

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203510Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203510

SUPPL # N/A

Trade Name

Generic Name phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%

Applicant Name Paragon BioTeck, Inc.

Approval Date, If Known March 21, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES

NO

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

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

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

YES

NO

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

NDA 203826 Phenylephrine Hydrochloride Injection

Discontinued NDAs

NDA 8306 Phenergen VC with Codeine syrup (promethazine, phenylephrine and codeine combo cough/cold syrup)
NDA 13296 Duo-Medihaler (isoproterenol/phenylephrine combo inhaler)
NDA 8604 Phenergan VC syrup (promethazine/phenylephrine combo cough/cold syrup)
NDA 7953 Prefrin-A ophth drops (phenylephrine/pyrilamine combo eye drops)

Marketed, OTC product

NDA 22565 Advil Congestion Relief (ibuprofen and phenylephrine combo tablet)

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

NOTE: The approval is literature based and the applicant will not qualify for exclusivity.

This product has been used for many years as an unapproved marketed drug. The NDA product was comparable with reports across a wide range of literature with regard to adverse reactions and effectiveness. The Division considers the data in the literature submitted in this NDA to be an adequate bridge for approval.

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:

The published literature contains sufficient clinical safety and efficacy information on multiple different concentrations of topical ophthalmic preparations of phenylephrine hydrochloride used in the induction and maintenance of mydriasis to support approval of this NDA.

(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: **Diana Willard**
Title: **Chief, Project Management Staff**
Date: **February 22, 2013**

Name of Office/Division Director signing form: **Renata Albrecht, M.D.**
Title: **Director, Division of Transplant and Ophthalmology Products**

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

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

/s/

DIANA M WILLARD
03/20/2013

RENATA ALBRECHT
03/21/2013

Submit Date: 9/21/12
Receipt Date: 9/21/12

Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%

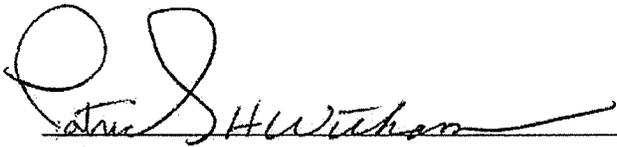
Paragon Biotech, Inc.

1.3. Administrative Information

NDA 203-510

3. DEBARMENT CERTIFICATION

Paragon Biotech, Inc. 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.



Patrick H. Witham

President and CEO

9-20-12

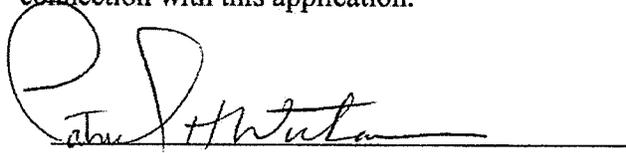
Date

Submit Date: 10/19/2011
Receipt Date: 10/21/2011

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Paragon Biotech, Inc. 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.



Patrick H. Witham
President and CEO

10/19/2011
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203510	NDA Supplement # N/A	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: phenylephrine hydrochloride Dosage Form: solution		Applicant: Paragon BioTeck, Inc. Agent for Applicant (if applicable): Point Guard Partners
RPM: Diana Willard		Division: Division of Transplant and Ophthalmology Products
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><u>NDA's and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> </div> <div style="width: 50%;"> <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input checked="" type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: March 21, 2013</p> <p>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.</p> </div> </div>		
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is March 21, 2013 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

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

² For resubmissions, (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).

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. <input checked="" type="checkbox"/> Not applicable as there are no patents that claim the drug for which approval is sought
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> N/A/(no paragraph III certification) Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

