CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208289Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval
NDA: 208289

NDA
Review #1

Drug Name/Dosage Form	Ephedrine Sulfate Injection, USP
Strength	50 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Flamel Ireland Limited
US agent, if applicable	The Weinberg Group

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

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeffery Medwid	OPQ/ONDP/DNP/BII
Drug Product	Christopher Hough	OPQ/ONDP/NDPII/BIV
Process	Yaodong Huang	OPQ/OPF/DIA/3BVIII
Microbiology		OPQ/OPF/DIA/IABII
Facility	Quallyna Porte	OPQ/OPF/DIA/BII
Biopharmaceutics	Vidula Kolhatkar	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO
Application Technical Lead	Julia Pinto	OPQ/ONDP
Laboratory (OTR)		
ORA Lead	Paul Perdue	
Environmental Assessment (EA)		

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	Ephedrine Sulfate		Nov 2015	Adequate
	Type III *(if applicable)*					
	Type IV *(if applicable)*					
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Ephedrine Sulfate Injection, USP is a (b) (4) sterilized aqueous solution consisting of ephedrine sulfate as the drug substance. The drug substance is under DMF (b) (4) and supplied by (b) (4) The DMF is adequate to support its use in the drug product.
The Drug Product is formulated in Saline using glacial acetic acid and sodium hydroxide as pH adjusters. The pH of the solution is 4.5 to 7 and the osmolality is about 300mOsmol/kg.
The manufacture of the drug product is by (b) (4) fill into clear glass vials.
The drug product must be diluted with saline or 5% dextrose prior to administration. The product cannot be administered as a bolus injection.
Satisfactory stability data is provided to support an expiry of 24 months for the drug substance, when stored at 25C.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

Ephedrine Sulfate, USP drug substance is supplied by (b) (4). The manufacture and control of the drug substance is referenced to DMF (b) (4) and reviewed by Jeff Medwid, Ph.D. The drug substance is adequately supported for use in the preparation of the drug product and has a retest period of (b) (4) months.

B. Drug Product [Established Name] Quality Summary

Ephedrine Sulfate Injection, USP is a (b) (4) sterilized aqueous solution consisting of ephedrine sulfate and Water for Injection, USP. Either sodium hydroxide or glacial acetic acid is added as (b) (4) solutions, for pH adjustment. The pH is controlled at approximately 5.0-5.5 and an osmolality of approximately 300 mOsmol/kg. The solution is (b) (4) (b) (4) . The solution is filled into (b) (4) clear glass vials and closed with a pharmaceutical grade stopper (13-mm diameter) and crimp seals. The vial is filled with (b) (4) mL of solution, which includes a slight overfill to allow for removal of 1.0 mL for dosing. The batch is then (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. The product cannot be administered as a bolus injection.

The granted expiry is 24 months when stored at 25C.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Akovaz
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	Hypotension associated with anesthesia
Duration of Treatment	As needed
Maximum Daily Dose	
Alternative Methods of Administration	none

D. Biopharmaceutics Considerations

A biowaiver was requested and granted.

E. Novel Approaches NA

F. Any Special Product Quality Labeling Recommendations NA

G. Life Cycle Knowledge Information (see Attachment A) NA

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

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

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE FOR NDA 208289

2.3.S **DRUG SUBSTANCE** [EPHEDRINE SULFATE, USP, (b) (4)

2.3.S.1 **General Information**

Applicant's Response:

1.1. Nomenclature

Recommended International Nonproprietary Name (INN) 1.1.1.
Ephedrine sulfate

Compendial Name 1.1.2.
Ephedrine Sulfate, USP

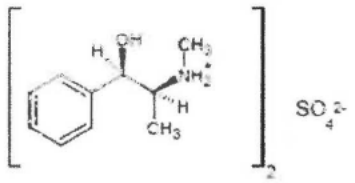
Chemical Names 1.1.3.
(-)-Ephedrine sulfate (2:1) (salt)

(1*R*,2*S*)-(-)-2-methylamino-1-phenylpropan-1-ol sulfate

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

Chemical Abstracts Services (CAS) Registry Number 1.1.4.
134-72-5

1.2. Structure



Molecular Formula:
$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$
$C_{20}H_{32}N_2O_6S$

Molecular Weight: 428.54

1.3.General Properties

Physical Form 1.3.1.
Colorless [redacted] (b) (4) powder, practically odorless

Solubility 1.3.2.
Water: freely soluble
Ethanol: freely soluble
Chloroform: very slightly soluble
Ether: practically insoluble

Hygroscopicity 1.3.3.
The substance is known to be hygroscopic.

