CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208943Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208943 SUPPL # HFD # 170

Trade Name Corphedra

Generic Name ephedrine sulfate injection

Applicant Name PAR Pharmaceuticals

Approval Date, If Known January 27, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☐ NO ☒

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

A biowaiver was granted for this application.

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

n/a

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

No

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

Product	NDA Number
AKOVAZ (Ephedrine Sulfate)	208289

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

Literature is sugfficient, no additional clinical data required. Literature reviewed to support the approval of NDA 208289/Akovaz/approved Apri; 29, 2016, did not get any exclusivity.

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

Investigation #1

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

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

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

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

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

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

a) For each investigation identified in response to question 3(c): if the investigation was 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:

Investigation #3
!
! NO ☐
IND # YES ☐ ! 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: Ogochukwu Ogoegbunam
Title: Regulatory Health Project Manager
Date: January 18, 2017

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

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

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

/s/

OGOCHUKWU U OGOEGBUNAM
01/27/2017

RIGOBERTO A ROCA
01/27/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208943 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Corphedra Established/Proper Name: Ephedrine Sulfate Dosage Form: Injection		Applicant: PAR Pharmaceuticals Agent for Applicant (if applicable):
RPM: Ogochukwu Ogoegbunam		Division: Anesthesia Analgesia and Addiction Products

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

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

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

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

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 01/27/17

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 January 26, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ 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, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

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

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

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

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

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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

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

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 01/26/17
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)*	05/16/16 05/13/16
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 01/26/17 ☐ None DMEPA: 12/15/16, 09/08/16 ☐ None DMPP/PLT (DRISK): ☒ None OPDP: 01/10/17 ☐ None SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	May 5, 2016 ☐ Not a (b)(2) 12/20/16
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain:	Did not trigger PREA due to recent approval of NDA 208289 for Akovaz (Ephedrine Sulfate Injection); therefore PeRC meeting not necssary
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	01/26/17, 01/25/17, 12/12/16, 11/21/16, 11/04/16, 10/17/16, 10/07/16, 10/04/16, 09/08/16, 09/07/16, 08/18/16, 07/15/16, 05/31/16, 05/16/16, 04/01/16, 03/31/16
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	PIND: 07/08/16

❖ 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 01/27/17
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☐ None 7
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	01/26/17, 03/18/16
• 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)*	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None

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

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 12/14/16, 05/16/16
❖ 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 12/20/16, 05/11/16
❖ 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
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 12/20/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	12/13/16
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 10/24/16 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ 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

Ogoegbunam, Ogochukwu

From: Ogoegbunam, Ogochukwu
Sent: Thursday, January 26, 2017 5:25 PM
To: 'English, Carla'
Subject: RE: NDA 208943 PI

Hi Carla,

Removing the "USP" from the Description section is your discretion. You can remove it for consistency.

Thanks,

Ogo

Ogochukwu U. Ogoegbunam, PharmD
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Ph: 240-402-8807
Email: Ogochukwu.ogoegbunam@fda.hhs.gov

From: English, Carla [mailto:Carla.English@parpharm.com]
Sent: Thursday, January 26, 2017 5:13 PM
To: Ogoegbunam, Ogochukwu
Subject: RE: NDA 208943 PI

Hi Ogo,

One other question, does the Agency want us to remove "USP" from the Description section as well? Refer to highlighted text below.

11 DESCRIPTION
Ephedrine sulfate is an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent. CORPHEDRA (ephedrine sulfate injection, USP) is a clear, colorless, sterile solution for intravenous injection. Each mL contains ephedrine sulfate 50 mg in water for injection as a single-dose product. The pH range is 4.5 to 7.0. The drug product must be diluted before intravenous administration. The chemical name of ephedrine sulfate is (1R,2S)-(-)-2-methylamine-1-phenylpropan-1-ol sulfate (2:1) (salt). Its molecular weight is 428.54.

Carla

Carla English | Senior Manager, Regulatory Affairs
Par Pharmaceutical | Six Ram Ridge Road | Chestnut Ridge, NY 10977
Phone: 845-573-5728 | Fax: 845-573-5795 | carla.english@parpharm.com
www.parpharm.com

From: Ogoegbunam, Ogochukwu [mailto:Ogochukwu.Ogoegbunam@fda.hhs.gov]
Sent: Thursday, January 26, 2017 5:01 PM

To: English, Carla
Subject: NDA 208943 PI

Hi Carla,

Attached is our recommended changes to the Corphedra PI. Provide your label as soon as possible, but no later than 12 p.m. Eastern Time, January 27, 2017.

Please review and accept all the changes you concur with, then submit a WORD copy to us via email that is as clean as possible. Please keep in mind that if Par is proposing more changes to the PI, email as soon as possible as it must be agreed upon by the Division. PAR would then submit a final copy of the agreed upon label to the NDA prior to the PDUFA date.

Please let me know if you have any questions.

Thanks,

Ogo

Ogochukwu U. Ogoegbunam, PharmD
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Ph: 240-402-8807
Email: Ogochukwu.ogoegbunam@fda.hhs.gov

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

/s/

OGOCHUKWU U OGOEGBUNAM
01/27/2017

From:	Ogoegbunam, Ogochukwu
To:	English, Carla (Carla.English@parpharm.com)
Subject:	NDA 208943 Package Insert
Date:	Wednesday, January 25, 2017 11:49:00 AM
Attachments:	corphedra-pacakge-insert 01.25.17.doc

Hi Carla,

Attached is our final set of recommended changes to the Corphedra PI. Provide your label as soon as possible, but no later than 5 p.m. Eastern Time, Wednesday, January 25, 2017.

Please review and accept all the changes you concur with, then submit a WORD copy to us via email that is as clean as possible. Please keep in mind that if Par is proposing more changes to the PI, email as soon as possible as it must be agreed upon by the Division. PAR would then submit a final copy of the agreed upon label to the NDA prior to January 26, 2017.

Please let me know if you have any questions.

Thanks,

Ogo

Ogochukwu U. Ogoegbunam, PharmD
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Ph: 240-402-8807
Email: Ogochukwu.ogoegbunam@fda.hhs.gov

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/s/

OGOCHUKWU U OGOEGBUNAM
01/27/2017

From: Ogoegbunam, Ogochukwu
To: English, Carla (Carla.English@parpharm.com)
Subject: NDA 208943 Information Request
Date: Monday, December 12, 2016 10:45:00 AM

Dear Carla,

Please see the Information Request below and acknowledge receipt. The review team requests a response by **5 PM Eastern Standard Time on Wednesday, December 14, 2016**.

1.The carton labeling currently states “Protect from light.” Add the phrase, “Store in carton.” to appear with the “Protect from light.” statement on the carton labeling.

Please provide this information via return email (attachment is fine) initially so that we can expedite the review. Please follow up with a duplicate hard copy to the IND.