<p>(Summary Reviews)).</p> <ul style="list-style-type: none">[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?</p> <p>(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If “Yes,” skip to question (4) below. If “No,” continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.</i></p> <p><i>If “No,” continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).</p> <p><i>If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.</i></p> <p>(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If “No,” continue with question (5).</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ⁴	<u>X</u>
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<u>X</u> Included
Documentation of consent/non-consent by officers/employees	<u>X</u> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date: AP/March 21, 2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<u>X</u> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<u>X</u> Included
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	<p>No proprietary name: Minutes from March 8, 2013, teleconference with applicant included in Action Package</p>
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA February 22, 2013 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) February 26, 2013 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<p>March 30, 2012: Filing Review for October 19, 2011, submission No Filing Review for September 21, 2012, submission</p> <p>February 27, 2013, e-mail from Beth Duvall stating that this NDA is cleared for approval by the 505(b)(2) Clearance Committee</p> <p>505(b)(2) Assessment: March 21, 2013</p>
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC March 6, 2013 If PeRC review not necessary, explain: _____ • Pediatric Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	<input checked="" type="checkbox"/> Included
❖ Internal memoranda, telecons, etc.	<input checked="" type="checkbox"/> Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	N/A
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) • 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	March 21, 2013
Deputy Division Director Summary Review (<i>indicate date for each review</i>)	March 20, 2013
Cross-Discipline Team Leader (CDTL) Review (<i>indicate date for each review</i>)	March 20, 2013
PMR/PMC Development Templates (<i>indicate total number</i>)	March 18, 2013
Clinical Information⁶	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	See March 20, 2013, CDTL Review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	March 5, 2013
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

<p>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)</p>	<p>From Page 8 of the March 5, 2013, primary clinical review: This is a 505(b)(2) supplemental application primarily based on literature. In accordance with 21 CFR Part 54, no financial disclosure is appropriate for this application. There are no “covered clinical studies” in this submission.</p>
<p>❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)</p>	<p><input checked="" type="checkbox"/> None</p>
<p>❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)</p>	<p><input checked="" type="checkbox"/> Not applicable</p>
<p>❖ Risk Management</p> <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<p><input checked="" type="checkbox"/> None</p>
<p>❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)</p>	<p><input checked="" type="checkbox"/> None requested</p>
<p>Clinical Microbiology <input checked="" type="checkbox"/> None</p>	
<p>❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)</p>	<p><input type="checkbox"/> None</p>
<p>Clinical Microbiology Review(s) (<i>indicate date for each review</i>)</p>	<p><input type="checkbox"/> None</p>
<p>Biostatistics <input type="checkbox"/> None</p>	
<p>❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)</p>	<p><input type="checkbox"/> None</p>
<p>Statistical Team Leader Review(s) (<i>indicate date for each review</i>)</p>	<p>March 1, 2013</p>
<p>Statistical Review(s) (<i>indicate date for each review</i>)</p>	<p>February 21, 2013</p>
<p>Clinical Pharmacology <input type="checkbox"/> None</p>	
<p>❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)</p>	<p><input checked="" type="checkbox"/> None</p>
<p>Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)</p>	<p>December 12, 2012 NOTE: Team Leader co-signed primary review</p>
<p>Clinical Pharmacology review(s) (<i>indicate date for each review</i>)</p>	<p>December 12, 2012</p>
<p>❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)</p>	<p><input checked="" type="checkbox"/> None</p>

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<u>X</u> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	February 20, 2013 NOTE: Team Leader co-signed primary review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	February 20, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<u>X</u> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<u>X</u> No carc
❖ ECAC/CAC report/memo of meeting	<u>X</u> None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<u>X</u> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<u>X</u> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	February 20, 2013 Note: Branch Chief co-signed primary review
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	February 20, 2013
❖ Microbiology Reviews <u>X</u> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	<u>X</u> Included January 3, 2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<u>X</u> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Categorical Exclusion Claim accepted; Page 44 of February 20, 2013, Product Quality review
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	N/A
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁷)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (see Page 41 of the February 20, 2013, Product Quality review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/s/

DIANA M WILLARD
03/22/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING DATE: March 8, 2013
TIME:
LOCATION: WO Bldg 22, Rm 4396
APPLICATION: NDA 203510
DRUG NAME: (b) (4) (Phenylephrine Hydrochloride Ophthalmic Solution)
TYPE OF MEETING: Proprietary Name Review Teleconference (b) (4)
APPLICANT: Paragon BioTech, Inc
MEETING CHAIR: Jamie Wilkins Parker, PharmD (DMEPA Team Leader)
MEETING RECORDER: Karen Townsend, Safety Regulatory Project Manager, OSE
FDA ATTENDEES: Jung Lee, RPh (DMEPA Safety Evaluator)
Jamie Wilkins Parker, PharmD (DMEPA Team Leader)
Karen Townsend, RPh (OSE PM DTOP)
SPONSOR ATTENDEES: Patrick Witham (President, Paragon BioTech, Inc)
William Stringer (Partner, Point Guard Partners)
Jeremy Brace (Partner, Point Guard Partners)

