CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204300Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204300	NDA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: Vazculep Established/Proper Name: phenylephrine HCl Dosage Form: injection		Applicant: Eclat Pharmaceuticals, LLC Agent for Applicant (if applicable): The Weinberg Group, Inc.
RPM: Kim Compton		Division: DAAAP

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

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

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

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 6/23/14

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 8/6/14	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR on 4/28/14
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

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

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

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 5
(confirm chemical classification at time of approval)

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

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

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

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

Comments:

❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ **Verified** ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ **Included**
Documentation of consent/non-consent by officers/employees	☒ **Included**

Action Letters

❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) **CR (original 1)- 4/28/14; and AP (original 1)- 6/27/14**

Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ **Included**
• Original applicant-proposed labeling	☒ **Included**
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ **Medication Guide** ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ **Included**
• Original applicant-proposed labeling	☐ **Included**
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ **Included**
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	**9/13/13** **9/13/13**
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None **9/6/13** DMEPA: ☐ None **2/13/14** DMPP/PLT: ☒ **None** OPDP: ☐ None **4/16/14** SEALD: ☐ None **4/17/14** CSS: ☒ **None** Other: ☒ **None**
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	**RPM Filing Rvw-9/6/13 (of resubmission); 4/9/13 (filing of original)** ☐ Not a (b)(2) **6/23/14; 4/2/14**
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ **Included**
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC **3/5/14** If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	**Various**
❖ 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	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ **N/A** or no mtg **6/3/14 (written responses only)**
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ **No mtg**
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg **9/27/12**
• Mid-cycle Communication *(indicate date of mtg)*	☒ **N/A**
• Late-cycle Meeting *(indicate date of mtg)*	☒ **N/A**
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	**PIND mtg—11/17/11; Type A mtg #1—1/30/13; Type A mtg #2—6/13/13**
❖ Advisory Committee Meeting(s)	☒ **No AC meeting**
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None **6/27/14 (cycle 2); 4/28/14**
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None **6/23/14 (cycle 2), combined with Clinical memo; 4/7/14**
PMR/PMC Development Templates *(indicate total number)*	☐ None **4 PMRs + 2 PMCs**
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	**See combined CDTL/CLIN Rvw (cycle 2); 3/20/14; 8/26/13 (filing of resubmission); 4/4/13 (filing of original)**
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	**See Clinical Review dated 3/20/14, page 15**
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None **Peds Review—2/10/14; Maternal Hlth Rvw—2/10/14 (labeling recommendations-see labeling rvw section)**

	DBRUP Cnsltv Rvw--1/30/14 **Drug Use Review-- 2/6/14**
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ **N/A**
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ **None**
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested **1/22/14**
Clinical Microbiology ☒ **None**	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ **No separate review**
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ **No separate review**
Statistical Review(s) *(indicate date for each review)*	☐ None **12/30/13**
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ **No separate review**
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ **No separate review**
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ **None 3/20/14; 8/26/13 (filing of resubmission); 3/28/13 (filing of original)**
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ **None requested**
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ **No separate review**
• Supervisory Review(s) *(indicate date for each review)*	☒ **No separate review**
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None **6/18/14 (cycle 2); 3/20/14; 8/7/13 (filing of resubmission); 3/26/13 (filing of original)**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ **None**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ **No carc**
❖ ECAC/CAC report/memo of meeting	☒ **None** Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ **None requested**

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ **No separate review**
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ **No separate review**
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None **Quality—6/17/14; 6/18/14 (cycle 2); 3/20/14; 8/26/13 (filing of resubmission); 2/28/13 (filing of original)** **Biopharm: 8/26/13 (filing of resubmission); 3/27/13 (filing of original)**
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)*	☐ Not needed **3/12/14; 8/5/13 (filing of resubmission); 2/28/13 (filing of original)**
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ **None**
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	**See Quality Review dated 3/20/14, page 6**
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: **DATE; 6/6/14** ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ **Not needed (per review)**

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

KIMBERLY A COMPTON
06/30/2014

EXCLUSIVITY SUMMARY

NDA # 204300/original 1 SUPPL # HFD #

Trade Name Vazculep

Generic Name phenylephrine HCl

Applicant Name Eclat Pharmaceuticals, LLC

Approval Date, If Known 6/27/14

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☐ NO ☒

The application contains only published literature to support the indication. The applicant did not conduct any clinical studies to support the safety and efficacy of this product.

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

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

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

NDA

NDA 203826	Phenylephrine Hydrochloride Injection, 10 mg/mL
NDA 205388	Ketorolac tromethamine; phenylephrine hydrochloride

Discontinued NDAs

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

Marketed, OTC product

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

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☒

The application contains only published literature to support the indication. The applicant did not conduct any clinical studies to support the safety and efficacy of this product.

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously

approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

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

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

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kim Compton
Title: Sr. Regulatory Project Manager
Date: 6-24-14

Name of Office/Division Director signing form: Rigoberto Roca, MD
Title: Deputy Division Director; application signatory authority

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

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

/s/

KIMBERLY A COMPTON
06/26/2014

RIGOBERTO A ROCA
06/27/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204300/Original 1

ACKNOWLEDGE -
CLASS 1 COMPLETE RESPONSE

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

Attention: Marla E. Scarola, MS
Senior Consultant, The Weinberg Group, Inc.

Dear Ms. Scarola:

We acknowledge receipt on June 6, 2014, of your June 6, 2014, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for VAZCULEP (phenylephrine hydrochloride) Injection, 10 mg/mL.

We consider this resubmission a complete, class 1 response to our action letter. Therefore, the user fee goal date is August 6, 2014.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

KIMBERLY A COMPTON
06/13/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Tuesday, June 03, 2014 11:11 AM
To: Marla Scarola
Cc: Sullivan, Matthew; Compton, Kimberly
Subject: RE: NDA 204300/Original 1: Questions re response to CRL

Hi Marla,

We have the following replies to your 3 questions below.

1. As the Agency is aware, Éclat sources phenylephrine hydrochloride API from (b) (4) On (b) (4) received a Warning Letter for issues at its manufacturing facility. Following receipt of the Warning Letter, (b) (4) corresponded with the FDA regarding the design and implementation of a corrective actions plan. FDA then returned to (b) (4) for a re-inspection of the facility on (b) (4). This inspection resulted in the issuance of a 483 with three observations. According to discussions with (b) (4), the recent re-inspection of the facility found (b) (4) to have made substantial progress on the Warning Letter commitments and the noted observations were not repeat issues from either earlier inspections or the Warning Letter. Furthermore, (b) (4) submitted a response to the recent 483 to FDA on (b) (4) to fully address all of the deficiencies noted at the most recent inspection. Éclat also notes that throughout this entire period (b) (4) has been allowed to continue to sell approved product and has not been banned from (b) (4)

   Further, (b) (4) has provided Éclat with assurances that phenylephrine hydrochloride API was not impacted by the issues cited in the Warning Letter; regardless, remediation activities have been implemented for all (b) (4)-manufactured APIs and we believe these afford a continued improvement of cGMP compliance of the phenylephrine hydrochloride API. In addition, Éclat continues to conduct release testing on the drug substance to ensure that it meets all acceptance criteria.

   On April 28, 2014, Éclat received a Complete Response Letter for NDA 204300/Original 1 with the following sole deficiency:

   > "During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

   Thus, it is Éclat's belief that with (b) (4) submission of the response to the recent 483 and the additional quality assurances in place, the deficiencies have been satisfactorily resolved. Éclat proposes to resubmit NDA 204300/Original 1 immediately. Does the Agency agree that a resubmission at this time is approvable?

   FDA Response
   Regarding the facility inspections element of the Complete Response action, the current status of the implicated facility does not prevent your response to the Complete Response action, however, we recommend that you respond to the Complete Response action at a point when (b) (4) has been notified by FDA that the observed deficiencies have been resolved.

2. In the Complete Response Letter issued for NDA 204300/Original 1, FDA requested a safety update be included in the resubmission. Éclat proposes to prepare a stand-alone clinical safety update report similar to that which was submitted 120 days after the original NDA submission (please refer to SN0009 submitted on October 25, 2013). We propose to conduct a PubMed search to identify literature reporting adverse events (AEs) associated with the use of phenylephrine hydrochloride. The search, covering literature published after October 11, 2013 (the date of the 120-day safety update search), will be focused on identifying clinical trials and case reports in which phenylephrine was delivered intravenously. Is this approach acceptable?

   FDA Response
   Yes, your approach is acceptable.

3. It is Éclat's understanding that resubmission of NDA 204300/Original 1 would be categorized as a Class 1 resubmission and would thus have a 2 month review goal under PDUFA V. Is that correct?

   FDA Response
   As it currently stands, your response would be classified as a Class 2 resubmission with a 6 month goal date as all manufacturing facilities listed in the application will require a current CGMP evaluation at the time of resubmission. Our evaluation may determine that inspections are needed in order to find facilities in current compliance with CGMP and take action on the application.

I will archive a copy of this email to document the interaction and advice provided.

Thanks
Kim

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Tuesday, June 03, 2014 9:59 AM
To: Sullivan, Matthew
Cc: Compton, Kimberly
Subject: RE: NDA 204300/Original 1: Questions re response to CRL

Hi Matt,

Sorry for the barrage. I left you a voicemail on this as well. Éclat was informed by their API manufacturer that the manufacturing site is now classified as acceptable by the FDA. We would like to resubmit the NDA as soon as possible, but require the Division's guidance on the format of the safety update. Would you please provide the Division's responses to Questions 2 and 3?

Best,
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

From: Marla Scarola
Sent: Thursday, May 29, 2014 10:03 AM
To: Sullivan, Matthew
Cc: Compton, Kimberly
Subject: RE: NDA 204300/Original 1: Questions re response to CRL

Hi Matt,

Do you have an update from your internal meeting regarding when we can expect the written responses and if we can get a teleconference on the calendar?

Thanks,
Marla

Marla E. Scarola, M.S.
Senior Consultant
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From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Wednesday, May 21, 2014 02:16 PM
To: Sullivan, Matthew
Cc: Compton, Kimberly
Subject: FW: NDA 204300/Original 1: Questions re response to CRL

Hi Matt,

I wanted to be sure that you received my email to Kim this morning. This is in regards to the responses to questions submitted in a Type A meeting request to NDA 204300 on 5/13. Kim had agreed to provide written responses this week and a follow-up teleconference, if necessary. Please let me know if you have any questions.

Thanks,
Marla

Marla E. Scarola, M.S.

Senior Consultant

The Weinberg Group

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Washington, DC 20036

P +1 202.730.4129

F +1 202.833.7057

weinberggroup.com

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Friday, May 09, 2014 9:55 AM
To: Compton, Kimberly
Subject: NDA 204300/Original 1: Questions re response to CRL

Hi Kim,

Long time, no talk after the flurry of activity around the PDUFA date! I hope you're well. Éclat is considering requesting a Type A meeting to discuss the path to getting NDA 204300/Original 1 (treatment indication) approved. We've prepared the attached meeting request letter that will be formally submitted to the NDA on Monday. Would you mind taking a look and letting me know if a formal meeting is necessary to answer these questions or if you could simply answer them for us via email? If a meeting is necessary, do you have an idea of timing? We're requesting a teleconference. Please let me know if you need any additional information.

Best,
Marla

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<image001.gif>

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/s/

KIMBERLY A COMPTON
06/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204300

DISCIPLINE REVIEW LETTER

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

Attention: Marla E. Scarola, M.S.
Senior Consultant, The Weinberg Group, Inc.

Please refer to your June 28, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenylephrine Hydrochloride Injection, 1%, USP.

We also refer to your amendments dated January 6, February 12 and 13, March 7, 11, and 24, 2014.

Our review of the clinical section of your submission is complete, and we have identified the following deficiencies:

(b) (4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kimberly Compton, Sr. Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, MS
Supervisory 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/

MATTHEW W SULLIVAN
04/04/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, April 04, 2014 5:34 PM
To: Marla Scarola (Marla.Scarola@weinberggroup.com)
Cc: Compton, Kimberly
Subject: items for N 204300

Hi Marla,

Many of the preliminary reviews are starting to roll in for this NDA and so we are now in a position to issue discipline review (DR) letters. As I am sure you know, the DR letters simply list out the deficiencies noted in the reviews so that the firm can remain informed as to what the Agency is finding during the review of the application. Right now I have one based on the clinical review. An e-copy is attached.

In addition, we have some requests from the nonclinical folks for post-marketing requirements to address some items they feel are needed for the product as well. I am attaching them also and if the firm would like we can have a short call to discuss/clarify them as needed next week. We would need the firm to agree to these and provide dates when the requested items would be submitted in an amendment to the application.

I also soon expect to be able to send you the labeling, marked up again from our team. They looked at the version Eclat sent back to us and have a few replies to queries in that were included for us, additional edits on sections that were not worked on before, and also marked it up to reflect the issue noted in the clinical DR letter. I am just waiting on the final clearance of that.

Have a nice weekend,
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
Please consider the environment before printing this e-mail. If you decide to print, please make double-sided copies.

PMR 1

Conduct a fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.

Final Protocol Submission:

Study Completion:

Final Report Submission:

PMR 2

Conduct an embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.

Final Protocol Submission:

Study Completion:

Final Report Submission:

PMR 3

Conduct an embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.