Thanks,

Ogo

Ogochukwu U. Ogoegbunam, PharmD
LT, USPHS Commissioned Corps
Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Ph: 240-402-8807
Email: Ogochukwu.ogoegbunam@fda.hhs.gov

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/s/

OGOCHUKWU U OGOEGBUNAM
12/12/2016

Compton, Kimberly

From: Compton, Kimberly
Sent: Monday, November 21, 2016 3:13 PM
To: Compton, Kimberly
Subject: FW: NDA 208943 - Corphedra

From: Compton, Kimberly
Sent: Friday, October 21, 2016 6:08 PM
To: 'English, Carla'
Cc: Ogoegbunam, Ogochukwu
Subject: RE: NDA 208943 - Corphedra

HI Carla,

Thank you for the updates.

Regarding your question on the set of IRs related to the specifications, our CMC team leader has provided the following clarification:

> There are two issues the team is requesting additional data for.
>
> The first is the request from our nonclinical team regarding the levels of the [redacted] (b) (4)
>
> The second, is from our CMC team, requesting that the impurity specifications at release and stability specifications be set in accordance with ICH Q3B and also, that both sets should be the same or, if not, Par should provide justification for needing a wider limit on stability.

I hope it is helpful to sort out what the Agency is requesting.

Thanks
Kim

From: English, Carla [mailto:Carla.English@parpharm.com]
Sent: Friday, October 21, 2016 2:13 PM
To: Compton, Kimberly
Cc: Ogoegbunam, Ogochukwu
Subject: RE: NDA 208943 - Corphedra

Hi Kim,

In regards the open items for Ephedrine (based on the 74-day letter and your email below), please see responses provided below.

FDA Comment from 10/12/2016 email
We note that in your July 13, 2016, letter responding to our 74 day letter, you state that you were working to provide an up-to-date ISS as soon as possible. Please let us know your timetable for provision of the updated ISS.

Par Update Status

We have been actively working on identification of the ephedrine enantiomer to provide a bridge between our drug product and the ephedrine product used in literature. Our last update was provided to FDA on 10/17/2016. Before moving forward with preparing the updated ISS, ISE and risk/benefit analysis, we are seeking FDA's agreement that the data we've provided to date is sufficient to establish a scientific bridge between the our product and the product used in literature. Once this has been confirmed, we can advise of the timetable for providing the updated ISS.

FDA Comment from 10/12/2016 email
Provision of an English translation of the Kanai paper.

Par Update Status
The translated journal articles will be completed by Oct. 31, 2016. We can submit this information in our November 7, 2016 Information Request response to the Agency October 7, 2016 CMC Information Request (email).

FDA Comment from 10/12/2016 email
Justification for the safety of the drug substance and drug product specifications for (b) (4) *exceeding ICH thresholds, or completion of the required toxicology studies outlined in our July 8, 2015, Pre-IND written responses.*

FDA Comment from 10/7/2016 IR email
In Section 3.2.P.5.1 Specifications the impurities limits listed are not supported by stability data and are not in alignment with ICH impurities guidance Q3B(R2). Tighten specifications to levels scientifically justified by the stability data and in alignment with ICH guidance.

FDA Comment from 74 Day Letter
Provide adequate justifications for the safety of the drug substance and drug product specifications that exceed ICH thresholds beyond the statement that ephedrine sulfate has been on the market in the E.U. and U.S. for several years using the same route of synthesis or submit the results of completed toxicology studies outlined in the July 8, 2015, Pre-IND written responses. Alternatively, you may tighten these specifications to comply with ICH.

Par Update Status
We've received the three comments above and would like the Agency to confirm whether these comments are related to the impurity limits for the drug substance and drug product or the (b) (4) limit. This is the first we are hearing of the comment related to the (b) (4) We believe the Agency is only requesting a response related to our impurity limits (DS/DP) but given that the last comment received included reference to the (b) (4) we'd like confirmation to ensure we adequately address the deficiency comment.

FDA Comment from 74 Day Letter

- *The container closure studies in test report 2012-271R are acknowledged. However, these studies did not utilize vials subjected to worst-case processing conditions. Specifically, a* (b) (4) *, equal to or worst-case to the production cycle, should be included prior to conducting the integrity test. Provide data that demonstrate the proposed commercial container closure system is adequate for use after* (b) (4)

- *Provide the maximum holding time from the* (b) (4) *for the commercial drug product vials.*

Par Update Status
We will provide a response to the comments above when filing our November 7, 2016 IR response.

Please let me know if you need any additional information.

Carla

Carla English | Senior Manager, Regulatory Affairs
Par Pharmaceutical | Six Ram Ridge Road | Chestnut Ridge, NY 10977
Phone: 845-573-5728 | Fax: 845-573-5795 | carla.english@parpharm.com
www.parpharm.com

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/s/

KIMBERLY A COMPTON
11/21/2016

From: Steven Kinsley
To: carla.english@parpharm.com
Cc: Ogochukwu Ogoegbunam
Subject: NDA 208943 CMC Information Request 11-4-16
Date: November 4, 2016

Dear Carla,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, November 29, 2016.

1) We note that you will continue the use of [redacted] (b) (4), and are currently performing USP [redacted] (b) (4), as well as, model solvent extractables studies on the [redacted] (b) (4). In the use of [redacted] (b) (4) [redacted] there is a possibility of residual acid from the [redacted] (b) (4) process that could affect the pH of the drug product, please provide these data reports to the Agency for evaluation.

2) We acknowledge that you have implemented strategies for protecting the drug product from light exposure during manufacturing. Please update the eCTD submission to include light exposure mitigation strategy for your blank commercial master records.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov

Steven
Kinsley

Digitally signed by Steven Kinsley
Date: 11/04/2016 03:02:20PM
GUID: 555cc3bc000836e194b17e8bf695ce5f

Compton, Kimberly

From: Compton, Kimberly
Sent: Monday, October 17, 2016 4:32 PM
To: 'English, Carla'
Cc: Ogoegbunam, Ogochukwu
Subject: RE: NDA 208943 - Corphedra - contact?
Attachments: NDA 208943 74-day letter.pdf

Hi Carla,

I have been trying to reach Rahana Hussain for about a week now and all my emails to her bounce back, and phone calls go to a VM for a name I do not know. I called Par's main # and they connected me to Janis Picurro in Reg Affairs who let me know Rahana is no longer with the company and that you are currently covering Corphedra so I am FWDing the email I originally sent to Rahana last week in the hopes that you can assist with responses.

Please let me know if you have any questions.

Thanks!
Kim Compton

From: Compton, Kimberly
Sent: Wednesday, October 12, 2016 12:40 PM
To: 'Hussain, Rahana'
Cc: Ogoegbunam, Ogochukwu
Subject: Information Requests for NDA 208943 - Corphedra

Hello Rahana,

The team asked me to check in with you on a few items from our May 31, 2106, 74-day latter that appear to still be outstanding. A copy of our original letter is attached for quick reference.

We note that in your July 13, 2016, letter responding to our 74 day letter, you state that you were working to provide an up-to-date ISS as soon as possible. Please let us know your timetable for provision of the updated ISS.

In addition, we note that, as stated in our 74-day letter, the ISE and Risk/Benefit analysis were also needed. Please state your timetable for provision of those items.

Also, we note that the 2 items in our 74-day letter listed under the heading of "Non-Clinical" do not seem to have yet been addressed:

1. Provision of an English translation of the Kanai paper

2. Justification for the safety of the drug substance and drug product specifications for (b) (4) exceeding ICH thresholds, or completion of the required toxicology studies outlined in our July 8, 2015, Pre-IND written responses

Please provide a timeline for provision of these items.