Background:

DMEPA requested this teleconference to notify you of our safety concerns with the proposed proprietary name, (b) (4)

Discussion:

Promotional Concerns with (b) (4)

The Office of Prescription Drug Promotion (OPDP) objects to the proposed proprietary name " (b) (4) . (b) (4) contains a common substance, phenylephrine hydrochloride, for which the limitations are readily recognized when listed by the established name [21 CFR 201.10(c)(3)]. (b) (4) evokes the word (b) (4) which is defined as " (b) (4) (<http://unabridged.merriam-webster.com/cgi-bin/unabridged>: accessed 02/07/2013). Therefore, the proposed proprietary name suggests a unique representation over other drugs with similar active ingredients.

Concerns with Foreign Product Name:

In addition, it has been noted that (b) (4) sounds like another product, (b) (4), which is a foreign product identified in Argentina containing the active ingredient (b) (4)

Concerns with the name (b) (4):

In addition, there is concern that the name (b) (4) is too similar to (b) (4) which is a topical product used in the (b) (4). Furthermore, (b) (4) was also stated to be very similar to (b) (4) by one of the participants in the Division of Medication Error Prevention and Analysis' prescription study, and was also identified during our initial evaluation of the name.

Although we show the product (b) (4) is discontinued and the application was voluntarily withdrawn by the Applicant, since it was not withdrawn for safety reasons, the probability exists for (b) (4) to return to the market at any time. Should you wish to pursue the name (b) (4) despite OPDP's objection, we will require additional data to show the name (b) (4) as well as the manufacturer are no longer viable to dismiss the safety concern with the proposed proprietary name, (b) (4)

Preliminary concerns with the proposed alternate name, (b) (4):

We performed a preliminary evaluation of your alternate proprietary name, (b) (4), and have found it is phonetically similar to and shares overlapping product characteristics with the currently marketed product (b) (4).

(b) (4) contains 3 syllables vs. 2 syllables in (b) (4) in which the first and last syllables of both names sound similar. However, the 2 syllable in (b) (4) is a vowel which may be dropped or not well enunciated when spoken, thus making the name sound phonetically similar to (b) (4). Furthermore, one verbal participant in our prescription study misinterpreted the name (b) (4) as (b) (4) further adding to our concern over possible name confusion.

Both products also share overlapping product characteristics that may increase the risk of confusion between this name pair. Both (b) (4) and (b) (4) have similar indications for use, similar setting of use, have the same route of administration (Ophthalmic), and the same dosage form (Solution) which may be omitted on a prescription order. For example, a prescription written for (b) (4)

Overall, these combined features contribute to the similarity of this name pair.

Options:

- 1) Withdraw the proposed name [REDACTED] (b) (4) and submit an alternate name(s) for review.
- 2) Wait for DMEPA to complete our review of [REDACTED] (b) (4) by our OSE PDUFA goal date of 04/18/2013 and issue a denial letter.

Questions:

Paragon: Is it a viable option to market the product with the generic name and submit a proprietary name later due to the overwhelming evidence not to pursue the name

[REDACTED] (b) (4)

FDA: Yes

FDA: When should we expect a withdrawal letter from your firm?

Paragon: You should expect it by Monday or Tuesday next week. Should we confirm this with an email? All 3 versions of the label submission were included when emailed to Diana (OND PM) including the generic version. We will email Diana to let her know to focus their efforts on the Phenylephrine label and let her know a formal submission will be forthcoming.

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/s/

KAREN F TOWNSEND
03/14/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: February 27, 2013

To: Mr. Jeremy Brace	From: Diana Willard Chief, Project Management Staff
Company: Paragon Biotech, Inc.	Division of Transplant and Ophthalmology Products
Email: jbrace@pointguardllc.com	Email: diana.willard@fda.hhs.gov
Telephone Number: 727-458-2823	Phone number: 301-796-1600
Subject: NDA 203510 – Labeling Comments	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1600. Thank you.

