CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208943Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208943
Review 1

Drug Name/Dosage Form	**Corphedra(Ephedrine Sulfate Injection, USP)/Injection**
Strength	**50 mg/mL**
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	**Par Sterile Products, LLC**
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeffrey Medwid	OPQ/ONDP/DNDPAPI/BII
Drug Product	Valerie Amspacher	OPQ/ONDP/DNDPII/BIV
Process	Peter Krommenhoek	OPQ/OPF/DPAIII/BVIII
Microbiology	Jessica Cole	OPQ/OPF/DMA/BIII
Facility	Rebecca Dombrowski	OPQ/OPF/DIA/BII
Biopharmaceutics	Mei Ou/Haritha Mandula	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Julia Pinto	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)	Valerie Amspacher	OPQ/ONDP/DNDPII/BIV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

B. DMF#	Type	Holder	Item Referenced	Status	Date Review completed	Comments
(b) (4)	II	(b) (4)	Ephedrine sulfate, USP	1	Nov 2015	Adequate
	III		(b) (4) Vial, 13 mm	4	N/A	N/A
	V		13 mm, (b) (4) (b) (4) (b) (4) Stopper - process	4	N/A	Jessica Cole looked at this as part of her review
	III		13 mm, (b) (4) Stopper - formulation	3	N/A	N/A

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

C. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS: NONE

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

Cophedra (Ephedrine Sulfate Injection, USP) is administered intravenously for the treatment of hypotension associated with anesthesia. It is a (b) (4) sterilized aqueous solution for injection, consisting of ephedrine sulfate as the drug substance. The drug product is in a concentration of 50mg/ml. The only excipient used in the preparation of the drug product is water. It is supplied in a (b) (4) clear glass vial stoppered with a (b) (4) Stopper with a yellow flip-off cap. The product pH is 4.5-7.0 and nothing is added to adjust pH. The data provided in this NDA satisfactorily supports the drug substance, drug product and the manufacturing process. All manufacturing facilities are recommended as adequate by the Office of Compliance and the Office of Process and Facilities. Sufficient stability data is provided to support an expiry of 24 months, for the product when stored at 25C, in its carton, away from light. Therefore this NDA is recommended for approval.

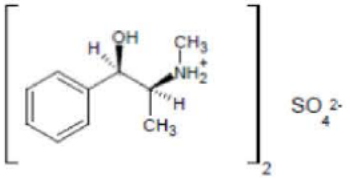
II. Summary of Quality Assessments

A. Product Overview

Drug Substance

The active ingredient is (-) ephedrine sulfate and is supported by DMF (b) (4), reviewed and deemed adequate for use in the preparation of the drug product, by Jeff Medwick, Ph.D. The impurity profile includes the (b) (4) with a proposed specification of (b) (4)%. However, this limit exceeds the limits under ICH Q3A. The PharmTox team, requested a lower limit. The Sponsor has tightened the spec for the (b) (4) of ephedrine sulfate to NMT (b) (4)%. Sufficient stability data is provided in the DMF to support a retest period of (b) (4)

Structure:



Chemical Name:

(-)-Ephedrine sulfate (2:1) (salt)
(1*R*,2*S*)-(-)-2-methylamino-1-phenylpropan-1-ol sulfate
[*R*-(*R**,*S**)]-Benzenemethanol, α-[1-(methylamino)-ethyl] sulfate (2:1) (salt)

Drug Product

Ephedrine Sulfate Injection, USP drug product is a clear, colorless solution in water with a (b) (4) and no other excipients. (b) (4) (b) (4) The product is designed to meet Ephedrine Sulfate Injection USP monograph requirements. The drug product must be diluted with saline or 5% dextrose prior to administration. (b) (4) . Sufficient stability data is provided to support an expiry of 24 months when stored at 25C in the carton, away from light.

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Cophedra
Non Proprietary Name of the Drug Product	Ephedrine Sulfate Injection, USP
Non Proprietary Name of the Drug Substance	Ephedrine Sulfate
Proposed Indication(s) including Intended Patient Population	Treatment of hypotension in adults having received anesthesia
Duration of Treatment	
Maximum Daily Dose	
Alternative Methods of Administration	

C. Quality Assessment Overview

D. Special Product Quality Labeling Recommendations (NDA only)

E. Final Risk Assessment (see Attachment)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

This NDA is recommended for approval.

Application Technical Lead Signature:

Julia C. Pinto, Ph.D.
Branch Chief(Acting)
ONDP/Division II/Branch IV

Julia Pinto

Digitally signed by Julia Pinto
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(b) (4)

R Regional Information

Environmental Analysis

Reviewer's Assessment: Adequate.

