

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209387Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, N.C. 28645
www.exelapharm.com

PATENT CERTIFICATION

Paragraph I Certification: No Orange Book Patents

The undersigned hereby certifies that to the best of our knowledge and in the opinion of Exela Pharma Sciences, LLC, based on the Electronic Orange Book (“Orange Book”) record available as of January 27, 2017, for NITROPRESS® (sodium nitroprusside injection), NDA N018450, held by Abbvie, Inc., patent information has not been submitted to FDA.

The Orange Book lists NDA N018450 as having been discontinued, with the notation that: “**Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**.” The Orange Book lists no patents for NDA N018450 and states that “There are no unexpired patents for this product in the Orange Book database.”

Phanesh
Koneru

Digitally signed by Phanesh Koneru
DN: cn=Phanesh Koneru, j=US, o=Exela Pharma
Sciences, LLC, email=pkoneru@exela.us, c=United
States, givenName=Phanesh Koneru
Date: 2017.01.27 10:48:53 -05'00'

January 27, 2017

Phanesh Koneru, Ph.D., J.D., LL.M.
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PATENT CERTIFICATION

In accordance with the Federal Food, Drug and Cosmetic Act (FDCA) and with the Code of Federal Regulations, the following patent certification is hereby provided for Exela Pharma Sciences, LLC (Exela's) Sodium Nitroprusside (b)(4) Injection, 0.5 mg/mL, 50 mg/100 mL. This certifications are made in accordance with Section 505(b)(2)(A) of the FDCA and 21 C.F.R. 314.50(i)(1)(i).

Paragraph I Certification: No Relevant Patents

The undersigned hereby certifies that to the best of our knowledge and in the opinion of Exela Pharma Sciences, LLC, there are no unexpired patents, which claim the reference listed drug, NITROPRESS® (sodium nitroprusside injection), ANDA 071961, held by Hospira, Inc.

Jonathan E.
Sterling

Digitally signed by Jonathan E. Sterling
DN: cn=Jonathan E. Sterling, o=Exela
Pharma Sciences, LLC, ou=Regulatory
Affairs, email=jsterling@exela.us, c=US
Date: 2016.05.06 12:16:02 -04'00'

Jonathan E. Sterling
Vice President of Quality and Regulatory Affairs
Exela Pharma Sciences, LLC

CONFIDENTIAL

FOOD AND DRUG ADMINISTRATION

SODIUM NITROPRUSSIDE (b) (4) INJECTION

NEW DRUG APPLICATION

EXELA PHARMA SCIENCES, LLC.

1.3.5.1 PATENT INFORMATION

2.0 EXCLUSIVITY

According to the FDA listed information published in the Electronic Orange Book, exclusivity applies for the Reference Listed Drug, NITROPRESS[®] (sodium nitroprusside injection), ANDA 071961.

An Exclusivity Certification has been provided in the Exclusivity Section of this application.

EXCLUSIVITY SUMMARY

NDA # 209387

SUPPL #N/A

HFD # 110

Trade Name Nipride RTU

Generic Name sodium nitroprusside

Applicant Name Exela Pharma Sciences, LLC.

Approval Date, If Known 03/08/2017

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)

b) 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.

This application relied on the Agency's previous finding of safety and effectiveness for the reference listed drug, Nitropress (sodium nitroprusside) Injectable (NDA 018450 by Abbvie Inc. The NDA was withdrawn on September 17, 2003. Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons. The Applicant requested a waiver of *in vivo* Bioavailability/Bioequivalence requirements for Exela's Sodium Nitroprusside ^{(b) (4)} Injection.

The proposed drug product is a parenteral solution for administration by injection, and the proposed drug product has the same active ingredient (sodium nitroprusside), and has the same dosage form, route of administration and indication as the LD. However, the proposed product and the listed drug product are different with regard to the inactive

ingredients [sodium chloride vs. dextrose] and the concentration of the active ingredient. The differences in inactive ingredients and the difference in the concentration of the active ingredient are not expected to affect the bioavailability of sodium nitroprusside in the proposed drug product when administered via IV infusion route.

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:

N/A

c) Did the applicant request exclusivity?

YES NO

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

--

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

YES NO

No, but pediatric studies were conducted and labeling updated as part of a NIH generated Written Request.

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

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 NO

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

NDA# 018450 Nitropress®

NDA# 017546 Nipride®

NDA# 018581 Sodium
nitroprusside

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

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:

Name of person completing form: Maryam Changi
Title: Regulatory Project Manager
Date: February 22, 2017

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MARYAM K CHANGI
03/08/2017

NORMAN L STOCKBRIDGE
03/08/2017



P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, N.C. 28645

May 6, 2016

Pre-Approval Manager
Food and Drug Administration
Atlanta - Southeast Regional Office
60 Eighth Street NE
Atlanta, GA 30309

**RE: Sodium Nitroprusside (b) (4) Injection, 0.5 mg/mL, 50 mg/100 mL
Manufacturing Site: Exela Pharma Sciences (Lenoir, NC)
NDA # To be assigned, Sequence 0000**

Dear Pre-Approval Manager:

Enclosed in this correspondence is a true and accurate electronic copy of the submission provided to the central FDA office. This copy is to serve as the field office copy of the referenced submission.

Sincerely,

Jonathan E. Sterling

Digitally signed by Jonathan E. Sterling
DN: cn=Jonathan E. Sterling, o=Exela Pharma
Sciences, LLC, ou=Regulatory Affairs,
email=jsterling@exela.us, c=US
Date: 2016.05.06 12:05:37 -0400

Jonathan E. Sterling
Vice President of Quality and Regulatory Affairs
Exela Pharma Sciences
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(828) 758-5474

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

/s/

JONATHAN T DOW
03/23/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209387	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Nipride RTU Established/Proper Name: sodium nitroprusside Dosage Form: Injection		Applicant: Exela Pharma LLC. Agent for Applicant (if applicable): Phanesh Koneru
RPM: Maryam Changi		Division: DCaRP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: _____</p> <p><i>Note: 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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>March 9, 2017</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ 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 _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approved, 03/08/2017
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included (Final labeling)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included (Final labeling)
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	Acceptable Letter: 03/07/2017 Review: 03/02/2017
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 07/07/2016 DMEPA: 10/18/2017- 01/31/2017 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: 01/31/2017 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i> ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Reviews:06/29/2016 07/07/2016- 03/08/2017 505(b)(2) 02/28/2017
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Completed

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: Same active ingredient, dosage form, route of administration, dosing regimen. Review team concurred 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	07/15/16-08/03/16-09/19/16-10/13/16-11/04/16-11/28/16-12/14/16-12/19/16-1/9/17/17-01/26/17(Two)-02/15/17-02/28/17-03/02/17-03/03/17
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg cancelled after Preliminary comments sent
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	N/A

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 03/07/2017
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 03/01/2017
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	N/A
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	N/A This is a 505(b)(2) application with no clinical data.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None "505b2 with no clinical data or safety concerns."
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	<input type="checkbox"/> None N/A
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input type="checkbox"/> None N/A
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 02/28/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) <i>(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: 02/27/2017 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done N/A (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done N/A
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

MARYAM K CHANGI
03/08/2017



NDA 209387

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Exela Pharma Sciences, LLC.
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

ATTENTION: Phanesh Koneru, Ph.D., J.D., LL.M.
President and CEO

Dear Dr. Koneru:

Please refer to your New Drug Application (NDA) dated May 6, 2016, received May 9, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sodium Nitroprusside in 0.9% Sodium Chloride, 0.5 mg/mL.

