CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208943Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208943
Supporting document/s:	SDN-1 and -12
Applicant's letter date:	March 18, 2016 and December 2, 2016
CDER stamp date:	March 18, 2016 and December 2, 2016
Product:	Corphedra (ephedrine sulfate injection, USP)
Indication:	The treatment of clinically important hypotension occurring in the setting of anesthesia
Applicant:	Par Pharmaceutical
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Marcus S. Delatte, PhD
Team Leader:	Newton H. Woo, PhD
Supervisor:	R. Daniel Mellon, PhD
Medical Officer:	Alla T. Bazini, MD
Division Director:	Sharon H. Hertz, PhD
Project Manager:	Ogoegbunam, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208943 are owned by Par Pharmaceutical or are data for which Par Pharmaceutical obtained a written right of reference.
Any information or data necessary for Par Pharmaceutical approval of NDA 208943 that Par Pharmaceutical does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208943.

TABLE OF CONTENTS

Table of Tables

1 Executive Summary

1.1 Introduction

The Applicant is seeking marketing approval for the use of ephedrine sulfate as an injectable intravenous solution for the treatment of clinically important hypotension occurring in the setting of anesthesia. There is extensive clinical history with the API, ephedrine sulfate, as it is used in a FDA-approved product and various marketed unapproved drug products. Initially, the Applicant submitted a 505(b)(2) NDA based on published literature. However, the Applicant amended the NDA to rely upon the safety and efficacy of Akovaz (ephedrine sulfate, NDA 208289) and relevant pharmacology, pharmacokinetics, and toxicology information in the approved label of the listed drug.

1.2 Brief Discussion of Nonclinical Findings

The Applicant is relying upon the Agency's previous finding of safety and efficacy of Akovaz to support marketing approval of their ephedrine sulfate drug product. There were no original nonclinical pharmacology or toxicology studies submitted in support of this NDA application. The final drug product is ephedrine sulfate in water; therefore, there are no novel excipients in the drug product formulation. All drug substance impurities and drug product degradants are adequately qualified for safety.

A post-marketing requirement (PMR) will be requested to conduct a leachables assessment of Corphedra in its container closure system over the course of stability. This leachables assessment is deemed acceptable as a PMR because the (b) (4) rubber stopper is used in several FDA-approved aqueous injectable drug products and the submitted information regarding the rubber stopper do not raise any significant cause for concern. As the referenced product's label and nonclinical literature do not adequately address Sections 8 and 13 of the Applicant's proposed label, several PMRs that include a full battery of reproductive and toxicology studies and an in vivo genotoxicity study will be issued to inform labeling for this product.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 208943 may be approved with the recommended PMRs (see below).

1.3.2 Additional Non Clinical Recommendations

Based on the review of the information submitted to date, the following studies are recommended as post-marketing requirements (PMRs), should this NDA be approved during this cycle:

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

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

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

4. Conduct a (b) (4)- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.

5. Conduct an in vivo micronucleus assay to evaluate ephedrine sulfate.

6. Conduct an adequate leachable safety assessment for the (b) (4) rubber stopper (13 mm).

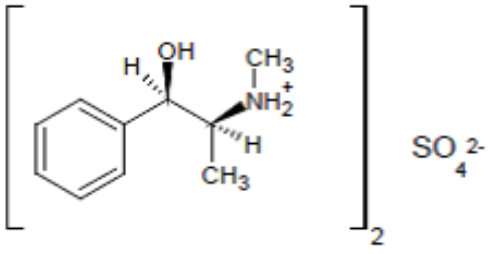
1.3.3 Labeling

The proposed label will be edited to be identical to the approved label of the listed drug. The reader is referred to the final action letter for final drug product labeling.

