CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201444Orig1s000

CHEMISTRY REVIEW(S)

NDA/ANDA 201-444

Nithiodote (Sodium Nitrite 30 mg/mL and Sodium Thiosulfate 250 mg/mL) solutions for injection

Hope Pharmaceuticals

Olen M. Stephens, Ph.D. and
Xiaobin Shen, Ph.D.
Pre-Marketing Division III for the

Division of Analgesia and Anesthetic Products

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Chemistry Review Data Sheet

1. NDA 201-444

2. REVIEW #: 3

3. REVIEW DATE: 10-Jan-2011

4. REVIEWERS: Olen Stephens and Xiaobin Shen

PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Review #1	27-Sep-2010
CMC Review #2	3-Nov-2010

SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment 0023	6-Dec-2010
Amendment 0024 Complete Response	22-Dec-2010

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Nithiodote
b) Non-Proprietary Name (USAN): Sodium Nitrite; Sodium Thiosulfate

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Sodium nitrite and sodium thiosulfate are indicated for sequential use for treatment of acute cyanide poisoning that is judged to be life-threatening.

- Use with caution if the diagnosis of cyanide poisoning is uncertain.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 300 mg (30 mg/mL; Sodium Nitrite) and 12.5 g (250 mg/mL; Sodium Thiosulfate)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

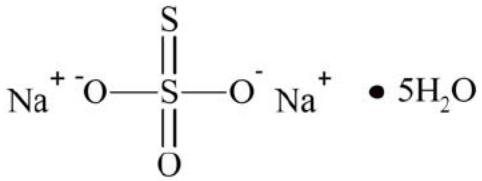
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

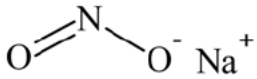
Sodium Thiosulfate

Chemical name: Sodium thiosulfate pentahydrate
United States Adopted Name (USAN): Sodium thiosulfate
Compendial name: Sodium thiosulfate pentahydrate, United States Pharmacopeia (USP)
Chemical structure:



Molecular formula: $Na_2O_3S_2 \cdot 5H_2O$
Molecular weight: 248.19 g/mol
Sodium thiosulfate anhydrous has a molecular formula of $Na_2O_3S_2$ and has a molecular weight of 158.11 g/mol.

Sodium Nitrite
Chemical name, USAN, and Compendial Name: Sodium Nitrite
Chemical structure:



Molecular formula: $NaNO_2$
Molecular weight: 69.0 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		3*	Adequate	14-Oct-2008	Reviewed by Dr. Donald Klein
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	V			7			Reviewed by Microbiologist Dr. Robert Mello
	III			7	Adequate	NA	USP Type 1 glass meets safety requirement per MAPP 5015.5

* The stopper used in this NDA is (b) (4). The base material (b) (4) information has been reviewed previously and deemed adequate to support various injection products. The most recent review was performed by Dr. Donald Klein on 14-Oct-2008. The stopper (b) (4) used in this NDA (on the non-drug contacting side of the stopper) has been previously reviewed by Dr. Mark Sassaman on 12-Apr-2007 and deemed adequate. The DMF was reorganized and resubmitted on 08-May-2009 with information related to other (b) (4) materials.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-166	Sodium Thiosulfate Reference Drug

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	21-Sep-2010	OC
Pharm/Tox	Approval	10-Jan-11	Dr. Marcus Delatte
Microbiology	Adequate	07-Sep-2010	Dr. Robert Mello
Biopharm	Adequate	21-May-2010	Dr. John Duan

The Chemistry Review for NDA 201-444

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, NDA 201-444 is recommended for approval.

Product quality concerns remain regarding [redacted] (b) (4) leachable(s); however, in the judgment of the clinical division, this CMC deficiency should not prevent the approval of this NDA on the basis of safety or efficacy deficiencies. Because this product is administered in life-threatening situations, the unknown risk of [redacted] (b) (4) leachable(s) is mitigated by the potential benefit of this antidote. Furthermore, the nonclinical review team is unaware of any safety signal associated with this class of impurity when administered intravenously. Without a clearly defined safety concern, product quality concerns were not sufficient to recommend a complete response by the clinical division. However, formal formal toxicology studies have not been performed to identify safety signals that may exist associated with [redacted] (b) (4) leachables, so the CMC deficiencies will be addressed through post-marketing requirements (see below) to further characterize the root cause of the leachables, its anticipated concentration, its rate of increase on storage, and potential strategies to minimize its concentration in the drug product solutions.

Notes:

1. The labeling comments are being routed through the project manager as part of the team review that involves DMEPA and DRISK.

[redacted] (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Requirements, Commitments, Agreements, and/or Risk Management Steps, if Approvable

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

2. 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.
3. 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 of (b) (4) sterilization (b) (4) may be investigated. Any manufacturing changes will be validated in context of the expected microbial load.
4. 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).

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

NDA 201-444 is submitted as a 505(b)(2), based on the approved NDA 20-166, Sodium Thiosulfate Injection. NITHIODOTE® contains sodium nitrite and sodium thiosulfate solutions for injection that are indicated for the treatment of acute cyanide poisoning that is judged to be life-threatening. The review was granted a priority review due to the lack of approved products with this formulation. The referenced product was developed by the Army, and approved in 1992 to be used in combination with sodium nitrite injection as a cyanide antidote, but is currently discontinued. Hope Pharmaceuticals received a waiver of *in vivo* bioequivalence studies for the sodium thiosulfate. The sodium thiosulfate (12.5 g/50 mL) and sodium nitrite (300 mg/10 mL) injection solutions, are co-packaged as the cyanide antidote in two single dose vials as sterile solutions.

The sodium nitrite drug substance is manufactured under cGMP from a food grade sodium nitrite source that complies with Food Chemicals Codex (FCC). (b) (4) Sufficient stability data is provided to grant a (b) (4) month retest date for the sodium nitrite drug substance.

Sodium thiosulfate drug substance is prepared (b) (4) Both starting materials are commercially available. Specifications for the starting materials, reagents, and in-process control are adequate. Only 6 months of stability data are available at both long term (25°C/60% RH) and accelerated conditions (40°C/75% RH). The provided results conformed to specifications except that the (b) (4) of batch 09/113

exceeded the limit of (b) (4) at (b) (4) at month 6 under accelerated conditions. An investigation was conducted and no assignable cause was identified. A retest period of (b) months is granted. Photostability, thermal stability, and open dish stability studies were conducted on both drug substances; no meaningful changes were noted.

The sodium nitrite and sodium thiosulfate drug products are formulated as solutions (b) (4) The sodium nitrite drug product is a simple solution (b) (4) the sodium thiosulfate drug product (b) (4) (b) (4) Both drug products are packaged in USP Type 1 (b) (4) glass vials and stoppered with (b) (4) stoppers and a (b) (4) aluminum overseal. Both vials are co-packaged in a (b) (4) box, the secondary container. Release and stability testing include testing for bacterial endotoxins, sterility, and container integrity testing. Photostability, thermostability, oxygen stress, and temperature cycling studies showed both drug products were insensitive to these stability stressors. Sufficient stability data is provided to allow a 12 month shelf life for both drug products. (b) (4)

A (b) (4) leachable material was observed for both drug products, where the sodium thiosulfate drug product is the main contributor. A worst case estimate based on linear extrapolation of two leachable data points would result in (b) (4) exposure from the sodium thiosulfate component and an additional (b) (4) exposure from the sodium nitrite drug product. This leachable impurity appears to arise as the result of the alkaline drug product solution hydrolyzing the Type I USP (b) (4) glass vial; (b) (4) (b) (4) (b) (4). The clinical and nonclinical review teams have no knowledge of a safety signal, but also cannot determine a safety margin for this class of impurity when administered intravenously. Post-marketing requirements are suggested above in an attempt to improve the product quality and assuage potential safety issues that have yet to be identified or quantified.

