CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201444Orig1s000

OTHER REVIEW(S)

NDA 201444
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A non-clinical study to assess the levels of (b) (4) leachables (in (b) (4) from multiple batches of an agreed upon Agency-approved parenteral product(s) packaged in Type I USP (b) (4) (b) (4)

PMR/PMC Schedule Milestones:

Final Protocol Submission:	03/2011
Study/Trial Completion:	05/2011
Final Report Submission:	06/2011
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

The NITHIODOTE® is a cyanide antidote drug for which there are no approved comparable products. It is intended for a potentially life threatening exposure to cyanide. The sodium thiosulfate drug product contains a (b) (4) leachable material that has not been fully characterized or qualified. Although there is no safety signal known for this class of impurity when administered intravenously, no toxicology studies have been performed to establish a NOAEL. Literature references suggest that this class of impurity may be present in a wider pool of approved parenteral products, but exposure levels are unclear at this time. Based on a clinical risk: benefit analysis, complete characterization of the leachable(s) and definitive risk assessment can be completed post-marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor has identified [redacted] (b) (4) leachables in the drug products that appear to increase with time on storage. These [redacted] (b) (4) leachables may result in adverse effects following intravenous administration; however, the toxicological profile has not been adequately characterized in terms of risk. As there are data to suggest that other FDA approved intravenous phenytoin drug products may also contain these same leachables at comparable levels, based on a clinical risk:benefit assessment for this product, confirmation of the leachables in order to confirm the risk characterization is being required as a post-marketing study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Hope will provide the levels of [redacted] (b) (4) leachables from [redacted] (b) (4) testing (ideally from multiple batches) of an Agency-approved parenteral product(s) packaged in Type I USP [redacted] (b) (4)

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)

Additional analytical data to establish (b) (4) phenomenon and establish (b) (4) leachable levels in currently Agency-approved products

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: An extractable study that individually investigates the rubber stopper and Type I USP (b) (4) vial using both the drug product solutions (in independent experiments) as the extraction medium.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	03/2011
Study/Trial Completion:	05/2011
Final Report Submission:	06/2011
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

The NITHIODOTE® is a cyanide antidote drug for which there are no approved comparable products. It is intended for a potentially life threatening exposure to cyanide. The sodium thiosulfate drug product contains a (b) (4) leachable material that has not been characterized or qualified. Although there is no safety signal known for this class of impurity when administered intravenously, no toxicology studies have been performed to establish a NOAEL. Literature references suggest that this class of impurity may be present in a wider pool of approved parenteral products, but exposure levels are unclear at this time. Based on a clinical risk: benefit analysis, complete characterization of the extractables(s) from the container closure and definitive risk assessment can be completed post-marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor has identified (b) (4) leachables in the drug products that appear to increase with time on storage. These (b) (4) leachables may result in adverse effects following intravenous administration; however, the toxicological profile has not been adequately characterized in terms of risk. As there are data to suggest that FDA approved intravenous phenytoin drug products may also contain these same leachables at comparable levels, based on a clinical risk:benefit assessment for this product, confirmation of the identify of the extractable materials necessary to complete the risk characterization is being required as a post-marketing study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Hope will report the results of an extractable study that individually investigates the rubber stopper and Type I USP (b) (4) vial using both the drug product solutions (in independent experiments) as the extraction medium.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

An inadequate extractable study was submitted with the NDA at the time of approval. A new study is needed to support the hypothesis regarding the source, identity, and maximum possible exposure to the (b) (4) leachable compound.

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Evaluate alternative container closure systems and (b) (4) sterilization methods that might result in a more acceptable leachable profile.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	04/2012
	Study/Trial Completion:	07/2012
	Final Report Submission:	08/2012
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☒ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☒ Theoretical concern
   ☐ Other

The NITHIODOTE® is a cyanide antidote drug for which there are no approved comparable products. It is intended to treat a life-threatening condition. The sodium thiosulfate drug product contains a (b) (4) leachable material that has not been characterized or qualified. Based on a clinical risk: benefit analysis, complete characterization of the leachable(s) from the container closure and definitive risk assessment can be completed post-marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Hope will conduct pharmaceutical development studies to explore the possibility of using alternative container closure systems and (b) (4) sterilization methods that might result in a more acceptable leachable profile. Robust extractable studies and stability data (including leachables) are required to support the manufacturing and packaging changes. Inverted (worst case) storage configurations and stress conditions will be examined. Qualification or safety justifications will be required for leachables from these manufacturing changes.