Specific Optical Rotation 1.3.4.
[redacted] (b) (4)

pH 1.3.5.
The pH value of an aqueous solution [redacted] (b) (4) is about 5.6.

pKa 1.3.6.
[redacted] (b) (4)

Partition Coefficient 1.3.7.
[redacted] (b) (4)

For additional general properties:
[redacted] (b) (4) under the DMF [redacted] (b) (4)

Reviewer's Assessment: Reviewer's Assessment: General Information, Structure and General Properties

Limited information is provided for the General Information, properties, and structure of Ephedrine Sulfate, USP in the NDA Submission. It is adequately and accurately provided. See DMF [redacted] (b) (4) for more detailed information.

The most recent CMC review of DMF [redacted] (b) (4) was completed by this reviewer, Jeffrey B. Medwid, PhD, on November 12, 2015 and approved by Donna F. Christner, Ph.D., Acting Chief, Branch II, Division of New Drug API November 12, 2015. The final recommendation was adequate. The November 12, 2105 DMF CMC review is the first review of this DMF

2.3.S.2 Manufacture

S.2.2 Description of the Manufacturing Process and Controls

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OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:

This NDA is recommended for approval from the CMC drug substance perspective. All CMC issues concerning the drug substance have been satisfactorily resolved. The manufacturing process and controls, specifications and analytical methods are all covered in detail in DMF (b) (4). The most recent DMF CMC review was completed by this reviewer, Jeffrey B. Medwid, PhD, on November 12, 2015 and approved by Donna F. Christner, Ph.D., Acting Chief, Branch II, Division of New Drug API November 12, 2015. The final recommendation was adequate.

Jeffrey B. Medwid, PhD., Senior Review Chemist, Branch II, Division of New Drug API. January 13, 2016

Secondary Review Comments and Concurrence:

I concur with Dr. Medwid's assessment that the drug substance information is adequate to support its use for NDA 208289.

Donna F. Christner, Branch Chief (Acting), Branch II, DNDAPI. January 13, 2016

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

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

Parameters*	Reference Product	Product under Review
Type	No RLD used	505 (b) (2)
Description	Efficacy supported by literature	Liquid Injection
Target Weight	Drug Product supported by USP	50 mg
Dimensions/Size		50 mg/mL
Container/Closure Design		(b) (4) clear glass vial
Excipients (not in RLD) which require label warning		Water for injection, USP, glacial acetic acid, USP, or sodium hydroxide, NF, to adjust pH to (b) (4).

P.1 Description and Composition

Ephedrine sulfate Injection, USP is just ephedrine sulfate, USP and water for injection, USP at 50 mg/mL.
The pH is adjusted by either sodium hydroxide or glacial acetic acid as a (b) (4) solution to between (b) (4)

Osmolality at release is approximately 300 mOsmol/kg. The following Table 1 describes the components of the drug product and its primary packaging.

Table 1: Components of Ephedrine Sulfate Injection, USP

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	Solvent	USP	*q.s.*	*q.s.*
Glacial acetic acid or sodium hydroxide ([redacted] (b) (4))	pH adjustment	USP/NF[b]	*q.s* to pH [redacted] (b) (4) if needed	*q.s* to pH [redacted] (b) (4) if needed
[redacted] (b) (4) clear glass vial of type 1 USP glass	Container	See specifications Section 3.	-	Each
[redacted] (b) (4) stopper	Closure	See specifications Section 3.	-	Each
Aluminum crimp seal	Closure	See specifications Section 3.	-	Each

USP: United States Pharmacopeia
NF: National Formulary
[a] Based on a delivery of 1.0 mL per vial, actual fill with overfill is [redacted] (b) (4)
[b] Both glacial acetic acid (USP) and sodium hydroxide (NF) [redacted] (b) (4), USP immediately before use for pH adjustment, if needed.
-Not available

Reviewer's Assessment: Adequate

2.3.P.2 Pharmaceutical Development

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

Ephedrine sulfate, USP, water for injection, USP, and [redacted] (b) (4) of NaOH or H_2SO_4 for pH adjustment are the components of the drug product.