Proposed Mode of Action: Sodium nitrite reacts with hemoglobin to form methemoglobin, which has a higher affinity for cyanide than cytochrome oxidase. Methemoglobin and cyanide form cyanmethemoglobin, keeping cyanide away from cytochrome oxidase and thus regenerating this enzyme's function. The resulting cyanmethemoglobin, in the presence of sulfurtransferase enzyme, catalyzes the attachment of sulfate to cyanide to form thiocyanate, which has relatively low toxicity and is eventually eliminated in the urine. The molecule of methemoglobin that is released is available to bind to another molecule of cyanide or it is reduced back to hemoglobin.

(b) (4) odium thiosulfate is used in conjunction with sodium nitrite to serve as a source of sulfate. The combined mechanism may be expressed in a chemical manner:

$$NaNO_2 + \text{hemoglobin} = \text{methemoglobin}$$

$$HCN + methemoglobin = cyanmethemoglobin$$
$$Na_2S_2O_3 + CN = SCN + Na_2SO_3$$

B. Description of How the Drug Product is Intended to be Used

The proposed dosing regimen, below, is identical to the referenced discontinued product. Sodium nitrite is administered first followed immediately by sodium thiosulfate. The same needle and vein may be used to administer both solutions.

Adults:

Sodium Nitrite: 10 mL of a 3% solution (300 mg) of sodium nitrite at the rate of 2.5 to 5 mL/minute.

Sodium Thiosulfate: 12.5 g (50 mL of a 25% solution) immediately following administration of sodium nitrite.

Redosing: If a patient does not respond to initial doses, treatment may be repeated with one-half the original dose of sodium nitrite followed by one-half the original dose of sodium thiosulfate

Children:

Sodium Nitrite: 0.2 mL/kg of a 3% solution (6 mg/kg or 6-8 mL/m^2 BSA) of sodium nitrite at the rate of 2.5 to 5 mL/minute not to exceed 10 mL (300 mg)

Sodium Thiosulfate: 1 mL/kg of body weight using a 25% solution (250 mg/kg or approximately 30-40 mL/m2 of BSA) not to exceed 50 mL (12.5 g) total dose.

Storage and Expiry:

NITHIODOTE® should be stored between 20°C and 25°C (68°F - 77°F); excursions permitted to 15 - 30°C (59°F - 86°F). Protect from direct light and keep the vials in their secondary container. Do not permit the drug products to freeze. NITHIODOTE® is limited to the expiry of either component with a maximum expiry of 12 months at this time.

C. Basis for Approvability or Not-Approval Recommendation

Chemistry, Manufacturing and Controls deficiencies for the drug substance and drug product were communicated and have been adequately addressed throughout the review cycle with the exception of the (b) (4) leachable material. The clinical review team has determined that the medical necessity of this product outweighs product quality concerns for the (b) (4) leachable(s). The nonclinical review team is unable to identify any safety signal associated with (b) (4) leachables administered intravenously; though, no toxicology studies have been performed to establish a safety threshold.

The facilities used in the manufacture and control of the drug substance and drug product have been submitted for evaluation to the Office of Compliance and received an overall acceptable cGMP recommendation.

The CMC recommendation for NDA 201-444 is for approval in light of the clinical determination of medical necessity. Without nonclinical concerns that warrant a complete response, CMC will address leachable concerns as a product quality issue in a post approval setting. Stability data and leachable data (via post-marketing requirements) should be regularly submitted as amendments to this NDA as it is available and will be reviewed for shelf life extension as appropriate.

III. Administrative

A. Reviewer's Signature
Olen Stephens (Sodium Nitrite)
Xiaobin Shen (Sodium Thiosulfate)

B. Endorsement Block

Chemist Name: Olen M. Stephens and Xiaobin Shen
Chemistry Branch Chief: Prasad Peri

C. CC Block

CMC Lead: Danae Christodoulou
Project Managers: Allison Meyer and Swati Patwardhan

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/s/

OLEN M STEPHENS

01/10/2011

CMC recommendation for approval;
PMR's and PMC's recommended

XIAOBIN SHEN

01/11/2011

PRASAD PERI

01/11/2011

I concur

Nithiodote® (Sodium Nitrite 300 mg and Sodium Thiosulfate 12.5 g) Solutions for Injection

NDA 201-444

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Hope Pharmaceuticals
16416 N. 92nd Street #125, Scottsdale, AZ 85260

Indication: Sodium nitrite and sodium thiosulfate are indicated for sequential use for treatment of acute cyanide poisoning that is judged to be life-threatening. Dosage and administration is shown in the table below.

Age	Intravenous Dose of Sodium Nitrite and Sodium Thiosulfate
Adults	**1.) Sodium Nitrite -**10 mL of a 3% solution (300 mg) of sodium nitrite at the rate of 2.5 to 5 mL/minute **2.) Sodium Thiosulfate -** 50 mL of a 25% solution (12.5 gram) of sodium thiosulfate immediately following administration of sodium nitrite.
Children	**1.) Sodium Nitrite -** 0.2 mL/kg of a 3% solution (6 mg/kg or 6-8 mL/m^2 BSA) of sodium nitrite at the rate of 2.5 to 5 mL/minute not to exceed 10 mL (300 mg) **2.) Sodium Thiosulfate -** 1 mL/kg of body weight using a 25% solution (250 mg/kg or approximately 30-40 mL/m^2 of BSA) not to exceed 50 mL (12.5 g) total dose.

Presentations: NITHIODOTE® consists of one 10 mL vial of sodium nitrite injection 30 mg/mL (300 mg sodium nitrite), and one 50 mL vial of sodium thiosulfate injection 250 mg/mL (12.5 grams of sodium thiosulfate).

EER Status: Acceptable as of 21-Sept-2010

Consults: **EA** – Granted
Methods Validation – Revalidation by Agency will not be requested since the methods listed are standard.
Pharmacology/Toxicology – Not acceptable. (See review dated 11/4/10)
Biopharmaceutics – Acceptable. (See review dated 9/7/10)
Quality Microbiology – Acceptable. (See review dated 7/8/10)

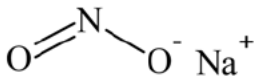
Original Submission: 27-May-2010

The review was granted a priority review due to the lack of approved products with this formulation and its importance in the national anti-terrorism stockpile of antidote kits. The referenced product was developed by the Army, and approved in 1992 to be used in combination with sodium nitrite injection as a cyanide antidote, but is currently discontinued. There are other unapproved marketed products in the stockpile.

Post-Approval CMC Commitments:

Drug Substance: Sodium nitrite is a white to off-white solid that is hygroscopic. It is soluble in water and slightly soluble in ethanol with a melting range of 281.1-281.3°C. Sodium nitrite is manufactured under cGMP from a food grade sodium nitrite source that complies with Food Chemicals Codex (FCC).

Chemical structure:



Molecular formula: $NaNO_2$
Molecular weight: 69.0 g/mol

(b) (4)

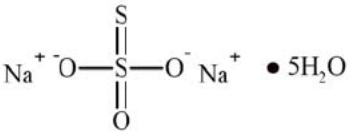
The drug substance is manufactured by (b) (4) This site and all testing sites have an acceptable EES recommendation from the office of compliance.

The drug substance specifications has acceptable controls for Appearance, ID, Loss on Drying, Heavy metals, Assay, pH of a (b) (4) Bacterial Endotoxins, and Microbial Limits.

Sodium nitrite drug substance is packaged in a (b) (4) high density polyethylene (HDPE (b) (4) Sufficient stability data are provided to grant a ( ) month retest date.