Dear Mr. Brace,

Please refer to your NDA 203510 for phenylephrine hydrochloride ophthalmic solution.

The following are comments pertaining to the labels for this NDA. Please let us know if you are in agreement with these comments/revisions and when you would be able to submit revised labels to this NDA.

- 1) To avoid selection error, revise the color scheme of the labeling (i.e., carton and container labeling) for one of the product strengths from (b) (4) to another color scheme so that they are well differentiated from each another.
- 2) Change the font color of the proprietary name on the carton and container to a color that provides better contrast against a (b) (4) background.
- 3) Ensure that the established name is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2). Remove the (b) (4) outline around the letters of the proprietary name unless you also utilize the (b) (4) outline on the established name.
- 4) The strength statement should directly follow after the established name on the principal display panel of the carton and container labels. For example: (b) (4) (phenylephrine ophthalmic solution) 2.5%.
- 5) Revise the net quantity statement to include a space between the number and the unit of measure. For example: 5mL should read 5 (space) mL.
- 6) Delete or relocate the word (b) (4) that appears directly below the strength statement to a location away from the strength statement.
- 7) The statement on the container labeling, “Do not use if imprinted seal on cap is torn, broken or missing,” is printed in a (b) (4) font color against a (b) (4) background. Change the font color to a color that provides better contrast against a (b) (4) background, such as black.

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Diana Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

DIANA M WILLARD
02/27/2013

Willard, Diana M

Subject: FW: NDA 203510 - cleared for action

From: Duvall, Beth A
Sent: Wednesday, February 27, 2013 1:26 PM
To: Willard, Diana M
Cc: Roeder, David L; Raggio, Miranda; Bertha, Amy
Subject: NDA 203510 - cleared for action

Diana,

Sorry for the delay. You are cleared for action from a 505(b)(2) perspective.

Please make the following changes to your draft 505(b)(2) assessment before archiving in DARRTS (assuming you are heading towards approval if you are not heading towards approval, please defer until you hear from us after the next clearance/review cycle):

Q3) Provide a statement as to the why the published literature that is necessary for approval is scientifically relevant or appropriate. [this would be along the lines of what you had indicated under Q2 below]

Beth

Beth Duvall

Associate Director for Regulatory Affairs
CDER/Office of New Drugs
Direct Phone Number: (b) (6)
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

Cuff, Althea

From: Jeremy Brace [jbrace@pointguardllc.com]
Sent: Thursday, February 21, 2013 3:00 PM
To: Cuff, Althea
Subject: Re: NDA 203510

Thanks Althea,

I confirm receipt of the email. I am sure this will be ok but I will speak with the sponsor and confirm

Regards

Jeremy

On Thu, Feb 21, 2013 at 2:25 PM, Cuff, Althea <Althea.Cuff@fda.hhs.gov> wrote:

Hi Jeremy,

We have completed review of the CMC module and have concluded that an expiration dating period of 18 months is appropriate for Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%, although you had requested an expiration dating period of (b) (4) in the NDA. You may extend the expiration dating to (b) (4) post-approval by either of the two options listed below:

1. At the next stability test point when you have 18, 12, and 12 months long-term stability data for the current exhibit batches for each strength, you may submit a prior-approval supplement to extend the expiration dating period to (b) (4). Approval of the extension will, of course, depend on review of the data that are submitted.
2. Alternatively, when you have accumulated 24 months of long-term stability data for 3 commercial scale batches of each strength, and the data show no out of specification results, you may extend the expiration dating period to (b) (4) via the Annual Report.

Thanks,

Althea Cuff, MS
Regulatory Health Project Manager
Food & Drug Administration, CDER
Office of New Drugs Quality Assessment II
301-796-4061

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/s/

ALTHEA CUFF
02/21/2013

MEMORANDUM OF TELECON

DATE: February 13, 2013

APPLICATION NUMBER: NDA 203510

BETWEEN:

Name: Bill Stringer, Patrick Witham, Jeremy Brace NAME
Representing: Paragon Biotech, Inc.