We also refer to:

- Your December 8, 2016, correspondence, received December 9, 2016, requesting a review of your proposed proprietary name, Nipride
- Our December 14, 2016, correspondence, requesting clarification of your proposed proprietary name
- Your December 14, 2016, amendment, received December 15, 2016, requesting a review of your proposed proprietary name, Nipride RTU
- Our December 19, 2016, information request
- Your December 21, 2016, amendment, received December 27, 2016, responding to the information request for your proposed proprietary name, Nipride RTU

We have completed our review of the proposed proprietary name, Nipride RTU and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in the above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Maryam Changi, Regulatory Project Manager in the Office of New Drugs, at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

VIKKI S KINSEY
03/07/2017

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/07/2017

Kord Bacheh Changi, Maryam

From: Kord Bacheh Changi, Maryam
Sent: Friday, March 03, 2017 9:38 AM
To: 'Tracie Watkins'; Phanesh Koneru
Cc: Aruna Koganti
Subject: RE: RE: RE: labeling NDA 209387
Attachments: SNP - MM.DOCX

Importance: High

Dear Dr. Koneru,

Please find attached, our proposed draft the revised labeling for NDA 209387, with the Agency's edits included. Please review with your team and let us know if these changes are acceptable as final version by end of the day today March 3, 2017.

Asper your question regarding submitting new sequence, you are welcome to keep sending in submissions with updated labeling, but it is not necessary.

Please confirm the receipt.

Best,

Maryam Changi, PharmD,

Regulatory Project Manager

Office of Drug evaluation 1

Division of Cardiovascular and Renal Products

Phone:(240) 402-2725

Email: Maryam.Kordbachehchangi@fda.hhs.gov

Address for desk and courtesy copies:

Food and Drug Administration

10903 New Hampshire Avenue

White Oak, Building 22, Room 4175

Silver Spring, MD 20993

Address for official submissions to your administrative file:

Division of Cardiovascular and Renal Products

FDA, CDER, HFD-110

5901-B Ammendale Rd.

Beltsville, MD 20705-1266

From: Tracie Watkins [mailto:twatkins@exela.us]
Sent: Thursday, March 02, 2017 7:00 PM
To: Kord Bacheh Changi, Maryam; Phanesh Koneru

Cc: Aruna Koganti
Subject: RE: RE: RE: labeling NDA 209387

Dear Dr. Changi,

Please see the revised package inserts to Sodium Nitroprusside NDA 209387. We greatly appreciate patience and kindness.

Sincerely,

Tracie Watkins

From: Kord Bacheh Changi, Maryam [<mailto:Maryam.KordBachehChangi@fda.hhs.gov>]
Sent: Thursday, March 02, 2017 6:49 PM
To: Phanesh Koneru
Cc: Aruna Koganti; Tracie Watkins
Subject: RE: RE: RE: labeling NDA 209387

No problem.

From: Phanesh Koneru [<mailto:phanesh@exela.us>]
Sent: Thursday, March 02, 2017 6:44 PM
To: Kord Bacheh Changi, Maryam
Cc: Aruna Koganti; Tracie Watkins
Subject: RE: RE: RE: labeling NDA 209387

Will do. Thanks very much.

On Mar 2, 2017 6:34 PM, "Kord Bacheh Changi, Maryam" <Maryam.KordBachehChangi@fda.hhs.gov> wrote:

Please email me the updated one tonight or early tomorrow morning. I will let you know tomorrow, if you need to submit a new sequence.

From: Phanesh Koneru [<mailto:phanesh@exela.us>]
Sent: Thursday, March 02, 2017 6:32 PM
To: Kord Bacheh Changi, Maryam
Cc: Aruna Koganti; Tracie Watkins
Subject: RE: RE: RE: labeling NDA 209387

Dr. Changi, one more time please accept our apologies. We just discovered that we have not updated the table of contents with the changes. Should we submit a new sequence? We will send the electronic version tonight and hand deliver the CD tomorrow morning in Maryland. Please advise. Thanks.

On Mar 2, 2017 6:20 PM, "Kord Bacheh Changi, Maryam" <Maryam.KordBachehChangi@fda.hhs.gov> wrote:

Thanks for the clarification.

From: Phanesh Koneru [mailto:phanesh@exela.us]
Sent: Thursday, March 02, 2017 5:26 PM
To: Kord Bacheh Changi, Maryam; Tracie Watkins; Aruna Koganti
Subject: Fwd: RE: RE: labeling NDA 209387

Dr. Changi, please see below. Please let me know if you have any follow up questions. Thanks.

----- Forwarded message -----

From: "Aruna Koganti" <akoganti@exela.us>
Date: Mar 2, 2017 5:09 PM
Subject: RE: RE: labeling NDA 209387
To: "Phanesh Koneru" <phanesh@exela.us>
Cc: "Tracie Watkins" <twatkins@exela.us>

Hi Phanesh,

Yes, the final labeling submitted today incorporates all of their recommendations received to date. Some of the comments we got today were already taken care of previously. I think today's comments were from one single reviewer who used a previous document to make additional comments. But all of the comments we received today were either already incorporated or were newly incorporated today.

I think Maryam's confusion may be because she is not seeing as many tracked changes as she sent us today and that is because we are making the changes in a more recent submission.

Hope this helps,

Aruna

From: Phanesh Koneru [mailto:phanesh@exela.us]
Sent: Thursday, March 02, 2017 4:58 PM
To: Aruna Koganti
Subject: Fwd: RE: RE: labeling NDA 209387

Aruna, can you please answer? Thanks

----- Forwarded message -----

From: "Kord Bacheh Changi, Maryam" <Maryam.KordBachehChangi@fda.hhs.gov>

Date: Mar 2, 2017 4:56 PM

Subject: RE: labeling NDA 209387

To: "Tracie Watkins" <twatkins@exela.us>

Cc: "Phanesh Koneru" <phanesh@exela.us>

Hi Tracie,

Would you please let me know that this is your final labeling based on all of our comments?

Thanks,

Maryam

From: Tracie Watkins [mailto:twatkins@exela.us]
Sent: Thursday, March 02, 2017 1:52 PM
To: Kord Bacheh Changi, Maryam; Phanesh Koneru
Cc: Aruna Koganti
Subject: RE: labeling NDA 209387

Dear Dr. Changi,

A courtesy copy of the revised proposed labeling to NDA 209387 is attached with this email. The official copy of the revised proposed labeling will be sent by UPS this afternoon for next day delivery. Please let us know if you need any additional information.