The team is meeting at the end of October and if at all possible, we would like to have these items in house well before that for the team to begin to review so we can discuss them together when we meet.

Thanks
Kim

Kimberly Compton

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

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/s/

KIMBERLY A COMPTON
10/21/2016

From: Lalmansingh, Anika
To: "janis.picurro@parpharm.com"
Cc: Kinsley, Steven (Steven.Kinsley@fda.hhs.gov)
Subject: NDA 208943 - Information Request, 10/7/2016
Date: Friday, October 07, 2016 3:59:00 PM
Attachments: image002.png

Information Request – CMC only

NDA 208943

Good Afternoon Ms. Picurro,

We request submission of the following information by **November 7, 2016**:

1. In Section 3.2.P.5.1 Specifications the impurities limits listed are not supported by stability data and are not in alignment with ICH impurities guidance Q3B(R2). Tighten specifications to levels scientifically justified by the stability data and in alignment with ICH guidance.

2. (b) (4)

3. In section 3.2.P.1 Description and Composition of the Drug Product it is stated "Each 1 mL single use vial contains 50 mg of Ephedrine Sulfate..." and in Table 4 Container Closure System the vial is listed as, (b) (4) Vial, 13 mm Spec #: 3000521." In section 3.2.P.7 Container Closure System Table 1 the vial is listed as, (b) (4) vial, 13 mm." Clarify if the container closure is a 1mL or (b) (4) vial. Clarify the number of milliliters of drug product present in the vial.

4. (b) (4)

(b) (4)

Kindly acknowledge receipt of this email and direct any questions to Steven Kinsley.

Kind Regards.

-Anika

Anika Lalmansingh, PhD
Regulatory Business Process Manager

Center for Drug Evaluations and Research (CDER)
Office of Pharmaceutical Quality (OPQ)
U.S. Food and Drug Administration
Tel: 240-402-0356
anika.lalmansingh@fda.hhs.gov

Anika Lalmansingh

Digitally signed by Anika Lalmansingh
Date: 10/07/2016 04:10:11PM
GUID: 55370d2000cfd6978662b28ff455c2a6

From:	Steven Kinsley
To:	carla.english@parpharm.com
Cc:	Ogochukwu Ogoegbunam
Subject:	NDA 208943 CMC Information Request 10-4-16
Date:	October 4, 2016

Dear Carla,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, October 18, 2016.

1. We acknowledge the risk assessment you provided for Extractable and Leachables in equipment report and wherein you indicate the move to a (b) (4) rather than the (b) (4) one. Please provide the status of implementation of (b) (4).

2. We note that from your development studies you have concluded that the drug product is not light sensitive; however, the USP monographs for the drug substance, Ephedrine Sulfate USP and drug product, Ephedrine Sulfate Injection, USP, recommend protecting from light. Please describe the steps you are taking to prevent exposure to light during manufacturing and storage throughout the shelf life of your drug product.

3. We acknowledge your intention to delete (b) (4) once sufficient data has been gathered from registration and validation batches and submit the data in an Annual Report. Please note that the proposed changes and supporting data are not annual reportable but should be submitted in a Supplement – Changes Being Effected in 30 days per "Guidance for Industry: Changes to an Approved NDA or ANDA".

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov

Steven
Kinsley

Digitally signed by Steven Kinsley
Date: 10/04/2016 01:01:40PM
GUID: 555cc3bc000836e194b17e8bf695ce5f

From: Steven Kinsley
To: Ms. Rahana Hussain
Cc: Ogochukwu Ogoegbunam
Subject: NDA 208943 CMC Information Request 9-8-16
Date: September 8, 2016

Dear Ms. Hussain,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA Thursday, September 22, 2016

1. We acknowledge that you have submitted a formal **Request for Waiver of In-Vivo Study** per 21 CFR §320.22(b)(1) in M.1.12.15. However, the biowaiver request should be submitted per 21 CFR §320.21(a)(2). Also, you need to provide supporting information and/or literature references regarding the in vivo bioavailability/bioequivalence data comparing to the similar drug products in market to permit FDA to assess the biowaiver request of your product.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
240-402-2773

Steven
Kinsley

Digitally signed by Steven Kinsley
Date: 9/08/2016 11:31:09AM
GUID: 555cc3bc000836e194b17e8bf695ce5f

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, September 07, 2016 12:46 AM
To: Hussain, Rahana
Cc: Jani, Parinda; Ogoegbunam, Ogochukwu
Subject: RE: NDA 208943 - Corphedra - Clinical Progress Update

Hello Rahana,

Parinda and Ogo are both out, so I shared your progress report with the team and they asked me to convey the following request to you:

> Provide a list of the 7 articles where you believe you've identified the correct (-) enantiomer.
>
> In addition, provide detailed information on how you were able to identify the correct enantiomer in each of those 7 articles.

Please let me know if you have any questions on our request.

Thanks
Kim Compton

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

From: Hussain, Rahana [mailto:Rahana.Hussain@parpharm.com]
Sent: Tuesday, September 06, 2016 9:08 AM
To: Jani, Parinda; Ogoegbunam, Ogochukwu; Compton, Kimberly
Subject: NDA 208943 - Corphedra - Clinical Progress Update

Dear All,

Please find below a summary of our Clinical Progress for this week:

Total Number of Authors Contacted: 52
Total Number of Authors Replied: 12
Total Number of Publications with (-) Ephedrine: 7

Regards,

Rahana

Rahana Hussain
Manager, Regulatory Affairs
Par Pharmaceutical Six Ram Ridge Road Chestnut Ridge, NY 10977
Phone: 845-573-5792 Fax: 845-573-5795
rahana.hussain@parpharm.com

From: Hussain, Rahana
Sent: Monday, August 22, 2016 3:01 PM
To: 'Jani, Parinda'; Ogoegbunam, Ogochukwu; Compton, Kimberly
Subject: NDA 208943 - Corphedra - Clinical Progress Update

Dear All,

Please find below a summary of our Clinical Progress:

Total Number of Authors Contacted: 52
Total Number of Authors Replied: 12
Total Number of Publications with (-) Ephedrine: 6

Regards,

Rahana

Rahana Hussain
Manager, Regulatory Affairs
Par Pharmaceutical Six Ram Ridge Road Chestnut Ridge, NY 10977
Phone: 845-573-5792 Fax: 845-573-5795
rahana.hussain@parpharm.com

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/s/

KIMBERLY A COMPTON
09/07/2016

Jani, Parinda

From: Jani, Parinda
Sent: Thursday, August 18, 2016 9:06 AM
To: 'rahana.hussain@parpharm.com'
Subject: NDA 208943/ Information Request

Dear Rahana:

Please submit a formal request to waive the requirement to conduct in vivo bioavailability or bioequivalence studies for your drug product per the requirements of 21 CFR 320.22. We would appreciate it if you can submit it by August 25, 2016.