Drug Substance: Sodium thiosulfate is a colorless and odorless crystal. (b) (4)

Chemical structure:



Molecular formula: $Na_2S_2O_3 \bullet 5H_2O$
Molecular weight: 248.19 g/mol

Sodium thiosulfate is manufactured (b) (4)

(b) (4)

The drug substance is manufactured by (b) (4) This site and all testing sites have an acceptable EES recommendation from the office of compliance.

The drug substance specifications has acceptable controls for Appearance, ID, Assay, Loss on Drying, Heavy metals, Odor, pH of a 10% solution, Appearance of 10% solution, (b) (4) Bacterial Endotoxins, and Microbial Limits.

Sodium thiosulfate is packaged in a (b) (4), high density polyethylene (HDPE) (b) (4) Sufficient stability data are provided to grant a (b) (4) month retest date.

Conclusion: The drug substances are satisfactory.

Drug Product:
The sodium nitrite and sodium thiosulfate drug products are formulated as solution (b) (4) The sodium nitrite drug product is a simple solution (b) (4) the sodium thiosulfate drug product is (b) (4) Both drug products are packaged in USP Type 1 (b) (4) glass vials and stoppered with (b) (4) stoppers and a (b) (4) aluminum overseal. Both vials are co-packaged in a (b) (4) box, the secondary container.

Cangene bioPharma, Inc. Baltimore, MD is the drug product manufacturer. (b) (4) is the drug product packager; (b) (4) are the drug product testing sites. All sites have an acceptable EES status as per Office of Compliance.

Specifications for the Sodium Nitrite Injection include testing for Appearance, ID, pH, Assay, Related Substances, Sterility, Particulate Matter, Bacterial endotoxins, Net contents, and Container Closure Integrity. The NDA registration lot scale was (b) (4) and the commercial lot scale is (b) (4)

Specifications for the Sodium thiosulfate Injection include testing for Appearance, ID, pH, Assay, Related Substances, Sterility, Particulate Matter, Bacterial endotoxins. The NDA registration lot scale was (b) (4) and the commercial lot scale is (b) (4)

A very limited stability data (3 months long term and accelerated) was provided for both drug products in the original NDA. Photostability, thermostability, oxygen stress, and temperature cycling studies showed both drug products were insensitive to these stability stressors except for **leachables in the drug product.** An updated stability results under accelerated conditions at the 6 month time point was recently reported which showed increased levels of leachables

containing (b) (4). Preliminary indications seem to allude that these leachables are from the container closure system (glass vial and rubber stopper) of the drug product. This is very likely since the pH of the formulations are in the 7-9.5 range and the glass vials are (b) (4) which has the potential for leaching (b) (4) from the glass.

Since the applicant has not conclusively identified the source and identity of the (b) (4) (b) (4) leachables; as a result a safety evaluation of the leachables in the drug products cannot be completed at this time. It is also not clear if the levels of (b) (4) leachables have attained an asymptote so that the levels observed can be assessed for safety. Pending this critical safety evaluation, ONDQA cannot recommend approval of the application.

(b) (4)

Conclusion: The drug product is NOT acceptable.

Additional Items:
Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

Overall Conclusion:
From a CMC perspective, the application is recommended for **a complete response. The following items must be addressed prior to approval of the drug product.**

1. **Establish the identity and source of (b) (4) impurity. Your attempts may include the methods used in your primary literature searches.**
2. **Explore new container closure systems that may have a smaller leachable profile. The new container closure system might include, but should not be limited to evaluation of the rubber stoppers (b) (4)), the glass vials, and polypropylene bottles.**
3. **Submit a robust extractable study performed using the drug product solutions to extract all components of the container closure system.**
4. **Submit six months of stability data (including leachables) using the new container closure system which includes results from testing at release, 3 months, and 6 months under real time storage and testing at release, 1 month, 3 months, and 6 months under accelerated stability conditions. Both conditions should include upright and inverted storage configurations.**

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/s/

PRASAD PERI
11/04/2010
Complete Response

CMC Memo to File

Date	1 Nov 2010
IND#	201-444 Amendments 0020 & 0021 Review and Final Recommendation
Sponsor:	Hope Pharmaceuticals
Drug:	Nithiodote (sodium thiosulfate injection (30 mg/mL), sodium nitrite injection (250 mg/mL))
Reviewer	Dr. Olen Stephens and Dr. Xiaobin Shen

Introduction:

Please refer to CMC Review #1, submitted 27-Sep-2010. In that first review, NDA 201-444 was recommended for approval pending review of non-clinical deficiencies for leachables substances from drug product container closure system, the proposed (b) (4) specifications for sodium nitrite, and the (b) (4) specification for sodium thiosulfate. During the review team wrap-up meeting 5-Oct-2010, the non-clinical team reported that the only remaining potential approvability issue regarded the (b) (4) leachable substance from the drug product container closure system.

Amendment 0009 provided a 4-month leachables stability update from drug product stored at 40°C/75% RH in the inverted orientation. The report identified three leachates with exposures more than (b) (4) from the sodium thiosulfate drug product (b) (4) was the only leachate above (b) (4) identified from the sodium nitrite drug product): (b) (4). The amount of (b) (4) impurity was later revised (see below) because of a more reliable analytical method.

At the time of the wrap-up meeting, no further information was available regarding the accuracy of the (b) (4) concentration, the methods employed for the leachables study, the quantitative amount of (b) (4) compound leaching from the sodium nitrite drug product, the identity of the leachate or the origin of the (b) (4) leachate. A telephone conference call was placed with the applicant to voice these concerns – Dr. Xiaobin Shen, Dr. Eric Duffy, Dr. Olen Stephens, Dr. Dan Mellon, Dr. Marcus DeLatte, Dr. Rigo Roca, and Allison Meyers (PM) were in attendance.

A list of review concerns were emailed to Hope Pharmaceuticals, to which a formal reply was received 15-Oct-2010 in Amendment 0020 (refer to the appendix for a fuller summary and review of the amendment). The primary review issue was the amount of (b) (4) leachate found in the sodium thiosulfate drug product, its

identity, the rate of leaching, the maximum exposure to this leachate, and the origin of this leachate.

Clarification regarding quantity of [redacted] *impurity:*

In amendment 0020 (15-Oct-2010), Hope clarifies that the leachable [redacted] was detected by ICP-OES, which is challenged by high salt solutions like the two drug products. Because the leachable [redacted] material out of the sodium nitrite drug product was below the level of detection [redacted], Hope reported a worst-case scenario of [redacted] exposure. Hope has since changed methods used to detect the [redacted] leachate to ICP-MS, which has a [redacted]. The change in analytical method is reasonable given the limitations of the ICP-OES method. Revised estimates of the [redacted] leachate were reported as follows:

- Duplicate 6-month inverted storage at 40°C sodium nitrite drug product samples assayed with the ICP-MS method yielded [redacted] leachable material. Samples from the 4-month leachables study were re-analyzed with the ICP-MS method and [redacted] A worst-case estimate of [redacted] exposure from the sodium nitrite drug product would be [redacted] at the highest drug product dose of 15 mL (1.5 vials of sodium nitrite drug product.)

- The concentration of [redacted] leachate from the sodium thiosulfate drug product remains a review issue from a non-clinical perspective. When 4-month and 6-month leachable samples are analyzed by the ICP-MS method concentrations [redacted] respectively, were observed. [redacted] concentration translates into [redacted] exposure (on a per molar basis of the [redacted]) of the [redacted]d leachate from the maximum prescribed dose of sodium thiosulfate.

Clarification of the <u>identity</u> of the [redacted] *impurity:*

Hope was asked to conclusively determine the source of the [redacted] impurity, provide reasonable evidence that establishes its identity and to provide more extractable data from the rubber stopper (20-Oct-2010). This information is particularly important for the non-clinical reviewer because the identity of the impurity factors heavily into the risk posed by the leachate. The [redacted] signal in the ICP methods is not sufficient to determine identity of the leachate, so reasonable evidence for identity will have to be established through other means.