The sponsor states, "Par Sterile Products, LLC hereby claims a categorical exclusion from the requirement to prepare an Environmental Impact Analysis statement. Par Sterile Products, LLC certifies that it is in compliance with federal, state and local environmental laws. To the applicant's knowledge, no extraordinary circumstances exist with this action in accordance with 21 CFR 25.21 and 40 CFR 1508.4, as the active and excipient compounds that comprise the Ephedrine Sulfate Injection, USP formulation are derived through synthetic means and the compound will not exceed 1 ppb entry into the aquatic environment."

Methods Verification Package

Reviewer's Assessment: N/A

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

Reviewer's Assessment: N/A

List of Deficiencies N/A

LABELING

{For NDA only}

R Regional Information

1.14 Labeling

Immediate Container Label

(b) (4)

[redacted]

Reviewer's Assessment: Adequate.
The immediate container label(s) comply with all regulatory requirements from a CMC perspective.

- ***Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))***
- ***Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))***
- ***Net contents (21 CFR 201.51(a))***
- ***Lot number per 21 CFR 201.18***
- ***Expiration date per 21 CFR 201.17***
- ***"Rx only" statement per 21 CFR 201.100(b)(1)***

- ***Storage conditions if space permits***
- ***NDC number per 21 CFR 201.2 (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)***
- ***Bar Code per 21 CFR 201.25(c)(2)***
- ***Name of manufacturer/distributor***

Carton Labeling

(b) (4)

[redacted]

Reviewer's Assessment: Adequate.
The sponsor didn't include the items in red and that is acceptable.

The carton label(s) comply with all regulatory requirements from a CMC perspective.

- **Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))**
- **Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))**
- **Net contents (21 CFR 201.51(a))**
- **Lot number per 21 CFR 201.18**
- **Expiration date per 21 CFR 201.17**
- **Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables unless the container is)[201.10(a), 21CFR201.100(b)(5)(iii)]**
- **Statement of Sterility if applicable**

- **"Rx only" statement per 21 CFR 201.100(b)(1)**
- **Storage Conditions**
- **NDC number per 21 CFR 201.2 (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)**
- **Bar Code per 21 CFR 201.25(c)(2)**
- **Name of manufacturer/distributor**
- **"See package insert for dosage information" (21 CFR 201.55)**
- **Route of Administration (not required for oral, 21 CFR 201.100(b)(3))**

List of Deficiencies:

1. In the Patient Insert Highlights section – Dosage Forms and Strengths - add "single dose" and "clear solution"

2. In the Patient Insert main body - Dosage Forms and Strengths - add "clear solution"

3. In the Patient Insert main body - How Supplied/Storage and Handling – change "single use" to "single dose" and add "clear solution" before 1mL vial

4. 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.

Julia Pinto

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Valerie Amspacher

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Date: 12/13/2016 03:41:35PM
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BIOPHARMACEUTICS

Product Background: The Applicant submitted this **NDA 208943** on 03/18/2016. The proposed drug product, Corphedra™ (Ephedrine Sulfate Injection, USP, 50 mg/mL), is indicated for increasing blood pressure in patients with clinically important hypotension in the setting of anesthesia.

The Listed Drug (LD) for this 505(b)(2) application is **AKOVAZ™ (ephedrine sulfate injection, USP, 50 mg/mL)**, which was approved under **NDA 208289** on 04/29/2016.

NDA: 208943

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

Route of Administration: Intravenous (IV)

Applicant Name: Par Sterile Products, LLC

Review Summary:

List Submissions being reviewed (table):

03/18/2016	Original submission
07/13/2016	Response to Biopharmaceutics Information Requests
08/18/2016	Response to Biopharmaceutics Information Requests
09/22/2016	Response to Biopharmaceutics Information Requests
12/02/2016	Response to Biopharmaceutics Information Requests

The Applicant submitted a formal and updated **Request for Waiver of In Vivo Bioavailability/Bioequivalence Studies** in M.1.12.15 on 12/02/2016, requesting "a waiver of the need to perform an *in vivo* bioequivalence study of the drug product, Corphedra™, in comparison to Akovaz™ per 21 CFR §320.21(a)(2)".

To support their biowaiver request, the Applicant provided the following supportive information:

a) The comparison of the active and inactive ingredients between the LD and the proposed drug product, in which the inactive ingredients are considered not affecting the in vivo pharmacokinetics performance of the proposed drug product compared to the LD;
b) Formal request to waive the requirement to conduct in vivo bioavailability/bioequivalence (BA/BE) studies in accordance with 21 CRF 320.22;
c) The physiochemical characteristics (i.e. pH and osmolality) data of the proposed drug product, which is comparable to the LD and within the physiological range;
d) The proposed drug product is a parenteral solution intended solely for administration by intravenous injection;
e) No additional convolution or dilution procedure for the proposed drug product.

For the enantiomers specification, the Applicant "acknowledged the Agency's request to justify the safety for the limit proposed for (b) (4) in the drug substance and drug product specifications or alternatively tighten these specifications to comply with ICH. The limit proposed for (b) (4) in the drug substance and drug product specification has been tightened to align with ICH requirements". Therefore, the review of the safety and efficacy of the enantiomers is pending the Office of Clinical Pharmacology (OCP) and clinical reviews.

