CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201444Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 201444 SUPPL # 000 HFD # 170

Trade Name Nithiodote

Generic Name sodium nitrite injection and sodium thiosulfate injection

Applicant Name Hope Pharmaceuticals

Approval Date, If Known January 14, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES X NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020166

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO X

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Allison Meyer
Title: Regulatory Project Manager
Date: January 11, 2011

Name of Office/Division Director signing form: Bob Rappaport, MD
Title: Director, HFD-170

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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
01/14/2011

BOB A RAPPAPORT
01/14/2011

1.3.3 Debarment Certification

Hope Pharmaceuticals 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.

Craig R. Sherman

Craig Sherman, M.D.

March 30, 2010
Date

President
Hope Pharmaceuticals

505(b)(2) ASSESSMENT

Application Information		
NDA # 201444	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Nithiodote Established/Proper Name: sodium nitrite and sodium thiosulfate Dosage Form: injection Strengths: 30 mg/mL and 250 mg/mL		
Applicant: Hope Pharmaceuticals		
Date of Receipt: May 21, 2010		
PDUFA Goal Date: February 22, 2010	Action Goal Date (if different): January 14, 2011	
Proposed Indication(s): for the treatment of (b) (4) cyanide poisoning		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Sodium Thiosulfate Injection, USP	Agency's previous findings of risk/benefit for NDA 020166
Magnesium Sulfate Injection	Sulfate levels in the sodium thiosulfate product
Sodium Chloride Injection	(b) (4) for sodium nitrite and sodium thiosulfate

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed

products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

As the proposed and referenced products are to be administered via the IV route of administration (100% bioavailable) with the same amount of active ingredients, the Agency waived the CFR's requirement for the submission of in vivo BA/BE data needed to bridge to the Agency's previous findings of safety and efficacy for sodium thiosulfate used in conjunction with sodium nitrate via NDA 020166 . The sponsor justified the safety of the levels of sulfate in their drug product via reference to sulfate levels in the approved magnesium sulfate injection product as per the dosing and administration section of the label. To justify the levels of the (b) (4), the sponsor analyzed levels in the referenced drug product and provided the data necessary to support the biowaiver request and scientific bridge to their product. These approaches were deemed scientifically valid and adequate by the review team.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Sodium Thiosulfate Injection, USP	NDA 020166	Yes
Magnesium Sulfate Injection	NDA 019316	Yes
Sodium Chloride Injection	NDA 018803	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*
*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:
   a) Approved in a 505(b)(2) application?

YES ☐ NO ☒
*If "**YES**", please list which drug(s).*
Name of drug(s) approved in a 505(b)(2) application:

   b) Approved by the DESI process?

YES ☐ NO ☒
*If "**YES**", please list which drug(s).*
Name of drug(s) approved via the DESI process:

   c) Described in a monograph?

YES ☐ NO ☒
*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

   d) Discontinued from marketing?

YES ☒ NO ☐
*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*
Name of drug(s) discontinued from marketing: Sodium Thiosulfate Injection

      i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the

archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a combination of Sodium Thiosulfate with Sodium Nitrite Injection.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(***Pharmaceutical equivalents*** *are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are*

listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" <u>and</u> there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☒ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Meyer, Allison

From: Duvall Miller, Beth A
Sent: Wednesday, January 05, 2011 1:22 PM
To: Meyer, Allison
Subject: RE: NDA 201444/Nithiodote - cleared for action

You can check it in at any time.

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Meyer, Allison
Sent: Wednesday, January 05, 2011 1:17 PM
To: Duvall Miller, Beth A; Jani, Parinda
Cc: Ripper, Leah W
Subject: RE: NDA 201444/Nithiodote - cleared for action

Ok, I have made the changes. Thanks Beth. I check this in on action day, correct?
Allison

From: Duvall Miller, Beth A
Sent: Tuesday, January 04, 2011 4:23 PM
To: Jani, Parinda; Meyer, Allison
Cc: Ripper, Leah W
Subject: NDA 201444/Nithiodote - cleared for action

Allison/Parinda,

Based on our discussion at today's meeting with Dr. Rappaport and the review team, this application is cleared for action from a 505(b)(2) perspective keeping in mind my advice about how reviews, or the action letter, should reference the generic phenytoin (or sodium bicarbonate) product(s) since Dr. Rappaport said that the (b) (4) leachate levels observed in those products are not necessary to support the safety of this product.

Please make the following changes to your 505(b)(2) assessment before archiving in DARRTS:

- Application information: The PDUFA goal date should be 2/22/11.
- Q2 and Q6: remove references to the generic sodium bicarbonate and phenytoin applications.

- Q3: remove the sentence (2nd to last) describing how the (b)(4) leachate levels were qualified
- Q14: Paragraph I should also be selected since the applicant submitted Paragraph I certification for their reliance on NDA 20-166, sodium thiosulfate.

That's it.

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Jani, Parinda
Sent: Tuesday, January 04, 2011 10:38 AM
To: Duvall Miller, Beth A; Meyer, Allison
Cc: Ripper, Leah W; Rappaport, Bob A; Roca, Rigoberto A; Mellon, Dan; Christodoulou, Danae D
Subject: RE: NDA 201444/Nithiodote - b2 clearance follow-up

Thanks!!!

Just some clarification. We did not advise the sponsor to reference ANDA products. We took a CR action on Nov 18th, and the next day sponsor submitted the leachables information for the two products cited and provided patent certification.

From: Duvall Miller, Beth A
Sent: Tuesday, January 04, 2011 10:34 AM
To: Jani, Parinda; Meyer, Allison
Cc: Ripper, Leah W
Subject: NDA 201444/Nithiodote - b2 clearance follow-up
Importance: High

Parinda/Allison,

We discussed this application at yesterday's clearance meeting.

Reliance on generic products in 505(b)(2) applications is almost always problematic, as it is in this case. Unfortunately, the advice given to Hope at the 12/21/10 meeting was not ideal; ideally they should have referenced an NDA product whose (b)(4) leachate levels were above their products to qualify the (b)(4) leachate levels in their product. The rationale behind this is that there is no finding of safety (or efficacy) in generic products – they were found to be bioequivalent to an innovator product where the finding of s/e was established by the conduct of studies.