Hope identified three possible sources for the [redacted] leachate (Amendment 0021; 22-Oct-2010): [redacted] that is applied to the *non-drug product contacting* surface of the rubber stopper, the glass vial that is made from Type 1 USP [redacted], and the drug product manufacturing process including the components of the drug product. Even though [redacted] is applied to the non-drug product side of the stoppers, [redacted] is a plausible source of [redacted] from a review perspective because it had not been conclusively ruled out as a source of [redacted] In

reference to the glass vials, Hope has provided primary literature references (Amendment 0021) that support the possibility that [redacted] leaches from the [redacted] Type I glass. Using a similar set of reasoning, because the manufacturing process uses [redacted], the same mechanism for [redacted] leaching from the glass vials may apply to the equipment used in the drug substance/product manufacturing processes.

In Amendment 0021, Hope outlines a reasonable argument to claim that the primary source of the [redacted] impurity is not the [redacted] from the rubber stopper. An evolved gas analysis/mass spectrometry (EGA-MS) method was chosen in an attempt to directly detect [redacted] The method is claimed to be non-quantitative, but Hope claims an LOD of 30 ppb and a [redacted] recovery of spiked samples (no further information was provided regarding the method.) When 4- and 6-month sodium nitrite and sodium thiosulfate samples were analyzed, only the 4-month sodium nitrite sample yielded a positive result [redacted] Hope now asserts that the [redacted] impurity is primarily not [redacted] From a review perspective, the new evidence supports the claim that the primary source of [redacted] leachates is not [redacted], which further implicates leaching from the other potential sources. However, because no details were provided regarding this EGA-MS method, the possibility remains that [redacted] is a minor contributor to the total [redacted] leachate.

[redacted] *leached from the glass vial:*

Hope has performed a literature search to identify other sources of [redacted] leachable material. [redacted]

Mass balance of [redacted] *leachate:*

Hope provided estimates for the amount of [redacted] that would arise from the sodium thiosulfate drug substance, the sodium thiosulfate drug product excipients, the rubber stopper, and glass vial. The sodium thiosulfate drug substance contained [redacted] impurity for three separate batches. Hope ascribes this [redacted] to the glass-lined reactors and possibly the [redacted] used in the manufacturing process. Estimates for the sodium thiosulfate excipients ranged from

(b) (4) from the sodium hydroxide to (b) (4) from the boric acid. However, the largest contributor is the glass vial, which Hope estimates to yield (b) (4) in the form of soluble (b) (4) This estimate for the glass vial is based on the primary literature references provided in amendment 0021. The total estimate summed (b) (4) leachate/50 mL vial of drug product, this is (b) (4) of that amount detected by ICP-MS in leachable studies. Therefore, Hope concludes that the remaining (b) (4) leachate must be leaching on storage. Other than the (b) (4) originating from the glass vial, the identity of the remaining (b) (4) leachate is undetermined.

Conclusions and CMC Recommendation:

> *Hope has provided evidence that suggests the identity of the (b) (4) (b) (4) leachate is (b) (4) in nature, arising from glass lining used in the drug substance/product manufacturing process and the glass vial container closure. Furthermore, the applicant presented a reasonable mass balance of the (b) (4) impurities that accounts for (b) (4) of the total leachate. However, Hope still has not conclusively provided adequate evidence or logical argument to account for (b) (4) of the mass balance of the (b) (4) leachate, its source, or its identity. The rate at which this impurity leaches and its maximum total concentration is unknown because inadequate extractable studies were performed on the container closure system. These CMC deficiencies are approvability issues that must be addressed in order to assure the quality of the product and to allow the non-clinical reviewers to perform a risk assessment for the identified impurities.*

Because the (b) (4) leachate has an undetermined source, has not been adequately identified, has an unknown rate of increase, and unknown maximum concentration, the CMC recommendation is for a complete response. Hope will be given a path forward to address this deficiency which includes identification of the leachable (b) (4) material, a mass balance accounting of the source of the leachate, a more robust leachable and extractable study to determine whether the leachate increases on storage & the maximum exposure that can be anticipated, and exploration into new container closure systems that may have a leachable profile with a lower risk potential.

The following CMC deficiencies must be addressed prior to approval:

1. **The identity, source, and mass balance of the (b) (4) leachate(s) has/have not been established.**
2. **Insufficient data is provided to determine whether the leachable (b) (4) material will continue to increase on storage and what the anticipated exposure will be.**

(b) (4)

To address the CMC deficiencies, provide the following information in the NDA re-submission:

1. **Establish the identity and source of (b) (4) impurity. Your attempts may include the methods used in your primary literature searches.**
2. **Explore new container closure systems that may have a smaller leachable profile. The new container closure system might include, but should not be limited to evaluation of the rubber stoppers (b) (4)), the glass vials, and polypropylene bottles.**
3. **Submit a robust extractable study performed using the drug product solutions to extract all components of the container closure system.**
4. **Submit six months of stability data (including leachables) using the new container closure system which includes results from testing at release, 3 months, and 6 months under real time storage and testing at release, 1 month, 3 months, and 6 months under accelerated stability conditions. Both conditions should include upright and inverted storage configurations.**

APPENDIX:

Information request sent 06-Oct-2010; Amendment 0020; Hope provided a response received 15-Oct-2010

FDA Comment 1: Clarify the amount of leachable elemental [redacted] that was detected by ICP-OES from 4-month inverted storage at 40 deg C of the sodium nitrite drug product.

Hope Response:
The amount of leachable [redacted] detected by the ICP-OES method from the 4-month inverted storage at 40°C of the sodium nitrite drug product was less than the limit of detection (LOD) [redacted] The ICP-OES method was performed by [redacted]. [redacted] cautioned that the ICP-OES analysis produced highly variable results, probably due to inference by salts in the drug product, and so Hope reported the [redacted] levels as greater than [redacted] at the high dose as a worst-case estimate.

Because of the high LOD of the ICP-OES method, the assay for [redacted] was changed to a new ICP-MS method that has a lower LOD [redacted]. Duplicate 6-month inverted storage at 40°C sodium nitrite drug product samples were assayed using the new ICP-MS procedure and the [redacted] leachables levels were reported to be [redacted] Duplicate 4-month inverted storage at 40°C sodium nitrite drug product samples were re-assayed using the new ICP-MS method and the [redacted] leachable levels were reported to be [redacted]. All samples came from the drug product lot 2098-106.

The [redacted] leachable result of [redacted] in the sodium nitrite drug product corresponds to an exposure of [redacted] at the highest labeled drug product dose of 15 mL (i.e., 1.5 vials).

EVALUATION: Adequate. Differences in the two methods can reasonably result in different leachable [redacted] impurities detected. The ICP-MS method is more appropriate for this analysis. Note that the method is not validated at this time.

FDA Comment 2: Clarify whether the amount of [redacted] obtained from the 4-month time point of your sodium thiosulfate leachable study obtained, [redacted]

Hope Response:
The amount of [redacted] obtained by [redacted] ICP-OES method in the 4-month time point of the sodium thiosulfate leachable study was reported to be [redacted] which corresponds to a [redacted] exposure based on administration of a high dose of 75 mL (i.e., 1.5 vials).

The suboptimal performance of the ICP-OES method lead to the decision to change the (b) (4) assay to a new ICP-MS method (refer to question 1). (b) (4) levels in a retained sample of the 4-month sodium thiosulfate drug product showed (b) (4) (b) (4) and duplicate analyses of the 6-month sample showed (b) (4) (b) (4) All samples came from the drug product lot 2107-101.