2 Drug Information

2.1 Drug

Table 1. Drug Substance Information

Generic Name(s)	(-)-ephedrine sulfate; (b) (4) (1R,2S)-(-)-ephedrine
Pharmacological Class	Alpha- and beta-adrenergic receptor agonist and norepinephrine releasing agent [Established Pharmacological Class]
Structure of (-) ephedrine	
Molecular Formula	$C_{20}H_{32}N_2O_6S$
IUPAC Name	(1R,2S)-2-(methylamino)-1-phenylpropan-1-ol; sulfuric acid
Molecular Weight	428.54 g/mol
CAS Registry Number	134-72-5

2.2 Relevant INDs, NDAs, BLAs and DMFs

Table 2. Relevant IND Application

Application No.	Holder	Product	Indication	Status (Date)
126012	Par Sterile Products, LLC	Ephedrine Sulfate	Increasing blood pressure in patients with clinically important hypotension resulting primarily from vasodilation, in such settings as anesthesia	Active (Nov 2015)

Table 3. Relevant DMFs

Application No.	Subject	Holder	DMF Type	Status
(b) (4)	(-)-Ephedrine Sulfate	(b) (4)	II	Active
	Glass Products (vial)		III	
	(b) (4) (related to Rubber Stopper; (b) (4)		II	Closed
	Pharmaceutical closure (stopper) – (b) (4)		V	Active
	(b) (4)		III	Active
	(b) (4) (related to Rubber Stopper; (b) (4)		III	Closed

Table 4. Relevant NDA Application (i.e., Referenced Drug)

Application No.	Sponsor	Product	Indication	Status (Date)
208289	Flamel Ireland Limited	Akovaz (ephedrine sulfate)	Treatment of clinically important hypotension in the setting of anesthesia	Approved (2016)

2.3 Drug Formulation

The drug product is formulated as an injectable solution that is intended for intravenous use. See the table below for excipients included in the drug product. This product is prepared in a single strength of 50 mg/mL with a fill volume of 1 mL.

Table 5. Ingredients Employed in the Drug Product

Component	Function	Total per vial	Acceptable (Yes/No)
Ephedrine Sulfate	Active Ingredient	50 mg	[redacted]
Water for injection	[redacted] (b) (4)	q.s. to 1 mL	Yes
[redacted]			(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product. See the table above for the ingredients employed in the drug product.

2.5 Comments on Impurities/Degradants of Concern

The drug substance and drug product specifications for impurities do not exceed ICH thresholds; therefore, there are no concerns.

Drug Substance

Table 6. Drug Substance Impurity Information

Impurity	Proposed Specification (NMT)	ICH Specification (NMT)	Acceptance (Yes/No)
[redacted]		(b) (4)	Yes

Table 7. Residual Solvent Information

Residual Solvent	Formula	Class	Proposed Specification (ppm)	ICH Specification (ppm)	Acceptable (Yes/No)
[redacted]				(b) (4)	Yes

Drug Product

Table 8. Drug Product Specifications

Test	Item	Proposed Specification (NMT)	ICH Specification or General Practice	Acceptable (Yes/No)
Impurities	(b) (4)	(b) (4)%	NMT 0.2%	Yes
	Specified degradation Product	(b) (4)%		
	Any unspecified degradation product	(b) (4)%		
Other	Osmolality	(b) (4) mOsm/kg	270 to 320 mOsm/kg*	

*The proposed osmolality range for this parenteral drug product is acceptable because normal serum osmolarity is approximately 290 mOsmol/L, parenteral solutions with comparable osmolalities have been used clinically for years, and there is considerable clinical experience with ephedrine sulfate as a marketed unapproved drug product.

