CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208424Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2016
See OMB Statement on Page 3.

NDA NUMBER
208424

NAME OF APPLICANT/NDA HOLDER
G. Pohl-Boskamp GmbH & Co. KG

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
to be defined-under assessment

ACTIVE INGREDIENT(S)	STRENGTH(S)
Nitroglycerin	400 mcg

DOSAGE FORM
powder

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
9,101,592 B2	Aug. 11, 2015	March 11, 2032

d. Name of Patent Owner	Address *(of Patent Owner)*	
G. Pohl-Boskamp GmbH & Co. KG	Kieler Straße 11	
	City/State: Hohenlockstedt	
	ZIP Code: 25551 Germany	FAX Number *(if available)*:
	Telephone Number: +49 48 26 59-256	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	14286-19 Beach Blvd #270	
	City/State: Jacksonville/Florida	
	ZIP Code: 32250	FAX Number *(if available)*: (815) 366-8260
Espero Pharmaceuticals, Inc.	Telephone Number: (904) 328-2210	E-Mail Address *(if available)*: qpham@esperopharma.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Publishing Services (301) 443-6740 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Dr Ulrike Küper Digitally signed by Dr Ulrike Küper DN: cn=Dr Ulrike Küper, o=G. Pohl-Boskamp GmbH & Co. KG, ou=Regulatory Affairs, email=u.kueper@pohl-boskamp.de, c=DE Date: 2015.11.20 12:49:52 +01'00'	11/23/2015

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Dr Ulrike Küper	
Address G. Pohl-Boskamp GmbH & Co. KG Kieler Straße 11	City/State Hohenlockstedt/Germany
ZIP Code 25551 Hohenlockstedt	Telephone Number +49 48 26 59 256
FAX Number *(if available)*	E-Mail Address *(if available)*

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"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 number."

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Identify the precise words of the approvel labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 208424 SUPPL # N/A HFD # 110

Trade Name GoNitro

Generic Name nitroglycerin

Applicant Name G. Pohl-Boskamp GmbH & Co. KG

Approval Date, If Known

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)(1)

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.

A CSR from Study P1202NL was submitted in Module 5.3.1.2 comparing the bioavailability of nitroglycerin powder to the applicant's approved Nitrolingual Pumpspray (NDA 18705).

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 ☒

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#	18705	Nitrolingual Pumpspray (sublingual spray)
NDA#	21780	Nitromist (sublingual aerosol)
NDA#	21045	Nitro-Dur (transdermal)
NDA#	19970	Nitroglycerin in Dextrose 5% (injection)
NDA#	21359	Rectiv (intra-anal)
NDA#	21134	Nitrostat (sublingual tablet)
ANDA#	74559	Nitroglycerin (transdermal)
ANDA#	72034	Nitroglycerin (injection)
ANDA#	87355	Nitroglycerin (transdermal ointment)

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:

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

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Bridget Kane
Title: Regulatory Health Project Manager
Date: 31 May 2016

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Division Director

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/

BRIDGET E KANE
06/04/2016

NORMAN L STOCKBRIDGE
06/05/2016

1.3.3 DEBARMENT CERTIFICATION

G. Pohl-Boskamp GmbH & Co. KG hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Hohenlockstedt, 17/06/2015

POHL BOSKAMP

Dr. Ulrike Küper
Director Regulatory Affairs

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208424	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: GoNitro Established/Proper Name: nitroglycerin Dosage Form: sublingual powder		Applicant: G. Pohl-Boskamp GmbH & Co. KG Agent for Applicant (if applicable): Espero Pharmaceuticals, Inc.
RPM: Bridget Kane		Division: DCRP

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

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is 10 June 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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 _____	☒ N/A
❖ 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)

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

(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

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

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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ 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 *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP – 8Jun16
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letters:1Jun15; 16Nov15 Reviews:29May15; 15Nov15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 8Jun16; 15Oct15 DMEPA: ☒ 23Mar16; 10Feb16 DMPP/PLT (DRISK): ☒ None OPDP: ☒ 4May16 SEALD: ☒ None CSS: ☒ None Product Quality ☒ 23May16 (primary review) Other: ☒ Patient Labeling – 5May2016
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	7Oct15 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

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

• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 4May2016 If PeRC review not necessary, explain:	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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.) *(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)*	Included
❖ 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)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ 22Jan13 and 18Sep14 (under IND 116608)
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ 4Jun16
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ 3Jun16
PMR/PMC Development Templates *(indicate total number)*	☒ None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ N/A
• Clinical review(s) *(indicate date for each review)*	N/A
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	CDTL memo – 3Jun16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A ☐ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ N/A
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review – CDTL memo – 3Jun16
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ 1Jun16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ 10Nov15

[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).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review N/A
• Supervisory Review(s) *(indicate date for each review)*	☒ Co-signatory of primary review 21Dec15
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ 21Dec15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ 23May2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	23May2016
☐ Review & FONSI *(indicate date of review)*	N/A
☒ Review & Environmental Impact Statement *(indicate date of each review)*	23May2016
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: 7Jun16 ☐ Withhold recommendation ☐ 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: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	**N/A**
• Finalize 505(b)(2) assessment	**N/A**
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	**N/A**
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	**N/A**
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	**N/A**
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

BRIDGET E KANE
06/13/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208424

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

G. Pohl-Boskamp GmbH & Co. KG
c/o Espero Pharmaceuticals, Inc.
14286-19 Beach Blvd #270
Jacksonville, Florida 32250

ATTENTION: Ulrike Küper
Director Regulatory Affairs

Dear Dr. Küper:

Please refer to your New Drug Application (NDA) dated August 6, 2015, received August 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nitroglycerin Sublingual Powder, 400mcg per packet.

We also refer to your correspondence, dated and received May 27, 2016, requesting reconsideration of your proposed proprietary name, GoNitro.

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

If any of the proposed product characteristics as stated in your May 27, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Bridget Kane, Regulatory Project Manager in the Office of New Drugs, at (240) 402-2170.

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/

TODD D BRIDGES
06/01/2016

MEMORANDUM of TELECONFERENCE

MEETING DATE: May 26, 2016

TIME: 2:30 P.M. EST

LOCATION: Teleconference

APPLICATION: NDA 208424

DRUG NAME: Nitroglycerin Sublingual Powder, 400 mcg

TYPE OF MEETING: Proprietary Name Review

MEETING CHAIRS: Todd Bridges Director, Division of Medication Error Prevention and Analysis (DMEPA)

MEETING RECORDER: Darrell Lyons, Safety Regulatory Project Manager (SRPM)

FDA ATTENDEES:

Office of Surveillance and Epidemiology
Todd Bridges, Director, DMEPA
Alice Tu, Team Leader, DMEPA
Darrell Lyons, Safety Regulatory Project Manager, PMS

SPONSOR ATTENDEES:

G. Pohl- Boskamp GmbH & Co. KG
Babette Reiken, Senior Director Market Access

Espero Pharmaceuticals, Inc.
Jeff Cole, President and CFO
Quang Pham, CEO

BACKGROUND:

On April 19, 2016, G. Pohl-Boskamp GmbH & Co. KG submitted a proposed Proprietary Name Review for (b) (4) is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

MEETING OBJECTIVES:

The purpose of the call was to let the sponsor know that DMEPA has concern with their proposed name (b) (4) and convey their preliminary findings.

DMEPA CONCERNS WITH THE PROPOSED NAME

DMEPA conveyed their concern with the potential for proprietary name confusion between the proposed proprietary name, [redacted] and the currently marketed product, [redacted] DMEPA further explained that the Applicant's previously proposed proprietary name, GoNitro would be an acceptable alternative to submit for review.

DISCUSSION

The Sponsor asked if withdrawing the current Proprietary Name and submitting a new Proprietary Name would start a new 90-day review clock. DMEPA confirmed that submitting a new Proprietary Name would start a new review clock however; since the proposed proprietary name, GoNitro was previously reviewed in November 2015, DMEPA's re-review should be completed in time for DCRP to take action on the application by the application PDUFA goal date of June 10, 2016.