Final Protocol Submission:

Study Completion:

Final Report Submission:

PMR 4

Conduct a peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

Final Protocol Submission:

Study Completion:

Final Report Submission:

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/s/

KIMBERLY A COMPTON
04/04/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, March 14, 2014 6:49 PM
To: Marla Scarola (Marla.Scarola@weinberggroup.com)
Cc: Compton, Kimberly
Subject: First draft of marked-up Phenylephrine PI

Hi Marla,

As I mentioned earlier, attached please find a very early draft showing some mark-ups (in tracked changes) to the proposed phenylephrine PI for N 204300.

We request that the firm go over the notes and proposed change shown and accept whatever they are OK with (so it would then show as normal text) and place any notes or counter proposals for items they are not willing to accept marked in tracked changes and save the doc in WORD format and send it back to me via email by COB Wed March 19 so we can look at the firm's position and keep moving forward in these negotiations.

I also need to emphasize that this is early in the process, reviews have not yet been completed and the signatory authority has not reviewed or cleared this version of the PI, we are simply using this as a starting point for labeling discussions while we continue to review the application. We also note that some sections of the label are still under review by the team on this end (you will see several notes to that effect in the document.)

Please let me know if you have any questions.

Thanks,
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
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13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KIMBERLY A COMPTON
03/24/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Monday, March 24, 2014 1:03 PM
To: Marla Scarola (Marla.Scarola@weinberggroup.com)
Cc: Sullivan, Matthew; Compton, Kimberly
Subject: N 204300 pediatric studies

Hi Marla,

We took the request for pediatric waiver submitted in the Eclat NDA for Phenylephrine (N 204300) to the PeRC team [redacted] (b) (4).

Instead they recommended that Eclat revise their pediatric plan as follows:

1. **Submit a revised request for a waiver of studies in pediatric patients from 0 to <12 years, with a justification for waiver.**

2. **Submit a request for a deferral for pediatric studies from age 12 to 16 years. The studies in this age group will include pharmacokinetics, efficacy and safety. We provide the following recommendations:**

[redacted] (b) (4)

(b) (4)

3. **Your revised plan must include a timeline for the required studies. The PeRC and Division suggest the following dates:**
   Final Protocol Submission: April 28, 2015
   Trial Completion: April 28, 2018
   Final Report Submission: November 1, 2018

Please let me know if you have any questions on this and when you believe you will be able to submit it.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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/s/

KIMBERLY A COMPTON
03/24/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, March 19, 2014 7:57 PM
To: Marla Scarola
Cc: Compton, Kimberly
Subject: RE: CMC issue as discussed in TC

Hi Marla,

This seems reasonable to our CMC team. Please submit the proposal to the NDA with a timeline included.

Thanks
Kim

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Tuesday, March 18, 2014 10:24 AM
To: Compton, Kimberly
Subject: RE: CMC issue as discussed in TC

Hi Kim,

Before setting a stability specification for sodium metabisulfite, Éclat would like to generate a full 24 months of stability data on the validation batches. Given the planned timing of validation batch manufacture, Éclat proposes the following (I've highlighted the changes from the Agency's proposal in red):

Based on available release data, Éclat commits to tighten the currently proposed tentative release acceptance criteria (b) (4) for the content of sodium metabisulfite in the drug product (b) (4) by March 1, 2015.

Éclat commits to establish final, data-based stability acceptance criteria for the content of sodium metabisulfite in the drug product (b) (4) by Oct 1, 2016.

(b) (4)

(b) (4)

(b) (4)

Furthermore, an evaluation of trends in sodium metabisulfite content in the context of changes in pH and impurity levels as well as impact of storage orientation will be included in the summary report as described in the response to Item 5 from the February 28, 2014 information request (please refer to 1.11.4.2 in SN0034 submitted on March 11, 2014). This report is scheduled to be submitted in March 2015 and updated in the Annual Report.

Please let me know if this proposal is acceptable or if you would like to discuss further.

Best,

Marla

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weinberggroup.com

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Friday, March 14, 2014 4:03 PM
To: Marla Scarola
Cc: Compton, Kimberly
Subject: CMC issue as discussed in TC

Hi Marla,

As we discussed in the teleconference this morning, assuming the application is approved in this review cycle, the CMC review team will be recommending the following be completed as a post-marketing commitment (PMC) to address the control strategy of sodium metabisulfite in the drug product:

Eclat commits to establish final, data-based acceptance criteria for the content of sodium metabisulfite in the drug product (b) (4) **by Oct 1, 2015.**

The currently proposed tentative release acceptance criteria (b) (4) **will be tightened, based on available release data, and the stability acceptance criteria will be established based on available stability data.**

(b) (4)

Please review and let us know if Eclat can commit to this.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and

Addiction Products
301-796-1191

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, March 19, 2014 7:55 PM
To: Marla Scarola
Cc: Compton, Kimberly
Subject: RE: NDA 204300: Leachables assessment update

HI Marla,

This proposal is acceptable from the CMC perspective.

Please include in the NDA amendment a statement that the results for leachable testing performed on samples at the expiry date will be submitted in the first annual report. If all results for (b) (4) are negative you don't need to include specificationss for leachables into the stability protocol.

Definitely we would want this as soon as possible and I appreciate you reminding us that with the vendor time added in, it can take longer to submit items to us. Therefore, yes, please email it to us as soon as it is ready and then follow it up with the official submission as soon as possible so we can complete reviews on this end.

Thanks
Kim

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Wednesday, March 19, 2014 2:19 PM
To: Compton, Kimberly
Subject: NDA 204300: Leachables assessment update

Hi Kim,

Éclat had already developed a validated method for detecting (b) (4)) for their neostigmine methylsulfate product (NDA 204078). Preliminary testing has shown that this same method is successful in detecting the (b) (4) The next steps towards generating the necessary data include (b) (4)

Assuming that the specificity protocol and sample analyses are completed without issue, Éclat should receive the final data by next Friday (3/28). We may be able to move this up a day or two; I'll keep you updated.

I would like to note that, as expected, (b) (4)

I would appreciate your guidance as to how best to handle the submission of the leachables data. As I believe I've mentioned, we use a vendor for publishing of the electronic submissions that adds at least a day on to our

timeline. If it would help, we can provide you with an email summary and the final data in advance of the official submission. For the submission, we intend to revise 3.2.P.2.4 to include a brief summary of the analysis that was conducted and a link to the report. Please let me know if you have any questions or concerns with that approach.

Best,
Marla

Marla E. Scarola, M.S.
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The Weinberg Group
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weinberggroup.com

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Tuesday, March 18, 2014 5:26 PM
To: Marla Scarola
Subject: RE: CMC issue as discussed in TC

Hi Marla,

Regarding the other issue we discussed in Friday's TC, the leachables (b) (4) the team has asked that Eclat provide us their response regarding the leachables issue and how they intend to approach it by tomorrow, Wed, March 19 at 4 PM so we can determine if this issue is resolved to our satisfaction or further discussion is needed. Our reviewers need to finalize their primary reviews by Thursday so we are down to the wire here.

Thanks
Kim

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/s/

KIMBERLY A COMPTON
03/19/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, February 28, 2014 6:08 PM
To: Marla Scarola (Marla.Scarola@weinberggroup.com)
Cc: Compton, Kimberly
Subject: Information Requests for N 204300

Hi Marla,

As I mentioned earlier this week, we have the following requests for additional information for N 204300.

As we are getting very near the end of the time in our review cycle for primary reviews to be complete, we are putting a short turnaround time on this. We request complete responses no later than 4 PM on Tues March 11, 2014.

As we are so near the end of our allotted time to review this and we'd like to minimize back and forths, we will make ourselves available for a TC to discuss the items and timing if you think that would be valuable. Please let me know if you'd like to pursue this and I will get it set up.

CMC Items:

1. We remind you of your agreement submitted to the NDA in an amendment dated January 6, 2014, to [redacted (b) (4)] in the drug product, and therefore request the following:

    a. Provide specifications with [redacted (b) (4)] in the drug product. [redacted (b) (4)]

    b. Submit a revised specification sheet for drug substance to include method(s) and interim acceptance criteria for limits on [redacted (b) (4)]. You may provide a footnote explaining that the proposed acceptance criteria may be revised as more commercial-scale data are available and complete method validation is finalized, which is anticipated by e.g., March 20, 2015.

2. As requested in the Agency Information Request dated December 6, 2013, submit revised specifications for the drug product,. The acceptance criteria should include interim limits for every attribute needed for a safety risk assessment for this intravenous product and the proposed limits should be supported by the collected data. In particular, include the following items in the drug product specification sheet:

    a. Specifications for the content of sodium metabisulfite. You may provide a footnote explaining that the proposed acceptance criteria are interim and might be revised as more commercial-scale data are available and complete method validation is finalized, which is anticipated by e.g., March 20, 2015. [redacted (b) (4)]

b. Tighten the acceptance criteria for pH to reflect the agreement provided in NDA amendment dated January 6, 2014.

c. Tighten the acceptance criteria for individual and total impurities to reflect the agreement provided in NDA amendment dated January 6, 2014.

(b) (4)

e. Include data-based acceptance criteria for osmolality.

3. We remind you to submit the results of in-use stability studies performed in response to comment #5, in Agency requset dated December 6, 2013. We acknowledge your progress report in NDA amendment dated February 13, 2014.

4. Submit revised stability protocol for the drug product to include the following:

a. (b) (4).

b. Method and interim acceptance criteria for content of leachables (b) (4). Provide supportive data to justify the proposed limits. We note your statement in the Pharmaceutical Development section of the NDA concerning the potential leachables (b) (4) however, no data documenting (b) (4) was provided.

c. Acceptance criteria for Osmolality until adequate manufacturing experience for commercial scale is established.

d. Storage in both orientation (b) (4) until adequate manufacturing experience for commercial-scale batches is gained and the comparability of data in each storage orientation is established.

5. Your response to comments #8 and #9, from the Agency request dated December 6, 2013, needs additional follow-up. (b) (4)

(b) (4)

6. The following comments pertain to the proposed draft labeling. Additional comments will be provided from the Division of Medication Error Prevention and Analysis (DMEPA—see below.)

    a. [redacted]. Express the concentration in mg/mL, i.e., Vazculep (phenylephrine hydrochloride) Injection, 10 mg/mL

    b. Add a statement "Must be diluted" for all labels. Since this statement pertains to the drug product safety we recommend prominent and different color fonts on the front panels of the cartons and on the immediate vial labels (see related DMEPA comment below.)

    c. Add information about the drug product manufacturer, e.g., Manufactured [redacted]… For Eclat… We recommend moving the manufacturing information to the side panel in order to provide additional space on the front panels.

DMEPA items:

Vial Labels

1. The 1 mL vial label uses the abbreviation "IV" which is listed on Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations. [redacted] with the word "intravenous" for clarity.

2. The 1 mL vial is meant as a single dose configuration; therefore, [redacted] to two statements "For Intravenous Use" and "Single Dose Vial".

3. The Éclat logo is the most prominent statement on the 5 mL and 10 mL vial labels. To help ensure that the proprietary name, established name, and strength statements are the most prominent information on the label, [redacted] as the required manufacturing information is listed on the bottom portion of the Principal Display Panel (PDP).

4. To improve readability, revise the presentation of the proprietary name from all capital letters "VAZCULEP" to title case "Vazculep".

5. The net quantity statements (1 mL, 5 mL, and 10 mL) appear in close proximity to the strength statements, which create clutter and may be confusing. Relocate the net quantity statements away from the strength statements, such as to the bottom portion of the PDP.

6. The Rx only statement appears in close proximity to the strength statements, which creates clutter. Minimize the size of the Rx only statement and relocate it away from the strength statements, such as to the top right portion of the PDP.

7. To ensure that the proprietary name, established name, and strength statements are the most prominent on the label, decrease the size of the manufacturing information. Additionally, to decrease clutter, [redacted] as per small label rules in 21CFR 201.10(i), since the information appears on the carton labeling.

8. As per 21CFR 201.17 and 21CFR 201.18, please indicate where the required lot number and expiration date will appear on the labels.

9. The Phenylephrine Hydrochloride USP monograph does not require the use of the 1% strength on labels and labeling. Additionally, to minimize the chance of a wrong strength error, the total drug content should be provided on all injectable dosage forms where the volume is greater than 1 mL and should appear more prominent than the strength per milliliter. Therefore, revise the presentations of the strength statements to appear as:

Vazculep

(Phenylephrine HCl Injection, USP)

10 mg/mL

Vazculep

(Phenylephrine HCl Injection, USP)

50 mg/5 mL

(10 mg/mL)

Vazculep

(Phenylephrine HCl Injection, USP)

100 mg/10 mL

(10 mg/mL)

10. For the pharmacy bulk 5 mL and 10 mL fill vials, as per FDA guidance for industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, (b) to a boxed statement to read "Pharmacy Bulk Package – Not for Direct Infusion". Locate the revised boxed statement directly below the strengths.

11. To help ensure appropriate use of the product, add the statement "must be diluted" under the strength statement on the 1 mL fill vial and under the boxed statement "pharmacy bulk package" for the 5 mL and 10 mL fill vials.

12. The help ensure correct storage add the statement "Protect from light" to the bottom potion of the PDP above the manufacturing information.