Sincerely,

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Tel # (301) 796-1232

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/s/

PARINDA JANI
08/18/2016

From: Steven Kinsley
To: janis.picurro@parpharm.com
Cc: Ogochukwu Ogoegbunam
Subject: NDA 208943 CMC Information Request 7-15-16
Date: July 15, 2016

Dear Janis,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA Friday, August 05, 2016.

1. Table 1.4.1 in Module 1 is where issuers of the Letters of Authorization (LOAs), e.g. DMF holders, place original LOA's. Remove Table 1.4.1 and show the copies of LOAs in section 1.4.2.
2. Remove the references to Biological Master Files, OB-MF (b) (4) and BB-MF (b) (4), from the table of LOAs.
3. (b) (4) are not listed on the 356h form. Submit a 356h listing DMFs (b) (4).

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
240-402-2773

This document is a PDF copy of an e-mail sent to the e-mail address and on the date given above.

Steven Kinsley -A

Digitally signed by Steven Kinsley -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Steven Kinsley -A, 0.9.2342.19200300.100.1.1=2001720189
Date: 2016.07.15 15:42:26 -04'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208943

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Par Sterile Pharma, LLC
Six Ram Ridge
Chestnut Ridge, NY 10977

Attention: Rusana Hussain
Manager, Regulatory Affairs

Dear Ms. Hussain:

Please refer to your New Drug Application (NDA) dated and received March 18, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Corphedra (Ephedrine Sulfate) Injection, 50 mg/mL.

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 January 18, 2017.

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 December 21, 2016.

We are not currently planning to hold an advisory committee meeting to discuss this application.

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

Clinical

1. The ISS, ISE, and risk/benefit analysis are missing. The Clinical Summary of Efficacy in Module 2.7.3 does not contain the required elements of an ISE as per the requirements of 21 CFR 314.50(d)(5)(v).

2. The scientific bridge that links your ephedrine product to the ephedrine products used in literature is missing. You have not identified which ephedrine enantiomer is used in the studies submitted to support efficacy and safety.

3. The rationale for the applicability of foreign data to U.S. practice is missing.

4. There are discrepancies in the dose selection within the submission. You propose dosing for (b) (4) treatment (b) (4) against anesthetic-induced hypotension; however, you are only seeking an indication for treatment.

5. Your proposed indication is for treatment of hypotension due to anesthesia, yet the majority of the publications you provided discuss use as (b) (4) against hypotension.

6. You have not specified which publications you want to use to support efficacy and which publications you want to use to support safety.

Non-Clinical

7. The drug substance and drug product specifications for (b) (4) exceed ICH thresholds. Also, you have neither provided adequate justifications for the safety of these specifications nor have you completed the required toxicology studies outlined in the July 8, 2015, Pre-IND written responses.

8. We also note that you cited findings from Kanai (1987); however, this paper was written in Japanese.

Clinical Pharmacology

9. Only four subjects have been used for each dose level of your PK/PD study. Whether the data can be used to support approval and labeling of your product will be a review issue based on quality of the data.

Chemistry, Manufacturing & Controls

10. The requested (b) (4) expiry does not appear to be a commercially viable product.

Biopharmaceutics

11. There is no formal request to waive the requirement to conduct in vivo bioavailability or bioequivalence studies for your drug product per 21 CFR 320.22.

12. The osmolality unit for the three registration batches in Table 2 of M.3.2.P.5.4.1 is unclear.

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

We request that you submit the following information:

1. Submit the ISS, ISE, and risk/benefit analysis.

2. Submit a scientific bridge that links your ephedrine product to the ephedrine products used in literature is missing. This could be accomplished via identification of the ephedrine enantiomer used in the studies submitted to support efficacy and safety.

3. All journal articles submitted as part of your NDA must be translated into English. Submit translations of all articles not in English along with the credentials of the person who translated the article.

4. Provide adequate justifications for the safety of the drug substance and drug product specifications that exceed ICH thresholds beyond the statemetn that ephedrine sulfate has been on the market in the E.U. and U.S. for several years using the same route of synthesis or submit the results of completed toxicology studies outlined in the July 8, 2015, Pre-IND written responses. Alternatively, you may tighten these specifications to comply with ICH.

5. The container closure studies in test report 2012-271R are acknowledged. However, these studies did not utilize vials subjected to worst-case processing conditions. Specifically, a (b) (4) equal to or worst-case to the production cycle, should be included prior to conducting the integrity test. Provide data that demonstrate the proposed commercial container closure system is adequate for use after (b) (4)

6. Provide the maximum holding time from the (b) (4) for the commercial drug product vials.

7. (b) (4)

8.

9. (b) (4)

10.

11.

12. We note the inclusion of a letter of authorization for DMF BB (b) (4). However, this DMF is not located within CDER and is not accessible to support this review. Please provide a letter of authorization for a CDER DMF that describes the (b) (4) process for the proposed stoppers.

13. Provide additional stability data at the 12-month time point to support a commercially viable expiry.

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

15. Clarify the osmolality unit for the three registration batches in Table 2 of M.3.2.P.5.4.1.

PRESCRIBING INFORMATION

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

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

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

1. White space is not present before each major heading in the Highlights (HL).

2. Each summarized statement or topic in HL does not reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information.

(b) (4)

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by June 21, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

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

PROMOTIONAL MATERIAL

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

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Ogochukwu Ogoegbunam, PharmD, Regulatory Project Manager, at (240) 402-8807.

Sincerely,

{See appended electronic signature page}

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

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/s/

SHARON H HERTZ
05/31/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208943

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Par Sterile Products, LLC
Six Ram Ridge
Chestnut Ridge, NY 10977

ATTENTION: Janis A. Picurro
Executive Director, Regulatory Affairs

Dear Ms. Picurro:

Please refer to your New Drug Application (NDA) dated and received March 18, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ephedrine Sulfate Injection, 50 mg/mL.

We also refer to your correspondence, dated and received March 18, 2016, requesting review of your proposed proprietary name, Corphedra.

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

If any of the proposed product characteristics as stated in your March 18, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Ogochukwu U. Ogoegbunam, Regulatory Project Manager in the Office of New Drugs, at (240) 402-8807.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
05/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208943

PROPRIETARY NAME ACKNOWLEDGEMENT

Par Sterile Products, LLC
Six Ram Ridge
Chestnut Ridge, NY 10977

ATTENTION: Janis A. Picurro
Executive Director, Regulatory Affairs

Dear Ms. Picurro:

Please refer to your New Drug Application (NDA) dated and received March 18, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ephedrine Sulfate Injection, USP, 50 mg/mL.

We acknowledge receipt of your correspondence, dated and received March 18, 2016, requesting a review of your proposed proprietary name, Corphedra.

If the application is filed, the user fee goal date will be June 16, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Ogochukwu Ogoegbunam, Regulatory Project Manager, in the Office of New Drugs at (240) 402-8807.

Sincerely,

{See appended electronic signature page}

Davis Mathew, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DAVIS MATHEW
04/01/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208943

NDA ACKNOWLEDGMENT

Par Sterile Products, LLC
Six Ram Ridge
Chestnut Ridge, NY 10977

Attention: Janis A. Picurro,
Executive Director, Regulatory Affairs

Dear Ms. Picurro:

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

Name of Drug Product: Corphedra (Ephedrine Sulfate Injection, USP) Injection 50 mg/mL

Date of Application: March 18, 2016

Date of Receipt: March 18, 2016

Our Reference Number: 208943

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 May 17, 2016, 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).

