

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203510Orig1s000**

**OTHER REVIEW(S)**

505(b)(2) ASSESSMENT

Application Information		
NDA # <b>203510</b>	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: <b>N/A</b>		
Established/Proper Name: <b>phenylephrine hydrochloride</b>		
Dosage Form: <b>solution</b>		
Strengths: <b>2.5% and 10%</b>		
Applicant: <b>Paragon BioTeck, Inc.</b>		
Date of Receipt: <b>September 21, 2012 (resubmission after December 16, 2011, RTF)</b>		
PDUFA Goal Date: <b>March 21, 2013</b>	Action Goal Date (if different):	
Proposed Indication: <b>To dilate the pupil</b> <span style="float: right;">(b) (4)</span>		

**GENERAL INFORMATION**

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

YES  NO

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



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

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

<b>Source of information* (e.g., published literature, name of referenced product)</b>	<b>Information provided (e.g., pharmacokinetic data, or specific sections of labeling)</b>
Published literature	Nonclinical (1987 National Toxicology Program report) and clinical

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

**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.**

**RELIANCE ON PUBLISHED LITERATURE**

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

YES  NO   
If “NO,” proceed to question #5.

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

YES NO X

If “NO”, proceed to question #5.

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

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

YES NO

**RELIANCE ON LISTED DRUG(S)**

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

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

YES NO X

If “NO,” proceed to question #10.

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

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

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

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

N/A      YES          NO   

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES                      NO   

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

Advil Congestion Relief (NDA 22565)

b) Approved by the DESI process?

YES          NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES                      NO   

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

Advil Congestion Relief (NDA 22565)

d) Discontinued from marketing?

YES                      NO   

*If "YES", please list which drug(s) and answer question d) i. below.*

*If "NO", proceed to question #9.*

Name of drug(s) discontinued from marketing:

NDA 07953/Prefin - A(WD FR effective 1/21/74)

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

YES          NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

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

This application provides for a new indication, dilation of the pupil (b) (4)

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

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

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

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

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

YES  NO

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

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

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
 NO

YES

*If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): none

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

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

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

YES        NO

If "NO", proceed to question #12.

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

   NO   

YES

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

YES        NO   

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

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

Pharmaceutical alternative:

Approved December 2012: NDA 203826/Phenylephrine Hydrochloride Injection, 10 mg/mL for increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia

Paragon Biotech, Inc. is NOT relying on NDA 203826 for approval of NDA 203510.

For completeness, there are a multitude of products that have been approved containing phenylephrine in combination with other products (many of these NDAs/ANDAs have been withdrawn or discontinued, but several are currently marketed). The applicant relied on none of these applications to support approval of NDA 203510.

**PATENT CERTIFICATION/STATEMENTS**

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

Listed drug/Patent number(s):

No patents listed  *proceed to question #14*

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

YES  NO

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

Listed drug/Patent number(s):

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

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

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

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

Patent number(s):

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

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

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

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

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?  
YES  NO   
*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.  
YES  NO   
*If "NO", please contact the applicant and request the documentation.*

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

Date(s):

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

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

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

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/s/  
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DIANA M WILLARD  
03/21/2013

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # 203510  
Product Name: Phenylephrine Hydrochloride

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PMR/PMC Description: Evaluate leachables present in the drug product: Analyze drug product that has been stored 6 months at accelerated (25C/60% RH) and 24 months long-term (refrigerated) storage conditions for the presence of leachables using a screening analytical method. Use an appropriate control solution for this analysis. Submit a report with numerical data to show the amount of leachables present, if any.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/2013</u>
	Study/Trial Completion:	<u>04/2015</u>
	Final Report Submission:	<u>06/2015</u>
	Other: <u>Interim Report</u>	<u>06/2014</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The NDA provides for a currently marketed unapproved product, phenylephrine hydrochloride ophthalmic solution, to dilate the pupil (b) (4). The product quality was found acceptable and the NDA is recommended for approval from the CMC-perspective. However, the NDA did not address container-closure leachables. As the drug product (unapproved) has been marketed for a number of years and its clinical efficacy and safety has been demonstrated, the above issue is not expected to affect safety. Therefore, we recommend the study be conducted as PMCs to further ensure reliable and consistent drug product quality. The company has agreed to conduct the study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Ophthalmic products with (b) (4) primary packaging components typically contain extractable/leachable data from a one-time study conducted through end of shelf-life. The NDA contained container-closure extractable data, but did not include results from a one-time leachable study through 24-months of storage. The applicant has agreed to institute this study and provide the data as it becomes available. The results obtained may determine whether or not any leachable compounds may need further identification or qualification and whether a control for leachables in the drug product specification is necessary.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