Sincerely,

Tracie Watkins

From: Kord Bacheh Changi, Maryam [mailto:Maryam.KordBachehChangi@fda.hhs.gov]
Sent: Thursday, March 02, 2017 10:35 AM

To: Phanesh Koneru
Cc: Tracie Watkins
Subject: RE: labeling NDA 209387

Great. Thanks.

From: Phanesh Koneru [<mailto:phanesh@exela.us>]
Sent: Thursday, March 02, 2017 10:28 AM
To: Kord Bacheh Changi, Maryam
Cc: Tracie Watkins
Subject: Re: labeling NDA 209387

Dear Dr. Changi, receipt is acknowledged. We will respond by 2 PM latest today. Thanks very much.

On Mar 2, 2017 10:24 AM, "Kord Bacheh Changi, Maryam" <Maryam.KordBachehChangi@fda.hhs.gov> wrote:

Dear Dr. Koneru,

Please find attached, our proposed draft the revised labeling for NDA 209387, with the Agency's comments included. Please review with your team and let us know if you can agree to these changes by end of the day today March 2, 2017.

Please confirm the receipt.

Thanks,

Maryam Changi, PharmD,

Regulatory Project Manager

Office of Drug evaluation 1

Division of Cardiovascular and Renal Products

Phone: [\(240\) 402-2725](tel:(240)402-2725)

Email: Maryam.Kordbachehchangi@fda.hhs.gov

Address for desk and courtesy copies:

Food and Drug Administration

10903 New Hampshire Avenue

White Oak, Building 22, Room 4175

Silver Spring, MD 20993

Address for official submissions to your administrative file:

Division of Cardiovascular and Renal Products

FDA, CDER, HFD-110

5901-B Ammendale Rd.

Beltsville, MD 20705-1266

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



Office of Process and Facilities
Division of Inspectional Assessment
10903 New Hampshire Avenue
Building 51, Room 3171
Silver Spring, MD 20993

TELEPHONE: (301) 796-3532
FAX: (301) 847-8742

February 15, 2017

Phanesh Koneru, Ph.D, LL.M
President and CEO
Exela Pharma Sciences LLC
1245 Blowing Rock Blvd
Lenoir, NC 28645-3618

Reference: FEI 3008563008

Dear Dr. Koneru,

We completed our review of the Establishment Inspection Report (EIR) for the inspection conducted at your pharmaceutical drug product manufacturing facility in Lenoir, NC by Investigator Seneca D. Toms from June 6 - 8, 2016. A Form FDA-483, Inspectional Observations, was not issued at the conclusion of the inspection.

We have some concerns, summarized below, that require clarification. We will determine the final recommendation for the acceptability of your facility in support of NDA 209387 after we receive the additional information as follows:

- 1) The majority of visual inspection rejects for batches XLNF1545, XLNF1546, XLNF1547, and XLNC1604 were for particulate matter.
 - a. Provide any SOPs related to the trending of particulate matter rejects and defects across multiple batches of a single product, across products made on the same line, and across all products for the facility itself. Also, clarify whether these SOPs apply to process simulation (i.e. media fill), commercial, and non-commercial batches.
 - b. Provide any SOPs that establish defect or reject thresholds and limits within a batch which would trigger an investigation. Provide any Quality SOPs that establish maximum defect limits which would result in rejecting or failing an entire batch.
 - c. If available, provide any recent defect trending data that includes process simulation (i.e. media fill), commercial, and non-commercial batches.

U.S. Food and Drug Administration
CDER Office of Pharmaceutical Quality
Office of Process and Facilities
www.fda.gov



2)

NON-RESPONSIVE

- 3) Please perform an AQL visual inspection of the Sodium Nitroprusside retain samples for lots XLNF1545, XLNF1546, XLNF1547, and XLNC1604, and any other sterile products made on the same filing line following these registration batches. Provide the AQL limits used and the rationale for these criteria.

Please reply to this letter in writing by February 22, 2017, and include your firm's FEI number: 3008563008. I would appreciate a courtesy digital copy (pdf) by email. Please address your response to:

Christina Capacci-Daniel
c/o Derek Smith
Division of Inspectional Assessment, Office of Process and Facilities
CDER / Office of Pharmaceutical Quality
WO51 RM3171
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If you have any questions regarding this letter, you may contact me by telephone at (301) 796-3532, or by email at: christina.capacci-daniel@fda.hhs.gov.

Sincerely,

Christina A.
Capacci-daniel -S

Digitally signed by Christina A. Capacci-daniel -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200127374
7, cn=Christina A. Capacci-daniel -S
Date: 2017.02.15 11:09:21 -05'00'

Christina Capacci-Daniel, PhD
Acting Quality Assessment Lead
Division of Inspectional Assessment
CDER/OPQ/OPF



**U.S. FOOD & DRUG
ADMINISTRATION**

cc: ORA ATL-DO, Pre-Approval Managers
cc: ORA ATL-DO, Recall Coordinator

**U.S. Food and Drug Administration
CDER Office of Pharmaceutical Quality
Office of Process and Facilities
www.fda.gov**



NDA 209387

INFORMATION REQUEST

Exela Pharma Sciences
Attention: Phanesh Koneru, Ph.D., J.D. LL.M
President and CEO
P.O. Box 818
1245 Blowing Rock Blvd
Lenoir, NC 28645

Dear Dr. Koneru:

Please refer to your New Drug Application (NDA) dated and received 9 May 2016, submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Sodium Nitroprusside (b)(4) Injection, 0.5 mg/mL, 50 mg/100 mL.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by **Monday, 30 January 2017** in order to continue our evaluation of your NDA.

1. We have received your response submitted Jan 23, 2017; however, you have not provided (b)(4) vials for the noted process simulation (b)(4) batches. For lots XLNA1500A, XLNA1500B, XLNA1500C, XLNA1604A, XLNA1604B, and XLNA1604C:



If you have any questions, please me at (301) 796-8427.

Sincerely,

Dahlia A. Woody, M.S., PMP
Regulatory Business Process Manager
Division of New Drug Product 1
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Dahlia Woody -S

Digitally signed by Dahlia Woody -S
DN: c=US, o=US Government, ou=HHS,
ou=FDA, ou=People, cn=Dahlia Woody -S,
e=9.2342.1920090.100.1.1-2000349125
Date: 2017.01.26 14:16:25 -0500

Kord Bacheh Changi, Maryam

From: Kord Bacheh Changi, Maryam
Sent: Thursday, January 26, 2017 12:54 PM
To: Phanesh Koneru
Subject: Information Request NDA 209387
Attachments: Final IR NDA 209387.pdf

Importance: High

Good Afternoon,

Please see attached the information request for NDA 209387. Please submit your response as an amendment to your NDA and email it to me by close of business day **on February 1, 2017**.