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

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

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

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

If you have any questions, contact me, at (240) 402-8807 or ogochukwu.ogoegbunam@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ogochukwu Ogoegbunam, PharmD
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/

OGOCHUKWU U OGOEGBUNAM
03/31/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

PIND 126012

**MEETING REQUEST-
WRITTEN RESPONSES**

Par Sterile Products, LLC.
One Upper Pond Road
Building D, 3rd floor
Parsippany, NJ 07054

Attention: Sharif Ahmed
Director of Regulatory Affairs

Dear Mr. Ahmed:

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

We also refer to your submission dated March 4, 2015, and received March 6, 2015, containing a pre-IND meeting request. The purpose of the requested meeting was to discuss the development program for Ephedrine Sulfate Injection.

Further reference is made to our Meeting Granted letter dated March 16, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting. The enclosed document constitutes our written responses to the questions contained in your March 30, 2015, background package.

If you have any questions, call me at (301) 796-1232.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	Type B
Meeting Category:	Pre-IND
Application Number:	PIND 126012
Product Name:	Ephedrine Sulfate Injection, USP
Indication:	Increasing blood pressure in patients with clinically important hypotension resulting primarily from vasodilation, in such settings as anesthesia.
Sponsor Name:	Par Sterile Products, LLC.
Regulatory Pathway:	505(b)(2)

1.0 QUESTIONS AND RESPONSES

A. REGULATORY QUESTIONS

Q.1) 505(b)(2) NDA Pathway

Background: Because of the long history of use of Ephedrine Sulfate Injection, the similarities to the recent 505(b)(2) NDA approvals of two phenylephrine hydrochloride injection drug products, and especially, the extensive publication of GLP nonclinical toxicology and well-controlled clinical studies, Par believes that adequate documentation of the efficacy, safety, and use exists in the literature and that it is appropriate to submit Ephedrine Sulfate Injection USP for approval under the 505(b)(2) NDA pathway.

Question: Does the Division agree with this approach? Does the Division have any specific recommendation regarding Par's use of an 505(b)(2) NDA regulatory pathway for the approval of Ephedrine Sulfate Injection USP?

FDA Response:
Submission of an application for ephedrine under the 505(b)(2) NDA pathway is an acceptable approach. Refer to the response to the response to Question 16, as well as the additional general comments below under "505(b)(2) Regulatory Pathway."

Q.2) Marketing Exclusivity
Background: If this 505(b)(2) NDA will be the first NDA to be submitted for Ephedrine Sulfate Injection USP, Par believes ephedrine may be considered a new chemical entity and therefore, entitled to 5 years of exclusivity after NDA approval.
Question: Does the Division agree that Ephedrine Sulfate Injection USP will be considered a NCE and be entitled to 5 years of data exclusivity after NDA approval?

FDA Response:
The Agency does not make exclusivity determinations pursuant to Sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food Drug and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA.

Q.3) Pediatric Assessment: PREA

Background: The Division approved two 505(b)(2) NDAs for Phenylephrine HCl Injection USP for treatment of clinically important hypotension resulting primarily from vasodilation in the last several years. The PREA pediatric study requirements were waived for these drug products for ages 0 to <12 years because necessary studies are impossible or highly impracticable. The submission of a pediatric study for ages ≥ 12 to 16 years was deferred until post-approval. Par believe a similar pediatric waiver for ages 0 to <12 year and a deferral of pediatric studies for ages ≥ 12 to 16 will be appropriate for Ephedrine Sulfate Injection, USP.

Question: Does the Division agree that a pediatric waiver for ages 0 to <12 year and a deferral of pediatric studies for ages ≥ 12 to 16 is likely to be appropriate for Ephedrine Sulfate Injection USP?

FDA Response:
We agree that it is reasonable to request a waiver from the PREA study requirements for patients between the ages of 0 and 12 years. However, you must provide supporting evidence that these studies are impossible or highly impractable.

Similarly, a request for a deferral in a particular age group must be accompanied by supporting evidence and/or rationale for the deferral. This assessment must also address the timing of the proposed pediatric clinical trials, which should begin when sufficient nonclinical and adult human data (if applicable) are available to conclude either that:

1. **The risk of administering an investigational product is no more than a minor increase over minimal risk, and thus could proceed under 21CFR §50.53 (assuming other conditions are met); or,**

2. **Administering an investigational product offers a sufficient prospect of direct benefit to justify the risk, and the relation of anticipated benefit to risk is comparable to available alternatives, and thus could proceed under 21 CFR §50.52.**

In addition, refer to the additional comments below under "PREA Requirements."

Additional Nonclinical comment:

Based on our preliminary review of the published literature a juvenile animal study will be required based on the lack of clinical and nonclinical data to support the safety of ephedrine intended for use in pediatric patients, particularly in regard to the potential impact of ephedrine administration to the developing juvenile brain. Therefore, you must provide a detailed outline of the juvenile animal study that will be conducted, including what CNS toxicological endpoints you will employ in the study design to address our concern for any adverse effects of ephedrine on juvenile brain development, along with a justification for your selection of species and the age of the animal to be tested. Refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf.

Also, because your drug product is centrally active and expected to cross the blood brain barrier, your juvenile animal study should include evaluation of at least seven brain slices rather than the standard three slices. We refer you to the following recent publications that discuss the rationale behind increasing the number of brain slices in toxicology studies. If you elect to evaluate alternative slices based on the predicted sensitivity of the specific tissues examined to your drug product, your protocol should include justification for the slices selected.

1. **Bolon,B., Garman,R.H., Pardo,I.D., Jensen,K., Sills,R.C., Roulois,A., Radovsky,A., Bradley,A., Andrews-Jones,L., Butt,M., and Gumprecht,L. (2013). STP position paper: Recommended practices for sampling and processing the nervous system (brain, spinal cord, nerve, and eye) during nonclinical general toxicity studies. Toxicol Pathol. 41, 1028-1048.**

2. **Rao,D.B., Little,P.B., Malarkey,D.E., Herbert,R.A., and Sills,R.C. (2011). Histopathological evaluation of the nervous system in National Toxicology Program rodent studies: a modified approach. Toxicol. Pathol. 39, 463-470.**

B. CHEMISTRY, MANUFACTURING, AND CONTROLS QUESTIONS

(b) (4)

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Question: Does the Division have any comments on Par's proposed commercial drug product specifications for Ephedrine Sulfate Injection USP?