AND

Name: Rapti Madurawe, Ph.D., Branch Chief, ONDQA
Bala Shamugam, Ph.D., CMC Lead, ONDQA
George Lunn, Ph.D., Chemist, ONDQA
Wiley Chambers, MD., Deputy Director, OND
William Boyd, MD., Lead, OND
Diana Willard, CPMS, OND

SUBJECT: Clarification of IR sent to Applicant September 20, 2012

The sponsor will test for leachables using the HPLC method (b) (4).
Unknowns will be referenced to (b) (4). FDA acknowledged that
making a sterile control (b) (4) may pose technical problems and the sponsor
agreed to use their best efforts in preparing a sterile solution. If there are any untoward results
we can discuss them when full data are available to evaluate the need to include a specification
for leachable(s).

(b) (4)
FDA may make this a post-
marketing commitment (internal consultations are on-going).

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/s/

ALTHEA CUFF
03/08/2013



NDA 203510

REFUSAL TO FILE

Paragon Biotech, Inc
Attention: Mr. Patrick H. Witham
President and CEO
11501 SW Pacific Highway
Suite 201
Tigard, OR 97223

Dear Mr. Witham:

Please refer to your New Drug Application (NDA) submitted October 19, 2011, received October 21, 2011, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

The NDA does not provide sufficient stability data to establish the stability profile of the drug product over the requested shelf-life. Per ICH Q1A (R2), 12-month long-term and 6-month accelerated stability data for three batches should be provided for us to be able to evaluate the stability of the drug product over the requested shelf-life.

Release data for the two exhibit batches, one each for the two strengths, 2.5% and 10%, have been provided in the NDA but the submission does not provide stability data for these batches. Stability data submitted for the historical batches are inadequate since they were only tested for a few quality attributes. Furthermore, the long-term and accelerated data were generated from different batches which limits evaluating stability of any one batch stored under different conditions.

Additionally, the NDA lacks data on freeze-thaw and weight loss studies.

In addition, we request that you submit patent certifications for the listed drugs to which you refer in your application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Victor Ng, Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
12/16/2011



NDA 203510

MEETING MINUTES

Paragon Biotech, Inc
Attention: Mr. Patrick H. Witham
President and CEO
11501 SW Pacific Highway
Suite 201
Tigard, OR 97223

Dear Mr. Witham:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%.

We also refer to the telecon between representatives of your firm and the FDA on December 16, 2011. The purpose of the meeting was to clarify any questions Paragon BioTeck, Inc might have in regards to the Refuse To File Letter.

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

If you have any questions, call Victor Ng, Project Manager at (301) 796-0735.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 16, 2011
TIME: 2:00 PM – 3:00 PM
LOCATION: Teleconference
APPLICATION: NDA 203510
DRUG NAME: phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%
TYPE OF MEETING: N/A

MEETING CHAIR: Wiley A. Chambers, M.D.

MEETING RECORDER: Victor Ng

FDA ATTENDEES:

Renata Albrecht, MD, Division Director
Terrance Ocheltree, PhD, Division Director, ONDQA
Wiley A. Chambers, MD, Deputy Director
William Boyd, MD, Clinical Team Leader
Rapti Madurawe, PhD, Branch Chief
Judith Milstein, Chief, Project Management Staff
Martin Nevitt, MD, Clinical Reviewer
Victor Ng, Regulatory Project Manager
Balajee Shanmugam, PhD, Product Quality Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Patrick Witham, President & CEO, Paragon BioTeck, Inc.
William Stringer, Manufacturing and Quality Partner, Point Guard Partners LLC
Barry Butler, Managing Partner, Point Guard Partners LLC
Jeremy Brace, Regulatory Partner, Point Guard Partners LLC

BACKGROUND:

Paragon BioTeck, Inc submitted a New Drug Application on October 19, 2011, for phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%, to dilate the pupil (b) (4). A filing meeting was held on December 5, 2011, and a decision was made to Refuse to File the application:

The NDA did not provide sufficient stability data to establish the stability profile of the drug product over the requested shelf-life. Per ICH Q1A (R2), 12-month long-term and 6-month accelerated stability data for three batches should have been provided in the application to be able to evaluate the stability of the drug product over the requested shelf-life.

Release data for the two exhibit batches, one each for the two strengths, 2.5% and 10%, have been provided in the NDA but the submission does not provide stability data for these batches. Stability data submitted for the historical batches were inadequate since they were only tested for a few quality attributes. Furthermore, the long-term and accelerated data were generated from different batches which limited evaluating stability of any one batch stored under different conditions.