Please kindly confirm the receipt.

Kind Regards,

Maryam Changi, PharmD,
Regulatory Project Manager
Office of Drug evaluation 1
Division of Cardiovascular and Renal Products
Phone:(240) 402-2725
Email: Maryam.Kordbachehchangi@fda.hhs.gov

Address for desk and courtesy copies:

Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4175
Silver Spring, MD 20993

Address for official submissions to your administrative file:

Division of Cardiovascular and Renal Products
FDA, CDER, HFD-110
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

Information Request:

Labeling:

- 1- In order to comply with the 21 CFR 201.100b5iii, we recommend you change the sentence on the carton from “ (b) (4) ” to “Each 100 mL of the solution in vial contains 50 mg of sodium nitroprusside, and 900 mg of sodium chloride.
- 2- We note the proposed proprietary name Nipride RTU is still under review. The labels and labeling with the proprietary name are acceptable only after the name is found acceptable.

We recommend the following be implemented prior to approval of this NDA:

a. General Comments (Container labels and carton labeling)

- i. Revise the container label and carton labeling presented with the proprietary name to reflect the proposed proprietary name. The proposed proprietary name currently under review is Nipride RTU (without the dash).

b. Carton Labeling

- i. Revise the carton labeling to include the lot number and expiration date. The lot number is required per 21 CFR 201.10(i), and the expiration date per 21 CFR 201.17.
- 3- The proposed labeling includes information related to the serious risk of decrease in blood pressure associated with the drug (b) (4). This presentation is misleading because it minimizes the risks associated with the product. Specifically, by only including information related to the risk of decreased blood pressure, it suggests that this is the only risk associated with the drug, when such is not the case. We recommend deletion of this risk information from the carton and container labeling

Regulatory:

- 4- You must also provide an appropriate patent certification or statement with respect to each patent listed in FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

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/s/

MARYAM K CHANGI
01/26/2017

Kord Bacheh Changi, Maryam

From: Kord Bacheh Changi, Maryam
Sent: Monday, January 09, 2017 3:17 PM
To: Phanesh Koneru
Cc: 'Tracie Watkins'
Subject: proposed labeling NDA 209387
Attachments: SNP to Applicant (2).docx

Importance: High

Dear Dr. Koneru

Please find attached, our proposed draft the revised labeling for NDA 209387, with the Agency's comments included. Please review with your team and let us know if you can agree to these changes.

Please also address the following comment:

- To facilitate our review, please submit representative samples of revised container label and carton labeling.

Please submit your response via email to me by **close of business day on January 23, 2017**. Please confirm the receipt.

Kind Regards,

Maryam Changi, PharmD,
Regulatory Project Manager
Office of Drug evaluation 1
Division of Cardiovascular and Renal Products
Phone:(240) 402-2725
Email: Maryam.Kordbachehchangi@fda.hhs.gov

Address for desk and courtesy copies:

Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4175
Silver Spring, MD 20993

Address for official submissions to your administrative file:

Division of Cardiovascular and Renal Products
FDA, CDER, HFD-110
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

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/s/

MARYAM K CHANGI
01/24/2017

Lyons, Darrell

From: Lyons, Darrell
Sent: Wednesday, December 14, 2016 9:00 AM
To: phanesh@exela.us
Cc: Kord Bacheh Changi, Maryam; twatkins@exela.us
Subject: NDA-209387 Sodium Nitroprusside - Information Request (IR)

Importance: High

Dear Dr. Koneru,

Please refer to your recent Proprietary Name (PNR) submission for NDA 209387 (SDN 14), dated December 8, 2016, received December 9, 2016.

Please clarify the following question regarding the Proprietary Name(s) you are requesting for review. The first paragraph of your submission requests "Nipride". The second paragraph states you would like to use the modifier "RTU", however the labels/labeling do not reflect the use of this modifier (see letter excerpt below). Please submit an amendment to your PNR request for NDA-209387 SDN 14 dated 12/9/2016 with the exact spelling of the name you are requesting for review.

To submit an amendment to a proprietary name request, please include the statement "**AMENDMENT TO REQUEST FOR PROPRIETARY NAME REVIEW**" in **bold** capital letters, at the top of your cover letter and on the first page of the main submission document (please refer to the complete submission guidance link below). The review of this name will be initiated when the amendment is received.

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

Please submit your response within **2 days** of this communication.

Primary Proposed Proprietary Name: **NIPRIDE**

Alternate Proposed Proprietary Name: [REDACTED] (b) (4)

2. *Intended Pronunciation of the Proposed Proprietary Name:*

Nī - Prīd

3. *Derivation of Proprietary Name*

[REDACTED] (b) (4)

4. *Intended Meaning of Proprietary Name Modifiers (e.g., prefix, suffix)*

Exela would like to add suffix RTU. RTU designates Ready-to-Use, which supports the product characteristic, which is a pre-diluted product, and requires no further dilution. The product's currently proposed labeling clearly states that aspect in multiple places. Having the RTU suffix accentuates the avoidance of dilution aspect and clearly differentiates from other sodium nitroprusside compositions that are (and were) on the market, which were all concentrated solutions that require dilution prior to administration. Please see Section E below for further discussion.

Best Regards,

Darrell Lyons, BSN, RN
Commander, USPHS
Safety Regulatory Project Manager
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
U.S. Food and Drug Administration
Tel: (301) 796-4092
darrell.lyons@fda.hhs.gov



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/s/

DARRELL LYONS
12/19/2016

Lyons, Darrell

From: Lyons, Darrell
Sent: Monday, December 19, 2016 7:36 AM
To: phanesh@exela.us
Cc: twatkins@exela.us; Kord Bacheh Changi, Maryam
Subject: NDA-209387 Sodium Nitroprusside - Information Request (IR)

Dear Dr. Koneru,

Please refer to your NDA 209387 Request for Proprietary Name Review submission dated December 14, 2016, for the proposed proprietary name Nipride RTU. You stated that the modifier "RTU" designates "ready to use." You also indicated that you conducted an internal assessment of the proprietary name.

Page 2 of submission:

4. Intended Meaning of Proprietary Name Modifiers (e.g., prefix, suffix)

Exela would like to add suffix RTU. RTU designates Ready-to-Use, which supports the product characteristic, which is a pre-diluted product, and requires no further dilution. The product's currently proposed labeling clearly states that aspect in multiple places. Having the RTU suffix accentuates the avoidance of dilution aspect and clearly differentiates from other sodium nitroprusside compositions that are (and were) on the market, which were all concentrated solutions that require dilution prior to administration. Please see Section E below for further discussion.