That said, Lee is trying to determine what the basis for the (b) (4) levels in the generic product is based on – data from the innovator's NDA, literature, studies conducted by the generic manufacturer?

So in the meantime, you'll need to sit tight until we sort this out. For future reference, any time an applicant (or division) proposes reliance on a generic product, a big alarm should go off in your head followed by an email to us so we can provide definitive advice for the applicant.

Beth

PS I'll also be sending a list of changes for the b2 assessment once we've sorted everything out, so please don't archive in DARRTS until you get that list of changes.

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Jani, Parinda
Sent: Tuesday, December 28, 2010 11:20 AM
To: Duvall Miller, Beth A
Subject: Re: (b)(2) clearance needed/NDA 201444/Nithiodote

Yes, very high priority.

Sent from my BlackBerry Wireless Handheld

From: Duvall Miller, Beth A
Sent: Tuesday, December 28, 2010 11:12 AM
To: Jani, Parinda
Subject: RE: (b)(2) clearance needed/NDA 201444/Nithiodote

I'm guessing you plan to approve, correct?

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

From: Jani, Parinda
Sent: Tuesday, December 28, 2010 8:44 AM
To: Duvall Miller, Beth A
Subject: RE: (b)(2) clearance needed/NDA 201444/Nithiodote

You are wonderful!!

From: Duvall Miller, Beth A

Sent: Tuesday, December 28, 2010 7:54 AM

To: Jani, Parinda; Quaintance, Kim M

Cc: Ripper, Leah W; Meyer, Allison

Subject: RE: (b)(2) clearance needed/NDA 201444/Nithiodote

Parinda,

Thanks for the heads-up – I will put this on the agenda for Monday's (1/3) clearance meeting.

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Jani, Parinda
Sent: Monday, December 27, 2010 9:59 AM
To: Duvall Miller, Beth A; Quaintance, Kim M
Cc: Ripper, Leah W; Meyer, Allison
Subject: (b)(2) clearance needed/NDA 201444/Nithiodote
Importance: High

Dear all:

Hope Pharmaceuticals have submitted their response to our November 18th CR letter. The reason for CR was the levels of (b) (4) leachables in the drug product. Hope has provided additional Paragraph II certifications for products which have similar or higher amount of these leachables. I have revised the (b)(2) assessments to reflect this new information.

Please note that it is urgent that we take an action on this product as soon as possible as the currently available Cyanide Antidote Kits containing Na Nitrite and Na thiosulfate are all unapproved marketed products (Keystone and Akorn). If I am not mistaken, because of manufacturing issues, Keystone can no longer manufacture/distribute this product. SO there is an urgency, that the product gets approved as soon as possible. We are targeting January 14th as our action date, hopefully, you will be able to clear this application before that.

Thanks and Have a Happy New Year!!!!

<< File: filing 505b2.doc >>

Parinda Jani

Chief, Project Management Staff

Division of Anesthesia and Analgesia Products

Office of Drug Evaluation II
Center for Drug Evaluation and Research

Tel # (301) 796-1232 or 2280

Fax # (301) 796-9713

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
01/14/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 201444 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Nithiodote Established/Proper Name: sodium nitrite and sodium thiosulfate Dosage Form: injection		Applicant: Hope Pharmaceuticals Agent for Applicant (if applicable):
RPM: Allison Meyer		Division: HFD-170

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 20166 - Sodium Thiosulfate Injection, USP

NDA 19316 - Magnesium Sulfate Injection

NDA 18803 - Sodium Chloride Injection

Provide a brief explanation of how this product is different from the listed drug.

The listed drugs contain pieces of supportive information for determinations of safety on the combination of sodium nitrite and sodium thiosulfate as indicated for the treatment of cyanide poisoning

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 1-13-2010

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 2/21/11	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR 11/18/10

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	January 14, 2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) CR 11/18/2010, AP 1/14/11
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	January 13, 2011
• Original applicant-proposed labeling	May 21, 2010
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	5/21/10
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	1/12/11
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	10/8/2010 Accepted
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA 9/1/2010, 10/7/10 ☐ DRISK ☒ DDMAC 11/3/2010, 1/10/11 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	10/19/2010, 11/15/2010 ☐ Not a (b)(2) 11/10/2010, 1/5/11 ☐ Not a (b)(2) 1/14/11
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	6/11/10, 6/15/2010, 8/24/2010, 8/25/2010, 9/14/2010, 9/23/2010,

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	10/6/2010, 10/20/2010, 10/28/2010
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 7/27/07
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	4/22/09
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11/18/10, 1/14/11
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See Division Summary Review
• Clinical review(s) *(indicate date for each review)*	11/18/10
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	No clinical trials performed
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☒ None 6/17/2010
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/15/10
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 11/4/2010, 1/10/11
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 7/15/2010, 11/4/2010, 1/10/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 11/4/2010, 1/11/11
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 6/17/2010, 7/8/2010, 7/15/2010, 9/27/2010, 11/3/2010, 1/11/11
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 6/2/2010, 9/7/2010
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9/27/2010
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: 9/21/2010 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ODE’s ADRA.

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
01/14/2011

From: Jani, Parinda
Sent: Wednesday, January 05, 2011 5:27 PM
To: 'sherman@hopepharm.com'
Cc: Meyer, Allison
Subject: RE: Post-Action Meeting for NDA 201,444

Dear Dr. Sherman:
Attached is the FDA proposed label for NDA 201444/Nithiodote.

There are three files:
1. Marked-up version of your proposed label
2. A clean copy of the FDA proposed label
3. References

If you decided to propose any revisions, please use the clean copy file (I have accepted all the changes of the first file) for the ease of our review.

If you have any questions, please contact me at the number listed below.

Regards,

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Tel # (301) 796-1232 or 2280
Fax # (301) 796-9713

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

(b) (4)

[redacted]

From: Jani, Parinda
Sent: Monday, January 10, 2011 4:24 PM
To: 'sherman@hopepharm.com'; Meyer, Allison
Subject: RE: Revisions to Draft Label

Dear Dr. Sherman:

we are making the following recommendation in lieu of the requirement for a quick reference guide:

"Repeat the boxed dosage and administration instructions, as stated in the Highlights section of the insert labeling, on the carton labeling to expedite retrieval of product information in a crisis. This information may be presented on the back panel or on the side panel. If the back panel is chosen, the current statements may be deleted since it is the same information as on the principle display panel. If the side panel is chosen, you may delete the statement, 'Parenteral drug products should be inspected . . . ' to make room for the revisions."