No clinical study is required for this PMC.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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/s/  
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BALAJEE SHANMUGAM  
03/18/2013

RAPTI D MADURawe  
03/18/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** February 26, 2013

**To:** Diana Willard, CPMS  
Division of Transplant and Ophthalmology Products (DTOP)  
Office of Antimicrobial Products (OAP)

**From:** Christine Corser, Regulatory Review Officer  
Division of Professional Drug Promotion (DPDP)  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **Phenylephrine HCl ophthalmic solution 2.5% and 10%**  
NDA #203510

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As requested in your consult dated January 30, 2013, DPDP has reviewed the draft PI for Phenylephrine HCl ophthalmic solution 2.5% and 10%.

DPDP's comments are based on the proposed, clean, substantially complete version of the PI sent to OPDP via email by Diana Willard on February 25, 2013.

Thank you for the opportunity to provide comments on this PI. If there are any questions, please contact me at 301-796-2653 or [Christine.corser@fda.hhs.gov](mailto:Christine.corser@fda.hhs.gov).

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

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/s/  
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CHRISTINE G CORSER  
02/26/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: February 22, 2013

Reviewer: Jung Lee, RPh  
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: (b) (4) (Phenylephrine HCl Ophthalmic Solution), 2.5%  
and 10%

Application Type/Number: NDA 203510

Applicant/sponsor: Paragon BioTeck, Inc

OSE RCM #: 2012-2718

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, and insert labeling for (b) (4) (NDA 203510) for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

The NDA 203510 for (b) (4) (Phenylephrine Hydrochloride Ophthalmic Solution) was originally submitted on October 19, 2011. The Application received a Refusal to File letter on December 16, 2011 due to insufficient stability data and lack of data on freeze-thaw and weight loss studies. On September 21, 2012, the Applicant resubmitted the application under NDA 203510 which has been designated as a priority review.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the September 21, 2012 submission.

- Active Ingredient: Phenylephrine Hydrochloride
- Indication of Use: To dilate the pupil (b) (4)
- Route of Administration: Ophthalmic
- Dosage Form: Solution
- Strength: 2.5% and 10%
- Dose and Frequency: One drop instilled at 3 to 5 minute intervals up to a maximum of 3 drops per eye
- How Supplied:
  - (b) (4) 2.5%--15 mL sterile dropper bottle
  - (b) (4) 10%--10 mL sterile dropper bottle
- Storage: Store in a refrigerator at 2°C to 8°C (36°F to 46°F)
- Container and Closure System:
  - (b) (4) 2.5%--15 mL, white LDPE bottle with dropper tip and red (b) (4) cap.
  - (b) (4) 10%--10 mL, white LDPE bottle with dropper tip and red (b) (4) cap.
  - The red cap color is consistent with the American Academy of Ophthalmology's policy statement "Color Code for Ocular Medications" which recommends a red cap color for mydriatics and cycloplegics.

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Phenylephrine medication error reports. We also reviewed the Phenylephrine labels and package insert labeling submitted by the Applicant.