Carton Labeling

1. See Vial Labeling Comments 2, 4, 5, 8, 9, 10, and 11 above.

2. To help ensure proper storage of the drug, relocate the statements "Protect from light" and "Store in carton until time of use" from the side panel to the bottom of the PDP, above the manufacturing information.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
Please consider the environment before printing this e-mail. If you decide to print, please make double-sided copies.

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/s/

KIMBERLY A COMPTON
02/28/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, January 29, 2014 4:33 PM
To: Marla Scarola (Marla.Scarola@weinberggroup.com)
Cc: Compton, Kimberly
Subject: Clinical Information Request for N 204300

Hi Marla,

The clinical team has the below request for the Eclat Phenylephrine NDA:

1. For the administration of phenylephrine hydrochloride by infusion, you have proposed a starting rate of 10 to 35 mcg/min, titrating to effect; not to exceed 200 mcg/min for the treatment of hypotension during anesthesia, (b) (4)
   a. Specify the minimum and maximum proposed duration of infusion for each indication.
   b. Specify the maximal total amount administered per day for each indication.

2. For the treatment of hypotension during anesthesia, you propose the following bolus intravenous injection regimen:

   Initial dose of 40 to 100 mcg; doses to be administered every 1-2 minutes as needed; not to exceed 200 mcg; and intravenous infusion: starting rate 10 to 35 mcg/min, titrating to effect; not to exceed 200 mcg/min.

   a. Clarify if "…not to exceed 200 mcg" for bolus intravenous injection, means the total amount, or any single bolus not to exceed 200 mcg. If the total amount, specify over what time period.
   b. If you mean as a single bolus, clarify how your recommendation is different from simply recommending a dosing range of 40 to 200 mcg.
   c. Clarify how the clinician should know whether to administer a second bolus, versus starting a continuous infusion for patients that do not reach the target BP.
   d. You have provided a range for the initial dose for bolus and infusion, but have not provided language in label for how the clinician is to decide on the dose, for example who should be started in 40, 100, 200 mcg respectively. Address this.

(b) (4)

(b) (4)

4. For the **treatment of hypotension** regimen, you propose a starting rate of 10 to 35 mcg/min, titrating to effect; not to exceed 200 mcg/min, (b) (4)

(b) (4)

We request a response to them by February 12, 2014. Please let me know if you have any questions on our request.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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/s/

KIMBERLY A COMPTON
01/29/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, January 22, 2014 12:26 PM
To: Marla Scarola (Marla.Scarola@weinberggroup.com)
Cc: Compton, Kimberly
Subject: Additional Information Request for N 204300

Hi Marla,

The micro team has reviewed the December 23, 2013, response to our previous information requests for NDA 204300 and has more additional requests for information. Please see them listed below. They team requests a response in 3 weeks. Please let me know if you have any questions on our request.

(b) (4)

(b) (4)

I will archive a copy of this request for documentation purposes.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
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KIMBERLY A COMPTON
01/23/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, January 15, 2014 2:35 PM
To: 'Marla Scarola'
Subject: RE: NDA 204300: SN0012 correction

Hi Marla,

The team has a response for the question of max daily dose. I have listed it below:

> Based on our review of the information provided and the clinical use literature, the Division has determined that the MDD is likely to be less than 10 mg for the majority of patients. As such, we will regulate your drug product specifications as per ICH Q3B(R2) such that the Identification thresholds should be based on a MDD of 1 mg to 10 mg, and the qualification threshold of (b) (4).

Please let me know if you have any questions on this and, if the team is awaiting anything else from us at this point.

Thanks
Kim

From: Marla Scarola [mailto:Marla.Scarola@weinberggroup.com]
Sent: Friday, January 10, 2014 3:20 PM
To: Compton, Kimberly
Subject: NDA 204300: SN0012 correction

Hi Kim,

We realized that there was a formatting issue in a couple of the figures in the revised 3.2.P.3.5 submitted in SN0012 on December 23. We plan to submit an amendment with a corrected version of the figures on Tuesday, January 14.

I thought I'd also check in again regarding the status of a response to our submission on December 20 on the maximum daily dose issue raised by the nonclinical reviewer.

Have a nice weekend!

Best,
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

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/s/

KIMBERLY A COMPTON
01/23/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, December 06, 2013 1:03 PM
To: Marla Scarola (Marla.Scarola@weinberggroup.com)
Cc: Compton, Kimberly
Subject: NDA 204300 - Information Request

Hi again Marla,

I have another set of information requests for Eclat's Phenylephrine NDA 204300. These are from the nonclinical and CMC groups.

1. Based on our review of your NDA application and other submissions to date, the maximum daily dose (MDD) of phenylephrine infused in a clinical setting is not clear. For example, under the NDA section for "Nonclinical Overview" the maximum total daily dose noted is 4 mg; which you appear to base your drug substance and drug product specifications on (pages 6-7). In the minutes for the End-of-Phase 2 meeting, the maximum total daily dose mentioned is 96 mg (see Question 4; Nonclinical). Finally, your proposed drug product labeling suggests that the safety of cumulative doses greater than 4 mg has not been established. Provide justification for the maximum total daily dose of phenylephrine via reference to clinical use data that support this dose.

2. The maximum daily dose is essential for the determination of the qualification threshold for impurities controlled by the drug product specifications. If the clinical use data suggest that the MDD is 96-100 mg/day, you must revise your drug product specifications for individual impurities to at least NMT (b) (4) (b) (4) /day, whichever is lower, or provide adequate safety data to qualify these degradants as recommended in ICH Q3B (R2) for a drug with a maximum daily dose between 10 mg and 100 mg. Based on the submitted stability data to date, we recommend tightening acceptance criteria for each unknown impurity to NMT (b) (4) %, for (b) (4)

3. Provide updated stability data with statistical evaluation of instability trends.

4. Define the maximum use time for the drug product in the clinic, from the initial penetration of the single-use vial to the end of administration to patients.

5. Provide supportive stability data demonstrating chemical stability of the drug product during the maximum time allotment for the dilution and administration procedures.

6. Update your labeling to reflect the data-based time restrictions for vial use.

7. Submit revised specifications for the drug product. In addition to the above requested changes for controls of impurities, include the following:

    a. Acceptance criteria and analytical method controlling the content of sodium metabisulfate (b) (4)

    b. Acceptance criteria and analytical method (b) (4)

c. Tighten the proposed acceptance criteria for pH. [redacted] (b) (4)

8. [redacted] (b) (4)

9. [redacted] (b) (4)

Please let me know if you have any questions on our requests and when you think you may be able to provide the firm's reply.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
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KIMBERLY A COMPTON
12/06/2013

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, December 04, 2013 9:15 PM
To: Marla Scarola
Cc: Compton, Kimberly
Subject: Information Request/ NDA 204300

Hi Marla,

I hope you are well and had a nice Thanksgiving. I have the below requests from the microbiology reviewer for Eclat's Phenylephrine NDA 204300.

Provide the following information or a reference to its location within the application:

(b) (4)

(b) (4)

Please let me know if you have any questions about our requests.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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KIMBERLY A COMPTON
12/04/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204300

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Marla E. Scarola
Senior Consultant

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) dated and received, June 28, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Phenylephrine Hydrochloride Injection, USP, 1%.

We also refer to your correspondences dated and received, July 1, 2013, and July 8, 2013, requesting review of your proposed proprietary name, Vazculep. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Vazculep, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If **any** of the proposed product characteristics as stated in your July 1, 2013 and July 8, 2013 submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vaishali Jarral, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4248. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kimberly Compton at (301)-796-1191.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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/

VAISHALI JARRAL
09/13/2013

CAROL A HOLQUIST
09/13/2013

From:	Sullivan, Matthew
To:	Marla Scarola (Marla.Scarola@weinberggroup.com)
Cc:	Compton, Kimberly
Subject:	Information Request/ NDA 204300
Date:	Tuesday, September 10, 2013 5:11:00 PM

Marla –

I also have received an information request for NDA 204300 that I wanted to send you. Please let me know if you have any questions.

> Provide the results of verification studies to support the endotoxin and sterility test protocols referenced in the drug product specification.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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MATTHEW W SULLIVAN
09/10/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204300

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

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

Attention: Marla E. Scarola, M.S.
Senior Consultant, The Weinberg Group, Inc.

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) dated April 30, 2013, received June 28, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Phenylephrine Hydrochloride Injection, 1%, USP.

We also refer to your amendments dated July 1 and 8, 2013.

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 28, 2014.

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 27, 2014.

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

1. White space must be present before each major heading in Highlights (HL.)

2. A horizontal line must separate the Table of Contents (TOC) from the Full Prescribing Info (FPI.)

We request that you resubmit labeling that addresses these issues by September 24, 2013. The resubmitted labeling will be used for further labeling discussions.

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:

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

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

If you have any questions, contact Kimberly A. Compton, R.Ph., Senior Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MATTHEW W SULLIVAN
09/10/2013
For Bob A. Rappaport, MD

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204300

ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE

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

Attention: Marla E. Scarola, M.S.
Senior Consultant, The Weinberg Group, Inc.

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act in response to our April 5, 2013, refusal to file letter for the following:

Name of Drug Product: Phenylephrine Hydrochloride Injection, 1%, USP

Date of Application: June 28, 2013

Date of Receipt: June 28, 2013

Our Reference Number: NDA 204300

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 27, 2013, in accordance with 21 CFR 314.101(a).

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

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

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

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

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

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 204300** submitted on June 28, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

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

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

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

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

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

If you have any questions, call me at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory 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/

KIMBERLY A COMPTON
07/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204300

MEETING MINUTES

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

Attention: Marla E. Scarola, M.S.
Senior Consultant, The Weinberg Group, Inc.

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food Drug and Cosmetic Act for Phenylephrine Hydrochloride Injection, 1%, USP.

We also refer to the meeting between representatives of your firm and the FDA on June 13, 2013. The purpose of the meeting was to discuss to discuss our April 5, 2013, refusal to file letter.

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 301-796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEETING MINUTES

Meeting Type:	Type A
Meeting Date and Time:	June 13, 2013, at 11:30 AM
Meeting Location:	White Oak Bldg 22, Conference Room 1313
Application Number:	NDA 204300
Product Name:	Phenylephrine Hydrochloride Injection, 1%, USP
Regulatory Status:	Refused to file
Proposed Indication:	Treatment (b) (4) of hypotension during anesthesia
Sponsor Name:	Éclat Pharmaceuticals, Inc.
Meeting Chair:	Christopher Breder, M.D. Ph.D., Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), Center for Drug Evaluation and Research (CDER)
Minutes Recorder:	Matthew Sullivan, M.S., Senior Regulatory Project Manager, DAAAP

Eclat Pharmaceuticals, Inc. Representatives	**Title**
Michael S. Anderson	President and Chief Executive Officer, Éclat
Scott A. Macke	Vice President of Operations, Éclat
Nicholas M. Fleischer, R.Ph., Ph.D.	Vice President, The Weinberg Group
Robert I. Roth, M.D., Ph.D.	Medical Director, The Weinberg Group
Marla E. Scarola, M.S.	Senior Consultant, The Weinberg Group
FDA	**Title**
Rigoberto Roca, M.D.	Deputy Director, DAAAP, CDER
Timothy Jiang, M.D.	Medical Officer, DAAAP, CDER
Christopher Breder, M.D. Ph.D.	Clinical Team Leader, DAAAP, CDER
Matthew Sullivan, M.S.	Sr. Regulatory Project Manager, DAAAP, CDER
Julia Pinto, PhD	CMC Lead, Office of New Drug Quality Assessment, CDER
Yun Xu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
David Lee, PhD	Clinical Pharmacology Reviewer, OCP

BACKGROUND

The product is Phenylephrine Hydrochloride Injection, 1%, USP. The Sponsor submitted a 505(b)(2) application that proposes to rely only on literature references for approval. The Sponsor has proposed that the product be indicated for the treatment (b) (4) of hypotension during anesthesia. The Agency refused to file (RTF) the application on April 5, 2013, for reasons related to the format and content of the Integrated Summaries of Safety and Efficacy.

The Sponsor has stated that their objectives for this Type A meeting are as follows:

> To obtain FDA input and guidance on whether the proposed revisions to the NDA adequately address the Agency's reasons for the RTF. Éclat is seeking assurance that a second submission of the NDA incorporating these revised sections will be accepted for filing.

The questions from the May 15, 2013, background package are shown below in *italic* font. The Divisions responses are shown in **bold** font. The Division provided preliminary comments to the Sponsor on June 12, 2013, and the Sponsor responded on the same day that they wished to discuss Questions 2 and 4. Discussion from the meeting is in normal font.