ACTION ITEMS

G. Pohl- Boskamp GmbH & Co. KG will withdraw the current proposed name "[redacted] and submit the proposed Proprietary Name "GoNitro" by Tuesday May 31, 2016.

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/s/

TODD D BRIDGES
05/27/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208424

PROPRIETARY NAME REQUEST ACKNOWLEDGEMENT/WITHDRAWAL

G. Pohl-Boskamp GmbH & Co. KG
c/o Espero Pharmaceuticals, Inc.
14286-19 Beach Blvd #270
Jacksonville, Florida 32250

ATTENTION: Ulrike Küper
Director, Regulatory Affairs

Dear Dr. Küper:

Please refer to your New Drug Application (NDA) dated August 6, 2015, received August 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (b) (4) (Nitroglycerin) Sublingual Powder, 400 mcg (b) (4).

We also refer to your correspondence, dated and received April 19, 2016, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4). Therefore, (b) (4) is considered withdrawn as of April 19, 2016.

Finally, we refer to your correspondence, dated and received April 19, 2016, requesting review of your proposed proprietary name, (b) (4) Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.

Therefore, the user fee goal date is July 18, 2016.

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 Bridget Kane, Regulatory Project Manager in the Office of New Drugs, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Darrell Lyons
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DARRELL LYONS
04/25/2016

Lyons, Darrell

From: Reiken, Babette <b.reiken@Pohl-Boskamp.de>
Sent: Tuesday, April 19, 2016 9:45 AM
To: Lyons, Darrell
Cc: Küper, Ulrike; Kane, Bridget
Subject: AW: Proposed Proprietary Name for NDA 208424
Attachments: emfinfo.txt

Dear Darrell,

thank you very much for providing us again procedural guidance within our current and future proposed proprietary name submission.

As promised yesterday, we are happy to inform you about the two sequences sent via ESG successfully today: First, our withdrawal of [redacted] (b) (4) as sequence 0020 and second the new sequence of "[redacted] (b) (4) as sequence 0021. Espero as our local agent is involved in every step regarding our NDA, Quang will get every email separately as long as he is waiting for FDA feedback on his secured email address.

Espero and Pohl Boskamp appreciate your support and we would be very delighted to receive a response on this new submission before the 90-days review time. Please let us know, if there would be anything from our side to do within our challenging proposed proprietary name review.

Best regards
Babette

Babette Reiken
Senior Director Market Access
G. Pohl-Boskamp GmbH & Co. KG
Germany

b.reiken@pohl-boskamp.de
Phone +49 (0)4826 59-354
Fax +49 (0)4826 59-377

Von: Lyons, Darrell [mailto:Darrell.Lyons@fda.hhs.gov]
Gesendet: Freitag, 15. April 2016 18:45
An: Reiken, Babette <b.reiken@Pohl-Boskamp.de>
Cc: Küper, Ulrike <u.kueper@Pohl-Boskamp.de>; Kane, Bridget <Bridget.Kane@fda.hhs.gov>
Betreff: RE: Proposed Proprietary Name for NDA 208424

Dear Babette,

You will have to withdraw the current proposed name [redacted] (b) (4) and the proposed name "[redacted] (b) (4) will require a new submission. Although the submission will start a new 90-day review clock, you should receive a response before 90-days as we are already evaluating the root name.

Best Regards,

Darrell

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
darrell.lyons@fda.hhs.gov

From: Quang Pham [mailto:qpham@esperopharma.com]
Sent: Thursday, April 14, 2016 11:51 AM
To: Lyons, Darrell
Cc: Ulrike; Reiken, Babette; Kane, Bridget
Subject: Re: Proposed Proprietary Name for NDA 208424

Dear Darrell,

Thank you again for your communication below.

Pohl Boskamp and Espero no longer desire to pursue the proposed proprietary name (b) (4) with the word " (b) (4) as a modifier. Please continue your review of " (b) (4) without the " (b) (4) modifier.

If it is necessary to submit a new sequence containing updated mock-ups without the " (b) (4) modifier, please let us know. We would provide it short term at the beginning of next week then.

We anticipate that this modification will not have any influence on the ongoing 90-day proprietary name review clock. Please confirm.

We appreciate your updates. Have a nice day.

Best regards,

Quang

On 4/13/16, 10:55 AM, "Lyons, Darrell" <Darrell.Lyons@fda.hhs.gov> wrote:

Thanks Quang.

From: Quang Pham [mailto:qpham@esperopharma.com]
Sent: Wednesday, April 13, 2016 10:54 AM
To: Lyons, Darrell
Subject: Re: Proposed Proprietary Name for NDA 208424

Thank you, Darrell. Message received. We will discuss and respond soon.

By the way, we have sent the GlobalSign SHA1 certificates weeks ago and are just waiting for acceptance from the IT Vendor at the FDA to approve us for secure email.

Best regards,

Quang Pham
CEO | Espero Pharmaceuticals

On 4/13/16, 10:34 AM, "Lyons, Darrell" <Darrell.Lyons@fda.hhs.gov> wrote:
Dear Quang Pham,

We note Comment #6 in the Information Request [CMC] dated March 2, 2016, communicated to you that "(b) (4) is not an accepted regulatory term for describing a package type. Given this information, please let me know within 7 days of this communication if you would still like to pursue the proposed proprietary name (b) (4) submitted March 4, 2016, with "(b) (4) as the modifier?

Best Regards,

Darrell Lyons

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
darrell lyons@fda hhs.gov <mailto:darrell.lyons@fda.hhs.gov>
x

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/s/

DARRELL LYONS
04/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208424

GENERAL ADVICE

Espero Pharmaceuticals, Inc.
Attention: Quang Pham
Chief Executive Officer
14286-19 Beach Blvd # 270
Jacksonville, FL 32250

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for nitroglycerin sublingual powder.

We have reviewed the referenced material and have the following comments/recommendations:

Biopharmaceutical:

- FDA agrees that a dissolution test or solubility test is not needed for drug product batch release. However, in order to ensure the consistent quality of the drug product, for post-approval changes in formulation or manufacturing process, we recommend that you compare the solubility of the pre-change and post-change batches using a validated method. It is recommended that for the pre-change and post-change drug product batches, not less than (b) (4)% of the drug product should be dissolved in (b) (4).

Process:

- Your proposed sampling plan and acceptance criteria for (b) (4) appear to be acceptable. However, please note that the final acceptability of the validation studies will be based on the review of the data during the future inspections. Also, refer to FDA's process validation guidance: General Principles and Practices (2011) for more information on continuous process verification.

If you have any questions, call Maryam Changi, Regulatory Business Process Manager, at (240) 402-2725.

Sincerely,

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

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/s/

MOHAN K SAPRU
03/28/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208424

INFORMATION REQUEST

G. Pohl Boskamp GmbH & Co. KG
c/o Espero Pharmaceuticals, Inc.
Attention: Quang Pham, CEO
14286-19 Beach Blvd #270
Jacksonville, Florida 32250

Dear Mr. Pham:

Please refer to your New Drug Application dated 06 August 2015, received 10 August 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for nitroglycerin powder (400 mcg) for sublingual use.

We also refer to your draft carton and container labels that were submitted as part of your NDA.

We have reviewed the reference material and have the following recommendations:

A. General Recommendations (container labels and carton labeling)
   1. Ensure the final container labels and carton labeling contain the conditionally accepted proprietary name.
   2. Revise the established name so that it is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21CFR201.10(g)(2).
   3. Revise the usual dosage statement (b) (4) to read "Usual dose: See Prescribing Information" because the proposed product can be dosed as one or two (b) (4)

B. Container Labels
   1. Provide clarification regarding the intent of the "X/XXXXXXXXX" designation on the individual (b) (4) container label. If this is a numerical designation, ensure that it is not located in close proximity to the lot number or expiration date where it can be mistaken as the lot number or expiration date.[1]

[1] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

C. Carton Labeling
   1. Increase the prominence of the strength statement. As currently presented, the strength lacks prominence on the carton labeling.