A biowaiver under regulation 21 CFR 320.22(b)(1) is not feasible for the proposed drug product due to difference in inactive ingredient (pH adjuster), however based on review of the totality of the provided information (comparative pH and osmolality data), from the Biopharmaceutics perspective, a bridge between the proposed drug product and the LD has been established in accordance with 21 CFR 320.24(b)(6) regulation.

OVERALL COMMENTS:

A bridge between the proposed drug product and the listed drug (AKOVAZ™ approved under NDA 208289) has been established. From the Biopharmaceutics perspective, this NDA 208943 for Corphedra™ (Ephedrine Sulfate Injection, USP, 50 mg/mL), is recommended for APPROVAL.

BCS Designation

Reviewer's Assessment: N/A for intravenous product

Solubility: The drug substance, Ephedrine sulfate, is freely soluble in water and ethanol; very slightly soluble in chloroform and practically insoluble in ether (from M.3.2.S.1.3).

Permeability: n/a

Dissolution: n/a

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: n/a

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: n/a

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: n/a

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: n/a

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: n/a

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: n/a

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: n/a

Bridging of Formulations

Reviewer's Assessment: As noted in M.2.3.P, the developmental formulation is the same as the commercial formulation, and no alternative formulations were investigated. The drug substance is very stable and water was chosen as the (b) (4). No anti-oxidant, no buffer, no

preservative were used in the drug product. Therefore, bridging between different formulations used during the development is not needed.

Biowaiver Request

Reviewer's Assessment:

(1) Regulatory history of Biowaiver request

The proposed drug product, Corphedra™ (Ephedrine Sulfate Injection, USP, 50 mg/mL), is a parenteral drug product intended for administration by intravenous infusion.

In PIND 126012 meeting minutes dated on 07/08/2015, the Office of Clinical Pharmacology (OCP/FDA) provided the following comments for the Applicant's question regarding a bioavailability waiver:

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.

(2) Biowaiver request of this 505(b)(2) application based on published literature

In the original submission dated on 03/18/2016, the Applicant did not submit any request for waiver for in vivo BA/BE studies for the proposed drug product. The final components and composition of the proposed drug product are given in Table 1 below.

Table 1: Drug product composition (from M. 2.3.P)

Ingredient	Grade	Function	Composition (per mL)
Ephedrine Sulfate	USP	Active Pharmaceutical Ingredient	50 mg
Water for Injection[1]	USP/EP	(b) (4)	QS
(b) (4)			---

[1]QS to 1 mL

(b) (4)

The multiple physicochemical characteristics testing results for drug product release and stability of three registration batches of the proposed drug product were submitted in M.3.2.P.5.4. The pH and osmolality of the proposed drug product were proposed as: (1) pH, limit as 4.5-7.0; (2) osmolality, limit as (b) (4) mOsm/kg. These proposed specifications were used as controls for drug product (b) (4), release and shelf-life testing for both of the registration and commercial drug products. The batch information, pH and osmolality data of these three registration batches are summarized in Table 2 and 3 below.

Table 2: Batch information of the proposed drug product (from M.3.2.P.5.4)

Batch #	Manufacturing Date	Manufacturing Site	Manufacturing Process	Container Closure System	Batch Use	Batch Size	Drug Substance Batch #
RC3270	5/18/2015	(b) (4)	(b) (4)1 (b) (4)	(b) (4) (b) (4) (b) (4) Vial 13 mm neck, (b) (4) (b) (4) Stopper and 13 mm Flip Off Cap.	Registration	(b) L	19710
RC3271	5/20/2015	(b) (4)			Registration	(b) L	19739
XC3272	5/21/2015	(b) (4)			Clinical/ Registration	(b) L	19710

Table 3: pH and osmolality of three registration batches of the proposed drug product (from M.3.2.P.5.4)

Specifications		Batch RC3270 Registration Stability	Batch RC3271 Registration Stability	Batch XC3272 Clinical/Registration Stability
pH	4.5-7.0	5.5	4.9	6.0
Osmolality	(b) mOsm/kg	303 mOsm/kg	302 mOsm/kg	301 mOsm/kg

The Applicant also conducted a single pharmacokinetic/pharmacodynamic (PK/PD) study in healthy volunteers (Study DCR15239, A Phase I, Randomized, Double-Blind, Placebo-Controlled, Pharmacokinetic and Pharmacodynamic Study of Ephedrine Sulfate in Normal Healthy Volunteers). This clinical study was submitted in M.2.7.1 and M.5.3.3, which will be reviewed by the Office of Clinical Pharmacology (OCP).

The Applicant did not conduct other clinical trials but relied on the published literature to support the efficacy and safety of the proposed drug product in the original submission.