This recommendation pertains to the revised label and labeling submitted September 17, 2010.

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Tel # (301) 796-1232 or 2280
Fax # (301) 796-9713

From: Jani, Parinda
Sent: Tuesday, January 11, 2011 11:01 AM
To: 'sherman@hopepharm.com'
Cc: Meyer, Allison
Subject: Nithiodote/PMRs and PMCs
Importance: High

Dear Dr. Sherman:

As discussed at our teleconference, we need you to agree to the following PMR/PMCs and send an official submission. Let me know if you have any questions.

Regards,

POSTMARKETING REQUIREMENTS:

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

Final Protocol Submission: 03/2011
Study Completion: 05/2011
Final Report Submission: 06/2011

2 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.

Final Protocol Submission: 03/2011
Study Completion: 05/2011
Final Report Submission: 06/2011

POSTMARKETING COMMITMENTS

3 Evaluate alternative container closure systems and (b) (4) sterilization methods that might result in a more acceptable leachable profile.

Final Protocol Submission: 04/2012
Study/Trial Completion: 07/2012
Final Report Submission: 08//2012

4. Amend the post-approval stability protocol to adequately monitor (b) (4) leachable material.

Final Report Submission: 02/2011

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Tel # (301) 796-1232 or 2280
Fax # (301) 796-9713

From: Jani, Parinda
Sent: Tuesday, January 11, 2011 3:49 PM
To: 'sherman@hopepharm.com'
Cc: Meyer, Allison
Subject: RE: Nithiodote/PMRs and PMCs

Dear Dr. Sherman:

Your proposed artwork of the Nithiodote carton is acceptable to the Division of Medication Error Prevention and Analysis team. I will forward the Package Insert to you tomorrow. You can submit the PDF and/or word version of the labels to the NDA for now, you can submit the SPL version post-action.

Thanks

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Tel # (301) 796-1232 or 2280
Fax # (301) 796-9713

From: Jani, Parinda
Sent: Wednesday, January 12, 2011 5:01 PM
To: 'sherman@hopepharm.com'
Cc: Meyer, Allison
Subject: FDA Proposed revision 011211.doc

Dear Dr. Sherman:

Attached is the revised label with minor changes. Let us know if you agree with these changes, or, would like to revise it further.

Thanks
Parinda

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

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/s/

PARINDA JANI
01/13/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201444

ACKNOWLEDGE --
CLASS 1 COMPLETE RESPONSE

Hope Pharmaceuticals
16416 North 92nd Street, Suite 125
Scottsdale, AZ 85260

Attention: Craig Sherman, M.D.
President

Dear Dr. Sherman:

We acknowledge receipt on December 22, 2010, of your December 22, 2010, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nithiodote (sodium nitrite Injection and sodium Thiosulfate Injection).

We consider this a complete, class 1 response to our November 18, 2010, action letter.

Therefore, the user fee goal date is February 22, 2011.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia and Analgesia
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
01/06/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Allison Meyer, ODE II/DAAP/301-796-1258	
DATE 12/23/10	IND NO.	NDA NO. 201444	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT 12/23/10
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION Priority		CLASSIFICATION OF DRUG Critical Care	DESIRED COMPLETION DATE 1/10/11

NAME OF FIRM: Hope Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: NEW NDA/Labeling

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: \\CDSESUB1\EVSPROD\NDA201444\201444.enx
We have received a new NDA 201444. We would like the labeling to be reviewed by DMEPA.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

ALLISON MEYER
12/23/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Allison Meyer, ODEII/DAAP/301-796-1258

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
12/23/10		201444	New NDA Complete Response

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
(b) (4)	Priority	Critical Care	1/10/10

NAME OF FIRM:

Hope Pharmaceuticals

PDUFA Date: 6/23/11

Action Date: 1/14/11 – management is taking early action

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
x PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☒ CARTON/CONTAINER LABELING
MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☒ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☒ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: \\CDSESUB1\EVSPROD\NDA201444\201444.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting:

Labeling Meetings: TBD

Wrap-Up Meeting:

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL ☐ HAND

Reference ID: 2883346

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/s/

ALLISON MEYER
12/23/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 201444

MEETING PRELIMINARY COMMENTS

Hope Pharmaceuticals
16416 North 92nd Street, Suite 125
Scottsdale, AZ 85260

Attention: Craig Sherman, M.D.
President

Dear Dr. Sherman:

Please refer to your New Drug Application (NDA) submitted May 21, 2010, received May 21, 2010, under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for sodium thiosulfate, 250 mg/mL and sodium nitrite, 30 mg/mL.

We also refer to your November 19, 2010, correspondence, received November 22, 2010, requesting a meeting to discuss the issues that were identified in the Agency's complete response letter of November 18, 2010.

We acknowledge your December 6, 2010, correspondence, received December 6, 2010, supplying additional patent and CMC information to the NDA. Any additional information that has been supplied since your action letter of November 18, 2010, should be resubmitted as part of your complete response document.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 21, 2010, at 4:00 pm between Hope Pharmaceuticals, and the Division of Anesthesia and Analgesia Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

Please let me know if you would like to change anything about our forthcoming meeting. If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SPONSOR MEETING AGENDA

