

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208289Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 208289

SUPPL #

HFD # 170

Trade Name Akovaz

Generic Name ephedrine sulfate injection

Applicant Name Flamel Inc.

Approval Date, If Known April 29, 2016

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

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

YES  NO

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

505(b)(2)

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

YES  NO

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

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

n/a

c) Did the applicant request exclusivity?

YES  NO

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

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

YES  NO

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

No

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).

Product	NDA Number
POTASSIUM IODIDE & SODIUM BROMIDE COMPOUND SOLUTION - 2GR/FL OZ, 16GR/FL OZ, 1/25MIN/FL OZ, 16GR/FL OZ - SOLUTION	001061
FORMULA#333 CAP - 1/16GR, 1/500GR, 0.5GR, 2GR, 0.125GR - CAPSULE	005498
EPHEDRINE & CYCLOPAL CAP - 3/8GR, 0.5GR - CAPSULE	002320
EPHEDRINE SUL CAP - 24MG - CAPSULE	004650
CETEDRIN DPS - 1.00%, 0.033% - DROPS	002907
EPHEDRINE AMINOPHYLLIN & PHENOBARBITAL TAB - 0.75GR, 3/8GR, 1.5GR - TABLET	001902
HEPARIN PITKIN MENSTRUM INJ - 25MG/2ML, 200MG/2ML, 1MG/2ML - INJECTION	006047
ISOTONIC SOL EPHEDRINE SUL 1PC - 4.56GR/FL OZ - SOLUTION	000788
MERCURIC OXIDE & EPHEDRINE SULFATE OPH ONT - 0.5%, 1% - OINTMENT	003270
SERPHEDRINE ECT - 16MG, 100MG, 0.1MG - TABLET, DELAYED ACTION, ENTERIC COATED	010324
PRIVATE FORMULA FOR DR L T WALLER CLINIC TAB - 0.25GR, 0.75GR, 0.25GR - TABLET	001830
SERPHYLLINE TAB - 16MG, 100MG, 0.1MG - TABLET	010322
BELPHEDRIBARB TAB - 0.5GR, 0.0004GR, 3/8GR, 0.0001GR, 0.0016GR - TABLET	001139
NESPAMAL SYR - 1GR/FL OZ, 8GR/FL OZ, 8/50GR/FL OZ - SYRUP	003991

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

### **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

Investigation #1

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

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

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



(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: Ayanna Augustus  
Title: Sr. Regulatory Health Project Manager  
Date: May 9, 2016

Name of Office/Division Director signing form: Rigoberto Roca, MD  
Title: Deputy Director, DAAAP

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

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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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AYANNA S AUGUSTUS  
05/10/2016

RIGOBERTO A ROCA  
05/10/2016

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 208289 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Akovaz Established/Proper Name: ephedrine sulfate Dosage Form: injection		Applicant: Flamel Ireland Limited Agent for Applicant (if applicable): Marla Scarola Senior Consultant, The Weinberg Group Inc.
RPM: Ayanna Augustus		Division: DAAAP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: April 28, 2016</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>April 30, 2016</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

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

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

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

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

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

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s)
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<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
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	September 3, 2015 August 28, 2015
• Acceptability/non-acceptability letter(s) (indicate date(s))	
• Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews)	RPM: <input type="checkbox"/> None July 30, 2016 DMEPA: <input type="checkbox"/> None September 17, 201, February 1, 2016 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None Other: <input type="checkbox"/> None MHT:
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting (indicate date of each review)	August 25, 2016
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) April 12, 2016
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<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"> <li>Date reviewed by PeRC <u>March 9, 2016</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i> )	7/7/15, 9/4/15, 9/18/15, 10/16/15, 10/22/15, 1/13/16, 1/19/16, 3/18/16, 3/22/16, 3/31/16, 4/1/16, 4/5/16, 4/13/16, 4/22/16 CMC 9/23/15, 11/9/15, 2/17/16,
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg    April 23, 2015
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg    November 19, 2013
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	December 19, 2015, April 9, 2014
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    April 28, 2016
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None    April, 2016 (5)
<b>Clinical</b>	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )		April 28, 2016
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )		No clinical studies were conducted
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> ) <sup>5</sup>		<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )		<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• 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>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )		<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b>		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None
<b>Biostatistics</b>		<input checked="" type="checkbox"/> None
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None
<b>Clinical Pharmacology</b>		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None March 22, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )		<input checked="" type="checkbox"/> None requested

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

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 4, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews <sup>6</sup>	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 1, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	April 1, 2016
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

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

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/s/  
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AYANNA S AUGUSTUS  
04/29/2016

PARINDA JANI  
04/29/2016

**From:** [Augustus, Ayanna](#)  
**To:** [Marla Scarola](#)  
**Cc:** [Augustus, Ayanna](#)  
**Subject:** RE: NDA 208289/Draft Label  
**Date:** Friday, April 22, 2016 4:34:14 PM  
**Attachments:** [proposed-tracked 04 14 16 to FDA.DOCX](#)  
**Importance:** High

---

Dear Marla,

Please find attached the revised draft labeling for Akovaz which contains some additional minor edits to the label. Please review and provide your response to this in clean and tracked changes. Please note that the Division's changes were made on the marked-up label you provide so it's difficult to identify the new revisions, but as I stated, they are minor editorial revisions.

Let me know if you have any questions.

Best Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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8 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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AYANNA S AUGUSTUS  
04/24/2016

**From:** [Augustus, Ayanna](#)  
**To:** [Marla Scarola \(Marla.Scarola@weinberggroup.com\)](mailto:Marla.Scarola@weinberggroup.com)  
**Cc:** [Augustus, Ayanna](#)  
**Subject:** NDA 208289/Draft Label  
**Date:** Wednesday, April 13, 2016 3:06:55 PM  
**Attachments:** [proposed-tracked 04 13 16 to sponsor.docx](#)

---

Hi Marla,

Please find attached the Division's revisions to the draft labeling for Akovaz. Please review and provided a response in clean and tracked changes by Monday, April 18, 2016.

Let me know if you have any questions.

Best Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

12 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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AYANNA S AUGUSTUS  
04/13/2016

**PeRC Meeting Minutes  
March 9, 2016**

**PeRC Members Attending:**

Lynne Yao

Hari Cheryl Sachs

Linda Lewis

Thomas Smith

Meshaun Payne

Michelle Roth-Kline

Wiley Chambers

George Greeley

Peter Starke (Did not review **NON-RESPONSIVE** )

Dionna Green

Barbara Buch

Adrienne Hornatko-Munoz

Andrew Mulberg (Did not review **NON-RESPONSIVE** )

Lisa Faulcon (**NON-RESPONSIVE** reviews only)

Raquel Tapia

John Alexander

Shrikant Pagay

Freda Cooner

Belinda Hayes

**Agenda**

9:00	NON-RESPONSIVE				
9:15					
9:30					
9:45					
10:05	NDA 208289	Akovz (ephedrine sulfate) Partial Waiver/Deferral/Plan (with Agreed iPSP)	DAAAP	Ayanna Augustus	Treatment of clinically important hypotension in the setting of anesthesia
10:20	(b) (4)				
10:30					
10:40					
11:00					
11:10					
11:20					
11:35					

3 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

**Akovaz (ephedrine sulfate) Partial Waiver/Deferral/Plan (with Agreed iPSP)**

- Proposed Indication: Treatment of clinically important hypotension in the setting of anesthesia
- This product triggers PREA new: active ingredient, indication, dosing regimen, route of administration, and dosage form. Akovaz has a PDUFA goal date of April 30, 2016.
- The Division noted that the pediatric plan for the NDA is consistent with the plan in the Agreed iPSP for the proposed indication.
  
- *PeRC Recommendations:*
  - PeRC agreed with the division to grant a waiver as agreed upon in the iPSP in patients (b) (4) years of age and deferred studies in patients (b) (4) years of age.
  - The PeRC recommends revising the reason for waiver to reflect that the studies would be impossible or highly impractical (b) (4)
  - The PeRC recommends that the division include the dates that were agreed to in the Agreed iPSP for the timeline and contact the sponsor to include any changes to the dates that the division would like to propose.

NON-RESPONSIVE

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/s/  
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GEORGE E GREELEY  
04/13/2016

**Note:** The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC’s recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

**Complete the section(s) of this template that are relevant to your *current submission*.**

***Definitions:***

***Deferral*** – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

***Full Waiver*** – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

***Partial Waiver*** – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

**Pediatric Assessment** – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

**Pediatric Plan** – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

**Pediatric Population/Patient**- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

**PREA Pediatric Record/Pediatric Page** – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

## Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

### BACKGROUND

Please check all that apply:  Full Waiver  Partial Waiver  Pediatric Assessment  Deferral/Pediatric Plan

**BLA/NDA#:** 208289

**PRODUCT PROPRIETARY NAME:** Akovaz

**ESTABLISHED/GENERIC NAME:** ephedrine sulfate injection

**APPLICANT/SPONSOR:** Flamel Ireland Limited

#### PREVIOUSLY APPROVED INDICATION/S:

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

#### PROPOSED INDICATION/S:

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

**BLA/NDA STAMP DATE:** June 30, 2015

**PDUFA GOAL DATE:** April 30, 2016

**SUPPLEMENT TYPE:** n/a

**SUPPLEMENT NUMBER:** n/a

***Does this application provide for (If yes, please check all categories that apply and proceed to the next question):***

***NEW***  ***active ingredient(s) (includes new combination);***  ***indication(s);***  ***dosage form;***  ***dosing regimen;*** or  ***route of administration? This is a marketed unapproved product.***

***Did the sponsor submit an Agreed iPSP? Yes***  ***No***

***Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes***  ***No***

***Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)***

***Yes***  ***No***

***Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes***  ***No***

***If Yes, PMR # \_\_\_\_\_ NDA # \_\_\_\_\_***

***Does the division agree that this is a complete response to the PMR? Yes***  ***No***

***If Yes, to either question Please complete the Pediatric Assessment Template.***

***If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.***

## WAIVER REQUEST

*Please attach:*

***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form. Proposed package insert is at the end of this document. Section 8.4 will likely not change.***

***Pediatric Record***

1 Pediatric age group(s) to be waived. <12 years-old

2 Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.***)

Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (***This reason is for Partial Waivers Only***)

*3 Provide justification for Waiver:*

Éclat requests a partial pediatric waiver for those for nine-years-old and under. Éclat states that patients aged zero to five-years-old do not usually become hypotensive as the result of anesthesia and that, while some patients aged five to ten-years-old require treatment with a pressor for hypotension, this appears to occur less frequently than in adults. Therefore, studying subjects nine-years-old and under would be difficult because most patients in that age group will not require treatment with ephedrine for hypotension in the setting of anesthesia.

Éclat also states that the tachycardia that results from ephedrine may be detrimental to patients in this age group, although they do not include a citation to substantiate this claim.

*4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*

Section 8.4 will likely not change. Draft package insert is attached to the bottom of this document.

**Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics**

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

    basal cell and squamous cell skin cancer

    bladder

    breast

    cervical

    colorectal

    endometrial

    esophageal

cancer (continued):

    follicular lymphoma

    gastric

    hairy cell leukemia

    hepatocellular

    indolent non-Hodgkin lymphoma

    lung (small & non-small cell)

    multiple myeloma

    oropharynx (squamous cell)

    ovarian (non-germ cell)

    pancreatic

    prostate

    refractory advanced melanoma

    renal cell

    uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)  
dry eye syndrome (keratoconjunctivitis sicca)  
erectile dysfunction  
essential thrombocytosis  
Huntington's chorea  
infertility & reproductive technology  
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke  
memory loss  
menopause and perimenopausal disorders  
mesothelioma  
myelodysplasia  
myelofibrosis & myeloproliferative disorders  
osteoarthritis  
overactive bladder  
Parkinson's disease  
paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders  
polycythemia vera  
postmenopausal osteoporosis  
prevention of stroke and systemic embolic events in atrial fibrillation  
psoriatic arthritis  
reduction of thrombotic cardiovascular events in patients with coronary artery disease  
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone  
retinal vein occlusions  
stress urinary incontinence  
temporary improvement in the appearance of caudal lines  
treatment of incompetent great saphenous veins and varicosities  
type 2 diabetic nephropathy  
vascular dementia/vascular cognitive disorder/impairment

## DEFERRAL REQUEST

*Please attach:*

*Pediatric Record (see DARRTS)*

1. **Age groups included in the deferral request:** 12-16-years-old

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

Eclat (Flamel) requests a partial pediatric waiver for <sup>(b)(4)</sup> years-old and under because “there is evidence strongly suggesting that the drug would be ineffective or unsafe in that age group, and the drug is not likely to be used by a substantial number of pediatric patients in that age group.”  
(Source: PIND 116266 page 7 of Initial Pediatric Study Plan)

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** *(Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division’s thinking.)*

a. Adult studies are completed and ready for approval

4. **Provide projected date for the submission of the pediatric assessment (deferral date):** May 31, 2021

5. **Did applicant provide certification of grounds for deferring assessments?**  Yes  No (we told them to defer until juvenile animal study was complete)

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?**  Yes  No

## SPONSOR’S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency?**  Yes  No

2. **Does the division agree with the sponsor’s plan?**  Yes  No

3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?  Yes  No

The Sponsor submitted a revised timeline for conducting the deferred study at the Division's request.

- a. Protocol Submission: May 31, 2017
- b. Study Completion: May 31, 2020
- c. Study Submission: May 31, 2021

4. Has a Written Request been issued?  Yes  No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
5. Has a PPSR been submitted?  Yes  No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

***Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.***

#### **DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL**

*Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.*

#### **Types of Studies/Study Design:**

#### **Nonclinical Studies: Juvenile rat toxicity study**

Rats will be treated daily with intravenous injections of ephedrine (b) (4) which correlates with the pediatric age range of (b) (4) to 16 years old. A dose-range finding study will be conducted to determine the dose levels for the definitive study. In general, the definitive study will employ standard in-life and terminal examination endpoints.

#### **Clinical Studies: Open-label, safety, PK/PD trial**

**Age group and population (indication) in which study will be performed:**

This section should list the age group and population exactly as it is in the plan.

For clinical trial:

[Redacted] (b) (4)

*Example:*

*Study 1: patients aged X to Y years.*

*Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.*

**Number of patients to be studied or power of study to be achieved:**

*For clinical trial:* [Redacted] (b) (4) *will be studied. This study will not be powered to demonstrate the efficacy of ephedrine.*

**Entry criteria:**

*For clinical trial: Inclusion and exclusion criteria are not known at this time.*

**Clinical endpoints:**

[Redacted] (b) (4)

**Timing of assessments:**

*For clinical trial: This trial will be centered around the administration of one anesthetic.*

**Statistical information (statistical analyses of the data to be performed):**

For clinical trial: *The statistical analysis of the data that will be performed is unknown at this time.*

**Division comments on product safety:**

*Are there any safety concerns currently being assessed?*  Yes  No **FAERS review of ephedrine is on-going.**

*Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies?*  Yes  No

*Will a DSMB be required?*  Yes  No

*Other comments:*

**Division comments on product efficacy:**

**Ephedrine appears to be efficacious for the treatment of hypotension in the setting of anesthesia.**

**Division comments on sponsor proposal to satisfy PREA:**

**None.**

**PeRC ASSESSMENT TEMPLATE**

*Please attach:*

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.*
- Pediatric Record*

**Date of PREA PMR:**

**Description of PREA PMR: (*Description from the PMC database is acceptable*)**

Was Plan Reviewed by PeRC?  **Yes**  **No** If yes, did sponsor follow plan?

**If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.**

**Indication(s) that were studied:**

This section should list the indication(s) exactly as written in the *protocols*.

*Example:*

*DRUG for the treatment of the signs and symptoms of disease x.*

**Number of Centers** \_\_\_\_\_

**Number and Names of Countries** \_\_\_\_\_

**Drug information:**

*Examples in italics*

- **Route of administration:** *Oral*
- **\*Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

*\*If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

**Types of Studies/ Study Design:**

*Example:*

*Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.*

*Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.*

**Age group and population in which study/ies was/were performed:**

*Example:*

*Study 1: patients aged X to Y years.*

*Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.*

**Number of patients studied or power of study achieved:**

*Example:*

*Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.*

***Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .***

**Entry criteria:**

This section should list pertinent inclusion/exclusion criteria.

*Example:*

*Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs*

*Patients had a negative pregnancy test if female.*

**Clinical endpoints:**

*Example:*

*Study 1: Clinical outcome and safety were the primary endpoints.*

*Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F*

**Statistical information (statistical analyses of the data performed):**

This section should list the statistical tests conducted.