Because the Applicant did not submit a biowaiver request for this application in the original submission, the Division of Biopharmaceutics (DB/ONDP/OPQ) had one Information Request (IR) comment to the Applicant to request a formal biowaiver request. The IR comments and responses are summarized below:

Biopharmaceutics IR comment #1 (conveyed on 06/01/2016):

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.

(No response was provided to the comment #1 in the 07/13/2016 submission).

Biopharmaceutics IR comment #2 (conveyed on 06/01/2016):

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

Response to the IR comment #2 (responded on 07/13/2016):

Please refer to the updated Table 2 which has been revised to provide the osmolality unit "mOsm/kg".

Reviewer's comment:

The osmolality unit was corrected and updated in Table 2 of M.3.2.P.5.4.1. However, due to the lack of response for IR comment #2, another IR was issued requesting the formal biowaiver request from the Applicant:

Biopharmaceutics IR comment #3 (conveyed on 08/17/2016):

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

Response to the IR comment #3 (responded on 08/18/2016):

Par Sterile Products, LLC requests a waiver of in vivo bioequivalence studies under 21 CFR §320.22(b)(1) based on the following:
i. Corphedra™ (ephedrine sulfate injection, USP) is a parenteral solution intended solely for administration by injection.

Reviewer's comment:

Due to the lack of supportive information for the biowaiver request in M.1.12.15 in 08/18/2016 submission, the following IR was issued requesting the additional information to support the biowaiver request:

Biopharmaceutics IR comment #4 (conveyed on 09/09/2016):

*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.*

Response to the IR comment #4 (responded 09/22/2016):

Current approved labeling for ephedrine contains no pharmacokinetic information and there is minimal published information. Therefore, in support of this NDA, Par conducted a randomized, double-blind, active- and placebo-controlled, pharmacokinetic (PK) and pharmacodynamic (PD) study in which dose proportionality of Corphedra was assessed in 24 healthy volunteers (DCR15239). This study characterizes the in vivo bioavailability of Par's proposed commercial formulation in doses that range from 0.05 to 0.2 mg/kg, similar to the range of expected doses (5 to 10 mg IV bolus). Results are summarized in Section 1 below (note, please refer to the OCP review for details).

Par is formally requesting a waiver of the need to perform an in vivo bioequivalence study of this drug product in comparison to similar drug products on the market (including any used in the published literature relied upon in this NDA) per 21 CFR §320.21(a)(2). Since the proposed product is a solution administered as an intravenous injection, the bioavailability is considered 100%. The other marketed products, whether in concentrations of 30 mg/mL or 50 mg/mL as the hydrochloride or sulfate salts, are also solutions for systemic injection the content of ephedrine base is similar between the ephedrine sulfate and ephedrine hydrochloride products. There is no expectation that the bioavailability of these products would differ and bioequivalence of

Corphedra and other marketed ephedrine products described in the published literature is thus self-evident. A comparison of Par's Corphedra to similar ephedrine injection products on the market, including the products used in the published literature supporting this NDA, is provided in Section 2.

Section 2 COMPARISON OF COMPOSITIONS

Par has attempted to contact the authors of the publications used in support of this NDA to determine the identity and formulation of the ephedrine products used during these studies. A log of the author's responses is provided in Appendix 1 (please note: the broken hyperlink has been communicated to the OCP, please refer to the OCP review). The Table 4 below compares Par's Corphedra product to the ephedrine products described in the literature as well as the ephedrine product used as a comparator in Par's PK/PD study described in section 1. The publications are separated based on pooled analysis groups in the forthcoming Integrated Summary of Safety.

Par's Corphedra product contains ephedrine sulfate while some of the publications submitted in support of this NDA describe clinical use of ephedrine hydrochloride injection products. The two ephedrine salt forms have a small difference in the amount of ephedrine base present (1 mg of ephedrine sulfate contains 0.77 mg of ephedrine base compared to 1 mg of ephedrine hydrochloride which contains 0.82 mg of ephedrine base.

Table 4: Comparison of Par's Proposed Formulation for Corphedra to Manufactured Formulations described in Published Literature (from M.1.12.15 of 09/22/2016 submission)