Additionally, the NDA lacked data on freeze-thaw and weight loss studies.

Paragon should also have submitted patent certifications for the listed drugs referred to in the application.

A Refuse to File letter was issued on December 16, 2011.

MEETING OBJECTIVES:

The Division requested this teleconference to clarify any questions Paragon BioTeck, Inc might have in regards to the Refuse To File Letter.

DISCUSSION POINTS:

- The Agency stated that the Refuse to File letter sent to Paragon BioTeck, Inc on December 16, 2011, was an official correspondence.
- The Agency stated that there was no stability data provided for the two exhibit batches of the drug product and that the data submitted on the older batches lacked continuity. The Agency further stated that the submitted stability data are not sufficient to establish product quality and an expiry period.
- The Agency stated sufficient stability data for the proposed commercial formulation is necessary to assure the quality of the product over the proposed expiry period. The Agency also reiterated that per ICH Q1A (R2), 12-months of long-term and 6-months accelerated stability data for three batches should be provided.

- The Agency noted that the concentration of the proposed Paragon product because of the (b) (4) differed from the labeled concentration of the marketed phenylephrine and stated the need for clinical data and stability data to support the proposed Paragon product. If data are missing, it would be premature to submit an application.
- The Agency recommended that Paragon BioTeck, Inc request a meeting with the Agency to discuss any questions that arose in preparing their application.

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/s/

WILEY A CHAMBERS
02/09/2012



NDA 203510

INFORMATION REQUEST

Paragon BioTeck, Inc.
c/o Point Guard Partners LLC
Attention: Jeremy Brace, B.Sc. (Hons)
400 N. Ashley Street, Suite 1950
Tampa, FL 33602

Dear Mr. Brace:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%.

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

1. Please describe how the drug product manufacturer assures the quality of the in-coming drug substance and which tests are conducted in house. If the assay and impurities are determined by HPLC testing please describe how the drug product manufacturer has validated the method or verified that it is suitable for use.
2. Provide a description of the HPLC method used for SOP SAS-037 (b) (4) described in extract-migration-study. How is the reporting limit of (b) (4) defined? (b) (4) with reference to what?
3. Conduct extraction and migration studies (in a similar fashion to those already carried out) for 1-3 batches after storage at 25°C/60% RH (accelerated) for 6 months and after storage refrigerated (long-term) through expiration. We recommend that the control be a sealed glass vial containing the drug product solution.
4. In the description of the manufacturing Process (3.2.P.3.3) you state (b) (4)

- (b) (4)
5. In 3.2.P.3.4.1 the in-process control is given as (b) (4)
Please reconcile.
 6. Provide a description of the sampling plan and representative analyses for the (b) (4)
 7. (b) (4)
Please provide a report verifying that it is suitable for its intended purpose.
 8. Please change the phenylephrine hydrochloride assay acceptance criterion to (b) (4)
label claim.
 9. We note that the highest observed Total Impurities value is (b) (4). Please consider reducing the Total Impurities acceptance criterion from (b) (4)
 10. Consider adding a chiral purity test to the drug product specification or provide a justification for not doing so.
 11. Please supply batch numbers, expiration dates, and assigned purities for all the reference standards.
 12. Provide specifications for the in-coming container-closure system components.
 13. Provide a description (including brand, type, and composition, as far as is known) of the labeling materials and inks that may be used for this product. Please note that these should not be changed without notifying the Agency.
 14. Provide a Methods Validation Package. This should consist of a list of samples that could be supplied and links to the various analytical methods.
 15. You state in 3.2.P.2.5 Microbiological Attributes that “ (b) (4)
 16. Test the (b) (4) for extractables.
 17. Test the drug product for endotoxins on stability, at least annually.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
12/05/2012

-DARRTS

Markos, Constantine

From: Markos, Constantine
Sent: Thursday, November 15, 2012 8:39 PM
To: 'Brace, Jeremy'
Cc: Patrick H. Witham; Monica Alamorian
Subject: Information Request (IR) for NDA 203510 - Phenylephrine Hydrochloride ophthalmic solution, 2.5% and 10% - Paragon BioTeck, Inc. - Clinical/Pharmacology-Toxicology/Microbiology (sterility).
Importance: High

Good Evening Jeremy,

The applicant was previously requested to have the following Italian article translated into English:

Filho AD et. al, Arq Bras Oftamol 2007; 70 (6); 961-6.