3.2.P.2.1.1 Drug Substance

Ephedrine sulfate, USP is manufactured by [redacted] (b) (4) according to the specification of the USP monograph. Testing of residual solvents in the drug substance is also done by [redacted] (b) (4). The specification of the drug substance is given below.

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OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:
I recommend Approval of this Ephedrine Application. The drug product described in this Application is assured of its identity, strength, purity, and quality.
Christopher J. Hough, Ph.D.

Secondary Review Comments and Concurrence:

I concur with Dr. Hough's review of the Drug Product.

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

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ASSESSMENT OF THE PROCESS

2.3.P DRUG PRODUCT

2.3.P.2.3 Manufacturing Process Development

16. Does the information described in the pharmaceutical development section support the proposed drug product manufacturing process?

Applicant's Response:
The rationale for the selection of the proposed manufacturing process is to produce an Ephedrine Sulphate 50 mg/mL solution for injection product filled in (b) (4) clear Type I USP glass vials and closed with a (b) (4) stopper (b) (4) and aluminum crimp seals. The vial is filled with (b) (4) of solution, which includes a slight overfill to allow for withdrawal of 1.0 mL for dosing. The batch is then (b) (4). The formulation is adjusted to pH 4.5-7.0.
The proposed process is based on the knowledge the applicant have gained during the scale-up from bench (b) (4)) to full-scale engineering batch ((b) (4)) and registration ((b) (4)) batches, and the manufacture of the clinical trial materials. Therefore, it is concluded that the applicant's rationale for the proposed commercial manufacturing process is adequately supported by the data provided in this submission.

I concur with this Approval recommendation.

Christina Capacci-Daniel, PhD – 3/24/2016
Acting QAL / Consumer Safety Officer, OPQ/OPF/DIA/IABII

ASSESSMENT OF THE BIOPHARMACUETICS

The applicant did not conduct any clinical trials but relied on the published literature to support this NDA.

After consultation with the Office of New Drugs, the Division of Biopharmaceutics requested the applicant to submit a formal biowaiver request. The following comments were communicated to the applicant in the 74-day letter:

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 Agency provided further clarification about the 74-day letter comments on October 16, 2015 as requested by the applicant. The following comments were conveyed to the applicant:

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

Applicant's Response:

The applicant submitted a formal biowaiver request on October 29, 2015 and stated that the applicant contends that the published literature included in the NDA fulfills the CFR requirements for submission of bioavailability and bioequivalence data (per 21 CFR 320.21(a)).

The applicant identified ephedrine as the (-) enantiomer for the key efficacy references. The proposed product, Ephedrine Sulfate Injection, USP, is a sterile solution for injection (50 mg/mL) intended for IV administration. It is a (b) (4) sterilized aqueous solution consisting of Ephedrine Sulfate, USP and Water for Injection, USP. Either sodium hydroxide or glacial, acetic acid may be added (b) (4) if needed, for pH adjustment. The resultant solution has an in-process controlled pH of approximately (b) (4) (drug product release specification is (b) (4)). The osmolality at release is

approximately 300 mOsmol/kg (drug product release specification is 280-320 mOsmol/kg). This is similar to normal serum osmolality (275 – 300 mOsmol/kg)[1].

The proposed product is designed to meet Ephedrine Sulfate Injection, USP monograph requirements.

Table 1: Components of Ephedrine Sulfate Injection, USP

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	Solvent	USP	*q.s.*	*q.s.*
Glacial acetic acid or sodium hydroxide (b) (4)	pH adjustment	USP/NF[b]	*q.s* to pH (b) (4) if needed	*q.s* to pH (b) (4) if needed
(b) (4) clear glass vial of type 1 USP glass	Container	See specifications Section 3.2.P.7	-	Each
(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, actual fill with overfill is (b) (4).
[b] Both glacial acetic acid (USP) and sodium hydroxide (NF) (b) (4) USP immediately before use for pH adjustment, if needed.
-Not available

The applicant identified the manufacturer of the ephedrine injection product used in the most key efficacy studies described in the published literature. The following table provides a comparison between the proposed formulation (manufactured by Éclat, which was acquired by the applicant) and the marketed formulations of the ephedrine sulfate and ephedrine hydrochloride injections cited in the published literature:

Table 4: Comparison of Éclat's Proposed Formulation to Cited Manufactured Parenteral Formulations (per mL)