Company	Salt	Enantiomer	Quantity (mg)	Water for Injection qs?	Other ingredients	Compendial Specification	Publications	
							Primary Safety and Efficacy Studies	Supportive Safety Studies
Par	Sulfate	(-)	50 mg/mL	Yes	None	USP	Study DCR15239	--
Akorn	Sulfate	(-)	50 mg	Yes	None	USP	Study DCR15239	--
Martindale	HCl	(-)	3 mg/mL, 30 mg/mL	Yes	none	BP, Ph Eur	Adigun et al. 2010	Austin et al. 2009, Cooper et al. 2002, Cooper et al. 2007, El Tahan et al. 2011, Hennebry et al. 2009, Loughrey et al. 2002
Sterop	HCl	(-)	10-50 mg/mL	Yes	NaCl (10 mg/mL only)	Unk	Simin et al. 2012, Lecoq et al. 2010[a], Yousefshahi et al. 2010[a]	Masjedi et al. 2014, Odagme et al. 2013[a]
DBL	Sulfate	(-)	30 mg/mL	Yes	NaCl	USP	Ngan Kee et al. 2000[c], Ngan Kee et al. 2001, Ngan Kee et al. 2008b,	Ngan Kee et al. 2000[c], Ngan Kee et al. 2008a, Ngan Kee et al. 2009
Streuli	HCl	(-)	50 mg/mL	Yes	Unk	Unk	Dolci et al. 2011[a]	--
Bichsel	HCl	(-)	5 mg/mL, 50 mg/mL	Yes	NaCl	Unk	Dolci et al. 2011[a]	--
Amgros	HCl	(-)	50 mg/mL	Yes	None	Ph. Eur	Nissen et al. 2010	--
KabiVitrum	HCl	(-)	Unk	Unk	Unk	Unk	Taivainen 1991	Wennberg et al. 1992
Neon Labs	Sulfate	Unk	Unk	Unk	Unk	Unk	--	Prakash et al. 2010[b], Gopalakrishna et al. 2007, Singh et al. 2014
Sumimota Dainipoon	HCl	Unk	Unk	Unk	Unk	Unk	--	Ishiyama et al. 2003[b]
Cristalia	Sulfate	Unk	50 mg/mL	Yes	May contain hydrochloric acid or sodium hydroxide	Unk	--	Aragaõ et al. 2014[b,c]
Osel	HCl	Unk	Unk	Unk	Unk	Unk	--	Gunusen et al. 2010[b,c]

Table 4: Comparison of Par's Proposed Formulation for Corphedra to Manufactured Formulations described in Published Literature (continued)

Company	Salt	Enantiomer	Quantity (mg)	Water for Injection qs?	Other ingredients	Compendial Specification	Publications	
							Primary Safety and Efficacy Studies	Supportive Safety Studies
Aguettant	HCl	Unk	3 mg/mL	Yes	NaCl, sodium citrate, (may contain hydrochloric acid or sodium hydroxide)	Unk	--	Guillon et al. 2010
Venus Pharma	Sulfate	(-)	50 mg/mL	Unk	Unk	USP	--	Iqbal et al. 2010
Northeast Pharmaceutical Group	HCl	Unk	30 mg/mL	Unk	Unk	Unk	--	Quan et al. 2013
Unknown	Unk	(-)	Unk	Unk	Unk	Unk	Berends et al. 2005[a]	--
Unknown	HCl	(-)	Unk	Unk	Unk	Unk	Meersschaert et al. 2002[a]	Foss et al. 2014
Unknown	HCl	Unk	Unk	Unk	Unk	Unk	--	Pennekamp et al. 2011[a,b]; Kansal et al. 2005[b]
Unknown	Unk	Unk	Unk	Unk	Unk	Unk	--	Belzarena 2006[b], Bhattarai et al. 2010[b], Ganeshanavar et al. 2011[a,b], Kasaba et al. 2000[b], Kitchen et al. 2014[a,b], Meng et al. 2011a and 2011b[a,b]

--=Not applicable; Unk=unknown at this time
[a] To be included in forthcoming submission
[b] Article is currently considered supportive since the ephedrine enantiomer has not been confirmed. If more information becomes available, the Author Contact Log (Appendix 1) will be updated and this publication may be considered primary.
[c] Denotes publication includes both treatment and prophylaxis data for ephedrine

Reviewer's comment:

The Applicant submitted a **Request for Waiver from *in vivo* Bioavailability Studies** in M.1.12.15 on 09/22/2016, requesting "a waiver of the need to perform an *in vivo* bioequivalence study of the proposed drug product in comparison to similar drug products on the market (including any used in the published literature relied upon in this NDA) per 21 CFR§320.21(a)(2) regulation".

To support their biowaiver request submitted on 09/22/2016, the Applicant provided the following supportive information:

a) The physiochemical characteristics (i.e. pH and osmolality) data of the proposed drug product, which is within the physiological range;
b) The justification that the different ephedrine salts (ephedrine sulfate in the proposed drug product vs. the ephedrine hydrochloride in some currently unapproved products on the market) have a small difference in the amount of ephedrine base (1 mg of ephedrine sulfate contains 0.77 mg of ephedrine base compared to 1 mg of ephedrine hydrochloride which contains 0.82 mg of ephedrine base);
c) The excipient (water) of the proposed drug product is the same as some of the products in some currently unapproved products on the market and products used in published literature;
d) The proposed drug product is a parenteral solution intended solely for administration by intravenous injection;
e) No additional convolution or dilution procedure for the proposed drug product.