We request that you resubmit revised carton and container draft labeling that address the above issues by 11 March 2016.

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

Cc: G. Pohl-Boskamp GmbH & Co. KG
Attention: Dr. Ulrike Küper
Director of Regulatory Affairs
Kieler Straße 11
Hohenlockstedt - Schleswig-Holstein
Germany 25551

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208424

INFORMATION REQUEST

G. Pohl Boskamp GmbH & Co. KG
c/o Espero Pharmaceuticals, Inc.
Attention: Quang Pham, CEO
14286-19 Beach Blvd #270
Jacksonville, Florida 32250

Dear Mr. Pham:

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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

Cc: G. Pohl-Boskamp GmbH & Co. KG
Attention: Dr. Ulrike Küper
Director of Regulatory Affairs
Kieler Straße 11
Hohenlockstedt - Schleswig-Holstein
Germany 25551

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/s/

NORMAN L STOCKBRIDGE
02/19/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208424

PROPRIETARY NAME REQUEST
WITHDRAWN

G. Pohl-Boskamp GmbH & Co. KG
c/o Espero Pharmaceuticals, Inc.
14286-19 Beach Blvd #270
Jacksonville, Florida 32250

ATTENTION: Ulrike Küper
Director Regulatory Affairs

Dear Dr. Küper:

Please refer to your New Drug Application (NDA) dated August 6, 2015, received August 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (b) (4) (Nitroglycerin) Sublingual Powder, 400 mcg (b) (4)

We also refer to:

- Your correspondence, dated and received November 27, 2015, requesting review of your proposed proprietary name, (b) (4)
- Our January 19, 2016, teleconference, identifying an issue with your proposed proprietary name, (b) (4)
- Your correspondence, dated and received on February 5, 2016, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4)

This proprietary name request is considered withdrawn as of February 5, 2016.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

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 Bridget Kane, Regulatory Project Manager in the Office of New Drugs, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Darrell Lyons
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DARRELL LYONS
02/12/2016

MEMORANDUM of TELECONFERENCE

MEETING DATE: January 19, 2016

TIME: 12:00 P.M. EST

LOCATION: Teleconference

APPLICATION: NDA 208424

DRUG NAME: [redacted] (b) (4) (Nitroglycerin) Sublingual Powder, 400 mcg [redacted] (b) (4)

TYPE OF MEETING: Proprietary Name Review

MEETING CHAIRS: Lubna Merchant, Deputy Director, Division of Medication Error Prevention and Analysis (DMEPA)

MEETING RECORDER: Darrell Lyons, Safety Regulatory Project Manager (SRPM)

FDA ATTENDEES:

Office of Surveillance and Epidemiology
Lubna Merchant, Deputy Director, DMEPA
Sarah Thomas, Safety Evaluator, DMEPA
Darrell Lyons, Safety Regulatory Project Manager, PMS

Office of New Drugs
Edward Fromm, Chief, Project Management Staff, DCRP
Bridget Kane, Regulatory Project Manager, DCRP

SPONSOR ATTENDEES:

G. Pohl- Boskamp GmbH & Co. KG
Thanusha Thanabalasingam, Manager Regulatory Affairs
Babette Reiken, Senior Director Market Access

Espero Pharmaceuticals, Inc.
Jeff Cole, President and CFO
Quang Pham, CEO

BACKGROUND:

On November 27, 2015, G. Pohl-Boskamp GmbH & Co. KG submitted a proposed Proprietary Name Review for [redacted] (b) (4) (Nitroglycerin) Sublingual Powder, 400 mcg [redacted] (b) (4) indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

MEETING OBJECTIVES:

The purpose of the call was to let Sponsor know that DMEPA has identified a safety concern with their proposed name (b) (4) and convey our preliminary findings to the sponsor.

DMEPA CONCERNS WITH THE PROPOSED NAME

The proposed proprietary name (b) (4)" contains the United States Adopted Name (USAN) stem (b) (4)

DMEPA also offered some options that the sponsor could consider to alleviate the concern of including a USAN stem in the name. The sponsor could consider replacing the (b) (4) name (b) (4)

REGULATORY OPTIONS

DMEPA recommended that G. Pohl- Boskamp GmbH & Co. KG consider these safety concerns with the name and can either withdraw the current proprietary name submission for (b) (4); and submit a new Request for Proprietary Name Review of their choice or we can continue the review of the proposed name and issue the denial letter by the OSE PDUFA date.

DISCUSSION

The Sponsor asked if submitting a new Proprietary Name would start a new 90-day review clock. DMEPA confirmed that submitting a new Proprietary Name would start a new 90-day review clock and the Sponsor would need to withdraw the current Proprietary Name submission prior to resubmitting another name for our review.

ACTION ITEMS

G. Pohl- Boskamp GmbH & Co. KG will notify the OSE SRPM on how they will proceed with their proposed proprietary name on or before January 22, 2016.

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/s/

LUBNA A MERCHANT
02/10/2016

Lyons, Darrell

From: Lyons, Darrell
Sent: Wednesday, February 03, 2016 7:50 AM
To: 'Quang Pham'
Cc: Reiken, Babette (b.reiken@Pohl-Boskamp.de); Thanabalasingam, Thanusha; Jeff Cole; Kane, Bridget
Subject: RE: NDA 208424 - Request for Teleconference

Dear Quang,

Thank you for notifying us of your plans. Because the current (b) (4) submission has a PDUFA goal date of 2/25/2016, we kindly request that you withdraw this Request for Proprietary Name Review submission by next Tuesday February 9, 2016.

With regards to a new submission for "GoNitro (b) (4) and your NDA PDUFA goal date of June 10, 2016, you may submit your name submission for "GoNitro (b) (4) We request you submit before March 10, 2016 as that would provide the 90-day review timeline needed for us, thus would be much appreciated.

Best Regards,

Darrell Lyons

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
darrell.lyons@fda.hhs.gov

From: Quang Pham [mailto:qpham@esperopharma.com]
Sent: Monday, February 01, 2016 2:56 PM
To: Lyons, Darrell
Cc: Reiken, Babette (b.reiken@Pohl-Boskamp.de); Thanabalasingam, Thanusha; Jeff Cole; Kane, Bridget
Subject: Re: NDA 208424 - Request for Teleconference

Hello Darrell,

Thank you very much for giving us this early feedback regarding the review issue of (b) (4) We really appreciate this courtesy.

As agreed in our teleconference, we would like to inform you about our decision on how to proceed: Espero and Pohl-Boskamp will withdraw Sequence 0009 about our proposed proprietary name, (b) (4)." We will submit a new sequence containing another proposed proprietary name as soon as possible but no later than March 2016. We plan to submit the withdrawal of sequence 0009 (b) (4) addressed in the cover letter of our new sequence as combination of our new proposed proprietary name – if you would prefer a different eCTD handling or the withdrawal of the sequence 0009 short term, please let us know.

Espero and Pohl-Boskamp remain excited about "GoNitro (b) (4) as the best choice for our new

product name. We understand that there is another product with a possibly conflicting name currently under FDA review. From FDA guidance, the product which will get approved first shall get the proposed proprietary name, “GoNitro.”

We are currently contemplating to take the chance to resubmit “GoNitro (b) (4) 90 days before our PDUFA goal date (June 10, 2016). Our legal team has advised us that the U.S. Patent & Trademark Office (USPTO) recently refused an application with “nitro” in its name (for dietary and nutritional supplements featuring nitrates) due to its mark merely being descriptive. We are not certain if that name application was the one that had conflicted with “GoNitro.”

If appropriate, Espero and Pohl-Boskamp would be grateful for an update or any input regarding a resubmission of “GoNitro (b) (4)

Thank you for your consideration.