### 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1.

<b>Table 1: FAERS Search Strategy</b>	
Date	December 7, 2012
Drug Names	Phenylephrine HCl (active ingredient) Phenylephrine HCl Ophthalmic (product name)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS search identified 135 cases. Each case was reviewed for relevancy and duplication. After individual review, 128 cases were not included in the final analysis for the following reasons:

- Cases related to phenylephrine HCl intravenous, oral, and nasal spray dosage forms

### 2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted October 21, 2011 (Appendix B)
- Carton Labeling submitted October 21, 2011 (Appendix C)
- Insert Labeling submitted October 21, 2011

## 3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the (b)(4) product design as well as the associated label and labeling.

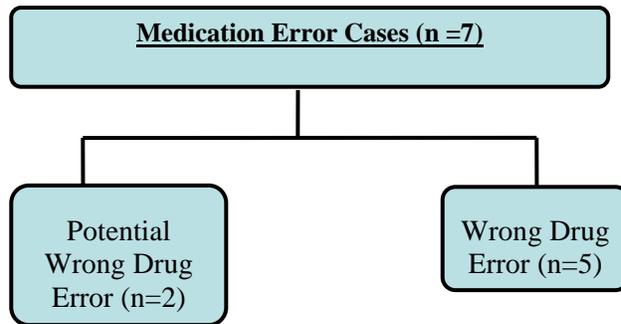
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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### 3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, seven (b) (4) medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter<sup>2</sup>. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix E provides listings of all case numbers for the cases summarized in this review.

**Figure 1:** (b) (4) medication errors (n = 7) categorized by type of error



#### Potential Wrong Drug Error (n=2):

Two cases report of a potential wrong drug error involving 2 different Bausch & Lomb ophthalmic products. The first case reports of Bausch & Lomb's phenylephrine hydrochloride and cyclopentolate product packaging looking very similar. The reporter also states the manufacturer's name is more prominent than the drug name and that nurses have placed one product into the bin for the other product so the potential for confusion is high. The second case refers to the packaging of Bausch & Lomb's tropicamide ophthalmic solution, due to recent labeling changes, it now looks identical to Bausch & Lomb's phenylephrine hydrochloride ophthalmic solution and that the nursing staff has to be especially careful in identifying the correct medication.

#### Wrong Drug Error (n=5):

All five cases describe how the packaging of Bausch & Lomb's products (tropicamide, phenylephrine, atropine, desmopressin acetate, and cyclopentolate) is very similar to each other resulting in the wrong product being dispensed. No outcome was reported in any of these cases. The root cause for the wrong drug errors may be attributed to similar packaging of Bausch & Lomb's ophthalmic and nasal products.

We reviewed these Bausch & Lomb's carton labeling with (b) (4) carton labeling to determine if the labels were sufficiently differentiated from one another. Our evaluation found the two manufacturer's carton labeling utilizes different colors and a different trade

<sup>2</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

dress which provides some differentiation (See Appendix D). However, the carton labeling for the Bausch & Lomb's products involved in the medication errors include boxes containing graphics, the strength statement, or the net quantity statement on the principal display panel (PDP) of the carton labeling which may have further contributed to their confusion. We note our proposed product, (b) (4), also contains two similar boxes on the PDP containing an eye graphic and the net quantity statement. To ensure our product is well differentiated from Bausch & Lomb's products, we will recommend the removal of the boxes on the principal display panel.

## 4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

### 4.1 COMMENTS TO THE DIVISION

#### A. Insert Labeling

1. In section 2 (Dosage and Administration) and section 16 (How Supplied/Storage and Handling), the symbol “ - ” (hyphen) is utilized in the insert labeling to represent “to.” This symbol can be easily overlooked resulting in the numbers being misinterpreted as a larger number than intended. For example “3-5” could be misinterpreted as “35”. Please revise the labeling to replace all “ - ” (hyphens) with the word “to.”
2. How Supplied/Storage and Handling (Section 16)  
The bottle package size is missing from the How Supplied section. Revise the How Supplied section to include the bottle package size for both strengths. For example: “Phenylephrine HCl Ophthalmic Solution, 2.5% is supplied as a sterile.... in a 15 mL opaque, white plastic bottle with a dropper tip and cap.”