Container Closure System

The container closure system proposed for use is a 3 mL glass vial and a 13mm rubber stopper (see CMC review for further details). In the NDA submission, the Applicant submitted a (b) (4) Stopper Report that contained several characterization reports and several biocompatibility assessments of the rubber stopper. However an extractables/leachables evaluation to support the safety of the container closure system was not submitted. Although a dedicated extractable/leachable assessment was not conducted for the container closure, the vial and rubber stopper are used in FDA-approved products with physiochemical properties that are similar to that of the product under review here. Therefore, the lack of leachables data is not an approval issue for this NDA. The Applicant will be required to conduct a leachable safety assessment for the (b) (4) rubber stopper (13 mm) used in the container closure system (see above the Post Marking Requirements or PMRs to be issued). This assessment will include leachable data from long-term stability studies testing at least three batches (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. The Applicant will be required to use this information to conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. Any leachable that contains a structural alert for mutagenicity should not exceed 120 mcg/day total daily exposure, or it must be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day. Overall, there does not appear to be evidence that suggests that there should be concerns of leachables from the container closure system and the container closure system is not novel for this type of drug product; therefore, the leachable testing may be conducted as a PMR.

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Ephedrine will be administered intravenously in patients with clinically important hypotension in the setting of anesthesia. The maximum recommended dose is 50 mg/ (b) (4) The ephedrine dose will likely be titrated to effect.

2.7 Regulatory Background

Ephedrine is listed in the Code of Federal Regulations as acceptable for use as an over-the-counter human drug as follows:

21 CFR Chapter	Acceptability of Use
§341.16	Bronchodilator Active Ingredient when used within the dosage limits established for each ingredient.
§341.20	Topical Nasal decongestant active ingredient when used within the dosage limits and dosage forms established for each ingredient.
§349.18	Ophthalmic vasoconstrictor (ephedrine hydrochloride 0.123 percent)

There are unapproved injectable products (i.e., intramuscular, intravenous, and subcutaneous; 50 mg/mL) that are marketed by (b) (4) Marketing for these products appeared to start in 2004 or later.

Although the Applicant did not meet with DAAAP for a preIND meeting, written responses were provided on July 8, 2015 to address questions provided by the Applicant prior to the submission of the IND. The questions were related to the Applicants plans to submit an IND application, followed by a 505(b)(2) NDA application. On April 13, 2016, a Pediatric Study Plan (PSP) was agreed upon between the Agency and the Applicant. The PSP included the requirement for a juvenile animal toxicity study. The NDA was submitted to the Agency on March 18, 2016 as a 505(b)(2) application relying upon published literature. Following the initial review of the application, DAAAP notified the Applicant that the enantiomer information in the referenced literature was not adequate and that this information must be revised to include findings from additional published studies that employed the enantiomer of ephedrine referenced to support the efficacy of ephedrine in non-obstetric patients. The Applicant submitted an amendment to the NDA and referenced the Agency's recent approval of Akovaz rather than revise their literature search. Therefore, the NDA is now relying on the findings of safety and efficacy for the approved product. This regulatory approach was deemed acceptable by DAAAP. As a result, the NDA no longer is required to conduct pediatric studies triggered by the Pediatric Research Equity Act (PREA). (b) (4)

3 Studies Submitted

The NDA is relying on the Agency's previous findings of safety and efficacy for the Akovaz product; therefore, nonclinical studies were not submitted to support its approval.

4 Pharmacology

Pharmacology studies were not submitted under this NDA. The following information on the pharmacology of ephedrine sulfate is from the referenced Akovaz label (Flamel Ireland LTD, 2016).

12.1 Mechanism of Action

Ephedrine sulfate is a sympathomimetic amine that directly acts as an agonist at α- and ß-adrenergic receptors and indirectly causes the release of norepinephrine from sympathetic neurons. Pressor effects by direct alpha- and beta-adrenergic receptor activation are mediated by increases in arterial pressures, cardiac output, and peripheral resistance. Indirect adrenergic stimulation is caused by norepinephrine release from sympathetic nerves.