MEETING DATE: December 21, 2010

TIME: 4:00 pm

LOCATION: FDA White Oak Campus
Silver Spring, MD

APPLICATION: NDA 201444

PRODUCT: Sodium thiosulfate and sodium nitrite

INDICATIONS: Treatment of cyanide poisoning

SPONSOR: Hope Pharmaceuticals

TYPE OF MEETING: Type A

MEETING CHAIR: Rigoberto Roca, M.D.; Deputy Division Director

MEETING RECORDER: Allison Meyer, Regulatory Project Manager, DAAP

FDA Attendees	Title
Bob A. Rappaport, M.D.	Division Director, Division of Anesthesia and Analgesia Products (DAAP)
Rigoberto Roca, M.D.	Deputy Division Director, DAAP
Xiaobin Shen, Ph.D.	Chemistry Reviewer, Office of New Drug Quality Assessment (ONDQA)
Olen Stephens, Ph.D.	Chemistry Reviewer, Office of New Drug Quality Assessment (ONDQA)
Danae Christodoulou, Ph.D.	CMC Lead, ONDQA
Prasad Peri, Ph.D.	Branch Chief (Acting), ONDQA
Eric Duffy, Ph.D.	Director, Division III, ONDQA
Marcus Delatte, Ph.D.	Pharmacology/Toxicology Reviewer
Dan Mellon, Ph.D.	Supervisor, Pharmacology/Toxicology
Allison Meyer	Regulatory Project Manager, DAAP
Sponsor Attendees	**Title**
Craig Sherman, MD	President
Hope Sherman	

The following comments are provided in response to your post-action meeting package (Amendment 0023; 6-Dec-2010) that responds to the key deficiencies for NDA 201444. As noted in the teleconference with the review Division on December 14, 2010, we believe the concerns you raised in your meeting package are best addressed by providing input regarding your proposed path to resolving the outstanding issues using your alternative approach to qualify the (b) (4) leachables.

The Agency acknowledges receipt of the new information and data contained within your post-action meeting package that suggests:

1. The (b) (4) leachables are primarily either (b) (4)

2. An FDA-approved phenytoin drug product appears to contain (b) (4) at levels that are comparable to or greater than those that would be administered via your NITHIODOTE® kit.

3. The leachables will increase at a slow rate relative to concentrations measured at release.

We have completed a preliminary review of the materials submitted and we believe that your alternative approach to resolve the deficiencies identified in the complete response letter may be a reasonable approach to address those deficiencies. However, a complete response submission for your NDA must include the following information for adequate review by the Chemistry, Manufacturing, and Controls (CMC) and pharmacology/toxicology teams. Please note that, while this information is essential for a complete understanding of your product's quality and safety, given our clinical risk-benefit assessment for NITHIODOTE® as a treatment for an emergent life-threatening condition, and its potential use in the setting of a terrorist attack, the additional in vitro studies noted in Items 8 and 9 may be performed as post-marketing study requirements. Also, should the information in Item 4 require the performance of an additional in vitro study, that study, too, may be submitted as a post-marketing requirement.

From a nonclinical perspective, provide the following information to establish a bridge to the previous finding of safety of phenytoin drug product:

1. In order to assure adequate compliance with the 505(b)(2) requirements, confirm that the phenytoin drug product you have analyzed was the Baxter product marketed under ANDA 84-307 and update your 356h form to include the referenced ANDA (84-307).

2. Assure that the complete response contains copies of the literature references you cited in your post-action meeting package.

From a CMC perspective, provide the following information:

3. Resubmit all of your NITHIODOTE® leachable data collected to date as a complete report that lists:

a. The batch/lot numbers, storage conditions, and age for each sample
b. The method of analysis used for each sample (i.e. ICP-OES or ICP-MS, method number, site of analysis, date of analysis)
c. Descriptions and sufficient method validation data for those methods
d. When different sites were used to analyze samples, adequate method robustness data to bridge the different data sets

4. Provide the levels of leachables from (b) (4) testing (ideally from multiple batches) in the comparator product(s) (e.g. phenytoin).

5. Using your leachables data collected for NITHIODOTE®, provide a statistical analysis evaluation (including graphs) that extrapolates the concentration of (b) (4) leachables over time in order to support your proposed expiry.

6. Provide in your resubmission an updated pH-time profile for your drug product solutions on stability.

7. Your meeting package (December 6, 2010) contains primary literature references that propose a mechanism for (b) (4) release from USP Type I (b) (4) glass under conditions of high pH and high heat. These primary literature references should be included in your resubmission.

Risk management post-approval:

8. To confirm the hypothesis that the bulk of the (b) (4) leachables originate from the USP Type I (b) (4) glass vial and follows the mechanism proposed in your primary literature references, provide an adequate extractable study as described in the 18-Nov-2010 complete response letter. This study should be conducted with the drug product solutions as the extraction medium and should be performed on both the stopper and vial.

9. Amend your post-approval stability protocol such that it adequately monitors leachables in your drug product. At a minimum, include monitoring at release, 3, and 6 months under accelerated stability conditions; include monitoring at release, 6, 12, 24, 36, 48, and 60 months under real time storage conditions in your post-approval stability batches.

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/s/

ALLISON MEYER
12/21/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 201444 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Nithiodote Established/Proper Name: sodium nitrite and sodium thiosulfate Dosage Form: injection		Applicant: Hope Pharmaceuticals Agent for Applicant (if applicable):
RPM: Allison Meyer		Division: Anesthesia and Analgesia

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 20166 - Sodium Thiosulfate Injection, USP

NDA 19316 - Magnesium Sulfate Injection

NDA 18803 - Sodium Chloride Injection

Provide a brief explanation of how this product is different from the listed drug.

The listed drugs contain pieces of supportive information for determinations of safety on the combination of sodium nitrite and sodium thiosulfate as indicated for the treatment of cyanide poisoning

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is November 21, 2010	☐ AP ☐ TA ☒ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	November 19, 2010
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☐ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) CR 11/18/2010
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	May 21, 2010
• Original applicant-proposed labeling	May 21, 2010
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	5/21/10
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	9/17/2010
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 10/8/2010 Accepted
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA 9/1/2010, 10/7/10 ☐ DRISK ☒ DDMAC 11/3/2010 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	10/19/2010, 11/15/2010
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 11/10/2010
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	6/11/10, 6/15/2010, 8/24/2010, 8/25/2010, 9/14/2010, 9/23/2010, 10/6/2010, 10/20/2010,

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	10/28/2010
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 7/27/07
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	4/22/09
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11/18/10
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See Division Summary Review
• Clinical review(s) *(indicate date for each review)*	
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	No clinical trials performed
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☒ None 6/17/2010
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/15/10
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 11/4/2010
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 7/15/2010, 11/4/2010
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 11/4/2010
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 6/17/2010, 7/8/2010, 7/15/2010, 9/27/2010, 11/3/2010
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 6/2/2010, 9/7/2010
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9/27/2010
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: 9/21/2010 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ODE’s ADRA.

