CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212909Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 212909
Review 1

Drug Name/Dosage Form	Phenylephrine Hydrochloride Injection USP
Strength	0.1 mg/mL and 10 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	SINTETICA SA
US agent, if applicable	Craig Kruman

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission (SD-01)	21-DEC-2018	All
Amendment (SD-04)	30-JAN-2019	Manufacturing (OPF)
Amendment (SD-05)	28-FEB-2019	Manufacturing (OPF), Drug Product, Microbiology
Amendment (SD-06)	26-MAR-2019	Drug Substance
Amendment (SD-07)	15-MAY-2019	Biopharmaceutics, Microbiology
Amendment (SD-09)	28-JUN-2019	Manufacturing (OPF), Drug Product, Microbiology
Amendment (SD-12)	14-AUG-2019	Drug Product
Amendment (SD-14)	04-SEP-2019	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sukhamaya (Sam) Bain	Donna F. Christner
Drug Product	Jizhou Wang	Julia Pinto
Process	Derek Smith	Edwin Jao
Microbiology	David Bateman	John Metcalfe
Facility	B. J. Ryan	Ruth Moore
Biopharmaceutics	Kamrun Nahar	Kelly M. Kitchens
Regulatory Business Process Manager	Anika Lalmansingh	N/A
Application Technical Lead	Sukhamaya (Sam) Bain	N/A
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A

Environmental	Sukhamaya (Sam) Bain	N/A

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

Form quality perspective, the NDA is recommended for approval for the 0.1 mg/mL strength of Phenylephrine Hydrochloride Injection USP based upon satisfactory evaluations of the drug substance, drug product, process and facilities (manufacturing), biopharmaceutics and microbiology sections.

II. Summary of Quality Assessments

A. Product Overview

The proposed drug product, Phenylephrine Hydrochloride Injection USP, is indicated for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia. The drug substance, Phenylephrine Hydrochloride USP, is a synthetic alpha-1 adrenergic receptor agonist, and produces dose-dependent vasoconstriction of cutaneous, muscular, mesenteric, splanchnic, and renal vasculature. It is the drug of choice for initial treatment of mild hypotension with normal or increased heart rate in the setting of general or regional anesthesia. The drug product is supplied in the strengths of 0.1 mg/mL for administration as an intravenous bolus. The maximum recommended single day dose is 200 µg. The applicant's basis for submitting this 505(b)(2) NDA 212909 is NDA 204300 for VAZCULEP (Phenylephrine Hydrochloride) Injection USP.

N/A	**Total Number of Comparability Protocols (ANDA only)**

Proposed Indication(s) including Intended Patient Population	Clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia
Duration of Treatment	During anesthesia
Maximum Daily Dose	200 mcg
Alternative Methods of Administration	Administered as an intravenous bolus

B. Quality Assessment Overview

For the drug substance CMC, the applicant has referenced DMF (b) (4) which has been found adequate by the Agency. The NDA includes the applicant's controls of the drug substance, which include (b) (4) (b) (4) Based upon the current adequacy of the DMF and upon

the information provided in the NDA, the drug substance manufacturing process, characterization, shelf-life specification, container closure system and stability are satisfactory.

In addition to the API, the drug product contains Water for Injection (b) (4) sodium chloride (b) (4) and (b) (4) hydrochloric acid for adjusting pH. (b) (4) (b) (4) The proposed product is designed for single use and immediate administration; thus, there is no preservative is in the product. The manufacturing process involves (b) (4) (b) (4)

All drug substance and drug product facilities are satisfactory based upon pre-approval inspection as well as history at the Agency's database.

The applicant has submitted the NDA for (b) (4) drug product, 0.1 mg/mL (b) (4) The qualities of the drug product components and of the finished drug product, including characterizations, specifications, test procedures and impurity profiles, have been found adequate. (b) (4) (b) (4) (b) (4) The lower, 0.1 mg/mL strength is recommended for approval, with an expiration dating of 36 months. (b) (4)

The applicant has requested a biowaiver in accordance with 21 CFR 320.22(b)(1), and provided adequate justification for the differences, in terms of inactive ingredients and physiochemical properties, between the proposed and the listed drug product. Consistent with 21 CFR 320.24 (b)(6), an adequate biobridge has been established between the listed and the proposed drug product. Thus, the NDA is recommended for approval from Biopharmaceutics perspective.

