CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204300Orig1s000

PHARMACOLOGY REVIEW(S)

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

PHARMACOLOGY TOXICOLOGY (PT) Memo

NDA number:	204300
SDN:	28
Sponsor:	Éclat Pharmaceuticals
PT Reviewer:	Marcus S. Delatte, PhD
PT Supervisor:	R. Daniel Mellon, PhD
CMC[1] Reviewer:	Eugenia M. Nashed, PhD
Medical Officer:	Timothy T. Jiang, MD
Project Manager:	Kimberly A. Compton, RPh
Division Director:	Bob A. Rappaport, MD

Recommendation: From a nonclinical pharmacology toxicology perspective, NDA 204300 may be approved with the originally recommended PMRs and pending agreement on labeling since there were neither nonclinical deficiencies to address nor new nonclinical information to review in the complete response submitted.

EXECUTIVE SUMMARY	The Sponsor submitted a complete response for NDA 204300 (Class 1 resubmission) on June 6, 2014 to address the deficiencies provided by DAAAP for NDA 204300/Original 1 – treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia (see SDN-28). Although the original application proposed two separate indications for the use of phenylephrine, the resubmission is a complete response to NDA 204300/Original 1 only. See the action letters finalized on April 28, 2014 for further information. The PT recommendation to approve this NDA will remain the same since there were neither nonclinical deficiencies to address nor new nonclinical information to review in the complete response submitted. Therefore, the NDA may be approved with the originally recommended PMRs and pending agreement on labeling.
DRUG INFO	
Drug Substance(s)	Phenylephrine HCl
Drug Product	VAZCULEP injection

[1]CMC stands for Chemistry, Manufacturing, and Controls.

Pharmacology	Phenylephrine is an alpha-1 adrenergic receptor agonist (Hoffman and and Taylor, 2001; Hoffman, 2001).
CLINICAL INFO	
Proposed Indication	Treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia (NDA 204300/Original 1).
Dose and Duration	The maximum dose recommended is < 10 mg/60 kg individual (i.e., < 0.17 mg/kg).
Previous Clinical Experience	There is an extensive literature on the clinical use of phenylephrine for the treatment of hypotension. See the Medical Officer's review for further information.
NON-CLINICAL INFO	
Studies Submitted/Required	Nonclinical studies were neither conducted nor required to support the NDA application.

Reference List

Hoffman BB (2001) Catecholamines, Sympathomimetic Drugs, and Adrenergic Receptor Antagoinist, in *Goodman and Gilman's The Pharmacological Basis of Therapuetics* (Hardman JG and and Limbird LE eds) pp 215-268, McGraw-Hill Medical Publishing Division.

Hoffman BB and and Taylor P (2001) Neurotransmission: The Autonomic and Somatic Motor Nervous Systems, in *Goodman and Gilman's The Pharmacological Basis of Therapuetics* (Hardman JG and and Limbird LE eds) pp 115-153, McGraw-Hill Medical Publishing Division.

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

/s/

MARCUS S DELATTE
06/18/2014

RICHARD D MELLON
06/18/2014
I concur.

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:	204300
Application Type:	505(b)(2)
Supporting document/s:	SDN-1, -6, and -19
Applicant's letter date:	February 8, 2013; June 28, 2013; and March 11, 2014
CDER stamp date:	February 8, 2013; June 28, 2013; and March 11, 2014
Product:	VAZCULEP (phenylephrine hydrochloride) injection
Indication:	For the treatment (b) (4) of hypotension during anesthesia
Applicant:	Éclat Pharmaceuticals Chesterfield, MO 63005
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products
Pharmacology/Toxicology (PT) Reviewer:	Marcus S. Delatte, PhD
PT Supervisor/Team Leader:	R. Daniel Mellon, PhD
Product Quality Reviewer:	Eugenia M. Nashed, PhD
Division Director:	Bob A. Rappaport, MD
Project Manager:	Kimberly A. Compton, RPh

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204300 are owned by Éclat Pharmaceuticals or are data for which Éclat Pharmaceuticals has obtained a written right of reference.
Any information or data necessary for approval of NDA 204300 that Éclat Pharmaceuticals 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 204300.

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1 Executive Summary

1.1 Introduction

The Applicant is seeking marketing approval for the use of phenylephrine HCl (PHE) as an injectable intravenous solution for the treatmen (b) (4) of hypotension during anesthesia via the 505(b)(2) pathway. PHE is not a New Molecular Entity. There is extensive clinical history of this drug substance. In addition to the many oral drug products containing phenylephrine, the Agency recently approved PHE-containing drug products for use via intravenous and intra-ocular routes of administration based, in part, on extensive findings from the published literature. See **Table 3** for information on these approved products. The Applicant is not relying upon an Agency finding of safety and effectiveness for either of these NDAs; rather, they are relying exclusively on information in the published literature to support this application.

1.2 Brief Discussion of Nonclinical Findings

There were no original nonclinical pharmacology or toxicology studies submitted in support of this NDA application. Findings in the published literature have demonstrated that PHE increases blood pressure by binding to and stimulating alpha 1-adrenergic receptors (see Shibasaki, et al., 1992; Zhou and Vargas, 1996).

There are no novel excipients in the drug product formulation. All drug substance impurities and drug product degradants have been adequately qualified for safety. The container closure system has been adequately qualified for safety.

In several meetings with the Applicant prior to submission of the NDA, the Division noted that if there is adequate clinical experience with the drug product, no general toxicology studies would be required to support the NDA. The Applicant was requested to provide a literature review to address the potential for genotoxicity, carcinogenicity, and reproductive and developmental toxicity of phenylephrine to inform product labeling. If upon review, these data were deemed inadequate to inform labeling, further studies may be required to be completed post-approval.

Adequate genetic toxicology studies have been reported in the literature. Although there was one positive finding in an in vitro mouse lymphoma assay, phenylephrine tested negative in the in vitro bacterial reverse mutation assay, an in vitro chromosomal aberration assay, an in vitro sister chromatid exchange assay, and an in vivo rat micronucleus assay.

Carcinogenicity studies were conducted in rats and mice treated with phenylephrine via their diet. Daily doses approximately 50 mg/kg (300 mg/m^2) in rats and 270 mg/kg (810 mg/m^2) in mice were not deemed carcinogenic following two years of treatment.

Review of the literature identified a few nonclinical studies that begin to characterize the potential impact of phenylephrine on reproductive and developmental endpoints. Specifically, reproductive toxicology studies in normotensive rabbits were conducted to evaluate the effect of phenylephrine administration during various stages of gestation. These studies indicate that subcutaneous administration of phenylephrine to pregnant rabbits (0.33 mg/kg, TID) resulted in premature labor onset, decreased litter weights, increased neonate deaths and still births, and histopathology findings in the placenta such as necrosis, thickened vascular walls, and narrowed lumina. Studies in normotensive pregnant sheep demonstrated that phenylephrine increases blood pressure and produces reflex bradycardia in both the ewe and the fetus and decreases uterine blood flow at doses that were slightly greater than the upper dosing range in humans. These findings, in normotensive animals, suggest the potential for risk and should be included in the drug product labeling at this point. However, none of the studies are deemed adequate by current standards, and the results from studies in normotensive animals may not reflect clinical conditions if the drug is used only to treat hypotension and restore blood pressure to normal. However, these study results may be clinically relevant with respect to the proposed use of the drug to (b) (4) hypotension, as there may be a period of increased blood pressure under this clinical use condition. Based on the limited data in the literature, the full reproductive and developmental toxicology study battery of studies are recommended as PMRs. Careful design of these studies to include assessment of clinically relevant conditions, if possible, should be discussed with the Sponsor.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 204300 may be approved with the recommended PMRs and pending agreement on labeling.

1.3.2 Additional Non Clinical Recommendations

Based on the data 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 phenylephrine hydrochloride.

2. Conduct an embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.

3. Conduct an embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.

4. Conduct a peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

1.3.3 Labeling

The labeling recommendations below have not been discussed with the entire review team or the Applicant. The reader is referred to the drug product labeling in the action letter for final labeling information.

Table 1. Labeling Recommendations

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
Highlights **Indication and Usage** PHENYLEPHRINE HYDROCHLORIDE INJECTION, USP, (b) (4) is an alpha-1 adrenergic receptor agonist (b) (4) for the treatment (b) (4) of hypotension during anesthesia.	**Highlights** **Indication and Usage** ~~PHENYLEPHRINE HYDROCHLORIDE INJECTION, USP,~~ (b) (4) VASCULEP (phenylephrine hydrochloride) injection, is an alpha-1 adrenergic receptor agonist (b) (4) for . . .	The FDA Established Pharmacological Class is correct. The brand name has been updated as per the review team recommendations.
Highlights **Use in Specific Populations**	Pregnancy: Based on animal data, may cause fetal harm. (8.1)	This statement is appropriate for a Pregnancy Category C drug where animal data suggest risk.
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Pregnancy Category C. There are no adequate or well-controlled studies of intravenous phenylephrine hydrochloride in pregnant women (b) (4)	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** Pregnancy Category C Risk Summary ~~Pregnancy Category C.~~ There are no adequate or well-controlled studies of intravenous phenylephrine hydrochloride in pregnant (b) (4)	In the spirit of the PLLR labeling initiative, human data is presented first. A risk summary statement will also be crafted to include human risk and animal risk.

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
	(b) (4) There are no adequate animal studies that evaluate the potential teratogenicity of intravenously administered phenylephrine. Published studies in normotensive pregnant rabbits suggest that phenylephrine treatment during gestation resulted in early onset of labor, decreased placental integrity, possible teratogenicity, and increased fetal and neonatal lethality. Published studies in normotensive pregnant sheep suggest that phenylephrine decreased uterine blood flow, decreased PaO_2, increased $PaCO_2$, and decreased blood pH in the fetus. Data Animal Data Studies in the published literature evaluating subcutaneously administered phenylephrine (0.33 mg/kg, TID) in normotensive pregnant rabbits treated during gestation reported an increase in fetal deaths, premature labor, and adverse histopathology findings in the placenta (necrosis, calcification and thickened vascular walls with narrowed lumen) and possible teratogenic effects at doses that were 1.9-times the total daily human dose of 10 mg/day based on a body surface area comparison. Published studies in pregnant normotensive sheep demonstrate that intravenous phenylephrine (4 mcg/kg/min for 30 minutes, equivalent to 3.6 to	The proposed nonclinical risk summary statement will be combined with a human risk summary statement in the final product labeling. The rabbit data was derived from the literature (see Shabanah, et al., 1969b; Shabanah, et al., 1969a) The data from pregnant sheep were published by Cottle and colleagues.

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
	4.1 mcg/kg/min human equivalent dose based on body surface area) decreased uterine blood flow by 42%. This dose is 1.1 to 1.2-times the human bolus dose of 200 mcg/60 kg person based on body surface area. Fetal blood pressure and heart rate fluctuated above and below controls by about 7% during the infusion. Fetal PaO_2 was significantly decreased by approximately 26% of control during the infusion. Likewise, $PaCO_2$ was increased and pH was decreased. The clinical significance of these findings is not clear; however, the results suggest the potential for cardiovascular effects on the fetus when phenylephrine is used during pregnancy.	
12 CLINICAL PHARMACOLOGY **12.1 Mechanism of Action** (b) (4) [redacted] .	**12 CLINICAL PHARMACOLOGY** **12.1 Mechanism of Action** Phenylephrine hydrochloride is (b) (4) [redacted] an α_1-adrenergic receptor agonist (b) (4) [redacted]	
13 NONCLINICAL TOXICOLOGY	**13 NONCLINICAL TOXICOLOGY**	
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**	

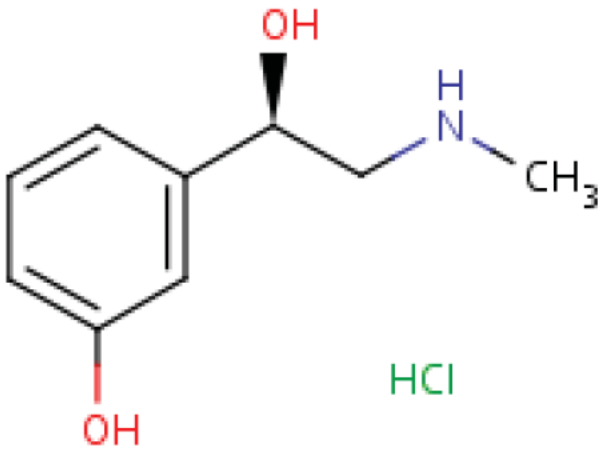
Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
Carcinogenesis: (b) (4) long-term animal (b) (4) to evaluate the carcinogenic potential of intravenous phenylephrine. (b) (4) .	*Carcinogenesis:* (b) (4) Long-term anima (b) (4) to evaluate the carcinogenic potential of intravenously administered phenylephrine hydrochloride. (b) (4) -in F344/N rats and B6C3F$_1$ mice were completed by the National Toxicology Program using the dietary route of administration. There was no evidence of carcinogenicity in mice administered approximately 270 mg/kg/day (131-times the maximum recommended daily dose of < 10 mg/day) or rats administered approximately 50 mg/kg/day (48-times the maximum recommended daily dose of < 10 mg/day based on body surface area comparisons).	These data provide evidence that dietary administration of phenylephrine in rats and mice does not produce carcinogenic effects up to doses markedly higher than the maximum recommended daily dose (see Bucher, et al., 1988; National Toxicology Program, 1987). The doses proposed by the Applicant were based on the highest of the two drug administered between males and females. The doses proposed by the review reflect the mean values reported in the NTP study abstract.
Mutagenesis: (b) (4)	*Mutagenesis:* (b) (4) –Phenylephrine hydrochloride tested negative in the in vitro bacterial reverse mutation assay (*S.typhimurium* strains TA98, TA100, TA1535 and TA1537), the in vitro	These data were obtained from a published report from NTP, an organization with extensive experience conducting these types of studies (National Toxicology Program,1987).