Based on the ICP-MS results, the highest (b) (4) level of (b) (4) for sodium thiosulfate corresponds to (b) (4) and the highest (b) (4) level of (b) (4) for sodium nitrite corresponds to (b) (4).

A preliminary method validation report was provided by the contract laboratory for the ICP-MS method.

Validation Criteria	***Result***
Linearity	(b) (4)
LOD	
LOQ	
Spike Recovery (sodium thiosulfate)	

Hope concludes the (b) (4) ICP-OES (b) (4) level data are unreliable for the sodium nitrite and sodium thiosulfate drug products. Hope concludes the ICP-MS (b) (4) level data is reliable and reflects true amount of (b) (4) in the drug product samples. The (b) (4) level in sodium thiosulfate drug product corresponds to (b) (4) and in sodium nitrite drug product corresponds to (b) (4)

EVALUATION: Adequate. At this time, the selection of the ICP-MS method appears appropriate. Further validation will be required as a post-marketing agreement.

FDA Comment 3: Provide a description of the analytical methods used for your leachables study along with their validation, for the observed leachates, including (b) (4)

Hope Response:
Descriptions of the analytical methods, with the exception of the new ICP-MS method for (b) (4) are provided in the (b) (4) extractables report that was included in the 3.2.P.2 folder of the sodium thiosulfate drug product section in the original NDA filing. These analytical methods used for the extractables studies are otherwise the same as those being used for the current leachables studies.

(b) (4)

(b) (4)

As discussed with FDA during the teleconference on October 6, 2010, none of the analytical methods have been validated at this time.

EVALUATION: Adequate. Further validation will be required as a post-marketing agreement.

FDA Comment 4: Clarify whether you are claiming that all (b) (4) detected by ICP-OES originates from (b) (4) and, if so, provide a mechanism for how sample preparations and detection result in the detection of (b) (4).

Hope Response:
Hope concludes at this time that the primary source of (b) (4) leachable in the drug products should be the stoppers as they are treated with (b) (4) This is the case regardless of whether the samples are assayed by either the ICP-OES method or the new ICP-MS method.

(b) (4)

EVALUATION: Adequate. New analytical data and literature sources have since changed Hope's response.

Information request sent 20-Oct-2010; Hope provided a response received 22-Oct-2010

FDA Comment 1: Provide documented analytical evidence and empirical reasoning for your conclusion that the (b) (4) leachate observed by the ICP-MS and ICP-OES methods is .

Hope Response:

Hope has now changed its claim regarding the source of (b) (4). EGA-MS data on drug product extracts suggest that (b) (4) is a minor contributor to the (b) (4) leachate. (b) (4) of the leachable (b) (4) can be accounted for from the Type 1 USP glass vial used as the container closure and through the manufacturing process. Hope has not accounted for the remaining (b) (4) of the leachate or its likely identity.

EVALUATION: Inadequate. Without assurance of the leachates identity, source, and likely maximum patient exposure, the drug products lack adequate quality for approval based on quality concerns that may impact safety.

FDA Comment 2: In your extractables study of the rubber stopper, provide the estimated amount of (b) (4) detected from the (b) (4) extractions.

Hope Response:
This data is not available and the contract analytical lab (b) (4)) did not perform this analysis.

EVALUATION: Adequate. Subsequent data suggests that (b) (4) from the stoppers are minor (b) (4) contributors.

HFD-/Division File
HFD-170
HFD-170/A. Meyer

Olen Stephens, Ph.D.
Chemistry Reviewer

Xiaobin Shen, Ph.D.
Chemistry Reviewer

Prasad Peri, Ph.D.
Branch Chief, ONDQA

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

/s/

OLEN M STEPHENS
11/01/2010
CMC recommendation: complete response

XIAOBIN SHEN
11/01/2010

PRASAD PERI
11/03/2010
I concur

NDA/ANDA 201-444

[redacted] (Sodium Nitrite 30 mg/mL and Sodium Thiosulfate 250 mg/mL) solutions for injection

Hope Pharmaceuticals

Olen M. Stephens, Ph.D. and
Xiaobin Shen, Ph.D.
Pre-Marketing Division III for the

Division of Analgesia and Anesthetic Products

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Chemistry Review Data Sheet

1. NDA 201-444

2. REVIEW #: 1

3. REVIEW DATE: 27-Sep-2010

4. REVIEWERS: Olen Stephens and Xiaobin Shen

PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	21-May-2010
Amendment 002 – Stability Update	25-Jun-2010
Amendment 003 – Stability Update	2-Jul-2010
Amendment 004 – Stability Update	9-Jul-2010
Amendment 006 – IR response	10-Aug-2010
Amendment 007 – IR response	18-Aug-2010
Amendment 008 – Labeling	19-Aug-2010
Amendment 009 – IR response and Stability Data	20-Aug-2010
Amendment 010 – IR response and Labeling	23-Aug-2010
Amendment 011 – IR response and master batch record amendment	30-Aug-2010
Amendment 012 – Labeling and IR response	31-Aug-2010
Amendment 013 – IR response	3-Sep-2010
Amendment 016 – Updated Labeling and Master Batch Records	13-Sep-2010
Amendment 017 – Labeling	17-Sep-2010
Amendment 018 – IR response	20-Sep-2010
Amendment 019 – IR response and PMR commitment	24-Sep-2010

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Nithiodote
b) Non-Proprietary Name (USAN): Sodium Nitrite; Sodium Thiosulfate

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antidote for [redacted] (b) (4) cyanide poisoning

11. DOSAGE FORM: Solutions for Injection

12. STRENGTH/POTENCY: 300 mg (30 mg/mL; Sodium Nitrite) and 12.5 g (250 mg/mL; Sodium Thiosulfate)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

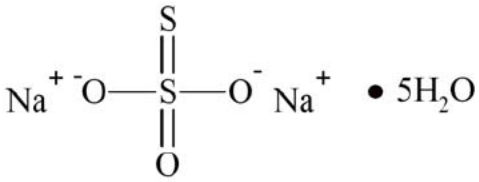
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

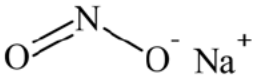
Sodium Thiosulfate
Chemical name: Sodium thiosulfate pentahydrate
United States Adopted Name (USAN): Sodium thiosulfate
Compendial name: Sodium thiosulfate pentahydrate, United States Pharmacopeia (USP)

Chemical structure:



Molecular formula: $Na_2O_3S_2 \cdot 5H_2O$
Molecular weight: 248.19 g/mol
Sodium thiosulfate anhydrous has a molecular formula of $Na_2O_3S_2$ and has a molecular weight of 158.11 g/mol.

Sodium Nitrite
Chemical name, USAN, and Compendial Name: Sodium Nitrite
Chemical structure:



Molecular formula: $NaNO_2$
Molecular weight: 69.0 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3*	Adequate	14-Oct-2008	Reviewed by Dr. Donald Klein
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	V			7			Microbiologist Dr. Robert Mello will review this DMF
	III			7	Adequate	NA	USP Type 1 glass meets safety

		(b) (4)					requirement per MAPP 5015.5

* The stopper used in this NDA is (b) (4). The base material (b) (4) information has been reviewed previously and deemed adequate to support various injection products. The most recent review was performed by Dr. Donald Klein on 14-Oct-2008. The stopper (b) (4) used in this NDA (on the non-drug contacting side of the stopper) has been previously reviewed by Dr. Mark Sassaman on 12-Apr-2007 and deemed adequate. The DMF was reorganized and resubmitted on 08-May-2009 with information related to other coating materials.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-166	Sodium Thiosulfate Reference Drug

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	21-Sep-2010	OC
Pharm/Tox	Pending	Pending	Dr. Marcus Delatte
Microbiology	Adequate	07-Sep-2010	Dr. Robert Mello
Biopharm	Adequate	21-May-2010	Dr. John Duan

The Chemistry Review for NDA 201-444

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, NDA 201-444 is approvable.