*Example:*

*Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.*

*Study 2: descriptive statistical methods for AUC, C max, Tmax, CI/F and compared to adults.*

**Timing of assessments:**

*Example:*

*Baseline, week 2, week, 6, and end of treatment*

**Division comments and conclusions (Summary of Safety and Efficacy)**

**Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.**

7 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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AYANNA S AUGUSTUS  
04/07/2016

**From:** [Augustus, Ayanna](#)  
**To:** [Marla Scarola \(Marla.Scarola@weinberggroup.com\)](mailto:Marla.Scarola@weinberggroup.com)  
**Cc:** [Augustus, Ayanna](#)  
**Subject:** Akovaz/NDA 208289/Advice  
**Date:** Friday, April 01, 2016 9:37:48 AM

---

Dear Marla,

The Division would like to remind you to discuss the projected needs of ephedrine with the DEA Office of Diversion Control since the importation and manufacturing of ephedrine is subject to the controls imposed by the Combat Methamphetamine Epidemic Act of 2005.

Best Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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/s/  
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AYANNA S AUGUSTUS  
04/05/2016

**From:** Augustus, Ayanna  
**To:** [Marla Scarola \(Marla.Scarola@weinberggroup.com\)](mailto:Marla.Scarola@weinberggroup.com)  
**Subject:** Akovaz/ephedrine sulfate/IR  
**Date:** Tuesday, April 05, 2016 1:45:00 PM

---

Hi Marla,

The Agency has the following comments on the draft container/carton labels for Akovaz. Please submit revised labels to me, via email, by COB, Friday, April 8<sup>th</sup>.

Use the same format and font sizes for the proprietary and non-proprietary names, that were on the original carton and container labels prior to the recent color changes.

Akovaz (ephedrine sulfate injection,USP)

Best Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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/s/  
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AYANNA S AUGUSTUS  
04/05/2016

**From:** Augustus, Ayanna  
**To:** ["Marla Scarola"](#)  
**Subject:** RE: Akovaz/Non-clinical PMRs  
**Date:** Thursday, March 31, 2016 10:54:00 AM  
**Importance:** High

---

Hi Marla,

The proposed milestone dates for the deferred pediatric study do not include a specific date as requested. Please provide this information to me via email as soon as possible, followed by a formal submission to the NDA.

Please provide the highlighted date for each milestone.

Final Protocol Submission: 05/XX/2017  
Study Completion: 05/XX/2020  
Final Report Submission: 05/XX/2021

Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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AYANNA S AUGUSTUS  
03/31/2016

**From:** [Augustus Ayanna](#)  
**To:** [Marla Scarola \(Marla.Scarola@weinberggroup.com\)](#)  
**Cc:** [Augustus Ayanna](#)  
**Subject:** Akovaz/Non-clinical PMRs  
**Date:** Tuesday, March 22, 2016 3:22:59 PM  
**Importance:** High

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Hi Marla,

The Division has determined that several non-clinical post-marketing required studies (PMRs) will be required should Akovaz be approved. Please review the PMR studies below and provide milestone dates for submission of the study protocol, study completion and final study report submission. Please provide a response by COB, Monday, March 28, 2016.

**1. Conduct a fertility and early embryonic development toxicology study in the rat model for ephedrine sulfate.**

Final Protocol Submission: XX/XX/XXXX  
Study/Trial Completion: XX/XX/XXXX  
Final Report Submission: XX/XX/XXXX

**2. Conduct an embryo-fetal developmental toxicology study using the rat model for ephedrine sulfate.**

Final Protocol Submission: XX/XX/XXXX  
Study/Trial Completion: XX/XX/XXXX  
Final Report Submission: XX/XX/XXXX

**3. Conduct an embryo-fetal developmental toxicology study using the rabbit model for ephedrine sulfate.**

Final Protocol Submission: XX/XX/XXXX  
Study/Trial Completion: XX/XX/XXXX  
Final Report Submission: XX/XX/XXXX

**4. Conduct a pre- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.**

Final Protocol Submission: XX/XX/XXXX  
Study/Trial Completion: XX/XX/XXXX  
Final Report Submission: XX/XX/XXXX

**5. Conduct an in vivo micronucleus assay with ephedrine sulfate.**

Study/Trial Completion: XX/XX/XXXX  
Final Report Submission: XX/XX/XXXX

Best Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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AYANNA S AUGUSTUS  
03/22/2016

**From:** [Augustus, Ayanna](#)  
**To:** [Marla Scarola \(Marla.Scarola@weinberggroup.com\)](mailto:Marla.Scarola@weinberggroup.com)  
**Cc:** [Augustus, Ayanna](#)  
**Subject:** NDA 208289/Akovaz/Information Requests  
**Date:** Friday, March 18, 2016 3:07:30 PM  
**Importance:** High

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Dear Marla,

Please provide a response to the following IRs by COB, Wednesday, March 23<sup>rd</sup>.

1. We note that the phenomenon of the development of tachyphylaxis to ephedrine has not been described in your NDA submission or in your proposed package insert. Submit information about this phenomenon to your NDA and submit language for your proposed package insert, or provide rationale for its exclusion.
2. Defossez 2007 was an abstract that you submitted to support the safety of Akovaz. However, the details of its publication are unclear. Submit a complete citation for this publication or indicate where a complete citation can be located in your NDA submission.
3. The Division has reviewed and presented your request for a partial deferral and partial waiver for pediatric studies to the Pediatric Review Committee (PeRC). Your request for a partial waiver for pediatric patients aged 0 to (b)(4)-years-old and deferral of pediatric studies for pediatric patients (b)(4) to 16-years-old has been granted. However the age group for the partial waiver has been revised to include patients aged 0 to 12-years-old and deferral of pediatric studies for patients 12 to 16-years old. Additionally, we suggest you conduct nonclinical and pediatric studies concurrently. This will necessitate adjustments to your proposed timeline for pediatric studies. Please provide a new timeline for your deferred pediatric study which should include the following:

<b>Protocol Submission:</b>	XX/XX/XXXX
<b>Study Completion:</b>	XX/XX/XXXX
<b>Study Submission:</b>	XX/XX/XXXX

4. Table 16 on page 87 of your Integrated Summary of Safety reports that 122 subjects overall experienced reactive hypertension. Is this number correct?
5. In section 7 of your proposed package insert, you state:

“ (b) (4)

- Guanethidine
- Rocuronium

- Epidural anesthesia
- (b) (4)
- Theophylline
- (b) (4)

Provide brief, additional, statements describing the drug interactions that may occur with ephedrine and the drugs listed above. Also describe appropriate interventions should this interaction occur.

6. In section 10 Overdose, you state: "Overdose of EPHEDRINE (b) (4) can cause a rapid rise in blood pressure." Describe appropriate interventions that could take place to mitigate the rapid rise in blood pressure should an overdose of ephedrine occur.

Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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AYANNA S AUGUSTUS  
03/21/2016



NDA 208289

**INFORMATION REQUEST**

Flamel Ireland Limited  
Attention: Marla Scarola, Senior Consultant  
The Weinberg Group  
1129 Twentieth St., NW, Suite 600  
Washington, DC 20036

Dear Ms. Scarola,

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ephedrine Sulfate Injection, USP, 50mg/mL strength.

We are reviewing the Chemistry, Manufacturing, and Controls sections 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. Please submit your response by Friday, March 4, 2016.

**Drug Product:**

- 1. Provide the method used for testing osmolality. If a non-compendial method is used, provide a full validation report in addition to the detailed method.**

**Microbiology:**

- 2. Please provide the maximum holding time [REDACTED] (b) (4)**  
[REDACTED] Please note that holding times are to be established and provided in the drug application and extensive hold times are to be validated prior to commercial manufacture of the product.

**Process:**

- 3. We evaluated extractable volume data that you provided for your engineering batch; however, we did not find data to support your proposed [REDACTED] (b) (4) /vial fill. Please provide extractable volume for the proposed [REDACTED] (b) (4)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

**fill or if this data was provided earlier, indicate its exact location in the submission. We also recommend that you provide extractable volume data for (b) (4) fill as a comparison.**

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

**Steven  
Kinsley -A**

Steven Kinsley, Ph.D.

Regulatory Business Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Digitally signed by Steven Kinsley -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Steven Kinsley -  
A,  
0.9.2342.19200300.100.1.1=2001720189  
Date: 2016.02.17 10:46:11 -05'00'

**From:** [Augustus, Ayanna](#)  
**To:** [Marla Scarola](#)  
**Cc:** [Augustus, Ayanna](#)  
**Subject:** RE: NDA 208289/Akovaz/ Labeling/ Additional comments  
**Date:** Tuesday, January 19, 2016 12:10:02 PM  
**Importance:** High

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Hi Marla,

We have an additional comment regarding the proposed package insert for Akovaz. Please provide a response (revised labeling in clean and tracked changes) as soon as possible.

Justify how the publications cited support the clinical pharmacology labeling. Check publications to confirm the drug substance used by authors was in fact (-)-ephedrine as proposed in your drug product. See the comments indicated in parenthesis. If appropriate publications cannot be submitted it may result in deletion of all material that is not supported.

The proposed labeling in section reads as follows in 12.3 Clinical Pharmacology: Pharmacokinetics



Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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AYANNA S AUGUSTUS  
01/19/2016

**From:** [Augustus, Ayanna](#)  
**To:** [Marla Scarola](#)  
**Cc:** [Augustus, Ayanna](#)  
**Subject:** RE: NDA 208289/Akovaz/ Labeling  
**Date:** Wednesday, January 13, 2016 12:47:53 PM  
**Importance:** High

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Hi Marla,

DMEPA has the following comment/recommendation regarding the carton labels for Akovaz.

**Carton Labeling and Container Labels**

There is inadequate differentiation between the labels and labeling for the 1 ml single dose Akovaz 50 mg/mL vials and the 1 mL single dose Vazculep 10 mg/mL vials. Consider the use of different colors, colored boxing of the strength statement, or some other means to provide adequate differentiation between the container labels and carton labeling.

Let me know if you have any questions. Please submit any revisions to the container labels as soon as possible.

Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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AYANNA S AUGUSTUS  
01/13/2016



NDA 208289

**INFORMATION REQUEST**

Flamel Ireland Limited  
Attention: Marla Scarola, Senior Consultant  
The Weinberg Group  
1129 Twentieth St., NW, Suite 600  
Washington, DC 20036

Dear Ms. Scarola,

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ephedrine Sulfate Injection, USP, 50mg/mL strength.

We are reviewing the Chemistry, Manufacturing, and Controls sections 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. Please submit your response by Tuesday, December 1, 2015.

1. **Specify how long you normally hold the bulk solution** [REDACTED] (b) (4)  
[REDACTED]
2. **Provide the** [REDACTED] (b) (4)  
[REDACTED]
3. **Provide the executed batch records for registration batch #00002 and #00003, and include the yield and reconciliation information.**
4. **Provide a blank master batch record for your proposed commercial batches.**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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**Food and Drug Administration  
Silver Spring MD 20993**

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

**Steven Kinsley**

-A

Steven Kinsley, Ph.D.

Regulatory Business Project Manager

Office of Program and Regulatory Operations

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research

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ou=FDA, ou=People, cn=Steven Kinsley -A,  
0.9.2342.19200300.100.1.1=2001720189  
Date: 2015.11.09 14:03:31 -05'00'

**From:** [Augustus, Ayanna](#)  
**To:** [Marla Scarola](#)  
**Cc:** [Augustus, Ayanna](#)  
**Subject:** RE: NDA 208289/Ephedrine Sulfate/Info Request  
**Date:** Thursday, October 22, 2015 1:24:34 PM  
**Importance:** High

---

Dear Marla,

Submit the formal biowaiver request in module 1.12.15 and include related information to support the request. The biowaiver request can include a reference and hyperlink to the information provided in module 2.7.1.

Best Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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**From:** Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]  
**Sent:** Tuesday, October 20, 2015 9:52 AM  
**To:** Augustus, Ayanna  
**Subject:** RE: NDA 208289/Ephedrine Sulfate/Info Request

Hi Ayanna,

We require some clarification regarding this request. The source of some of our confusion is likely from the EOP2 meeting held for Éclat's Neostigmine Methylsulfate Injection (NDA 204078). At this meeting, Éclat explained the intention to submit an in vivo BA/BE waiver request. It was explained that because there was not an FDA-approved product that could serve as a reference for the proposed product that a waiver request should not be submitted. Instead, Éclat was instructed to include the available published BA/BE information in the appropriate sections of the NDA submission to fulfill the CFR requirements for the in vivo BA/BE data. (Please see page Question 7 on page 9-10 of the attached EOP2 meeting minutes).

As explained in the response to the FDA IR (74-day letter) submitted on September 22, 2015, Éclat believes that the published literature included in the Ephedrine NDA fulfills the CFR requirements for the in vivo BA/BE data.

Would you please help me understand what needs to be included in this next submission? Does the information related to in vivo BA/BE presented in 2.7.1 need to be placed in an official waiver request (1.12.15)?

Thanks,  
Marla

Marla E. Scarola, M.S.  
Senior Consultant  
The Weinberg Group  
1129 Twentieth St, NW, Suite 600  
Washington, DC 20036  
P +1 202.730.4129  
F +1 202.833.7057  
[weinberggroup.com](http://weinberggroup.com)



---

**From:** Augustus, Ayanna [<mailto:Augustus.Ayanna@fda.hhs.gov>]  
**Sent:** Friday, October 16, 2015 10:15 AM  
**To:** Marla Scarola <[Marla.Scarola@weinberggroup.com](mailto:Marla.Scarola@weinberggroup.com)>  
**Cc:** Augustus, Ayanna <[Augustus.Ayanna@fda.hhs.gov](mailto:Augustus.Ayanna@fda.hhs.gov)>  
**Subject:** NDA 208289/Ephedrine Sulfate/Info Request  
**Importance:** High

Hi Marla,

We acknowledge that there is no FDA-approved drug product that can serve as a reference product for your proposed product. Per 21 CFR 320.21(a)(2), you need to provide information to permit FDA to waive the submission of evidence measuring in vivo bioavailability. Submit a formal request to waive the requirement to conduct in vivo bioavailability or bioequivalence studies for your drug product. You may include literature references to support your justification. Note that our previous reference to 21 CFR 320.22 was an oversight.

We request the response by October 30, 2015.

Let me know if you have any questions.

Best Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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AYANNA S AUGUSTUS  
10/22/2015

**From:** [Augustus, Ayanna](#)  
**To:** [Marla Scarola](#)  
**Cc:** [Augustus, Ayanna](#)  
**Subject:** NDA 208289/Ephedrine Sulfate/Info Request  
**Date:** Friday, October 16, 2015 10:15:03 AM  
**Importance:** High

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Hi Marla,

We acknowledge that there is no FDA-approved drug product that can serve as a reference product for your proposed product. Per 21 CFR 320.21(a)(2), you need to provide information to permit FDA to waive the submission of evidence measuring in vivo bioavailability. Submit a formal request to waive the requirement to conduct in vivo bioavailability or bioequivalence studies for your drug product. You may include literature references to support your justification. Note that our previous reference to 21 CFR 320.22 was an oversight.

We request the response by October 30, 2015.

Let me know if you have any questions.

Best Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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AYANNA S AUGUSTUS  
10/16/2015



NDA 208289

**INFORMATION REQUEST**

Flamel Ireland Limited  
Attention: Marla Scarola, Senior Consultant  
The Weinberg Group  
1129 Twentieth St., NW, Suite 600  
Washington, DC 20036

Dear Ms. Scarola,

Please refer to your original New Drug Application received June 30, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (Ephedrine Sulfate) Injection, 50mg/mL strength.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, October 13, 2015.

1. **Please indicate whether the units were subjected to the proposed** (b) (4)  
**prior to container/closure integrity validation testing.**

2. **Please indicate the maximum hold time** (b) (4)  
**Please note that extensive hold times are to be validated prior to approval.**

3. **Please provide the routine production load size(s)** (b) (4)

4. **In regard to** (b) (4)

(b) (4)



5. In regard to [REDACTED] (b) (4)

[REDACTED] (b) (4)

6. The method description provided for validation of the drug product bacterial endotoxins test method are acknowledged; however please provide the actual method suitability data for BET validation and specify the actual drug product dilution used for the validation study and also the dilution to be used for routine testing of commercial batches.

7. Please provide a method suitability validation summary report for the drug product sterility test. Please indicate the number of units tested [REDACTED] (b) (4)

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,  
Steven

Kinsley -S

Steven Kinsley, Ph.D.