Company	Ephedrine Salt	Quantity of Ephedrine Salt	Water for injection qs	Other Ingredients
Éclat (b) (4)	Sulfate	50 mg	Yes	Glacial acetic acid or sodium hydroxide (as (b) (4))
	Sulfate	50 mg	Yes	Sodium hydroxide and/or hydrochloric acid qs pH
	Sulfate	50 mg	Yes	N/A
	Sulfate	30 mg	Yes	Sodium chloride (b) (4)
	Hydrochloride	30 mg	Yes	Sodium chloride Dilute hydrochloric acid (b) (4)
	Hydrochloride	15 mg – 30 mg	Yes	N/A
	Hydrochloride	10 mg – 50 mg	Yes	Sodium chloride
	Hydrochloride	50 mg	Yes	N/A
	Hydrochloride	50 mg	Yes	(b) (4)

qs: sufficient quantity

The Applicant Flamel Ireland Limited acquired Eclat.

The differences noted between Éclat's formulation and the other formulations are in the ephedrine salt form, or in ingredients for altering pH or tonicity. The above table lists the Cristalia formulation (used in the study by Belzarena, 2006[2]), DBL formulation (used in the study by Ngan Kee *et al* 2001[3] and Ngan Kee *et al* 2008b[4]), Martindale Pharma formulation (used in the study by Desalu and Kushimo 2005[5]), Cardinal health formulation (used in the study by Meng et al 2011a[6] and Meng et al 2011b[7]), Neon laboratories formulation (used in the study by Nag, 2010[8]) Sterop formulation (used in the study by Lecoq et al 2010[9]), Amgros formulation (used in the study by Nissen et al 2010[10]) and Pharmachemie formulation (used in the study by Pennekamp et al 2011[11]).

The pH adjusters (sodium hydroxide and/or hydrochloric or acetic acid) are typically used in very small amounts and their use is not expected to have an effect on safety or efficacy. The addition of sodium chloride to alter tonicity is also used in a small amount and therefore is not expected to have an effect on safety or efficacy. In addition, the applicant obtained currently marketed ephedrine injection products and performed several tests including assay, impurity profile, and enantiomeric purity, and demonstrated similarity to their proposed Ephedrine Sulfate Injection, USP product.

The formulations of currently marketed unapproved products and products used in published studies have been shown to be comparable or identical to Éclat's proposed formulation.

The applicant has stated that although they were not able to confirm the enantiomeric composition, salt form, or formulation of the ephedrine product in all efficacy, clinical pharmacology, and safety studies cited in this NDA, some results from those studies are included in the application as supportive information. Results across the efficacy, safety, and clinical pharmacology studies are consistent, despite possible differences in formulation, enantiomeric composition, or salt form. The applicant has stated that they have established a bridge between the clinical data presented as supportive of the primary data and the proposed formulation.

The applicant has further stated that the proposed product is a parenteral product intended for intravenous (IV) administration, and it does not contain any other ingredients that would affect the bioavailability of the drug. The applicant has therefore not conducted any original biopharmaceutics or clinical pharmacology studies in support of this NDA and is relying on published literature to demonstrate that information.

The applicant has established a scientific bridge between the proposed formulation and the formulations used in the literature studies. This was confirmed with CMC reviewer Dr. Julia Pinto and medical officer Dr. Amelia Luckett. The proposed formulation will be administered as an intravenous solution and does not contain any ingredients that are expected to affect the bioavailability of the proposed product. Therefore, published literature is adequate to demonstrate bioavailability of the proposed product.

Overall, the applicant has provided adequate information to waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence for the proposed drug product from the biopharmaceutics perspective.