The pending deficiencies are the non-clinical evaluations of leachables substances from drug product container closure system, the proposed (b) (4) specifications for sodium nitrite, and the (b) (4) specification for sodium thiosulfate.

Notes:

1. The labeling comments are being routed through the project manager as part of the team review that involves DMEPA and DRISK.

(b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. Updated stability data is anticipated before the PDUFA action date. An expiry will be determined at that time in light of the new data.
2. (b) (4)
3. There is an outstanding confirmation method validation request at the Agency's St. Louis Labs. The outcome does not affect the application's approvability, but may affect Risk Management steps post-approval.
4. (b) (4)
5. Hope Pharmaceuticals has agreed to a Phase 4 commitment to tighten the sodium nitrite drug substance manufacturing process parameters for step (b) (4) (b) (4) and acceptable yield for commercial batches.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

NDA 201-444 is submitted as a 505(b)(2), based on the approved NDA 20-166, Sodium Thiosulfate Injection. The [redacted] kit contains sodium nitrite and sodium thiosulfate solutions for injection that are indicated for the treatment of acute cyanide poisoning that is judged to be life-threatening. The review was granted a priority review due to the lack of approved products with this formulation and it's importance in the national anti-terrorism stockpile of antidote kits. The referenced product was developed by the Army, and approved in 1992 to be used in combination with sodium nitrite injection as a cyanide antidote, but is currently discontinued. Hope Pharmaceuticals has requested a waiver of *in vivo* bioequivalence studies for the sodium thiosulfate, which was granted. The sodium thiosulfate (12.5 g/50mL) and sodium nitrite (300 mg/10 mL) injection solutions, are co-packaged as the cyanide antidote kit in two single dose vials as sterile solutions.

The sodium nitrite drug substance is manufactured under cGMP from a food grade sodium nitrite source that complies with Food Chemicals Codex (FCC). The sodium nitrite is [redacted]. The sodium nitrite drug substance is [redacted] Sufficient stability data is provided to grant a [redacted] month retest date for the sodium nitrite drug substance.

Sodium thiosulfate drug substance is prepared [redacted] Both starting materials are commercially available. Specifications for the starting materials, reagents, and in-process control are adequate. Only 6 months of stability data are available at both long term (25°C/60% RH) and accelerated conditions (40°C/75% RH). The provided results conformed to specifications except that the [redacted] of batch 09/113 exceeded the limit of [redacted] month 6 under accelerated conditions. An investigation was conducted and no assignable cause was identified. An retest period of [redacted] months is granted. Photostability, thermal stability, and open dish stability studies were conducted on both drug substances; no meaningful changes were noted.

The sodium nitrite and sodium thiosulfate drug products are formulated as solutions followed by [redacted] The sodium nitrite drug product is a simple solution [redacted] the sodium thiosulfate drug product [redacted] Both drug products are packaged in USP Type 1 [redacted] glass vials and stoppered with [redacted] stoppers and a [redacted] aluminum overseal. Both vials are co-packaged in a [redacted] box, the secondary container. Release and stability testing include testing for bacterial endotoxins, sterility, and container integrity testing. Photostability, thermostability, oxygen stress, and temperature cycling studies showed both drug products were insensitive to these stability stressors. Sufficient stability data is provided to allow a 6 month shelf life for both drug products. [redacted]

Proposed Mode of Action: Sodium nitrite reacts with hemoglobin to form methemoglobin, which has a higher affinity for cyanide than cytochrome oxidase.

Methemoglobin and cyanide form cyanmethemoglobin, keeping cyanide away from cytochrome oxidase and thus regenerating this enzyme's function. The resulting cyanmethemoglobin, in the presence of sulfurtransferase enzyme, catalyzes the attachment of sulfate to cyanide to form thiocyanate, which has relatively low toxicity and is eventually eliminated in the urine. The molecule of methemoglobin that is released is available to bind to another molecule of cyanide or it is reduced back to hemoglobin.

(b) (4)

Sodium thiosulfate is used in conjunction with sodium nitrite to serve as a source of sulfate. The combined mechanism may be expressed in a chemical manner:

$$NaNO_2 + \text{hemoglobin} = \text{methemoglobin}$$
$$HCN + \text{methemoglobin} = \text{cyanmethemoglobin}$$
$$Na_2S_2O_3 + CN = SCN + Na_2SO_3$$

B. Description of How the Drug Product is Intended to be Used

The proposed dosing regimen, below, is identical to the referenced discontinued product. Sodium nitrite is administered first followed immediately by sodium thiosulfate. The same needle and vein may be used to administer both solutions.

Adults:

Sodium Nitrite: 10 mL of a 3% solution (300 mg) of sodium nitrite at the rate of 2.5 to 5 mL/minute.

Sodium Thiosulfate: 12.5 g (50 mL of a 25% solution) immediately following administration of sodium nitrite.

Redosing: If a patient does not respond to initial doses, treatment may be repeated with one-half the original dose of sodium nitrite followed by one-half the original dose of sodium thiosulfate

Children:

Sodium Nitrite: 0.2 mL/kg of a 3% solution (6 mg/kg or 6-8 mL/m^2 BSA) of sodium nitrite at the rate of 2.5 to 5 mL/minute not to exceed 10 mL (300 mg)

Sodium Thiosulfate: 1 mL/kg of body weight using a 25% solution (250 mg/kg or approximately 30-40 mL/m2 of BSA) not to exceed 50 mL (12.5 g) total dose.

Storage and Expiry:

The (b) (4) kit should be stored between 20°C and 25°C (68°F - 77°F); excursions permitted to 15 - 30°C (59°F - 86°F). Protect from direct light and keep the kit in its secondary container. Do not permit the kit to freeze. The kit is limited to the expiry of either component with a maximum expiry of 6 months at this time.

C. Basis for Approvability or Not-Approval Recommendation

Chemistry, Manufacturing and Controls deficiencies for the drug substance and drug product were communicated and have been adequately addressed throughout the review cycle.

The facilities used in the manufacture and control of the drug substance and drug product have been submitted for evaluation to the Office of Compliance and are acceptable in its overall recommendation.

The CMC recommendation for NDA 201-444 is for approval. Stability data will be regularly submitted as amendments to this NDA as it is available and will be reviewed for shelf life extension as appropriate.

III. Administrative

A. Reviewer's Signature
Olen Stephens (Sodium Nitrite)
Xiaobin Shen (Sodium Thiosulfate)

B. Endorsement Block

Chemist Name: Olen M. Stephens and Xiaobin Shen
Chemistry Branch Chief: Prasad Peri

C. CC Block

CMC Lead: Danae Christodoulou
Project Managers: Allison Meyer and Swati Patwardhan

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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/

OLEN M STEPHENS
09/27/2010
CMC recommendation for approval
stability data supports 6 month shelf life at this time

XIAOBIN SHEN
09/27/2010

PRASAD PERI
09/27/2010
I concur

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Correction to page 2 of the Initial Quality Assessment

The last paragraph described the manufacturing process of sodium thiosulfate as (b) (4) [redacted]. The description of the reaction is corrected to read as the following:

The principal manufacturing process of sodium thiosulfate consists of (b) (4) [redacted]

Comments from the Filing Review:

1. Provide a stability update (including a summary) for the primary batches of the two drug substances and products, as soon as the six-month data become available.
2. Provide a Letter of Authorization (LoA) to (b) (4) [redacted]s DMF (b) (4) [redacted] referenced in M3.
3. Clarify if the (b) (4) [redacted] and (b) (4) [redacted] stoppers are (b) (4) [redacted]
4. Monitor and report leachables in the drug product, at the 6, 9, and 12 month time interval.