Regulatory Business Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

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ou=FDA, ou=People, cn=Steven Kinsley -  
S,  
0.9.2342.19200300.100.1.1=2001720189  
Date: 2015.09.23 11:16:29 -0400

**From:** Augustus, Ayanna  
**To:** "[Marla\\_Scarola](#)"  
**Subject:** NDA 208289/Ephedrine Sulfate/labeling IR  
**Date:** Friday, September 18, 2015 12:40:00 PM  
**Importance:** High

---

Dear Marla,

The clinical reviewer with the Division of Maternal and Pediatric Health (DMPH) has conducted a preliminary review of the proposed labeling for ephedrine sulfate and has the following comments/request for information. Please provide a response by **November 16, 2015**.

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

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

**Submit the following information on ephedrine sulfate use in pregnant and lactating women by November 15, 2015:**

- a review and summary of all available published literature regarding [drug name],
- a review and summary from your pharmacovigilance database,
- interim ongoing or final report on a closed pregnancy registry (if applicable).
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

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

Let me know if you have any questions.

Best Regards,  
Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

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/s/  
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AYANNA S AUGUSTUS  
09/18/2015



NDA 208289

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Flamel Ireland Limited  
c/o The Weinberg Group, Inc.  
1129 Twentieth St. NW, Suite 600  
Washington, DC 20036

Attention: Marla Scarola, MS  
Senior Consultant

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Ephedrine Sulfate Injection, 50 mg/mL.

We also refer to your amendment dated July 21, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 30, 2016. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 30, 2016.

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

**Chemistry, Manufacturing, and Controls (CMC):**

1. Assay specification at release of the drug product and stability should be the same. Explain why two different assay specifications are used for release and stability of the drug product.
2. The stability data demonstrate that [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] Provide additional data to demonstrate that the (-)ephedrine analytical method is fully validated.
3. Explain the variability in the stability data for [REDACTED] (b) (4) impurity at the [REDACTED] (b) (4)  
[REDACTED].
4. Tighten the pH specification or justify the wide specification for pH at release and stability of the drug product.
5. The photostability study looked at the change in pH with light exposure. Provide data to demonstrate whether or not degradation occurs when the product in the vial is exposed to light. Data should include determination of assay and impurities.

**Biopharmaceutics**

6. Submit a formal request to waive the requirement to conduct in vivo bioavailability or bioequivalence studies for your drug product per 21 CFR 320.22.

**Clinical**

7. We are unable to find justification for the maximum daily dose of ephedrine in your submission. Provide justification for the maximum daily dose of ephedrine or indicate where it can be found in your submission.
8. We noted a variety of adverse events with ephedrine in the FAERS data that you submitted that were not included in the proposed labeling. Clarify how you determined which adverse events to include and which ones to leave out of the proposed labeling.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

## **PRESCRIBING INFORMATION**

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

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

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

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

## **PROMOTIONAL MATERIAL**

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

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

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

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Anesthesia, Analgesia, and Addiction Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Ayanna Augustus, PhD, RAC, Sr. Regulatory Project Manager, at (301) 796-3980.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Director  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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SHARON H HERTZ  
09/04/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 208289

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Flamel Ireland Limited  
c/o The Weinberg Group Inc.  
1129 Twentieth St. NW, Suite 600  
Washington, DC 20036

Attention: Marla Scarola, MS  
Senior Consultant

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) dated and received June 30, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ephedrine Sulfate Injection, 50 mg/mL.

We also refer to your correspondence, dated and received July 1, 2015, requesting review of your proposed proprietary name, Akovaz.

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

If any of the proposed product characteristics as stated in your July 1, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lisa Skarupa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301)796-2219. For any other information regarding this application, contact Ayanna Augustus, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3980.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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TODD D BRIDGES  
09/03/2015



NDA 208289

**NDA ACKNOWLEDGMENT**

Flamel Ireland Limited  
c/o The Weinberg Group, Inc.  
1129 Twentieth St. NW, Suite 600  
Washington, DC 20036

Attention: Marla Scarola, MS  
Senior Consultant

Dear Ms. Scarola:

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: Ephedrine Sulfate Injection, 50 mg/mL

Date of Application: June 30, 2015

Date of Receipt: June 30, 2015

Our Reference Number: NDA 208289

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 **August 29, 2015**, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

If you have any questions, call me at (301) 796-3980.

Sincerely,

*{See appended electronic signature page}*

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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AYANNA S AUGUSTUS  
07/07/2015



PIND 116266

**MEETING MINUTES**

Éclat Pharmaceuticals, LLC  
c/o The Weinberg Group Inc.  
1129 Twentieth St. NW, Suite 600  
Washington, DC 20036

Attention: Marla Scarola, MS  
Senior Consultant

Dear Ms. Scarola:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ephedrine sulfate injection.

We also refer to the meeting between representatives of your firm and the FDA on April 23, 2015. The purpose of the meeting was to discuss the development of an NDA for ephedrine sulfate injection, USP 50 mg/mL.

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

If you have any questions, call me at (301) 796-3980.

Sincerely,

*{See appended electronic signature page}*

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** April 23, 2015; 10:30-11:30 a.m.  
**Meeting Location:** White Oak, Bldg. 22; Room 1419

**Application Number:** 116266  
**Product Name:** ephedrine sulfate  
**Indication:** treatment of clinically important hypotension in the setting of anesthesia

**Sponsor/Applicant Name:** Éclat Pharmaceuticals, LLC  
**Meeting Chair:** Rigoberto Roca, MD, Deputy Director  
**Meeting Recorder:** Ayanna Augustus, PhD, RAC, Sr. Regulatory Project Manager

<b>FDA Attendees</b>	<b>Title</b>
Sharon Hertz, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director
Amelia Lockett, MD	Clinical Reviewer
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor
Newton Woo, PhD	Acting Pharmacology/Toxicology Team Leader
Ciby Abraham, PhD	Acting Quality Assessment Lead, OPQ
Julia Pinto, PhD	Acting Branch Chief, OPQ
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer
Yun Xu, PhD	Clinical Pharmacology Team Leader
Thomas Permutt, PhD	Director, Division of Biometrics II
Ayanna Augustus, PhD, RAC	Sr. Regulatory Health Project Manager
Charles Lee, MD	Sr. Medical Advisor, Office of Compliance/Office of Unapproved Drugs and Labeling Compliance (OUDLC)
Barbara Wise	Project Manager, OUDLC
Aaron Weisbuch	Regulatory Counsel, OUDLC
Wendy Brown	Safety Project Manager, Office of Surveillance and Epidemiology
Alan Trachtenberg, MD, MPH	Medical Officer, Controlled Substance Staff
<b>Sponsor Attendees</b>	<b>Title</b>

Michael Anderson	President and Chief Executive Officer; Éclat Pharmaceuticals, LLC
Scott A. Macke	Vice President, Operations; Éclat Pharmaceuticals, LLC
(b) (4)	
Marla Scarola, M.S.	Senior Consultant, The Weinberg Group, Inc.
(b) (4)	

## 1.0 BACKGROUND

The purpose of this meeting is to provide guidance on the adequacy of the published literature the Sponsor intends to provide to support the approval of a 505(b)(2) NDA for Ephedrine Sulfate Injection, USP, 50 mg/mL for the treatment of clinically important hypotension in the setting of anesthesia. The Sponsor has developed ephedrine sulfate injection, USP as a sterile 50 mg/mL solution for intravenous injection. Ephedrine sulfate is a sympathomimetic drug with mixed adrenergic agonist activity. The Sponsor plans to submit a 505(b)(2) application supported by nonclinical and clinical literature. There are currently several unapproved marketed versions of ephedrine sulfate.

During the PIND meeting held on December 19, 2012, the Division provided guidance on the Sponsor's development program for ephedrine sulfate. During the End-of-Phase 2 (EOP2) meeting held on November 19, 2013, the Division provided guidance on the adequacy of the Chemistry, Manufacturing and Controls (CMC), nonclinical, and clinical information the Sponsor intends to submit to support a 505(b)(2) NDA. The Sponsor also submitted a request for a Type C guidance meeting to discuss their effort to address several concerns raised during the EOP2 meeting, which included the stereoisomer composition of the drug product used in referenced studies, the scope of the proposed indication, and the limited information on the patient population that would benefit from (b) (4) administration of ephedrine sulfate and how to measure a clinical benefit.

The Sponsor received the preliminary comments on Monday, April 20, 2015. The meeting questions are presented below in *italicized* text, Agency responses prepared prior to the meeting are **bolded**. The Sponsor's responses submitted before the meeting are in bold italics and the discussion is presented in normal text.

## 2. DISCUSSION

### 2.1. Chemistry, Manufacturing, and Controls (CMC)

***Question 1:***

*The proposed commercial drug substance specification is provided in Attachment 1. Does the Agency agree that this is an acceptable drug substance specification?*

**FDA Response to Question 1:**

**From a CMC perspective, the proposed drug substance acceptance criteria appear reasonable. Further evaluation is deferred to the NDA submission, where the data can be reviewed in its totality.**

No further discussion was needed.

**Question 2:**

*The proposed commercial drug product specification is provided in Attachment 1. Please note that per the Agency's request at the EOP2 meeting (November 19, 2013), the specification has been modified to include specific acceptance criteria for the (b) (4) impurity (b) (4) as a separate test. Also, a separate analysis and acceptance criteria has been added for (b) (4) combined in one assay. Does the Agency agree that this is an acceptable drug product specification?*

**FDA Response to Question 2:**

**From a CMC perspective, the acceptance criteria for the (b) (4) appear reasonable. Further evaluation is deferred to the NDA submission, where the data can be reviewed in its totality.**

No further discussion was needed.

**Question 3:**

*Éclat is using the same rubber stoppers for Ephedrine Sulfate Injection, USP as are currently in use for their approved Bloxiverz (NDA 204078) and Vazculep (NDA 204300) products. As described in Attachment 2, an evaluation of extractables was performed by the stopper manufacturer and provided to Éclat. Based on the simple formulation for Ephedrine Sulfate Injection, USP (ephedrine sulfate and water), Éclat contends that no leachables testing needs to be performed on registration batches. Does the Agency agree?*

**FDA Response to Question 3:**

**No, we cannot agree based on the information provided in the meeting package. The drug product container closure systems for both NDA 204078 and 204300 employed (b) (4) stopper (b) (4). Although (b) (4) appears to be made of (b) (4) rubber, it is not clear from the meeting package if this stopper model is manufactured using the exact same process and includes identical additives. If you believe there is adequate information in the referenced DMF, include reference to specific page number of submission dates in the DMF to support your conclusions that the extractable/leachable profile of the two products (b) (4). The adequacy of the data can only be determined upon review of the NDA and reference DMF materials. In the absence of adequate justification otherwise, an assessment of leachables over the course of stability will be required.**

No further discussion was needed.

**Question 4:**

*Eclat is currently conducting a chiral analysis on Ephedrine Sulfate Injection, USP to evaluate the purity of the enantiomeric composition and any changes over time. Thus far, this analysis has demonstrated the enantiomeric composition of Ephedrine Sulfate Injection, USP does not change over time. Given that Eclat's formulation is the same as those used in the published literature (i.e., ephedrine salt and water), Éclat assumes that the degradation profile data generated on Ephedrine Sulfate Injection, USP can be used to address any concerns over the purity of drug used in the published studies. Does the Agency agree?*

**FDA Response to Question 4:**

**From a CMC perspective, we do not agree. To address potential degradation, we suggest that you perform forced degradation studies on your product to evaluate the degradation profile of Ephedrine Sulfate. However, this will not address the complete purity profile of the Ephedrine drug used in the literature, since the process impurities and any drug substance impurities are still unknown.**

Discussion:

The Sponsor stated that they will submit forced degradation study data with their NDA. However, the Sponsor noted that this study was conducted prior to chiral testing of the drug product. The Division clarified that the forced degradation studies were requested in order to confirm that the drug product does not undergo (b) (4). The Sponsor intends to provide 18-month long-term stability data and 6-month accelerated data for the drug product.

**2.2. Nonclinical**

**Question 5:**

*Eclat believes that the impurities and potential leachables are adequately qualified based on QSAR and existing toxicity data assuming a maximum daily dose of 50 mg (see Attachments 2 and 3). Does the Agency agree?*

**FDA Response to Question 5:**

**Yes, we generally agree with your approach. However, the adequacy of your justification will be determined during the review of your NDA. We note that your drug substance specification for (b) (4) exceeds ICH Q3A(R2) thresholds and must be adequately qualified for safety, which generally entails:**

- 1. A complete minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
- 2. A repeat-dose toxicology study of 14-days duration to support the proposed acute indication.**

Discussion:

The Sponsor agreed to ensure that the drug substance specification for [REDACTED] (b) (4) aligns with ICH Q3A(R2) thresholds.

**Question 6:**

*Éclat has not conducted nonclinical studies to support this application. Éclat has developed a detailed integration of the available nonclinical literature on ephedrine in Section 2.4 (Attachment 2) and limited written and tabular study summaries in Section 2.6 (Attachment 3) due to the limited nature of the details present in the published literature. Does the Agency agree with this approach?*

**FDA Response to Question 6:**

**Yes, your approach appears reasonable. The adequacy of the submitted information contained in Sections 2.4 and 2.6 will be determined during the review of your NDA. We remind you that the referenced genetic, reproductive, and developmental toxicology literature do not appear to be adequate to support labeling for your drug product. These studies will likely be required as post-marketing requirements (PMRs).**

No additional discussion was needed.

**Additional Nonclinical Comments:**

1. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2) and ICH Q3B(R2). In order to provide adequate qualification:
  - a. You must complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
  - b. In addition, you must conduct a repeat-dose toxicology of appropriate duration to support the proposed indication. In this case, a study of 14 days must be completed.

Refer to guidance for industry: *Q3A Impurities in New Drug Substances* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>

and

guidance for industry: *Q3B (R2) Impurities in New Drug Products* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

- 2. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICH Q3A(R2) and Q3B(R2) qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**
- 3. Include in your NDA submission a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**
- 4. Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to ICH M7 guidance document titled: *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying or controlling these impurities, available at, [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Multidisciplinary/M7/M7\\_Step\\_4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf). Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.**
- 5. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system should include specific assessments for residual monomers, solvents, polymerizers, etc. The choice of solvents and conditions for the extraction studies should be justified. The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables. Although a toxicological risk assessment based on the results of the extraction studies may be**

adequate to support the safety assessment during development, you should still evaluate the drug product over the course of your stability studies and base the final safety assessment on the levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen. As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, refer to the FDA guidance for industry, *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf> and the FDA guidance for industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure for a chronic indication or be adequately qualified for safety. From a genetic toxicology perspective, we will allow up to 120 mcg/day for an acute indication for most potentially genotoxic impurities. However, a toxicological risk assessment must be provided for any non-genotoxic leachable that exceeds 5 mcg/day. The risk assessment should be based on the levels of leachables detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

6. We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the recommended qualification thresholds or novel excipients that are not justified for safety or if the application lacks adequate safety justification for extractables and leachables from the container closure system.

No additional discussion was needed.

### 2.3. Clinical

**Question 7:**

*Through contacting study authors, manufacturers, hospital pharmacies, etc., Éclat was able to confirm the identity of study drug administered in a number of clinical studies. A table listing the documentation that was gathered on the study drug identity for each of the key efficacy and safety papers is provided in Section 2.7.1 (Attachment 4). Is the level of evidence provided for each study drug identity considered to be adequate?*

**FDA Response to Question 7:**

**The level of evidence provided for the ephedrine in each study in Tables 5 and 6 appears adequate. However, you did not confirm the purity of the compound. Whether or not the journal articles are adequate to support an NDA will be a matter of review.**

Discussion:

The Sponsor stated that all of the marketed unapproved ephedrine sulfate products comply with USP standards, however, there is no USP specification for purity. To address the Division's concerns regarding the purity of the drug product, the Sponsor proposed requesting information on the purity profile of ephedrine sulfate products from current manufacturers, however it is unlikely that existing manufacturers will have this information. The Division recommended the Sponsor try to obtain samples of ephedrine sulfate from current manufacturers and provide a comparison of the purity profile of these products with the Sponsor's drug product. The Sponsor agreed to conduct an HPLC analysis of existing ephedrine sulfate products on the market, even if those products may not be the products used in the literature to support their NDA. The Sponsor will compare the impurity profile, degradation and amount of ephedrine in each product compared to their drug product. The Sponsor reassured the Division that their final drug product will conform to ICH specification for impurities and degradants.