Best regards,

Quang Pham
CEO | Espero Pharmaceuticals, Inc.
+1 904 328 2210

On 1/22/16, 9:45 AM, "Lyons, Darrell" <Darrell.Lyons@fda.hhs.gov> wrote:

Thanks Quang.

You have a good weekend too.

Best,
Darrell

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
darrell.lyons@fda.hhs.gov

From: Quang Pham [mailto:qpham@esperopharma.com]
Sent: Friday, January 22, 2016 3:34 PM
To: Lyons, Darrell
Cc: Reiken, Babette (b.reiken@Pohl-Boskamp.de); Thanabalasingam, Thanusha; Jeff Cole
Subject: Re: NDA 208424 - Request for Teleconference

Darrell,

Our decision on proceeding with our proposed proprietary name will be made during next week. Thank you again for the call on Tuesday.

Have a nice weekend.

Regards,

Quang Pham
CEO | Espero Pharmaceuticals
(904) 328-2210

On 1/14/16, 10:12 AM, "Lyons, Darrell" <Darrell.Lyons@fda.hhs.gov> wrote:
Hi Quang,

Thank you for confirming Tuesday 1/19/16 at 12pm EST.

Darrell

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
darrell.lyons@fda.hhs.gov

From: Quang Pham [mailto:qpham@esperopharma.com]
Sent: Thursday, January 14, 2016 12:20 PM
To: Lyons, Darrell
Cc: Reiken, Babette (b.reiken@Pohl-Boskamp.de); Thanabalasingam, Thanusha; Jeff Cole
Subject: Re: NDA 208424 - Request for Teleconference

Hello Darrell Lyons,

Thanks for your email.

We would like to request Tue 1/19/16 at 12pm EST. Our Pohl Boskamp Partners will also join the call.

Thanusha Thanabalasingam (Manager Regulatory Affairs)
Babette Reiken (Senior Director Market Access)

Here is the teleconference number for all particpants.

(b) (4) Participants code: (b) (4)

Germany Toll Free: (b) (4)
Germany Local: (b) (4)

Best regards,

Quang Pham
CEO
Espero Pharmaceuticals

On 1/14/16, 5:51 AM, "Lyons, Darrell" <Darrell.Lyons@fda.hhs.gov> wrote:
Dear Quang Pham,

Our review team has identified an issue with your proposed proprietary name, (b) (4) . We would like to schedule a 30-minute teleconference to discuss this matter further. Please let me know if you are available for any of the following dates/times:

Tuesday January 19th 12:00 – 12:30 p.m. (EST)
Tuesday January 19th 3:00 – 3:30 p.m. (EST)
Thursday January 21st 11:00 – 11:30 a.m. (EST)
Friday January 22nd 10:00 – 10:30 a.m. (EST)
Friday January 22nd 11:00 – 11:30 a.m. (EST)
Friday January 22nd 12:00 – 12:30 p.m. (EST)

Best Regards,
Darrell Lyons

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
darrell.lyons@fda.hhs.gov <mailto:darrell.lyons@fda.hhs.gov>

Best regards,

Quang Pham
Espero Pharmaceuticals

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/s/

DARRELL LYONS
02/08/2016

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2015. 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	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
G POHL BOSKAMP GMBH AND CO KG Ulrike Kueper Kieler Strasse 11 Hohenlockstedt 25551 DE	208-424
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 0049-482659 256	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? [ ] YES [X] 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: [ ] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME Nitroglycerin	6. USER FEE I.D. NUMBER PD3015300

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? [ ] YES [X] 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 COMMERCIALLY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] 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.

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE
Küper	DF	30-07-2015

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$1,167,600.00

Form FDA 3397 (08/13)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208424

PROPRIETARY NAME REQUEST
UNACCEPTABLE

G. Pohl-Boskamp GmbH & Co. KG
c/o Espero Pharmaceuticals, Inc.
14286-19 Beach Blvd #270
Jacksonville, Florida 32250

ATTENTION: Ulrike Küper
Director Regulatory Affairs

Dear Dr. Küper:

Please refer to your New Drug Application (NDA) dated August 6, 2015, received August 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nitroglycerin Powder, 400mcg (b) (4).

We also refer to your August 18, 2015, correspondence, received August 20, 2015, requesting review of your proposed proprietary name, GoNitro.

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

> We have completed our review of the proposed proprietary name, GoNitro, and conclude that this name could result in medication errors due to confusion with another product that is also under review. Therefore, the ultimate acceptability of your proposed proprietary name, GoNitro, is dependent upon which underlying application is approved first. If another product is approved prior to your product, with a name that would be confused with your proposed name of GoNitro, you will be requested to submit another name.

We note that you have proposed an alternate proprietary name in your submission dated August 18, 2015. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, 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 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 Bridget Kane, Regulatory Project Manager in the Office of New Drugs, at (240) 402-2170.

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/

TODD D BRIDGES
11/16/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208424

FILING COMMUNICATION -
NO FILING REVIEW ISSUES IDENTIFIED

G. Pohl-Boskamp GmbH & Co. KG
Attention: Dr. Ulrike Küper
Director of Regulatory Affairs
Kieler Straße 11
Hohenlockstedt - Schleswig-Holstein
Germany 25551

Dear Dr. Küper:

Please refer to your New Drug Application (NDA) dated 06 August 2015, received 10 August 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for GoNitro (nitroglycerin powder) 400mcg for sublingual use.

We also refer to your amendments received 14 and 20 August 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is 10 June 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by 12 May 2016.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. During our preliminary review of your submitted labeling, we found that you did not provide a review and summary of the available information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

   Resubmit the following information by December 1, 2015:
   - A review and summary of all available published literature regarding nitroglycerin use in pregnant and lactating women,
   - A revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

   Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. The highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns. Please amend them accordingly.
2. Please amend the headings in HL so that they are bolded and presented in the center of a horizontal line. The horizontal line should also extend over the entire width of the column.

3. The formatting of the referenced section or subsection of each summarized statement or topic in HL is inconsistent. Please place the referenced section or subsection number [e.g., (1.1)] outside of the period.
4. In the HL, please list all contraindications listed in the Full Prescribing Information (FPI). Currently, "Circulatory Failure and Shock" is not included in Highlights.
5. Please update the Table of Contents (TOC) so that all subsection headings are in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
6. In Section 6.2 of the FPI, "Postmarketing Experience", please place a dash (-) between "post" and "approval" in the disclaimer statement.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by 13 November 2015.The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and the Patient Instructions for Use (IFU). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Patient Instructions for Use (IFU), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

Sincerely,

{See appended electronic signature page}

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

Cc: Espero Pharmaceuticals, Inc.
Attention: Quang Pham
Chief Executive Officer, US Agent
14286-19 Beach Blvd. #270
Jacksonville, FL 32250

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/s/

NORMAN L STOCKBRIDGE
10/21/2015

Bui Nguyen, Tri

From: Bui Nguyen, Tri
Sent: Tuesday, August 18, 2015 2:17 PM
To: 'reg.affairs@pohl-boskamp.de'
Subject: Proposed Proprietary Name for NDA 208424

Dear Dr. Kueper:

Please refer to your NDA 208424 for Nitroglycerin Powder, 400 mcg.

We also refer to your correspondence, dated August 12, 2015, and received August, 14 2015, requesting a review of your proposed proprietary name.

Upon preliminary review of your submission, we have determined that it is not a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names* because there was no data on the CD received by the FDA.

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,

Tri Bui-Nguyen, Ph.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: tri.bui-nguyen@fda.hhs.gov

Office: (240) 402-3726

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/s/

TRI M BUI NGUYEN
08/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208424

NDA ACKNOWLEDGMENT

G. Pohl-Boskamp GmbH & Co. KG
Attention: Dr. Ulrike Kueper
Director, Regulatory Affairs
Kieler Straße 11
Hohenlockstedt - Schleswig-Holstein
Germany 25551

Dear Dr. Kueper:

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

Name of Drug Product: nitroglycerin powder for sublingual use, 400 mcg (b) (4)

Date of Application: 6 August 2015

Date of Receipt: 10 August 2015

Our Reference Number: NDA 208424

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on 10 October 2015, in accordance with 21 CFR 314.101(a).