For the enantiomers specification, the proposed drug product has both enantiomers with the proposed specification for the ephedrine (b) (4) is NMT (b) (4)%. The approved drug product, Akovaz™, has both enantiomers combined with the approved specification for the (b) (4) (b) (4) is NMT (b) (4)%, and the review of the safety and efficacy of the enantiomers is pending the OCP and clinical reviews. The Applicant showed the proposed drug product has the same ephedrine (-) isomer as many currently unapproved drug products on the market and in the literature (see Table 4 above).

Upon review of the provided data and justification, from the Biopharmaceutics perspective, a bridge between the proposed drug product and the drug products used in the literature studies can be established in accordance with 21 CFR 320.24(b)(6) regulation when this 505(b)(2) application was based on published literature.

(3) Biowaiver request of this 505(b)(2) application based on approved NDA

In original submission, this 505(b)(2) application was based on published literature. On 06/24/2016, clinical review team communicated with the Applicant regarding the potential 505(b)(2) route through the LD AKOVAZ™ (under approved NDA 208289), summarized as:

Clinical IR comment (email) (Please DARRTS document dated on 06/24/2016):

From: Ogoegbunam, Ogochukwu
To: Hussain, Rehana (Rehana.Hussain@parpharm.com)
Subject: NDA 208943 Telecon Follow Up
Date: Friday, June 24, 2016 1:11:00 PM

Dear Ms. Hussain,

Please find below the response to Par's inquiry regarding requirements for a biowaiver during Par's telecon with DAAAP.

> In order to reference the newly approved listed drug product, Akovaz (ephedrine sulfate Inj.), under NDA 208289, approved on April 29, 2016, you must 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. The request for the biowaiver should also contain the following information:
>
> a. A table of side-by side comparison of the active and inactive ingredients between the listed drug and your proposed dug product.
>
> b. Your justification for any differences between the two formulations and to demonstrate that the difference for each active and/or inactive ingredient, would not affect the pharmacokinetic performance towards any difference in clinical safety and/or efficacy outcome. You may include literature data and/or you study reports to support your new biowaiver request.

Thank you,

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

The Applicant would continue the application through published literature and submitted the biowaiver request and justification after the above teleconference communication (*please see the above review section (2)*).

On 11/18/2016, the Applicant communicated with the RBPM, regarding to change their 505(b)(2) application route to the approved NDA 208289, summarized as:

"*Par would like to re-confirm that we could rely on the Agency's previous finding of safety and efficacy for the listed drug Akovaz by amending our pending NDA with the items listed above. In addition, Par will provide an updated 356h and revised patent certification statement with this amendment. Does the Agency agree this is acceptable.*"

On 11/21/2016, the clinical RBPM communicated with the Applicant as:

If you intend to amend your pending application in order to rely on the Agency's previous finding of safety and efficacy for the listed drug Akovaz, you must submit the following:

- *A table of a side-by-side comparison of the active and inactive ingredients between the listed drug and your proposed drug product.*
- *Justification for any difference between the two formulations and to demonstrate that the differences for each active and/or inactive ingredient would not affect the pharmacokinetic performance towards any difference in clinical safety and/or efficacy outcome.*
- *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 referencing the approved listed drug product, Akovaz (ephedrine sulfate Inj.), under NDA 208289.*
- *Literature data and/or study reports to support a new biowaiver request to reflect NDA 208289.*
- *An updated 356h and revised patent certification statement.*

The above information should be submitted as soon as possible.

On 11/29/2016, FDA had a teleconference with the Applicant. During the teleconference, the Applicant confirmed to change the 505(b)(2) application route from published literature to the approved LD AKOVAZ™ (under NDA 208289).

On 12/02/2016, the Applicant submitted an updated and formal **Request for Waiver of In Vivo Bioavailability/Bioequivalence Studies** in M.1.12.15 on 12/02/2016, requesting "a waiver of the need to perform an *in vivo* bioequivalence study of the drug product, Corphedra™, in comparison to Akovaz™ per 21 CFR §320.21(a)(2)".

According the Applicant:

Par has decided to no longer pursue a 505(b)(2) new drug application that relies solely on the literature provided in the original NDA 208943 to support the safety and efficacy of Corphedra. At this time we are amending our application in order to rely on the Agency's previous finding of safety and efficacy for the reference listed drug (RLD) Akovaz™. Therefore, the requested ISS, ISE and risk benefit analysis information is no longer applicable to this NDA.

In support of this amendment, the following information is provided in Module 1:

- Side-by side comparison of the active and inactive ingredients between the listed drug and our proposed product (Refer to Section 1.12.11 and Section 1.12.12).
- Formal request to waive the requirement to conduct in vivo bioavailability/bioequivalence studies in accordance with 21 CRF 320.22 (Refer to Section 1.12.15).
- An updated 356h form.
- Revised Patent Certification Statement (Refer to Section 1.3.5.1 and Section 1.3.5.2).
- Updated labeling (package insert), including a side-by-side comparison to the listed drug (Refer to Section 1.14.1 and Section 1.14.3). For ease of review, a copy of the RLD package insert is also provided in Section 1.14.3.