**Question 8:**

*In the Agency's Type C WRO dated April 10, 2014, Éclat was informed that if documentation that supports the determination about drug product identity in each (-)ephedrine sulfate paper is provided, and that chiral purity and stability has been addressed, then those papers would be considered pivotal support of the efficacy of Éclat's product. Of potentially equal importance to the (-)ephedrine sulfate studies are studies with (-)ephedrine hydrochloride, if Éclat is able to provide satisfactory information regarding the drug product and a sound rationale for its relevance despite its different salt. Éclat has provided a rationale for the applicability of the data generated in studies using (-)ephedrine hydrochloride to (-)ephedrine sulfate in Section 2.7.1 (Attachment 4). Does the Agency agree that this rationale is adequate and that the (-)ephedrine hydrochloride literature can be used as pivotal support for the efficacy and safety of Ephedrine Sulfate Injection, USP for the proposed indication?*

**FDA Response to Question 8:**

**The rationale that (-)ephedrine hydrochloride literature can be used to support the efficacy and safety of Ephedrine Sulfate Injection appears reasonable. To assure that the strengths of ephedrine are compared appropriately, convert the strengths of ephedrine sulfate and ephedrine HCl to the free base form of ephedrine.**

Discussion:

The Sponsor stated that they intend to include tables that convert the strength of ephedrine sulfate and ephedrine HCl as a table in their NDA submission.

**Question 9:**

*Éclat has identified 15 studies with confirmed relevant study drug (i.e., either (-)ephedrine sulfate or (-)ephedrine hydrochloride, referred to collectively as (-)ephedrine). Nine of these studies were conducted during C-sections, two were conducted under spinal anesthesia (non-C-section) and four were conducted under general anesthesia. Éclat intends to use this literature as pivotal support for the efficacy and safety of Ephedrine Sulfate Injection, USP for the treatment of hypotension in the setting of anesthesia. Does the Agency agree that data described in the draft Section 2.7.3 and Integrated Summary of Efficacy (Attachments 6 and 9, respectively) are adequate to support the approval of Ephedrine Sulfate Injection, USP for the proposed indication?*

**FDA Response to Question 9:**

**We are concerned about the following aspects of the literature you have presented to support the efficacy of ephedrine:**

- 1. Chiral purity of the ephedrine has not been confirmed. See the answer to Question 7.**
- 2. The number of surgical subjects receiving ephedrine under general anesthesia is relatively small.**

**Whether or not the data you have described will be adequate to support the approval of Ephedrine Sulfate Injection, USP for the proposed indication will be a matter for NDA review. We encourage you to continue to obtain more data to support the efficacy of your product for its proposed indication. Additionally, the analysis of the literature submitted to support your Neostigmine 505(b)(2) NDA should also be provided in your NDA for ephedrine sulfate.**

**Discussion:**

The Sponsor inquired about the implication of the limited data from subjects receiving general anesthesia on the fileability and/or review of their NDA submission. The Sponsor suggested that perhaps the product labeling would be the appropriate mechanism to address the limited data in this population by describing that the data on the use of ephedrine sulfate in the setting of general anesthesia are limited. The Division stated that the lack of data in this setting would not be a filing issue, but would be reviewed and could potentially be addressed in product labeling. However, it is too early to know how this issue will be addressed until the NDA is submitted and reviewed. The Division agreed that the limited data on ephedrine sulfate use in general anesthesia may be used to support the overall safety of the ephedrine sulfate, but additional internal discussions would be needed and would occur during the review of the NDA. The Sponsor was advised to summarize the data to support safety and efficacy and to also distinguish the robust literature material from the less supportive literature in their submission. The Sponsor agreed to submit all of the literature data on the use of ephedrine sulfate in general anesthesia and parse out the better literature references (i.e., the literature in which the identity of ephedrine used has been confirmed) from the less supportive

references (i.e., the literature in which the identity of the ephedrine used has not been confirmed).

The Division clarified that the analysis of the literature that was submitted to support the Sponsor's Neostigmine 505(b)(2) NDA should be used as an example for the analysis that they will provide in their NDA for ephedrine sulfate.

**Post-Meeting Note:**

The Neostigmine NDA is an example of a well-written 505(b)(2) NDA. The format of the Neostigmine NDA may not necessarily be appropriate to use as the format for the Ephedrine 505(b)(2) submission.

**Question 10:**

*... Does the Agency agree that the concerns regarding the reliance on foreign clinical data, GCP status of studies and investigator competence have been adequately addressed?*

**FDA Response to Question 10:**

**Whether or not the studies you have cited are applicable to the U.S. population and medical practice will be a matter of review of the articles you intend to submit. We note your attempt to obtain information about the conditions under which foreign clinical data was obtained and we encourage you to continue this. Please refer to guidance for industry, *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions*, available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf>**

No additional discussion was needed.

**Question 11:**

*Éclat intends to use safety data generated in studies of (b)(4) use of ephedrine as supportive of the safety of Éclat's proposed product and indication (see discussion of Supplementary Safety Literature in 5.3.5.3 Integrated Summary of Safety Section 1.1.3 provided in Attachment 10). Does the Agency agree?*

**FDA Response to Question 11:**

**Ephedrine literature pertaining to (b)(4) use may not support the safety of ephedrine sulfate for the treatment of hypotension because, from a safety standpoint, the effects of ephedrine in a normotensive individual receiving ephedrine may differ from the effects in a hypotensive individual. If you would like to submit safety data generated in studies of (b)(4) use of ephedrine as supportive of the safety of your ephedrine product, provide a rationale for why the data can be extrapolated from one population to the other.**

Discussion:

The Sponsor stated that they believe the literature data on the (b)(4) use of ephedrine sulfate may support overall safety for ephedrine sulfate because patients' exposure is thought to be higher in this patient population. The Division advised the

Sponsor to include and describe in their NDA submission how data from studies pertaining to (b) (4) use of ephedrine sulfate could support the overall safety of ephedrine sulfate.

**Question 12:**

*Éclat has identified a number of studies of ephedrine of unknown stereoisomeric composition. Based on the Agency's Type C WRO (April 10, 2014), Éclat does not intend to summarize the data from these studies in either the efficacy or safety sections of the NDA. Is this acceptable to the Agency?*

**FDA Response to Question 12:**

**For the efficacy section of the NDA, it is acceptable to include data only from studies in which the stereoisomeric composition of the ephedrine used is known. However, for the safety section of the NDA, you may include data from studies in which the stereoisomeric composition of ephedrine is unknown. To the extent possible, compare the safety findings to determine if there are any differences between ephedrine that may be composed of the (-) stereoisomer versus data that may reflect both the (-) and (+) isomers. Clearly identify data from literature that does not provide information on the composition and purity of the ephedrine.**

No further discussion was needed.

**Question 13:**

*Because Éclat's NDA submission has remained uncertain, a Pediatric Study Plan (PSP) was only recently submitted to the PIND on February 13, 2015. Understanding that failure to include an Agreed PSP is grounds for a refuse to file action, Éclat respectfully requests consideration for an accelerated review by the Pediatric Research Committee.*

**FDA Response to Question 13:**

**FDA has established procedures for review of Pediatric Study Plans. We intend to respond to your initial PSP submission by May 14, 2015.**

No further discussion was needed.

**Question 14:**

*Éclat has determined that the risk of abuse for Ephedrine Sulfate Injection, USP is low based on its acute use in patients under anesthesia, its prescription only status and its dispensation and administration in a highly-controlled setting. This argument is summarized in the Drug Abuse section of the ISS (see Attachment 10). Does the Agency agree that no further abuse potential information is required in the NDA?*

**FDA Response to Question 14:**

**Ephedrine is controlled by the DEA as a List 1 chemical, due to its common use as a precursor in the illicit manufacture of methamphetamine.**

**While there may be no need for any new abuse potential studies with the application, you must still submit an abuse potential assessment and the full information on which it is based. This will be reviewed as part of the NDA.**

Discussion:

The Division clarified that ephedrine sulfate is not a controlled substance, but is a List 1 chemical controlled by the DEA. No new or additional abuse liability studies will be needed to support an NDA for ephedrine sulfate. However, the Sponsor must include an abuse liability assessment for us to review as part of a complete NDA. This could take the format of an eight factor analysis, although this particular format is not required (Please see Post-Meeting Note for clarification). Summaries based on a complete review of the existing literature on ephedrine abuse will be sufficient. The specific circumstances of the injectable product (marketing, intended use, etc.) may be cited as potentially significant variables in determining a low risk for abuse or risk for the illicit use of the product as a precursor of Methamphetamine.

**Post-Meeting Note:**

The Sponsor should provide an overview of the abuse potential of the formulation. This overview should include a description of the drug product, and a literature review on the abuse potential of ephedrine. This information should be included in the NDA ((Module 1.11.4, Multiple Module Information Amendment) as a summary. An eight factor analysis is not needed for ephedrine.

The Sponsor was instructed to discuss the projected needs of ephedrine with the DEA Office of Diversion Control because the importation and manufacturing of ephedrine is subject to the controls imposed by the Combat Methamphetamine Epidemic Act of 2005. This Act mandates that DEA establish total annual requirements, and individual import, manufacturing, and procurement quotas for three List 1 chemicals: ephedrine, pseudoephedrine, and phenylpropanolamine.

**Additional Clinical Comments:**

**In your NDA submission, provide data to support the ephedrine dose, frequency of dosing, and maximum dose.**

Discussion:

The Division stated that Sponsor's package indicates that ephedrine sulfate is renally excreted; however the package did not address dosing in special populations, particularly those with renal impairment. The Sponsor was advised to address the use of ephedrine sulfate in patients with renal impairment in their NDA submission.

**Additional Comments Regarding Marketed Unapproved Products:**

**The Agency encourages firms to voluntarily comply with the law by submitting applications for previously marketed unapproved new drugs. This process benefits public health by increasing assurance that marketed drugs are safe and effective for**

**their intended uses as well as manufactured consistent with current good manufacturing practice. When a company obtains approval of an NDA for which other companies market unapproved versions, the FDA is more likely to consider a compliance action. However, FDA considers several factors such as the effect on public health of proceeding immediately to remove the unapproved products from the market, the ability of the applicant holder to meet patient needs by supplying the entire market, assuring that the components and finished drug products are manufactured under quality standards, and efficient use of Agency resources. We encourage your firm to consider these important factors as the application progresses through the review process and to open discussions with the Drug Shortage Staff when appropriate. We refer you to the Agency website which provides additional guidance on the compliance actions for marketed unapproved products,**  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/default.htm>.

### **3.0 ADDITIONAL REGULATORY COMMENTS**

#### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our February 12, 2015, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

## **PREA REQUIREMENTS**

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

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

In addition, your PSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf>.

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

development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

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

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

## **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

## **MANUFACTURING FACILITIES**

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

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

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

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

Corresponding names and titles of onsite contact:

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

## **505(b)(2) REGULATORY PATHWAY**

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

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

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

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

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

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

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

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

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

#### **4.0 ACTION ITEMS**

1. The Sponsor agreed to change the drug substance specification for (b)(4) so that they aligns with ICH Q3A(R2) thresholds.
2. The Sponsor plans to include all literature references with data on the use of ephedrine sulfate in general anesthesia in their NDA and separate the supportive studies from those that are less supportive.
3. The Sponsor will consider including an eight factor analysis for ephedrine sulfate in their NDA submission.
4. The Division advised the Sponsor to include and describe in their NDA submission how data from studies pertaining to (b)(4) use of ephedrine sulfate support the overall safety of ephedrine sulfate.
5. The Sponsor agreed to address dosing of ephedrine sulfate in their NDA submission.

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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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AYANNA S AUGUSTUS  
05/21/2015



PIND 116266

**MEETING REQUEST-  
WRITTEN RESPONSES**

Éclat Pharmaceuticals, LLC  
c/o The Weinberg Group Inc.  
1129 Twentieth St. NW, Suite 600  
Washington, DC 20036

Attention: Marla Scarola, MS  
Senior Consultant

Dear Ms. Scarola:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ephedrine sulfate injection.

We also refer to your submission dated January 29, 2014, containing a meeting request. The purpose of the requested meeting was to discuss the development of an NDA for ephedrine sulfate injection.

Further reference is made to our Meeting Granted letter dated January 31, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your January 29, 2014, background package.

If you have any questions, contact me at [ayanna.augustus@fda.hhs.gov](mailto:ayanna.augustus@fda.hhs.gov) or (301) 796-9380.

Sincerely,

*{See appended electronic signature page}*

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Written Responses



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**WRITTEN RESPONSES**

**Meeting Type:** Type C  
**Meeting Category:** Guidance

**Application Number:** 116266  
**Product Name:** ephedrine sulfate injection  
**Indication:** (b) (4) the hypotensive (b) (4)  
anesthesia

**Sponsor/Applicant Name:** Eclat Pharmaceuticals, LLC  
**Regulatory Pathway:** 505(b)(2)

**1.0 BACKGROUND**

The Sponsor seeks to obtain guidance from the Division on their efforts to address several concerns raised during the EOP2 meeting held on November 19, 2013. These concerns include the stereoisomer composition of the drug product used in referenced studies, the scope of the proposed indication, and the limited information on the patient population that would benefit from (b) (4) administration of ephedrine sulfate and how to measure a clinical benefit. The Division also provided guidance on the Sponsor's development program for ephedrine sulfate during the PIND meeting held on December 19, 2012.

There are currently several unapproved marketed versions of ephedrine sulfate, a sympathomimetic drug with mixed adrenergic agonist activity. Éclat Pharmaceuticals, LLC, has developed ephedrine sulfate injection, USP as a sterile 50 mg/mL solution for intravenous (b) (4) injection. The Sponsor plans to submit a 505(b)(2) application supported by nonclinical and clinical literature.

**2.0 QUESTIONS AND RESPONSES**

**2.1. Clinical and CMC**

Question 1a:

*...Éclat considers the eight studies with (-)-ephedrine sulfate to provide the most direct and relevant literature support for the use of ephedrine sulfate for anesthesia-induced hypotension. Does FDA agree that these papers should be considered the top tier of supportive studies? If not, would other literature be considered equally important?*

**FDA Response to Question 1a:**

**Assuming you can provide documentation that supports your determination about drug product identity in each (-) ephedrine sulfate paper, and you have addressed chiral purity and stability, then study design and conduct should be weighed in order to determine the amount of support each study provides. Of potentially equal importance to the (-) ephedrine sulfate studies are studies with (-) ephedrine hydrochloride, if you provide satisfactory information regarding the drug product and a sound rationale for its relevance despite its different salt. See our response to Question 3.**

**Because all relevant studies were conducted outside the U.S., the requirements of 21 CFR 314.106 need to be met. You will need to provide a rationale for why the data from outside the U.S. may be generalized to the U.S. population. Your rationale should include a description of the medical practice associated with the indication and a characterization of the patient population. Additional requirements of 21 CFR 314.106 are performance of the studies by investigators of recognized competence and FDA ability to validate data through on-site inspection or other means. Per 21 CFR 312.120, the studies should also have been conducted in accordance with good clinical practice.**

**You will need to provide evidence-based rationale that ephedrine provides a clinical benefit beyond simply raising blood pressure and heart rate. The most supportive studies will include outcomes that either directly demonstrates a benefit to the patient or that include data you can use to develop a rationale based on the weight from different lines of evidence supporting your reasoning.**

**Question 1b:**

*Does FDA recommend that dosing directions be principally derived from this specific literature of 8 studies, or more broadly from the entire ephedrine literature identified for the NDA?*

**FDA Response to Question 1b:**

**Dosing directions will be derived from only those studies for which you have adequate information about the drug product, and not from the entire ephedrine literature. We note that you have identified only three treatment studies by two investigators and each was conducted in the setting of neuraxial anesthesia for Cesarean section. It is unlikely that those few papers provide sufficient data for dosing directions for the entire labeled population that includes non-parturient patients and patients undergoing general anesthesia.**

**Question 2a:**

*Through Éclat's efforts to identify study drug, we were able to confirm seven additional clinical studies in which subjects were administered the sulfate salt of ephedrine but for which the enantiomeric composition could not be determined (Table 3). These studies fill gaps in the (-)-ephedrine sulfate literature: studies are primarily from the U.S. and are mostly placebo or volume-controlled. Does FDA concur that these studies are pertinent to the evaluation of Ephedrine Sulfate Injection, USP, 50 mg/mL for its intended indications?*