FDA Response:
We have the following comments regarding the proposed drug product specifications:

1. **Include testing for osmolality as part of the release testing.**

2. **Include a specification for appearance, color and visibility of any precipitation.**

3. **Two methods of identification are required as part of drug product testing.**

4. **Testing for** (b) (4) **must be maintained throughout stability testing. Once there is sufficient product history, a request to** (b) (4) **may be submitted via a CBE-30 supplement.**

Q.6) Drug Product Stability Data

Question: Given the simple and stable formulation of Par's Ephedrine Sulfate Injection USP, the packaging presentation that is the same as currently marketed in the U.S., and the ongoing shortage of this drug product in the US, would it be acceptable to the Division for Par to submit its 505(b)(2) NDA with (b) (4) *of long-term stability data (25 ± 2°C/60 ± 5% RH) and 6 months of accelerated stability data (40 ± 2°C/ 75 ± 5% RH) in both upright and inverted orientations from 3 Primary Stability lots. Additional long-term stability data would be provided during the Agency review of the NDA.*

FDA Response:
No, we do not agree with your proposal. Per ICH Q1A(R2), 12 months of data under long-term storage conditions and 6 months of data under accelerated conditions is expected at the time of submission. (b) (4) **stability data would not be sufficient to allow us to grant a commercially viable expiry period. Refer to the guidance for industry: *Q1A(R2) Stability Testing of New Drug Sustances and Products,* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073369.pdf**

Q.7)Future Development Questions about Par's Ephedrine Sulfate Injection USP Drug Product

Background: Par is in the initial stages of its development of Ephedrine Sulfate Injection USP drug product. No specific issues or difficulties are anticipated during the development of this parenteral dosage form with a simple formulation and standard container closure system.

Question: If Par has additional CMC questions related to its development of Ephedrine Sulfate Injection USP drug product, may these be sent to the Division in a written format if Par has not yet submitted an NDA?

FDA Response:
Yes, you may send additional CMC questions to the Division.

C. CMC AND NONCLINICAL QUESTION

Q.8) Qualification of Drug Product Degradation Products

Background: Par intends to manufacture 3 registration/primary stability lots of Ephedrine Sulfate Injection USP drug product using Ephedrine Sulfate USP from the commercial drug substance manufacturer, (b) (4) *Forced degradation studies will be conducted in parallel with long-term and accelerated stability studies to evaluate the degradation product profile in Ephedrine Sulfate Injection USP drug product at release and during storage.*

Question: In case any degradation products in Par's Ephedrine Sulfate Injection USP are present at, and need to be controlled at, levels above the ICH Q3B qualification threshold of (b) (4) *%, does the Division agree with a strategy to qualify the general safety of any such degradation products by a GLP-compliant, comparative 2-week repeat-dose studies in one rodent species [e.g., vehicle control, drug substance alone, and drug substance spiked with the impurity(ies)]?*

FDA Response:
Although your proposal is consistent with ICH Q3B(R2) guidance, we strongly recommend that you conduct the GLP repeat-dose toxicology study with the isolated drug product degradant. This study design provides far greater ability to characterize the safety of the actual drug product degradant as it permits the use of multiple doses of the compound and eliminates the confounding impact of the ephedrine molecule. If you cannot test the isolated impurity, you may provide a detailed discussion why you cannot test the isolated impurity and you may then test the ephedrine spiked with the impurity. In this case, we recommend that you still test at least three different doses of the impurity in order to provide a toxicological characterization of the compounds effects.

We remind you that to qualify any impurity or degradant that exceeds ICH qualification thresholds, you must also conduct a minimal genetic toxicology screen with those impurity(ies) that exceed the relevant ICH qualification threshold. See Additional Nonclinical Comment 3 below for further information.

D. NONCLINICAL QUESTIONS

Q.9) General Toxicity

Background: The National Toxicology Program (NTP) conducted GLP rat and mouse 14-day and 13-week in-feed oral general toxicity studies, to support rat and mouse 2-year carcinogenicity (CA) studies. Although the route of administration was oral in-feed, and not intravenous, these published studies provide good safety evaluation data. The main effect of treatment with ephedrine for 14 days and 13 weeks was significant reductions in body weights, indicating a maximum tolerated dose (MTD) was achieved.

Question: Does the Division agree that the published toxicology data provided in the NTP rat and mouse repeat-dose toxicity studies are likely to be adequate to support a 505(b)(2) NDA for Ephedrine Sulfate Injection USP?

FDA Response:

No, we do not agree. Oral toxicology studies are not likely to result in comparable exposures in terms of C_{max} to provide coverage for the expected exposures via your drug product and will not address the blood compatability and local tissue toxicity assessments generally required for intravenous drug product formulations. However, given the clinical experience with ephedrine we are willing to review the published toxicology data from the NTP rat and mouse repeat-dose toxicity studies to support a 505(b)(2) NDA application. Your NDA must include these data together with all relevant nonclinical literature data in the public domain to support filing a 505(b)(2) application. If a detailed review of the clinical safety database from the published literature suggests any unexpected toxicity, intravenous toxicology studies may be necessary to support approval. Final determination of the adequacy of the submitted materials can only be determined at the time of NDA review.

Q.10) Carcinogenicity and Genotoxicity

Background: The National Toxicology Program (NTP) conducted GLP rat and mouse 2-year carcinogenicity studies. No ephedrine-related neoplasms were reported.

Several genotoxicity studies have been reported for ephedrine, with and without the addition of S9 metabolizing enzymes, including: S. typhimurium mutagenicity, Chinese hamster ovary (CHO) cell chromosome aberration, CHO cell sister-chromatid exchange and mouse in vitro lymphoma L5178Y mutagenicity. There are no reports of any in vivo genotoxicity performed, including no in vivo bone marrow micronucleus studies. However, since rat and mouse CA studies have been done, with negative results, there would be no added value to conduct an in vivo genotoxicity study.

Question: Does the Division agree that the published carcinogenicity data and the genotoxicity data are likely to be sufficient to support a 505(b)(2) NDA for Ephedrine Sulfate Injection USP?

FDA Response:
Based on the previous human experience, we are willing to review the NTP genetic toxicology and carcinogenicity data to support filing your NDA. The adequacy of these data to support approval of your NDA can only be determined upon formal review of the studies. Although as per the guidance for industry: *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074931.pdf, a standard battery of genotoxicity studies consisting of both in vitro and an in vivo genotoxicity studies is required for marketing approval of drug products, we may be willing to either waive the in vivo genetic toxicology study with ephedrine or defer the study to a post-marketing requirement. This will be determined during the NDA review.

Q.11) Reproductive Toxicity

Background: A review of published literature and available data has not identified any reproductive safety concerns that are not already well known for ephedrine. No formal nonclinical reproductive toxicity studies have been published. However, there is a large published database on reproductive effects and fetal safety in humans, particularly when ephedrine is administered during C-section surgery. These data in humans can provide the information necessary for reproductive safety labeling in the Prescribing Information for Ephedrine Sulfate Injection USP, without further nonclinical reproductive toxicity studies.

Question: Does the Division agree that the published nonclinical and human data on the effects of ephedrine on reproductive function are likely to be adequate to support a 505(b)(2) NDA for Ephedrine Sulfate Injection USP?

FDA Response:
No, we do not agree. The published nonclinical and human data do not appear to contain adequate information regarding the impact on reproductive and developmental toxicity of ephedrine. Therefore, developmental and reproductive toxicology studies may be necessary. Given the clinical history of use, it may be acceptable to submit of the results from these studies as postmarketing requirements (PMRs). However, if you elect to not complete these studies to support your initial NDA submission, the drug product will likely be labeled with a risk statement equivalent to a Pregnancy Category C due to lack of adequate nonclinical reproductive and developmental toxicity data. In the absence of adequate clinical data for these endpoints, the lack of these nonclinical studies will likely impact your final drug product labeling with respect to use during C-sections. Final determination regarding whether PMRs will be required can only be provided upon detailed review of the referenced literature studies.