DISCUSSION

Clinical Questions

Integrated Summary of Efficacy

Question 1

The overall organization of the ISE includes a brief introduction followed by separate sections for the treatment (b) (4) *indications. Each indication section includes subheadings that follow the outline provided in Draft Guidance to Industry: Integrated Summary of Effectiveness, i.e., Background and Overview, Tabular Results of Individual Studies, Comparisons and Analyses of Efficacy Results Across Studies, Comparison of Results in Subpopulations, Analysis of Clinical Information Relevant to Dosing Recommendations, Persistence of Efficacy and/or Tolerance Effects and Exploratory Investigations. Does this organization address the Agency's deficiency that the discussions in the ISE were not appropriately separated by indication?*

FDA Response

The format seems to have followed the Guidance. However, the adequacy of the content will be determined during the course of the review.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 2

Given that the application is based solely on published literature from studies of differing design and conduct, mathematical integration of aggregated data is not possible. The section, Integrated Data Analyses has been included for both indications (ISE Section 2.3.4 for the treatment indication (b) (4) *however, rather than providing integrated data, the reasons these analyses could not be conducted are listed. Is this sufficient? Please note that a similar approach was used for Éclat's paper based application for neostigmine methylsulfate injection (NDA 204078) and was found to be acceptable.*

FDA Response

We appreciate that, as in the case for your NDA 204078, you may not have access to much individual subject data from publications. As such, we do not expect a mathematical integration, or re-analysis of that data. However, you should provide a summary that describes the range of data, and the most common or average of the findings. You also should provide a description of the outlying results and what condition might explain them.

We note that you did include an ISE and ISS in NDA 204078 and while the NDA was reviewed and ultimately approved, the integration of this data was not well done. This is why we have provided further guidance on what should be included in the Phenylephrine NDA.

Please note, when you describe Modules, include the whole number sequence, e.g., "the ISS Section 3.3.4" should be written as "Module 5.3.3.4," with the option of preceding it with your description, e.g., ISS Section.

Discussion:
The Sponsor acknowledged that the Division stated that we did not expect a mathematical integration of the data, but they sought clarification regarding the extent of summarization that would be required. The Division responded that since the source data would likely not be available to the Sponsor, they should endeavor to synthesize and discuss the data that is available in each published article. Additionally, outliers (both whole studies and subjects within a study) should be discussed, and possible explanations provided supporting why they may be outside the norm.

The Division also noted that the Sponsor should compose separate tables for each indication as well as a combined table for all indications, and include discussions of the data presented.

Additionally, the Sponsor should ensure that an annotated label is provided which clearly links each section to the tables and summary discussion supporting that section.

The Sponsor inquired if they should group studies with similar endpoints together, or keep them separate. The Division responded that studies with clinically meaningful endpoints should be grouped and discussed together, but that all individual studies should be presented as well.

The Division stated that the Sponsor should critically examine the information provided by the studies, and seek to identify any "gaps" that may need to be addressed. These "gaps" should be discussed and, if appropriate, justification provided supporting their conclusion that the product can be safely used in spite of the "gap."

Question 3

Éclat believes that it is following the Agency's guidance that was provided for Question 15 at the End-of-Phase 2 meeting held on September 27, 2012 as well as the Draft Guidance to Industry: Integrated Summary of Effectiveness and the Guidance to Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. Does the Agency consider the revised ISE to be adequately constructed?

FDA Response

The format of your ISE seems to have followed the advice at the End-of-Phase 2 meeting minutes and the Guidances to which you have referred. However, the adequacy of the content will be determine during the course of the review.

Discussion:
There was no discussion beyond the Division's initial written response.

Integrated Summary of Safety

Question 4

Given that Éclat is seeking approval of two different, but related, indications, the safety findings from literature in which phenylephrine is used to treat hypotension during anesthesia is presented first, (b) (4) . In each of these sections, deaths, adverse events (serious, common and other significant), dropouts, laboratory findings and vital signs are discussed. Éclat has identified supportive safety literature from the clinical use of phenylephrine: in other indications; for the specific clinical safety endpoint of fetal health; and for miscellaneous topics of interest such as safety pharmacology, carcinogenicity, etc. Discussion of this supportive information is provided in a subsequent section and is considered to be relevant to both the treatment (b) (4) indications. The final section of the ISS is the postmarketing experience, i.e. analysis of the FDA AERS database. Does this organization address the Agency's deficiency that the discussions in the ISS were not appropriately separated by indication? Does the Agency agree that the supportive literature relevant to both indications can be included in an independent section and does not need to be repeated for each indication?

FDA Response

Your revised ISS seems to have appropriately separated two indications. You should separate the supportive literature for the indication it is meant to support. If there is literature supporting both indications, the summaries of those literature articles may follow both in a section that explains the literature's utility. Please note that even the supportive literature should be summarized and integrated into the discussion for each specific indication.

Discussion:
The Sponsor asked how literature on the use of phenylephrine for indications other than the (b) (4) treatment of hypotension during anesthesia should be captured in the NDA resubmission. The Division said that the information from literature for indications such as septic shock, which have little relevance to the indications proposed by the Sponsor, should be discussed but separately from the data specifically supporting the two proposed indications.

The Division stated that some studies in the literature are for *both* treatment (b) (4) of hypotension, and these studies should be included in a separate section of the ISS, rather than included in the sections for the individual indications. Additionally, the Division stated that numerous articles

exist about how when phenylephrine is used to support maternal blood pressure, umbilical arterial pH may be affected. This literature should be comprehensively reviewed and synthesized as it relates to each of the indications.

(b) (4)

Question 5

Éclat believes that it is following the Agency's guidance that was provided for Question 15 at the End-of-Phase 2 meeting held on September 27, 2012 as well as the Reviewer Guidance Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review. Does the Agency consider the revised ISS to be adequately constructed?

FDA Response

The format of your ISE seems to have followed the advice at the End-of-Phase 2 meeting minutes, and the Guidance to which you referred. However, the adequacy of the content will be determined during the course of the review. The following FDA document will be helpful in directing you on issues related to eCTD granularity: *The Comprehensive Table of Contents Headings and Hierarchy*
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163175.pdf.

Discussion:
There was no discussion beyond the Division's initial written response.

Use of Foreign Data

Question 6

Per the Agency's request (RTF letter), Éclat has provided a rationale for the use of some publications that contain the results of studies conducted outside of the United States. Is this sufficient to address the Agency's concerns? Please note that for the resubmission Éclat plans to incorporate this rationale into Section 2.5.

FDA Response

We note that this issue was not considered a deficiency that served as a basis for refusing to file. Your response will be evaluated during the review of the NDA.

Discussion:
There was no discussion beyond the Division's initial written response.

Regulatory Questions

Question 7

Based on discussion with Kimberly Compton, Éclat understands that the RTF letter included a comprehensive list of reasons for the decision. Thus, if Éclat adequately addresses each of these deficiencies and does not alter any other section of the NDA in any substantive manner, the NDA will be accepted for filing. Does the Agency agree? Will the Agency commit to notifying Éclat of the fileability of the application earlier than 74 days after receipt of the submission?

FDA Response

Within 60 days after FDA receives your NDA, the Agency will determine whether the application may be filed. If FDA finds that none of the reasons in 21 CFR 314.101(d), (e) apply, then the application will be filed and the agency will notify you in writing in accordance with 21 CFR 314.101.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 8

Éclat does not intend to replace any administrative information in Module 1, e.g., financial certification, debarment certification, patent certifications, etc. Does the Agency agree that the documents signed and dated October 2012 and January 2013 will be considered acceptable for filing?

FDA Response

If you are amending your previously submitted 505(b)(2) application to address the deficiencies that precluded filing, and the original certifications remains accurate, then new certifications are not required. Ensure that links to all previously-submitted materials function in the resubmission

Discussion:
There was no discussion beyond the Division's initial written response.

ADDITIONAL COMMENTS:

CMC:

When you resubmit your NDA, include the most recent stability updates for the drug substance and drug product.

Discussion:
The Sponsor stated that they would submit their 9 month and 12 month stability update with the NDA resubmission.

General Discussion:
The Division inquired as to when the Sponsor plans to resubmit the NDA, to which the Sponsor responded that it was likely days to weeks, and not months.

Action Items:

1. The Sponsor will revise their ISE to include an explanation for outliers, both at the study level, and at the subject level.
2. The Sponsor will ensure that all sections of the labeling are appropriately supported, and that references to the supportive data are clearly identified.
3. The Sponsor will identify and discuss any "gaps" in the data and will provide a justification, as appropriate, discussing the "gap" and supporting the safe use of the product in spite of the "gap."
4. The Sponsor will group studies with clinically meaningful endpoints together and ensure that these are fully discussed.

OTHER IMPORTANT INFORMATION

PEDIATRIC 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 a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).

- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

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/s/

MATTHEW W SULLIVAN
07/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 113044

MEETING PRELIMINARY COMMENTS

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

Attention: Marla E. Scarola, M.S., RAC
Senior Consultant

Dear Ms. Scarola:

Please refer to your Pre-Investigational New Drug (PIND) file for Phenylephrine HCl Injection, USP.

We also refer to your December 31, 2012, correspondence, received January 2, 2013, requesting a Type A meeting to discuss issues related to the 505(b)(2) filing strategy planned for your New Drug Application (NDA.)

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type/Category: Type A
Meeting Date and Time: January 30, 2013 at 12:00 noon
Meeting Location: Teleconference
Application Number: PIND 113044
Product Name: Phenylephrine HCl Injection, USP
Regulatory Status: Pre-Submission
Indication: For the treatment (b) (4) of hypotension during anesthesia
Sponsor Name: Éclat Pharmaceuticals
Meeting Chair: Christopher Breder, M.D., Ph.D., Clinical Team Leader
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAAP

Éclat Pharmaceuticals Representatives	**Title**
Michael S. Anderson	President and Chief Executive Officer, Éclat
Scott A. Macke	Vice President, Operations, Éclat
Nicholas M. Fleischer, R.Ph., Ph.D.	Vice President, The Weinberg Group Inc.
Carolyn S. Rabe, Ph.D.	Senior Consultant, The Weinberg Group Inc.
Robert I. Roth, M.D., Ph.D.	Medical Director, The Weinberg Group Inc.
Marla Scarola, M.S.	Senior Consultant, The Weinberg Group Inc.
FDA	**Title**
Bob A. Rappaport, M.D.	Director, DAAAP
Rigoberto Roca, M.D.	Deputy Director, DAAAP
Leah Crisafi, M.D.	Medical Officer, DAAAP
Christopher Breder, M.D., Ph.D.	Clinical Team Leader, DAAAP
Parinda Jani	Chief, Project Management Staff, DAAAP
Nisha Shah, J.D.	Regulatory Counsel, Office of Regulatory Policy (ORP)
Jay Sitlani, J.D.	Senior Regulatory Counsel, ORP
Kim Compton	Sr. Regulatory Project Manager, DAAAP

INTRODUCTION

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 30, 2013, at 12:00 noon, between Éclat and the Division. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact me if that is the case). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from

face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

BACKGROUND

The Sponsor states that the purpose for this meeting is to obtain the Agency's feedback regarding the acceptability of their proposed indications for filing an NDA for Phenylephrine Hydrochloride Injection, USP, 1%. In addition, it appears the firm is interested in obtaining input on submitting their application following the recent approval of another product with the same ingredient and indication.

Their product is phenylephrine hydrochloride 1% injection, USP. It is predominantly an α1-agonist that causes vasoconstriction. Phenylephrine has little activity on α2 or β-receptors. The major action is on the cardiovascular system, with stimulation of vascular α1-receptors but little direct action on the heart itself. The firm plans to submit a 505(b)(2) NDA application relying on literature only as support for the clinical evidence of safety and efficacy. They do not currently market the product. The firm had an End of Phase 2 (EOP2) meeting with the Agency on September 27, 2012.

DISCUSSION

Question 1
At this time, Éclat requests that the Agency confirm that Éclat's proposed indication (i.e., treatment (b) (4) *of hypotension during anesthesia) are different enough from West-Ward's approved indication to allow Éclat to file a 505(b)(2) NDA.*

FDA Response

You have proposed indications for "the treatment (b) (4) **of hypotension during anesthesia." The FDA-approved indication for West-Ward's phenylephrine hydrochloride (NDA 203826) is for "increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia." This approved indication seems to subsume your indication for the treatment of hypotension during anesthesia.** (b) (4) **It appears that a 505(b)(2) NDA may be appropriate for your proposed phenylephrine product.**

(b) (4)

(b) (4)

Question 2
In addition to feedback regarding the proposed indications, guidance is being sought on whether Éclat is required to reference West-Ward's approved NDA for phenylephrine hydrochloride injection. Éclat's submission has been prepared based on the published literature (b) (4)

FDA Response
It appears that, although West-Ward has approval for a phenylephrine hydrochloride injection product, (b) (4) **You may rely on FDA's findings of safety or effectiveness for a listed drug, or on published literature.**

If you intend to rely on FDA's previous findings of safety or effectiveness for a listed drug(s) (i.e., a drug with a current approval as reflected in the Orange Book), 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. This is consistent with FDA's policy to rely to the greatest extent possible on what is already known about an approved drug product.

You will need to provide a scientific bridge between your product and each listed drug upon which you plan to rely. We also refer you to the Meeting Minutes from our September 27, 2012, meeting, wherein we discussed the requirement for a scientific bridge when referring to information from the literature (see our response to Question 9).