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
	chromosomal aberrations assay, the in vitro sister chromatid exchange assay, and the in vivo rat micronucleus assay. Positive results were reported in only one of two replicates of the in vitro mouse lymphoma assay.	
Impairment of Fertility: (b) (4)	*Impairment of Fertility:* (b) (4) Studies to evaluate the effect of phenylephrine on fertility have not been conducted.	Adequate studies have not been completed. The proposed statement (b) (4)

2 Drug Information

2.1 Drug

Table 2. Drug Substance Information

Drug Substance	Phenylephrine HCl
Pharmacological Class	alpha-1 adrenergic receptor agonist (FDA Established Pharmacological Class)
Structure	
Manufacturer	(b) (4)
CAS Registry #	(b) (4)

Drug Substance	Phenylephrine HCl
Molecular Formula	$C_9H_{13}NO_2$•HCL
IUPAC Name	3-[(1R)-1-hydroxy-2-(methylamino)ethyl]phenol, hydrochloride
Molecular Weight	203.67 g/mol

2.2 Relevant INDs, NDAs and DMFs

The Agency has approved two NDA applications for phenylephrine drug products. These products are listed in **Table 3** and are listed here for informational purposes only. These products were neither referenced by the Applicant nor reviewed by the PT Reviewer to support the safety of the drug product under review here (i.e., the Vazculep drug product).

Table 3. Phenylephrine Drug Products Approved by the FDA

NDA #	Product Name (Approval Date)	Dosage Form (Route)	Applicant	Indication
203826	Phenylephrine HCl injection, USP (Dec 2013)	Solution (10 mg/mL, IV infusion)	West Ward Pharmaceutical Corp.	For increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia
203510	Phenylephrine HCl (Mar 2013)	Solution/Drops (2.5 and 10%, Ophthalmic)	Paragon Biotech, Inc.	Dilation of pupils

Table 4. Referenced DMF Information

Master File (MF) Number	Subject	Holder	MF Type	Active Status Date	Comments
[redacted] (b) (4)			II	May 1985	Deemed adequate for other FDA-approved applications
			III	June	The specific

	(b) (4)		1994	(b) (4) been deemed adequate for other FDA-approved products.
(b) (4)		III	Oct 2007	Adequate as per ONDQA
		III	Oct 1995	Adequate as per ONDQA

2.3 Drug Formulation

The drug product is formulated as an injectable solution that is intended for intravenous use. See **Table 5** for excipients included in the drug product. This product is prepared in one strength at 10 mg/mL. The fill volumes are 1 mL, 5 mL, and 10 mL in glass vials (fitted with gray rubber stoppers, aluminum seals and flip off caps (see **Figure 1** for details).

Table 5. Excipients Included in Drug Product and Their Safety Status

Excipient (Function)	Quantity (mg/mL)	Maximum Amount[1] (mg)	Acceptable (Yes/No)
Sodium Chloride (b) (4)	3.5	3.5	**YES**
Sodium Citrate Dihydrate (b) (4)	4	4	
Citric Acid Monohydrate (b) (4)	1	1	
Sodium Metabisulfite (b) (4)	2	2	
Sodium Hydroxide (b) (4)	As needed	---	**---**

[1]This value is based on <10 mg as the top clinical dose of phenylephrine.

Excipient (Function)	Quantity (mg/mL)	Maximum Amount[1] (mg)	Acceptable (Yes/No)
(b) (4)			
Hydrochloric Acid (b) (4)	As needed	---	---
Water (b) (4)	q.s. to 1 mL	---	---

Figure 1. Container Closure Information[2]

Component	Manufacturer/Supplier	DMF	Specification	Certificate of Analysis
(b) (4)				CofA
				CofA
				CofA

2.4 Comments on Novel Excipients

There are no novel excipients. All of the excipients are common excipients in injectable drug products at comparable concentrations and doses.

[2]Excerpt from 3.2.P.7 Container Closure System

2.5 Comments on Impurities/Degradants of Concern

There are no concerns about the impurities/degradants reported, as none of them exceed ICH levels based on the maximum recommended clinical dose (b) (4) individual, see Tables 6 and 7). Both drug product degradants identified in Table 7 (b) (4) were predicted to be negative for Salmonella mutagenicity based on internal computational assessment at the Agency (see Figure 3, excerpt from report)

Table 6. Drug Substance Impurities[3]

Impurity Type	Impurity	Structure	Proposed specification	Reviewer Comment
Starting Material	(b) (4)			Acceptable. Complies with ICH Q3A(R2)
Process Impurities				

[3]Reproduced from NDA 204300 Section 3.2.S.3 Characterization and 3.2.S.4 Control of Drug Substance

Figure 2. Proposed Specifications for Phenylephrine Drug Substance[4]

Table 1: Proposed Regulatory Specifications for Phenylephrine Hydrochloride, USP

Test Parameter	Method	Acceptance Criteria
Appearance	ATP007 (Visual)	A white or almost white crystalline powder
Identification	ATP008 (FT-IR)	Conforms to reference spectrum
	Test B (USP)	Complies
Melting range	USP <741>	140 °C – 145 °C
[redacted]		(b) (4)

Test Parameter	Method	Acceptance Criteria
Certificate of Analysis must be received from Éclat Pharmaceuticals, confirming that the material: Conforms to supplier specifications Has been controlled according to GMP regulations Has been released for use		Certificate of Analysis including compliance statements received
[redacted]		(b) (4)

[4]Excerpt from NDA 204300 Section 3.2.S.4 Control of Drug Substance

Table 7. Proposed Drug Product Specifications

Degradation Products	Structure	Proposed specification	Reviewer Comment
(b) (4)		(b) (4)	**Acceptable, complies with ICH Q3B(R2)**
	Individual Unknown Impurities		
	Total Related Substances		

Figure 3. Excerpt from FDA Computational Service Report on Drug Product Degradants from Phenylephrine HCl

2. (b) (4)

***Salmonella* Mutagenicity**[1]

(b) (4)

Software	*Salmonella* Mutagenicity
Derek Nexus	(b) (4)
Model Applier	–
CASE Ultra	–
Overall Software Prediction	–
Overall Expert Prediction	–

(b) (4) is predicted to be negative for *Salmonella* mutagenicity.

3. (b) (4)

***Salmonella* Mutagenicity**[1]

(b) (4)	Software	*Salmonella* Mutagenicity
	Derek Nexus	(b) (4)
	Model Applier	
	CASE Ultra	–
	Overall Software Prediction	–
	Overall Expert Prediction	–

(b) (4)

Container Closure Leachables/Extractables

The container closure system has been used (b) (4) The system contains a Type 1 clear glass vial (tubular ISO 10R, 10 mL, 20 mm neck) and a (b) (4) rubber stopper (b) (4) (b) (4) An extractable/leachable assessment of this rubber stopper was conducted using water for injection (WFI), isopropanol, and hexane as solvents. This assessment included testing under the following conditions:

- Autoclave extraction at 121°C into water for injection at three pH levels (3, 6, and 11) for 1 hour followed by dichloromethane liquid/liquid extraction
- Reflux extraction for 30 minutes in isopropanol
- Reflux extraction for 30 minutes in hexane

According to the extractables report, the typical rubber stopper evaluated was (b) (4) g/stopper. Also, the stopper was not cut or otherwise altered for these studies. The final test article surface to solvent ratio was 2 cm^2/mL across the conditions employed. See **Table 8** for further information about the rubber stopper evaluated. The findings are briefly discussed below.

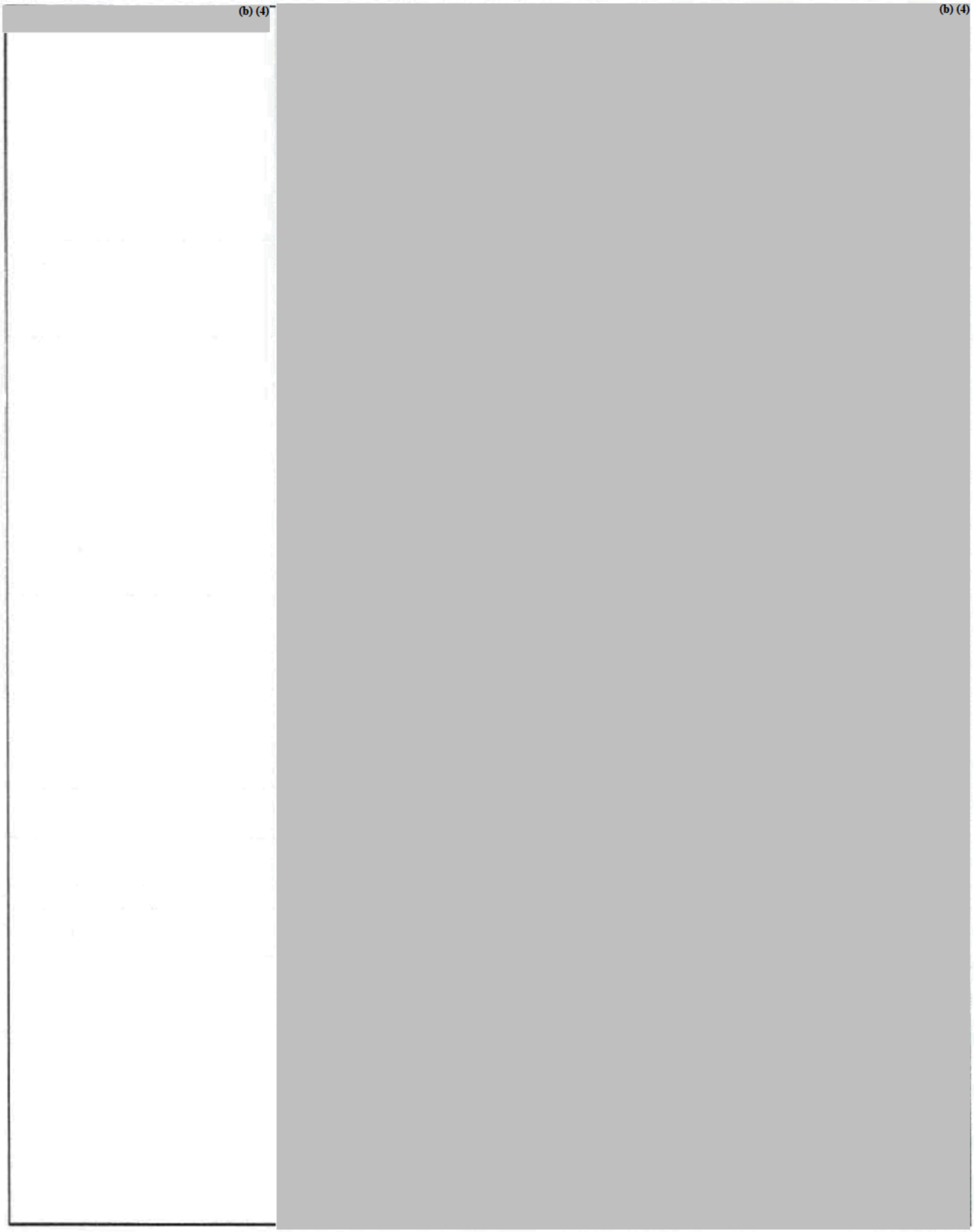
Table 8. Properties of the Rubber Stopper Proposed

Test Item ID		(b) (4)	
Lot/Batch #			
Typical Unit Weight			
Unit Surface Area			
Unit Volume			

A variety of compounds were identified during the extraction studies. See **Figure 4** for a list of these compounds. According to the study report reviewed, the source of these compounds was attributed to the ingredients used and manufacturing steps employed during production of this product. To assess the safety of the extractables detected, the Applicant determined the analytical evaluation threshold (AET) based on the following equation: AET (mcg/g stopper) = safety concern threshold ÷ maximum total stopper exposure ÷ 2. The safety concern threshold employed was 120 mcg/day, a value based on the use of the drug product for ≤ 1 month of the lifetime of the patient (see ICH M7 guidance document). An AET value of 117 mcg/g stopper was determined for materials from the 1 mL fill volume product, which is expected to have the highest ratio of stopper per unit volume of the drug formulation compared to the other fill volume products employed. Based on the Applicants calculations no substances were extracted into any aqueous media (pH 3, pH 7, and pH 11) or isopropanol at levels that exceeded the AET value determined.

Figure 4. Summary of Detected Compounds

Analysis	Compound	Concentrations (mg/kg)				
		WFI	pH3	pH11	IPA	hexane
		(b) (4)				


(b) (4)
(b) (4)

Leachable Measurements

Based on the extraction studies, there are a variety of substances that may potentially leach from the stopper employed. The Applicant concluded that there are only (b) (4) that may potentially leach into the drug product from the stopper based on the findings from the extraction study and taking into consideration the solvents tested and chemical composition of the drug product solution. The Applicant and Division agreed that there was no need to monitor these predicted leachables in ongoing stability studies since each is consumed in the diet and naturally found throughout the body at levels higher than were obtained in the extraction study (see End of Phase 2 meeting minutes). Separately, the CMC Reviewer concluded that (b) (4)) was a potential leachate of concern based on its levels detected in the extractable study when hexane is employed as a solvent, and (b) (4) in its structure. To address this concern the Applicant agreed to the CMC Reviewer's recommendation to conduct tests to evaluate (b) (4) levels in multiple batches of the drug product and submit the data in the first annual report. The Applicant agreed to test nine batches that will include three registration batches from each fill (1 mL, 5 mL, and 10 mL). These three batches will be stored inverted (b) (4) for ~22 months. The Applicant reported that preliminary analysis showed the (b) (4) levels in the phenylephrine drug product currently on stability are less than the limit of quantification. These results are consistent with findings from another FDA-approved drug product (b) (4)) that consists of the same container closure system and displays similar, if not harsher, physiochemical properties to the product under review here. The review team concluded that these preliminary findings with the drug product under review may be leveraged as evidence that the container closure system is safe given the lack of evidence that (b) (4) leaches out from the container closure system and the use of this container closure system in other approved drug products. Also, the CMC review team concluded that a specification was

not needed for (b) (4) if it is not detected in the batches of drug product tested. See the CMC review for further information.