a. Alternative container closure systems may include alternative rubber stoppers (e.g., (b) (4)), different glass vial sources, and polypropylene bottles.
b. Alternative methods (b) (4) will be investigated. Any manufacturing changes will be validated in context of the expected microbial load.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Amend the post-approval stability protocol to adequately monitor (b) (4) leachable material.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	02/2011
Study/Trial Completion:	
Final Report Submission:	
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☒ Theoretical concern
   ☐ Other

   Based on a clinical risk: benefit analysis, complete characterization of the leachable(s) from the container closure and definitive risk assessment can be completed post-marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Hope will amend the post-approval stability protocol to include leachable monitoring in the two drug products. The protocol will include monitoring at release, 3, and 6 months under accelerated stability conditions and monitoring at release, 6, 12, 24, 36, 48 and 60 months under real time storage conditions for the post-approval stability batches (at least the first three commercial batches).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial

☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
The original post-approval stability protocol was inadequate to monitor (b) (4) leachables. The amended post-approval stability protocol is necessary to fulfill post-approval stability testing of the first three NDA production batches, and annual stability batches.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

PARINDA JANI
01/13/2011

LARISSA LAPTEVA
01/13/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: January 10, 2011

To: Allison Meyer – Regulatory Project Manager
Division of Anesthesia, and Analgesia Products (DAAP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 201444 NITHIODOTE (sodium nitrite injection 300 mg and sodium thiosulfate injection 12.5 g) for intravenous infusion

DDMAC has reviewed the proposed revised product labeling (PI) for NITHIODOTE (sodium nitrite injection 300 mg and sodium thiosulfate injection 12.5 g) for intravenous infusion (Nithiodote), submitted for DDMAC review on December 23, 2010.

The following comments are provided using the updated draft PI sent via email on January 7, 2011, by Allison Meyer. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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/s/

MATHILDA K FIENKENG
01/10/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Oen Stephens and Xiaobin Shen, Reviewing Chemist, HFD-170
E-mail Address: olen.stephens@fda.hhs.gov, xiaobin.shen@fda.hhs.gov
Phone: (301)-796-3901; 796-1411
Fax: (301)-796-9747

FROM: FDA
Division of Pharmaceutical Analysis, HFD-920
James Allgire
Room 1002
1114 Market Street
St. Louis, MO 63101

Through: B. J. Westenberger, Deputy Director, HFD-920
Phone: (314)-539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA 201-444

Name of Product: (b) (4) (Sodium Nitrite 30 mg/mL and Sodium Thiosulfate 250 mg/mL) solutions for injection

Applicant: Hope Pharmaceuticals

Applicant's Contact Person: Craig Sherman, M.D. President

Address: 16416 N. 92nd Street; Scottsdale, AZ 85260

Telephone: 480-607-1970 Fax: FAX Number

Date NDA Received by DPA: 07/21/2010

Date Samples Received by DPA: 10/04/2010

Date Analytical Completed by DPA: 12/08/2010

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☐
2. Methods are acceptable with modifications (as stated in accompanying report). ☒
3. Methods are unacceptable for regulatory purposes. ☐

Comments:

The cover memo and summary of results are attached.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3897

Date: November 12, 2010

To: Olen Stephens, Ph.D. & Xiaobin Shen Ph.D., Reviewing Chemist, HFD-170

Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)

From: Wei Ye & Anna Wokovich, Chemist (HFD-920)

Subject: Method Validation for NDA 201-444
(b) (4) (Sodium Nitrite 30 mg/mL and Sodium Thiosulfate 250 mg/mL) solution for injection
Hope Pharmaceuticals Inc.

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

- Detection of (b) (4) Impurities in Sodium Nitrite Drug Product Samples Using (b) (4) Electrode (Method: (b) (4) Document Number: PHR-190.00, page 1-6)

The following methods were evaluated and will be acceptable for quality control and regulatory purposes with modifications.