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
11/19/2010

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, October 28, 2010 2:11 PM
To: 'sherman@hopepharm.com'
Subject: Manufacturing facility

Craig,
When will the new manufacturing facility be up and running?

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia and
Analgesia Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Friday, June 11, 2010 9:01 AM
To: 'sherman@hopepharm.com'
Subject: FW: NDA 201444

Importance: High

Sodium nitrite, sodium thiosulfate drug substances and products have been submitted with one-month stability data. Based on dates of batch manufacture, additional stability data may be available. When will the 3-month stability update be amended to the NDA for all drug substances and products?

Thanks,
Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia and
Analgesia Products
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Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, June 15, 2010 11:08 AM
To: 'sherman@hopepharm.com'
Subject: RE: Trade name

Craig,
This has to be resubmitted to the NDA. Please submit this ASAP, along with any background/rationale for this name and any correspondence you received to the IND with this.
Thanks,
Allison

-----Original Message-----
From: Craig Sherman [mailto:sherman@hopepharm.com]
Sent: Tuesday, June 15, 2010 11:00 AM
To: Meyer, Allison
Subject: Re: Trade name

Dear Ms. Meyer:

A request for proprietary name review was submitted to the FDA under PIND 78,597 Serial # 0000 on February 23, 2010.

Sincerely,

Craig Sherman, M.D.
President
Hope Pharmaceuticals
16416 N. 92nd Street #125
Scottsdale, AZ. 85260

------Original Message------
From: Meyer, Allison
To: sherman@hopepharm.com
Sent: Jun 15, 2010 7:41 AM
Subject: Trade name

Have you submitted your trade name for proprietary name review to the NDA?

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia and
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Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
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Sent from my Verizon Wireless BlackBerry

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, June 15, 2010 12:36 PM
To: 'sherman@hopepharm.com'
Subject: Financial disclosure

Craig,
You did not include financial disclosure forms with your application. You will need to submit form 3454 or 3455, whichever is appropriate to your application.
Thanks,

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia and
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Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, August 24, 2010 10:42 AM
To: 'sherman@hopepharm.com'
Subject: NDA 201444

"What is the frequency of requalification of the production [redacted] (b) (4). Briefly describe the re-qualification studies that are performed."

Thanks,

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia and
Analgesia Products
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Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, August 24, 2010 4:37 PM
To: 'sherman@hopepharm.com'
Subject: IR for NDA 201-444

You failed to provide adequate response regarding controlling the limit of (b) (4) in sodium thiosulfate. We reiterate our previous request regarding that you provide test and appropriate limit for the amount of (b) (4) in sodium thiosulfate. Therefore, you should provide the requested information as soon as possible so that we will be able to complete reviewing your NDA in timely manner. Please note that USP has a specification for (b) (4) in sodium sulfite at NMT (b) (4)

Allison Meyer
Sr. Regulatory Health Project Manager
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Meyer, Allison

From: Meyer, Allison
Sent: Wednesday, August 25, 2010 4:10 PM
To: 'sherman@hopepharm.com'
Subject: FW: IR for NDA 201-444

Please see CMC response to the applicant below:

Provide responses as outlined in Options 1 & 2. You can also include the safety justifications outlined in Option 4 as additional information.

Thanks!

From: Craig Sherman [mailto:sherman@hopepharm.com]
Sent: Wednesday, August 25, 2010 12:30 AM
To: Meyer, Allison
Subject: Re: IR for NDA 201-444

Dear Ms. Meyer:

Thank you for clarification of Request 1 of the August 19, 2010 Informational Request. Our August 23 response to Request 1 was based on our interpretation of the wording of the request to mean that we should monitor for the presence o [(b) (4)] in the final drug substance, which we are in fact doing now (i.e., as of yesterday per our response to FDA).

We also interpreted the request as meaning that we are to then establish an appropriate specification and do so on the basis of the actual [(b) (4)] levels measured in the above monitoring. In other words, specifications are normally appropriately set on the basis of actual values from actual batches. The [(b) (4)] values for the final drug substance batches are not available yet; the drug substance batches are being assayed for [(b) (4)] now but the [(b) (4)] levels for two recent batches will not be available until Friday due to laboratory scheduling issues. [(b) (4)] levels for the three validation batches of sodium thiosulfate as reported in the NDA will not be available for another week or more again due to scheduling issues.

Based on your clarification today, we now understand that the meaning of the request is to both monitor for [(b) (4)] immediately and set a specification immediately. Our best efforts to comply with this request include the following options. We are requesting that these options be presented to the reviewing chemist to select the option that constitutes an adequate response for FDA, which we will then implement immediately. We will then prepare a formal revised response to Request 1 containing the adequate response selected by FDA as a formal amendment to the NDA.

Response Option 1: We are assaying two of the available batches of final drug substance for [(b) (4)] now, and the results will be available on Friday August 27. These two batches were recently manufactured by [(b) (4)] in anticipation of volume requirements needed for process validation of the drug product at Cangene in the near future. On the basis of these results, a [(b) (4)] specification will be set and the new assay and specification amended immediately to the NDA. The formal amendment will be submitted by Tuesday August 31.

In addition, [(b) (4)] were able to test six (6) batches of the sodium sulfite starting material during the past few days. The [(b) (4)] results show that [(b) (4)] levels in the sodium sulfite batches are no more than [(b) (4)] in any of the six batches. Based on these data, Hope considers it possible to set a specification requirement for [(b) (4)] in the final sodium thiosulfate drug substance of NMT [(b) (4)] of [(b) (4)]

In summary, the (b) (4) specification for the final drug substance will be set on the values from these two batches. This is normally too few batches upon which to set a specification, therefore the specification will be set high enough to account for a larger range of (b) (4) that might be seen when more batches are assayed.

Response Option 2: (b) (4) data will be available for the original three validation batches of the sodium thiosulfate drug substance and an additional two batches recently manufactured on or about September 3, 2010. Hope will amend the NDA at this time with the available data for (b) (4) content of the sodium thiosulfate drug substance by September 5, 2010. An updated analytical procedure and validation data for the analytical procedure will take at least another month to complete and so cannot be submitted until about 3 November 2010 however.