12.2 Pharmacodynamics

Ephedrine stimulates heart rate and cardiac output and variably increases peripheral resistance; as a result, ephedrine usually increases blood pressure. Stimulation of the α-adrenergic receptors of smooth muscle cells in the bladder base may increase the resistance to the outflow of urine. Activation of ß-adrenergic receptors in the lungs promotes bronchodilation. The overall cardiovascular effect from ephedrine is the result of a balance among α-1 adrenoceptor-mediated vasoconstriction, ß-2 adrenoceptor-mediated vasoconstriction, and ß-2 adrenoceptor-mediated vasodilatation. Stimulation of the ß-1 adrenoceptors results in positive inotrope and chronotrope action. Tachyphylaxis to the pressor effects of ephedrine may occur with repeated administration

5 Pharmacokinetics/ADME/Toxicokinetics

Pharmacokinetics/ADME/toxicokinetic studies were not submitted under this NDA. The following information on human pharmacokinetic parameters of ephedrine sulfate is from the referenced Akovaz label (Flamel Ireland LTD, 2016).

12.3 Pharmacokinetics

Publications studying pharmacokinetics of oral administration of (-)-ephedrine support that (-)-ephedrine is metabolized into norephedrine. However, the metabolism pathway is unknown. Both the parent drug and the metabolite are excreted in urine. Limited data after IV administration of ephedrine support similar observations of urinary excretion of drug and metabolite. The plasma elimination half-life of ephedrine following oral administration was about 6 hours.

6 General Toxicology

General toxicology studies were not submitted under this NDA.

7 Genetic Toxicology

Genetic toxicology studies were not submitted under this NDA. The following information on the genetic toxicology of ephedrine sulfate is from the referenced Akovaz label (Flamel Ireland LTD, 2016).

> Mutagenesis: Ephedrine sulfate tested negative in the in vitro bacterial reverse mutation assay, the in vitro mouse lymphoma assay, the in vitro sister chromatid exchange, and the in vitro chromosomal aberration assay.

An in vivo genotoxicity study evaluating ephedrine sulfate will be required as a postmarketing requirement.

8 Carcinogenicity

Carcinogenicity studies were not submitted under this NDA. The following information on the carcinogenicity of ephedrine sulfate is from the referenced Akovaz label (Flamel Ireland LTD, 2016).

> Carcinogenesis: Two-year feeding studies in rats and mice conducted under the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate at doses up to 10 mg/kg/day and 27 mg/kg/day (approximately 2 times and 3 times the maximum human recommended dose on a mg/m^2 basis, respectively).

9 Reproductive and Developmental Toxicology

Reproductive and developmental studies were not submitted under this NDA. The following information on the reproductive and developmental toxicology of ephedrine sulfate is from the referenced Akovaz label (Flamel Ireland LTD, 2016).

> Animal reproduction studies have not been conducted with ephedrine sulfate.
>
> Impairment of Fertility: Studies to evaluate the effect of ephedrine on fertility have not been conducted.

A full battery of reproductive and developmental toxicology studies will be conducted as a post-marketing requirement since the nonclinical literature was deemed insufficient to inform labeling. Reproductive and developmental toxicology studies that evaluated ephedrine are briefly discussed below; however, the findings were not used to inform labeling since either the study design does not comply with the ICH S5A guidance or the information provided was not sufficient to verify that the test article was l-ephedrine. For example, teratogenicity data with ephedrine were reported in rats following intraperitoneal administration (Kanai, 1987) and chick embryos following topical administration (Nishikawa et al., 1985). The findings in the chick embryos are limited given the route of administration. Findings from Kanai et al. (1987) are informative given that hazards were identified in fetuses obtained from dams with plasma levels of ephedrine of 19.2 mcg/mL (1 hour following treatment). These findings suggest that toxicities occurred in rat fetuses at clinically relevant ephedrine exposure levels. However, the usefulness of these findings are limited based on a variety of factors that include the lack of information in the publication to indicate if the formulation administered consisted of both isomers of ephedrine or an individual isomer and that these findings were not published in a peer-reviewed journal. See below for a brief discussion of the studies mentioned.