Page 3 of submission:

E. Applicant's Assessment of Proprietary Name, Packaging, and/or Labeling

Exela conducted an internal assessment of the proprietary name, packaging and labeling. Exela has on staff seven pharmacists that have varied practical experiences in the dispensing of pharmaceuticals. Exela's team also included senior marketing and sales members that

Did your internal assessment include evaluation of the proposed modifier, RTU, such as data showing that healthcare providers understand the intended meaning of RTU as "ready to use"? If so, we request that you submit such data for our review of your proposed proprietary name, Nipride RTU. To facilitate our review, we request that you respond within 5 business days from receipt of this request.

Best Regards

Darrell Lyons, BSN, RN
Commander, USPHS
Safety Regulatory Project Manager
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
U.S. Food and Drug Administration
Tel: (301) 796-4092
darrell.lyons@fda.hhs.gov





APPEARS THIS WAY ON ORIGINAL

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

/s/

DARRELL LYONS
12/19/2016

Kord Bacheh Changi, Maryam

From: Kord Bacheh Changi, Maryam
Sent: Monday, November 28, 2016 9:08 AM
To: Tracie Watkins
Cc: 'phanesh@exela.us'
Subject: Information Request NDA 209387

Importance: High

Good Morning Tracie,

Please refer to your New Drug Application received May 9, 2016, we are reviewing your application and have the following information request:

- Regarding drug product labeling, please note that usage of term “(b) (4) injection” is not acceptable. To comply with *USP General Chapter <1121> Nomenclature*, we recommend labeling your proposed product as follows:
Sodium Nitroprusside in 0.9% Sodium Chloride Injection or Proprietary name (Sodium Nitroprusside) in 0.9% Sodium Chloride Injection.

Please submit your response as an amendment to your application and via email to me by close of business day on **December 9, 2016**. Please do not hesitate to contact me if you have any questions.

Please confirm the receipt.

Kind Regards,

Maryam Changi, PharmD,
Regulatory Project Manager
Office of Drug evaluation 1
Division of Cardiovascular and Renal Products
Phone:(240) 402-2725
Email: Maryam.Kordbachehchangi@fda.hhs.gov

Address for desk and courtesy copies:

Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4175
Silver Spring, MD 20993

Address for official submissions to your administrative file:

Division of Cardiovascular and Renal Products
FDA, CDER, HFD-110
5901-B Ammendale Rd.

APPEARS THIS WAY ON ORIGINAL

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

/s/

MARYAM K CHANGI
11/29/2016



NDA 209387

INFORMATION REQUEST

Exela Pharma Sciences
Attention: Johnathan E. Sterling
Vice President of Quality and Regulatory Affairs
P.O. Box 818
1245 Blowing Rock Blvd
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) dated and received November 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sodium Nitroprusside (b) (4) Injection, 0.5 mg/mL, 50 mg/100 mL.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by **Friday, 18 November 2016** in order to continue our evaluation of your NDA.

1. As (b) (4) in the manufacturing of the finished drug product, please update the batch formula accordingly to include this as a component. Also include supporting information and related specifications within section (b) (4).
2. The drug substance (DS) is slightly hygroscopic. Also, it was noted that drug product was protected from light (b) (4).
3. Provide a side-by-side comparison of all equipment used in the manufacturing of the drug product (b) (4) between registration batches and future commercial production. The information should include make, model, capacity, material of construction, and operation principles. Discuss any differences and their potential impact on the drug product quality. Also include all process parameters wherever is applicable (b) (4). Parameters should be defined as set-point and/or ranges with lower and upper limits. Parameters should be established based on data collected from manufacturing of all developmental and registration batches, and any scale dependent change to parameters should be discussed.
4. Provide with study data the sensitivity of your product to (b) (4). There was no discussion in your product or process development report as why there is a need to (b) (4).

(b) (4) Further, we cannot locate any in-process testing/controls of (b) (4) in your filled vials upon its replacement with (b) (4) (for example (b) (4)). Explain how this replacement of (b) (4) was performed and how the procedure is suitable to (b) (4). Provide a summary of development data to support your conclusion. Also describe the drug product rejection procedure if a vial does not meet the limit of (b) (4).

5. Confirm that all formulation contacting (b) (4) used in the manufacturing of the drug product (b) (4).
6. Provide equipment compatibility data to demonstrate that the drug product impurity (b) (4).
7. We note that your (b) (4).
8. As per CFR 211.103 and CFR211.186(b)(7) provide consolidated reconciliation tables for all exhibition batches including theoretical yield, target yield specification, and actual yield for each unit operation and total production, wherever is applicable. Provide justification for any significant waste and/or rejections and batch to batch variability.

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

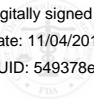
Sincerely,

Dahlia A. Woody, M.S., PMP
Regulatory Business Process Manager
Division of New Drug Products I
Cardiovascular and Renal Products
CDER/OPQ/ONDP



Dahlia
Woody

Digitally signed by Dahlia Woody
Date: 11/04/2016 03:35 36PM
GUID: 549378e2002d59c90ffeba218024f890



Lyons, Darrell

From: Lyons, Darrell
Sent: Monday, October 03, 2016 1:02 PM
To: 'jsterling@exela.us'
Subject: Proprietary Name for NDA 209387

Importance: High

Dear Mr. Sterling:

Please refer to your NDA 209387 for Sodium Nitroprusside, USP, 0.05 mg/mL IV.

We also refer to your correspondence, dated May 6, 2016, received May 9, 2016, requesting review of your original NDA.

If you intend to have a proprietary name for the above-referenced product, you should submit a request for proprietary name review within **7 days** of this communication.

Include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold capital letters, at the top of your cover letter and on the first page of the main submission document (please refer to the complete submission guidance link below). The review of this name will be initiated when the new submission is received.

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding any other aspects of the proprietary name review process, feel free to contact me directly.

Best Regards,

Darrell Lyons, BSN, RN
Commander, USPHS
Safety Regulatory Project Manager
FDA, Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office: (301) 796-4092

APPEARS THIS WAY ON ORIGINAL

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

/s/

DARRELL LYONS
10/13/2016



NDA 209387

INFORMATION REQUEST

Exela Pharma Sciences
Attention: Johnathan E. Sterling
Vice President of Quality and Regulatory Affairs
P.O. Box 818
1245 Blowing Rock Blvd
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) dated and received November 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sodium Nitroprusside (b) (4) Injection, 0.5 mg/mL, 50 mg/100 mL.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by **Friday, September 23, 2016** in order to continue our evaluation of your NDA.

Drug product:

1. In the initial NDA submission for the drug product specification, you provided separate tables for lot release (1.1.1) and stability (1.1.2). Since the regulatory drug product specification table should include both the lot release and stability tests information, we recommend you to combine the information in the Tables 1.1.1 and 1.1.2 into a single table. The tests that are conducted during stability may be indicated in the footnote of the revised table.
2. In the NDA submission, you provided 9 months of long-term stability data for the primary stability drug product batches XLNF1545, XLNF1546, and XLNF1547. In compliance with the FDA Guidance for Industry document *entitled "Q1A(R2) Stability Testing of New Drug Substances and Products (November 2003, ICH, Revision 2)"* that recommends a minimum of 12-month stability data, provide the updated long-term stability data for these batches.
3. We note that you have provided no stability data for the drug product batches that were manufactured with the drug substance manufactured by the alternate supplier. Since the selection of drug product batches should include batches that are manufactured by using drug substance from an alternate manufacturer, therefore, provide long-term and accelerated stability data for the drug product batch # XLNC1604.