**FDA Response to Question 2a:**

**No, we do not agree. You have proposed that we consider literature regarding ephedrine with the same salt as your proposed drug product (i.e., ephedrine sulfate), but unknown stereoisomer. Without information about the stereoisomeric composition of the drug product used in these studies, they cannot be considered in the evaluation of ephedrine sulfate injection or in the determination of dosing directions.**

**Question 2b:**

*Does FDA concur that these studies are relevant to the determination of dosing directions for Ephedrine Sulfate Injection, USP, 50 mg/mL?*

**FDA Response to Question 2b:**

**Refer to the Division's response to Question 2a.**

**Question 3a:**

*Through Éclat's efforts to identify study drug, we were able to confirm that six clinical papers administered (-)-ephedrine hydrochloride for the (b) (4) indication (Table 4) and 11 papers administered ephedrine hydrochloride of unknown stereoisomer composition for treatment and (b) (4) indications (Table 5). Éclat intends to consider these papers supportive of the safety and efficacy of Ephedrine Sulfate Injection, USP, 50 mg/mL. Does FDA concur that these studies are pertinent to the evaluation of Ephedrine Sulfate Injection, USP, 50 mg/mL for its intended indications?*

**FDA Response to Question 3a:**

**Regarding the six (-) ephedrine hydrochloride (b) (4) studies, they would be pertinent to the evaluation of ephedrine sulfate injection and determination of dosing if you provide sufficient information about the drug product used in each study and a sufficient rationale for the applicability of data regarding (-) ephedrine hydrochloride to (-) ephedrine sulfate. Your rationale for the applicability of the (-) ephedrine hydrochloride data should address, at a minimum, the different quantity of active moiety for a given dose, or mass, of (-) ephedrine sulfate vs. (-) ephedrine hydrochloride.**

**Regarding the eleven studies of ephedrine hydrochloride where the stereoisomer is unknown, without information about the enantiomeric composition of the drug product used in these studies, they cannot be considered in the evaluation of ephedrine sulfate injection or in the determination of dosing directions.**

**Question 3b:**

*Does FDA concur that these studies can be used to determine dosing directions for Ephedrine Sulfate Injection, USP, 50 mg/mL?*

**FDA Response to Question 3b:**

**Refer to the Division's response to Question 3a.**

**Question 4:**

*At the EOP2 meeting, the Agency required that Éclat provide information about the stereoisomer, including its purity and its salt form, for a sufficient number of published studies that are of adequate design and conduct to support the safety and efficacy of the proposed indications and labeling claims. In response, Éclat obtained information on the study drug identity for a number of studies as shown in Table 1 through Table 5 and discussed in the questions above. Thus, Éclat believes that the Agency's request has been satisfied. Does the Agency agree?*

**FDA Response to Question 4:**

**No, we do not agree. See our responses to Questions 1-3.**

**Question 5a:**

*...Consequently, Éclat concludes, with more certainty than not, that all studies conducted in the United States used the sulfate salt form of ephedrine. Does the Agency agree that the studies conducted in the United States using non-specific ephedrine product can be considered to have used ephedrine sulfate?*

**FDA Response to Question 5a:**

**No, we do not agree. We have found several references that have used ephedrine hydrochloride, for example, Yen, 1981; Gomez, 2005; Hood, 2003.**

**Question 5b:**

*...it is Éclat's contention that all studies conducted within the United States would have used USP-compliant ephedrine sulfate injection, i.e., (-)-ephedrine sulfate. Does the Agency agree?*

**FDA Response to Question 5b:**

**No we do not agree. Most of the references provided refer to only "Ephedrine", not "Ephedrine, USP." Unless "USP" is included in the name, it cannot be assumed that *all* Ephedrine products are USP compliant. Further, the USP monograph from 1970 does not provide for testing of any related substances that are now part of the European Pharmacopoeia and British Pharmacopoeia monographs. Therefore, the purity of the products used in the referenced literature is still not known with any certainty.**

Question 5c:

*Does FDA agree that these papers should be considered equally important to the eight studies that are confirmed to be using (-)-ephedrine sulfate in terms of providing support for the use of Éclat's drug product and for deriving dosing directions?*

**FDA Response to Question 5c:**

**No, we do not agree that you have provided sufficient information regarding the drug product used in the U.S. studies for them to be considered equally important to studies where the use of (-) ephedrine sulfate has been verified.**

Question 6a:

*...Can the Agency please clarify whether this analytic approach was suggested as an option for addressing the issue of drug substance purity in the event that data cannot be identified specifically for the drug product used in the literature citations?*

**FDA Response to Question 6a:**

**The purity and stability of the drug product, including isomeric purity over time, should be established for the products studied in the literature in order to support those clinical studies. Without establishing the integrity of the study drug throughout the study period, the literature reference may not be considered as relevant by the clinical team. Therefore, since it may be difficult to establish the integrity of the literature products, the CMC team suggested that by establishing the stability, purity and chiral integrity of the NDA drug product, one could possibly establish a bridge to the literature drug products, if the two formulations are similar in terms of pH and other characteristics that may influence impurities.**

Question 6b:

*Éclat is currently conducting a chiral analysis on Ephedrine Sulfate Injection, USP, 50 mg/mL to evaluate the purity of the enantiomeric composition and any changes over time. Given that Éclat has demonstrated that a number of the study drugs used in the published clinical studies were USP compliant and that the drug product formulations are simple ((-)-ephedrine sulfate and water), Éclat assumes that the degradation profile data generated on Ephedrine Sulfate Injection, USP, 50 mg/mL can be used to address any concerns over the purity of drug used in the published studies. Does the Agency agree?*

**FDA Response to Question 6b:**

**Yes, we agree. The analyses could possibly support the literature products if no degradation or racemization is found in current test product stored over a long period and if the starting composition of the drug products were similar.**

### **3.0 ADDITIONAL REGULATORY COMMENTS**

#### **PREA REQUIREMENTS**

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

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

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

#### **505(b)(2) REGULATORY PATHWAY**

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

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge"

(e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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

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

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

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

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

<p><b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature</b></p>
--

<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

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

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/s/  
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AYANNA S AUGUSTUS  
04/09/2014



PIND 116266

**MEETING REQUEST-  
WRITTEN RESPONSES**

Éclat Pharmaceuticals, LLC  
c/o The Weinberg Group Inc.  
1129 Twentieth St. NW, Suite 600  
Washington, DC 20036

Attention: Marla Scarola, MS  
Senior Consultant

Dear Ms. Scarola:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ephedrine sulfate injection.

We also refer to your submission dated January 29, 2014, containing a meeting request. The purpose of the requested meeting was to discuss the development of an NDA for ephedrine sulfate injection.

Further reference is made to our Meeting Granted letter dated January 31, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your January 29, 2014, background package.

If you have any questions, contact me at [ayanna.augustus@fda.hhs.gov](mailto:ayanna.augustus@fda.hhs.gov) or (301) 796-9380.

Sincerely,

*{See appended electronic signature page}*

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Written Responses



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**WRITTEN RESPONSES**

**Meeting Type:** Type C  
**Meeting Category:** Guidance

**Application Number:** 116266  
**Product Name:** ephedrine sulfate injection  
**Indication:** (b) (4) the hypotensive (b) (4)  
anesthesia

**Sponsor/Applicant Name:** Eclat Pharmaceuticals, LLC  
**Regulatory Pathway:** 505(b)(2)

**1.0 BACKGROUND**

The Sponsor seeks to obtain guidance from the Division on their efforts to address several concerns raised during the EOP2 meeting held on November 19, 2013. These concerns include the stereoisomer composition of the drug product used in referenced studies, the scope of the proposed indication, and the limited information on the patient population that would benefit from (b) (4) administration of ephedrine sulfate and how to measure a clinical benefit. The Division also provided guidance on the Sponsor's development program for ephedrine sulfate during the PIND meeting held on December 19, 2012.

There are currently several unapproved marketed versions of ephedrine sulfate, a sympathomimetic drug with mixed adrenergic agonist activity. Éclat Pharmaceuticals, LLC, has developed ephedrine sulfate injection, USP as a sterile 50 mg/mL solution for intravenous (b) (4) injection. The Sponsor plans to submit a 505(b)(2) application supported by nonclinical and clinical literature.

**2.0 QUESTIONS AND RESPONSES**

**2.1. Clinical and CMC**

Question 1a:

*...Éclat considers the eight studies with (-)-ephedrine sulfate to provide the most direct and relevant literature support for the use of ephedrine sulfate for anesthesia-induced hypotension. Does FDA agree that these papers should be considered the top tier of supportive studies? If not, would other literature be considered equally important?*

**FDA Response to Question 1a:**

**Assuming you can provide documentation that supports your determination about drug product identity in each (-) ephedrine sulfate paper, and you have addressed chiral purity and stability, then study design and conduct should be weighed in order to determine the amount of support each study provides. Of potentially equal importance to the (-) ephedrine sulfate studies are studies with (-) ephedrine hydrochloride, if you provide satisfactory information regarding the drug product and a sound rationale for its relevance despite its different salt. See our response to Question 3.**

**Because all relevant studies were conducted outside the U.S., the requirements of 21 CFR 314.106 need to be met. You will need to provide a rationale for why the data from outside the U.S. may be generalized to the U.S. population. Your rationale should include a description of the medical practice associated with the indication and a characterization of the patient population. Additional requirements of 21 CFR 314.106 are performance of the studies by investigators of recognized competence and FDA ability to validate data through on-site inspection or other means. Per 21 CFR 312.120, the studies should also have been conducted in accordance with good clinical practice.**

**You will need to provide evidence-based rationale that ephedrine provides a clinical benefit beyond simply raising blood pressure and heart rate. The most supportive studies will include outcomes that either directly demonstrates a benefit to the patient or that include data you can use to develop a rationale based on the weight from different lines of evidence supporting your reasoning.**

**Question 1b:**

*Does FDA recommend that dosing directions be principally derived from this specific literature of 8 studies, or more broadly from the entire ephedrine literature identified for the NDA?*

**FDA Response to Question 1b:**

**Dosing directions will be derived from only those studies for which you have adequate information about the drug product, and not from the entire ephedrine literature. We note that you have identified only three treatment studies by two investigators and each was conducted in the setting of neuraxial anesthesia for Cesarean section. It is unlikely that those few papers provide sufficient data for dosing directions for the entire labeled population that includes non-parturient patients and patients undergoing general anesthesia.**

**Question 2a:**

*Through Éclat's efforts to identify study drug, we were able to confirm seven additional clinical studies in which subjects were administered the sulfate salt of ephedrine but for which the enantiomeric composition could not be determined (Table 3). These studies fill gaps in the (-)-ephedrine sulfate literature: studies are primarily from the U.S. and are mostly placebo or volume-controlled. Does FDA concur that these studies are pertinent to the evaluation of Ephedrine Sulfate Injection, USP, 50 mg/mL for its intended indications?*

**FDA Response to Question 2a:**

**No, we do not agree. You have proposed that we consider literature regarding ephedrine with the same salt as your proposed drug product (i.e., ephedrine sulfate), but unknown stereoisomer. Without information about the stereoisomeric composition of the drug product used in these studies, they cannot be considered in the evaluation of ephedrine sulfate injection or in the determination of dosing directions.**

**Question 2b:**

*Does FDA concur that these studies are relevant to the determination of dosing directions for Ephedrine Sulfate Injection, USP, 50 mg/mL?*

**FDA Response to Question 2b:**

**Refer to the Division's response to Question 2a.**

**Question 3a:**

*Through Éclat's efforts to identify study drug, we were able to confirm that six clinical papers administered (-)-ephedrine hydrochloride for the (b) (4) indication (Table 4) and 11 papers administered ephedrine hydrochloride of unknown stereoisomer composition for treatment and (b) (4) indications (Table 5). Éclat intends to consider these papers supportive of the safety and efficacy of Ephedrine Sulfate Injection, USP, 50 mg/mL. Does FDA concur that these studies are pertinent to the evaluation of Ephedrine Sulfate Injection, USP, 50 mg/mL for its intended indications?*

**FDA Response to Question 3a:**

**Regarding the six (-) ephedrine hydrochloride (b) (4) studies, they would be pertinent to the evaluation of ephedrine sulfate injection and determination of dosing if you provide sufficient information about the drug product used in each study and a sufficient rationale for the applicability of data regarding (-) ephedrine hydrochloride to (-) ephedrine sulfate. Your rationale for the applicability of the (-) ephedrine hydrochloride data should address, at a minimum, the different quantity of active moiety for a given dose, or mass, of (-) ephedrine sulfate vs. (-) ephedrine hydrochloride.**

**Regarding the eleven studies of ephedrine hydrochloride where the stereoisomer is unknown, without information about the enantiomeric composition of the drug product used in these studies, they cannot be considered in the evaluation of ephedrine sulfate injection or in the determination of dosing directions.**

**Question 3b:**

*Does FDA concur that these studies can be used to determine dosing directions for Ephedrine Sulfate Injection, USP, 50 mg/mL?*

**FDA Response to Question 3b:**

**Refer to the Division's response to Question 3a.**

**Question 4:**

*At the EOP2 meeting, the Agency required that Éclat provide information about the stereoisomer, including its purity and its salt form, for a sufficient number of published studies that are of adequate design and conduct to support the safety and efficacy of the proposed indications and labeling claims. In response, Éclat obtained information on the study drug identity for a number of studies as shown in Table 1 through Table 5 and discussed in the questions above. Thus, Éclat believes that the Agency's request has been satisfied. Does the Agency agree?*

**FDA Response to Question 4:**

**No, we do not agree. See our responses to Questions 1-3.**

**Question 5a:**

*...Consequently, Éclat concludes, with more certainty than not, that all studies conducted in the United States used the sulfate salt form of ephedrine. Does the Agency agree that the studies conducted in the United States using non-specific ephedrine product can be considered to have used ephedrine sulfate?*

**FDA Response to Question 5a:**

**No, we do not agree. We have found several references that have used ephedrine hydrochloride, for example, Yen, 1981; Gomez, 2005; Hood, 2003.**

**Question 5b:**

*...it is Éclat's contention that all studies conducted within the United States would have used USP-compliant ephedrine sulfate injection, i.e., (-)-ephedrine sulfate. Does the Agency agree?*

**FDA Response to Question 5b:**

**No we do not agree. Most of the references provided refer to only "Ephedrine", not "Ephedrine, USP." Unless "USP" is included in the name, it cannot be assumed that *all* Ephedrine products are USP compliant. Further, the USP monograph from 1970 does not provide for testing of any related substances that are now part of the European Pharmacopoeia and British Pharmacopoeia monographs. Therefore, the purity of the products used in the referenced literature is still not known with any certainty.**

Question 5c:

*Does FDA agree that these papers should be considered equally important to the eight studies that are confirmed to be using (-)-ephedrine sulfate in terms of providing support for the use of Éclat's drug product and for deriving dosing directions?*

**FDA Response to Question 5c:**

**No, we do not agree that you have provided sufficient information regarding the drug product used in the U.S. studies for them to be considered equally important to studies where the use of (-) ephedrine sulfate has been verified.**

Question 6a:

*...Can the Agency please clarify whether this analytic approach was suggested as an option for addressing the issue of drug substance purity in the event that data cannot be identified specifically for the drug product used in the literature citations?*

**FDA Response to Question 6a:**

**The purity and stability of the drug product, including isomeric purity over time, should be established for the products studied in the literature in order to support those clinical studies. Without establishing the integrity of the study drug throughout the study period, the literature reference may not be considered as relevant by the clinical team. Therefore, since it may be difficult to establish the integrity of the literature products, the CMC team suggested that by establishing the stability, purity and chiral integrity of the NDA drug product, one could possibly establish a bridge to the literature drug products, if the two formulations are similar in terms of pH and other characteristics that may influence impurities.**

Question 6b:

*Éclat is currently conducting a chiral analysis on Ephedrine Sulfate Injection, USP, 50 mg/mL to evaluate the purity of the enantiomeric composition and any changes over time. Given that Éclat has demonstrated that a number of the study drugs used in the published clinical studies were USP compliant and that the drug product formulations are simple ((-)-ephedrine sulfate and water), Éclat assumes that the degradation profile data generated on Ephedrine Sulfate Injection, USP, 50 mg/mL can be used to address any concerns over the purity of drug used in the published studies. Does the Agency agree?*

**FDA Response to Question 6b:**

**Yes, we agree. The analyses could possibly support the literature products if no degradation or racemization is found in current test product stored over a long period and if the starting composition of the drug products were similar.**

### **3.0 ADDITIONAL REGULATORY COMMENTS**

#### **PREA REQUIREMENTS**

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

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

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

#### **505(b)(2) REGULATORY PATHWAY**

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

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge"

(e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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

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

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

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

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

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

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

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/s/  
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AYANNA S AUGUSTUS  
04/09/2014



PIND 116266

**MEETING MINUTES**

Éclat Pharmaceuticals, LLC  
c/o Beckloff Associates  
7400 West 110th Street, Suite 300  
Overland Park, Kansas 66210

Attention: Wayne F. Vallee, RPh, RAC  
Director, Managing Consultant

Dear Mr. Vallee:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ephedrine sulfate injection.