2.6 Proposed Clinical Population and Dosing Regimen

Phenylephrine has been proposed for intravenous administration in patients as a (b) (4) treatment for anesthesia-induced hypotension. See **Figure 5** for the dosing regimens proposed by the Sponsor for each indication below. Based on the proposed regimens the highest total exposure level expected was 12 mg the day of a given procedure (200 mcg/min for 60 min = 12,000 mcg = 12 mg). However, the Division clinical review team will not include a maximum duration of treatment in the dosing and administration section of the drug product labeling. After further discussions within the Division, based on typical usage patterns, although some rare individuals may be exposures to more than 10 mg, the Division determined that a reasonable maximum recommended daily dose to < 10 mg/60 kg individual (i.e., < 0.17 mg/kg).

Figure 5. Original Dosing Regimen Proposed for PHE for the [redacted] (b) (4) Treatment of Hypotension[5]

Method of Administration	Starting Dose Recommendation
Bolus intravenous dose administered to treat anesthesia-induced hypotension, with repeat dosing if needed	40 to 100 µg Doses to be applied every 1-2 minutes as needed Not to exceed 200 µg
Intravenous infusion administered to treat anesthesia-induced hypotension	10 to 35 µg/min starting dose, titrating to effect Not to exceed 200 µg/min
[redacted] (b) (4)	

The safety of cumulative doses >4 mg has not been evaluated.

2.7 Regulatory Background

There are numerous PHE-containing products approved by the Agency. Please see **Table 3** for information on approved NDA applications for single entity PHE products. Neither of these applications are being referenced by the Applicant in support of NDA 204300. The information in **Table 3** is provided for historical purposes, to document the approval history of products containing phenylephrine and why this drug substance is not considered a new chemical entity. As mentioned above, the Applicant has decided to base the safety and efficacy of the drug product for the NDA under review here on findings from the published literature. The Applicant has meet with DAAAP in person twice and received formal advice several times. See **Figures 6** and **7** for excerpts from advice letters/meeting minutes provided to the Applicant.

[5]Excerpts from Clinical Overview (Section 2.5) of the NDA application

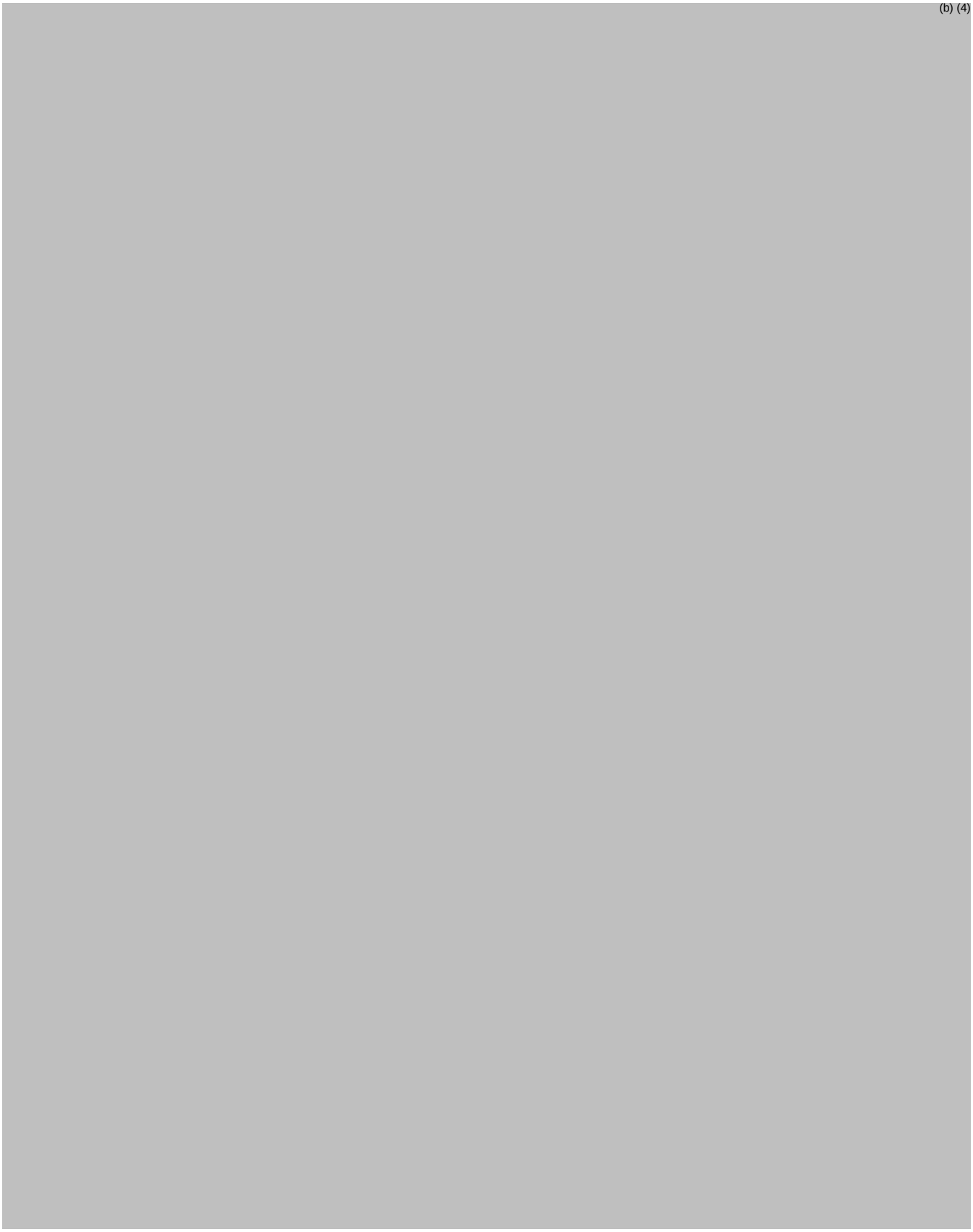
Figure 6. Meeting Minutes Pre-IND Meeting Held on November 17, 2011

DISCUSSION

The Sponsor opened the meeting by stating that they intended to bring this marketed product under NDA approval in line with the marketed, unapproved drugs guidance. They stated that they intended to rely on literature to support the application.

NONCLINICAL

(b) (4)



Additional Nonclinical Comments pertaining to your NDA submission:

1. **For the NDA submission, any impurity or degradant that exceeds ICH thresholds must be adequately qualified for safety as per (ICH Q3A(R2), ICH Q3B(R2)). Adequate qualification must include:**

    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. **Repeat dose toxicology of appropriate duration to support the proposed indication.**

    Note, impurities that contain a structural alert for mutagenicity or are demonstrated to be genotoxic or carcinogenic must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequately justified based on FDA 2008 Draft Guidance "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches". This guidance can be found on the CDER website at the following location: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative in vitro bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled "Guidance on Specific Aspects of Regulatory Genotoxity Tests for Pharmaceuticals". Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, unless otherwise justified.

2. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and determination if the impurity contains a structural alert for mutagenicity, and how these levels compare to ICH Q3A(R2) and Q3B(R2) qualification thresholds, and 1.5 mcg/day for genotoxic impurity threshold. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

    The NDA submission must contain information on potential leachables and extractables from the drug container closure system. Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled specified route of administration. The approach for toxicological evaluation of the safety of extractables must be based on good scientific

principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). This should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission.

3. **Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and specifically address how the information impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**

4. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained.**

5. **We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity, degradant, or residual solvent that exceeds the ICH qualification thresholds or if you fail to provide safety justification for extractable/leachables.**

Discussion
There was no further discussion on this point.

Figure 7. Excerpts from Meeting Minutes for End of Phase 2 Meeting Held on September 27, 2012

Additional CMC Comments

(b) (4)

[redacted]

We suggest you refer to the following guidance documents as you proceed with your IND and your NDA.

1. **Guidance for Industry:** ***Content and Format of Investigational New Drug Applications (INDs) Including Well-Characterized, Therapeutic, Biotechnology-derived Products***
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf

2. **Guidance for Industry:** ***INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information***
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070567.pdf and the 21 CFR 312.23.

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

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

5. **Guidance for Industry:** ***Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances***

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm134966.htm

6. **Guidance for Industry:** ***Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation*** http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070551.pdf

7. **Guidance for Industry:** ***Q2A Text on Validation of Analytical Procedures*** http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073381.pdf.

8. **ICH guidance for industry,** ***Q2B Validation of Analytical Procedures: Methodology,*** **available at** http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073384.pdf.

9. **Guidance for Industry:** ***Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*** http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf

Discussion
There was no further discussion of this point.

Nonclinical

Question 4
Éclat has calculated the maximum total daily dose of Phenylephrine Hydrochloride Injection, USP, 1% as 96 mg based on the maximum infusion rate of 200 µg/min for a total of 8 hours. This calculation is based on the following assumptions:

- *A continuous intravenous infusion throughout a surgical procedure will result in the highest exposure compared to the other proposed dosing regimens.*
- *Surgical procedures generally last less than 8 hours. This is a conservative estimate based on numbers reported in the published literature. For example, a study comparing surgical times and rates of infection found that, in the United States, across 14 categories of surgical procedures, at least 75% of procedures lasted 277 minutes or less (Leong et al. 2006). In a study conducted in Germany, over 250,000 operations falling into 8 different procedure categories were included in an analysis; it was reported that at least 75% of procedures lasted no longer than 179 minutes (Gastmeier et al. 2011).*

Does the Agency agree with Éclat's method for calculating maximum total daily dose for the purpose of assessing the safety of impurities and extractables?

FDA Response

Your method of calculating total daily dose appears reasonable from a clinical perspective. If the review of your NDA suggests that a greater daily dose may be required, this assessment will need to be reconsidered.

A maximum 8-hour in-use time combined with the proposed 6-hour hold after preparation from pharmacy bulk packaging would result in a total hold of 14 hours after initial package penetration. The length of time following initial penetration, combined with the use of (b) (4) as a diluent for the drug product, could result in a significant risk for the proliferation of microbial contaminants.

If you propose these time periods in your labeling, you should provide justification in your NDA that microbial proliferation will not occur during the hold period. For example, you could provide microbiological data to demonstrate that the drug product infusion solution does not support growth. Generally, "no growth" is interpreted as not more than a 0.5 $\log_{10}$ increase from the initial count; however other evidence of growth may be significant. Such testing should be run at the proposed storage conditions, be conducted for 2- to 3-times the proposed hold period, and use the diluted drug product inoculated with low numbers (≤100 CFU/mL) of challenge microbes. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

Discussion

There was no further discussion of this point.

Question 5

Éclat believes that the excipients present in the formulation are adequately qualified based on their common use in intravenous injection and infusion products at levels greater than or equal to those present in the phenylephrine formulation. Does the Agency agree?

FDA Response

Yes. The excipients in your proposed drug product formulation appear to be found in other FDA-approved intravenous drug products at comparable levels and appear to be adequately qualified for safety.

Discussion

There was no further discussion of this point.

Question 6

Éclat believes that the impurities are adequately qualified based on QSAR and existing toxicity data. Does the Agency agree?

FDA Response

Your proposed drug substance impurity specifications of (b) (4) (96 mcg/day) for (b) (4) appear to be acceptable based on the lack of structural alerts via a DEREK analysis. Based on the structures provided, we do not anticipate any genotoxic concerns. However, you should be aware that ongoing ICH M7 discussions appear to be suggesting that use of an expert-rule based model alone (such as DEREK) may not be acceptable and that a second statistical-based model evaluation is also recommended. At the time of your NDA submission, if new structures are identified that raise concerns, the Agency will likely submit the structures of your anticipated impurities to our internal Computational Toxicology Services, which typically run four different models. Should these results suggest concern, an actual Ames assay may be required. We will work with you to identify and resolve any concerns.

Discussion

There was no further discussion of this point.

Question 7

Based on the extraction profiles obtained using three different solvent systems, Éclat believes that (b) (4) *leachables during the stability analysis. Does the Agency agree with this approach?*

FDA Response

Based on the information provided in your meeting package, your proposed approach is considered to be acceptable as long as the toxicological risk assessment based on the extraction studies for each of the potential leachables adequately justifies their safety. Final determination of the adequacy of methodology and the study results can only be determined upon review of the NDA.

Discussion

There was no further discussion of this point.

Question 8

Éclat has not conducted nonclinical studies on phenylephrine to support this application. Éclat has developed a detailed integration of the available nonclinical literature on phenylephrine which has been provided for the Agency's review in Attachment C Section 2.4. In the NDA, limited written and tabular study summaries will be provided in Section 2.6 due to the limited nature of the details present in the published literature. Does the Agency agree with this approach?

FDA Response

Your approach appears acceptable. Your NDA submission should include details regarding the literature search criteria used and include copies of the articles you referenced. As noted in the pre-IND meeting minutes from November 17, 2011, if the literature references do not contain adequate information regarding the mutagenic potential and impact on reproductive and developmental toxicity of phenylephrine, these studies may be required as post-marketing requirements (PMRs). Prior to the qualified nonclinical studies being submitted, the drug product will likely be labeled a Pregnancy Category C due to lack of adequate nonclinical reproductive and developmental toxicity data. Final determination of whether PMRs will be needed or not can only be provided upon detailed review of the referenced literature studies.

Discussion

There was no further discussion of this point.

Additional Nonclinical Comments

1. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. Unless otherwise justified, adequate qualification must include:**

    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. **Repeat-dose toxicology study of appropriate duration to support the proposed indication. For this acute use drug product, the study should be at least 14 days in duration.**

2. **Drug substance manufacturing process intermediates may include compounds with structural alerts for genotoxicity. Refer to the Guidance for Industry: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf. As noted in this draft guidance, impurities which are carcinogenic must be reduced to levels in the drug substance or drug product which would limit human exposure to NMT 1.5 mcg/day. Impurities which are genotoxic or contain a structural alert for genotoxicity must be reduced to this same level unless you provide adequate safety qualification. For an impurity with a structural alert for mutagenicity, an adequate safety qualification requires a negative in vitro bacterial reverse mutation (Ames) assay, ideally with the isolated impurity tested to the appropriate highest concentration of the assay as outlined in ICH S2(R1) guidance, Guidance for Industry: *Guideline on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use.***

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074931.pdf

3. **Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day or otherwise justified, which may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model**

4. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

5. **The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. Based on identified leachables you will need to provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics* and *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure or be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day.**

6. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product or literature references, the exposure margins provided in the label must accurately reflect exposures from your product. If the referenced studies employ a**

different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.