Question 3
It is Éclat's understanding that if the Agency accepts Éclat's NDA for review, that the Agency has committed to reviewing both the (b) (4) *treatment indications even though the treatment indication would likely be considered a duplicate of the West-Ward indication. Éclat would like to understand if referencing the West Ward product as the listed drug would impact the Agency's commitment to review the treatment (duplicate) indication. It was never Éclat's intent to rely on the Agency's finding of safety and effectiveness of the*

West-Ward product to support Éclat's application. Does the "administrative" acknowledgement that the West-Ward product is the first approved and therefore the "listed drug" in any way jeopardize the Agency's commitment to review (b) (4) *the duplicate treatment indication. Éclat would like to retain the possibility that approval could be based on treatment,* (b) (4)

FDA Response

It appears that you are proposing to submit your NDA for both the treatment (b) (4) **indications. If so, you must provide information to support both indications, which may include, among other things, published literature and reliance on FDA's finding of safety and effectiveness for a listed drug. If you intend to rely on the Agency's finding of safety and effectiveness for West-Ward's approved phenylephrine hydrochloride drug product for the treatment indication, and on published literature** (b) (4)**, any reliance on the former would not itself bar the filing or review of a 505(b)(2) NDA for** (b) (4) **treatment indications.**

As a separate matter, we note that the proposed strength of your product is phenylephrine hydrochloride 10 mg/mL supplied in three vial sizes: 1 mL, 5 mL and 10 mL. The strength of West-Ward's approved product is phenylephrine hydrochloride 10 mg/mL supplied as a 1 mL single dose vial. As you may know, the Agency interprets "same strength" for parenterals to mean the "same concentration and total drug content." Thus, Éclat's 5 and 10 mL presentations would not be considered to have the same strength as and, therefore, would not be considered to be pharmaceutically equivalent to West-Ward's approved product.

OTHER IMPORTANT INFORMATION

PREA PEDIATRIC STUDY PLAN

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies.

CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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.

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/s/

KIMBERLY A COMPTON
01/28/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

PIND 113044

MEETING MINUTES

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

Attention: Marla E. Scarola, M.S., RAC
Senior Consultant

Dear Ms. Scarola:

Please refer to your Pre-Investigational New Drug (PIND) file for Phenylephrine HCl Injection, USP.

We also refer to the End-of-Phase 2 (EOP2) meeting between representatives of your firm and the FDA on September 27, 2012. The purpose of the meeting was to discuss plans for continuing development of your product.

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 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type/Category: Type B (EOP2)
Meeting Date and Time: September 27, 2012, at 1:30 PM
Meeting Location: White Oak, Bldg 22, Rm 1311
Application Number: PIND 113044
Product Name: Phenylephrine HCl Injection, USP
Regulatory Status: Pre-Submission
Indication: For the treatment (b) (4) of hypotension during anesthesia
Sponsor Name: Éclat Pharmaceuticals
Meeting Chair: Christopher Breder, M.D., Ph.D., Clinical Team Leader
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAAP

Éclat Pharmaceuticals Representatives	**Title**
Michael S. Anderson	President and Chief Executive Officer, Éclat
Scott A. Macke	Vice President, Operations, Éclat
(b) (4)	
Nicholas M. Fleischer, R.Ph., Ph.D.	Vice President, The Weinberg Group Inc.
Carolyn S. Rabe, Ph.D.	Senior Consultant, The Weinberg Group Inc.
Robert I. Roth, M.D., Ph.D.	Medical Director, The Weinberg Group Inc.
Joel I. Falk	Executive Vice President, The Weinberg Group Inc.
Marla Scarola, M.S.	Senior Consultant, The Weinberg Group Inc.
(b) (4) (b) (4)	
FDA	**Title**
Bob A. Rappaport, M.D.	Director, DAAAP
Rigoberto Roca, M.D.	Deputy Director, DAAAP
Leah Crisafi, M.D.	Medical Officer, DAAAP
Christopher Breder, M.D., Ph.D.	Clinical Team Leader, DAAAP
David Lee, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader
Huiqing Hao, Ph.D.	Pharmacology/Toxicology Reviewer, DAAAP
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAAAP
Ramesh Raghavachari, Ph.D.	CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Prasad Peri, Ph.D.	Branch Chief, Branch VIII, ONDQA
Erika Pfeiler, Ph.D.	Microbiology Reviewer, New Drug Microbiology Staff
Albert Chen, Ph.D.	Biopharmaceutics Reviewer, ONDQA
Jennifer Stevens, J.D.	Regulatory Counsel, Office of Regulatory Policy (ORP)
Leah Ripper	Associate Director, Regulatory Affairs, Office of Drug Evaluation II
Charles Lee, M.D.	Senior Medical Advisor, Office of Unapproved Drugs and Labeling Compliance (OUDLC)
Judy Park	Senior Regulatory Reviewer, OUDLC
Luz Rivera, Psy.D.	Project Manager, ONDQA
Kim Compton	Sr. Regulatory Project Manager, DAAAP

BACKGROUND

The Sponsor stated that the purpose for the meeting was to obtain FDA feedback on the adequacy of the chemistry manufacturing and controls (CMC), nonclinical, and clinical information package intended to be filed in a 505(b)(2) NDA. Specifically, the firm stated they have the following objectives for the meeting:

1. To obtain input from FDA on the adequacy of nonclinical information for NDA submission and approval
2. To obtain input from FDA on the adequacy of clinical efficacy and safety information for NDA submission and approval
3. To obtain agreement that several nonclinical and CMC issues raised in prior meetings with the Agency have been adequately addressed, and
4. To share details of Éclat's efforts to obtain original study data from authors of relevant publications, which will be included in the NDA as supporting the safety and efficacy of phenylephrine for the proposed indication

In addition, the firm was interested in obtaining input on submitting their application if another identical product receives prior approval for the same indication, and how to proceed should the company wish to pursue multiple indications for their product.

The product is phenylephrine hydrochloride 1% injection, USP. It is an α1-agonist, acting as a post-synaptic alpha-receptor stimulant that causes vasoconstriction. Phenylephrine has little activity on α2- or β-receptors. The firm plans to submit a 505(b)(2) NDA application relying on literature only. They do not currently market the product, which is not FDA approved though it is widely marketed by other companies. The firm had a Pre-IND meeting with the Agency on November 17, 2011.

The Agency's preliminary responses for the Type B meeting were sent via email on September 26, 2012. The firm indicated that they would like to discuss the Questions 18, 17, 12, 1, and 15 from the preliminary responses.

The Sponsor's questions are incorporated below in *italics* followed by the FDA Response or Comment to the question in **bold**. Discussion that took place at the meeting is captured following the question to which it pertains in normal text.

DISCUSSION

Chemistry Manufacturing and Controls (CMC)

Question 1
As described in Attachment A, Éclat intends to submit 6 months of accelerated and real time stability data on nine registration batches and will be supplementing with the 12 month data in an amendment. Does the Agency agree with this approach?

FDA Response
No we do not agree. We expect 12 months of long-term stability data and 6 months of accelerated stability data when the application is submitted.

Discussion
The Sponsor stated that they would like to file their application as soon as possible and so would like to submit with the stability data they have on hand. The firm stated that they are prepared to accept a shorter expiry and could amend their application with updated data once it is available. The Agency reiterated our expectations regarding stability data and stated that, if Éclat chooses to submit the application with less than the recommended stability data, the Agency would discuss the acceptability of the submission at that time.

Question 2
Éclat's proposed label will include information for diluting Phenylephrine Hydrochloride Injection, USP, 1%. Information on the compatibility of Éclat's formulation with the recommended diluents is based on literature reports as summarized in Attachment A. Does the Agency agree with this approach?

FDA Response
Data to support the compatibility of the Éclat formulation (any one presentation) with every diluent should be provided to support the labeling. Labeling information will be a subject of review during the NDA.

Discussion
There was no further discussion of this point.

Question 3
The 5 and 10 mL vials of Phenylephrine Hydrochloride Injection, USP, 1% are considered single-use pharmacy bulk packages. In order to comply with the USP requirements for pharmacy bulk package labeling outlined in USP general chapter <659>, (b) (4) *Does the Agency agree with this approach?*

FDA Response
The term "single-use pharmacy bulk package" is not currently recognized by FDA, and it is unclear what your intention for the drug product is from the description in the meeting package. (b) (4) **). Information on PBPs can be found in USP <659> and define a PBP as "a container of a sterile preparation for parenteral use that contains many single doses." Contents of PBPs are intended to be prepared as pharmacy admixtures in a suitable setting, such as a laminar flow hood. Closures on PBPs should only be penetrated one time after constitution and should be done with an adequate**

sterile transfer device. Additionally, PBPs must "contain or refer to information on proper technique to help assure safe use of the product." This information should be submitted as part of an NDA and would be evaluated during the NDA review. Typically, hold times of greater than 4 hours from time of penetration must be justified, and this justification would also be evaluated as part of the NDA review.

Discussion
The Sponsor stated that the product container is intended to be penetrated only once. The Agency stated that the firm should refer to USP Chapter 659 noting that, if the product will be used within four hours or less, no additional studies would be needed. (b) (4) These issues can be addressed in labeling, but the firm should provide any information or data from studies on microbiological stability of the product.

Additional CMC Comments

(b) (4) **Clarify if any** (b) (4) **extractables are observed (** (b) (4) **) that could potentially be a leachable in the drug product.**

We suggest you 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

Discussion
There was no further discussion of this point.

Nonclinical

Question 4
Éclat has calculated the maximum total daily dose of Phenylephrine Hydrochloride Injection, USP, 1% as 96 mg based on the maximum infusion rate of 200 µg/min for a total of 8 hours. This calculation is based on the following assumptions:

- *A continuous intravenous infusion throughout a surgical procedure will result in the highest exposure compared to the other proposed dosing regimens.*
- *Surgical procedures generally last less than 8 hours. This is a conservative estimate based on numbers reported in the published literature. For example, a study comparing surgical times and rates of infection found that, in the United States, across 14 categories of surgical procedures, at least 75% of procedures lasted 277 minutes or less (Leong et al. 2006). In a study conducted in Germany, over 250,000 operations falling into 8 different procedure categories were included in an analysis; it was reported that at least 75% of procedures lasted no longer than 179 minutes (Gastmeier et al. 2011).*

Does the Agency agree with Éclat's method for calculating maximum total daily dose for the purpose of assessing the safety of impurities and extractables?

FDA Response
Your method of calculating total daily dose appears reasonable from a clinical perspective. If the review of your NDA suggests that a greater daily dose may be required, this assessment will need to be reconsidered.

(b) (4)

(b) (4)

Discussion
There was no further discussion of this point.

Question 5
Éclat believes that the excipients present in the formulation are adequately qualified based on their common use in intravenous injection and infusion products at levels greater than or equal to those present in the phenylephrine formulation. Does the Agency agree?

FDA Response
Yes. The excipients in your proposed drug product formulation appear to be found in other FDA-approved intravenous drug products at comparable levels and appear to be adequately qualified for safety.

Discussion
There was no further discussion of this point.

Question 6
Éclat believes that the impurities are adequately qualified based on QSAR and existing toxicity data. Does the Agency agree?

FDA Response

Your proposed drug substance impurity specifications of [redacted] (b) (4) for [redacted] (b) (4) appear to be acceptable based on the lack of structural alerts via a DEREK analysis. Based on the structures provided, we do not anticipate any genotoxic concerns. However, you should be aware that ongoing ICH M7 discussions appear to be suggesting that use of an expert-rule based model alone (such as DEREK) may not be acceptable and that a second statistical-based model evaluation is also recommended. At the time of your NDA submission, if new structures are identified that raise concerns, the Agency will likely submit the structures of your anticipated impurities to our internal Computational Toxicology Services, which typically run four different models. Should these results suggest concern, an actual Ames assay may be required. We will work with you to identify and resolve any concerns.

Discussion

There was no further discussion of this point.

Question 7

[redacted] (b) (4) *. Does the Agency agree with this approach?*

FDA Response

Based on the information provided in your meeting package, your proposed approach is considered to be acceptable as long as the toxicological risk assessment based on the extraction studies for each of the potential leachables adequately justifies their safety. Final determination of the adequacy of methodology and the study results can only be determined upon review of the NDA.

Discussion

There was no further discussion of this point.

Question 8

Éclat has not conducted nonclinical studies on phenylephrine to support this application. Éclat has developed a detailed integration of the available nonclinical literature on phenylephrine which has been provided for the Agency's review in Attachment C Section 2.4. In the NDA, limited written and tabular study summaries will be provided in Section 2.6 due to the limited nature of the details present in the published literature. Does the Agency agree with this approach?

FDA Response

Your approach appears acceptable. Your NDA submission should include details regarding the literature search criteria used and include copies of the articles you referenced. As noted in the pre-IND meeting minutes from November 17, 2011, if the literature references do not contain adequate information regarding the mutagenic potential and impact on reproductive and developmental toxicity of phenylephrine, these studies may be required 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.

Discussion

There was no further discussion of this point.

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), 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:**

    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 study of appropriate duration to support the proposed indication. For this acute use drug product, the study should be at least 14 days in duration.**

2. **Drug substance manufacturing process intermediates may include compounds with structural alerts for genotoxicity. Refer to the Guidance for Industry: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf. As noted in this draft guidance, 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, Guidance for Industry: *Guideline on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*.**

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074931.pdf

3. **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**

4. **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 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.**

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 or device 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 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 (chronic or short-term dosing). 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, consult the Guidance for Industry: *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*.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.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.**

6. **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 or literature references, the exposure margins provided in the label must accurately 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.

7. **NOTE: 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 of if there is a missing or inadequate extractable leachable safety assessment for the container closure system.**

Discussion
There was no further discussion of this point.