4. The proposed commercial drug product solution vial is expected to contain a minimum of 100 mL of the sodium nitroprusside injection and, a health care personnel is expected to withdraw 100 mL of the solution from the vial. To comply with the excess volume recommendations prescribed by the USP, specify the fill, overfill and extractable volumes that can reproducibly permit withdrawal and administration of the labeled volumes.

Microbiology:

5. Regarding environmental monitoring of the facility, provide the following information:
 - a) The monitoring frequencies, media used and incubation conditions for air, surface and personnel monitoring samples.
 - b) Descriptions/plans/frequencies for environmental monitoring of yeasts and molds.
 - c) WFI monitoring frequencies, as well as endotoxins acceptance criteria.
 - d) The actions to be taken when levels are exceeded for air, surfaces, personnel, and WFI monitoring samples.
6. It is noted that the microbial retention validation study included a two-hour filter contact time with the drug product. Please clarify the maximum drug filtration time (product contact time) for commercial production. If the proposed duration is longer than the validated two hours, new bacterial retention study to support that duration will need to be provided.
7. With regard to the holding periods in the drug production:
 - a) Provide the maximum duration proposed for each major step of the manufacturing process, including time for [REDACTED] (b) (4).
 - b) Provide microbiological study to demonstrate that during the proposed duration of [REDACTED] (b) (4), bioburden does not exceed acceptance criterion.
 - c) [REDACTED] (b) (4)
8. With regard to the media fill, [REDACTED] (b) (4)
9. Regarding the bacterial endotoxins testing:
 - a) Clarify what dilution of the drug product will be used for the routine testing during drug production.
 - b) It is noted that Maximum Valid Dilution (MVD) was calculated using a bacterial endotoxins specification of [REDACTED] (b) (4) EU/mg. However, the bacterial endotoxins specification is [REDACTED] (b) (4)/mg. Please clarify this discrepancy.

10. Page 1 of the package insert states,

(b) (4)

However, the Dosage and Administration section of the labeling states,

(b) (4)

Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Generally, "no growth" is interpreted as not more than a $0.5 \log_{10}$ increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers (<100 CFU/mL) of challenge microbes. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the storage period of the diluted drug product is not more than 4 hours at room temperature or 24 hours under refrigeration.

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

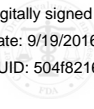
Sincerely,

Mohan Sapru, Ph.D.
CMC Lead Cardiovascular Renal Products
Division of New Drug Product 1
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Mohan
Sapru

Digitally signed by Mohan Sapru
Date: 9/19/2016 11:32:24AM
GUID: 504f82160000ec6d20b59d2b68eb3d2





NDA 209387

INFORMATION REQUEST

Exela Pharma Sciences
Attention: Johnathan E. Sterling
Vice President of Quality and Regulatory Affairs
P.O. Box 818
1245 Blowing Rock Blvd
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) dated and received November 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sodium Nitroprusside (b) (4) Injection, 0.5 mg/mL, 50 mg/100 mL.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by **Friday, 9 September 2016** in order to continue our evaluation of your NDA.

1. Provide a single table for the drug product specification by combining the information in the current tables for the lot release specification and stability specification. Those tests that are conducted during stability may be indicated in the footnote of the revised table.
2. Provide updated long-term stability data for the drug product lots XLNF1545, XLNF1546, and XLNF1547.
3. Provide long-term and accelerated stability data for the drug product lot# XLNC1604 that was manufactured with the API from the alternate supplier.

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427.

Sincerely,

Mohan Sapru, Ph.D.
CMC Lead Cardiovascular Renal Products
Division of New Drug Product 1
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Form Approved: OMB No. 0910 - 0297 Expiration Date: March 31, 2019. See instructions for OMB Statement, below.

**DEPARTMENT OF HEALTH AND HUMAN
SERVICES
FOOD AND DRUG ADMINISTRATION**

**PRESCRIPTION DRUG USER FEE
COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>EXELA PHARMA SCIENCES LLC Jonathan Sterling P.O. Box 818 1245 Blowing Rock Blvd. Lenoir NC 28645 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>209-387</p>
<p>2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE</p> <p>828-7585474</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>
<p>3. PRODUCT NAME</p> <p>Sodium Nitroprusside (b)(4) Injection</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3016078</p>
<p>7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p>PRIORITY REVIEW VOUCHER NUMBER:</p>	
<p>8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.</p> <p><input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)</p> <p><input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act</p> <p><input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY</p>	

FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

If a waiver has been granted, include a copy of the official FDA notification with your submission.

Privacy Act Notice:

This notice is provided pursuant to the Privacy Act of 1974, 5 U.S.C. 552a. The collection of this information is authorized by 21 U.S.C. 371, 379, 379e, 379h, 379h-1, 379j, 379j-12, 379j-21, 387s, and 393(d)(2); 42 U.S.C. 263b(r)(1); 5 U.S.C. 301 and 552; and 42 U.S.C. 3101. FDA will use the information to assess, collect and process user fee payments, and, facilitate debt collection under the Debt Collection Improvement Act. FDA may disclose information to courts and the Department of Justice in the context of litigation and requests for legal advice; to other Federal agencies in response to subpoenas issued by such agencies; to HHS and FDA employees and contractors to perform user fee services; to the National Archives and Records Administration and General Services Administration for records management inspections; to the Department of Homeland Security and other Federal agencies and contractors in order to respond to system breaches; to banks in order to process payment made by credit card; to Dun and Bradstreet to validate submitter contact information, and to other entities as permitted under the Debt Collection Improvement Act. Furnishing the requested information is mandatory. Failure to supply the information could prevent FDA from processing user fee payments. Additional detail regarding FDA's use of information is available online: <http://www.fda.gov/RegulatoryInformation/FOI/PrivacyAct/default.htm>.

OMB Statement:

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

\$1,187,100.00

Form FDA 3397 (03/16)

Form Approved: OMB No. 0910 - 0297 Expiration Date: March 31, 2019. See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET
---	--

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm>

1. APPLICANT'S NAME AND ADDRESS EXELA PHARMA SCIENCES LLC Jonathan Sterling P.O. Box 818 1245 Blowing Rock Blvd. Lenoir NC 28645 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 000-000
---	--

2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 828-7585474 104	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
--	---

3. PRODUCT NAME Sodium Nitroprusside (b) (4) Injection	6. USER FEE I.D. NUMBER PD3015970
--	---

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? YES NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION

736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
 THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?
 YES NO

If a waiver has been granted, include a copy of the official FDA notification with your submission.