7. **NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds of if there is a missing or inadequate extractable leachable safety assessment for the container closure system.**

Discussion
There was no further discussion of this point.

3 Studies Submitted

3.1 Studies Reviewed

Original nonclinical studies were not submitted for review under this application.

3.2 Studies Not Reviewed

Not applicable

3.3 Previous Reviews Referenced

None.

4 Pharmacology

Phenylephrine is an alpha-1 adrenergic receptor agonist (Hoffman and and Taylor, 2001; Hoffman, 2001). For the purposes of this review, the findings from published in vitro and in vivo studies[6] that evaluated phenylephrine will be discussed below.

4.1 Primary Pharmacology

The NDA under review proposes the use of phenylephrine to either treat (b) (4) hypotension during anesthesia. Published findings in multiple animal species demonstrate that under various conditions phenylephrine increases blood pressure, an effect that is mediated via the alpha-1 receptor (Shibasaki, et al., 1992; STANTON, et al., 1988; Zhou, et al., 1996). In vitro findings demonstrate that phenylephrine binds to the alpha 1B-, alpha 1C-, and alpha 1A/D-adrenergic receptor subtypes, which provides further insight into the mechanism by which phenylephrine may produce its various effects (Minneman, et al., 1994). Overall, the primary pharmacology of phenylephrine encompasses a variety of effects mediated via alpha adrenergic receptors. These effects provide evidence of the potential effects of phenylephrine in various organ systems at doses that are, in many cases, lower than the maximum recommended clinical dose (<0.17 mg/kg or 6.2 mg/m^2). See below for a brief discussion of these findings. The effects of phenylephrine on blood pressure and other cardiovascular endpoints are briefly discussed in the **Safety Pharmacology** section below.

Thermal hyperalgesia

Dogrul et al. (2006) published findings that thermal hyperalgesia was observed following the subcutaneous administration of phenylephrine (0.04, 0.4, or 1.2 mg/kg[7]) at $\geq$ 0.4 mg/kg (or 1.2 mg/m^2) in adult male Balb/C mice (0.025 to 0.030 kg) evaluated with the radiant heat tail-flick test. This effect was substantially reduced when the alpha-1 receptor antagonist prazosin (1 mg/kg, IP) was administered 20 minutes prior to phenylephrine (1.2 mg/kg or 3.6 mg/m^2, SC). **These findings provide evidence that the thermal hyperalgesia observed following phenylephrine treatment in mice was mediated by the alpha-1 receptor at 1.2 mg/kg (3.6 mg/m$^{2)}$; a dose that is 1.8-fold lower than the maximum recommended clinical dose (<0.17 mg/kg or 6.2 mg/m^2) when based on body surface area.**

Antinociception

Tasker et al., (1992) published findings that antinociception and paw swelling, respectively, were increased and decreased following the subcutaneous administration

[6]None of the studies conducted were identified as GLP studies. Pharmacology studies are no required to be completed under GLPs.
[7]Doses based on the administration of 1, 10, or 30 mcg (i.e., 0.001, 0.01, or 0.03 mg) at the lowest weight measured in rats (0.025 g).

of L-phenylephrine (≤ 10 mg/kg) in **Long Evans rats** tested with the Formalin test. The ED_{50} value for L-phenylephrine was 2.96 mg/kg based on % analgesia. Antinociception was substantially antagonized when the alpha-1 receptor antagonist prazosin (0.15 mg/kg, IP) was administered 5 minutes prior to phenylephrine (3 and 10 mg/kg, SC). The reduction in swelling observed was not significantly antagonized in rats pretreated with the same dose of prazosin. Separately, fall latency was not significantly altered following the administration of L-phenylephrine (≤ 10 mg/kg) in rats performing a rotorod task, which suggests the alpha-1 mediated antinociception effects occurred in the absence of sedative-like effects. **These antinociceptive effects were observed in phenylephrine-treated rats at up to 10 mg/kg (60 mg/m^2, SC); a dose that is approximately 10-fold higher than the maximum recommended clinical dose (<0.17 mg/kg or 6.2 mg/m^2) when based on body surface area.**

Thurston and Helton (1996) published findings that tail flick reflex and blood pressure were increased in a dose- and time-related manner in lightly anesthetized **rats** (0.3 to 0.6 grams) following the intravenous infusion of phenylephrine (0.001, 0.0025, or 0.01 mg[8]/min, 21-minute infusion period). At the top dose (0.7 mg/kg), the averaged value for blood pressure was increased to > 160 mmHg at 3 minutes post injection, which was the peak time to effect. Also, the mean value for tail flick latency was increased to approximately 9 seconds at 12 minutes post injection, which was the peak time to effect. Neural activity of ON and OFF cells monitored in the rostral ventral medulla varied following treatment with the various doses, suggesting that it was not correlated with the other two endpoints measured. **In rats, tail flick latency and blood pressure were increased following the administration of intravenous phenylephrine up to 0.7 mg/kg (4.2 mg/m^2); which is slightly lower than the maximum recommended clinical dose (<0.17 mg/kg or 6.2 mg/m^2) when based on body surface area.**

Intraurethral and Intraluminal Pressure

Noguchi et al. (2008) published findings that dose-related increases in intraurethral and intraluminal pressure of vas deferens were observed in anesthetized **male beagle dogs** (n = 4) following the intravenous administration of phenylephrine (0.0003, 0.001, 0.003, 0.01, or 0.03 mg/kg). The highest dose (0.03 mg/kg) increased intraurethral pressure and intraluminal pressure of the vas deferens by > 30 cmH_2O. At the same dose, these effects were significantly reduced in dogs (n=5) pretreated with alpha 1 receptor antagonists that include alfuzosin (≥ 30 mcg/kg), naftopidil (≥ 30 mcg/kg), prazosin (≥ 3 mcg/kg), silodosin (≥ 0.3 mcg/kg), and tamsulosin (≥ 1 mcg/kg). **These findings provided evidence that alpha-1 receptor mediated increases in intraurethral and intraluminal pressure were observed in dogs following IV administration of phenylephrine up to 0.03 mg/kg (0.6 mg/m^2), which is approximately 11-fold lower than the maximum recommended clinical dose proposed (<0.17 mg/kg or 6.2 mg/m^2) when based on body surface area.**

[8]Amounts originally presented as mcg/min (i.e., 1, 2.5, or 10 mcg/min) in the published study.

Contractile Activity

Wilson et al. (1973) published findings that seminal vesicles in anesthetized **rabbits** (n=6) deemed sexually mature contracted following the intravenous administration of 0.1 mg/kg. At this dose, the maximum contraction of the seminal vesicle was 53.2 mm when measured 25 seconds after the phenylephrine injection. This contraction lasted 80 to 129 seconds. **These findings provide evidence that ejaculation was altered in anesthetized rabbits following intravenous administration of a dose of phenylephrine (0.1 mg/kg or 1.2 mg/m^2) that is approximately 5-fold lower than the maximum recommended clinical dose (<0.17 mg/kg or 6.2 mg/m^2) when based on body surface area.**

Acritopoulou-Fourcroy and Marcais-Collado (1988) published findings that the spontaneous uterine contractions in anesthetized pro-estrus **rats** was increased following intravenous injection of cumulative doses of phenylephrine (0.010 and 0.040 mg/kg). Rats were observed with contractions in which the amplitude was increased by 25% at 0.01 mg/kg and duration was of increased by $\geq$ 33%, alterations that were deemed statistically significant when compared to control. The contractile activity observed following the cumulative administration of 0.040 mg/kg of phenylephrine was reportedly abolished in rats when followed by intravenously administered phentolamine (1 mg/kg). Separately, rats administered the same dose of phentolamine alone were observed with contractions in which the amplitude was decreased by 41% and the duration was increased by 7%, findings deemed statistically significant when compared to control. **Together, these findings provided evidence that spontaneous uterine contractions in rats were increased following intravenous administration of phenylephrine up to a cumulative dose (0.04 mg/kg or 0.24 mg/m^2), a dose that is approximately 4-fold lower than the maximum recommended clinical dose < 0.17 mg/kg or 6.2 mg/m^2) when based on body surface area.**

4.3 Safety Pharmacology

Cardiovascular

Numerous studies have demonstrated that phenylephrine alters cardiovascular endpoints in animal species under a variety of experimental conditions (Cottle, et al., 1982; Shibasaki, et al., 1992; STANTON, et al., 1988; Zhou, et al., 1996). In particular, intravenously administered phenylephrine (4 mcg/kg/min or 120 mcg/kg, 30-minute infusion) increased mean arterial blood pressure and decreased heart rate in pregnant normotensive sheep (45 to 64 kg) within 5-8 minutes following the start of treatment (Cottle, et al., 1982). Although fetal heart rate and blood pressure were not significantly altered, partial pressure of oxygen and carbon dioxide in arterial blood were significantly depressed in fetus up to 40 minutes following the start of treatment in ewes. Also, fetal blood pH was significantly decreased up to 40 minutes following the start of treatment in

ewes. **Together, these effects were observed at 0.12 mg/kg (equivalent to 0.11 mg/kg to 0.12 mg/kg human dose), a dose that is slightly lower than the maximum recommended clinical dose (< 0.17 mg/kg). Therefore, these findings in pregnant sheep and fetus are relevant to clinical studies in normotensive individuals administered PHE (b) (4).**

Gastrointestinal System

DiMarino and Cohen (1973) evaluated lower esophageal sphincter (LES) pressure and blood pressure in anesthetized opossum (males and females; 2.2 to 3.6 kg, n ≥ 10) following intravenous administration of phenylephrine (55 mcg/kg, 30-second bolus). Following treatment LES pressure and blood pressure, respectively, were increased in the opossum by approximately 40% and 30%. In regard to LES pressure, these findings in opossum are presumed to be mediated via an alpha adrenergic mechanism based on findings that the alpha adrenergic antagonist phentolamine alone reduced LES pressure. **The dose of PHE that increased LES pressure and blood pressure (0.055 mg/kg; equivalent to 0.018 mg/kg to 0.021 mg/kg human dose[9]) is ≥8-fold lower than the maximum recommended clinical dose (< 0.17 mg/kg) when based on a body surface area comparison.**

Pahlin and Kewenter (1976) evaluated ileocecal sphincter (ICS), ileal, and colonic motility in anesthetized **cats** (male and female, n=5, **weight not provided**) following intravenous administration of phenylephrine at 2-11 mcg/kg (0.002 to 0.011 mg/kg). Based on the published findings motility in the ICS was increased, whereas in the ileum and colon it was decreased following phenylephrine administration. The increased motility observed in the ICS of phenylephrine-treated cats was reportedly blocked when the alpha adrenergic antagonist phenoxybenzamine (5 mg/kg) was intravenously administered. These changes in motility in the ICS, ileum, and colon were measured following IV doses ≤ 85-fold lower than the maximum recommended clinical dose (0.17 mg/kg) when compared on a mg/kg basis (weight of animals were not provided).

Respiratory System

Studies evaluating the effects of PHE on respiratory function in animal species were not identified for review here by the PT Reviewer.

Central Nervous System (CNS)

[9]The HED was determined, as per the FDA Start Dose Guidance as follows: HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$ and assumed a 60 kg person.

Standard stand alone CNS Safety Pharmacology studies evaluating PHE were not identified in the published literature. PHE has been demonstrated to produce convulsions and decrease motor activity in rodents from toxicology studies (see below).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

There are very few studies in the published literature that evaluated the pharmacokinetics of phenylephrine following intravenous administration in experimental animals. Findings from these studies are briefly discussed below.

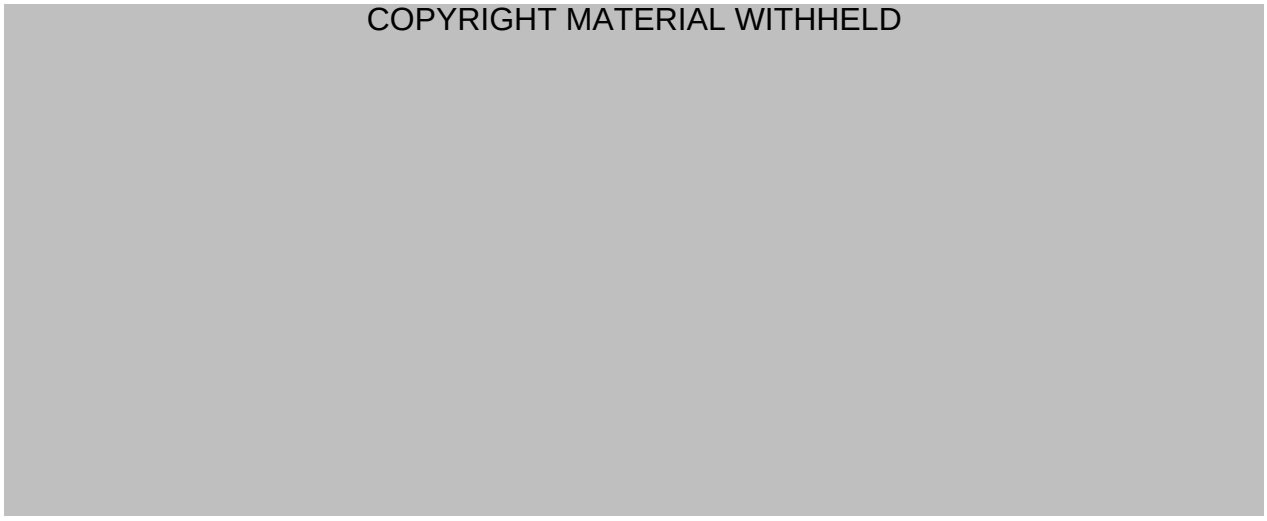
Absorption

Although the PT Reviewer did not identify any studies in the published literature that evaluated the absorption of phenylephrine following intravenous administration in experimental animals, it should be 100% bioavailable and absorbed rapidly.