Kanai et al (1987) evaluated the effects of ephedrine (0.1, 1, 10, or 50 mg/kg) injected intraperitoneally (IP) in pregnant Wistar-Imamichi rats on Gestation Days (GDs) 9, 10, or 11. Fetuses were collected on GD 20 when the dams were sacrificed. In a separate group of dams, toxicokinetic assessments were made on GD 10 following the intraperitoneal injection of 50 mg/kg of ephedrine. Cardiovascular anomalies were observed in 20.5% of the fetuses collected. The frequency of this finding increased in a dose-related manner. The cardiovascular anomalies observed were all ventricular septal defects, two of which were associated with overriding aorta. There was reportedly no significant difference in the malformation rate among the fetuses across the GDs in which dams were treated. Extracardiac malformations were not reported in the fetuses collected. In regard to serum levels, the concentrations of ephedrine in dams were 19.2, 7.2, 1.9, and 0 mcg/mL, respectively, at 1, 3, 6, and 12 hours following the IP injection of 50 mg/kg. The concentrations of ephedrine in fetus tissue were 34.9, 9.5, 2.7, and 0 mcg/g, respectively, at 1, 3, 6, and 12 hours following treatment. **Overall, these data provide evidence that cardiovascular teratogenicity occurred in fetus across the treatment levels on either GD 9, 10, or 11 in dams. Although these findings in rats are informative, this information will not be used for labeling purposes given that the publication does not indicate whether the racemic form or an individual isomer of ephedrine was tested in rats, the study was not conducted under GLP conditions, and there is no clear indication that the article was peer-reviewed. In addition, the Applicant will be required to conduct a full battery of reproductive toxicology studies post approval (i.e., PMR).** (b) (4)

Nishilawa et al (1985) evaluated cardiovascular teratogenicity and embryotoxicity endpoints in chick embryos (White Leghorn eggs) treated with L-ephedrine. L-ephedrine topically applied to eggs decreased survival and increased cardiovascular malformations in the embryonic chick in a dose-related manner. In an initial dose range finding study that topically applied L-ephedrine (0.5, 1, 5, 10, or 20 mcmol/egg) at four days of incubation, the percentage of survival for embryonic chicks was decreased in a statistically significant manner at 20 mcmol/egg. The percentage of malformations was increased in a statistically significant manner at $\geq$ 1 mcmol/egg. The malformations observed included cardiac anomalies and aortic arch anomalies. In the experiment that followed in which chick embryos (2.5 to 6 days old) were treated topically with an optimal dose (14 mcmol) selected from the previous experiment on Incubation Day 4 and returned to the incubator until Day 14, comparable incidences of aortic arch anomalies were reported. In contrast, the incidence of simple ventricular septal defects and conotruncal anomalies were markedly less in the older group (5 to 6 days) compared to the two younger groups. **Although these data provide evidence of cardiovascular teratogenicity and embryotoxicity in chick embryos following exposure to L-ephedrine, the clinical relevance of these findings is not clear given the species tested and route of administration employed.**

10 Special Toxicology Studies

Local Tolerance

Although the Applicant did not conduct local tolerance studies, the Reviewer identified published findings from a study employing rabbits observed with thrombosis in the vein following the administration of a 5% ephedrine sulfate solution (or 50 mg/mL) via three or four bolus intravenous injections at $\geq$ 16.6 mg/kg (Chen, 1926). This concentration equals the concentration of the clinical formulation proposed for clinical use. This nonclinical finding is likely not clinically relevant given that the finding appears to be limited to the study mentioned and not observed at the clinical doses studied in the published literature (see the Medical Officers review). Given the extensive clinical history of the marketed unapproved drug product under review here, the Division agreed to permit the local tissue toxicity of the drug product to be addressed based on clinical experience. Further nonclinical studies are not required.

11 Integrated Summary and Safety Evaluation

NDA 208943 was submitted via the 505(b)(2) regulatory pathway with the Akovaz product (NDA 208289) as the referenced product. The clinical history of ephedrine sulfate is extensive. Ephedrine is an established sympathomimetic agent that stimulates both alpha- and beta-adrenergic receptors directly and indirectly enhances the release of norepinephrine from sympathetic neurons. Ephedrine is known to increase blood pressure by binding to and stimulating alpha adrenergic receptors. Based on the long history of clinical use, repeat-dose toxicology and local tolerance studies evaluating ephedrine were not required for approval of this NDA application. The impurities/degradants are controlled at acceptable levels in both the drug substances and the drug product. There are no toxicologic concerns when the product is used at levels up to the maximum recommended daily dose (50 mg (b) (4) individual). Therefore, NDA 208943 may be approved with the recommended PMRs (see above).