### 4.2 COMMENTS TO THE APPLICANT

#### A. Container Labels (2.5% and 10%)

1. Revise the color scheme of the labeling for one of the product strengths from (b) (4), to another color scheme so they are well differentiated from one another to avoid selection error.
2. Remove the (b) (4) shaded circle from the background, and shadow behind the font of the strength statement to improve readability of this important information. After revision and removal, revise the font color to one with sufficient contrast against the background coloration.
3. The proprietary name is printed in a (b) (4) font color against a (b) (4) background. Change the font color of the proprietary name to a color that provides better contrast against a (b) (4) background. Also, remove the (b) (4) outline around the letters of the proprietary name to allow for improved readability.

4. 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).
5. Relocate the route of administration statement, “For Ophthalmic Use Only” to the principal display panel (PDP) as this information is important for the proper administration of the product.
6. Delete or relocate the word “(b) (4)” that appears directly below the strength statement to a location away from the strength statement.
7. 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.
8. Decrease the prominence and size of the manufacturer’s name and logo on the principal display panel (PDP) to be in accordance with 21 CFR 201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter; as it appears overly prominent and distracts from the most important information on the label such as the proprietary name, established name, and strength statement.
9. Relocate the “RX Only” statement and the manufacturer’s name to appear below the established name and strength.
10. Relocate the strength statement to follow after the established name on the PDP as this is the customary placement of the strength statement, and therefore the location most familiar to users. To allow for additional space, consider removing the circle graphic over the strength. For example:

(b) (4)  
Phenylephrine Hydrochloride Ophthalmic Solution  
2.5%

11. Debold and decrease the prominence of the net quantity statement so it does not have greater prominence than that of the strength statement and the established name.
12. The statement on the side panel “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.

B. Carton Labeling (2.5% and 10%)

1. See comments A1 to A8.
2. Relocate the manufacturer's name to appear below the established name and strength statement and away from the top half of the principal display panel (PDP).
3. Remove the (b) (4) streak across the PDP and side panel as this is intervening matter and distracts from the most important information on the label such as the proprietary name, established name, and strength statement.
4. Remove the square box containing the graphic of the eye and the box containing the net quantity statement at the bottom of the PDP as no standards have been established for the use of these symbols for ophthalmic products and have been the source of errors.
5. Include a net quantity statement at the bottom of the PDP ensuring that it does not have greater prominence than the strength statement and is located away from the strength statement.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

## **APPENDICES**

### **APPENDIX A. DATABASE DESCRIPTIONS**

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

**Appendix E:** Listings of all case numbers for the cases summarized in this review

Case Numbers	Type of Medication Error	Narrative
3985918-1	Potential Wrong Drug	<p>medication error</p> <p>The two products are dangerously similar in appearance. The "Bausch &amp; Lomb" is much more prominent than the drug name. Both have red caps, (b)(4) striped safety seals, drug names in small (b)(4) print, and the words "2 mL" at the bottom. The "2 mL" and the company name are both more prominent than the drug name. Nurses put one product into the bin for the other. Many patients get both of these products, so the potential for error is very high.</p>
6955011-1	Potential Wrong Drug	<p>Bousch and Lomb Ophthalmic solutions: Phenylephrine Hydrochloride Solution USP 2.5% Tropicamide POphthalmic solution USP 1% Identical Packaging making medication error due to misidentification of drug a possibility. Packaging was recently change and new packaging is also identical. Put side by side both bottles appear to be the same. Nursing staff reported that they have be very careful when they admisnister these medications that they identify the correct medication. Medication Error</p>
3946958-1	Wrong Drug	<p>Labeling revision on Tropicamide Ophthalmic Solution 1% was made 2/97, changing from a large distinguishable "1" overlay on the label to a small 1%. Label and packaging are now similar to other 2mL products in the Bausch &amp; Lomb line. Tropicamide was administered to a patient instead of Phenylephrine Hydrochloride 2.5%. See page 2 for copy of the labels.</p> <p>medication error drug maladministration</p>
4059564-1	Wrong Drug	<p>DRUG MALADMINISTRATION SEE IMAGE</p> <p>Bausch and Lomb manufactured vaso-dilating eye drop packaging looks virtually the same. Atropine, Tropicamide, and Phenylephrine, out of the box, look exactly the same except for the labeled name. They all have a red cap, the same size dropper bottle, the same (b)(4) label, the name in small black print, and the strength in red. Incorrect eye drops were used in dilating a patient's eyes for an exam.</p>
5792845-1	Wrong Drug	<p>THE PROBLEM OCCURRED ON 1/18/93. BOTH OF THESE PRODUCTS ARE IDENTICAL IN APPEARANCE (SHAPE, SIZE, COLOR, AND PROTECTIVE CAPPING, ETC). WHEN THESE PRODUCTS ARE SENT TO THE NURSING UNITS IN EMERGENCY ROOM, ETC., FOR THEIR STOCK, THEY CAN EASILY BE MISTAKEN FOR ONE ANOTHER. THE LABELS COULD APPEAR DIFFERENTLY OR THE BOTTLES SHAPED DIFFERENTLY.</p> <p>MEDICATION ERROR</p>

