytical method verification studies?	Yes		Section 3.2.P.3.5
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	None requested by product quality microbiology
9	Is this NDA fileable? If not, then describe why.	Yes		**Submission is fileable**

Additional Comments: Eight Comments for the Applicant are attached (see the review which follows).

Robert J. Mello, Ph.D.
Reviewing Microbiologist Date

John W. Metcalfe, Ph.D.
Microbiology Secondary Reviewer Date

This is a 505(b)(2) NDA submission. The Reference Listed Drug is Sodium Thiosulfate Injection, USP (NDA 20-166), which was approved in conjunction with sodium nitrite injection, USP for the treatment of cyanide poisoning.
The drug product is a cyanide antidote kit consisting of co-packaged sodium nitrite injection, USP 30 mg/mL (300mg in 10 mL) and sodium thiosulfate injection, USP 250 mg/mL (12.5g in 50 mL).

The proposed specifications for bacterial endotoxins and microbial limits for the two drug substances meet the Agency's requirements for sodium thiosulfate and sodium nitrite.

Manufacturing of both of the drug products (sodium thiosulfate injection and sodium nitrite injection) will be performed at Cangene bioPharma, Inc. (formally known as Chesapeake Biological Labs, Inc.).

(b) (4)

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(b) (4)

Overall, **the submission is fileable**. The following microbiology product quality comments should be conveyed to the NDA Applicant:

1. The sodium thiosulfate release and stability specifications for bacterial endotoxins listed in Table 1 of Section 3.2.P.5.1 and Table 1 of Section 3.2.P.8.1 are NMT (b) (4) while all other references to this specification list it as NMT (b) (4) Please clarify the proposed bacterial endotoxin specification for sodium thiosulfate drug product and correct all parts of the submission that are in error.

2. Please provide the protocol used for the container closure integrity (b) (4) test for the sodium thiosulfate drug product. The sensitivity of the test method using both visual and the spectrophotometric methods of assessment should also be provided.

3. In support of the (b) (4) period for the formulated sodium thiosulfate drug product, please provide a copy of SOP 1351: Procedures for Performing a Hold Time Study. Also include a copy of the final report for the study.

4. The bacterial endotoxin specification units for the sodium nitrite drug product are listed both as EU/mg and EU/ml throughout the submission. Please clarify the proposed bacterial endotoxin specification for the sodium nitrite drug product and correct all parts of the submission that are in error.

5. Please provide the protocol used for the container closure integrity (b) (4) test for the sodium nitrite drug product. The sensitivity of the test method using both visual and the spectrophotometric methods of assessment should also be provided.

6. For both the sodium thiosulfate and sodium nitrite drug products, no data were presented to support the maximum (b) (4) hold time period (b) (4) to the

completion of (b) (4) sterilization of the batch. While it appears that the drug products may be (b) (4), no (b) (4) validation data were provided in the submission. Please provide (for each drug product) either a (b) (4) sterilization bioburden specification along with data to support the (b) (4) (b) (4) holding time (prior to (b) (4) sterilization), or state that the drug products are (b) (4) sterilization. If the latter is chosen, then you should supply the necessary validation studies to support (b) (4) of the drug product.

7. The individual bacterial endotoxin specifications for the two drug products appear to meet the threshold safety limit of (b) (4) However, the drug products are specifically designed to be co-administered to the patient within a one hour time period. As such, from an endotoxin perspective, the combined exposure to bacterial endotoxin, derived from the maximum dosing of both products must be considered when setting the individual drug product specification. The current combined specifications could result in the administration of a bacterial endotoxin dose that would be in excess of the threshold safety limit of (b) (4). Please submit revised specifications for bacterial endotoxin for the drug products such that they (together) do not exceed the (b) (4). In setting these limits, please consider maximum pediatric dosing. If the maximum pediatric dosing results in a lower specification than calculations for adult dosing then it should be used to set the drug product specification for bacterial endotoxin.

8. The current NDA submission contained 2 manufacturing floor plans for the manufacture of the drug products - (b) (4) The current NDA submission will be reviewed in light of the facility that was used to produce the process validation/stability batches of the drug products. (b) (4)

- END -

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/s/

ROBERT J MELLO
06/02/2010

JOHN W METCALFE
06/02/2010
I concur.