In order to support their biowaiver request, the Applicant provided the following information:

In M.1.12.11:

1. Basis for 505(b)(2) New Drug Application: Corphedra™ (ephedrine sulfate injection, USP) 50 mg/mL manufactured by Par Sterile Products, LLC for the treatment of clinically important hypotension occurring in the setting of anesthesia, seeks to rely on the Agency's previous finding of safety and efficacy for the Reference Listed Drug, Akovaz™, NDA 208289. Corphedra™ utilizes the same active ingredient (ephedrine sulfate) and inactive ingredients (water for injection) as the Reference Listed Drug, Akovaz™. Corphedra™ is Q1/Q2 to the RLD formulation.

2. The Route of Administration, Dosage Form and Strength: [(21 CFR 314.94(a)(6)(i)]: The route of administration, dosage form and strength of Par Sterile Product's Corphedra™ is the same as that of the reference listed drug, Akovaz™, manufactured by Flamel Ireland Limited.

3. The reference listed drug product Akovaz™ is referred by Par Sterile Products as a reference for the annotated labeling as shown in this module (Module 1.14) of this New Drug Application.

In M.1.12.12:

As required by 21 CFR §314.94(a), the following information is provided to demonstrate that the reference listed drug is the same as the proposed drug.

Parameters	Reference Listed Drug (RLD)	Proposed Product for this NDA
Product Name	Akovaz™ (ephedrine sulfate injection, USP)	Corphedra™ (ephedrine sulfate injection, USP)
Condition of Use	An alpha-and beta-adrenergic agonist and a norepinephrine-releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.	An alpha-and beta-adrenergic agonist and a norepinephrine-releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.
Active Ingredient	Ephedrine Sulfate, 50 mg	Ephedrine Sulfate, 50 mg
Inactive Ingredients	Water for Injection	Water for Injection
Route of Administration	Intravenous	Intravenous
Dosage Form	Solution, Injection	Solution, Injection
Strength(s)	50 mg/mL	50 mg/mL

Condition of Use:

The condition of use prescribed, recommended or suggested in the labeling proposed for the drug product are similar to those conditions previously approved for the Reference Listed Drug (RLD), Akovaz™, according to NDA 208289 held by Flamel Ireland Limited.

APPEARS THIS WAY ON ORIGINAL

In M.1.12.15:

1.12.15 Updated Request for Waiver of In-Vivo Bioavailability/Bioequivalence Studies

Par Sterile Products, LLC (Par) has developed Corphedra™ (ephedrine sulfate injection, USP) as a treatment for anesthesia-induced hypotension. The active ingredient is ephedrine sulfate ([1R,2S]-[-]-methlyamino-1-phenyl-1-propanol sulfate), a nonspecific α- and β-adrenergic agonist that raises blood pressure mainly by increasing cardiac output via stimulation of cardiac β_1 receptors, with a smaller contribution from vasoconstriction. It is provided as a sterile, nonpyrogenic solution for intravenous use in a concentration of 50 mg/mL.

Par submitted an 505(b)(2) NDA for Corphedra on March 18, 2016 based on published literature.

Subsequently, Par submitted an amended biowaiver request to NDA 208943 on September 22, 2016 Since this time, Par has decided to rely on the Agency's prior finding of safety and efficacy of ephedrine for the treatment of anesthesia-induced hypotension based on the approval of the Reference Listed Drug (RLD) Akovaz™ (Flamel Ireland Ltd. [Flamel]; NDA 208289 approved April 29, 2016).

Par is formally requesting a waiver of the need to perform an *in vivo* bioequivalence study of the drug product, Corphedra™, in comparison to Akovaz™ per 21 CFR §320.21(a)(2). As the criteria for a waiver outlined in 21 CFR §320.22(b)(1) are met, bioequivalence is self-evident. Specifically, the proposed product is a solution intended for intravenous injection. The composition of the proposed product and the RLD are identical, namely active drug in the same concentration and water for injection. Thus, there is no excipient that could alter systemic availability or distribution. A comparison of Par's Corphedra™ to Akovaz™ is provided below in Table 1.

Table 1. Comparative Compositions of Par's Corphedra™ and the RLD Akovaz™

Ingredient	Content (mg/mL)	
	Corphedra™ (Par)	Akovaz™ (Flamel)
Ephedrine Sulfate, USP	50 mg	50 mg
Water for injection	qs to 1 mL	qs to 1 mL

qs=quantity sufficient

Reviewer's assessment:

The components and composition of the approved LD AKOVAZ™ (under NDA 208289) are given in Table 5 below.