- Determination of Sodium Nitrite Assay, and (b) (4) Impurity in Sodium Nitrite Drug Substance and Drug Product Samples by Ion Chromatography with Conductivity Detection (Method: Analytical Method of (b) (4))

- Higher Sensitivity Elements in Sodium Thiosulfate (Method: (b) (4)

- Lower Sensitivity Elements in Sodium Thiosulfate (Method: (b) (4)

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to these methods

- **Determination of Sodium Nitrite Assay, and (b) (4) Impurity in Sodium Nitrite Drug Substance and Drug Product Samples by Ion Chromatography with Conductivity Detection**

(b) (4)

2. In (b) (4) Data and Calculations on page 6, the formula of percent difference between duplicate preparations should have a subtract in the numerator (Drug Substance or drug production). It should be $\frac{|\text{Assay, Pre.1} - \text{Assay, Pre.2}|}{(\text{Assay, Pre.1} + \text{Assay, Pre.2})/2} \times 100$ Instead of $\frac{|\text{Assay, Pre.1} + \text{Assay, Pre.2}|}{(\text{Assay, Pre.1} + \text{Assay, Pre.2})/2} \times 100$

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/s/

JAMES F ALLGIRE
12/10/2010

BENJAMIN J WESTENBERGER
12/10/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: November 3, 2010

To: Allison Meyer – Regulatory Project Manager
Division of Anesthesia, and Analgesia Products (DAAP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 201444 NITHIODOTE (sodium nitrite injection 300 mg and sodium thiosulfate injection 12.5 g) for intravenous infusion

DDMAC has reviewed the proposed product labeling (PI), and Carton and Container labels for NITHIODOTE (sodium nitrite injection 300 mg and sodium thiosulfate injection 12.5 g) for intravenous infusion (Nithiodote), submitted for DDMAC review on July 15, 2010.

The following comments are provided using the updated draft PI sent via email on November 2, 2010 by Allison Meyer, and the carton and container labels submitted by the sponsor via EDR on September 17, 2010. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

Carton and Container Label

DDMAC has reviewed the carton and container labels and has no comment.

9 Page(s) of Draft Labeling have been Withheld in Full as vb4 (CCI/TS) immediately following this page

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

/s/

MATHILDA K FIENKENG
11/03/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 201444 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Sodium Nitrite Injection and Sodium Thiosulfate Injection Dosage Form: Injection Strengths: 30 mg/mL and 250 mg/mL		
Applicant: Hope Pharmaceuticals Agent for Applicant (if applicable): N/A		
Date of Application: May 21, 2010 Date of Receipt: May 21, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: November 21, 2010	Action Goal Date (if different): November 19, 2010	
Filing Date: July 19, 2010	Date of Filing Meeting: June 16, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) **1 copackaged drug**		
Proposed indication(s)/Proposed change(s): treatment of [redacted] (b) (4) cyanide poisoning		

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☒ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):				
List referenced IND Number(s): 78597				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	XX			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	XX			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	XX			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		XX		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	XX			Orphan designation

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		XX		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		XX		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		XX		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		XX		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***	xx			
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***		xx		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		XX		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		XX		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			XX	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	XX			
Index: Does the submission contain an accurate comprehensive index?	XX			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	XX			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:* **March 18, 2010**		**XX**		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	XX			
Are all establishments and their registration numbers listed on the form/attached to the form?	XX			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?		XX		Patent Certification was submitted
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	XX			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	XX			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	XX			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			XX	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		XX		A full waiver is requested due to orphan designation.
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			xx	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	XX			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	XX			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		XX		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	XX			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	XX			
Is the PI submitted in PLR format?	XX			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			XX	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	XX			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			XX	
REMS consulted to OSE/DRISK?			XX	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	XX			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***				

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		XX		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** August 24, 2007 ***If yes, distribute minutes before filing meeting***	XX			As a PIND, no IND was opened.
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		XX		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 16, 2010

BLA/NDA/Supp #: 201444

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: Sodium Nitrite Injection, USP and Sodium Thiosulfate Injection, USP

DOSAGE FORM/STRENGTH: Injection 30 mg/mL and 250 mg/mL

APPLICANT: Hope Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of (b) (4) cyanide poisoning