12 Appendix/Attachments

Bibliography

Chen K (1926) The Effect of Repeated Administration of Ephedrine. *J Pharmacol Exp Ther* **27**:77-86.

Kanai T (1987) The Effects of Ephedrine on the Fetal Rat Heart. *Tokyo Women's Medical Journal* **57**:347 -357.

Nishikawa T, Bruyere HJ, Jr., Takagi Y, Gilbert EF and Uno H (1985) Cardiovascular teratogenicity of ephedrine in chick embryos. *Toxicol Lett* **29**:59-63.

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/s/

MARCUS S DELATTE
12/20/2016

NEWTON H WOO
12/20/2016

RICHARD D MELLON
12/20/2016
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 208943 **Applicant:** Par Sterile Products, LLC **Stamp Date:** March 18, 2016

Drug Name: CORPHEDRA (Ephedrine Sulfate Injection, USP) **NDA Type: 505(b)(2)**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		No new nonclinical studies of ephedrine were conducted for this NDA nor were they required in order to file the NDA. Given the long clinical history of use, the Division agreed to permit review based on clinical experience and published literature with any deficiencies in toxicology of ephedrine addressed via PMRs. Only nonclinical literature references were submitted to support the b2 application were submitted. The submitted acute toxicology studies appear to be the only toxicology studies in which ephedrine was intravenously administered. The Sponsor provided what appears to be a peer-reviewed article evaluating the potential teratogenicity and embryotoxicity effects of ephedrine (intraperitoneal) in rats; however, the text was not translated to English (with the exception of the abstract). The Sponsor did not identify published peer-reviewed articles that reported findings from fertility, pre- and postnatal development, and local tolerance

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
				studies; however, this was not deemed a filing issue.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	-	-	Not applicable. See above.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	-	-	Not applicable. See above.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	-	-	Not applicable. No new nonclinical studies were required for this NDA.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		Two impurity specifications exceed ICH thresholds and will be noted in the 74-day letter. These issues are not filing deficiencies, as it would appear that the specifications can be tightened to meet ICH thresholds based on submitted stability data. A qualitative extractable report was submitted to this b2 application to support the safety of the container closure system (i.e., rubber stopper); however, it was deemed inadequate. The rubber stopper can be deemed safe for use based on the Agency's previous finding of safety used in for FDA-approved intravenous aqueous products that

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
				used the same stopper. Note that the pH ranges for these products overlap with that of the product under review, which reduces the probability that the integrity of the stopper will be impacted differently over time.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	-	-	This parameter is not applicable to the application under review.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		The Sponsor provided a rationale to support the reliance to the nonclinical literature.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __YES_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The comments below should be communicated to the Applicant.

1. We note that your drug substance and drug product specifications for (b) (4) exceed ICH thresholds. Also, you have neither provided adequate justifications for the safety of these specifications nor have you completed the required toxicology studies outlined in the PreIND written responses. Your safety justification that ephedrine sulfate has been on the market in the E.U. and U.S. for several years using the same route of synthesis is not adequate. You must either tighten these specifications to comply with ICH or qualify them.

   As we previously stated, for the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2) and ICH Q3B(R2). In order to provide adequate qualification:

   a. You must complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14-days duration should be completed.

Refer to
Guidance for Industry: *Q3A(R2) Impurities in New Drug Substances*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf

and

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

2. We also note that you cited findings from Kanai (1987); however, this paper was written in Japanese. You are reminded that journal articles submitted as part of your NDA must be translated into English. Submit a translated articled along with the credentials of the person who translated the article.

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/s/

MARCUS S DELATTE
05/11/2016

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