Distribution

The distribution of intravenously administered ^{11}C-phenylephrine was evaluated in female Sprague Dawley rats (del Rosario, et al., 1996). The tissue distribution of radioactivity from ^{11}C-phenylephrine in rats (n=4; 100-200 mcCi via the femoral vein) was ranked from greatest to least 30-minutes post-treatment as follows: submaxillary gland > liver > heart ventricles > spleen > kidney > lung > blood > brain. At 60-minutes following treatment, the distribution pattern was comparable to that at 30 minutes in the tissues evaluated. See **Figure 8** for findings at 30- and 60-minutes following treatment. These data suggest that the distribution of ^{11}C-phenylephrine is predominately to peripheral sites, and not to central sites such as the brain at the amounts studied.

Figure 8. Tissue Distribution of ^{11}C-Phenylephrine (Percent Dose/g)[10]



Metabolism

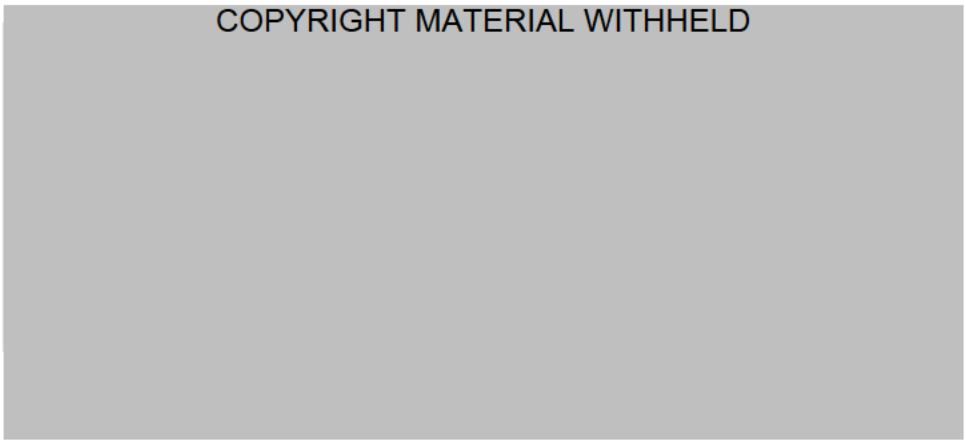
The PT Reviewer did not identify studies that evaluated the metabolic profile of phenylephrine following intravenous administration in experimental animals. A study that evaluated the metabolic profile of phenylephrine following nasal inhalation in humans was identified in the published literature (Ibrahim, et al., 1983). The following metabolites were measured in the urine of humans following the inhalation of phenylephrine: m-hydroxymandelic acid (MHMA), m-hydroxyphenylglycol (MHPG) sulfate, phenylephrine sulfate, and phenylephrine glucuronide. Unchanged phenylephrine was measured also. These findings provide evidence that phenylephrine administered via nasal inhalation is metabolized; however, studies evaluating the pharmacological activity of these metabolites were not identified.

Excretion

Ibrahim et al. (1983) evaluated the urinary excretion of R-(-)-m-synephrine (aka phenylephrine, 1 mg/kg) in three rats following an intraperitoneal injection. The rats were housed in separate metabolism cages over a 24-hour period for urine collection. Conjugates in the urine were hydrolysed by adding acid, beta-glucuronidase, sulphatase, or nothing to the samples collected. The authors identified phenylephrine and its metabolites (MHMA and MHPG) in the samples analyzed. See **Figure 9** for the mean excretion (calculated as a percentage of the total dose) of phenylephrine and its metabolites over a 24-hour period. Across the methods of hydrolysis, the percentage of phenylephrine recovered in the urine samples ranged from 7 to 16% of the total dose administered.

[10]The excerpt provided was obtained from Section 2.6.4 Pharmacokinetics Written Summary from the NDA Application. This figure was prepared based on findings from del Rosario et al. (1996).

Figure 9. Mean Excretion (Calculated as a Percentage of the Total Dose) of m-Synephrine (phenylephrine) and its Metabolites over a 24-Hour Period



6 General Toxicology

6.1 Single-Dose Toxicity

The PT Reviewer created a toxicology profile for a single treatment of phenylephrine in experimental animals below based on findings from several published papers (DUNGAN, et al., 1965; Marvola, 1976; Richards, et al., 1970; Stockhaus and Wick, 1969; Weikel, Jr. and Harper, 1972). Across the studies cited, the LD_{50} value was 0.44 mg/kg (or 2.6 mg/m^2) in rats and $\geq$ 4.8 mg/kg (or 14.4 mg/m^2) in mice. These findings suggest that the rat is more sensitive to the lethal effects of intravenously administered phenylephrine than the mouse. Toxicities observed in rats included "preliminary depression,[11]" labored respiration, and convulsions immediately after intravenous administration of phenylephrine. According to the authors, death usually occurred within five minutes following drug administration. Separately, toxicities observed in mice included ataxia, decreased rate and increased depth of respiration at sublethal doses (see Weikel, Jr., et al., 1972). At lethal doses, evidence of toxicities such as Straub-tail reaction and asphyxia convulsions were observed in the same study. In regard to the lethality of phenylephrine, published findings demonstrated that in mice it is increased when ambient temperature is increased in laboratory settings. For example, Richards et al. (1970) demonstrated that the LD_{50} value in mice was 7.4 mg/kg at 23°C and 1.12 mg/kg at 35°C. Note that 23°C is within the thermoneutral range established for mice; therefore, the increased potency of phenylephrine at 35°C is likely mediated at least in part by the physiological adaption(s) by this species to the increases in ambient temperature above that recommended for laboratory studies (see **Table 10,** created from information from Committee for the Update of the Guide for the Care and Use of Laboratory Animals, 2011). Such findings highlight the role of ambient temperature in mediating the toxicological effects of drugs such as phenylephrine and the potential limitations of interpreting findings from the cited studies that did not provide ambient temperature values. Despite these limitations, the findings discussed provided insight to the toxicity profile of phenylephrine. In particular, the LD_{50} values in rats and mice, respectively, were **24-fold** lower and 2.2-fold higher than the maximum recommended clinical dose (0.17 mg/kg or 6.2 mg/m^2) when compared based on body surface area.

Table 9. LD_{50} Values Estimated for Phenylephrine Intravenously Administered in Rats and Mice

[11]"Preliminary depression" was not defined by Hutcheon et al. (1955)

Table 10. Recommended Daily Dry-Bulb Macroenvironmental Temperatures for Common Laboratory Animals

Species	Ambient Temperature Ranges	
	Celsius (°C)	Fahrenheit (°F)
Mouse, rat, hamster, gerbil, guinea pig	20-26	68-79
Rabbit	16-22	61-72
Cat, dog, nonhuman primate	18-29	64-84
Farm animals, poultry	16-27	61-81

6.2 Repeat-Dose Toxicity

Repeat-dose toxicology studies evaluating intravenous phenylephrine in experimental animals were not identified in the published literature either by the Applicant or the reviewer. The Applicant provided findings from repeat-dose toxicology studies in rats and mice administered phenylephrine daily via their diet for 2 and 12 weeks. These studies, completed by the National Toxicology Program (NTP), were primarily conducted to select doses for carcinogenicity testing of phenylephrine in the species mentioned. The results are discussed below.

Rats

F344/N rats (n=5/sex/group, 6-7 weeks old) served as subjects in the 2- and 12-week repeat-dose study of oral phenylephrine. These animals were group housed in an animal room maintained at 20-25°C, which is within the range for thermoneutral temperatures for this species. Also, these animals were treated with the test article via their diet. See **Table 11** for treatment information. The endpoints employed across these studies included histopathology, body weight, food consumption, and clinical signs. The results are briefly discussed below.

2-Week Repeat-Dose Toxicology Study

There were no test article-related toxicities observed in rats exposed to phenylephrine up to 2000 ppm daily via their diet. The NOAEL in rats is estimated at 2000 ppm[12] (i.e., high dose) based on the lack of toxicity.

12-Week Repeat-Dose Toxicology Study

A variety of toxicities were observed in rats exposed to up to 20000 ppm of phenylephrine daily via their diet. Mortalities were observed in male rats at ≥ 5000 ppm (n ≤ 4/10). Final mean body weight was markedly decreased in a toxicologically significant manner in all of the treatment groups, except in females at 1250 ppm (i.e., low dose group). See **Figure 10** for final weight values relative to controls (percent). See **Table 12** for the target organs of toxicity identified by the PT Reviewer. Toxicologically significant histopathology findings observed included chronic keratitis in the eye (n ≤ 8/10/sex, severity not mentioned) at ≥ 10000 ppm, as well as testicular atrophy (n = 4/8 males, minimal to mild), seminal vesicle atrophy (n=5/6 males; severity not mentioned), and ovarian atrophy (n=5/10 females, mild to moderate) at 20000 ppm. **Overall, the PT Reviewer estimated the NOAEL at 1250 ppm in females based on the toxicologically significant decrease in the averaged body weight and observation of histopathology findings at higher doses, and < 1250 ppm in males given that toxicities were observed across each treatment level (see above).**

Table 11. Treatment Information in Rats from 2- and 12-Week Repeat-Dose Toxicology Studies

Study Duration (weeks)	Treatment (ppm)
2	0
	125
	250
	500
	1000
	2000
12	0
	1250
	2500
	5000
	10000
	20000

[12]The value represented in ppm represents a concentration of the test article. The Sponsor did not provide the actual amount or dose administered represented by this concentration in rats treated daily for either a 2- or 12-week period.

Table 12. Target Organs of Toxicity in Rats from 2- and 12-Week Repeat-Dose Toxicology Study

Study Duration (weeks)	Target organ of Toxicity	Notable Findings
2	NONE	
12	Brain	Hyperexcitability (M/F, ≥ 10000 ppm)
	Eye	Chronic Keratitis (M/F, ≥ 10000 ppm)
	Testicles	Atrophy (M, 20000 ppm)
	Seminal Vesicle	Atrophy (M, 20000 ppm)
	Ovarian	Atrophy (F, 20000 ppm)

Figure 10. Survival, Mean Body Weight, and Food Consumption of Rats Administered Phenylephrine Daily for up to 12-Weeks

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Wk 1	Wk 12
MALE							
0	10/10	107 ± 3	363 ± 7	+256 ± 6	--	13.3	14.9
1,250	10/10	107 ± 3	324 ± 6	+217 ± 5	89	12.5	14.2
2,500	10/10	108 ± 3	246 ± 4	+38 ± 5	68	8.4	11.3
5,000	(e) 9/10	108 ± 3	206 ± 5	+98 ± 3	57	7.4	12.1
10,000	(f) 8/10	108 ± 2	165 ± 6	+56 ± 6	45	6.5	10.4
20,000	(g) 6/10	107 ± 2	127 ± 6	+16 ± 6	35	3.5	9.1
FEMALE							
0	10/10	92 ± 1	211 ± 3	+119 ± 3	--	10.0	10.7
1,250	10/10	92 ± 2	202 ± 3	+110 ± 2	96	9.5	9.0
2,500	10/10	95 ± 2	178 ± 2	+83 ± 3	84	8.0	8.5
5,000	10/10	90 ± 3	147 ± 3	+57 ± 3	70	7.0	9.2
10,000	10/10	89 ± 2	122 ± 2	+33 ± 2	58	5.4	8.8
20,000	10/10	91 ± 2	107 ± 3	+16 ± 2	51	3.8	8.4

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams of feed per animal per day
(e) Week of death: 1
(f) Week of death: 3,3
(g) Week of death: 3,5,7,8

Mice

B6C3F$_1$ mice (n=5/sex/group, 6-8 weeks old) served as subjects in the 2- and 12-week repeat-dose study of oral phenylephrine. These animals were group housed in an animal room maintained at 20-25°C, which is within the range for thermoneutral

temperatures for this species. Also, these animals were treated with the test article via their diet. See **Table 13** for treatment information. The endpoints employed across these studies included histopathology, body weight, food consumption, and clinical signs. The results are briefly discussed below.

Table 13. Treatment Levels of Oral Phenylephrine in Mice

Study Duration (weeks)	Treatment (ppm)
2	0
	63
	125
	250
	500
	1000
12	0
	1250
	2500
	5000
	10000
	20000

2-Week Repeat-Dose Toxicology Study

There were reportedly no toxicities observed in rats following exposure to phenylephrine up to 1000 ppm daily via their diet. However, the final mean body weight was decreased by approximately 10-12% below control levels at ≤ 250 ppm in females. Although not addressed in the published report, this alteration is likely test article related based on the magnitude of the change and its occurrence across several concentrations. Given the reported findings the PT Reviewer estimated the NOAEL at 2000 ppm[13] in males based on the lack of test article-related toxicities and at < 63 ppm in females based on the observation of decreases in body weight (≥ 10%).