6363632-1	Wrong Drug	<p>Pyxis fill error: Desmopressin Acetate Nasal Solution 0.01% in Pyxis in place of Phenylephrine HCl Ophthalmic Solution 2.5%. Outside boxes of products look very similar - color scheme (b) (4) similar font, etc. Front of ophthalmic box has graphic of an eye; front of nasal solution has graphic of nose. Pharmacy had placed inventory sticker (e.g. price sticker) over the nose graphic, obscuring this clue. Did not reach patient. Hospital pharmacy. Desmopressin Acetate Nasal Solution 0.01%, Bausch &amp; Lomb 5 mL bottle Phenylephrine HCl Ophthalmic Solution 2.5%, Bausch &amp; Lomb, 2 mL bottle Discovered by RN during Pyxis removal. Educate pharmacy staff not to place inventory stickers on front of box, obscuring graphic. Request B&amp;L to vary color scheme so boxes are not look-alike.</p> <p>Submitted via ISMP</p> <p>Did not reach patient</p> <p>Outside boxes of products look very similar - color scheme (b) (4), similar font, etc. Front of ophthalmic box has graphic of an eye; front of nasal solution has graphic of nose. Pharmacy had placed inventory sticker (e.g. price sticker) over the nose graphic, obscuring this clue.</p> <p>medication error</p>
6990482-1	Wrong Drug	<p>Two Bausch &amp; Lomb products with nearly identical packaging. Cyclopentolate HCl 1% ophthalmic solution 2ml -NDC 24208-735-01- Phenylephrine HCl 2.5% ophthalmic solution 2ml -NDC 24208-740-59- Dispensing errors have occurred in the pharmac where the wrong medication was filled in the Pyxis stations. No dosing error has been reported.</p> <p>Medication Error</p>

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JUNG E LEE  
02/22/2013

JAMIE C WILKINS PARKER  
02/22/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # <b>203510</b> BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: <b>(none submitted)</b> Established/Proper Name: <b>phenylephrine hydrochloride</b> Dosage Form: <b>ophthalmic solution</b> Strengths: <b>2.5% and 10%</b>		
Applicant: <b>Paragon BioTeck, Inc</b> Agent for Applicant (if applicable):		
Date of Application: <b>October 19, 2011</b> Date of Receipt: <b>October 21, 2011</b> Date clock started after UN: <b>N/A</b>		
PDUFA Goal Date: <b>N/A</b>	Action Goal Date (if different):	
<b>Note: A Refuse to File letter issued for this application on December 16, 2011.</b>		
Filing Date: <b>This application was not filed based on the October 19, 2011 submission.</b>	Date of Filing Meeting: <b>December 5, 2011</b>	
Chemical Classification: (1,2,3 etc.) (original NDAs only) <b>7</b>		
Proposed indication(s)/Proposed change(s): <b>To dilate the pupil</b> <span style="float: right;">(b) (4)</span>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> <b>505(b)(2)</b> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> <b>Priority</b>  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <b>N/A</b>	Resubmission after refuse to file? <b>N/A</b>	
Part 3 Combination Product? <b>No</b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