Privacy Act Notice:

This notice is provided pursuant to the Privacy Act of 1974, 5 U.S.C. 552a. The collection of this information is authorized by 21 U.S.C. 371, 379, 379e, 379h, 379h-1, 379j, 379j-12, 379j-21, 387s, and 393(d)(2); 42 U.S.C. 263b(r)(1); 5 U.S.C. 301 and 552; and 42 U.S.C. 3101. FDA will use the information to assess, collect and process user fee payments, and, facilitate debt collection under the Debt Collection Improvement Act. FDA may disclose information to courts and the Department of Justice in the context of litigation and requests for legal advice; to other Federal agencies in response to subpoenas issued by such agencies; to HHS and FDA employees and contractors to perform user fee services; to the National Archives and Records Administration and General Services Administration for records management inspections; to the Department of Homeland Security and other Federal agencies and contractors in order to respond to system breaches; to banks in order to process payment made by credit card; to Dun and Bradstreet to validate submitter contact information, and to other entities as permitted under the Debt Collection Improvement Act. Furnishing the requested information is mandatory. Failure to supply the information could prevent FDA from processing user fee payments. Additional detail regarding FDA's use of information is available online: <http://www.fda.gov/RegulatoryInformation/FOI/PrivacyAct/default.htm>.

OMB Statement:

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE
--	-------	------

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$1,187,100.00

Form FDA 3397 (03/16)

INSTRUCTIONS FOR COMPLETING PRESCRIPTION DRUG USER FEE COVER SHEET FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency, unless specifically exempted below. Form FDA 3397 should be placed in the first volume of the application with the application (FORM FDA 356(h)) form. Form FDA 3397 is to be completed on-line at https://userfees.fda.gov/OA_HTML/pdufaCAcdLogin.jsp. If you need assistance in completing the form call 301-796-7200 or email: userfees@fda.gov.

NOTE: Form FDA 3397 need not be submitted for:

CDER

505(j) applications
Supplements to 505(j) applications
351(k) applications

CBER

Any supplement that does not require clinical data for approval.
Applications and supplements for:

- * Products for further manufacturing use only
- * Whole blood or blood components for transfusion
- * Bovine blood product for topical application licensed before September 1, 1992
- * A crude allergenic extract product
- * An in vitro diagnostic biological product licensed under Section 351 of the PHS Act
- * 351(k) applications

ITEM NO.	INSTRUCTIONS
1-2.	Self-explanatory
3.	PRODUCT NAME: Include generic or proper name and trade name, as applicable.
4.	BLA STN / NDA NUMBER - FOR AN ORIGINAL BIOLOGIC LICENSE APPLICATION (BLA) - Indicate the 6-digit BLA number (Submission Tracking Number (STN)) if pre-assigned, otherwise leave blank. For A SUPPLEMENT enter the BLA STN. FOR DRUG PRODUCTS: Indicate the new drug application (NDA) number. NDA numbers can be obtained by completing the information at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm114027.htm .
5.	CLINICAL DATA: The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on FDA's web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf .
6.	USER FEE I.D. NUMBER: Please include the ID number (generated when completing Form FDA 3397) on the application payment check.
7.	PRIORITY REVIEW VOUCHER: If you are redeeming a priority review voucher awarded to a sponsor of a tropical disease product application (see section 524 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)), please include the priority review voucher number assigned when the voucher was initially granted. See FDA's Guidance for Industry: Tropical Disease Priority Review Vouchers for further information. FDA's guidance can be found on FDA's web site: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf .
8.	EXCLUSIONS: The application is for an orphan drug product. Under section 736(a) (1) (F) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement. A copy of the FDA letter granting orphan designation should be included with the BLA/NDA submission.
9.	WAIVER: Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the BLA/NDA submission.

Form FDA 3397 (03/16) (BACK)

[Close](#) [Print Cover sheet](#)

APPEARS THIS WAY ON ORIGINAL



P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, N.C. 28645

Financial Certification

Not Applicable to this application.

No new clinical data is presented in support of Exela's proposed drug product, Sodium Nitroprusside (b)(4) Injection, 0.5 mg/mL, 50 mg/100 mL.

Jonathan E.
Sterling

Digitally signed by Jonathan E. Sterling
DN: cn=Jonathan E. Sterling, o=Exela Pharma
Sciences, LLC, ou=Regulatory Affairs,
email=jsterling@exela.us, c=US
Date: 2016.05.06 14:02:57 -04'00'

Jonathan E. Sterling
Vice President, Quality and Regulatory Affairs

Date

EXELA

PHARMA SCIENCES

P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, N.C. 28645

Pediatric Administrative Information

Request for Waiver of Pediatric Studies

FDA regulations require that “each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration” must contain “data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric populations...” Federal Food, Drug, and Cosmetic Act, Section 505B (Pediatric Research Equity Act).

The undersigned hereby requests a full waiver of that requirement for the proposed product under the Federal Food, Drug, and Cosmetic Act, Section 505B as Exela’s proposed drug product has the same active ingredient, and same indication, dosage form, dosing regimen, and route of administration as that of the reference drug, NITROPRESS® (sodium nitroprusside, ANDA holder, Hospira).

Jonathan E. Sterling

Digitally signed by Jonathan E. Sterling
DN: cn=Jonathan E. Sterling, o=Exela Pharma Sciences, LLC,
ou=Regulatory Affairs, email=jssterling@exela.us, c=US
Date: 2016.05.06 12:06:14 -04'00'

Jonathan E. Sterling
Vice President, Quality and Regulatory Affairs

Date



PIND 127676

ADVICE LETTER

Exela Pharma Sciences, LLC
Attention: Jonathan E. Sterling
Vice President of Quality and Regulatory
PO Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your Pre-Investigational New Drug (PIND) file concerning Sodium Nitoprusside (b) (4) Injection 0.5 mg/mL in 0.9% Sodium Chloride.

We also refer to your 20 January 2016 correspondence requesting guidance related to your proposed Potential Medication Error Mitigation Plan, requested by the Division in our Preliminary Comments correspondence dated 07 October 2015.

We have the following recommendations and comments:

A. Questions for the Agency

1. Does the division agree that the above presented risk mitigation plan is adequate to address the risk for dosing errors with Exela's Sodium Nitroprusside (b) (4) Injection (b) (4) in 0.9% Sodium Chloride?

FDA Response:

Yes.

2. Does the division accept Exela's NDA application for review even if the above presented risk mitigation plan is considered not adequate, with the assurance that Exela will work with the Division to address its concerns while the application is being reviewed?

FDA Response:

Generally, the type of concern arising from reviewing your PIND package impacts drug safety. Consequently, the risk/benefit assessment would be impacted that would directly affect a regulatory recommendation. Therefore, you are urged to resolve this concern prior to submitting the NDA. See response to question # 1.