We note that all NDA applications filed after June 30, 2015, must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In

order to prepare for this new labeling format, you should conduct a thorough review of the existing clinical and nonclinical literature for the drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm .

Q.12) No Additional Nonclinical Studies

Background: Par does not plan to conduct any further nonclinical studies to support a 505(b)(2) NDA for Ephedrine Sulfate Injection USP. It is proposed that the published literature and the extensive data on use in patients, and particularly women of child-bearing potential, are sufficient to support a 505(b)(2) NDA and to write the nonclinical portions as well as the reproductive portions of the Prescribing Information (pregnancy, labor and delivery, nursing and fertility) for Ephedrine Sulfate Injection USP.

Question: Does the Division agree that no further nonclinical studies are needed to support a 505(b)(2) NDA for Ephedrine Sulfate Injection USP?

FDA Response:
No, we cannot agree at this time as additional nonclinical qualification studies may be required (see Additional Nonclinical Comments). In addition your drug product may be administered intravenously (IV) and therefore your NDA submission must provide data to demonstrate blood compatibility and lack of adverse local tissue irritation. This may be addressed via tonicity data and clinical use data in the published literature if you can provide data to show that the formulations tested in the literature are comparable to your proposed formulation and the lack of any apparent novel excipients via the parenteral route of administration in your proposed formulation. Final determination of the adequacy of the submitted materials can only be provided at the time of NDA review.

Q.13) Nonclinical Content of the 505(b)(2) NDA

Background: The nonclinical content of the 505(b)(2) NDA for Ephedrine Sulfate Injection USP will summarize the results of the literature search for nonclinical data on ephedrine as it relates to the proposed clinical indication. The literature search strategy will be provided, and PDF files of pertinent published papers will be provided.

Question: Does the Division have any comments or recommendation regarding the proposed nonclinical content of the 505(b)(2) NDA for Ephedrine Sulfate Injection USP?

FDA Response:
Your proposed nonclinical content appears reasonable. Include in your NDA submission a detailed discussion of the nonclinical information in the published literature and specifically address how the published literature 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.

Note that any reference to published literature should specifically indicate what stereoisomers were tested and provide justification for why those data are relevant to your drug product.

Additional Nonclinical Comments:

1. **The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.**

2. **We remind you that any novel excipients added to your drug product must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the guidance for industry: *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients,* available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guida nces/ucm079250.pdf. As noted in the document cited above, "the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance), and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration." (emphasis added)**

3. **Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICH Q3A(R2), and ICH Q3B(R2) guidances. In order to provide adequate qualification, you must conduct:**

    a. **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. A repeat-dose toxicology study of appropriate duration to support the proposed indication (in this case, a study of at least 14-day duration should be completed).

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

and

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

4. **Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This guidance is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.**

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

6. **The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product**

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

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

8. **For general toxicology and supporting nonclinical toxicokinetic studies, we encourage you to both use Standards for the Exchange of Nonclinical Data (SEND) for regulatory submissions and to submit sample or test data sets before implementation becomes required. Sponsors will be provided feedback on the**

suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

E. CLINICAL QUESTIONS

Q.14) Clinical Indication

Background: In the early 1920's, ephedrine was characterized as a sympathomimetic agent capable of increasing blood pressure. Since the 1920's, parenteral ephedrine has been widely used to treat clinically important hypotension in a variety of patient populations. This usage is well-documented in the medical literature and standard usage manuals, such as the American Hospital Formulary Service (AHFS) Manual.

For the setting of maternal hypotension during spinal anesthesia for Cesarean delivery, 44 randomized, controlled studies encompassing 3,127 women were identified in which ephedrine was used to prevent or treat clinically significant hypotension. Many of these studies were summarized in a comprehensive 2006 Cochrane Collaboration Review by Cyna et al. entitled "Techniques for preventing hypotension during spinal anaesthesia for caesarean section". In this review, the authors identified 7 controlled studies comparing ephedrine to control (N=472), 4 controlled studies comparing ephedrine to crystalloid (N=293), and 9 controlled studies comparing ephedrine plus crystalloid to crystalloid alone (N=529). In each of these studies, ephedrine was found to be superior to the control condition, with relative risk ratios of 0.51 (95% CI: 0.33 to 0.78), 0.70 (0.50 to 0.96), and 0.71 (0.53 to 0.96), respectively. These authors also identified 3 controlled studies (N=97) comparing ephedrine to phenylephrine. For this comparison, ephedrine and phenylephrine were found to be similarly efficacious (0.95 [0.37 to 2.44]) for the prevention of clinically significant maternal hypotension. In addition to these studies, 13 additional randomized, controlled studies (N=1,004) were identified in which ephedrine was used to prevent or treat clinically significant hypotension in a variety of elective surgery populations. As above, ephedrine was found to be safe and effective in these non-pregnant patient populations.

Based on available data, Par believes the following clinical indication can be well-supported by the published medical literature and usage manuals:

- *Ephedrine sulfate is indicated for increasing blood pressure in patients with clinically important hypotension resulting primarily from vasodilation, in such settings as anesthesia.*

This indication is included in the Prescribing Information for both of the recent 505(b)(2) NDAs approved for the intravenous use of Phenylephrine Hydrochloride Injection.

Question: Does the Division have any comments or recommendation regarding Par's planned indication for Ephedrine Sulfate Injection USP?

FDA Response:
The final agreed-upon wording of the indication will be dependent upon the review of the data submitted in the NDA. However, the proposed language is a reasonable starting point.

Q.15) No Additional Clinical Studies

Background: Par does not plan to conduct any further clinical studies to support a 505(b)(2) NDA for Ephedrine Sulfate Injection USP. Given the parenteral dosage form, simple formulation, and intravenous route of administration, Par believes that no clinical studies bridging to unapproved Ephedrine Sulfate Injection currently marketed in the US are warranted.

Question: Does the Division agree that no further clinical studies are needed to support a 505(b)(2) NDA for Ephedrine Sulfate Injection USP?

FDA Response:
The list of published efficacy studies from the literature listed in the meeting package appears reasonable to support submission of your NDA. However, whether these are supportive of your proposed indication will be determined upon submission and review of your NDA. Also see our response to Question 17.

Q.16) Bioavailability Waiver

Background: There are no approved Ephedrine Sulfate Injection drug products so there is no Reference Listed Drug for Ephedrine Sulfate Injection. Therefore, meaningful bioequivalence studies per 21 CFR 320 with Par's Ephedrine Sulfate Injection are not possible.