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

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call:

Alison Blaus, RAC
Senior Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief Project Management Staff
Division of Cardiovascular & Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc: Espero Pharmaceuticals, Inc.
Attention: Quang Pham, Chief Executive Officer, US Agent
14286-19 Beach Blvd #270
Jacksonville, FL 32250

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

/s/

EDWARD J FROMM
08/13/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 116608

MEETING MINUTES

G. Pohl-Boskamp GmbH & Co. KG
z. Hd. Babette Reiken
Director Regulatory Affairs
Kieler Straße 11
D-25551 Hohenlockstedt
Germany

Dear Ms. Reiken:

Please refer to your Pre-Investigational New Drug Application (PIND) file for nitroglycerin oral powder ((b) (4)).

We also refer to the meeting between representatives of your firm and the FDA on September 18, 2014. The purpose of the meeting was to the clinical and CMC development program in preparation for a NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-IND

Meeting Date and Time: September 18, 2014 1:00-2:30 pm
Meeting Location: Building 22, room 1311

Application Number: PIND 116,608
Product Name: nitroglycerin oral powder (b) (4)
Indication: acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease
Sponsor/Applicant Name: G. Pohl-Boskamp GmbH & Co. KG

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Meeting Recorder: Alexis Childers, RAC

FDA ATTENDEES

**Division of Cardiovascular and Renal Products*

Norman Stockbridge, M.D., Ph.D.	Director
Tom Marciniak, M.D.	Clinical Team Leader
Khin U, M.D.	Clinical Reviewer
Alexis Childers	Regulatory Health Project Manager
Edward Fromm, R.Ph., RAC	Chief, Regulatory Health Project Manager

**Office of New Drug Quality Assessment*

Kasturi Srinivasachar, Ph.D.	Chemistry Pharmaceutical Assessment Lead
Akm Khairuzzaman, Ph.D.	Chemist
Sandra Suarez, Ph.D.	Master Biopharmaceutics Reviewer

**Office of Clinical Pharmacology*

Sudharshan Hariharan, Ph.D.	Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Thomas Wittig, M.D.	Senior Director Medicine and Clinical Research
Christina Siedschlag, Ph.D.	Manager Regulatory Affairs
Babette Reiken	Senior Director Market Access
Henrick Hesse	Senior Director Product Development/Licensing

1.0 BACKGROUND

Nitroglycerin is an established treatment for angina pectoris. G. Pohl-Boskamp GmbH & Co. KG markets Nitrolingual Pumpspray (NDA 18705). They are developing a new dosage form as an oral powder for sublingual administration. The sponsor met with the Division in January 2013 to discuss both the clinical and CMC development program to ensure adequate support for an NDA

submission. The sponsor has since completed a BA study and further CMC development. The sponsor requested a pre-NDA meeting to ensure there is sufficient information to submit an NDA.

2. DISCUSSION

Preamble: Plasma exposures of nitroglycerin following 0.4 mg nitroglycerin oral powder administered sublingually is in the range of exposures observed for other nitroglycerin products administered sublingually at the same dose i.e., 0.4 mg. Therefore, the Division does not see a need for dose-adjusting the 0.4 mg nitroglycerin oral powder. Moreover, as exposures from (b) (4) 0.4 mg nitroglycerin oral powder are expected to be different by only (b) (4) %, the Division does not see a value in having (b) (4) nitroglycerin oral powder. If there is a reasonable case for it, there are several CMC and biopharmaceutics issues which would require generating additional data (b) (4) as noted below.

Meeting Discussion: The Division questioned the clinical utility of having the (b) (4) strength. The sponsor stated that it is based on (b) (4) experience. They would like physicians and patients to have options if a patient experiences side effects. They would also like to position this product as an alternative to the Nitrostat® tablets which is available at various strengths.

2.1 PROPOSED GENERAL QUESTIONS

1. Applicant's additional comment in preparation of the pre-NDA-Meeting: Furthermore a Prior Approval (Labelling) (b) (4)

   Does the FDA agree?

   FDA Preliminary Response: Yes, a BA study that showed no unexpected adverse drug reactions may be sufficient (b) (4).

   Meeting Discussion: No further discussion.

2.2 PROPOSED STUDY QUESTIONS

2. In agreement with the Division we conducted a randomized, controlled, open, crossover BA study in healthy volunteers to describe and compare the in vivo biopharmaceutical properties of the investigational nitroglycerin oral powder vs Nitroglycerin (GTN) sublingual spray (Nitrolingual® Pumpspray as marketed in the US), each containing 0.4 mg GTN. The Division requested "the SE around the geometric mean ratio should be no more

than 20%". Therefore, the study aimed to determine the geometric mean ratios (test vs. reference) for AUC(0-t_z) and C_{max} of GTN with this certain precision. The Division agreed to obtain a maximum standard error of 0.2 around the log-transformed geometric mean ratio. This target could have been hit for AUC(0-t_z) of GTN with a standard error of 0.139 and for C_{max} with a standard error of 0.156 (standard error of treatment difference, obtained from the ANOVA of the log-transformed PK parameters) (for details see Enclosure 1).

The applicant assumes that this measure of SE fully complies with the Division´s requirement. Taken the estimates of the true mean treatment ratios into account, the applicant proposes to adjust the dosage of nitroglycerin oral powder (see below) to (b) (4) The applicant also assumes that the Division takes it as a given that measure of SE then does not have to recalculated. Does the Division agree?

FDA Preliminary Response: An estimate of relative bioavailability between nitroglycerin oral powder versus Nitrolingual® Pumpspray has been calculated with a precision that is acceptable to the Division.

Meeting Discussion: No further discussion.

3. In the above mentioned BA study it was agreed to define C_{max} and AUC (0-tz) for GTN as primary variables. Provided the geometric mean ratios of C_{max} and AUC (0-tz) indicate a significant superiority for GTN, the Division recommended to consider a dose adjustment. In fact, the geometric mean ratios of AUC(0-t_z) and C_{max} of GTN were 155.16% and 207.26%, respectively, with corresponding 90% confidence intervals ([122.45%; 196.59] and [158.92%; 270.29%], respectively) (for details see the table below).

BEST AVAILABLE COPY

Summary of the statistical analysis of GTN (PK set)

	GTN oral powder / Nitrolingual® Pumpspray		
Parameter	**Geometric mean ratio (%)**	**90% Confidence interval (%)**	**CV%***
AUC(0-t_z)	155.16	(122.45, 196.59)	60.42
C_{max}	207.26	(158.92, 270.29)	69.24
AUC(0-inf)	156.08	(122.05, 199.60)	56.78
	Difference	**90 % Confidence interval**	
t_{max}	0.547	(-0.380; 1.383)	

*Intra-individual CV estimated from the residual mean squares

With reference to the secondary variables, the geometric mean ratio for C_{max} of 1,2-GDN was 142.94% wit
In addition, geometric mean ratios of C_{max} of 1,3-GDN was 134.39% with a 90% confidence interval of (1
On balance, these primary and secondary variables indicate higher exposures for GTN and its metabolites 1,2 active metabolites supports rather a dose close to 0.4 mg GTN. Therefore, the applicant considers to adjust the dosage for nitroglycerin oral powder to (b) (4) (see for details the attached expert statement, enclosure 2).
Does the Division agree to the considered dose (b) (4)?

FDA Preliminary Response: Plasma exposure of nitroglycerin following 0.4 mg nitroglycerin oral powder administered sublingually is in the range of exposures observed by other nitroglycerin products at 0.4 mg dose administered sublingually [exposures

(b) (4)

Meeting Discussion: No further discussion.