Studies in humans may not be conducted under this PIND. Before you may conduct studies in humans, you must submit a full Investigational New Drug Application (IND, see 21 CFR Part 312, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>) by amending this PIND with the required information. Include the above PIND number in Box 6 of the form FDA 1571 submitted with your IND. Send your IND submission in triplicate to the address below.

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

If you have any questions, please contact Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Division Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
03/10/2016



PIND 127676

MEETING REQUEST CANCELLED

Exela Pharma Sciences, LLC
Attention: Jonathan E. Sterling
Vice President of Quality and Regulatory Affairs
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Sodium Nitroprusside (b) (4) Injection 0.5 mg/mL in 0.9% Sodium Chloride.

We also refer to your 09 October 2015 email communication requesting cancellation of the meeting we scheduled on 13 October 2015 in response to your 18 August 2015 meeting request because you indicated our preliminary comments sent 07 October 2015 were sufficient and a meeting was not warranted. Therefore, the 13 October 2015 meeting was cancelled.

If you have any questions, please call me at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Bridget Kane, MS
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

BRIDGET E KANE
11/06/2015



PIND 127676

MEETING PRELIMINARY COMMENTS

Exela Pharma Sciences, LLC
Attention: Jonathan E. Sterling
Vice President of Quality and Regulatory Affairs
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Sodium Nitroprusside
(b) (4) Injection 0.5 mg/mL in 0.9% Sodium Chloride.

We also refer to your 18 August 2015 correspondence, received 21 August 2015, requesting a meeting to discuss the appropriate regulatory pathway for your product.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to me, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting at least 2 business days in advance. In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please call me at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Bridget Kane, MS
Regulatory Project Manager
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-IND
Meeting Date and Time: 13 October 2015
Meeting Location: Teleconference
Application Number: 127676
Product Name: Sodium Nitroprusside (b) (4) Injection
Indication: Blood pressure reduction in hypertensive crisis
Sponsor Name: Exela Pharma Sciences, LLC (Exela)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion (via teleconference) scheduled for 13 October 2015 from 900-1000 EST between Exela Pharma Sciences, LLC and the Division of Cardiovascular and Renal 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). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Sodium nitroprusside is a vasodilator approved (Hospira - NDA 021572) for the following indications:

- immediate reduction of blood pressure in hypertensive crisis
- the production of controlled hypotension to reduce bleeding during surgery
- treatment of acute (b) (4) heart failure

NDA 021572 is supplied in single-dose 50 mg/2 mL vials for dilution.

Exela is planning to file a NDA for sodium nitroprusside (b) (4) injection (0.5 mg/mL in 0.9% sodium chloride packaged in 100-mL vials) relying upon data from literature to satisfy requirements for safety and efficacy. Exela states that the differences between their product and the one approved under NDA 021572 (e.g., the volume and rate of infusion) are not expected to affect the overall safety and efficacy.

The purpose of the meeting is to discuss this planned NDA under the 505(b)(2) pathway using Hospira's Nitropress (NDA 021572) Injection as the designated reference listed drug and Exela's request for a bio-waiver.

2.0 DISCUSSION

2.1. Questions for the Agency

1. Does the Division concur that the appropriate regulatory pathway for Exela's Sodium Nitroprusside (b) (4) Injection is the 505(b)(2) pathway?

FDA Preliminary Response

Yes, we agree that the 505(b)(2) is the appropriate regulatory pathway.

2. Does the Division agree that Nitropress (Sodium Nitroprusside) Injection 25mg/mL of Hospira, approved under NDA #021572, is the appropriate reference listed drug ("RLD")?

FDA Preliminary Response

We typically do not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, your proposal to rely on Nitropress (Sodium Nitroprusside injection) 25 mg/mL appears acceptable.

3. Does the Division grant a bio-waiver?

FDA Preliminary Response

21 CFR § 320.22 (b)(1) states that FDA shall waive the requirement for the submission of data demonstrating bioequivalence if the drug product is a parenteral solution for injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.

Although the final amounts of Sodium Nitroprusside administered is the same for the listed drug and the proposed drug product, there is a difference in the concentration of Sodium Nitroprusside and administered volume between your proposed drug product and the listed drug product, In addition, your proposed product contains NaCl as additional inactive ingredients whereas the listed product, upon dilution, contained dextrose. Therefore, there might be a difference in pH, (b) (4) and osmolality between the two

products. FDA will consider a biowaiver request for your product if you provide sufficient justification with supporting data (e.g., published literature, study data, etc.) demonstrating that the differences in drug concentration, administered volume, pH, (b) (4), and osmolality between your product and the listed product, addition of NaCl and lack of 5% dextrose will not have any impact on the pharmacokinetics, efficacy, and safety of your product, as compared to those of the listed drug product.

Note that FDA does not grant biowaivers of the required BA/BE studies during the IND stage. Our recommendation on granting the biowaiver for your product will be made during review of the NDA. Note also that if your justification and data do not support the biowaiver request, a bioequivalence study will be needed.

To permit FDA to evaluate a request to waive the requirement for the submission of in vivo bioavailability (BA) and or bioequivalence (BE) data, you must include in the NDA submission a BA/BE biowaiver request along with information demonstrating that the physiological disposition of Sodium Nitroprusside for the proposed and listed drug products is similar.

In addition, include the following information in the NDA:

- Formulation (qualitative composition) before and after reconstitution or dilution, dosage form, administered volume, etc., for the proposed drug product and the listed drug in a side-by-side comparison table.
 - Comparative physicochemical data for the proposed drug product and listed drug product. The measurements should be done in triplicate for each lot tested. Include justification for any differences in the formulation's composition, pH, osmolality, dosage, mode of administration, drug concentration, administered volume, etc., relative to the listed drug product.
4. Exela proposes to make three (3) NDA 505(b)(2) submission stability batches of the new formulation, Sodium Nitroprusside (b) (4) Injection, and generate stability data, at accelerated and controlled room conditions, on all the 3 batches. Nitropress was on drug shortage previously and currently only one supplier is on the market. This supplier has demonstrated a history of cGMP non-compliance. Thus, there is a potential for Nitropress to become a shortage drug. Given this background, Exela requests that it be permitted to file the NDA with three (3) months stability data (accelerated and room temperature conditions), and provide additional stability data as they become available. Exela is willing to accept shelf life that is commensurate with the stability data on record with the Division.

Does the Division grant the request?

FDA Preliminary Response

No, we do not agree with the justification for a short expiry based on a potential drug shortage. In general, we recommend that stability data adequately support a commercially

viable product expiration dating period. Specifically, it is our expectation that the NDA will include at least twelve (12) months of long-term stability data and six (6) months of accelerated stability data at the time of submission as per ICH QIA(R2).

2.2. Additional comments

Because of differences of unit concentrations between your product and the reference drug, different volume to be administered is different between two products. This could be a source for dosing error and is of significant concern. Please provide information on how you plan to mitigate this potential medication error.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the

Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdere-data@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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

/s/

BRIDGET E KANE
10/07/2015