Information requests generated from our review of the application thus far:

Drug Substances:

1. *Provide the Certificates of Analysis (CoA) for the desiccant pouch and* (b) (4) [redacted] *liner used as the primary container closure system for the sodium nitrite and sodium thiosulfate drug substances. Provide the letter of reference for the DMF's and identify the suppliers for the desiccant pouch and drum liner.*
2. *Several of your analytical methods appear to be similar if not identical for the drug substances and drug products, though the methods have different names and numbers. Where applicable, indicate which methods are identical to facilitate our review. Provide a tabulated summary of method comparison for drug substances and products.*
3. *In the acceptance criteria of your sodium nitrite starting materials and solvents, clarify what is meant by "tests required for retest".*
4. *Provide the Certificate of Analysis (or additional documentation) to confirm the manufacturer of the sodium nitrite starting material. Amend your application to include the CoA with functional hyperlink. Note that the hyperlink you provided is not linked to the sodium nitrite CoA.*
5. *For your* (b) (4) [redacted] *methods, provide the following information:*
   a. *In your validation reports for sodium nitrite, you report* (b) (4) [redacted]. *However, based on your batch records, the LOD appears to be* (b) (4) [redacted] *Clarify the discrepancy between these two values.*
   b. *Clarify what the LOD and LOQ are for the NPOC methods for both the sodium thiosulfate and sodium nitrite.*
   c. *Clarify the limiting factor in obtaining lower LOD's and LOQ's.*

d. *Report NPOC as a quantitative result or "< LOQ" or "< LOD" with a footnote to define the LOQ or LOD for that sample.*
e. *What is the sample sequence for your NPOC methods?*
f. *Currently, we interpret the NPOC values for the sodium thiosulfate registration batches to mean that they contain NPOC below the limit of detection (< LOD), but the LOD changes between batches. Clarify whether new LOD's are determined for each drug substance batch in your NPOC method.*

6. *Provide the batch numbers of the USP sodium thiosulfate standards used. Provide a summary of information of other standards used in sodium thiosulfate drug substance characterization and analysis, include standard name, purity, manufacturer/supplier, batch/lot number.*
7. *Justify why the sodium thiosulfate appearance specification for stability has changed* (b) (4) *Alternatively, use the same acceptance criterion.*
8. *Demonstrate that the ICP-MS method used to determine residual Ca in place of the USP method is equivalent to the USP method with respect to sensitivity.*
9. *For analytical method PHR-178:*
   a. *Your method stated that the carryover or interference in the diluent injection at the retention time of thiosulfate should be NMT* (b) (4) *of the area response of the reference working standard (RWS). Tighten this limit or provide appropriate justification.*
   b. (b) (4) *of sodium thiosulfate drug substance and standard should be determined shortly before sample and standard preparation to avoid using a biased* (b) (4) *for calculation.*
   c. *Clarify in the method if the sodium thiosulfate drug substance sample and its reference standard are weighed immediately* (b) (4)
   d. *On page 2 of Section 3.2.S.4.2, the equation (shown below) does not appear to be correct. Demonstrate that it is correct with actual data or rectify the page.*

(b) (4)

Drug Products

10. *Your manufacturing process description does not provide sufficient process details (e.g. equipment type and size, batch size, process parameters). Submit a master batch record and revise section 3.2.P.3.3 to provide a comparably detailed process description.*
11. *Calculate and report the tonicity for your sodium thiosulfate and sodium nitrite drug products.*
12. *In the sodium thiosulfate drug product manufacturing process, after pH adjustment in* (b) (4) *the solution is held until QC authorizes continuation of the process. Specify a time range for this holding period. Clarify if this holding period is part of or additional to the proposed* (b) (4).
13. *The assay results in critical control Table 8 (Section 3.2.P.3.4) show consistently higher sodium thiosulfate assay value than 100%. Even though no overage is planned, it*

appears that your manufacturing process has built in a (b) (4) *overage. Identify the overage source and correct as appropriate.*

14. *In your label under Dosage and Administration, you state that the same needle and vein may be used to administer both the sodium nitrite and sodium thiosulfate. Confirm that our understanding of that passage is correct. If this is correct, include data in your application to demonstrate compatibility of the two drug products when using the same needle and vein, e.g., assay(s), impurities/degradants and particulate matter.*
15. *Clarify whether your* (b) (4) *kit will be supplied with syringes and needles or only with the two drug product vials.*

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

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/s/

XIAOBIN SHEN
07/15/2010
Addendum to IQA and information request thus far.

PRASAD PERI
07/15/2010
I concur

Initial Quality Assessment
Office of New Drug Quality Assessment
Division III, Branch VIII
Division of Anesthesia, Analgesia and Addiction Products

OND Division:	Anesthesia, Analgesia and Addiction
NDA:	201444
Chemical Classification	4S
Applicant:	Hope Pharmaceuticals
Stamp date:	May 21, 2010
PDUFA Date:	November 21, 2010
Trademark:	(b) (4) ™
Established Name:	Sodium Nitrate Injection, USP; Sodium Thiosulfate Injection, USP
Dosage Form:	Intravenous Injection(s), 30 mg/ml; 250 mg/ml
Route of Administration:	Parenteral (IV)
Indication:	Treatment of cyanide poisoning
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

The application is submitted as a 505(b)(2), based on the approved NDA 20-166, Sodium Thiosulfate Injection, USP. A priority review is requested (6-month clock). The referenced product was developed by the Army, and approved in 1992 to be used in combination with sodium nitrite injection as a cyanide antidote, but is currently discontinued. Note that other marketed unapproved products exist, using this drug combination as a cyanide antidote. The application is filed based upon the applicant's request for a waiver of *in vivo* bioequivalence studies for the sodium thiosulfate, as per 21 CFR 320.22. The applicant references the July 27, 2007, pre-NDA meeting with the Agency.

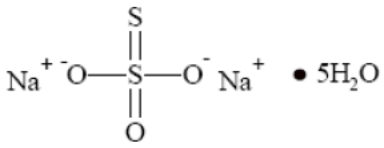
The sodium thiosulfate and sodium nitrite injection solutions, are co-packaged as the cyanide antidote kit, in the two single dose vial presentations of 12.5 g/50ml and 300 mg/10 ml, respectively. The proposed dosing regimen, below, is claimed to be identical to the referenced discontinued product:

1. Inject intravenously 10 mL of a 3% solution (300 mg) of sodium nitrite at the rate of 2.5 to 5 mL/minute. The recommended dose of a 3% solution of sodium nitrite for children is 6 to 8 mL/m^2 of body surface area (approximately 0.2 mL/kg of body weight) but is not to exceed 10 mL of a 3% solution (300 mg).
2. Immediately thereafter, inject 50 mL of a 25% solution (12.5 g) of sodium thiosulfate for adults. The recommended dose of a 25% solution of sodium thiosulfate for children is 30 to 40 mL/m^2 of body surface area (approximately 1.0 mL/kg of body weight); but dosage should not exceed 50 mL of a 25% solution (12.5 g). The same needle and vein may be used.