Response option 3: Hope can set the specification for (b) (4) in the drug substance immediately (i.e., now) at (b) (4) without waiting for the (b) (4) results on Friday. A specification of (b) (4) ppm the same as the (b) (4) specification for sodium sulfite USP, as FDA has pointed out.

This option poses two immediate concerns however. The first is that setting specifications without actual data from actual batches is not accepted practice (i.e., unless controlling for impurities that pose a known safety risk). The second is that within 3 days, we might learn that the specification was too narrow because more than (b) (4) of (b) (4) might be found in the drug substance, in which case the specification needs to be changed.

Response option 4: This response is similar to our original response: we will monitor for (b) (4) starting now and set an appropriate specification on the basis of the results of a larger number of batches of drug substance, and report the specification to the NDA in the annual report per 21 CFR 314.70. However, this version of the response includes two significant changes:

1. Hope will add an acceptance specification of (b) (4) for the sodium sulfite starting material. This will help ensure that (b) (4) in the drug substance is controlled at the most likely source of (b) (4) being introduced into the manufacture of the drug substance.

2. A justification is included to support this option on the basis that (b) (4) poses minimal toxicological concerns at significantly higher concentrations than the USP specification of (b) (4) set for sodium sulfite. This justification should remove safety concerns for additional (b) (4) being introduced into the drug substance from sources other than the sodium sulfite starting material. This justification is

explained below.

(b) (4)

(b) (4)

(b) (4)

[redacted] (b) (4)

I await your guidance on this matter.

Sincerely,

Craig Sherman, M.D.

President

Hope Pharmaceuticals

16416 N. 92nd St. #125

Scottsdale, AZ 85260

Tel: (480) 607-1970

Fax: (480) 607-1971

Email: sherman@hopepharm.com

Meyer, Allison <Allison.Meyer@fda.hhs.gov> wrote:

You failed to provide adequate response regarding controlling the limit of [redacted] (b) (4) in sodium thiosulfate. We reiterate our previous request regarding that you provide test and appropriate limit for the amount of [redacted] (b) (4) in sodium thiosulfate. Therefore, you should provide the requested information as soon as possible so that we will be able to complete reviewing your NDA in timely manner. Please note that USP has a specification for [redacted] (b) (4) in sodium sulfite at NMT [redacted] (b) (4)

Allison Meyer
Sr. Regulatory Health Project Manager
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Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, September 14, 2010 10:26 AM
To: 'sherman@hopepharm.com'
Subject: NDA 201444 labeling comments

Revise the labeling accordingly:

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.

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'.

Container Labels (Sodium Nitrite and Sodium Thiosulfate)

A. We note that the container labels for the sodium nitrite and sodium thiosulfate have the (b) (4) [redacted]

B. Relocate the statement 'Single Dose Vial' away from the net quantity 'XX mL' and revise to read 'Single Use Only. Discard Unused Portion'.

Allison Meyer
Sr. Regulatory Health Project Manager
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Meyer, Allison

From: Meyer, Allison
Sent: Thursday, September 23, 2010 12:51 PM
To: 'sherman@hopepharm.com'
Subject: NDA 201-444 IR

Craig,
Please respond to the following by Friday:

1. Commit to using USP compendial grade [redacted] (b) (4) for the manufacturing process of the sodium nitrite and sodium thiosulfate drug substances.

2. As a Phase 4 post-marketing commitment, commit to tightening your manufacturing process parameters for the sodium drug substance. Specifically, tighten your process parameters for the Step [redacted] (b) (4) and the yield that is acceptable for commercial batches.

Thanks,

Allison Meyer
Sr. Regulatory Health Project Manager
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10903 New Hampshire Avenue
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Meyer, Allison

From: Meyer, Allison
Sent: Thursday, September 23, 2010 1:04 PM
To: 'sherman@hopepharm.com'
Subject: FW: NDA 201-444 IR, please

Please change the request to the following:

2. As a Phase 4 post-marketing commitment, commit to tightening your manufacturing process parameters for the sodium nitrite drug substance. Specifically, tighten your process parameters for the Step [redacted] (b) (4) and the yield that is acceptable for commercial batches.

Thanks,

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia and
Analgesia Products
Office of New Drugs II

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
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Meyer, Allison

From: Meyer, Allison
Sent: Wednesday, October 06, 2010 2:06 PM
To: 'sherman@hopepharm.com'
Subject: FW: (b) (4)

1. Clarify the amount of leachable (b) (4) that was detected by ICP-OES from 4-month inverted storage at 40 deg C of the sodium nitrite drug product.
2. Clarify whether the amount of (b) (4) obtained from the 4-month time point of your sodium thiosulfate leachable study obtained, was (b) (4) (b) (4)
3. Provide a description of the analytical methods used for your leachables study along with their validation, for the observed leachates, including (b) (4).
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).
5. If you can provide adequate evidence to support the your conclusion that the (b) (4) determine the levels of (b) (4) that would be infused into the patient and provide references to support the conclusion that those levels do not represent a safety concern.
6. Submit the references you used to conclude that the levels of (b) (4) do not represent a safety concern.
7. To support the conclusion that the stoppers do not represent a unique safety concern due to their widespread use in other FDA products, provide data to show that there are other FDA approved intravenous products that would result in comparable daily IV exposure to (b) (4) and provide data to show that the levels of (b) (4) in the leachates from this product are comparable to that found in saline leachates.

As per this morning's discussion.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia and
Analgesia Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993

301-796-1258
301-796-9713 (fax)

Meyer, Allison

From: Meyer, Allison
Sent: Wednesday, October 20, 2010 8:45 AM
To: 'sherman@hopepharm.com'
Subject: FW: IR for 201-444

Craig,

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

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia and
Analgesia Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
11/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201444

METHODS VALIDATION MATERIALS RECEIVED

Hope Pharmaceuticals
Attention: Craig Sherman, M.D.
President
16416 N. 92nd Street #125
Scottsdale, AZ 85260

Dear Dr. Sherman:
:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (Sodium Nitrite 30 mg/L and Sodium Thiosulfate 250 mg/mL) Solution for Injection and to our 08/10/2010, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 08/18/10, 08/25/2010 and 10/4/10, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
10/12/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 201444

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Hope Pharmaceuticals
16416 N. 92nd Street #125
Scottsdale, Arizona 85260

ATTENTION: Craig Sherman, MD
President

Dear Dr. Sherman:

Please refer to your New Drug Application (NDA) dated May 21, 2010, received May 21, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sodium Nitrite Injection, 30 mg/mL and Sodium Thiosulfate Injection, 250 mg/mL.