References:

[1] Howard Ansel *Pharmaceutical calculations* 13th edition 2010 Wolters Kluwer Health Lippincott Williams & Wilkins

[2] Belzarena, SD *Ephedrine and Etilefrine as Vasopressor to Correct Maternal Arterial Hypotension during Elective Cesarean Section under Spinal Anesthesia. Comparative Study* Rev Bras Anestesiol; 56 (3), 223-229, 2006
[3] Ngan Kee *et al Comparison of Metaraminol and Ephedrine Infusions for Maintaining Arterial Pressure during Spinal Anesthesia for Elective Cesarean Section* Anesthesiology; 95, 307–13, 2001
[4] Ngan Kee *et al Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective Caesarean section* Anaesthesia; 63, 1319–1326, 2008
[5] Desalu I and Kushimo O.T. *Is ephedrine infusion more effective at preventing hypotension than traditional prehydration during spinal anaesthesia for caesarean section in African parturients?* International Journal of Obstetric Anesthesia; 14, 294–299, 2005
[6] Meng L. *et al Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients* British Journal of Anaesthesia; 107, 209-217, 2011
[7] Meng L. *et al The impact of phenylephrine, ephedrine, and increased preload on third-generation vigileo-flotrac and esophageal doppler cardiac output measurements* Anesthesia & Analgesia; 113, 751-757, 2011
[8] Nag K *One year randomized clinical trial to compare the efficacy of intravenous bolus phenylephrine and ephedrine in maintaining arterial blood pressure during spinal anaesthesia in caesarean section* Department of Anaesthesiology, Jawaharlal Nehru Medical College, Belgaum – 10 Karnataka; Dissertation 2010
[9] Lecoq JP H. *et al Norepinephrine and ephedrine do not counteract the increase in cutaneous microcirculation induced by spinal anaesthesia* British Journal of Anaesthesia; 105, 214-219, 2010
[10] Nissen P. et al *Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension* Neurocrit Care; 12, 17-23, 2010
[11] Pennekamp CWA *et al Differential effect of phenylephrine and ephedrine on cerebral haemodynamics before carotid cross-clamping during carotid endarterectomy* Correspondence British Journal of Anaesthesia; 109, 831-833, 2012

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature: Adequate

The waiver for in vivo bioavailability studies for Ephedrine Sulphate Injection, 50 mg/mL, is granted. From the Biopharmaceutics perspective, NDA 208289 for Ephedrine Sulphate Injection, 50 mg/mL, is recommended for approval.

Reviewer's Signature
Vidula Kolhatkar, Ph.D.
Branch II
Division of Biopharmaceutics/ONDP

03/28/2016

Secondary Review Comments and Concurrence:

I have reviewed the Biopharmaceutics Assessment, and I concur with the recommendation of approval.

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Quality Assessment Lead (Acting)
Division of Biopharmaceutics, Branch II
March 28, 2016

ASSESSMENT OF MICROBIOLOGY

27. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: The following information is summarized below:

P.1 Description of the Composition of the Drug Product

- Description of drug product – The drug solution is a [redacted] (b) (4) sterilized aqueous solution.

- Drug product composition –

Component	Quality Standard	Function	Concentration (mg/mL)	Total/vial
Ephedrine Sulfate	USP	Active Ingredient	50 mg/mL	50 mg
Water for Injection	USP	Solvent	q.s.	q.s. to 1.0 mL
Glacial acetic acid or sodium hydroxide [redacted] (b) (4)	USP/NF	pH adjustment	q.s. to pH [redacted] (b) (4)	q.s. to pH [redacted] (b) (4)

- Description of container closure system –

Component	Description	Manufacturer
Vials	USP Type- I Clear Glass vial, [redacted] (b) (4)	[redacted] (b) (4)
Stoppers	[redacted] (b) (4) stoppers	
Seals	[redacted] (b) (4) aluminum seals [redacted] (b) (4)	

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity – Report CC166.13, dated 9/25/13 by [redacted] (b) (4) is provided. Container closure integrity testing was performed using a microbial ingress method.
  Media fill units [redacted] (b) (4) from the exhibit batch manufactured using the same vials and stoppers proposed for production batches were used for the study. [redacted] (b) (4)

(b) (4)

- Antimicrobial Effectiveness – N/A; no preservatives in the formulation. Single use/dose, multiple dose not indicated in package insert.

Reviewer's Assessment: This section was concluded Acceptable following sterility assurance review of the IR response submitted to the Agency on 10/2/2015.

The following comment (in italics) was conveyed to the sponsor via an Agency IR dated 9/23/15 following the product quality microbiology review:

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

Response: The applicant indicates that Container/closure integrity validation testing was performed (b) (4). No further questions are asked.

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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Reviewer's Assessment:N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment: The submission was concluded Acceptable following product quality microbiology review of the NDA and the IR responses submitted to the Agency on 10/2/2015 and 3/11/2016.