Clinical Pharmacology

Question 9
The majority of published clinical pharmacology, efficacy and safety studies that will be included in the NDA do not identify the manufacturer or the trade name of the phenylephrine drug product used. However, one paper used by Éclat to support both safety and efficacy and a few others included in the clinical pharmacology section do identify the source of the phenylephrine injection used in the study (refer to Attachment E Section 2.7.1). The formulations of the products used in these studies as well as the formulations currently marketed as unapproved products are believed to be essentially identical to Éclat's product. Because of this similarity and the fact that Éclat's to-be-marketed product is a parenteral product intended for intravenous use, Éclat believes that the requirements to demonstrate bioavailability of their product have been fulfilled. Does the Agency concur?

FDA Response
From a clinical pharmacology perspective, your rationale for using literature information to support the bioavailability of your product appears to be adequate.

As per 21 CFR 320.21(1) and §320.21(2), you are required to include in your NDA submission either evidence of measuring the in vivo bioavailability (BA) of the drug product that is the subject of the NDA or information to permit the Agency to waive the submission of evidence measuring in vivo bioavailability. To satisfy the BA evidence requirement, you may provide pharmacokinetic literature data, in lieu of the drug product specific BA studies, so that you may request a BA waiver. Our acceptance of the provided literature data as evidence of satisfying the BA requirement or supporting the biowaiver request is contingent on the appropriateness of the provided literature as well as the scientific bridge between the formulations used in the literature studies and your proposed formulation. Therefore, provide in your NDA:

1. **Legible copies of each cited published PK reference**

2. **A brief summary of the information included in each cited reference**

3. **A summary table comparing the composition of the formulation and route of administration of each cited PK reference vs. your proposed product – If any information is lacking include a justification.**

The adequacy of the above information supporting the bioavailability of your product will be determined at the time of NDA review.

Please see response to Questions 17 and 18 and Additional Regulatory Comments for information related to submission of literature to support approval of a 505(b)(2) application.

Discussion
There was no further discussion of this point.

Question 10
Does the Division agree that the clinical pharmacology data provided are adequate to support submission of an NDA for the use of Phenylephrine Hydrochloride Injection, USP, 1% to treat (b) (4) *hypotension during anesthesia in adults and children?*

FDA Response
From a clinical pharmacology perspective, the information submitted in the meeting package may not be sufficient to support the submission of an NDA because you did not include in your package all the clinical pharmacology information we previously requested (see our comment below). However, based on extensive clinical use of this product, no additional clinical pharmacology studies may be needed for NDA approval. As conveyed in our November 17, 2011 pre-IND meeting, you are further encouraged to obtain the following information and address the dosing in special populations.

1. **Address all pertinent clinical pharmacology information related to the following aspects, including but not limited to:**

   a. **Absorption, Distribution, Metabolism and Elimination of your product**

   b. **PK and dosing in special populations (effect of age, gender, hepatic and renal impairment, etc.)**

   c. **Drug-drug interaction potential (in vitro enzyme induction and inhibition properties of your drug)**

2. **This information may be obtained from your own studies or from the public domain (if information of adequate quality is available in the published literature). If literature articles are used for obtaining this information, full articles must be included in the NDA.**

Discussion
There was no further discussion of this point.

Clinical

Clinical Question 11
Per the Agency's request at 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 the briefing package (see Attachment K Integrated Summary of Efficacy Section 6.2) and will also be included in the NDA. Despite these efforts, we were unable to obtain any protocols or study data to include in the NDA. However, Éclat believes that the consistency of safety and efficacy findings across multiple studies, regions and research institutions validates the efficacy and safety of the product for the proposed uses. Does the Agency agree?

FDA Response
Your ability to obtain original protocols and data from studies you reference will help to confirm their contribution to your submission and facilitate accurate labeling. We recognize that it may not be possible to obtain protocols and original data from many studies because of the time that has elapsed since they were conducted. Consideration will be given to the consistency of results reported across a number of studies conducted at various centers. We consider the reliability of findings from a particular study to be enhanced when it is corroborated by similar studies conducted by other individuals at different institutions or from studies conducted at multiple institutions versus a single center.

Discussion
There was no further discussion of this point.

Question 12
Four different treatment paradigms are proposed in this briefing package as follows:

a. Treatment of hypotension

i. bolus administration

ii. infusion administration

(b) (4)

Does the Agency agree that the data provided in the briefing package adequately support the proposed methods of administration and indications?

FDA Response

The adequacy of the data submitted to support each proposed indication will be a matter of review upon submission of your NDA. In general, the bolus treatment indication is reasonable.

We have concerns regarding the safety of infusions related to the pharmacodynamic (e.g., tachyphylaxis) effects of prolonged alpha receptor stimulation. You will need to provide supportive evidence for efficacy in the specific populations included in your labeling, as well as regarding the toxicities demonstrated in nonclinical and human studies, including renal, splanchnic, and cardiac effects employing this route of administration.

(b) (4)

For both the treatment (b) (4) indications, you should prioritize the literature based on the quality of the studies and their relative contribution to supporting the indication and proposed labeling. We have provided suggestions regarding information that should be included in your study summaries in the additional clinical comments.

Discussion

(b) (4)

The efficacy of the indication "for the treatment of hypotension with a continuous infusion" appears to be supported by evidence in the published literature. However, the literature in support of the safety of administration by this route, including renal and cardiovascular effects, appears to be sparse. (b) (4)

(b) (4)

Question 13
Does the Agency agree that the published clinical efficacy data provided are adequate to support the submission of an NDA for the use of Phenylephrine Hydrochloride Injection, USP, 1% for the treatment and (b) (4) *of hypotension during anesthesia in adults and children?*

FDA Response
This question has been answered with regard to adults in our response to Question 12.

With regard to the pediatric population, the body of evidence is inadequate and, with respect to some of the literature, probably not generalizable. You should consider for which pediatric populations phenylephrine is not generally used or not appropriate and consider requesting a partial waiver so your labeling will be more clinically appropriate.

You should include adequate, well controlled studies in patients, as well as Phase 1 laboratory studies or published reports (e.g., baroreceptor evaluations in healthy normal subjects) as contributory evidence for efficacy and to describe the dose/response relationship.

Discussion
There was no further discussion of this point.

Question 14
In the Integrated Summary of Safety, Éclat plans to provide a review of data available in the literature as well as an analysis of reported adverse events from the AERS MedWatch program. The summarized safety information will focus on intravenous administration of phenylephrine as a pressor agent and will not include safety findings associated with topical or locally-administered drug. Does the Agency agree with this proposal?

FDA Response
In order to provide a complete assessment of the safety of your product, you must include information from the literature describing the adverse effects of phenylephrine when administered in a manner where pharmacodynamically active levels are reached in the systemic circulation. This includes the intranasal and intraocular routes, in addition to intravenous administration. It is not necessary to include information related to oral administration, such as with combination products for cough and cold symptoms.

You may separate this information by route in your ISS. Your table of adverse events should be based on the intravenous route of administration. You should include systemic effects as well as local effects at the administration site.

Discussion
There was no further discussion of this point.

Question 15
In lieu of individual study synopses in Section 2.7.6, Éclat has provided detailed tables of the study design and results of the efficacy studies (see Attachment J). In addition, a written summary is provided for each of these studies in the Integrated Summary of Efficacy. Does the Agency agree with this approach?

FDA Response
Your NDA should be organized in the following manner:

1. **Section (S) 2.5 – Clinical overview of your major findings from the published literature and how they contribute to your proposed labeling. Each indication you propose should be in a separate subheading (e.g., 2.5.1. Treatment… &** (b) (4)

2. **Section 2.7 – This section should include Clinical Summaries of Efficacy (S2.7.3) and Safety (S2.7.4). Each indication you propose should be in a separate subheading (e.g., 2.7.3.1. Treatment Efficacy… &** (b) (4) **). Each should be initiated with a tabular summary of the studies relevant to that Section. The content of these sections should be directed by ICH M4E and S. Since the NDA relies on published literature as the sole source of substantial evidence, the actual references should be placed in Module 5, rather than 2.7.5, where references are typically inserted. Your synoptic outlines should be placed in S2.7.6.**

3. **Section 5.3 – Your references from published literature should be included in the appropriate Subsection of 5.3, depending on the type of study in each paper. Your Integrated Summary of Efficacy and Safety should be in Section 5.3.5.3. Safety analyses from AERS should be included n Section 5.3.6 with individual Medwatch forms included in 5.3.7.**

4. **In general, you should provide hyperlinking throughout these sections to facilitate review of your application.**

These recommendations are consistent with the following documents.

1. **Guidance for Industry: *ICH M2 EWG Electronic Common Technical Document Specification* http://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0435-gdl0002-vol1.pdf**

2. **Guidance for Industry*: M4: Organization of the CTD* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129873.pdf**

3. **Guidance for Industry: *M4E: The CTD – Efficacy***
   http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129865.pdf

Discussion
The Sponsor stated that they will organize the application as the Agency prefers, but they were not clear how this was different from their Neostigmine NDA. The Division stated that, if the application is mapped well and items can be easily found, it would probably be acceptable, but the Division prefers the organizational method that we have specified.

Regulatory

Question 16
Does the Agency agree that the indications "for the treatment of hypotension during anesthesia" (b) (4) *are appropriate for this product? Would bundling these two indications in a single submission be considered acceptable?*

FDA Response
As stated, whether your proposed indications for this product are acceptable will be determined upon review of your NDA. An initial NDA submission permits submission of any number of indications in one application for one user fee. "Bundling" is a term more often applied to subsequent supplemental NDA (sNDA) submissions following NDA approval, and/or grouping of sNDAs which propose the same change to multiple applications. Each sNDA may provide for only one change, but the Agency may decide to "bundle" several together and review them together for efficiency.

Discussion
There was no further discussion of this point.

Question 17
According to the announcement for the September 13, 2012 Cardiovascular and Renal Drugs Advisory Committee meeting, West-Ward Pharmaceutical Corp., has submitted an NDA for phenylephrine hydrochloride injection. It is Éclat's understanding that if West-Ward is granted approval after Éclat's 505(b)(2) NDA has been submitted, the Agency will continue to review our 505(b)(2) NDA. We also understand that at the end of Éclat's review, it will be possible, given the acceptability of the submission, for the Agency to grant approval of a second 505(b)(2) NDA for the same drug product. Would the Agency please confirm that this understanding is correct?

FDA Response
If a pharmaceutically equivalent product is 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), then FDA may refuse to file your application as

a 505(b)(2). Certain changes to a product that would normally allow for submission as an ANDA under a suitability petition are not permitted for injectable products. Refer to 21 CFR 314.94(a)(9)(iii) for further details on this matter.

If a (b)(2) application is submitted that contains indications other than or in addition to the indication(s) approved in a pharmaceutically equivalent product, we will evaluate the submission to determine whether the evidence is sufficient to support the additional indications.

Discussion
The Agency clarified that the wording "may refuse to file" is taken directly from the regulations (21 CFR 314.101(d)(9)), but noted that the policy currently is interpreted as we would refuse to file the newer application if the formulations are identical. The Division noted that, for injectable drug products, when certain components (e.g., tonicity agents, etc.), differ between formulations, as specified in the regulations, the latter product cannot be a generic (ANDA) application. The Sponsor stated that they do not know how their product formulation compares to the Westward formulation at this time.

Regarding the indication, the Agency stated that it may be hard to generalize the use of the product to larger populations. The Sponsor will need to justify whatever they propose and clarify how the data they are providing are supportive of the proposal. The Division stated that the firm would need to explain why they were "carving out" a specific indication, if they were to propose such an approach.

Question 18
The announcement for the September 13, 2012 Cardiovascular and Renal Drugs Advisory Committee meeting listed the indication for West-Ward's phenylephrine hydrochloride injection NDA as "to increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension." Éclat's proposed indication is for the treatment (b) (4) *of hypotension during anesthesia. If West-Ward is granted marketing approval prior to Éclat's NDA submission, would the indications be considered different enough to allow the submission of Éclat's 505(b)(2) NDA?*

FDA Response
The indication for West-Ward's product will not be finalized until the time of approval of their NDA. Whether or not two products have the same or different indications can only be determined after the first product has been approved and the second product's application has been submitted.

Discussion
The Sponsor stated that they intend to submit a 505(b)(2) NDA relying on literature for the application's approval. They are aware that there is another phenylephrine NDA from Westward Pharmaceuticals currently under review by the Agency and that it may have an impact on their application. The firm stated that they do not know if the Westward NDA will be approved, or what indication it would have, and inquired how these issues may affect their

ability to submit their NDA. The firm stated that they agree with the Agency that the (b) (4) and believe it is, therefore, different enough from the Westward NDA to permit submission of Éclat's application as a 505(b)(2). The Division observed that there would be two separate issues regarding the submission of a 505(b)(2) application. The first would be the clinical appropriateness of the indication, and the second would be the regulatory status. In either case, the Agency cannot comment on the possible outcomes for the Westward NDA.

In regard to the issue of clinical appropriateness, as was noted in the discussion of Question 12, the Division stated that there appears to be a substantial body of literature regarding the treatment of hypotension with phenylephrine via bolus dosing. But the Division also noted that there appears to be a limited amount of published data regarding treatment by infusion dosing. (b) (4) (b) (4) Finally, the Division stated that it is unusual to accept a "paper" NDA (one which relies totally on literature and no actual trials with the product) for a new indication, noting that the data from literature studies are probably not of the same quality, and are probably not as complete, as that which we would normally have from two, adequate and well-controlled clinical trials.