12-Week Repeat-Dose Toxicology Study

A variety of toxicities were observed in mice exposed to up to 20000 ppm of phenylephrine daily via their diet. Mortalities were observed at ≥ 10000 ppm in males only (n ≤ 3/10). Final mean body weight was markedly decreased in a toxicologically

[13]The value represented in ppm represents a concentration of the test article. The Sponsor did not provide the actual amount or dose administered represented by this concentration in rats treated daily for either a 2- or 12-week period.

significant manner in males at ≥ 10000 ppm and in females at all of the treatment levels. See **Table 14** for the target organs of toxicity identified by the PT Reviewer. Toxicologically significant histopathology findings observed included inflammatory eye lesions (acute keratitis, panophthalmitis or phthisis, severity not provided; n ≤ 3/10/sex) at 20000 ppm. The observation of eye lesions in mice was consistent with that observed in rats (see above) **Overall, the PT Reviewer estimated the NOAEL at 5000 ppm in males based on the mortalities, toxicologically significant decreases in the averaged body weight, and observation eye lesions at higher doses, and < 1250 ppm in females given that toxicities were observed across each treatment level (see above).**

Table 14. Target Organs of Toxicity in Mice Administered Phenylephrine Orally in Their Diet Daily for 12 Weeks

Study Duration (weeks)	Target Organ	Finding
2	NONE	
12	Brain	Hyperexcitability (M/F; ≥ 10000 ppm)
	Eye	Chronic Keratitis (M/F; ≥ 10000 ppm)
	Testicles	Atrophy (M; 20000 ppm)
	Seminal Vesicle	Atrophy (M; 20000 ppm)
	Ovarian	Atrophy (F; 20000 ppm)

7 Genetic Toxicology

Findings from published studies demonstrate that phenylephrine is negative for producing gene mutations, chromosomal aberrations, and micronuclei. See the **Figure 11**.

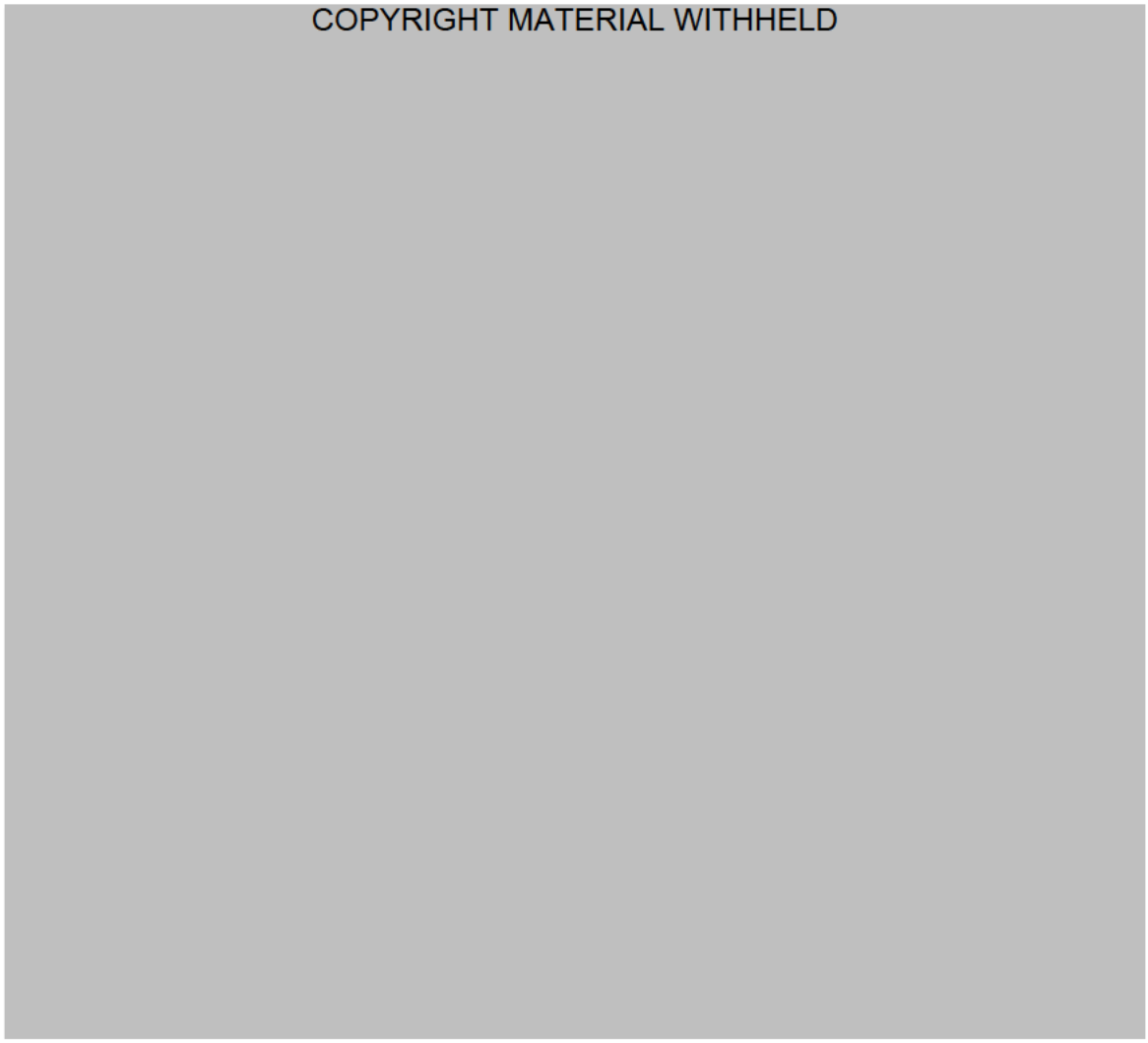
Figure 11. Sponsor's Summary Table of Published Genetic Toxicology Studies of Phenylephrine.

Test System	Endpoint	Concentration	Results	Reference
Salmonella typhimurium TA100, TA1535, TA1537, TA98	Bacterial gene mutation	± metabolic activation (S9) Up to 10,000 µg/plate	Negative	NTP 1987
L5178Y $Tk^{+/-}$ mouse lymphoma cells	Mammalian gene mutation	– metabolic activation Up to 1500 µg/mL	Equivocal (positive at toxic doses [12.2% relative growth]; not reproduced in replicate study)	NTP 1987
Chinese hamster ovary cells	Sister chromatid exchange	– metabolic activation (S9) Up to 2,500 µg/mL + metabolic activation (S9) Up to 10,000 µg/mL	Negative	NTP 1987
Chinese hamster ovary cells	Chromosomal aberrations	– metabolic activation (S9) Up to 2,500 µg/mL + metabolic activation (S9) Up to 10,000 µg/mL	Negative	NTP 1987; Galloway et al. 1998
Rat primary hepatocytes	DNA damage	3, 7, 10 mM	Negative	Storer et al. 1996
Fischer 344 Rat	Bone marrow and peripheral blood micronuclei	0, 4, 8, 17 or 35 mg/kg i.p. 3x, 72 hours	Negative	NTP 1993

Of the studies cited above, those published by NTP were deemed reasonably adequate to include in the label for this product. This decision is based on the quality of experiments conducted by NTP and the extensive experience of this group in the use of the mentioned assays to evaluate small molecules from various drug classes.

Of note, the Ames assay conducted by NTP did not include all of the modern bacterial strains to be deemed a current assay. Specifically, the study did not include an *S.typhimurium* strain TA102 or *E.coli* WP2*uvrA* or WP*uvrA* (pKM101) which are included in the standard battery to detect point mutations in AT sites. As such the study is not ideal by current standards. The description of the study results in the labeling should include the strains tested, to inform toxicologists about this deficiency.

The in vitro mouse lymphoma assay was deemed equivocal by the NTP but called positive by Myhr et al. (1990).[14] The results, as presented by Myhr are reproduced below:



As noted above, the first study demonstrated positive findings only at a relative total growth of 5%, which is outside of the valid study range (underlined values are statistically significant). The second trial demonstrated positive findings at 1000 mcg/mL and 1500 mcg/mL at RTG of greater than 10%, which is deemed positive in this assay.

The Galloway et al. (1998)[15] publication confirmed the results of the NTP study that phenylephrine tested negative in the in vitro assay for chromosomal aberrations. The

[14]Myhr B, McGregor D, Bowers L, Riach C, Brown AG, Edwards I, McBride D, Martin R and Caspary WJ (1990) L5178Y Mouse Lymphoma Cell Mutation Assay Results with 41 Compounds. Environmental and Molecular Mutagenesis Volume 16, Supplement 18:138-167.

study was designed to follow up both negative and positive chromosomal aberrations results of numerous compounds with assessments of DNA synthesis as an indirect mechanism of action for clastogens demonstrating no direct DNA reactivity.

The study by Storer et al. (1996)[16] was designed to study potential genetic toxicity using the in vitro alkaline elution assay in rat hepatocytes. The publication summarizes the results of a total of 81 compounds tested by this laboratory, including phenylephrine. As this is not part of the standard battery of studies, although negative results were reported, these data will not be included in the drug product labeling.
Based on the overall weight-of-evidence of all the genetic toxicology and carcinogenicity data, this positive/equivocal finding in the mouse lymphoma assay does not suggest a concern for genotoxicity.

[15]Galloway SM, Miller JE, Armstrong MJ, Bean CL, Skopek TR and Nichols WW (1998) DNA synthesis inhibition as an indirect mechanism of chromosome aberrations: comparison of DNA-reactive and non-DNA-reactive clastogens. Mutation Research 400:169-186.
[16]Storer RD, McKelvey TW, Kraynak AR, Elia MC, Barnum JE, Harmon LS, Nichols WW and DeLuca JG (1996) Revalidation of the in vitro alkaline elution/rat hepatocyte assay for DNA damage: improved criteria for assessment of cytotoxicity and genotoxicity and results for 81 compounds. Mutation Research 368:59-101.

8 Carcinogenicity

Carcinogenicity studies were not conducted by the Sponsor to evaluate the drug product under review here. The Sponsor is relying on findings from the published literature to support the safety of the drug product (Bucher, et al., 1988; National Toxicology Program,1987). The Bucher et al., (1988) manuscript is a summary of the data generated in the studies conducted by the National Toxicology Program (NTP). These findings were obtained from 2-year studies that employed F344 rats (0, 620, or 1250 ppm) and B6C3F1 mice (0, 1250, or 2500 ppm) treated with phenylephrine hydrochloride via their diet. USP grade phenylephrine hydrochloride was employed in these studies. According to the NTP report, based on evaluation of food consumption, the mean amount of phenylephrine hydrochloride consumed per day by male and female rats was approximately 24 mg/kg in low dose rats and 50 mg/kg daily doses in the high-dose rats. In the mouse study, the mean daily dose (males and females) in the low dose animals was 133 mg/kg and in the high dose animals 270 mg/kg. The study demonstrated no evidence of carcinogenicity in rats and mice under the testing conditions employed. The dose of 50 mg/kg (300 mg/m^2) in rats is 48-fold the human dose and the dose of 270 mg/kg (810 mg/m^2) in mice is 131-fold the maximum daily human dose of 10 mg/60 kg person (0.17 mg/kg or 6.3 mg/m^2) based on body surface area comparisons.

A comparison of the doses tested in the 2-year studies is below:

Species	Food Content (ppm)	Estimated Daily Dose (mg/kg)	Estimated Daily Dose (mg/m^2)	Exposure Margin based on body surface area
Mouse	1250	133	399	64
	2500	270	810	131
Rat	620	24	144	23
	1250	50	300	48
Human		0.167 (10 mg/60 kg)	6.2	

As this study was completed by the National Toxicology Program and appears to be consistent with current standards for carcinogenicity studies, the results should be included in the product labeling.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

A fertility and early embryonic development study was not completed by the Applicant. The Applicant conducted a literature search to identify published data that may address these standard endpoints. There are no standard studies to characterize the effects of phenylephrine on male fertility. Studies of female fertility were limited to studies using artificial insemination.

Hodgson et al. (1975) evaluated fertility endpoints in female rabbits (3.5 to 4 kg) intramuscularly administered phenylephrine 16 hours following artificial insemination. These endpoints included mean number of corpora lutea, rate of pregnancy, percentage of ovulated ova that implanted, and percentage of ovulated ova that implanted and were observed with normal gross morphology of placenta and fetus. Rabbits were injected with either 2 mg administered 4 to 6 times per day (3 days) or 1 mg administered every hour 16-48 hours after HCG treatment. Fertility parameters were decreased in rabbits treated with 2 mg (0.50 to 0.57 mg/kg); however, it should be noted that this dose was also associated with an increased incidence of mortality (two of eight rabbits died, likely due to hypertensive crisis). Phenylephrine decreased the mean percentage of ovulated ova implanted approximately 2-fold lower than that in controls. In the same rabbits, the percentage of implanted ova that reportedly appeared normal based on gross morphology of the placenta and fetus was approximately 3-fold lower than control. Separately, resorbed fetuses were observed in three rabbits. **Together, the endpoints for fertility were altered in a toxicologically significant manner following intramuscular phenylephrine at 2 mg (4-6 times per day, 3 days); however, given that two of the animals reportedly died due to cardiovascular crisis these findings may, at least in part, be due to maternal toxicities. Therefore, these alterations suggest a potential impact on fertility and early embryonic development at the dose levels tested (≥ 2 mg/kg or 24 mg/m^2, HED of ≥ 0.2 mg/kg) at maternally toxic doses, but are not adequate to inform product labeling as the studies are not typical study design and the dosing regimen cannot be readily extrapolated to a clinical setting.** No adverse effects were noted in animals treated with 1 mg every hour for 32 hours (i.e., a total dose of 8 to 9.1 mg/kg, equivalent to 3.13 mg/kg to 3.87 mg/kg human dose based on body surface area).

Hawk et al. (1982) evaluated sperm count in various parts of the reproductive tract, urterine contractions, and ovum fertilization in sexually mature New Zealand rabbits following intramuscularly administered phenylephrine. Sperm count in the oviducts was substantially increased, uterus, and cervices of rabbits administered 1.3 mg/kg of phenylephrine after mating or artificial insemination (HED is 25 mg/60 kg person). In a separate study evaluating multiple doses (0, 0.25, 1.3, or 6.25 mg/kg), this effect increased in a dose-related manner following separate injections of phenylephrine at ≤ 1.3 mg/kg when administered following artificial insemination. At 6.25 mg/kg, sperm count in the oviducts was increased compared to control; but, the magnitude of this effect was less than that measured at 1.25 mg/kg across the organs mentioned above.