The overall manufacturing controls described in the submission are adequate to minimize patient risk. The proposed compendial release tests and specifications are appropriate and method suitability has been verified for the drug product. The product quality microbiology review is recommended.

Reviewer's Assessment and Signature: The product quality microbiology review is recommended.

Nandini Bhattacharya, Ph.D.
Microbiologist
CDER/OPF/DMA/BRANCH II
3.23.2016

Secondary Review Comments and Concurrence: I concur with the recommendation to approve from a microbiology standpoint.

Bryan S. Riley, Ph.D.
Branch Chief (acting)
CDER/OPQ/OPF/DMA/Branch II
3/23/2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The Applicant has provided the following statement regarding the environmental assessment.

In accordance with 21 CFR 25.15(d), Flamel Ireland Limited affirms that the requested action, approval of the NDA for Ephedrine Sulfate Injection, USP qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(b). The estimated introduction concentration of the active moiety into the aquatic environment will be several orders of magnitude below 1 part per billion (ppb). In addition, to the applicant's knowledge there are no extraordinary circumstances indicating that the proposed action would significantly affect the quality of the human environment (21 CFR 25.21).

Reviewer's Assessment: Adequate

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: I concur with the request for a categorical exclusion from preparation of an environmental assessment.

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

Secondary Review Comments and Concurrence:

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For NDA only

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Carton Label:

(b) (4)

Vial Label:

(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Akovaz (Ephedrine Sulfate Injection, USP)	
Dosage form, route of administration	Intravenous solution in a 1ml single dose vial.	
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	One strength of 50mg/ml	

Conclusion: Adequate

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Intravenous Solution	
Strengths: in metric system	50mg/ml	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Clear Colorless Solution	

Conclusion:Adequate

#11: Description (21CFR 201.57(c)(12))
(Attach proposed text)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Akovaz	
Dosage form and route of administration	Intravenous Solution	
Active moiety expression of strength with equivalence statement for salt (if applicable)	Ephedrine Sulfate	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Water, sodium hydroxide and glacial acetic acid	
Statement of being sterile (if applicable)	Sterile solution for single use administration	
Pharmacological/ therapeutic class	Adrenergic agonist	
Chemical name, structural formula, molecular weight	Ephedrine Sulfate	
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa, solubility, or pH)		

Conclusion:
Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))
(Attach proposed text)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	50mg/ml	
Available units (e.g., bottles of 100 tablets)	Single use vials	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		
Special handling (e.g., protect from light, do not freeze)		
Storage conditions	Store (b) (4) (ephedrine sulfate) Injection, 50 mg/mL at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].	

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Eclat	

Conclusion:

Adequate

2. Container and Carton Labeling (SEE ABOVE)

1) Immediate Container Label

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
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))		
Route of administration 21.CFR 201.100(b)(3))		
Net contents* (21 CFR 201.51(a))		
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**		
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 (not required)		
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 (21 CFR 201.1)		
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

2) **Carton Labeling**
(Attach the proposed carton labeling here)

Item	Comments on the Information Provided in NDA	Conclusions
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((d)(2))		
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)[201.10(a), 21CFR201.100(d)(2)]		
Sterility Information (if applicable)		
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		
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)		
"Keep out of reach of children" (optional for Rx, required for OTC)		
Route of Administration (not		

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion:

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
Adequate

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

Secondary Review Comments and Concurrence:

II. List of Deficiencies To Be Communicated

Drug Substance

Drug Product

Process

Facility

Biopharmaceutics

Microbiology:

IR 1:

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

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

3. Please provide the routine production load size(s) [redacted] (b) (4).

4. In regard to [redacted] (b) (4)

   [redacted] (b) (4)

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

   [redacted] (b) (4)

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

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

IR 2:

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

Environmental

Label/Labeling

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208289 **Submission Type:** NDA **Established/Proper Name:** Ephedrine Sulfate Injection, USP

Applicant: Flamel Ireland Limited **Letter Date: June 30 2015** **Dosage Form:** IV injection

Chemical Type: **Stamp Date: June 30 2015** **Strength:** 50 mg/mL

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	x		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?	x		Comments for 74-day letter for CMC and Biopharm, listed in Appendix I.