4. The applicant plans to submit in addition (b) (4) a second strength of nitroglycerin oral powder containing 0.4 mg GTN for approval. The in-vitro pharmaceutical performance should justify the dose-proportionality and extrapolation from (b) (4) 0.4 mg. Literature data with different GTN formulations will confirm the safety of the proposed therapeutic range (b) (4). the applicant assumes that there is no reason to conduct further efficacy and/or safety studies for approval (see for details the attached expert statement, enclosure 3). Does the Division agree?

   FDA Preliminary Response: No, we do not agree. Given that your proposed product is a drug-device combination, an in vivo study is needed to address the dose-proportionality between the proposed strengths. Also refer to the preamble comments.

   Post meeting comments: It is noted that the reviewer mistakenly wrote " your proposed product is a drug-device combination" in the above preliminary response. This error does not change the need for the requested information.

   Meeting Discussion: The Division stated that since the (b) (4) strength is not being tested in clinical trials, its approval needs to be supported by an in vivo dose-proportionality study. Establishing dose proportionality could be accomplished by either: 1) applying the power equation, or 2) showing dose-proportionality to the 0.4 mg strength by means of calculating 90% confidence intervals for the relevant PK parameters. The Division confirmed that a reference was not needed to be included in the study. The Division also confirmed the study can be conducted in Germany.

2.3 PROPOSED CHEMISTRY QUESTIONS

5. **Regulatory Pathway**

   Applicant's additional comments in preparation of the pre-NDA-Meeting:
   We intend to submit the application as NDA using the 505(b)(1) pathway with the reference product being Nitrolingual Pumpspray (NDA 18-705). We furthermore intend to close possible gaps with literature and/or rely on the FDA's findings of safety or effectiveness for which we do not have right of reference. Does the FDA agree?

   FDA Preliminary Response: Please refer to our original response in the document dated January 14, 2013. If you are only referencing NDA 18705, this NDA would be a 505(b)(1). A 505(b)(2) application is one in which *at least some of the information required for approval* comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. An NDA will be a 505(b)(2) application if any of the specific information necessary for approval is obtained from the literature or from another source to which the applicant does not have a right of reference, even if the

applicant also provides data of their own (e.g., reference to underlying data contained in their own approved marketing application) to support approval.

Meeting Discussion: The sponsor asked for confirmation that they can refer to their NDA 18705 instead of resubmitting all study reports. The Division confirmed they can cross reference NDA 18705. They also asked if the application would still be considered a 505(b)(1) if some literature references are provided. The Division stated that if the literature provided is essential to approval of the sponsor's application, the application is a 505(b)(2) application and the sponsor will need to establish that reliance on the studies described in the literature is scientifically appropriate. If the literature provided is only supportive (not essential to approve the application) then the sponsor's application is a 505(b)(1).

Post meeting note: Please note that 505(b)(2) applicants that rely on published literature that describes a listed drug(s)*, which FDA considers to be reliance on FDA's finding of safety and/or effectiveness for that listed drug(s), the b2 applicant should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. The regulatory requirements for a b2 application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

*that the b2 applicant does not own or to which the b2 applicant does not have right of reference

5 (b) (4)

Meeting Discussion: No further discussion.

Post meeting note, clarification to preliminary comments: Based on the information you've provided, the initial application fee will probably be one half of the full fee at the time of submission. This is

dependent on the clinical data requirement for approval of the application when it is submitted and is not dependent on whether the application is a 505b1 or b2.

Generally, multiple strengths of the same dosage form and active ingredient may be submitted in the same NDA and are included in the same application fee.

After approval, establishment and product fees are assessed annually. Each separate strength is assessed the annual product fee. In general, establishment fees are assessed for each site where each of the products is manufactured in final dosage form unless no manufacture occurs for a fiscal year. If you only plan to market one of the two strengths you may request that the second strength be listed in the discontinued section of the Orange Book until you market the product. This should occur upon approval to avoid listing in the active portion of the Orange Book and incurring user fees. More information can be found at the following link: www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069943.htm . For other user fee questions, please call the PDUFA staff at 301-796-7900.

6. **Drug Substance**

US-DMF No. (b) (4) has already been submitted to and evaluated by the FDA; however, the DMF is in non-eCTD-format.
We intend to submit our NDA in the eCTD format. Our eCTD-dossier will contain a respective LOA as well as the Open Part of the DMF. Does the FDA agree?

FDA Preliminary Response: Yes.

Meeting Discussion: No further discussion.

8. **Drug Product**

The batch formula of both strengths remains unchanged. The only difference is the (b) (4) from 200 mg (0.4 mg, "W200") (b) (4)

For the strength (b) (4) we intend to rely on data and experience gained with the 0.4 mg sublingual powder presentation. This is based on the fact that the composition remains unchanged. This results in comparability of stability data and mostly of analytical methods. Therefore data obtained until now can be used as supporting data. Analytical methods will be further validated where necessary. Does the FDA agree?

FDA Preliminary Response: Per ICH Q1A (R2), stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied. Additionally, data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. If you intend not to use (b) (4) In terms of the amount of data that should be submitted at the time of NDA submission, you may follow the provisions of ICH Q1C guidance for a reduced stability database if justified.

Meeting Discussion: The sponsor has four batches of the 0.4 mg strength (b) (4)

(b) (4)

9. **Development**

(b) (4)

FDA Preliminary Response: This is being reviewed by the Agency's nomenclature group and at this stage the Agency does not have any further update.

Meeting Discussion: No further discussion.

10. **Manufacturing**

a. During the development phase only batches of 0.4 mg GTN oral powder (b) (4) were produced together with the respective stability data. We intend to submit the data as part of the NDA application. (b) (4) Does the FDA agree?

FDA Preliminary Response: No, we do not agree. Batches (b) (4) should be manufactured prior to the NDA submission and stability data from those batches are necessary as stated in the response to Question 8.

Meeting Discussion: No further discussion.

b. As described in Section "2.1 Description and Composition of the Product" of this meeting request letter we act on the assumption that data gained from the 0.4 mg strength are applicable as supporting data (b) (4). We therefore intend to apply for (b) (4) the 0.4 mg strength.

With this application we intend to submit manufacturing data (b) (4) (Note: For stability see Section "2.7 Stability Investigations" of this MRL). Does the FDA agree?

(b) (4)

Meeting Discussion: No further discussion.

(b) (4)

Meeting Discussion: No further discussion.

(b) (4)

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(b) (4)

Meeting Discussion: No further discussion.

Additional discussion during meeting:

(b) (4)

The Division stated that applications are supposed to be complete at the time of submission. Sending data on an additional strength after submission is not considered a complete application. The sponsor should submit all data at once (b) (4)

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, 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 (PSP) within 60 days of an End of

Phase (EOP2) meeting. 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.

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 Pediatric and Maternal Health Staff 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.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

None.