Could you please provide a translated copy to us; if you have already provided us a translated copy, could you point out where it is in the submission.

Also,

In Module 4, please provide copies of all non-clinical literature publications cited in the NDA. In the integrated summaries (Module 2), provide discussion regarding how the data contained within the cited publications supports the NDA based on the clinical dosing regimen proposed. Published literature is viewed at the same level of scrutiny as original data, and expected to be of comparable/sufficient quality to support the NDA. The potential impact of study shortcomings (e.g., lack of GLP quality data, insufficient animal numbers or endpoint analyses, formulation differences, inadequate test article characterization, etc.) should be discussed in Module 2.

(b) (4)



Thank you Jeremy.

Constantine

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager
FDA/CDER/OND/OAP/DTOP
P--301-796-3871
F--301-796-9881
Constantine.Markos@FDA.HHS.GOV

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/s/

CONSTANTINE J MARKOS
11/29/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203510

MEETING MINUTES

Paragon BioTeck, Inc.
c/o Point Guard Partners, LLC
Attention: Mr. Jeremy Brace
Partner, Point Guard Partners
400 N. Ashley St., Suite 1950
Tampa, FL 33602

Dear Mr. Brace:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%.

We also refer to the teleconference between representatives of your firm and the FDA on February 10, 2012. The purpose of the meeting was to discuss options for responding to the issues outlined in the December 16, 2011 Refuse to File letter.

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

If you have any questions, call Victor Ng, Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes

Meeting Preliminary Comments
Division of Transplant and Ophthalmology Products

Telecon Date/Time: February 10, 2012 at 2:00pm – 3:00pm.
Meeting Type: Type B meeting (scheduled within 30 days)
Application: NDA 203510
Drug: phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%
Sponsor: Paragon BioTeck, Inc

The following are the Division's preliminary responses to the questions posted in your briefing package dated January 17, 2012 for phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%.

If these answers and comments to your questions are clear to you and you determine that further discussion is not required, you have the option of canceling the teleconference.

Please note that if there are any major changes to your development plan, or the purpose of the meeting, or new questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting to be held on February 10, 2012. The minutes of the teleconference will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

Paragon BioTeck, Inc submitted NDA 203510 on October 19, 2011. The Agency issued a Refuse To File Letter on December 16, 2011. A follow-up teleconference was held on December 16, 2011. The purpose of that meeting was to clarify any questions Paragon BioTeck, Inc might have in regards to the Refuse To File Letter. Paragon BioTeck, Inc has requested a Type A meeting to discuss options for the Refuse To File issues described in the letter for resubmission of the NDA.

For the purposes of this response, your questions are in **bold** font and our responses are in *italics* font.

2. OPTIONS FOR RE-SUBMITTING NDA 20-3510

2.1. Option ONE

The preferred approach is to keep the labeled phenylephrine HCl potency as originally proposed in NDA 203-510 (2.5% and 10%). The sponsor will re-submit this NDA in February, 2012 with the following changes:

- Requested Shelf Life of 18 months
- 3 months stability data at accelerated (25°C) and labeled storage condition (2-8°C) from the first exhibit batches
- Release data on 2 additional exhibit batches of both products (2.5% and 10%)
- Supply 6 month stability results on first exhibit batches and 3 month stability results on second set of exhibit batches during review (June 2012)

2.2. Option TWO

The Sponsor is prepared to convert the labeled potency to that containing the (b) (4) if the Agency will accept the previously generated stability data. In this case, NDA 203-510 will be resubmitted in February, 2012 with the following changes:

- Requested Shelf Life of 18 months

- Release data on 3 new exhibit batches of each product (b) (4)
- Retain sample analysis to support shelf life review
- Supply 6 month stability results on three each new exhibit batches (August 2012)

Agency Response:

The product proposed to be marketed should be based on the product which was used in the supportive clinical trials. If the product used in the supportive clinical trials contains (b) (4) then the proposed NDA should contain the same concentration. If there is data to support the safety and efficacy of the lower 2.5% concentration, a 2.5% product with corresponding stability data should be submitted. You should identify which of your supporting studies used the 2.5% and which used the (b) (4).