Par intends to request a waiver from the requirement for the submission of evidence measuring the in vivo bioavailability of its Ephedrine Sulfate Injection USP drug product per 21 CFR 320.22. In accordance with 21 CFR 320.22(b)(1)(i), the bioavailability of Ephedrine Sulfate Injection can be considered "self-evident" since the drug product is a small volume (1 mL) parenteral solution intended solely for administration by injection. The formulation is only 50 mg/mL ephedrine sulfate in water for injection. The sterile solution has a pH of 4.5 – 7 and contains no bacteriostat, antimicrobial agent or added buffer. Ephedrine Sulfate Injection USP with the same formulation has been marketed in the US by a number of pharmaceutical companies over the years.

Question: Does the Division agree that no comparative pharmacokinetic studies are needed to support a 505(b)(2) NDA for Ephedrine Sulfate Injection USP?

FDA Response:
Comparative PK studies may not be needed for your proposed product. However, since you intend to submit a 505 (b)(2) application based on literature, we have the following comments that you must address in your NDA.

It is generally acceptable to submit good quality publications addressing the clinical pharmacology of ephedrine sulfate considering the history of use and extensive clinical experience. Provide a detailed summary for each literature report you plan to use and describe how the data in the literature will be used to support your application. However, final determination of the adequacy of the submitted materials will be a review issue. As the literature may use a different ephedrine product, provide adequate justification for why the literature data can be used to support your product since the formulation, dosing regimen, and patient population in the literature may be different from your proposed product. Publications should have an adequate description of bioanalytical method validation and PK analysis criteria.

Based on the information provided in your package, it does not appear that you have completely captured all required clinical pharmacology information needed to support a NDA submission, which is listed below. The follow must be addressed in your NDA submission.

1. **PK of ephedrine and its metabolites.**

2. **Bioavailability of ephedrine sulfate and its metabolites following proposed administration routes.**

3. **We understand that ephedrine may exist as different enantiomers. In such a situation, the pharmacokinetics of each enantiomer should be evaluated in the initial PK studies.**

    a. **If the pharmacokinetic profile is the same for both isomers or a fixed ratio between the plasma levels of enantiomers is demonstrated in the target population, an achiral assay or an assay that monitors one of the stereoisomers should suffice for later evaluation.**

    b. **Refer to FDA's policy statement for the Development of New Stereoisomeric Drugs at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm**

    c. **It is unclear whether the ephedrine isomer ratio is the same between your proposed product and the product(s) used in the literature. Therefore, you must provide adequate justification that the results from the literature can be used to support your proposed product.**

4. **For each clinical pharmacology literature study that you reference in the NDA,**

summarize the bioanalytical method validation information. For example, the precision and accuracy of the calibrators and the quality control samples used for measuring the analytes.

5. **If a range of ephedrine doses may be administered, provide dose-proportionality information across the proposed doses.**

6. **Provide information about the metabolism of ephedrine based on in vitro metabolism studies or in vivo mass balance studies.**

7. **Provide information on drug-drug interactions.**

8. **Provide dosage adjustment recommendation in the product label based on available publications or clinical data for the following special populations:**

    a. **Patients with hepatic impairment**

    b. **Patients with renal impairment**

    c. **PK or PD drug interactions with respect to perioperative medications**

    d. **Elderly patients**

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

Q.17) Clinical Sections of NDA

Background: The clinical content of the 505(b)(2) NDA for Ephedrine Sulfate Injection USP will summarize the results of the literature search for clinical data on ephedrine as it relates to the proposed clinical indication. The literature search strategy will be provided, and PDF files of pertinent published papers will be provided. Summaries of published clinical studies and available safety data to confirm the safety and efficacy of ephedrine will be provided in Module 2 and copies of the publications will be provided in Module 5.

Question: Does the Division have any comments or recommendation regarding the proposed clinical content of the 505(b)(2) NDA for Ephedrine Sulfate Injection USP?

FDA Response:

The briefing package contains a summary of the literature supporting the efficacy and safety of ephedrine. The NDA submission must also contain your assessment of the relevant literature data upon which you intend to rely for this application, and must be comprehensive, including published studies on ephedrine injection with either positive or negative outcomes. The studies must be individually assessed with discussion of their strength and weakness or deficiency, including comparability of the study drug to your proposed ephedrine injection, such as

stereoisomer composition and formulation. If such drug information is unavailable, you must provide justification for why data from cited literature is acceptable as a source of information to support your submission.

Whether or not the studies you have cited are applicable to the U.S. population and medical practice will be a matter of review of the articles you intend to submit. Refer to guidance for industry, *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions*, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf

The following points may be helpful as you prepare your submission:

Literature references:

1. **Focus on providing evidence to support the efficacy and safety of the drug for which you seek approval.**
2. **Indicate which articles you will rely most heavily.**
3. **Clearly articulate why the data from one clinical population can be extrapolated to support the use of ephedrine in another clinical population (for example, the applicability of data from the treatment of maternal hypotension in the peripartum period to the non-pregnant patient populations, and data evaluating the use of ephedrine to prevent clinically significant hypotension to using ephedrine to treat hypotension).**
4. **Provide a detailed discussion of how the information provided or referenced support your application.**

Assessment of Efficacy:

1. **Summarize each individual study you reference.**
2. **Make tables and narratives comparing study results.**
3. **Summarize available dosing recommendations.**
4. **Summarize drug efficacy differences in specific special populations.**

Assessment of Safety:

1. **Explain why specific adverse events will or will not be included labeling.**
2. **Provide explicit detail of how your literature search was conducted.**
3. **Describe all adverse events in articles you reference.**
4. **Analyze adverse events by category.**

5. Analyze adverse events by specific special populations.

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

F. PRESCRIBING INFORMATION QUESTION

Q.18) Prescribing Information for Ephedrine Sulfate Injection USP

Background: A review of published literature and available data has not identified any safety issues that should be of concern during the use of Ephedrine Sulfate Injection for the proposed indication. Because of the long, published history of clinical use, Par intends to support the Dosing and Administration, Adverse Reactions, Drug Interactions, etc. sections of the Prescribing Information for Ephedrine Sulfate Injection with available data, peer-reviewed publications, and well-established standard usage manuals and guidelines.

It is proposed that the published medical literature and the extensive data on use in patients, and particularly women of child-bearing potential, are sufficient to support a 505(b)(2) NDA and to write the clinical portions of the Prescribing Information for Ephedrine Sulfate Injection USP.

A preliminary proposal for the HIGHLIGHTS OF PRESCRIBING INFORMATION for Par's Ephedrine Sulfate Injection USP is provided on the following page.

Question: Does the Division have any comments or recommendation regarding Par's proposed approach for development of the Prescribing Information for Ephedrine Sulfate Injection USP?

Question: Does the Division have any specific comments on the preliminary proposal for the HIGHLIGHTS OF PRESCRIBING INFORMATION for Par's Ephedrine Sulfate Injection USP?

(b) (4)

FDA Response:
There will be modifications requested based upon the review of the data in the NDA submission, but overall, the proposal appears reasonable.

2.0 General Comments

PREA REQUIREMENTS

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

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

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

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical

and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

505(b)(2) REGULATORY PATHWAY

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

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

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

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

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

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

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

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

4.	

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

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food Drug and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. . As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

FDA has made a preliminary determination that the application for this product would not be reviewed as a new molecular entity (NME) and would not be subject to the Program under PDUFA V. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

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/s/

AYANNA S AUGUSTUS
07/08/2015