We also refer to your September 8, 2010, correspondence, received September 8, 2010, requesting review of your proposed proprietary name, Nithiodote. We have completed our review of the proposed proprietary name, Nithiodote and have concluded that it is acceptable.

The proposed proprietary name, Nithiodote, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your September 8, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Allison Meyer at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201-444

REQUEST FOR METHODS VALIDATION MATERIALS

Hope Pharmaceuticals
Attention: Craig Sherman, M.D.
President
16416 N. 92nd Street #125
Scottsdale, AZ 85260

Dear Dr. Sherman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (b) (4) (Sodium Nitrite 30 mg/L and Sodium Thiosulfate 250 mg/mL) Solution for Injection.

We will be performing methods validation studies on [redacted] (b) (4) (Sodium Nitrite 30 mg/L and Sodium Thiosulfate 250 mg/mL) Solution for Injection as described in NDA 201-444.

In order to perform the necessary testing, we request the following sample materials and equipments:

Equipment (Items will be returned on completion of method validation)

[redacted] (b) (4)

Reagents/Standards

[redacted] (b) (4)

(b) (4)

Sample
(b) (4)
(b) (4)
(b) (4)
(b) (4)

Sodium Nitrite Drug Substance
Sodium Thiosulfate Drug Substance
solutions for injection
Sodium Nitrite

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

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/s/

JAMES F ALLGIRE
08/10/2010

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

METHODS VALIDATION REQUEST

TO: **FDA**
Division of Pharmaceutical Analysis, HFD-920
Attn: Nick Westenberger
Room 1002
1114 Market Street
St. Louis, MO 63101

FROM: Olen 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

Through: Dr. Prasad Peri, Chemistry Team Leader, HFD-170
Phone: (301)-796-1730
and
Michael Folkendt, ONDC Methods Validation Coordinator, HFD-800
Phone: 301-827-5173

SUBJECT: Methods Validation Request

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 #125; Scottsdale, AZ, 85260

Telephone: 480-607-1970 Fax: Applicant contact's FAX number

Date NDA Received by CDER: **5/21/2010** Chemical/Therapeutic Type:

Date of Amendment(s) containing the MVP: **5/21/2010** Special Handling Required: No

DATE of Request: **July 20, 2010** DEA Class: N/A

Requested Completion Date: **10/21/2010** **Format of Methods Validation Package**

PDUFA User Fee Goal Date: **11/19/2010** ☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request Form*. Upon receipt of the samples, perform the tests indicated in item 3 of the attached *Methods Validation Request Form* as descr bed in the MV package. We request your report to be submitted in DFS promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the reviewing chemist of the date the validation process begins. If the requested completion date cannot be met, please promptly notify the reviewing chemist and the ONDC Methods Validation Coordinator.
Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying Methods Validation Report Summary). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DFS. Send the complete report, with the DFS signed *Methods Validation Report Summary*, by overnight courier to the above reviewing chemist. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

ATTACHMENT(S): *Methods Validation Request Form*, NDA Methods Validation Package (if not available in the EDR).

APPEARS THIS WAY ON ORIGINAL

MVP Reference #	METHODS VALIDATION REQUEST	NDA # 201-444

← SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT		
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION

↑ Contents of Attached Methods Validation Package:	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	3.2.P.1
Specifications/Methods for New Drug Substance(s)	3.2.S.4.1
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5.1
Supporting Data for Accuracy, Specificity, etc.	3.2.S.4.3
Applicant's Test Results on NDS and Dosage Forms	3.2.S.4.4 3.2.P.5.4
Other:	

→ **REQUESTED DETERMINATIONS** (Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.)

Method ID	Method Title	Volume/Page	MV Request Category (see attached page)	Comments
PHR-177	Assay and Related Substances by HPIC for Sodium Nitrite	3.2.S.4.2 under sodium nitrite	**7**	Applicant proposes to replace the monograph method with this HPIC method
PHR-190	(b) (4) by limit test by potentiometric detection	3.2.P.5.2 under sodium nitrite	**7**	Novel method
SS_SN_0003 and SS_SN_0004	ICP-MS for residual metals	3.2.S.4.2 under sodium thiosulfate	**7**	Product will be used in emergency situations without time for triage. Products have a higher potential for residual metal contamination. Nature of the product complicates analysis
CH-PRO-294	Total (b) (4)	3.2.S.4.2	**7**	The applicant claims that (b) (4) of the drug product/substances adversely affect the analysis. We would like a better understanding of this method's capabilities

Additional Comments:

APPEARS THIS WAY ON ORIGINAL

Methods Validation Request Criteria

MVP Request Category	Description
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason.

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

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/s/

OLEN M STEPHENS
07/20/2010

XIAOBIN SHEN
07/21/2010

PRASAD PERI
07/21/2010
I concur. The rationale for submitting this is to verify the validation data provided by the applicant for this high profile, critical care drug product to be used in emergency situations. Some of the methods described, although standard, are critical to ensure the quality of the drug product. An assessment of the LODs and LOQs for the NPOI is critical.

MICHAEL M FOLKENDT
07/21/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 201444

FILING COMMUNICATION

Hope Pharmaceuticals
16416 North 92nd Street, Suite 125
Scottsdale, AZ 85260

Attention: Craig Sherman, M.D.
President

Dear Dr. Sherman:

Please refer to your new drug application (NDA) dated May 21, 2010, received May 21, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) containing co-packaged sodium nitrite injection and sodium thiosulfate injection.

We also refer to your submissions dated June 15 and 25, and July 2 and 9, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is November 21, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 29, 2010.