B. Review, Comments and Recommendations

Drug Substance Sodium Thiosulfate Pentahydrate

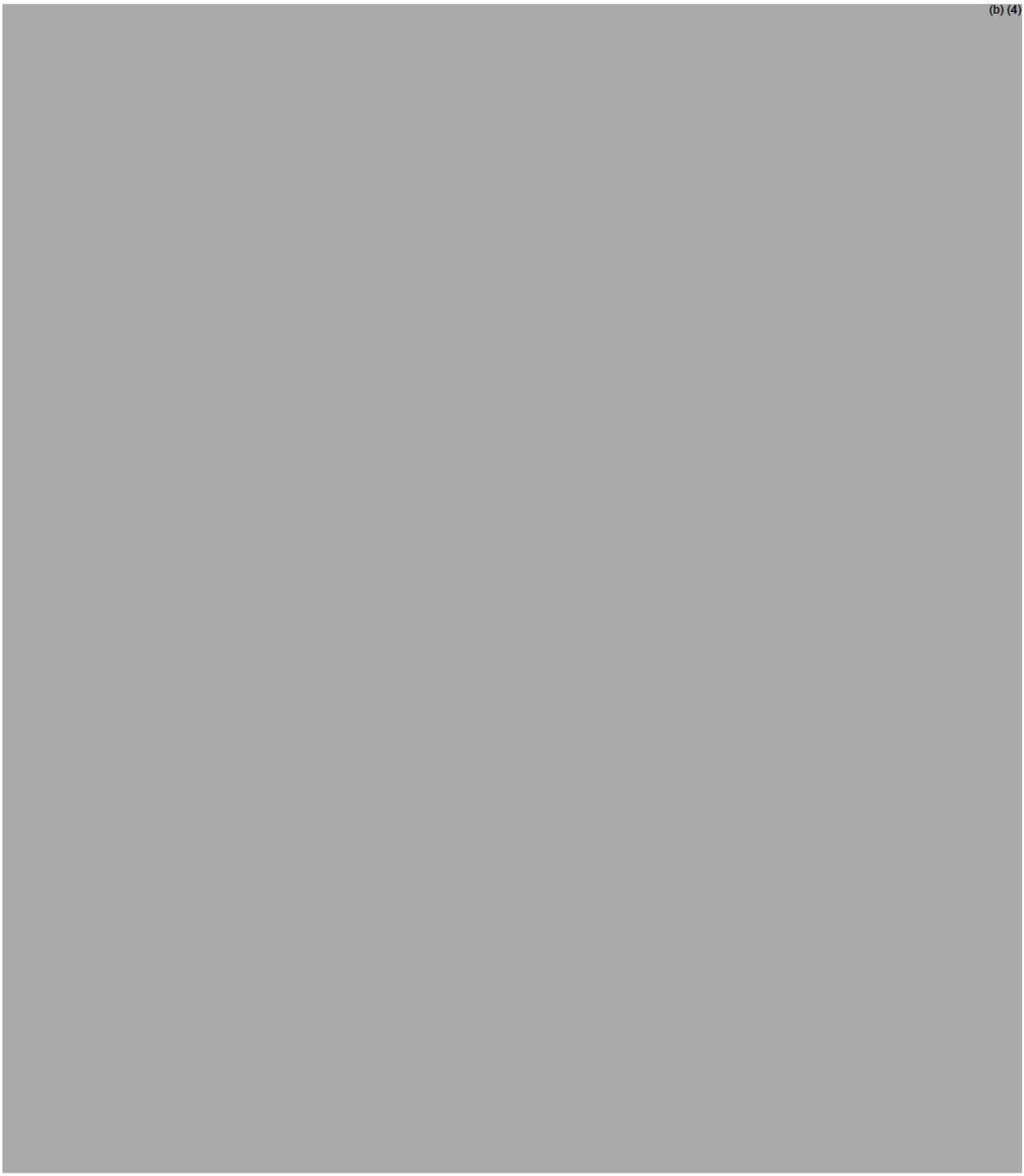
Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



Chemical Name(s): sodium thiosulfate
Molecular formula: $Na_2O_3S_2$
Molecular weight: 158.11
CAS: 10102-17-7

(b) (4)

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



Labeling: Labeling information on the container labels and packaging insert should be assessed with respect to CMC information. SPL labeling has been included in M1.

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. **Drug Substances:** The manufacturing processes, raw material specifications and in-process controls should be assessed. Specifications of impurities are based on the USP monograph and ACS specifications as per agreements with the Agency. Drug substance specifications should be assessed as per ICH Q3A(R2) in consultation with the Toxicology division and as per the agreements with the Agency.
2. Suitability of analytical methods for drug substances, validation and LOD/LOQs should be assessed as per ICHQ2b(R), in particular for HPIC method and the (b) (4) determination method (b) (4) Changes in certain specification limits as proposed by the Agency based on the applicant's validated methods and levels of exposures from other LVP and SVP products, containing these ions, should be assessed.
3. Suitability of the manufacturing process, for the drug products, which includes (b) (4) in-process controls, microbiolgical integrity of the container/closures should be assessed in consultation with the Microbiology division.
4. Hold times of drug product intermediates and absence of oxygen from manufacturing conditions should be assessed.
5. The suitability of (b) (4) overage of $Na_2S_2O_3$.
6. Manufacturing operation Step (b) (4) should be clarified for manual adjustment (b) (4).
7. The extractables/leachables studies and lack of leachable data thereof and the acceptability of the proposal of assessing leachables post-approval should be assessed in consultation with the Toxicology division.
8. Suitability and specifications of the container/closure system, and review of appropriate packaging DMFs.
9. Specifications (in-process and end product testing) for critical attributes of the drug product, e.g., pH and osmolality, as discussed in p. 4 and 6.
10. Specifications for drug product impurities/degradants as discussed in 2 above for the drug substance.
11. Proposed expiration dating of (b) (4) (b) (4)

D. Comment for the 74-day Letter:

1. Provide a stability update with updated summary for the primary batches of drug substances and products, as soon as the three and six-month data on drug substances and products becomes available.
2. Provide LoA to (b) (4), referenced in M3.
3. Clarify if the (b) (4) stoppers are (b) (4) (b) (4)
4. Monitor and report leachables at the 3 and 9- month time interval.

E. **Recommendation for fileability**: The NDA may be filed based on the need for cyanide antidote kits for the nation's stockpile. OCTEC should be consulted to advice on the immediate

need for this particular product with short proposed expiry, as one approved product exists (NDA 22-041, hydroxocobalamin).
Sufficient number of primary stability batches, and 3-month real time stability data will be amended in July 2010, as per email communication of the firm to the Project Manager, Allison Meyer.

Recommendation for Team Review: The NDA is recommended for team review. The drug substances are not NMEs, the formulation does not include novel excipients and the manufacturing process for the drug product does not present complexity, e.g., novel delivery or device issues, nor significant development, however the priority review timeline is appropriate for team review of the two individual components of the kit.

Consults:

Microbiology consult was requested.
Biowaiver assessment was requested.
The primary reviewers should initiate Toxicology consults for the impurities/degradants and extractables/leachables evaluation, when they are submitted.

Danae D Christodoulou, Ph.D. — 6/14/2010
CMC Lead — Date

Prasad Peri, Ph.D. — 6/15/2010
Acting Branch VIII Chief, ONDQA — Date

Established/Proper Name:

NDA Number: 201444 **Supplement Number and Type: 4S** **Sodium thiosulfate injection**

Sodium nitrite injection

Applicant: Hope **Letter Date: 05/21/2010** **Stamp Date: 05/21/2010**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		EOP2 2/5/2009

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		Clarifications and communications with OC.
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		X	Clarifications and communications with OC.

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?			
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Limited real time stability data: 1 month Proposed interim expiry: (b) (4)
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	3	(b) (4)	(b) (4)	3/16/2010	(b) (4)
	3			3/16/2010	
	3			3/13/2010	
	3			1/12/2010	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		Based on pre-NDA agreements
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	See above

{See appended electronic signature page}

Name of
CMC Lead: Danae Christodoulou 6/14/10 Date
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Name of
Branch Chief (Acting): Prasad Peri Date
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment

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

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/s/

DANAE D CHRISTODOULOU
06/17/2010
Initial Quality Assessment

PRASAD PERI
06/18/2010
I concur. During the filing meeting, the division expressed an opinion that this is an important drug to have in the market and should be a priority. Similar views were expressed by OCTET staff.