The two options presented in the meeting package are not acceptable given the limited data you propose to provide in the original NDA submission.

Per 21st Century Review Practices the NDA should be complete at the time of submission. Therefore, based on ICH Q1A (R2) Guidance the original submission should include 12-months long-term and 6-months accelerated stability on three batches for each strength that corresponds to clinical and to-be marketed concentrations. The stability studies should include testing for critical quality attributes such as appearance, assay, impurities, pH, osmolality, particulate matter, sterility, etc. The requested data will help us make a reasonable evaluation of the stability data and to establish stability profile over the shelf-life.

In addition to the primary stability data, you are encouraged to provide supportive stability data (long-term and accelerated) to support the proposed expiry period.

Due to the stringent internal review timelines and availability of resources any data submitted after the initial submission may or may not be reviewed during the current review cycle. The expiry period may be determined using only the data included in the original submission. We therefore recommend that the NDA be submitted with sufficient stability data so as to facilitate filing and review of your application.

Additional Comments

1. Please provide in the NDA, data on freeze-thaw, weight loss, (b) (4) and leachables/extractables studies.
2. Please ensure that all manufacturing and testing facilities comply with cGMP and are ready for inspection at the time of NDA submission.

If you have any questions, call me at (301) 796-1600.

Sincerely,

Victor Ng
Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

VICTOR F NG
02/08/2012



NDA 203510

MEETING REQUEST GRANTED

Paragon Biotech, Inc
Attention: Mr. Patrick H. Witham
President and CEO
11501 SW Pacific Highway
Suite 201
Tigard, OR 97223

Dear Mr. Witham:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%.

We also refer to your January 17, 2012, correspondence requesting a teleconference to discuss options for responding to the issues described in the Refuse to File Letter. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The teleconference is scheduled as follows:

Date: February 10, 2012
Time: 2:00 PM – 3:00 PM
Phone Arrangements: [REDACTED] (b) (4)

Tentative CDER Participants:

Division of Transplant and Ophthalmology Products

Renata Albrecht, MD, Division Director
Wiley Chambers, MD, Deputy Division Director
William Boyd, MD, Clinical Team Leader
Phil Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader
Terry Miller, PhD, Acting Pharmacology and Toxicology Team Leader
Martin Nevitt, MD, Clinical Reviewer
Victor Ng, Project Manager
Lin Qi, PhD, Product Quality Reviewer
Mushfiqur Rashid, PhD, Statistical Reviewer
Bryan Riley, PhD, Product Quality Microbiology Reviewer
Aaron Ruhland, PhD, Pharmacology and Toxicology Reviewer

Balajee Shanmugam, PhD, Product Quality Team Leader
Yan Wang, PhD, Statistical Team Leader
Diana Willard, Chief, Project Management Staff
Eric Yongheng Zhang, PhD, Clinical Pharmacology Reviewer

Submit background information for the meeting (three paper copies or one electronic copy to the application and 18 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by January 31, 2012, we may cancel or reschedule the meeting.

Submit the 18 desk copies to the following address:

If sending via USPS, please send to:

Victor Ng
Food and Drug Administration
Center for Drug Evaluation and
Research
White Oak Building 22, Room: 6109
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS
(e.g., UPS, DHL), please send to:

Victor Ng
Food and Drug Administration
Center for Drug Evaluation and
Research
White Oak Building 22, Room: 6109
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Victor Ng
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

VICTOR F NG
01/30/2012



NDA 203510

NDA ACKNOWLEDGMENT

Paragon Biotech, Inc
Attention: Mr. Patrick H. Witham
President and CEO
11501 SW Pacific Highway
Suite 201
Tigard, OR 97223

Dear Mr. Witham:

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

Name of Drug Product: phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%

Date of Application: October 19, 2011

Date of Receipt: October 21, 2011

Our Reference Number: NDA 203510

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 December 20, 2011, 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).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, do not include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to NDA 203510 submitted on October 19, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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 Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Victor Ng
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

VICTOR F NG
11/10/2011