During our filing review of your application, we have identified the following potential review issues:

1. The sodium thiosulfate release and stability specifications for bacterial endotoxins listed in Table 1 of Section 3.2.P.5.1 and Table 1 of Section 3.2.P.8.1 are NMT (b) (4) while all other references to this specification list it as NMT (b) (4) Clarify the

proposed bacterial endotoxin specification for sodium thiosulfate drug product and correct all parts of the submission that are in error.

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

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

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

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

6. For both the sodium thiosulfate and sodium nitrite drug products, no data were presented to support the maximum (b) (4) completion of (b) (4) sterilization of the batch. While it appears that the drug products may be (b) (4) If the latter is chosen, you should supply the necessary validation studies to support (b) (4) of the drug product.

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

8. The current NDA submission contained two manufacturing floor plans for the manufacture of the drug products - one "Interim" for current production of the stability batches and possibly initial commercial batches, and another "Future" for a modification

to the [redacted] (b) (4). The current NDA submission will be reviewed in light of the facility that was used to produce the process validation/stability batches of the drug products. Post-approval modifications to a facility or filling line that directly impact the manufacture of an approved drug product will require the submission of a supplement to the New Drug Application (NDA). Alternatively, an extensive Comparability Protocol (CP), covering the modifications and their subsequent validation studies, could be submitted as an amendment to the current submission. You are advised that if the CP is submitted to the current application and it is found to be deficient, then the application in its entirety would be considered deficient.

9. 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.

10. Provide a Letter of Authorization (LoA) to [redacted] (b) (4), referenced in M3.

11. Clarify if the [redacted] (b) (4) stoppers are [redacted] (b) (4)

12. Monitor and report leachables in the drug product, at the 6, 9, and 12-month time interval.

13. Submit a toxicological risk assessment for the maximum daily exposure to each identified extractable from the [redacted] (b) (4) stoppers noted in Report 1003/21489 titled [redacted] (b) (4) [redacted] (b) (4) as outlined in the FDA Guidance for Industry titled "Container Closure Systems for Packaging Human Drugs and Biologics." In general, the evaluation of extractables and leachables from the drug container closure system must include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents "Container Closure Systems for Packaging Human Drugs and Biologics" and "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation." Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.

14. Although discussed in the submission, we are not able to locate the justification for the proposed drug product specification for nitrate, which exceeds the ICHQ3B(R2)

qualification threshold of NMT (b) (4) Please identify where in the submission this discussion is located or provide rationale for the safety of the proposed specification.

We also request that you submit the following information:

Drug Substances:

15. Provide the Certificates of Analysis (CoA) for the desiccant pouch and drum 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.

16. 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.

17. In the acceptance criteria of your sodium nitrite starting materials and solvents, clarify what is meant by "tests required for retest."

18. 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.

19. For your (b) (4) methods, provide the following information:

    a. In your validation reports for sodium nitrite, you report an LOD of 0.1 ppm and an LOQ of 0.4 ppm. However, based on your batch records, the LOD appears to be 5.6 ppm. 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 LODs and LOQs.

    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 LODs are determined for each drug substance batch in your NPOC method.

20. 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, and batch/lot number.

21. Justify why the sodium thiosulfate appearance specification for stability has changed from the colorless crystals at release to white to off-white solid. Alternatively, use the same acceptance criterion.

22. 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.

23. 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. Water content of sodium thiosulfate drug substance and standard should be determined shortly before sample and standard preparation to avoid using a biased water content 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

24. 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.

25. Calculate and report the tonicity for your sodium thiosulfate and sodium nitrite drug products.

26. 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 [redacted] (b) (4)

27. 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 [redacted] (b) (4). Identify the overage source and correct as appropriate.

28. 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.

29. Clarify whether your [redacted] (b) (4) kit will be supplied with syringes and needles or only with the two drug product vials.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

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/s/

BOB A RAPPAPORT
07/20/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Allison Meyer, ODE II/DAAP/301-796-1258

DATE 7/15/10	IND NO.	NDA NO. 201444	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT 5/21/10

NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG Critical Care	DESIRED COMPLETION DATE 8/30/10

NAME OF FIRM: Hope Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: NEW NDA/Labeling

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: \\CDSESUB1\EVSPROD\NDA201444\201444.enx
We have received a new NDA 201444. I have scheduled Planning, MC and WU meetings. We would like the labeling to be reviewed by DMEPA.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

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/s/

ALLISON MEYER
07/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Allison Meyer, ODEII/DAAP/301-796-1258

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
7/15/10		201444	New NDA

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
(b) (4)	Priority	Critical Care	8/30/10

NAME OF FIRM:

Hope Pharmaceuticals

PDUFA Date: 11/19/10

Action Date: 8/30/10 – management is taking early action

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
x PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☒ CARTON/CONTAINER LABELING
MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☒ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☒ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: \\CDSESUB1\EVSPROD\NDA201444\201444.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: 8/3/10

Labeling Meetings: TBD

Wrap-Up Meeting: 10/5/10

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL ☐ HAND

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NDA-201444	ORIG-1	HOPE PHARMACEUTICALS	SODIUM NITRITE INJECTION

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/s/

ALLISON MEYER
07/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 201444

NDA ACKNOWLEDGMENT

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

Attention: Craig Sherman, M.D.
President

Dear Dr. Sherman:

We have received your New Drug Application (NDA) submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Sodium Nitrite injection

Date of Application: May 21, 2010

Date of Receipt: May 21, 2010

Our Reference Number: NDA 201444

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 20, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

If you have any questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

ALLISON MEYER
05/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Sylvia Gantt, 301-796-2123	FROM *(Name, Office/Division, and Phone Number of Requestor)*: Swati Patwardhan, ONDQA, Division of Post-Marketing Assessment, 301-796-4085

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/21/10	NA	20-1444	N-000	5/21/10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(b) (4)	Priority		8/21/10

NAME OF FIRM: Hope Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: New NDA for (b) (4) containing co-packaged sodium nitrite injection and sodium thiosulfate injection for the treatment of (b) (4) cyanide poisoning.
This NDA is expected to receive priority consideration.

\\CDSESUB1\EVSPROD\NDA201444

The PDFUA goal date is : 11/21/10

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Swati Patwardhan	☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

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/s/

SWATI A PATWARDHAN
05/21/2010

DANAE D CHRISTODOULOU
05/21/2010