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	x ☐	
2.	Botanical[1]	☐	x ☐	
3.	Naturally-derived Product	☐	x ☐	
4.	Narrow Therapeutic Index Drug	☐	x ☐	
5.	PET Drug	☐	x ☐	
6.	PEPFAR Drug	☐	x ☐	
7.	Sterile Drug Product	x ☐	☐	
8.	Transdermal[1]	☐	x ☐	
9.	Pediatric form/dose[1]	☐	x ☐	
10.	Locally acting drug[1]	☐	x ☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
11.	Lyophilized product[1]	☐	x ☐	
12.	First generic[1]	☐	x ☐	
13.	Solid dispersion product[1]	☐	x ☐	
14.	Oral disintegrating tablet[1]	☐	x ☐	
15.	Modified release product[1]	☐	x ☐	
16.	Liposome product[1]	☐	x ☐	
17.	Biosimiliar product[1]	☐	x ☐	
18.	Combination Product _____	☐	x ☐	
19.	Other_____	☐	x ☐	

	Regulatory Considerations				
20.	USAN Name Assigned			☐	☐
21.	End of Phase II/Pre-NDA Agreements			x☐	☐
22.	SPOTS (Special Products On-line Tracking System)			☐	x ☐
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application			☐	x ☐
24.	Comparability Protocol(s)[2]			☐	x ☐
25.	Other_____			☐	☐
	Quality Considerations				
26.	Drug Substance Overage			☐	x ☐
27.	Design Space	Formulation		☐	☐
28.		Process		☐	☐
29.		Analytical Methods		☐	☐
30.		Other		☐	☐
31.	Real Time Release Testing (RTRT)			☐	☐
32.	Parametric Release in lieu of Sterility Testing			☐	☐
33.	Alternative Microbiological Test Methods			☐	☐
34.	Process Analytical Technology[1]			☐	☐
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product		☐	☐
36.		Excipients		☐	☐
37.		Microbial		☐	☐
38.	Unique analytical methodology[1]			☐	☐
39.	Excipients of Human or Animal Origin			☐	☐
40.	Novel Excipients			☐	☐
41.	Nanomaterials[1]			☐	☐
42.	Hold Times Exceeding 30 Days			☐	☐
43.	Genotoxic Impurities or Structural Alerts			☐	☐

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44.	Continuous Manufacturing	☐	☐	
45.	Other unique manufacturing process[1]	☐	☐	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	☐	☐	
47.	New delivery system or dosage form[1]	☐	☐	
48.	Novel BE study designs	☐	☐	
49.	New product design[1]	☐	☐	
50.	Other	☐	☐	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	x☐	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	x☐	☐	☐	
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and	x☐	☐	☐	

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C. FILING CONSIDERATIONS					
	function identified for each facility, and ❑ DMF number (if applicable)				
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☐	☐	☐	
	DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	x☐	☐	☐	DMF (b) (4)
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials	x☐	☐	☐	DMF (b) (4)

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C. FILING CONSIDERATIONS					
	❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
	DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for	x☐	☐	☐	

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C. FILING CONSIDERATIONS					
	product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☒	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☒	☐	The applicant has stated that the bioavailability of IV administered ephedrine is self-evident (21 CFR 320.22) but did not submit a biowaiver request.
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
	REGIONAL INFORMATION AND APPENDICES				
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	x☐	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x☐	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and	☐	☐	x☐	

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C. FILING CONSIDERATIONS					
	non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients				
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	☐	☐	☐	

Julia C. Pinto -A

Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.08.18 20:28:36 -04'00'

Julia C. Pinto, Ph.D.

Branch Chief (Acting)

Division II, Branch IV ONDP

Vidula R. Kolhatkar -S

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Date: 2015.08.18 20:40:46 -04'00'

Vidula Kolhatkar, Ph.D.

Biopharm Reviewer

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Appendix I

Biopharmaceutics 74-day letter comments

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.

CMC 74-day Letter Comments:

1. Assay specification at release of the drug product and stability should be the same. Explain why two different Assay specifications are used for release and stability of the drug product.
2. The stability data demonstrates that (b) (4) Further demonstrate that the (-) ephedrine analytical method is fully validated.
3. Explain the variability in the stability data for (b) (4) impurity at the (b) (4)

4. Tighten the pH specification or Justify the wide specification for pH at release and stability of the drug product.

5. Photostability study looked at the change in pH with light exposure. Provide data to demonstrate that whether degradation occurs when the product in the vial is exposed to light. Data should include determination of assay and impurities.