We also refer to the meeting between representatives of your firm and the FDA on November 19, 2013. The purpose of the meeting was to discuss the suitability of the draft NDA sections to support a 505(b)(2) marketing application for ephedrine sulfate injection.

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

If you have any questions, contact me at [ayanna.augustus@fda.hhs.gov](mailto:ayanna.augustus@fda.hhs.gov) or, at (301) 796-3980.

Sincerely,

*{See appended electronic signature page}*

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** End-of-Phase 2  
**Meeting Date and Time:** November 19, 2013; 12:00 PM  
**Meeting Location:** White Oak, Bldg 22, Room 1419

**Application Number:** 116266  
**Product Name:** ephedrine sulfate injection  
**Indication:** (b) (4) the hypotensive (b) (4)  
anesthesia

**Sponsor/Applicant Name:** Eclat Pharmaceuticals, LLC

**List of Attendees:**

<b>FDA Attendees</b>	<b>Title</b>
Rigoberto Roca, MD	Deputy Division Director
Leah Crisafi, MD	Clinical Reviewer
Christopher Breder, MD, PhD	Clinical Team Leader
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor
Marcus S. Delatte, PhD	Pharmacology/Toxicology Reviewer
Julia Pinto, PhD	Acting CMC Lead, ONDQA
Prasad Peri, PhD	Branch Chief, ONDQA
Yun Xu, PhD	Clinical Pharmacology Team Leader
Ayanna Augustus, PhD	Sr. Regulatory Health Project Manager
Assad Noory, PhD	Biopharmaceutics Reviewer
Janice Derr, PhD	Biostatistics, Team Lead
Lisa Skarupa	Regulatory Project Manager, OSE
Martin Pollock, PharmD	Safety Evaluator, OSE/DPVII
Mary Lockett, MD	Clinical Reviewer
Charles Lee, MD	Sr. Medical Advisor, Office of Compliance/Office of Unapproved Drugs and Labeling Compliance
<b>Sponsor Attendees</b>	<b>Title</b>
Michael Anderson	President and Chief Executive Officer; Éclat Pharmaceuticals, LLC
Scott A. Macke	Vice President, Operations; Éclat Pharmaceuticals, LLC
(b) (4)	

(b) (4)	
Wayne F. Vallee, RPh, RAC	Director, Managing Consultant; Beckloff Associates, Inc.

## 1.0 BACKGROUND

The purpose of this meeting is to discuss the adequacy of the Chemistry, Manufacturing and Controls (CMC), nonclinical, and clinical information the Sponsor intends to submit to support a 505(b)(2) NDA for ephedrine sulfate injection. During the PIND meeting held on December 19, 2012, the Division provided guidance on the Sponsor's development program for ephedrine sulfate. Éclat Pharmaceuticals, LLC, has developed ephedrine sulfate injection, USP as a sterile 50 mg/mL solution for intravenous (b) (4) injection. Ephedrine sulfate is a sympathomimetic drug with mixed adrenergic agonist activity. The Sponsor plans to submit a 505(b)(2) application supported by nonclinical and clinical literature.

Prior to the meeting, the Sponsor provided a list of questions that required further discussion during the meeting. The meeting questions are presented below in *italicized* text, Agency responses prepared prior to the meeting are **bolded** and the discussion is presented in normal text.

## 2. DISCUSSION

### Introductory Comments:

**We have concerns regarding your proposed NDA application that will impact whether it may be filed and, ultimately, approved. Based on what you have submitted at this time, our primary concerns are:**

- **The lack of information regarding the stereoisomer composition of the drug used in the studies you have referenced**
- **The restricted scope of your proposed treatment indication**
- **The limited information to characterize the population who will benefit from (b) (4) administration of ephedrine and how that benefit may be measured**

These issues are briefly described below.

### Stereoisomer Composition

**In our December 19, 2012, PIND meeting, the Division requested that you clarify the exact stereoisomer used in the clinical trials referenced in the literature. You have identified only one paper containing isomeric information for the ephedrine drug product, and that paper alone does not contain sufficient substantial evidence for the evaluation of safety and**

**efficacy. You have provided, as a bridge between your product and the published literature, a supposition that the (-) isomer was used in the clinical trials in the literature because the U.S., Japanese, and European monographs describe the (-) isomer. However, a supposition alone, without supporting data, is insufficient. Furthermore, you have not provided any evidence from the literature to support the purity of the isomer used in these published clinical trials.**

**Your ability to reference the published literature as the sole source of evidence supporting your NDA is dependent on knowing the identity of the drug used in these studies. Therefore, the Division suggests the following approaches that could lead to approval of ephedrine sulfate injection:**

- **Revisit the literature, and obtain information from the publications and their authors about the exact form of ephedrine used in the clinical trials referenced in the literature. You will need to provide information about the stereoisomer, including its purity and its salt form. We understand that you will not be able to obtain this information for all clinical trials in the published literature. However, you must be able to provide this information for a sufficient number of studies that are of adequate design and conduct to support the safety and efficacy of your proposed indications and labeling claims.**
- **Design and conduct adequate and well-controlled clinical trials to support your proposed indication(s).**

Discussion:

The Sponsor stated that the majority of the selected published studies on ephedrine sulfate are 15 to 20 years old and, therefore, it would be difficult to determine the composition of the drug product used in those studies. Although the Sponsor was able to contact several of the study authors via email, they were unable to obtain additional information on the drug product composition used in those published studies. The Sponsor proposed contacting the ephedrine sulfate manufacturers who may have provided the study authors with the ephedrine sulfate drug substance used in the published studies. The Sponsor will attempt to obtain information on the composition and quality of the ephedrine sulfate manufactured and used during that timeframe. The Sponsor inquired about the adequacy of providing such information as a bridge between the composition of the drug product used in the published studies and their drug product. The Division replied that the information about the drug product would need to be provided at the level of the study and that the Sponsor must provide the composition of the ephedrine drug product. If the Sponsor can provide data that demonstrates that the drug substance used in each of the published studies started out as the (-) isomer, was pure and did not contain and other isomers, and remained pure throughout the study, the Sponsor may be able to establish a bridge to their drug product. The Sponsor would need to provide analytical data to demonstrate that the purity of the drug substance did not change over the course of the clinical studies.

The Division encouraged the Sponsor to broaden their literature search. Inclusion of more recent publications may facilitate the determination of the composition of the ephedrine sulfate drug product used in the study(ies). The Division also advised the Sponsor to consult with an anesthesiologist to help determine which references discovered in their search might contain useful information that might not be obvious from the titles, and to facilitate contacting study authors. Depending on the quality of the references, the Sponsor may only need a few well-documented studies of adequate design and conduct to support the safety and efficacy of the proposed indications and labeling claims.

The Sponsor inquired about what other options they should pursue if they are unable to adequately characterize the drug product composition used in the published studies. They also asked about conducting a bioavailability study with pharmacodynamic assessments. The Division responded that the Sponsor will need to provide data that are generalizable and inform about dosage and administration. Furthermore, the PK/PD relationship has not been characterized. Therefore, the Sponsor may need to design and conduct an adequate and well-controlled clinical trial or trials to support their proposed indication(s). The Division noted that the trial(s) would need to cover the use of ephedrine sulfate in the settings of both general anesthesia and neuraxial anesthesia. Trial design could be discussed and guidance provided to the Sponsor via teleconference, face-to-face meeting, or written responses, following receipt of the Sponsor's briefing document which should include the protocol synopsis(es). Dr. Roca noted, however, that given the apparent challenges of determining drug product composition and the nature of the ephedrine papers, the Sponsor will need to decide whether pursuit of the clinical trial pathway to approval might be easier than continued pursuit of a pure literature-based application.

Should the Sponsor decide to open an IND to conduct a clinical trial, no nonclinical studies for ephedrine will be required based on the extensive clinical experience with the drug product. However, the Sponsor would still need to provide relevant CMC information on the drug product to be used in any clinical trials.

**Post Meeting Note:**

It would help the CMC review team if you could perform a chiral HPLC analysis of available drug products that are currently being marketed and assess the levels of isomers of ephedrine sulfate that may be present. The results could be compared to the results from the analysis of your ephedrine sulfate injection product. This comparison can help establish a potential degradation profile for ephedrine sulfate injection and the potential levels of isomers of ephedrine that may be present in currently marketed products and those likely present in products used in previous clinical trials. Results from such a comparison may help formulate future recommendations for potential pathways in your drug development.

**Scope of the treatment indication**

The indication you have proposed, i.e., to treat (b) (4) anesthesia-induced hypotension in women 18 years of age or older undergoing Cesarean delivery, is too restricted in scope. Ephedrine sulfate injection has been used for the management of hypotension associated with other types of anesthesia (e.g., general and regional) and in the context of other surgical procedures and, if approved, is expected to be widely used. Such a narrow indication requires a justification based upon efficacy or safety data that demonstrate that the product should not be used in scenarios other than those you propose for the indication. In such a situation, the labeling would need to contain wording to restrict the use. Based on our current understanding of ephedrine, we suggest the following wording for your indication:

*...for increasing blood pressure in adults with clinically important hypotension in the setting of anesthesia.*

Discussion:

Discussion of the scope of the proposed indication focused on its impact on the pediatric assessment. Therefore, this discussion follows the Division's response to Question 10.

(b) (4)

## 2.1. Chemistry, Manufacturing and Controls (CMC)

### Question 1:

*Does the Agency have any comments regarding the acceptability of the proposed drug product specifications for use as a commercial product specification?*

### **FDA Response to Question 1:**

**Final acceptability of the drug substance and drug product specifications will be conducted during the NDA review. However, the specifications for the drug substance and drug product should include testing for chiral purity** (b) (4)

**using a validated analytical procedure.**

**Also note that the referenced DMF** (b) (4) **is for the hydrochloride salt of (-) ephedrine. Provide a letter of authorization to reference the DMF for the sulfate salt of the (-) ephedrine API to be used in the drug product.**

**From nonclinical pharmacology toxicology perspective, your proposal to qualify any drug substance impurities or drug product degradants that exceed ICH Q3A(R2) and Q3B(R2) qualification thresholds is appropriate. We remind you that, for the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. Unless otherwise justified, adequate qualification must include:**

- **Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay**
- **Repeat-dose toxicology study of appropriate duration to support the proposed indication**

No further discussion was needed.

### Question 2:

*Is the provision of 6 months of stability data for 3 registration batches adequate for the NDA to be filed?*

### **FDA Response to Question 2:**

**No, we do not agree. As per ICH Q1A(R2) Guidance for Industry: Q1A(R2) – Stability Testing of New Drug Substances and Products**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073369.pdf>, 12-months of data under long term storage conditions and 6-months of data under accelerated conditions for at least three batches, are expected at the time of submission. The proposal to provide 6-month stability data for three batches would not be sufficient to allow us to grant a commercially viable expiry period. Furthermore, we cannot guarantee review of any stability data submitted 6 months into the review cycle.

No further discussion was needed.

Question 3:

*Does the Agency agree with the strategy to not perform leachables testing on registration stability batches?*

**FDA Response to Question 3:**

We cannot provide a definitive response to this question since your meeting package does not clearly define the rubber formulation of the stopper or indicate which Master File includes that information, and the specific name for the vial proposed for use has not been provided. Leachables testing may not be required if you use a stopper with a rubber formulation deemed safe based on its extractable/leachable profile in an approved product with comparable drug product formulation characteristics. Your meeting package references the same formulation as that employed for your neostigmine drug product; however, the product code appears to be different and it is not clear what differences, if any, exist between these two products. As we noted previously, your NDA submission must contain information on potential leachables and extractables from the drug container closure system unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system should include specific assessments for residual monomers, solvents, polymerizers, etc.

Based on identified leachables you will need to provide a toxicological evaluation to determine the safe level of exposure via the label-specified routes of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). Many residual monomers are known genotoxic agents, therefore, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the following FDA guidance documents:

- **Guidance for industry, *Container Closure Systems for Packaging Human Drugs and Biologics - Chemistry, Manufacturing and Controls Documentation*, available**

at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf>

- **Guidance for Industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf>.**

For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure or be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day. The risk assessment should be based on the levels of leachables detected in long-term stability samples that include any intended primary container closure system(s) unless otherwise justified.

No further discussion was needed.

## 2.2. Nonclinical

### Question 4:

*Does the Agency agree that the summarized nonclinical information from the scientific literature contained in the briefing document appears to be sufficient for review to support the safety and efficacy of Ephedrine Sulfate Injection, USP, 50 mg/mL leading to approval?*

### **FDA Response to Question 4:**

The summarized nonclinical information from the scientific literature contained in the briefing document appears sufficient for review. However, the final determination of its adequacy to support the safety and efficacy of Ephedrine Sulfate Injection, USP cannot be determined until the review of your NDA application. As noted previously, based on the review of your meeting package, the referenced nonclinical genetic toxicology and reproductive and developmental toxicology literature still does not appear to be adequate to support labeling for your drug product. These studies will likely be required to be completed post marketing.

### **Additional Nonclinical Comments for your NDA submission:**

1. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

- 2. Impurities which are carcinogenic must be reduced to levels in the drug substance or drug product which would limit human exposure to NMT 1.5 mcg/day. Impurities which are genotoxic or contain a structural alert for genotoxicity must be reduced to this same level unless you provide adequate safety qualification. For an impurity with a structural alert for mutagenicity, an adequate safety qualification requires a negative in vitro bacterial reverse mutation (Ames) assay, ideally with the isolated impurity tested to the appropriate highest concentration of the assay as outlined in ICH S2(R1) guidance document entitled "Guideline on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use." Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified which may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.**
- 3. We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds or contains a structural alert and exceeds current standard levels without adequate safety qualification.**
- 4. Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**
- 5. The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.**

No further discussion was needed.

### **2.3. Clinical Pharmacology**

Question 5:

*... Because Éclat's ephedrine formulation is simple, containing only Ephedrine, USP, and water for injection, USP, Éclat does not believe that any minor differences in the formulations would have an impact on the bioavailability, safety, or efficacy of the ephedrine*

*injection. Éclat, therefore, believes that the requirements to demonstrate bioavailability of their product have been fulfilled and will submit a request to waive the requirement to conduct an in vivo bioavailability study in the NDA. Does the Agency agree?*

**FDA Response to Question 5:**

**Submit sufficient justification via literature and/or other source(s) to demonstrate that minor differences in you proposed formulations would not have an impact on the bioavailability, safety, or efficacy of the ephedrine injection. Whether a biowaiver will be granted will be determined after review of this information.**

No further discussion was needed.

**Question 6:**

*. . . Given that the Éclat ephedrine product contains only (-) ephedrine, Éclat concludes that it is appropriate to rely on these studies as evidence of safety and efficacy of their proposed product. Does the Agency agree?*

**FDA Response to Question 6:**

**We remind you of our comments in the PIND meeting on using literature data to support you NDA submission. Specifically, you will need to identify if there is any difference between the drug product (including both active moiety and formulation) used in literature and your proposed product, and provide an adequate rationale to explain why the study results in the literature apply to your product.**

**When selecting publications, ensure the references are primary sources describing original research. Provide a copy of the manuscripts from peer-reviewed journals. For example, the following reference is not a primary source:**



No further discussion was needed.

**2.4. Clinical**

**Question 7:**

*As suggested in the pre-IND meeting, Éclat engaged in a good-faith effort to obtain original study data from the authors of the clinical efficacy articles that will be cited in the NDA. A detailed description of these efforts is provided in Attachment 8, Section 2.7.3, Appendix 2.7.3.6.2, of the briefing document. Despite the efforts, Éclat was unable to obtain any additional information to include in the NDA. However, Éclat believes that the consistency*

*of the safety and efficacy findings across multiple studies and regions validates the safety and efficacy of Ephedrine Sulfate Injection, USP, 50 mg/mL for the proposed indications. Does the Agency agree?*

**FDA Response to Question 7:**

See our Introductory Comments for a discussion of the need for a bridge between your to-be-marketed product and the published literature.