Uterine contractions (primary and secondary) were increased ≥ 2-fold for up to 80 minutes in rabbits following the administration of 1.3 mg/kg when compared to control. Pretreatment with phenoxybenzamine (5 mg/kg, IM) fully antagonized the increase in sperm count in the oviducts and uterine contractions in rabbits following the injection of phenylephrine (1.3 mg/kg). In regard to ovum fertilization, it was increased by 3-fold following the administration of 1.5 mg/kg of phenylephrine in rabbits after artificial insemination. **Together, these findings suggest that under various experimental conditions sperm count in the oviduct, uterine contractions, and ovum fertilization were substantially increased following the administration of phenylephrine at ≥ 1.3 mg/kg (15.6 mg/m^2), which is approximately ≥ 2-fold higher than the maximum dose proposed for use (0.17 mg/kg or 6.3 mg/m^2) when based on body surface area. These data suggest that phenylephrine does not have an adverse effect on female fertility following insemination, the study employs a different route of administration and does not include all standard parameters of a modern fertility and early embryonic development study and therefore should not be used to support the drug product labeling.**

9.2 Embryo-Fetal Development

Embryo-fetal development studies have not been completed for phenylephrine. The Applicant did identify two published studies that included some endpoints consistent with a standard embryo-fetal development study. These data are summarized here and, although the data may not be ideal, the adverse findings should be included in the drug product labeling.

In vivo

Shabanah et al. (1969b) evaluated fetal growth and development in mated New Zealand white rabbits (3 kg) subcutaneously administered 0.33 mg/kg (1 mg/3 kg, TID) of phenylephrine treatment during various periods of gestation.

Group 1a	GD 3 to GD 10 (n=2)
Group 1b	GD 3 to parturition (n=3)
Group 2	GD 7 to parturition (n=3)
Group 3	GD 12 to parturition (n=10)
Controls	Untreated (n=3)

Specifically pregnant rabbits were treated from Gestation Day (GD) 3 to GD 10 or parturition, GD 7 to parturition, or GD 12 to parturition. Collectively this dosing period covers the period of organogenesis (typically GD 6-18 in the rabbit); therefore, the study dosing regimen is fairly consistent with that of a modern embryo-fetal development study. The placentas from animals in each group were obtained and evaluated histologically following delivery; however, the fetuses were not evaluated for teratogenic effects or individual pup weights. The authors report that phenylephrine treatment decreased the mean litter weights compared to controls, increased the occurrences of neonate deaths and still births, and produced histopathological findings in the placenta

(only tissue evaluated). The averaged litter weight following daily PHE treatment was decreased to 66 to 82% of control. PHE-treated rabbits were observed with stillbirths, the level of which increased the later treatment was initiated during pregnancy. Separately, increased incidence of neonate deaths were observed in rabbits from Groups 1 and 2 but not Group 3, suggesting that exposure earlier in pregnancy may result in embryocidal effects. Also, treatment-related findings in rabbits were observed in the placenta, including areas of necrosis and calcification, thickening of the vascular walls, narrowing of the lumina, and lipid deposition/fatty degeneration of the placenta. A NOAEL was not determined in this study.

Table 15. Findings in Rabbits Subcutaneously Administered 0.33 mg/kg Daily up to Delivery (Shabanah et al., 1969b)

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It is not clear stated in the publication if all offspring were specifically evaluated for teratogenicity. However, as noted in the table below, upon gross evaluation the authors noted that a single rabbit from Group 1 was observed with rudimentary tail, exstrophy in the bladder (part of the bladder outside of the body), and partial development of the intestine. One stillborn animal from a Group 1 animal showed macroglossia (unusually large tongue) and clubbing of the feet. Based on the low incidence of these findings it is difficult to determine if they are test-article related in the absence of historical controls. These findings suggest the potential for teratogenicity.

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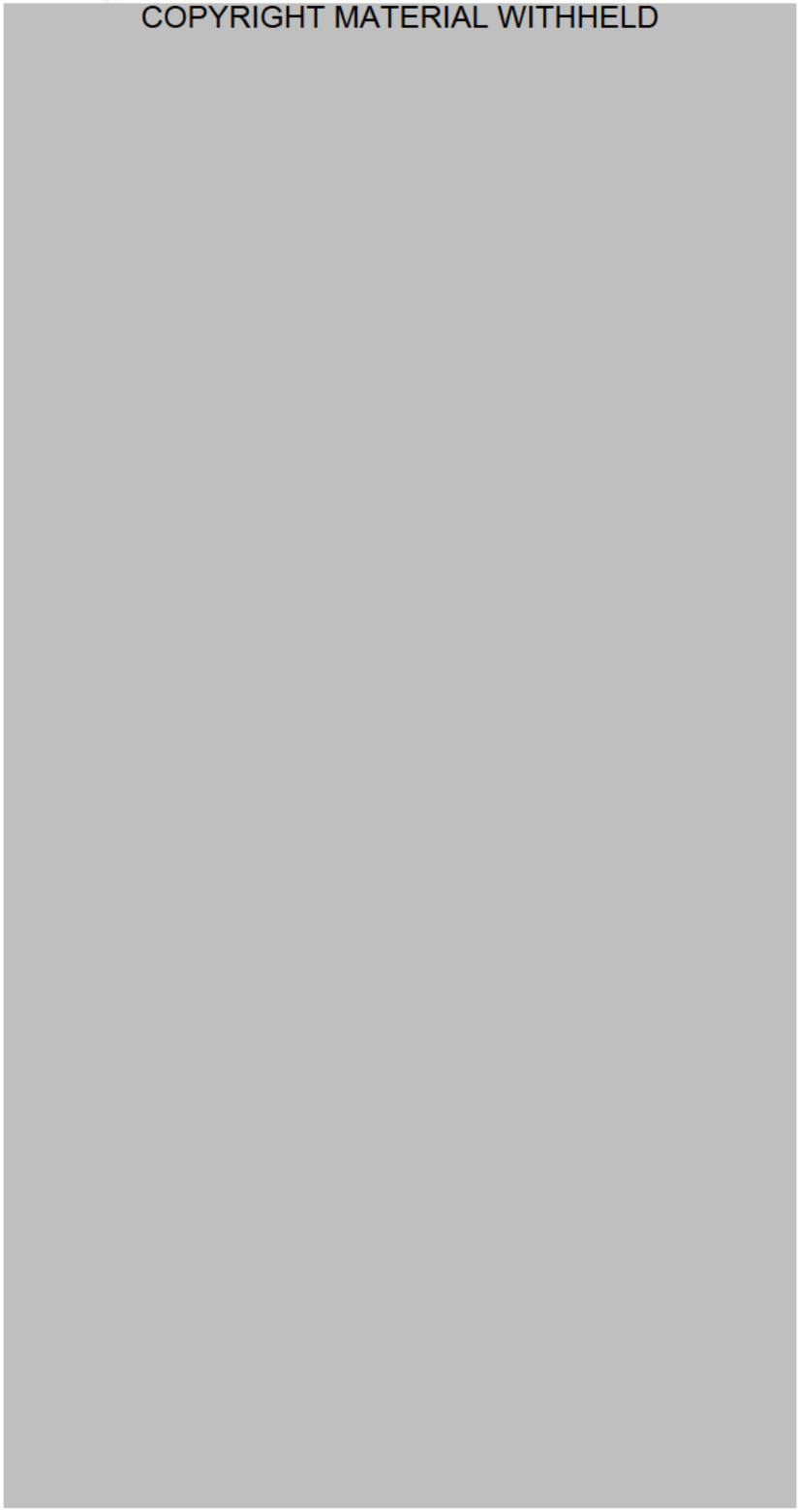
Collectively, these data suggest that phenylephrine during the course of gestation results in decreased mean litter weights, increased neonatal deaths and still births, alterations in the placenta, and possible teratogenicity following subcutaneous injection of phenylephrine at 0.33 mg/kg **(3.96 mg/m^2, TID). The total dose administered daily (i.e., 1 mg/kg/day or 12 mg/m^2) is 1.9-fold higher than the maximum recommended total daily clinical dose of 10 mg (0.17 mg/kg or 6.2 mg/m^2) when based on body surface area comparison. Given that this hazard was observed in rabbits at a dose that is slightly higher the maximum recommended clinical dose when based on body surface area the PT Reviewer recommends that it is included in the label for this product in the absence of definitive GLP embryo-fetal development studies.**

These adverse effects could be attributable to decreased placental perfusion and the resulting deprivation of the fetus to oxygen. However, it is difficult to extrapolate these findings to humans, given the differences in dosing regimen and the fact that the animals were normotensive to begin with and therefore the drug would induce a hypertensive crisis rather than treat a hypotensive crisis. When used as labeled, the drug is intended to restore blood pressure to the normal range rather than increase the blood pressure above normal. The single bolus dose of 0.33 mg/kg in the rabbit corresponds to a human equivalent dose of 6.4 mg/60 kg person. As single bolus doses of not more than 200 mcg/60 kg person every 1-2 minutes are given clinically, the rabbit bolus dose is 32 times the bolus dose in humans. Therefore, the clinical significance of these findings is not clear.

Cottle and colleagues (1982) examined the effect of phenylephrine on uterine and fetal blood pressure in normotensive sheep pregnant Dorset-Finn Suffolk ewes (45-64 kg) during the third trimester of pregnancy. The authors implanted chronic cannulas into the femoral artery of the ewes and into the saphenous vein of the fetus through the wall of the amnionic sac. In addition, cannula were inserted into the carotid artery and jugular vein of the ewes to monitor for blood oxygenation and an electromagnetic flow transducer was placed around the main branch of the middle uterine artery to monitor uterine blood flow. Phenylephrine (Neo-Synephrine, a marketed unapproved product) was infused intravenously into ewes at a mean Gestation Day 127 (full term is generally 145 days). The dose tested was 4 mcg/kg/min for 30 minutes (or a total dose of 0.12 mg/kg; equivalent to 0.11 to 0.12 mg/kg human dose based on body surface area)[17]. These HEDs in pregnant sheep are slightly lower than the maximum recommended clinical dose of PHE (< 0.17 mg/kg) based on a body surface area comparison. As depicted in the figure below, reproduced from the publication, phenylephrine infusion decreased uterine blood flow up to ~42%. Maternal mean arterial blood pressure

[17] The HED was determined, as per the FDA Start Dose Guidance as follows: HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$ and assumed a 60 kg person.

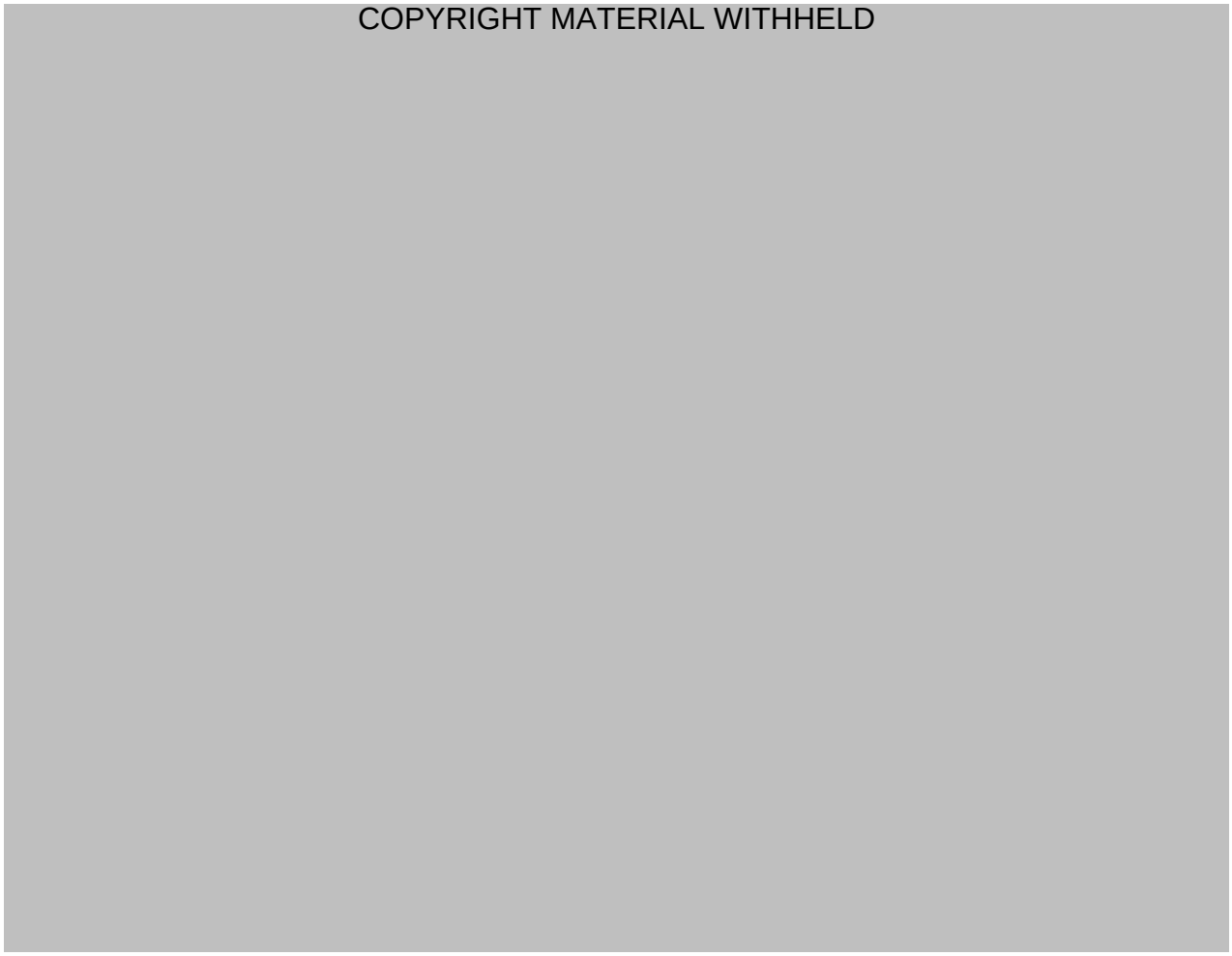
significantly increased and heart rate decreased reflexively. Maternal blood respiratory gasses, pH, hemoglobin, and hematocrit “changed little” during the infusion. Fetal mean arterial blood pressure also increased and heart rate decreased about 7% compared to controls.