BACKGROUND: This is a 505(b)(2) application for a product that is currently marketed by Keystone, but is unapproved. This is a priority review.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Allison Meyer	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Rigo Roca		Y
Clinical	Reviewer:	Art Simone	Y
	TL:	N/A	
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	

Clinical Pharmacology	Reviewer:	David Lee	Y
	TL:	Suresh Doddapaneni	N
Biostatistics	Reviewer:	Kate Meaker	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Marcus Delatte	Y
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Xiaoben Shen and Olen Stephens	Y
	TL:	Danae Christodoulou	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Bob Mello	Y
	TL:	N/A	
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	TBD	N
	TL:	TBD	N
OSE/DMEPA (Carton & Container)	Reviewer:	Denise Baugh	N
	TL:	Carol Holquist	N
OSE/DRISK (REMS)	Reviewer:	N/A	N
	TL:	N/A	N
Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:	N/A	

Other reviewers	Angelica Dorantes, Biopharm Marty Pollock	N Y
Other attendees	Brad Leissa Sally Loewke Alice Shapiro Matt Sullivan Sue Yang	Y Y Y Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No Clinical Studies, only bioequivalence studies. Clinical Pharmacology will consult DSI for BioPharm inspections.	☐ YES ☒ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Will not request inspections from DSI	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: nitrate specifications needed and extractable/leachable info needed for chlorobutyl stoppers	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments: need additional stability data, LOAs, stopper clarification, leachable information on drug product, CoAs, batch numbers, analytical method info, and manufacturing process information	☒ Review issues for 74-day letter

Environmental Assessment	☐ Not Applicable
• Categorical exclusion for environmental assessment (EA) requested?	☒ YES ☐ NO
If no, was a complete EA submitted?	☐ YES ☐ NO
If EA submitted, consulted to EA officer (OPS)?	☐ YES ☐ NO
Comments:	
Quality Microbiology (for sterile products)	☐ Not Applicable
• Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☒ YES ☐ NO
Comments: comments in 74-day letter	
Facility Inspection	☐ Not Applicable
• Establishment(s) ready for inspection?	☒ YES ☐ NO
▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?	☒ YES ☐ NO
Comments:	
Facility/Microbiology Review (BLAs only)	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only)	☒ Not Applicable
Comments:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Curt Rosebraugh **21st Century Review Milestones** (optional): Mid-Cycle = August 3, 2010 Wrap-Up = October 5, 2010 Labeling Comments and PMRs due to Sponsor October 8, 2010 Action Goal Date = November 19, 2010 PDUFA Date = November 21, 2010	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): CMC and Nonclinical Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74 – To be sent by July 19, 2010
☒	Other – Request Dosing device samples from the Sponsor to go to CMC, DMEPA, and Clinical disciplines.

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

ALLISON MEYER
10/19/2010

PARINDA JANI
10/19/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	September 1, 2010
To:	Bob Rappaport, MD, Director Division of Anesthesia and Analgesia Products (DAAP)
Through:	Todd Bridges, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Denise V. Baugh, PharmD, BCPS Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name:	(b) (4) 1 vial of Sodium Nitrite Injection, USP, 300 mg/10 mL (30 mg/mL) 1 vial of Sodium Thiosulfate Injection, USP, 12.5 grams/50 mL (250 mg/mL)
Application Type/Number:	NDA 201444
Applicant:	Hope Pharmaceuticals
OSE RCM #:	2010-1361

1 INTRODUCTION

This review responds to a request from the Division of Anesthesia and Analgesia Products (DAAP) for DMEPA's assessment of labels and labeling (b) (4) for their vulnerability to medication errors.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis[1] (FMEA), the Division of Medication Error Prevention and Analysis (DMEPA) evaluates container labels, carton and insert labeling. This review focuses on the label and labeling submitted by the Applicant on August 19, 2010 (see Appendices A and B; no image of insert labeling). Additionally, the Applicant submitted an actual carton for our review on the same date.

3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be clarified and improved upon to minimize the potential for medication errors. Section 3.1 *(Comments to the Division)* contains our recommendations for the insert labeling. Section 3.2 (*Comments to the Applicant)* contains our recommendations for the container label and carton labeling. We request these recommendations be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cherye Milburn, OSE Regulatory Project Manager, at 301-796-2084.