Regarding the regulatory issues, the Agency stated that, if Éclat submits their NDA seeking a single or multiple indications before the Westward NDA is approved, the Agency would accept it for review, assuming that it met all of the requirements for filing. If, however, another sponsor's application for an identical indication were to be approved prior to Éclat's submission, we would refuse to file a 505(b)(2) application because your product would be a "duplicate" of a listed drug. If the indication(s) proposed in Éclat's NDA was different from any approved application for the product, we would file and review the application.

Additional Regulatory Comments

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 Draft Guidance for Industry: *Applications Covered by Section 505(b)(2)* 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).

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 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(s) upon which a sponsor relies. You must also 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 must 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 is scientifically appropriate.

Discussion
There was no further discussion of this point.

Additional Clinical Comments

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

    a. **Study title, authors, and bibliographic data (hyperlinked to reference)**

    b. **Population demographics including average (avg) and range of age, avg and range of weight, and gender and ethnicity composition, a summary of the major comorbidities if presented**

    c. **Medical or surgical procedure of the study, anesthetic technique including anesthetic drug regimens**

    d. **Treatment arms, #s of subject on each treatment, average treatment duration**

    e. **Total dose and range for each treatment arm, as well as the initial dose and titration regimen**

f. Primary endpoint (defined *a priori*), secondary and PK endpoints, method of primary analysis

g. Subject disposition – Percentage by study status

h. Brief efficacy results with tabular support as relevant

i. For each study, you should provide a brief statement characterizing the adequacy of the safety data. Tabulated safety data should list adverse event rates relative to the comparator. Important but uncontrolled safety data should be summarized following this.

j. Your summary of the efficacy and safety data should include comments on the exposure or dose/response data.

Refer to ICH E3 for definitions and guidance on this section.

2. In each section, your discussion of studies should be grouped in the following manner (using accepted CTD bulleting):

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

3. The clinical appropriateness and response to phenylephrine therapy is thought to be dependent on the patient's physiological state, including volume status. You should provide a summary of data on these factors to guide dosing and administration.

Discussion
There was no further discussion of this point.

OTHER IMPORTANT INFORMATION

PREA PEDIATRIC STUDY PLAN

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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.

ADDITIONAL GENERAL COMMENTS FOR PRE-NDA STAGE OF DRUG DEVELOPMENT

Refer to Attachment 1 (below)

ISSUES REQUIRING FURTHER DISCUSSION

1. **Post-Meeting Note #1**

The issue of separating out indications and fileability was addressed again shortly after the meeting. Ms. Jennifer Stevens of ORP and members of the Division held a brief teleconference with the Sponsor on September 28, 2012. During the call another question arose which the Sponsor conveyed via email to the Division after the call. The Division provided an e-mailed response to the question that had been received from the Sponsor. Both the Sponsor's question and our response are reproduced below.

Assuming the following:

a) West-Ward receives approval of a treatment indication prior to Éclat's 505(b)(2) NDA submission;
b) Éclat's NDA is submitted with both treatment (b) (4) indications;
c) both Éclat indications are accepted for review; and
d) during the review, (b) (4) there is adequate support for the approval of the treatment indication (which is a duplicate of West-Ward's approved indication);

Will the Agency grant approval of Éclat's treatment indication alone?

FDA Clarification

As you know, under 21 CFR 314.101(d)(9), the Agency may refuse to file an application submitted through the 505(b)(2) pathway for a duplicate of a listed drug that is eligible for approval under section 505(j). However, a person seeking approval of a drug product that represents a change from a listed drug (including a new indication) and for which investigations, other than BA or BE studies are essential to approval, may submit an application through the (b)(2) pathway under 21 CFR 314.54(a). If the Agency determines your application is fileable, both indications will be reviewed. An ultimate determination that the application does not support the second (non-duplicate) indication will not result in the Agency forcing you to withdraw your application to resubmit it through the 505(j) pathway. Please note, however, that this response does not address any patent issues that may arise under this scenario.

2. **Post-Meeting Note #2**

The following question was raised by the firm via email on October 17, 2012, after the meeting took place. The Division agreed to provide guidance in a Post-Meeting Note.

During the meeting, Éclat asked for clarification regarding the organization of 2.7.3 and 2.7.4 as well as the ISE and ISS. In the briefing package submitted to the Division on August 13, 2012, the firm included all detailed discussion of the efficacy and safety findings in the ISE and ISS, respectively. In Sections 2.7.3 and 2.7.4, the firm had included only brief, high-level summaries of the key information contained in the ISE and ISS, respectively. Their reasoning

behind taking this approach was feedback that was received from the Division during Éclat's meeting on May 16, 2012 to discuss their neostigmine NDA.

Based on the preliminary responses and feedback received during this meeting however, it appears that the clinical reviewer (Dr. Breder) would prefer that the bulk of the discussion of the efficacy and safety findings be housed in Module 2. It is the firm's intention to move the detailed presentation in the ISE and ISS submitted in the briefing package to Module 2. However, they are unclear as to what information should then be presented in the ISE and ISS for the NDA given that they only have published literature thus making true integration of data impossible. The firm considers there to be a number of options and would appreciate guidance as to which of these is preferred.

- Option 1: Include all detailed discussion in 2.7.3 and 2.7.4. Include brief, high-level summaries of the key efficacy and safety information in the ISE and ISS.

- Option 2: Include all detailed discussion in 2.7.3 and 2.7.4, but link to detailed tables housed in the ISE and ISS.

- Option 3: Present essentially identical information in Module 2 and Module 5.

FDA Clarification
We have provided our preferred organization for the NDA in the response to Question 15. This format is based on the Guidances, which were also included in these comments. Module 2 should be used for summaries and not for detailed discussion. Your third option is only appropriate if your application is based on either a single study or a very small body of literature (e.g., 2 or 3 papers).

ACTION ITEMS (Includes Sponsor Summary of Issues)

1. The Sponsor understands that, if their proposed indication were to be approved with Westward's phenylephrine NDA before Éclat submits their application, then we would not file the Éclat NDA if their formulation was identical to the Westward formulation or differed only in terms of a preservative, buffer, or antioxidant as per 21 CFR 314.94(a)(9)(iii) . If Éclat proposes additional indications which were not approved for the Westward product at the time of Éclat's NDA submission, they would be filed and reviewed, assuming the NDA was otherwise acceptable for filing. [See clarification on this point in Post-Meeting Note #1 above.]

2. The Sponsor understands that, if the Westward NDA were to be approved with an identical indication to that which Éclat is proposing, (b) (4)

3. The Sponsor understands that, if the formulations and indications of the two products are the same or differ only in terms of a preservative, buffer or antioxidant (as per 21 CFR 314.94(a)(9)(ii)), the

application must be filed as an ANDA. If the formulation contained an ingredient(s) that the regulations specify would preclude the application from being an ANDA, it could be filed as a 505(b)(2) NDA.

4. The Sponsor understands that timing is critical. If the Westward NDA has not yet been approved at the time of submission of the Éclat NDA, the Éclat NDA could be filed for Agency review.

5. The Sponsor understands that, if they propose use of the product in a specific population, they will need to provide appropriate justification and support for that proposal.

(b) (4)

7. The Sponsor understands that, if they submit their application with less than the required stability data, we may determine that the application cannot be filed.

8. The Sponsor indicated that they would follow Chapter 659 for sterility issues.

9. The Division committed to having additional interaction with the firm if and when the Westward NDA is approved to help them determine if their proposed indications are "different enough" from that approved in the Westward NDA to allow a 505(b)(2) filing.

ATTACHMENTS AND HANDOUTS
See "Attachment 1" below. This was provided to the firm with the Division's preliminary responses.

Attachment 1:
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. 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/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 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/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf).

   Note that you may only rely on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling for the listed drug(s). You may not reference data in the Summary Basis of Approval or other FDA reviews obtained via the Freedom of Information Act or publically posted on the CDER website to support any aspect of your development program or proposed labeling of your drug product. Reviews are summary data only and do not represent the Agency's previous finding of safety and effectiveness.

   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). 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 is scientifically appropriate.

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. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.

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.

6. Refer to the following guidance when submitting the NDA application:
Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, available at
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072171.pdf.)

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

Pediatric Plan

You must submit a pediatric plan with the NDA submission regarding studies in pediatric patients to be conducted to fulfill the requirements of the Pediatric Research Equity Act (PREA). The plan must include the studies to be conducted; a timeline for the studies that states for each study, the date of final protocol submission, date of study start, date of study completion, and date of final study report to be submitted to the Agency; requests for waivers and deferrals with justifications; and, where possible, protocol synopses of the proposed studies.

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 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 HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT 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		

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

/s/

KIMBERLY A COMPTON
10/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 113044

MEETING MINUTES

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

Attention: Theresa Allio, Ph.D.
Senior Consultant

Dear Dr. Allio:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Phenylephrine HCl Injection, USP.

We also refer to the meeting between representatives of your firm and the FDA on November 17, 2011. The purpose of the meeting was to address questions related to preparations for submitting a New Drug Application for this product.

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) 301-796-1191

Sincerely,

{See appended electronic signature page}

Kimberly A. Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND
Meeting Date and Time: November 17, 2011, 12:00 noon
Meeting Location: White Oak Conference Room 1309
Application Number: 113044
Product Name: phenylephrine HCl injection, USP
Indication: (b) (4)
Sponsor/Applicant Name: Eclat Pharmaceuticals
Meeting Chair: Rigoberto Roca, M.D. Deputy Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAAP

Industry Representatives	**Title**
Michael S. Anderson	President and Chief Executive Officer, Éclat Pharmaceuticals
Scott A. Macke	Director of Operations, Éclat Pharmaceuticals
(b) (4)	
Joel I. Falk	Executive Vice President, The Weinberg Group Inc.
Nicholas M. Fleischer, R.Ph., Ph.D.	Vice President, The Weinberg Group Inc.
Robert I. Roth, M.D., Ph.D.	Medical Director, The Weinberg Group Inc.
Carolyn S. Rabe, Ph.D.	Senior Consultant, The Weinberg Group Inc.
Theresa Allio, Ph.D.	Senior Consultant, The Weinberg Group Inc.
FDA	**Title**
Bob A. Rappaport, M.D.	Director, DAAAP
Rigoberto Roca, M.D.	Deputy Director, DAAAP
Arthur Simone, M.D., Ph.D.	Medical Officer, DAAAP
Huiqing Hao, Ph.D.	Pharmacology/Toxicology Reviewer, DAAAP
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAAAP
David Lee, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader
Sally Loewke, M.D.	Unapproved Drugs Coordinator, Office of New Drugs (OND)
Kim Compton	Senior Regulatory Project Manager, DAAAP

BACKGROUND

The purpose of the meeting was to discuss the suitability of the current scientific literature to support the submission of a new drug application (NDA) for the product. No prior discussion or interactions on this product have taken place between this Division and this Sponsor.

On November 13, 2011 (prior to the November 17, 2011, meeting), the Agency forwarded to the firm our comments and responses to the questions posed by the Sponsor in their October 6, 2011, meeting package.

The meeting entailed further discussion of the General Clinical Comments as well as Questions 1, 2 and the Clinical Pharmacology Comments.

Presented below are the Agency's November 13, 2011, comments and responses to questions in the background meeting package, followed by a summary of relevant discussion that took place at the meeting itself. The Sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. Discussion that took place at the meeting is captured in normal text following the question to which it pertains.

DISCUSSION

The Sponsor opened the meeting by stating that they intended to bring this marketed product under NDA approval in line with the marketed, unapproved drugs guidance. They stated that they intended to rely on literature to support the application.

NONCLINICAL

Question 1
Does the Agency agree that the toxicology information described in this package is adequate to support the submission of an NDA for phenylephrine hydrochloride injection (b) (4)

FDA Response
For a 505(b)(2) application that relies on information in the public domain, the referenced nonclinical literature dose 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 phenylephrine drug should be necessary to support an NDA application. Nevertheless, as the existing data do not appear to contain adequate information regarding the mutagenic potential and impact on reproductive and developmental toxicity of phenylephrine, 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 has not previously 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 given the similarity of formulations currently marketed 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.

Discussion

The Division stated that, based on the meeting package, the available data are inadequate to meet the current standards, lacking in vivo genotoxicity data, and a complete battery of reproductive toxicology studies. The Sponsor contended that the available two carcinogenicity studies would be adequate to cover the need for genotoxicity studies. The Division clarified that the genotoxicity studies are designed differently from the carcinogenicity studies and address different questions; for example, the doses used in the in vivo genotoxicity study are much higher than carcinogenicity studies. In addition, the Division indicated that the carcinogenicity studies were completed via the oral route and, therefore, the systemic exposure may have been much lower than that of in vivo genotoxicity studies. The Division stated that these tests are part of the standard battery and that we were not aware of any available genotoxicity data. However, the Division will review the submitted data and justification in the NDA and determine at that time if further studies are warranted. If the submitted data are not deemed adequate, further studies will be considered as post-marketing requirements.