Whether the literature is adequate to support your application will be determined upon submission and review of your NDA.

Regarding your efforts to obtain study data, you must include a description of your activity related to this in your NDA submission. You must also incorporate any data or supporting materials (e.g., original protocols) you obtain in your NDA submission.

No further discussion was needed.

**Question 8:**

*Does the Agency agree with the format and content of the ISS and ISE as outlined in the briefing document?*

**FDA Response to Question 8:**

The outline of your ISS and ISE provided in the briefing package is reasonable (b) (4). However, note that your discussion should also be organized according to type of anesthesia, surgical procedure, and method of administration (e.g., bolus versus infusion).

For the ISE, we recommend that you follow the draft guidance to industry: *Integrated Summary of Effectiveness*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>.

For the ISS, we recommend that you follow the reviewer guidance: *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf>.

For a NDA based on literature, we also recommend that you follow the appropriate sections in the Guidance to Industry: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf>.

**In addition, we acknowledge that the body of ephedrine literature is limited in quantity. However, your literature findings seem incomplete, which may be a result of your search methodology. The worldwide medical literature on ephedrine is not completely represented in review articles and meta-analyses. You must conduct a comprehensive search to support your risk/benefit analysis and proposed labeling.**

No further discussion was needed.

Question 9:

*Does the Agency agree that the clinical information contained in this briefing document appears to be sufficient for review to support the safety and efficacy of Ephedrine Sulfate Injection, USP, 50 mg/mL leading to approval?*

**FDA Response to Question 9:**

**No, we do not agree. Without the content of the ISS and ISE to review, we cannot determine that the clinical information you plan to provide is sufficient for review.**

**See our introductory comments for a discussion of the need for a bridge between your to-be-marketed product and the published literature and our response to Question 8 for comments on the adequacy of your literature search.**

No further discussion was needed.

Question 10:

*Please confirm the acceptability of the proposed strategy to meet the Pediatric Research Equity Act requirement.*

**FDA Response to Question 10:**

**We do not agree that pediatric studies of ephedrine sulfate injection should be waived; you will need to study ephedrine sulfate injection for hypotension in an age-appropriate pediatric model. However, should you wish to further pursue a waiver, you will need to provide evidence and justification for your assertion that a waiver or deferral for certain pediatric age cohorts should be granted based on the terms described in the guidance for industry: *How to Comply with the Pediatric Research Equity Act*, available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf>.**

Discussion:

The Sponsor inquired about the age-appropriate pediatric population in which to conduct studies to fulfill the PREA requirement. The Division advised the Sponsor to consult with pediatric anesthesiologists to determine the clinical context and limitations of ephedrine sulfate's use in pediatric patients. The Division also clarified that, while important for establishing safe use in obstetric populations, the published literature that includes safety data related to placental transfer of ephedrine sulfate would not provide

PREA-mandated safety and efficacy data in the neonatal population. Data from direct administration of the drug product to the pediatric population of patients will need to be submitted to satisfy the PREA requirement.

Question 11:

*Éclat proposes to include*

(b) (4)

**FDA Response to Question 11:**

(b) (4)

No further discussion was needed.

**3.0 Additional Regulatory Comments**

**PREA REQUIREMENTS**

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*, available at:

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

[CM360507.pdf](#). In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for Sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

## **505(b)(2) REGULATORY PATHWAY**

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

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

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

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

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

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

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

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

3. Example: NDA YYYYYY "TRADENAME"	Previous finding of safety for Carcinogenicity, labeling section XXX
4.	

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

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

#### **5.0 ACTION ITEMS**

1. The Sponsor will consider expanding their efforts to obtain information on the composition and quality of the drug product used in the selected publications using ephedrine sulfate to treat hypotension in the setting of anesthesia.
2. The Sponsor will consider broadening their search of relevant literature on ephedrine sulfate use to treat hypotension in the setting of anesthesia.
3. The Sponsor will consider consulting a pediatric anesthesiologist to help design their pediatric clinical trials.

#### **6.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting minutes.

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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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AYANNA S AUGUSTUS  
12/05/2013



PIND 116266

**MEETING MINUTES**

Èclat Pharmaceuticals, L.L.C  
c/o Beckloff Associates  
7400 West 110<sup>th</sup> Street, Suite 300  
Overland Park, Kansas 66210

Attention: Wayne F. Vallee, R.Ph., RAC  
Director, Managing Consultant

Dear Mr. Vallee:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ephedrine sulfate injection.

We also refer to the meeting between representatives of your firm and the FDA on December 19, 2012. The purpose of the meeting was to discuss the development program for ephedrine sulfate injection.

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

If you have any questions, contact me at [ayanna.augustus@fda.hhs.gov](mailto:ayanna.augustus@fda.hhs.gov) or, at (301) 796-3980.

Sincerely,

*{See appended electronic signature page}*

Ayanna Augustus, Ph.D.  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** PIND  
**Meeting Date and Time:** December 19, 2012  
**Meeting Location:** White Oak, Bldg 22, Room 1311  
**Application Number:** 116266  
**Product Name:** ephedrine sulfate injection  
**Indication:** (b) (4) the hypotensive (b) (4) anesthesia  
**Sponsor/Applicant Name:** Eclat Pharmaceuticals, L.L.C.

FDA Attendees	Title
Rigoberto Roca, M.D.	Deputy Division Director
Leah Crisafi, M.D.	Clinical Reviewer
Christopher Breder, M.D. Ph.D.	Clinical Team Leader
Dan Mellon, Ph.D.	Pharmacology/Toxicology Supervisor
Marcus S. Delatte, Ph.D.	Pharmacology/Toxicology Reviewer
Ramesh Raghavachari, Ph.D.	CMC Lead, ONDQA
Prasad Peri, Ph.D.	Branch Chief, ONDQA
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader
Ayanna Augustus, Ph.D.	Regulatory Health Project Manager
Martin Pollock, Pharm.D.	OSE/DPVII
Kimberly Lehrfeld	OSE/DRISK
Sponsor Attendees	Title
Michael Anderson	President and Chief Executive Officer; Éclat Pharmaceuticals, L.L.C.
Scott A. Macke	Vice President, Operations; Éclat Pharmaceuticals, L.L.C.
Wayne F. Vallee, R.Ph., R.A.C.	Director, Managing Consultant; Beckloff Associates, Inc.

## 1.0 BACKGROUND

Éclat Pharmaceuticals, L.L.C., has developed a sterile ephedrine sulfate injection, USP as a sterile 50 mg/mL solution for intravenous (b)(4) injection. Ephedrine sulfate is a sympathomimetic drug with mixed adrenergic agonist activity. The Sponsor plans to submit a 505(b)(2) application supported by nonclinical and clinical literature. The Sponsor does not plan to conduct any nonclinical or clinical studies for the NDA.

## 2.0 DISCUSSION

### 2.1. Chemistry, Manufacturing, and Controls

Question 1:

*Does the agency agree with the proposed drug substance and drug product specifications?*

**FDA Response:**

**We have the following comments on the specifications for drug substance and drug product.**

- 1. Clarify the exact stereoisomer used in the clinical trials referenced in the literature.**
- 2. The specifications proposed for the drug substance states R,S enantiomer; clarify if it is a pure enantiomer or a mixture.**
- 3. Clarify if you will have a chiral HPLC method for ephedrine impurities.**
- 4. Institute an orthogonal test for identity.**
- 5. We expect a HPLC method for the characterization and quantifications of related substances.**

No further discussion was needed.

Question 2:

*Does the agency agree with the proposed stability protocol for the drug product registration stability batches?*

**FDA Response:**

**Your proposed stability protocol appears to be acceptable.**

No further discussion was needed.

Question 3:

*Does the Agency agree with the proposed strategy of providing stability data as described during review of the submission?*

**FDA Response:**

**We do not agree. We expect at least 12-months, long-term stability data and 6-months accelerated stability data along with your supporting data.**

Sponsor's Response:

*Would submission of six months long-term and accelerated stability data in the NDA result in a refusal-to-file? If not, would we have the opportunity to provide additional data during the review cycle?*

Discussion:

The Division reiterated the expectation that all NDA applications must be complete at the time of submission. Any submissions that contains less than the required information needed to conduct a substantive review will be assessed for whether it can be filed at the time of submission. The Sponsor acknowledged the requirement and agreed to submit a complete NDA package which would include 12-month, long-term stability data.

## 2.2. Nonclinical

Question 4:

*Does the Agency agree that the representative summarized nonclinical information from the scientific literature contained in this briefing document appears to be sufficient for review to support the safety and efficacy of Ephedrine Sulfate Injection, USP, leading to approval?*

**FDA Response:**

**For a 505(b)(2) application that relies on information in the public domain, the referenced nonclinical literature does not appear to be adequate to support an NDA application. However, assuming a detailed review of the clinical safety database from the published literature does not suggest any unexpected toxicity, no nonclinical studies for ephedrine drug substance should be necessary to support an NDA application. Nevertheless, as the existing data do not appear to contain adequate information regarding the in vivo mutagenic potential and impact on reproductive and developmental toxicity of ephedrine, these studies may be necessary as post-marketing requirements (PMRs). Prior to the qualified nonclinical studies being submitted, the drug product will likely be labeled a Pregnancy Category C due to lack of adequate nonclinical reproductive and developmental toxicity data. Final determination of whether PMRs will be needed or not can only be provided upon detailed review of the referenced literature studies.**

**As your product will be administered via the intravenous (IV) route of administration and it does not appear to have been studied in humans, your IND submission must provide data to demonstrate blood compatibility and lack of adverse local tissue irritation prior to the initiation of clinical studies. This may be addressed via tonicity data and clinical use data in the published literature if you can provide data to show that the formulations tested in the literature are comparable to your proposed formulation and the lack of any apparent novel excipients via the IV route of administration in your proposed formulation. However, final determination of the adequacy of the submitted materials can only be provided at the time of NDA review.**

No further discussion was needed.

Question 5:

*Does the Agency agree that if, upon review, the information provided is deemed acceptable, no nonclinical studies would be required for approval?*

**FDA Response:**

**See response to Question 4 and the general nonclinical pre-NDA comments, provided in Appendix 1.**

No further discussion was needed.

### 2.3. Clinical

Question 6:

*Does the agency agree that the clinical information contained in this briefing document appears to be sufficient for review to support the safety and efficacy of Ephedrine Sulfate Injection, USP, leading to approval?*

**FDA Response:**

**Before we are able to comment on whether the clinical information provided in the briefing packet is adequate, we offer the following observations and suggestions regarding your proposed indications and dosing schema:**

1. **(b) (4) anesthesia is a more appropriate term than conduction anesthesia if your intent is to provide guidance for ephedrine dosing (b) (4).**
2. **The proposed indication listed in Part (3), “(b) (4) the hypotensive (b) (4) anesthesia,” seems to imply a treatment of hypotension and, as such, is not consistent with Part (4), *Dosage Form, Route of Administration, and Dosing Regimen*, which prescribes ephedrine doses (b) (4).**

3. Each dosing regimen for an injectable solution should specify method of administration, e.g., bolus or infusion.
4. In the dosing for [REDACTED] (b) (4) hypotension, you mention repeat ephedrine dosing, which suggests a treatment of hypotension. This constitutes [REDACTED] (b) (4) indication, and requires its own supportive evidence.
5. In the proposed dosing regimen for patients [REDACTED] (b) (4) of age or older, the circumstance for use of ephedrine that you specified (“...during surgery”) should also indicate the type of anesthetic [REDACTED] (b) (4).

Whether the literature and rationale are adequate to support your proposed indications can only be determined after review. However, preliminary assessment of the clinical summary reveals the following issues:

1. With few exceptions, the literature provided in the briefing package that discusses the efficacy or safety of ephedrine for [REDACTED] (b) (4) anesthesia-induced hypotension is specific to parturients. A rationale must be provided for extrapolating the data in parturients to the entire patient population for which you seek ephedrine’s approval.
2. Included throughout the clinical summary are references to literature regarding the use of ephedrine in the setting of general anesthesia. If your proposed indication is for ephedrine in the setting of [REDACTED] (b) (4) anesthesia, the data regarding ephedrine use with general anesthetics is not relevant.
  - a. Several of the trials upon which you propose to base your dosing regimen evaluated ephedrine for the [REDACTED] (b) (4) of hypotension during the induction of general anesthesia and, therefore, provide no support for the proposed dosing.
  - b. Similarly, “...the efficacy of ephedrine [REDACTED] (b) (4) -anesthesia-induced hypotension” is claimed on the basis of five controlled clinical studies, but only one of these five studies evaluated the efficacy of intravenous ephedrine for [REDACTED] (b) (4) -anesthesia-induced hypotension. Furthermore, the authors of the only study of [REDACTED] (b) (4) anesthesia-induced hypotension determined that intravenous ephedrine was not effective in [REDACTED] (b) (4) anesthesia-induced hypotension. Therefore, none of the five cited articles seem to support your efficacy claim.
3. The adverse events associated with ephedrine administration at the proposed doses are not adequately addressed in the clinical summary. [REDACTED] (b) (4)

*Summary of Ephedrine Safety Studies from*

**Literature), goes without mention in the safety summary. The safety of ephedrine at the proposed intravenous (b)(4) doses needs to be analyzed and discussed in detail to support your assessment of the risk-benefit profile of the proposed dose regimens.**

No further discussion was needed.

**Question 7:**

*Does the agency agree that if, upon review, the information provided is acceptable, no clinical studies would be required for approval?*

**FDA Response:**

**Clinical Comments**

**Whether your evidence is adequate to support the intended labeling will be a matter of review. It appears, on preliminary review of the briefing document, that the literature provided does not adequately support your proposed dosing and populations. We have provided several examples of this issue in our response to Question 6. A clinical trial will be needed in order to demonstrate safety and/or effectiveness if the proposed uses, routes, doses, or populations are not adequately supported by the literature.**

**Biopharmaceutics Comments:**

**As per 21 CFR 320.21(a), all NDA applicants are required to include in the NDA submission, either (1) evidence measuring the in vivo bioavailability of the proposed drug product that is the subject of the NDA or (2) information to permit FDA to waive the submission of evidence measuring in vivo bioavailability. Therefore, you must provide:**

- 1. Data from an in vivo bioavailability study using your product, or**
- 2. A request to waive the requirement to conduct an in vivo bioavailability study along with supporting information (i.e., pharmacokinetic (PK) or bioavailability data from the published literature and justification for the similarity, e.g., composition, osmolarity, pH, of the proposed drug product and the product(s) used in the published literature)**

**Clinical Pharmacology Comments:**

**It is generally acceptable to submit good quality publications addressing the clinical pharmacology of ephedrine sulfate considering the history of use and extensive clinical experience. However, final determination of the adequacy of the submitted materials will be a review issue at the NDA review stage. Publications should have an adequate description of bioanalytical validation and PK analysis criteria. Utilizing available publications or in-house clinical data, address the following and provide information as requested:**

1. **PK of ephedrine and its metabolites following IV (b) (4) administration**
2. **Bioavailability of ephedrine sulfate and its metabolites following (b) (4) administration**
3. **Important considerations for selection of publications describing PK of ephedrine:**
  - a. **We understand that ephedrine may exist as different enantiomers. In such a situation, pharmacokinetics of each enantiomer should be evaluated in the initial PK studies.**
  - b. **If the pharmacokinetic profile is the same for both isomers or a fixed ratio between the plasma levels of enantiomers is demonstrated in the target population, an achiral assay or an assay that monitors one of the stereoisomers should suffice for later evaluation.**
  - c. **Please refer to FDA's policy statement for the development of new stereoisomeric drugs at <http://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm>.**
  - d. **It is unclear whether the ephedrine isomer ratio is the same between your proposed product and the product(s) used in the literature. Therefore, you will need to provide adequate justification that the results from the literature can be used to support your proposed product.**
4. **It appears that a range of ephedrine doses may be administered. Provide dose-proportionality information across the proposed doses.**
5. **Limited metabolism of ephedrine based on in vitro metabolism studies or in vivo mass balance studies.**
6. **Provide information on drug-drug interactions.**
7. **From a safety perspective, provide dosage adjustment recommendation in the product label based on available publications or clinical data for the following special populations:**
  - a. **Patients with hepatic impairment**
  - b. **Patients with renal impairment**
  - c. **PK or PD drug interactions with respect to perioperative medications**

**d. Elderly patients**

**8. Address the risk of QT-prolongation by ephedrine using adequate published literature or clinical data for which you have a right of reference.**

**Sponsor's Response:**

***Are there any other areas, other than mentioned, where support of the dosing and populations is lacking?***

Discussion:

The Division noted that additional deficiencies exist in the submission, as the Sponsor did not provide either clear information on the proposed indication(s) and dosing schema, or a thorough analysis of the literature.