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

/s/

NORMAN L STOCKBRIDGE
10/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 116,608

MEETING MINUTES

G. Pohl-Boskamp GmbH & Co. KG
z. Hd. Babette Reiken
Director Regulatory Affairs
Kieler Straße 11
D-25551 Hohenlockstedt
Germany

Dear Ms. Reiken:

Please refer to your Pre-Investigational New Drug Application (PIND) file for nitroglycerin oral powder (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on January 22, 2013. The purpose of the meeting was to discuss the clinical and CMC development program.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Alexis Childers, Regulatory Project Manager at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-IND
Meeting Date and Time:	January 22, 2013 9:30-11:00 am
Meeting Location:	Building 22, room 1315
Application Number:	PIND 116,608
Product Name:	nitroglycerin oral powder (b) (4)
Indication:	acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease
Sponsor/Applicant Name:	G. Pohl-Boskamp GmbH & Co. KG
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Alexis Childers, RAC

FDA ATTENDEES

**Division of Cardiovascular and Renal Products*	
Norman Stockbridge, M.D., Ph.D.	Director
Tom Marciniak, M.D.	Clinical Team Leader
Khin U, M.D.	Clinical Reviewer
Philip Gatti, Ph.D.	Pharmacologist
Al DeFelice, Ph.D.	Pharmacology Team Leader
Alexis Childers	Regulatory Health Project Manager
**Office of New Drug Quality Assessment*	
Kasturi Srinivasachar, Ph.D.	Chemistry Pharmaceutical Assessment Lead
**Office of Clinical Pharmacology*	
Martina Sahre, Ph.D.	Clinical Pharmacology Reviewer
Raj Madabushi, Ph.D.	Clinical Pharmacology Team Leader
**Office of Biostatistics, Division of Biometrics I*	
Fanhui Kong, Ph.D.	Statistician

SPONSOR ATTENDEES

Thomas Wittig	Senior Director Medical & Regulatory Affairs
Thomas Zimmeck	Director Research & Development
Michaela Gorath	Medical & Preclinical Advisor
Babette Reiken	Director Regulatory Affairs
Laurence J. Downey	Vice President Medical and Scientific Affairs
Allison Lowry	Director Regulatory Affairs

1.0 BACKGROUND

Nitroglycerin is an established treatment for angina pectoris. G. Pohl-Boskamp GmbH & Co. KG markets nitrolingual Pumpspray (NDA 18705). They are developing a new dosage form as an oral powder for sublingual administration. The sponsor would like to discuss the both the clinical and CMC development program to ensure adequate support for an NDA submission.

2. DISCUSSION

2.1. General Questions

1. Is the plan to submit a 505(b)(2) application appropriate?

   FDA Preliminary Response: It appears from your briefing document that you plan to reference your approved NDA 18-705 for Nitrolingual Pumpspray to support approval of your proposed application for nitroglycerin oral powder for sublingual administration. As you are also the current owner/applicant for approved NDA 18-705, your reference to that application to support your proposed oral powder application does not constitute reliance on our finding of safety and/or effectiveness of a listed drug, as pertains to 505(b)(2) applications, but rather on the underlying data contained in that application. Therefore, your nitroglycerin oral powder application would be a 505(b)(1) application. If, however, you intend to rely instead or also on our finding of safety and/or effectiveness for a different listed drug and/or published literature which you do not own or for which you do not have right of reference, your application may be a 505(b)(2) application. Please confirm your plans.

   Discussion during meeting: The Division explained that if the sponsor only intends to rely on NDA 18-705, for which, they are the current owner/applicant, the application would be a 505(b)(1). If the sponsor relies on FDA's findings of safety or effectiveness for any other listed drug for which they are not the owner/applicant, or if they intend to rely on literature or studies in which they have no right of reference, then the application would be a 505(b)(2).

2. There is no recent in-vitro or in-vivo trial with nitroglycerin oral powder upon which reference could be taken. It is planned to conduct a descriptive pharmacokinetic study and an efficacy study (ETT study) aiming at an improved exercise tolerance time in a single treadmill study in order to claim an acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease as approved indications. Does the Division agree that such a plan is both appropriate and also a basis for approval?

   FDA Preliminary Response: This plan is acceptable; however, a single relative bioavailability study with your approved Nitrolingual Pumpspray as the reference may be sufficient to achieve the intended purpose. We refer you to the Draft Guidance on Nitroglycerin for designing your bioavailability study. The link to the study is provided:
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201265.pdf

   Discussion during meeting: The Division explained that the demonstration of BE is not necessary. The relative bioavailability must be characterized with as much precision as possible; for example, the SE around the geometric mean ratio should be no more than 20%. Following the Draft Guidance on Nitroglycerin for designing your bioavailability study increases the likelihood of achieving the desired precision. .

2.2. Study P1208NL Questions

3. Subjects (1): Standard pharmacokinetic descriptions will be obtained only for the dose used in the ETT study (see below), but in healthy volunteers – not patients with angina. Does the Division approve such an approach?

   FDA Preliminary Response: A single relative bioavailability study with your approved Nitrolingual Pumpspray as the reference may be sufficient to achieve the intended purpose.

   Discussion during meeting: No additional discussion.

4. Subjects (2): It is planned to include male and female subjects aged between 18 and 45 years; female subjects of childbearing potential will only be enrolled provided they are using medically adequate contraception. No further limitations are planned e.g. in terms of age or race. Does the Division approve this approach?

   FDA Preliminary Response: Yes, for subjects enrolled in a relative bioavilability study with your approved Nitrolingual Pumpspray as reference.

   Discussion during meeting: No additional discussion.

5. Subjects, type (3): It cannot be ruled out that the experimental formulation might yield higher than expected plasma concentrations. Subjects will be investigated at screening to be healthy (in accordance with conventional criteria including clinical laboratory testing and 12-lead ECG), without orthostatic hypotension and without predisposition to or history of vascular headache. Does the Division recommend also including further baseline evaluations (e.g. serology for hepatitis B and C, alcohol test or urine test for substances of abuse upon recruitment)?

   FDA Preliminary Response: Yes, for subjects enrolled in a relative bioavailability study with your approved Nitrolingual Pumpspray as reference.

   Discussion during meeting: No additional discussion.

6. Medications/treatments: To emphasize the descriptive nature of the pharmacokinetic study, only 0.4 mg nitroglycerin oral powder will be evaluated. The administration of only one single dose (0.4 mg nitroglycerin) is proposed. No control arm is planned. Does the Division agree?

   FDA Preliminary Response: We reached no consensus. This will need to be discussed.

   Discussion during meeting: No additional discussion.

7. Administration of nitroglycerin oral powder: It is proposed to administer the medications according to a strict application protocol. The sponsor proposes to emphasize (and justify) in the trial protocol that this mode of administration is an experimental protocol also used in previous GTN-investigations carried-out by the sponsor and that this protocol is chosen only to minimise undue formulation unrelated variability? Does the Division agree that this precaution does not need to result in corresponding limitations in the dosage and administration instructions of future labeling if authorisation were to be granted?

FDA Preliminary Response: This remains to be seen in actual clinical practice situations where patients with angina may need to self-administer the nitroglycerin oral powder promptly, and may not be able to follow the protocol (b) (4) .

Discussion during meeting: No additional discussion.

8. May the sponsor conduct this descriptive pharmacokinetic study either in Europe or in the United States of America, provided the study will be carried out in accordance with international GCP-principles and national GCP-provisions applicable in the country of conduct?

FDA Preliminary Response: You can conduct the relative bioavailability study either in Europe or in the United States of America, provided the study will be carried out in accordance with international GCP-principles and national GCP-provisions applicable in the country of conduct.

Discussion during meeting: No additional discussion.

2.3. Study P1206NL Questions

9. Design: A cross-over trial design is proposed. This approach is taken while the within-subject variability of the study criteria can be expected to be distinctly lower than the between-subject variability. On the other hand, this might have a negative impact on the recruitability of suitable subjects. Does the Division agree with the proposed cross-over trial design?

FDA Preliminary Response: Yes. However, as stated in response to Question 2.1 (2) above, a single relative bioavailability study with your approved Nitrolingual Pumpspray as the reference may be sufficient to achieve the intended purpose.

Note: Because a single relative bioavailability study may be sufficient, questions 10 through 19 are not relevant at this time.

Discussion during meeting: No additional discussion.

10. Sample size calculation: A formal estimate of the appropriate sample size was derived from previous study RG-83608-601 conducted by the sponsor (Nitrolingual® Pumpspray (Application Number N018705, respectively Thadani U, Wittig T. Clin. Med. Insights Cardiol. (2012) 6: 87-95). In this study, the mean time to onset of angina was 5.43 minutes and 5.93 minutes for placebo and for 0.4 mg GTN, respectively. The mean treatment difference (investigational ETT-times not corrected for baseline- or control-ETT) was 0.50 minutes with a standard deviation of the within-subject (intra-patient) treatment difference of 1.185 min. Based on this, a desirable sample size of 62 patients was estimated for parametric treatment contrasts (ANOVA-based t-test) with 90% power and a two-sided alpha-risk of 0.05. Does the Division agree with this estimate?