The Division stated that it would be ideal to have peri- and postnatal development and embryo-fetal developmental toxicity data to provide good information on use of the product for procedures such as cesarean sections. In the absence of adequate animal data, the product will be labeled as a Pregnancy Category C. The Division stated that clinical experience could be useful in this regard and suggested that the Sponsor compile all the information they have for the Division to review. If there are adequate and well-controlled human studies that support the conclusion that there is no apparent risk, the product may be labeled a Pregnancy Category B; however, it may be difficult to extrapolate oral exposure to intravenous (IV) exposure. The Division reminded the Sponsor that conclusions based entirely on case reports is different from data obtained via use in a clinical trial.

The Division stated that the Sponsor should analyze the existing information and provide clear justification for how that data support their proposed labeling. The Division also noted that the information appropriate to support labeling should be based on studies that specifically attempted to identify safety signals, and not articles that only describe routine clinical use.

With regard to blood compatibility and local tissue irritation potential, the Sponsor stated that they do not believe that there will be hematocompatability concerns as only a small volume of the product is actually used and there have not been adverse events reported with the currently marketed unapproved drug products that employ the same formulation. The Division indicated that the Sponsor should include their justification in their submission.

Additional Nonclinical Comments pertaining to your NDA submission:

1. **For the NDA submission, any impurity or degradant that exceeds ICH thresholds must be adequately qualified for safety as per (ICH Q3A(R2), ICH Q3B(R2)). Adequate qualification must 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.**

    Note, impurities that contain a structural alert for mutagenicity or are demonstrated to be genotoxic or carcinogenic must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequately justified based on FDA 2008 Draft Guidance "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches". This guidance can be found on the CDER website at the following location: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf. 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 ICHS2A guidance document titled "Guidance on Specific Aspects of Regulatory Genotoxity Tests for Pharmaceuticals". Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, unless otherwise justified.

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 determination if the impurity contains a structural alert for mutagenicity, and how these levels compare to ICH Q3A(R2) and Q3B(R2) qualification thresholds, and 1.5 mcg/day for genotoxic impurity threshold. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

    The NDA submission must contain information on potential leachables and extractables from the drug container closure system. Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled specified route of administration. The approach for toxicological evaluation of the safety of extractables 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). This should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission.

3. **Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and specifically address how the information 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.**

4. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained.**

5. **We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity, degradant, or residual solvent that exceeds the ICH qualification thresholds or if you fail to provide safety justification for extractable/leachables.**

Discussion
There was no further discussion on this point.

CLINICAL

Clinical Comments

On review of your meeting package, we have the following general comments that should be taken into consideration as you prepare your NDA:

1. **The proposed indication:** (b) (4) **A more appropriate wording would be "for the treatment of hypotension during anesthesia." The latter wording more accurately reflects the pharmacodynamic effect of phenylephrine, i.e., it raises blood pressure, and its use during anesthesia, i.e., to counteract the vasodilatory effects of various anesthetic agents and techniques.**

2. **Provide a dosing regimen for the use of phenylephrine that incorporates its pharmacodynamic parameters; specifically, the change in blood pressure that can be expected for a given dose and the duration for which that change will persist.**

The Division-recommended indication allows studies demonstrating the efficacy of phenylephrine for treating hypotension due to drugs used in general anesthesia to be considered as evidence of efficacy when those same drugs are used for sedation. This indication also allows for a finding of efficacy without providing evidence for each anesthetic agent or combination thereof. Specifically, the Division will consider evidence that phenylephrine is effective for treatment of hypotension caused by one inhaled anesthetic agent as evidence of its effectiveness for treatment of hypotension caused by all such agents. This does not mitigate the need to thoroughly search the literature and provide all the evidence that is available to the Agency for review, but it may reduce or eliminate the need to conduct clinical studies to generate data missing from the published literature.

The provision of sufficient clinical data to support a proposed dosing regimen and adequately characterize the risk profile of phenylephrine for that dosing regimen are the other key considerations for determining whether studies reported in the literature will be adequate for supporting an approval of the NDA. In this regard, data from the various clinical studies should be evaluated individually and, to the extent possible, should be integrated to allow a meaningful benefit-risk analysis.

As phenylephrine has been used in the clinical practice of anesthesia for decades, the Division will also consider information contained in standard anesthesia texts regarding the safety and efficacy of dosing regimens of phenylephrine in its benefit-risk assessment. Consistency in dosing regimens between texts and over the course of several editions suggests the regimens are considered relatively safe and effective by the clinical community. While this information alone would not be adequate to support filing of an NDA, it can be considered along with the published literature, some of which was likely to have been the bases for the recommendations in the texts.

The responses to the clinical questions below are based upon a preliminary review of the literature in your submission and the comments made above.

Discussion

The Division advised the Sponsor that they needed to be able to describe appropriate use of the product in the label and suggested that the Sponsor limit the recommended route of administration to the one with the most safety, efficacy and dosing data to support it.

Ultimately, the Division will need [redacted] (b) (4) The Division understands that the dose-response is variable and that the product is typically titrated to effect, but the labeling will have to give a sense of how much of a change a practitioner can expect with a specific dose. If this information is available for only one route, the NDA may be approved for that route alone, but if the data are available for others routes of administration, that information needs to be included in the NDA as well, if only for further characterizing the risk profile despite a limited indication. The Division stated that reporting a

range for dosing could be acceptable, but the goal should be to narrow the range as much as possible. In addition, the Agency will require information about dosing in specific populations for the labeling. This information is also used by the Agency to evaluate the overall risk-benefit balance of the product for determination of approval. If there is not enough information in the literature, it may have to be obtained from other sources.

The Division stated that it would be receptive to a scientific rationale for why evidence of dosing, safety and efficacy for phenylephrine, when used for a particular anesthetic agent, could be applied to all products in that drug class when used for the same anesthetic technique, e.g., the hypotension associated with spinal anesthesia occurs by the same mechanism regardless of the local anesthetic agent used; therefore, evidence of safety and efficacy for a particular dose of phenylephrine for one local anesthetic may serve as evidence of the same for all local anesthetics when used in this fashion.

Question 2
Does the Agency agree that the existing published safety data are adequate to support submission of an NDA for the use of phenylephrine hydrochloride injection for (b) (4)

FDA Response
As noted above, the proposed indication would need to be modified; but regardless of what the final wording is, in order to appropriately label phenylephrine, there needs to be sufficient evidence of safety and efficacy to support the proposed dosing regimen. The label will need to provide clinicians with the following information about phenylephrine:

- (b) (4) **proposed dose and method of administration (i.e., intravenous bolus or infusion)**
- **the risks associated with the proposed dose**
- **dosing modifications, if any, that need to be made for special patient populations,** (b) (4)

The studies provided in the submission do not appear to be adequate, on preliminary review, to provide the needed information. (b) (4)

In our assessment of the safety evaluations performed in the literature submitted, it was noted that, for the El-Tahan (2011) study that you cited, you reported "No additional

data" under the Safety Findings in Table 11-3. However, in the article abstract, the authors note the following:

> **Patients received 0.15 mg/kg of ephedrine showed additional increased heart rate and frequent ischemic episodes ($P < 0.001$). However, those who received phenylephrine showed greater rise in SVRI, reduced CI, SVI, and LVSWI and more frequent ischemic episodes.**

This highlights that an important consideration in the Agency's assessment of published literature and determination of the quality of the data, and thus its adequacy, is the availability of the original protocols and original data from each of the studies. Access to complete protocols allows a more thorough evaluation of the adequacy of the study to assess efficacy and monitor safety. Having access to the original data allows confirmation of the study findings and additional analyses of safety and efficacy. As a greater emphasis can be placed on the findings of studies where this information is available, a diligent effort needs to be made to obtain it for each study cited.

Note that for the Agency to consider published literature in its assessment of the safety (or efficacy) of phenylephrine, you will need to verify that the information from the studies cited is either in the public domain or that you have obtained a right of reference to it.

Discussion

The Division stated that the Sponsor needs to determine whether the use of phenylephrine requires special consideration (e.g., dosing adjustments) or raises unique safety risks (e.g., possible effects on uterine blood flow) for certain patient populations. If information to address these issues can be found in the literature, the Sponsor should submit that to the Agency. In addition, the Sponsor could make the argument that the use of the product is expected to be of very limited duration and, therefore, special dosing, safety and efficacy concerns may not exist for certain conditions, e.g., renal or hepatic insufficiency.

Question 3

Does the Agency agree that the existing published effectiveness data are adequate to support the submission of an NDA for the use of phenylephrine hydrochloride injection (b) (4)

FDA Response

The study by Imran et al. appears to have been designed to capture the types of data necessary to determine the treatment effect of phenylephrine and, therefore, may be supportive of a finding of efficacy for a specific dose of phenylephrine.

The study by El-Tahan evaluated the effects of a single dose of phenylephrine when given prior to induction, along with intravenous infusion of 5 to 7 ml/kg of 6% hydroxyethyl starch 130/0.4. This study may be supportive for phenylephrine use with general anesthesia but only if the extent of the treatment effect of phenylephrine can be discerned from that of the hydroxyethyl starch.

Discussion
There was no further discussion on this point.

Question 4
Does the Agency agree that the existing data from published studies, including randomized, controlled, multicenter studies, provides sufficient documentation to support the safety and efficacy of phenylephrine hydrochloride injection for approval?

FDA Response
As indicated above, the information contained in your submission is not adequate to support filing an NDA, and you will need to identify an appropriate dosing regimen to guide in the gathering of suitable data to allow a benefit risk analysis when the NDA is submitted. The determination of whether the data provided to the Agency are sufficient for an approval will be a matter of review when the NDA is submitted.

Note that safety data related to higher-than-labeled doses of phenylephrine may help support a finding of safety; for lower-than-labeled doses, safety data will be used to identify potential risks but will not be sufficient to support a finding of safety.

Discussion
There was no further discussion on this point.

Question 5
Does the Agency agree that the studies selected as adequate and well-controlled studies fulfill the regulatory requirements and could form the basis of substantial evidence for an NDA?

FDA Response
For the reasons noted in the previous responses, the studies cited in your submission are not adequate, by themselves, to support an NDA submission.

Discussion
There was no further discussion on this point.

Clinical Pharmacology Comments
Address all pertinent clinical pharmacology information related to the following aspects, including but not limited to:

1. **Absorption, Distribution, Metabolism and Elimination of your product**

2. **PK and dosing in special populations (effect of age, gender, hepatic and renal impairment, etc.)**

3. **Drug-drug interaction potential (in vitro enzyme induction and inhibition properties of your drug)**

This information may be obtained from your own studies or from the public domain (if information of adequate quality is available in the published literature). If literature articles are used for obtaining this information, full articles must be included in the NDA.

Discussion
The Division stated that the Sponsor will need to provide information for the label on special populations, drug-drug interactions, and the absorption, distribution, metabolism, and excretion of the product. If any of this information is available in the literature, the Sponsor should provide it for Agency review. The Sponsor will need to address each special population. Ultimately, the Division will need to be able to characterize the risk profile of the product, including for the special populations. These issues must be addressed, and not with hypothetical statements alone. Any data or rationales the Sponsor can provide will be useful in this effort.

The Sponsor stated that they were hoping to assemble a package that would outline their full plan for the NDA submission and discuss it with the Division at an End-of-Phase 2 meeting. This is acceptable to the Division with the understanding that the feedback will be as to whether the planned package appears filable, and that the determination of approvability of the NDA will take place following the review of the submission. The Division encouraged the Sponsor to summarize and integrate, to the extent possible, the data they have available, instead of simply providing the literature.

It was also noted that there may be issues when this product is combined with other products, so the Sponsor should address that as well.

The Sponsor ensured the Agency that it would make a diligent effort to obtain the data that are available for studies reported in the literature, but noted that, in some cases, this will be very difficult or impossible. The Agency stated that the Sponsor should document their efforts in that regard and noted that data supporting dosing, safety and efficacy coming from multiple institutions carries greater weight than data coming from a single source.

Regulatory Comments

1. **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).**

2. **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 must 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 is scientifically appropriate.**

3. **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.**

4. **You indicated that you plan to file this product under a 505b(2) pathway by only relying on literature data. If you plan to rely on the Agency's findings of safety and efficacy of an NDA-approved product as reference, then you need to establish appropriate link to the reference product.**

ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion

SPONSOR SUMMARY OF MEETING (Includes Action Items)

1. The Sponsor understands that they are welcome to propose, in the package insert, as many dosing paradigms as they choose to (e.g., bolus dosing, infusions), provided there are adequate safety and efficacy data to support each paradigm.

2. The Sponsor understands that they may employ the rationale that demonstration of efficacy of phenylephrine treating hypotension induced by one agent in a class implies efficacy for all agents in the class, provided the mechanism by which those agents induce hypotension is identical.

3. The Sponsor understands the nonclinical concerns raised by the Division and that post-marketing requirements may be necessary to address them if the available data are not sufficient.

4. The Sponsor will provide any data that are available and a rationale to support the use of the product in special populations and in order to label it properly in the package insert.

5. The Sponsor understands that the overall goal of the application should be to provide sufficient safety and efficacy information in order for the Division to perform a benefit risk analysis for each indication and dosing paradigm sought and to adequately label the product should it be approved.

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/s/

KIMBERLY A COMPTON
12/19/2011