As an initial step in addressing the deficiencies, the Division offered two strategies for determining indications and finding support in the literature. The Sponsor might consider first identifying a clinically meaningful indication and then seek literature that supports the proposed indication. As an alternative strategy, the sponsor might first review the existing literature, and then decide what clinically meaningful indication(s) has/have the best support in the available literature. The NDA must contain a thorough analysis of how the literature supports the proposed indication.

**Post-meeting note:**

**The Division would like to emphasize that a complete review of the related literature was not performed in preparation for the meeting, and that it will be the Sponsor's responsibility to analyze the literature and identify its deficiencies prior to submitting the NDA. The Division, however, offers one specific example: the proposed dose of ephedrine in patients <sup>(b)(4)</sup> years of age is well outside of the range of doses used in the supportive literature provided, and it (and all other proposed doses) must be carefully considered before proposing dosing guidelines.**

**2.4. Regulatory**

**Question 8:**

***Please confirm the acceptability of the proposed application as a 505(b)(2) NDA.***

**FDA Response:**

**We agree that the 505(b)(2) regulatory pathway may be an appropriate approach for submission of an NDA for your product. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dockets/04p0231/04p-0231-c000001-Exhibit-29-vol4.pdf>)).

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

#### Clinical Comment

As was noted in the Clinical Pharmacology comments following Question 7, it is not clear whether the ephedrine isomer ratio is the same between your proposed product and the product(s) used in the literature. Therefore, you will also need to provide evidence that the results from the *clinical* literature can be used to support your proposed product from the perspective of the enantiomeric composition of the drug used in the references.

#### Sponsor's Response:

*It appears that the level of information requested from studies using clinical literature references is similar to that expected from sponsors conducting their own studies. We will try to obtain as much information, including protocols, as possible from the authors. Would FDA accept clinical literature references if such requested data was not available?*

#### Discussion:

The Division stated that the level of evidence required for approval of NDAs submitted via the 505(b)(2) and the 505(b)(1) pathway is the same. The Sponsor was informed that the literature may not provide all of the information needed to determine the safety and efficacy of the drug product, and may not enable the Division to conduct a risk/benefit assessment. The adequacy of the clinical literature provided in lieu of clinical data sets is a matter of review. In addition, the adequacy of any data submitted on the clinical use of the product to support the Sponsor's application would depend on the strength of the data provided, (e.g., data from testimonials would not be as supportive as clinical use data). The Sponsor should assess the strength of the literature references and available clinical data and determine if additional clinical studies may be needed to demonstrate the safety and

efficacy of their drug product for the proposed indication and to support product labeling.

The Sponsor agreed to document its efforts to obtain clinical data sets and protocols from authors and provide this documentation in their NDA. The Sponsor also agreed to provide integrated summaries of safety and efficacy and not simply a list of literature references. In addition, the Sponsor agreed to identify any deficiencies in the clinical data from the literature and provide a rationale for why the data support the proposed indication(s) and populations/sub-populations for which the product is intended for use.

Since it is unclear what stereoisomer of ephedrine sulfate was used in the clinical pharmacology studies and clinical trials referenced in the literature, the Sponsor must also provide justification for why data from cited literature is applicable to their drug product.

The Sponsor plans to submit a request for an End-of-Phase 2 (EOP2) meeting with the Division to obtain feedback from on the content of their NDA submission. The Sponsor should include in their EOP2 meeting package descriptions of the study designs and data summaries in a format consistent with an NDA application. For the clinical pharmacology study literature, the Sponsor should also review the bioanalytical section and include adequate description of bioanalytical validation. The need for a pre-NDA meeting will be determined at the conclusion of the EOP2 meeting.

*Question 9:*

*Please confirm the acceptability of the proposed strategy to meet the Pediatric Research Equity Act (PREA) requirement.*

**FDA Response:**

**We do not agree. Data from IMS's Inpatient HealthCare Utilization System reveals that ephedrine is used in pediatric patients. You will need to provide evidence for your assertion that a waiver should be granted based on the terms described in the Guidance for Industry How to Comply with the Pediatric Research Equity Act**

**<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf>**

No further discussion was needed.

## 2.5. Additional Comments

### CMC Comments

**Refer to the following guidance documents as you proceed with your IND and your NDA.**

1. **Guidance for Industry: *Content and Format of Investigational New Drug Applications (INDs) Including Well-Characterized, Therapeutic, Biotechnology-derived Products***  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf>
2. **Guidance for Industry: *INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information***  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070567.pdf> and the 21 CFR 312.23.
3. **Guidance for Industry: *Q3A (R) Impurities in New Drug Substances***  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>.
4. **Guidance for Industry: *Q3B (R2) Impurities in New Drug Products***  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>
5. **Guidance for Industry: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances***  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm134966.htm>
6. **Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation***  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070551.pdf>
7. **Guidance for Industry: *Q2A Text on Validation of Analytical Procedures***  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073381.pdf>.
8. **ICH guidance for industry, *Q2B Validation of Analytical Procedures: Methodology*, available at**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073384.pdf>.
9. **Guidance for Industry: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches***  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf>

### **Additional Clinical Comments**

**In each section of your NDA application, the discussion of studies should be grouped in the following manner; the following bulleting is not meant to correspond to the expected eCTD granularity format:**

- 1. Studies supporting Treatment of Hypotension**
  - 1.1. Bolus Administration**
    - 1.1.1. Neuraxial Anesthesia Setting**
      - 1.1.1.1. Obstetric population**
      - 1.1.1.2. Non-obstetrical surgical population**
      - 1.1.1.3. Other**
    - 1.1.2. General Anesthesia**
      - 1.1.2.1. Obstetric population**
      - 1.1.2.2. Non-obstetrical surgical population**
      - 1.1.2.3. Other**
  - 1.2. Infusion administration etc...**

**Important considerations in the submission of an application that relies upon literature are found in the guidance on providing evidence of effectiveness available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf>. Examples include the selected doses and indications, the quality of data, the types of data, and the quantity of data.**

**Access to complete protocols allows a more thorough evaluation of the adequacy of studies, and original data enables confirmation of study findings. Therefore, a greater emphasis can be placed on the findings of studies where this information is available and a diligent effort needs to be made to obtain protocols and original data for each study cited. Where Éclat is unsuccessful at obtaining critical study details, its efforts should be documented, and the NDA should include a rationale for why the existing literature alone is sufficient.**

**With respect to safety, considerations in providing evidence on the basis of published literature, while not explicitly covered in the effectiveness guidance, are similar, and include selected doses and indications, level of detail in published reports, and full accounting of all enrolled subjects. As much as possible, the NDA should make it easy for the Division to consider how the studies were designed to capture adverse events, the types and duration of monitoring, demographics of subjects evaluated, and their underlying medical conditions. In addition, a comparison of occurrence of adverse events with placebo or alternate doses of ephedrine is more informative than simple listings of adverse events noted during the administration of ephedrine.**

**In your summary outlines, you should include the following study data, as well as any other information you wish to convey:**

- 1. Study title, authors, and bibliographic data, hyperlinked to reference**
- 2. Population demographics**
  - a. Average and range of age**
  - b. Average and range of weight**
  - c. Gender**
  - d. Ethnicity**
  - e. Major comorbidities, with attention to the subjects' cardiovascular status**
- 3. Medical or surgical procedure performed**
- 4. Anesthetic technique and drug regimens**
  - a. Include intraoperative and post-operative medications including doses and adjustments**
  - b. Include other interventions affecting blood pressure, e.g. intravenous fluid boluses, changes in patient positioning**
- 5. Intraoperative events relevant to subjects' physiologic status, such as blood loss and fluids administered**
- 6. Treatment (reported per arm)**
  - a. Number of subjects**
  - b. Average treatment duration**
  - c. Total dose and range**
  - d. Initial dose and titration regimen**
- 7. Primary endpoint (defined *a priori*)**
- 8. Secondary and PK endpoints**
- 9. Method of primary analysis**
- 10. Efficacy results with tabular support as relevant**
  - a. Blood pressure and heart rate before, at the time of, and following administration of the study drug**

- b. Time to onset, maximal response, and cessation of effect**
  - c. Duration of response**
- 11. A brief statement characterizing the adequacy of the safety data for each study**
  - a. Tabulated safety data should list adverse event rates relative to the comparator**
  - b. Important but uncontrolled safety data should be subsequently summarized**
- 12. Your summary of the efficacy and safety data should include comments on the exposure or dose/response data.**

### **3.0 ADDITIONAL REGULATORY COMMENTS**

#### **PREA PEDIATRIC STUDY PLAN**

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

#### **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues that require further discussion.

### **5.0 ACTION ITEMS**

1. The Sponsor will include 12-month stability data in their NDA at the time of submission.
2. The Sponsor will address the quality of the literature submitted and will provide integrated summaries of safety and efficacy in their NDA submission.
3. The Sponsor will document all efforts to obtain clinical data sets and protocols from the authors of literature referenced in their NDA.
4. The Sponsor plans to request an EOP2 meeting.

## **6.0 ATTACHMENTS AND HANDOUTS**

These are standard comments given to all applicants at the pre-NDA stage of drug development. Read these comments carefully to determine the applicability of the comments to your drug development program, and address accordingly.

### **Additional Comments for Pre-NDA Stage of Drug Development**

#### **Nonclinical Comments**

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.
2. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.
3. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance for industry, *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients*.

As noted in the document cited above, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently **proposed level of exposure, duration of exposure, or route of administration.**” (emphasis added).

4. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICH Q3A(R2) and ICH Q3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
  - b. Repeat dose toxicology of appropriate duration to support the proposed indication.
5. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative *in vitro* bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICH S2A guidance document titled “Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.” Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.
  6. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICH Q3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.
  7. The NDA submission must contain information on potential leachables and extractables from the drug container closure system as outlined in the FDA Guidance for Industry titled “Container Closure Systems for Packaging Human Drugs and Biologics.” The

evaluation of extractables and leachables from the drug container closure system must include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents “Container Closure Systems for Packaging Human Drugs and Biologics” and “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation.” Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at [http://www.pqri.org/pdfs/LE\\_Recommendations\\_to\\_FDA\\_09-29-06.pdf](http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf).

8. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

### **Chemistry, Manufacturing and Control (CMC) Comments**

1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
2. Include at least 12 months of real time data and 6 months of accelerated data in the NDA.
3. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.
4. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.
5. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and

trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

**The Abuse Potential section of the NDA is submitted in the eCTD as follows:**

*Module 1: Administrative Information and Prescribing Information*

1.11.4 Multiple Module Information Amendment

This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (nonclinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

*Module 2: Summaries*

2.4 Nonclinical Overview

This section should include a brief statement outlining the nonclinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

*Module 3: Quality*

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

*Module 4: Nonclinical Study Reports*

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence

This section should include:

- A complete discussion of the nonclinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

*Module 5: Clinical Study Reports*

5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

**General Clinical Comments**

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events
4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions
7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

**Sites for Inspection**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested, as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

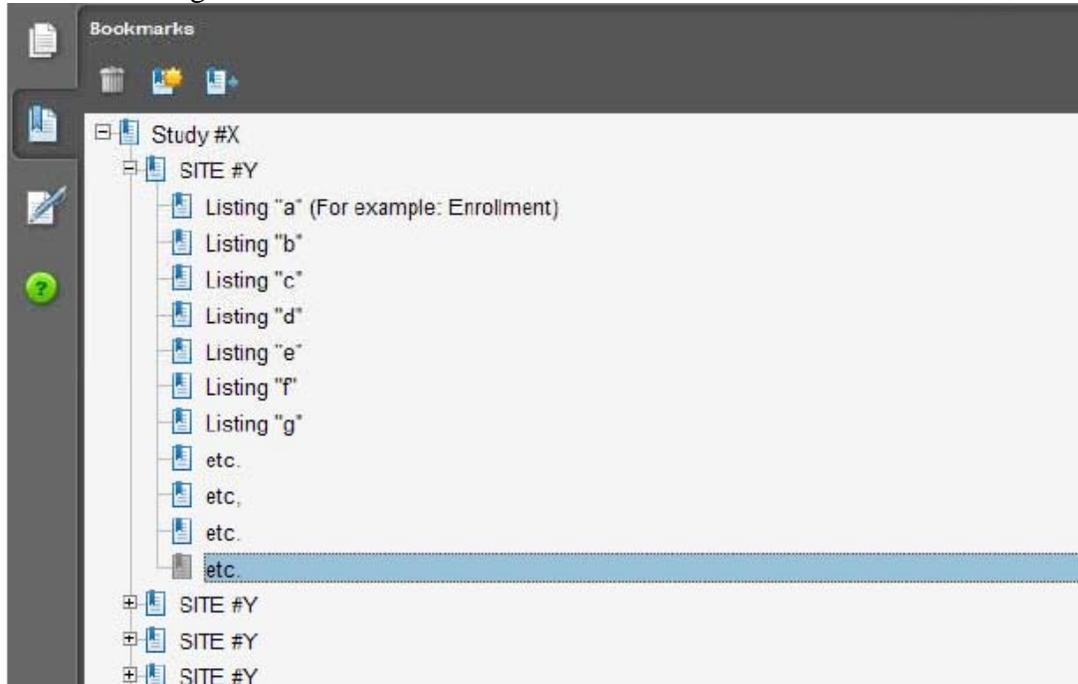
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Subpart 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

**I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Number of subjects screened for each site by site
  - b. Number of subjects randomized for each site by site, if appropriate
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
  - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
  - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
  - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
  - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

**II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
  
2. We request that one PDF file be created for each pivotal Phase 3 study using the following format:



### III. Request for Site Level Dataset

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OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Subpart 1, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

## Subpart 1

### 1. Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

#### 1.1. Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

#### 1.2. Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

#### *Site-Specific Efficacy Results*

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

**Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)**

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

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Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

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Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

**Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)**

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

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MINITAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

**Subpart 2**  
**Technical Instructions:**  
**Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clnsite.xpt.”

<b>DSI Pre-NDA Request Item<sup>1</sup></b>	<b>STF File Tag</b>	<b>Used For</b>	<b>Allowable File Formats</b>
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>

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FDA eCTD web page  
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

## **Pediatric Plan**

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

## **Common PLR Labeling Errors**

### **Highlights:**

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)
7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]
12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
15. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

**Contents (Table of Contents):**

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
20. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy  
8.3 Nursing Mothers (not 8.2)

8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)

21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Full Prescribing Information (FPI):**

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
24. Do not refer to adverse reactions as “adverse events.” Refer to the guidance for industry, *Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>  
:
25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)].
28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under

the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.

30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
32. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. See guidance for industry, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements*. The same applies to PPI and MG.
33. For fictitious examples of labeling in the new format, refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
34. For a list of error-prone abbreviations, symbols, and dose designations, refer to the Institute of Safe Medication Practices’ website, <http://www.ismp.org/Tools/abbreviationslist.pdf>

### **SPL Submission**

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); guidance for industry, *Providing Regulatory Submissions in Electronic Format – Content of Labeling*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email [spl@fda.hhs.gov](mailto:spl@fda.hhs.gov) for individual assistance.

### **Integrated Summary of Effectiveness**

Please refer to the guidance for industry, *Integrated Summary of Effectiveness*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

Please refer to guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

## **CDER Data Standards Reference Guide/Checklist**

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

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

### **Dataset Comments**

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
  - b. Study/protocol number
  - c. Patient's treatment assignment
  - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
  - e. Dosing at time of adverse event
  - f. Dosing prior to event (if different)
  - g. Duration of event (or start and stop dates)
  - h. Days on study drug at time of event
  - i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
  - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
  - k. Marker for serious adverse events
    - l. Verbatim term
2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.
  3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the

MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.

4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the *ICH MedDRA Term Selection: Points to Consider* document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
13. All datasets must contain the following variables/fields (in the same format and coding):

- a. Each subject must have one unique ID across the entire NDA
  - b. Study number
  - c. Treatment assignment
  - d. Demographic characteristics (age, race, gender, etc.)
14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.
15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
16. For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
17. With reference to the table on the following page, note that the HLG and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLG terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

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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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AYANNA S AUGUSTUS  
01/10/2013