Table 5: Components of AKOVAZ™ (Ephedrine Sulfate Injection, USP) (from M.2.3 of NDA 208289)

Component	Function	Reference to Quality Standards	Concentration	Total/Vial
Ephedrine Sulfate, USP	Active	Certificate of Analysis	50 mg/mL	50 mg[a]
Water for injection	(b) (4)	USP	*q.s.*	*q.s.*
Glacial acetic acid or sodium hydroxide (b) (4)	pH adjustment	USP/NF[b]	*q.s* to pH (b) if needed	*q.s* to pH (b) if needed
(b) (4) clear glass vial of (b) (4) USP glass	Container	See specifications Section 3.2.P.7	-	Each
13-mm (b) (4) stopper	Closure	See specifications Section 3.2.P.7	-	Each
Aluminum crimp seal	Closure	See specifications Section 3.2.P.7	-	Each

USP: United States Pharmacopeia
NF: National Formulary
[a] Based on a delivery of 1.0 mL per vial (b) (4)
[b] Both Glacial Acetic Acid (USP) or Sodium Hydroxide (NF) are mixed with Water for Injection, USP (b) (4) for pH adjustment, if needed.
-Not available

Compared to the proposed drug product, LD has additional glacial acetic acid or sodium hydroxide (b) (4) as pH adjuster in formulation. However, the physicochemical characteristics of the LD, such as pH and osmolality, were reviewed and approved as (1) pH, limit as 4.5-7.0; (2) osmolality, limit as (b) (4) mOsm/kg. The batch information, pH and osmolality data of the LD are summarized in Table 6 below.

Table 6: pH and osmolality of three registration stability batches of the LD, AKOVAZ™ (from M.3.2.P.5.4 under NDA 208289)

Specifications		Batch 00001	Batch 00002	Batch 00003
		Registration Stability	Registration Stability	Registration Stability
pH	4.5-7.0	5.9	6.0	5.9
Osmolality	(b) (4) mOsm/kg	304 mOsm/kg	297 mOsm/kg	300 mOsm/kg

Therefore, after the internal discussion within the Biopharmaceutics review team, the pH and osmolality of the proposed drug product (Table 3 above) and the LD (Table 6) are considered comparable. The lack of pH adjusters in the proposed drug product is considered not affecting the in vivo pharmacokinetics performance compared to the LD.

Therefore, the overall assessment of this biowaiver request for this 505(b)(2) application based on approved LD AKOVAZ™ are:

a) The comparison of the active and inactive ingredients between the LD and the proposed drug product, in which the inactive ingredients are considered not affecting the in vivo pharmacokinetics performance of the proposed drug product compared to the LD;

b) Formal request to waive the requirement to conduct in vivo BA/BE studies in accordance with 21 CRF 320.22;
c) The physiochemical characteristics (i.e. pH and osmolality) data of the proposed drug product, which is comparable to the LD and within the physiological range;
d) The proposed drug product is a parenteral solution intended solely for administration by intravenous injection;
e) No additional convolution or dilution procedure for the proposed drug product.

Per the listed drug labeling, the listed drug is to be diluted before administration. (b) (4)

Please refer to clinical pharmacology/labeling reviews for additional details.

A biowaiver under regulation 21 CFR 320.22(b)(1) is not feasible for the proposed drug product due to difference in inactive ingredient (pH adjuster), However, upon review of the totality of the submission (comparative pH and osmolality data), from the Biopharmaceutics perspective, a bridge between the proposed drug product and the listed drug (AKOVAZ™ approved under NDA 208289) can be established in accordance with 21 CFR 320.24(b)(6) regulation.

OVERALL COMMENTS:

A bridge between the proposed drug product and the listed drug (AKOVAZ™ approved under NDA 208289) has been established. From the Biopharmaceutics perspective, this NDA 208943 for Corphedra™ (Ephedrine Sulfate Injection, USP, 50 mg/mL), is recommended for APPROVAL.

R Regional Information

Comparability Protocols

Reviewer's Assessment: n/a

Post-Approval Commitments

Reviewer's Assessment: n/a

Lifecycle Management Considerations

n/a

List of Deficiencies:

n/a

Primary Biopharmaceutics Reviewer Name and Date:

Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality
11/17/2016 for 505(b)(2) route based on published literature
12/6/2016 for 505(b)(2) route based on approved NDA 208289

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Kelly M. Kitchens, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality
November 21, 2016

Haritha Mandula, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality
12/12/2016

Tertiary Reviewer Name and Date (and Tertiary Summary, as needed):

Tapash Ghosh, Ph.D.
Acting Branch Chief
Division of Biopharmaceutics, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality

Haritha Mandula

Digitally signed by Haritha Mandula
Date: 12/20/2016 03:17:02PM
GUID: 508da8fb000282df41459408f32a1ce0

Mei Ou

Digitally signed by Mei Ou
Date: 12/20/2016 03:19:11PM
GUID: 54ca8d7000073c57d2eb7cc8e42c05bb