DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208943

NDA APPROVAL

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

Attention: Carla English
Senior Manager Regulatory Affairs

Dear Ms. English:

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.

This new drug application provides for the use of CORPHEDRA (ephedrine sulfate) Injection, for the treatment of clinically important hypotension occurring in the setting of anesthesia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on December 14, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in*

Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 208943**." Approval of this submission by FDA is not required before the labeling is used.

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.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of teratogenicity, serious embryo-fetal developmental, and/or post-natal developmental adverse events, organ system toxicity, genetic toxicity, or cancer from ephedrine or leachables from the container closure system.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3145-1 Conduct a fertility and early embryonic development toxicology study in the rat model for ephedrine sulfate.

The timetable you submitted on December 14, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2017
Study Completion:	03/2018
Final Report Submission:	12/2018

3145-2 Conduct an embryo-fetal developmental toxicology study using the rat model for ephedrine sulfate.

The timetable you submitted on December 14, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2017
Study Completion:	12/2017
Final Report Submission:	10/2018

3145-3 Conduct an embryo-fetal developmental toxicology study using the rabbit model for ephedrine sulfate.

The timetable you submitted on December 14, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2017
Study Completion:	03/2018
Final Report Submission:	01/2019

3145-4 Conduct a pre- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.

The timetable you submitted on December 14, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2017
Study Completion:	02/2019
Final Report Submission:	02/2020

3145-5 Conduct an in vivo micronucleus assay with ephedrine sulfate.

The timetable you submitted on December 14, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2017
Study Completion:	12/2017
Final Report Submission:	06/2018

3145-6 Conduct an adequate leachable safety assessment for the (b) (4) rubber stopper (13 mm) used in your container closure system. This assessment must include leachable data from long-

term stability studies testing at least three batches (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. Using this information, conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 120 mcg/day total daily exposure, or it must be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day.

The timetable you submitted on December 14, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2017
Study Completion:	07/2017
Final Report Submission:	09/2017

3145-7 Conduct an extractable study using model solvents, (b) (4) Using this information, extrapolate the worst-case daily exposure via the drug product and conduct a toxicological risk assessment justifying the safety of the extractables that could be present in the final drug product formulation, taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 120 mcg/day total daily exposure, or it must be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day.

The timetable you submitted on December 14, 2016, states that you will conduct this study according to the following schedule:

Study Completion:	03/2017
Final Report Submission:	05/2017

Submit the protocol(s) to your IND 126012 with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a

safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

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

/s/

RIGOBERTO A ROCA
01/27/2017