In vitro

Hodach et al. (1975) evaluated chick embryos for gross malformations and cardiovascular anomalies following a single in vitro treatment with L-phenylephrine (≤ 20 x 10^{-9} mol) via a micropipette. These embryos were obtained from medium-sized fertile white Leghorn eggs incubated in a forced-draft incubator. The incubation period was planned for up to 14 days. Phenylephrine was placed on the extra-embryonic membranes directly above the developing embryo in ovo on Day 5 of incubation. The study was designed such that eggs were re-incubated following treatment and checked for survivors 24 hours later. Phenylephrine was typically lethal within the first 24 hours of treatment. A number of embryos that did not survive until Day 14 were not examined because of severe postmortem degeneration. The survival rate in phenylephrine-treated embryos decreased in a concentration-related manner. At the top concentration (20 x 10^{-9} mol), survival rate was 66.1% (survival in the saline control animals was 84.5%). Similarly, the percentage of embryos with cardiovascular anomalies increased in a concentration-dependent manner in phenylephrine-treated embryos. The percentage of embryos with anomalies was 19.2% at 20 x 10^{-9} mol, which was greater than the saline-treated controls (3.4%). The cardiovascular anomalies observed include anomalies of the aortic arches, ventricular septal defect, double outlet right ventricle, aortic hypoplasia, and truncus arteriosus. See **Figure 12** for qualitative findings related to the defects observed (no quantitative findings specifically for phenylephrine-treated embryos was provided). No gross malformations were observed in treated embryos.

Figure 12. Classification of Cardiovascular Anomalies Observed in Embryos following Treatment with Phenylephrine and Other Sympathomimetic Amines[18]



Overall, these findings demonstrate that death and cardiovascular anomalies increased in a concentration-related manner in embryos following in vitro exposure to phenylephrine. Although these in vitro findings suggest the potential for risk under the conditions tested, as drug clearance does not occur in this system, the clinical relevance is not clear. Given the confounding treatment conditions, these results are not deemed appropriate to inform drug product labeling.

9.3 Prenatal and Postnatal Development

The PT Reviewer did not identify any studies in the published literature that specifically evaluated prenatal and postnatal development in animals administered phenylephrine. One published study did treat pregnant rabbits late in gestation which roughly

[18]This excerpt was obtained from Hodach et al. (1975).

corresponds to a pre- and post-natal development study; however, as standard endpoints, including post-natal development were not included in the study the study would not be deemed adequate by current standards. Nonetheless, it is summarized here as adverse effects were suggested which should be included in the drug product labeling.

Shabanah et al. (1969a) evaluated fetal growth and length of gestation in mated female rabbits (3 kg) subcutaneously administered 0.33 mg/kg (1 mg/3 kg, TID) during the later portion gestation. The normal gestational period in the rabbit is 28-31 days. The animals were divided into the following treatment groups:

Group 1 GD 22 to parturition on GD 26 (0.33 mg/kg, TID, n=7)
Group 2 GD 22 to parturition on GD 31-32 (0.33 mg/kg, TID, n=5)
Group 3 GD 16 to parturition on GD 29 or 32 (TID, n=2)

Treatment Groups 1 and 2 also included 3 and 5 control animals, respectively, that were not treated (authors note that saline injections were without effect in their other studies). These groups were apparently treated the same but analyzed separate by the authors as they were evaluated at different times. Several placentas (4-5) from each of the two animals in Group 3 were obtained and evaluated histologically following delivery. Based on the results provided the mean values for birth weight in Groups 1 and 2 and day of labor onset across groups were decreased compared to control (see **Table 16**). The mean values for birth weight were markedly decreased in PHE-treated rabbits, as they were 61-72% of control. As for the mean day for labor onset, it occurred about 2 to 3 days earlier in PHE-treated rabbits when compared to control who typically delivered on GD 32 or 33. Evaluation of the placentas in the two Group 3 treated animals did not reveal clear treatment related findings given the lack of control placenta and limited specimens examined. In the Group 3 rabbit that delivered on GD 29, there were a few placenta that showed evidence of necrosis in areas of placental detachment from the uterine wall. There were no adverse placental findings in the Group 3 rabbit that delivered on GD 32. Collectively, t**hese findings suggest that daily subcutaneous injection of phenylephrine at 0.33 mg/kg (3.96 mg/m^2, TID) late in pregnancy may increase the likelihood of earlier onset of labor in pregnant rabbits and reduce birth weight of the animals in the litter following. The reduced birth weight may be due the early delivery; however, we cannot rule out a direct effect of the drug on the fetus. The total dose administered daily (i.e., 0.99 mg/kg or 11.88 mg/m^2) is 1.9-fold higher than the maximum recommended clinical dose (0.17 mg/kg or 6.3 mg/m^2) when based on body surface area. This is not a standard pre- and post-natal development study, in which pregnant animals would be dosed from implantation through weaning (Gestation Day 6 through weaning). Likewise, the study does not include any evaluation of post-natal development and cannot be considered an adequate pre- and post-natal development study. However, given that this hazard was observed in rabbits at a dose that is slightly higher the maximum recommended clinical dose when based on body surface area the PT Reviewer recommends that it is included in the label for this product.**

Table 16. Findings in Rabbits Subcutaneously Administered 0.33 mg/kg (TID) During Late Gestation (Shabanah, et al., 1969a)

9.4 Lactation

Although the PT Reviewer did not identify any published findings on the exposure levels of phenylephrine in milk ejected by treated animals, there are published findings of marked reductions in milk ejection from cows following phenylephrine administration (Bruckmaier, et al., 1991; Bruckmaier, et al., 1997). For example, Bruckmaier et al. (1997) provided findings that milk yield was reduced to 24% of control in cows following intravenous administration of phenylephrine at 30 mcg/kg (or 0.03 mg/kg), a dose that is 5.6-fold lower than the maximum daily clinical dose of 10 mg/60 kg person (0.17 mg/kg). After milk flow ceased in these animals, the alpha adrenergic receptor antagonist phentolamine (100 mcg/kg) was intravenously administered and milk flow started within two minutes. The total milk yield returned to 90% of control following treatment with phentolamine. Overall, these data suggest that milk ejection in cows involves an adrenergic-receptor mechanism. This finding is informative, but is unlikely to have any significant clinical implications given the acute indications proposed and the short half-life of phenylephrine.

10 Special Toxicology Studies

Local Tolerance

Studies on the local toxicity of phenylephrine are limited (see DUNGAN, et al., 1965). Duncan et al. (1965) provided findings that albino rats intracutaneously administered 2.7% of phenylephrine in the abdomen skin were observed with local irritation in areas near the injection site. As the drug product is a 1% solution that is diluted prior to use, the findings do not appear to have clinical relevance. Given the extensive clinical history of comparable drug products containing this drug substance, the local tissue

toxicity of the drug product can be addressed via clinical experience. Further nonclinical studies are not required.

11 Integrated Summary and Safety Evaluation

The clinical history of phenylephrine HCl is extensive. Phenylephrine is an established alpha 1-receptor agonist that can increase blood pressure under various conditions in humans and other animal species (see Hoffman, 2001). Based on the long history of clinical use, nonclinical studies for phenylephrine were not required for approval of this NDA application. Studies from the published literature were used to support the safety of the phenylephrine HCL product reviewed here. Based on findings from the published literature phenylephrine administered intravenously to rats is distributed to sites that include the submaxillary gland, liver, heart ventricles, spleen, kidney, lung, and brain. Phenylephrine and its metabolites are excreted via urine from rats. Also, data from human and animal studies demonstrate the fast onset of effects and short half-life of phenylephrine. For example, in single-dose toxicology studies mortalities in rodents occurred minutes after phenylephrine administration. Other findings such as the alteration of respiration, as well as the exhibition of behaviors that include ataxia and convulsions occur immediately following intravenous injection of phenylephrine. Findings from single-dose toxicology studies provided evidence that the target sites of toxicity for phenylephrine are the CNS and the lungs. In multiple-dose toxicology studies in rodents the target sites of toxicity included the brain (hyperactivity), eye (chronic keratitis), testicles (atrophy), seminal vesicles (atrophy), and ovaries (atrophy) following 12 weeks of treatment.

In evaluations of the genotoxic potential of phenylephrine, it was deemed positive in an in vitro mouse lymphoma assay; whereas, it was deemed negative in an in vitro bacterial reverse mutation assay, an in vitro chromosome aberration assay, an in vitro sister chromatid exchange assay, and an in vivo rat micronucleus assay. This positive finding was not deemed toxicologically relevant given that phenylephrine was not deemed carcinogenic in the rat and mice 2-year carcinogenicity studies conducted by NTP. Based on the data in the published literature, further genetic toxicology and carcinogenicity studies are not warranted.

In regard to reproductive toxicology, PHE administration to normotensive animals produced adverse effects at doses that are comparable to those proposed for clinical use. For example, subcutaneous administration of phenylephrine to pregnant normotensive rabbits (0.33 mg/kg, TID) resulted in premature labor onset, decreased litter weights, increased neonate deaths and still births, and histopathology findings in the placenta such as necrosis, thickened vascular walls, and narrowed lumina. Separately, studies in normotensive pregnant sheep demonstrated that phenylephrine increases blood pressure and produces reflex bradycardia in both the ewe and the fetus and decreases uterine blood flow at clinically relevant doses. Although adequate reproductive and developmental studies were not identified in the published literature, these findings from the studies described provide insight on potential adverse effects of

phenylephrine in pregnant normotensive animals. As definitive studies were not identified in the literature and the literature references available suggest adverse effects with unclear clinical significance, the full battery of reproductive and developmental toxicology studies should be completed for this drug product. These may be completed post-marketing, given the extensive clinical experience. Until definitive data are provided, the adverse effects noted in normotensive animals should be included in the product labeling. The design of the definitive GLP reproductive and developmental toxicology studies should be discussed with the Applicant. Ideally, they should mimic the clinical use of the drug in order to dissociate, if possible, any direct effects of the drug from the indirect pharmacodynamics effects of the drug on the cardiovascular system.

Based on the information provided to date, from a nonclinical pharmacology toxicology perspective, NDA 204300 may be approved with post-marketing requirements and pending agreement on drug product labeling.

12 Appendix/Attachments

NOTE: Due to network software malfunction, additional references can be found in footnotes.

Reference List

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Ref Type: Report

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/s/

MARCUS S DELATTE
03/20/2014

RICHARD D MELLON
03/20/2014

I concur with Dr. Delatte's recommendation that, from a nonclinical pharmacology toxicology perspective, NDA 204300 may be approved with the recommended PMRs and pending agreement on final product labeling.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 204300 **Applicant: Éclat Pharmaceuticals Stamp Date: Jun 28, 2013**

Drug Name: Phenylephrine HCl **NDA Type: 505(b)(2)**

resubmission resulting from RTF letter

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

	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		
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).		X	The acute toxicology studies submitted appear to be the only toxicology studies in which phenylephrine was administered intravenously. As these studies were not specifically required for this NDA, this Is not deemed a filing issue.
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?		X	Other than the acute toxicology studies, the other toxicology studies cited typically used routes other than IV. The Sponsor believes that the existing toxicology findings are sufficient to accurately predict safety signals that may occur with a single-dose IV treatment with the drug product. As these studies were not specifically required for this NDA, this Is not deemed a filing issue.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
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?		X	The Sponsor did not identify/submit findings from GLP studies or provide an explanation for any significant deviations. As these studies were not specifically required for this NDA, this Is not deemed a filing issue.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		DAAAP informed the Sponsor that if the literature references submitted do not contain adequate information regarding the mutagenic potential and impact on reproductive and developmental toxicity of phenylephrine, these studies may be required as post-marketing requirements (see EOP2 meeting minutes); however, these types of studies have not been requested as part of the recent approval for a intravenous and a ophthalmic formulation of phenylephrine.
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 – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?		X	The Reviewer did not identify any nonclinical sections of the application that addressed issues related to the abuse potential of the drug product. This is an issue that will be addressed by CSS, rather than Pharmacology Toxicology.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	-	-	Not Applicable

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

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

There are no comments at this time for the 74-day letter.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

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

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

MARCUS S DELATTE
08/07/2013

RICHARD D MELLON
08/07/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 204300 **Applicant: Éclat Pharmaceuticals** **Stamp Date: February 8, 2013**

Drug Name: Phenylephrine HCl **NDA Type: 505(b)(2)**

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

	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		
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).		X	The acute toxicology studies submitted appear to be the only toxicology studies in which phenylephrine was administered intravenously. As these studies were not specifically required for this NDA, this Is not deemed a filing issue.
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?		X	Other than the acute toxicology studies, the other toxicology studies cited typically used routes other than IV. The Sponsor believes that the existing toxicology findings are sufficient to accurately predict safety signals that may occur with a single-dose IV treatment with the drug product. As these studies were not specifically required for this NDA, this Is not deemed a filing issue.
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?		X	The Sponsor did not identify/submit findings from GLP studies or provide an explanation for any significant deviations. As these studies were not specifically required for this NDA, this Is not deemed a

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
				filing issue.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		DAAAP informed the Sponsor that if the literature references submitted do not contain adequate information regarding the mutagenic potential and impact on reproductive and developmental toxicity of phenylephrine, these studies may be required as post-marketing requirements (see EOP2 meeting minutes); however, these types of studies have not been requested as part of the recent approval for a intravenous and a ophthalmic formulation of phenylephrine.
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 – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?		X	The Reviewer did not identify any nonclinical sections of the application that addressed issues related to the abuse potential of the drug product. This is an issue that will be addressed by CSS, rather than Pharmacology Toxicology.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	-	-	Not Applicable

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

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

There are no comments at this time for the 74-day letter.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

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

Reviewing Pharmacologist	Date
Team Leader/Supervisor	Date

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/s/

MARCUS S DELATTE
03/26/2013

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