		products <input type="checkbox"/> Other (drug/device/biological product)			
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):					
List referenced IND Number(s):					
<b>Goal Dates/Product Names/Classification Properties</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>		X			
Are the <b>proprietary, established/proper</b> , and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>		X			<b>Note: No proprietary name was submitted in the October 19, 2011 submission.</b>
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>		X			<b>Priority</b>
<b>Application Integrity Policy</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>  <b>If yes, explain in comment column.</b>			X		
<b>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</b>					
<b>User Fees</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input checked="" type="checkbox"/> <b>Waived (e.g., small business, public health)</b>  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> <b>Not in arrears</b>  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  <b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> <b>Mixed (paper/electronic)</b>  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>	Forms, cover letter, admin information, reference section, pediatrics, labeling, clinical and quality summaries/overviews, study reports, literature references			
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>		X		
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  If no, explain.				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  If yes, BLA #			X	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			No relevant patents are claimed
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X			
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			Form 3674 was submitted on 12/6/2011
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with	X			

authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>		X		

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Full waiver of pediatric studies
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			Full waiver of pediatric studies
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<b>BPCA (NDAs/NDA efficacy supplements only):</b> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> <b>Package Insert (PI)</b> <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> <b>Carton labels</b> <input checked="" type="checkbox"/> <b>Immediate container labels</b> <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		X		<b>Note: A Refuse to File letter issued on December 16, 2011.</b>
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)		X		<b>Note: A Refuse to File letter issued on December 16, 2011.</b>
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?		X		<b>Note: A Refuse to File letter issued on December 16, 2011.</b>
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>		X		
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>		X		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** December 5, 2011

**BLA/NDA/Supp #:** 203510

**PROPRIETARY NAME:** none submitted

**ESTABLISHED/PROPER NAME:** phenylephrine hydrochloride

**DOSAGE FORM/STRENGTH:** ophthalmic solution, 2.5% and 10%

**APPLICANT:** Paragon BioTeck, Inc

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

**BACKGROUND:** Paragon BioTeck, Inc submitted this NDA on October 19, 2011. It was received on October 21, 2011. On December 16, 2011, the Agency issued a Refuse to File letter.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Victor Ng	Y
	CPMS/TL:	Diana Willard	Y
Cross-Discipline Team Leader (CDTL)	William Boyd		Y
Clinical	Reviewer:	Martin Nevitt	Y
	TL:	William Boyd	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Eric Zhang	Y
	TL:	Phil Colangelo	Y
Biostatistics	Reviewer:	Rashid Mushfiqu	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Aaron Ruhland	Y
	TL:	William Taylor	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Lin Qi	Y
	TL:	Balajee Shanmugam	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Bryan Riley	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> <b>FILE</b> <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspection(s) needed?</li> </ul> <p><b>If no, explain:</b> The application contains no clinical studies. It is a 505(b)(2) and references NDA 22565, NDA 07953, ANDA 84300, and published literature.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> <b>FILE</b> <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> <b>NO</b>
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> <b>FILE</b> <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> <b>FILE</b> <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> See Regulatory Conclusions/Deficiencies for CMC Refuse to File comments</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input checked="" type="checkbox"/> <b>REFUSE TO FILE</b> <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> <b>YES</b> <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> <b>YES</b> <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> <b>Not Applicable</b></p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Renata Albrecht, M.D.</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b> A Refuse to File letter issued for this application on December 16, 2011. No milestones were established for this application.</p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<p><input checked="" type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p> <p>The December 16, 2011 Refuse to File letter states:</p> <p>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.</p>
<p><input type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p>

	<input type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

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Regulatory Project Manager

Date

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Chief, Project Management Staff

Date

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

VICTOR F NG  
03/30/2012

DIANA M WILLARD  
03/30/2012