3.1 COMMENTS TO THE DIVISION

Insert Labeling

A. Revise the presentation of the established name appearing under the Highlights of Prescribing Information heading (b) (4) to "(sodium nitrite injection, USP and sodium thiosulfate injection, USP)".

B. The instructions in the Dosage and Administration section of the Highlights of Prescribing Information and the Full Prescribing Information preclude rapid understanding of how to prepare (b) (4) DMEPA recommends the Applicant develop a quick reference guide for emergency personnel to use in the event that they have not familiarized themselves with the preparation of this drug product. This reference guide should include dosing information for the pediatric population. As cyanide poisoning is rapidly fatal, the development of such a reference may save lives.

C. Remove references to percentages (b) (4) in the Dosage and Administration section of Highlights and Full Prescribing Information. Their presence may confuse the reader and they are unnecessary in the administration of this product.

[1] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

D. In the Dosage and Administration section of the Highlights of Prescribing Information and the Full Prescribing Information, revise the sentence [redacted] to read "If signs of poisoning reappear, repeat treatment using one-half the original dose of both sodium nitrite and sodium thiosulfate."

E. To improve readability of the Dosage Forms and Strengths section of Highlights and Full Prescribing Information, separate the two active ingredients from each other by bulleting each product. For example,

[redacted] consists of:

- One vial of sodium nitrite injection, USP, (300 mg/10 mL) 30 mg/mL and
- One vial of sodium thiosulfate injection, USP, (12.5 grams/50 mL) 250 mg/mL

F. In the last paragraph of the Indications and Usage section in Full Prescribing Information, revise the abbreviation, "≥", to read "greater than or equal to". The greater than or equal to symbol is considered an error-prone abbreviation. As part of a national campaign to warn healthcare practitioners and consumers not to use error-prone abbreviations, acronyms, dose designations, or symbols, including trailing zeroes, FDA agreed not to use such error prone designations in their approved product labeling.

G. The WARNINGS AND PRECAUTIONS section of Full Prescribing Information contains the statements [redacted] However, the Dosage and Administration sections do not contain instructions to administer sodium thiosulfate over several minutes. We request you add explicit directions for the rate of administration for sodium thiosulfate (e.g., administer over X minutes).

H. In Section 5.4 of the Full Prescribing Information, revise the statement "1-2 mg/kg" to read "1 mg/kg to 2 mg/kg" to minimize the potential for misinterpretation of this information.

3.2 COMMENTS TO THE APPLICANT

3.2.1 General Comments

A. The product strengths for sodium nitrite and sodium thiosulfate do not follow the current recommendations of USP injections General Chapter <1> which states: "For single-dose and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses." Revise so that the total drug content is prominently presented (bolded) and followed by the concentration per mL (which should be in a smaller font size). For example,

Sodium Nitrite Injection, USP	Sodium Thiosulfate Injection, USP
300 mg/10 mL	**(12.5 grams/50 mL)**
(30 mg/mL)	250 mg/mL

B. The expression of the units of measurement for Sodium Thiosulfate as 'g' may be misinterpreted. Anywhere this statement of strength is expressed, revise to 'grams' (e.g., 12.5 grams) for clarity.

3.2.2 Carton Labeling

A. The storage statement and statement to inspect parenteral drug products are repeated multiple times. Revise so that these statements appear only once on the side panel to minimize the cluttered appearance.

B. Relocate the statement 'Any unused portion of a vial should be discarded' to immediately follow the statement 'Single Use Only'.

3.2.3 Container Labels (Sodium Nitrite and Sodium Thiosulfate)

A. (b) (4) Revise the color scheme of the container labels so that each container label is distinctively different from the other. Additionally, the color scheme for the vial labels should be different from the color scheme utilized for the carton labeling.

B. Relocate the statement (b) (4) away from the net quantity 'XX mL' and revise to read 'Single Use Only. Discard Unused Portion'.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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

/s/

TODD D BRIDGES on behalf of DENISE V BAUGH
09/01/2010

CAROL A HOLQUIST
09/01/2010