FDA Preliminary Response: Deferred.

Discussion during meeting: No additional discussion.

11. Subjects: It is planned to include adult male and female subjects aged 18 years or older. No further limitations are planned e.g. in terms of race, diversity or defining an upper limit of 80 years. Does the Division agree?

    FDA Preliminary Response: Deferred.

    Discussion during meeting: No additional discussion.

12. Patient selection (1): At visit 2 all patients will run a single treadmill exercise testing for eligibility. Only patients with an angina limited ETT-testing and a ST-segment depression (≥ 1 mm) at the baseline ETT will continue the study and will be randomized. There will be no requirement for 2 exercise tolerance tests to be within 20% of one another at baseline. Does the Division agree with that plan?

    FDA Preliminary Response: Deferred.

    Discussion during meeting:

13. Patient selection (2): There will be no requirement for patients to be demonstrated nitrate responders to enter the randomization phase of the trial. Does the Division agree with that plan?

    FDA Preliminary Response: Deferred.

    Discussion during meeting: No additional discussion.

14. Criteria & Methods (1): It is proposed to define the primary end point as time to end of ETT-testing; investigational ETT-testing (visit 3 and 4) is stopped a) upon the patient´s decision or b) physician's decision to stop (with or without angina/ECG-changes) – the latter is based on common safety criteria acc. to pertinent guidelines. Does the Division agree with that plan?

    FDA Preliminary Response: Deferred.

    Discussion during meeting: No additional discussion.

15. Criteria & Methods (2): It is proposed to test the mean treatment differences for the primary criterion for statistical significance at a 2-sided alpha-level of 0.05 and a power of 90%. Does the Division agree that such a plan - a single trial that demonstrates superiority of 0.4 mg nitro-glycerin oral powder versus placebo - is both appropriate and also a basis for approval?

    FDA Preliminary Response: Deferred.

    Discussion during meeting: No additional discussion.

16. Criteria & Methods (3): The time to end of ETT-testing (exercise tolerance time, ETT) is proposed as primary criterion. It is not planned to carry out any control-ETT without treatment within each period. Furthermore, it is not planned to correct the estimates of the mean treatment differences for the baseline-ETT. Does the Division agree?

    FDA Preliminary Response: Deferred.

Discussion during meeting: No additional discussion.

17. Criteria & Methods (4): Secondary end point will be time to onset of ≥ 1 mm ST-segment depression during exercise. Its mean treatment differences will be analyzed in a similar fashion as the primary end point and will be tested hierarchically at a 2-sided alpha-level of 0.05, i.e. the significance test can only be interpreted in a confirmatory way if a statistical significant difference was detected for the primary endpoint. Due to the hierarchical testing procedure no adjustment of the type I error is required. Does the Division agree?

    FDA Preliminary Response: Deferred.

    Discussion during meeting: No additional discussion.

18. Handling missing data: Provided Division agrees to cross-over design, this procedure will require a suitable approach to account for subjects who fail to complete the study for the two investigational trial treatments/periods. It is proposed to consider an ETT-testing evaluable if a) the observations were not confounded by major protocol deviations and b) the ETT was stopped either by the physician's or c) the patient's decision (with or without angina). Furthermore, it is proposed that patients without evaluable ETT-testing at visit 3 will be replaced. Patients with an evaluable ETT-testing for visit 3, but not for visit 4 will not be replaced; for the ITT, the missing ETT at visit 4 will be replaced by Last Observation Carried Forward (LOCF) from visit 3. Does the Division agree with this proposal?

    FDA Preliminary Response: Deferred

    Discussion during meeting: No additional discussion.

19. To emphasize the descriptive nature of the above mentioned pharmacokinetic study (study identifier P1208NL), although unlikely, it might be that there is no ability to document plasma concentrations of the (b) (4) formulation. Provided that the 0.4 mg dose is superior to placebo with a $p<0.05$ in the proposed ETT study P1206NL, even if the pharmacokinetic study fails to document PK-data of the (b) (4) the sponsor thinks that there would still be a basis of approval. Does the Division agree?

    FDA Preliminary Response: Deferred. However, please explain this inconsistency in the context of the statement in Question 5 in the PK study in healthy volunteers: "*It cannot be ruled out that the experimental formulation might yield higher than expected plasma concentrations…..*"

    Discussion during meeting: No additional discussion.

2.4. CMC Questions

20. Development: Does the FDA agree with the term (b) (4)"?
    Would the FDA prefer (b) (4) "sublingual powder"?
    Would there be consequences the applicant should take into account when choosing the exact term?

    FDA Preliminary Response: "Sublingual powder" may be acceptable. However, this has to be discussed internally before a final decision can be made. You will be notified of our recommendation before your NDA is submitted.

Discussion during meeting: The sponsor felt that the new product has some similarities to the tablet and since both dosage forms are given under the tongue, they would like to know if they can use the USP monograph for sublingual tablets specifications. The Division explained that sublingual powder is not a compendial dosage form. An internal nomenclature committee will be consulted to determine how this product will be classified prior to NDA submission.

21. Control of excipients: In addition to the listed information we intend to submit suitable certificates of analysis for the excipients. Does the FDA agree with this concept?

    FDA Preliminary Response: Yes.

    Discussion during meeting: No additional discussion.

22. Manufacturing: We intend t (b) (4) the active substance?

    FDA Preliminary Response: (b) (4)

    Discussion during meeting: (b) (4) It was suggested again that the sponsor should have a PRE-NDA CMC meeting.

23. Manufacturing: The manufacturing site will be (b) (4). This site is already audited for (b) (4).
    Therefore we act on the assumption that no additional FDA audit is required before launch of this new dosage form. Does the FDA agree?

    FDA Preliminary Response: All manufacturing, packaging and testing sites should be ready for inspection when the NDA is submitted. Our Office of Compliance will decide which sites to inspect.

    Discussion during meeting: No additional discussion.

24. Manufacturing: Does the FDA agree with the proposed in-process controls?

    FDA Preliminary Response: Since the amount of drug in the formulation is very low, you should consider (b) (4)

    Discussion during meeting: No additional discussion.

25. Specifications: Does the FDA agree with the proposed specification?

    FDA Preliminary Response: The tests proposed seem appropriate. No comments are provided on the proposed acceptance criteria for various test attributes as this is a review issue.

    Discussion during meeting: (b) (4)

(b) (4)

26. Specification - microbiological purity: We expect no OOS results due to the characteristics of the product and the excipients. Therefore microbiological purity will be tested on release of the first 5 commercial batches only.
Does the FDA agree?

FDA Preliminary Response: No, you should perform the microbial limits test on every batch. Any sunset provision should be submitted for review in the NDA with a strong justification, not merely the absence of OOS results on a few batches.

Discussion during meeting: No additional discussion.

27. Packaging: Does the FDA accept pack sizes (b) (4) ?

FDA Preliminary Response: Yes

Discussion during meeting: No additional discussion.

28. Stability investigations: Is this stability program satisfactory?

FDA Preliminary Response: Yes. A minimum of 12 months' long term and 6 months' accelerated data are expected at the time of submission of the NDA. (b) (4)

Discussion during meeting: No additional discussion.

29. Conclusion: Which additional information will help the FDA to evaluate this dossier?

FDA Preliminary Response: You should request a pre-NDA CMC specific meeting and submit a detailed briefing package for discussion incorporating the changes recommended above.

To facilitate any future CMC and other changes by serving as a bridge, consider the development of a dissolution method for your proposed powder formulation which reflects physiological relevance while serving as a QC test.

Discussion during meeting: No additional discussion.

Additional discussion during meeting: Although not required, if no studies are performed in the United States, the Division recommended that the sponsor open an IND and ask for comment on the single protocol since that study will be the basis for approval.

3.0 PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

None.

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

/s/

NORMAN L STOCKBRIDGE
02/05/2013