The drug product manufacturing process involves (b) (4) (b) (4) Based upon evaluations of the manufacturing process, bioburden of bulk solution, ampoule depyrogenation, container closure integrity, and specifications and test results involving Bacterial Endotoxins and Sterility, the drug product has been found adequate from Microbiology perspective.

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

Satisfactory; see Attachment I

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(b) (4)

[redacted]

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

Labeling & Package Insert

1. Package Insert

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

BiorPHEN 0.5 mg/mL

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Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	BiorPHEN (phenylephrine hydrochloride) for 0.5 mg/mL (b) (4)	Acceptable for 0.5 mg/mL
Dosage form, route of administration	Dosage: injection for intravenous	Acceptable Acceptable
Controlled drug substance symbol (if applicable)	N/A	Acceptable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	an injectable solution containing 0.1 mg/ml (b) (4) (b) (4)	Acceptable

Conclusion: Acceptable with the required data elements as summarized above

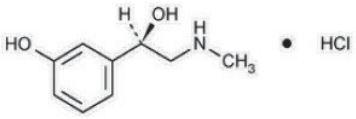
(b) "Full Prescribing Information" Section

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

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	injectable solution	Acceptable
Strengths: in metric system	0.5 mg/mL (b) (4)	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not provided *Clear and colorless*	Not Acceptable

Conclusion: Not Acceptable with the required data elements as summarized above

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	BiorPHEN (phenylephrine hydrochloride) for 0.5 mg/mL (b) (4)	Acceptable for 0.5 mg/mL
Dosage form and route of administration	a sterile, nonpyrogenic solution for intravenous use	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each mL contains: phenylephrine hydrochloride 0.1 mg	Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	sodium chloride water, hydrochloric acid	Acceptable
Statement of being sterile (if applicable)	sterile injection	Acceptable
Pharmacological/ therapeutic class	an alpha-1 adrenergic receptor agonist	
Chemical name, structural formula, molecular weight	 (-)-*m*-hydroxy-α-[(methylamino) methyl] benzyl alcohol hydrochloride, Molecular Formula: *Not provided* (b) (4) Molecular weight: *Not provided* 203.6 (b) g/mol	Not Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	N/A	N/A

Conclusion: **Not** Acceptable with the required data elements as summarized above

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

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	0.1 mg/mL (b) (4)	Acceptable
Available units (e.g., bottles of 100 tablets)	pack of 10 ampules	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4) NDC No. 71863-202-05 For 5 mL ampule; for single use	Acceptable
Special handling (e.g., protect from light, do not freeze)	(b) (4) (b) (4) Discard any unused portion	Acceptable
Storage conditions	20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]	Acceptable

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

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	**Manufactured for:** Eton Pharmaceuticals, Inc. Deer Park, IL 60010 USA	Acceptable

Conclusion: Acceptable with the required data elements as summarized above

2. Labels

1) Immediate Container Label

(b) (4)

Reviewer's Assessment:
Acceptable for 0.5 mg/mL. See summary in the table below [redacted]

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	BiorPHEN (phenylephrine hydrochloride) for 0.1 mg/mL [redacted]	Acceptable for 0.1 mg/mL [redacted]
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	0.1 mg/mL [redacted]	Acceptable
Net contents (21 CFR 201.51(a))	See above	Acceptable
Lot number per 21 CFR 201.18	Yes	Acceptable
Expiration date per 21 CFR 201.17	Yes	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	Acceptable
Storage (not required)	Yes	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Acceptable
Name of manufacturer/distributor	Cumberland Pharmaceuticals Inc.	Acceptable
Others	N/A	N/A

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

Conclusion: Acceptable for [redacted] 0.1 mg/mL, [redacted]

2) Cartons

500 mcg/5 mL (0.1 mg/mL)

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Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	BiorPHEN (phenylephrine hydrochloride) for 0.1 mg/mL (b) (4)	Acceptable for 0.1 mg/mL (b) (4)
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	500 mcg/5mL (b) (4)	Acceptable
Net contents (21 CFR 201.51(a))	See above	Acceptable
Lot number per 21 CFR 201.18	Yes	Acceptable
Expiration date per 21 CFR 201.17	Yes	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	sodium chloride water, hydrochloric acid	Acceptable
Sterility Information (if applicable)	sterile injection	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	Acceptable
Storage Conditions	20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	(b) (4) NDC No. 71863-202-05	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Acceptable
Name of manufacturer/distributor	Eton Pharmaceuticals, Inc.	Acceptable
"See package insert for dosage information" (21 CFR 201.55)	Yes	Acceptable
"Keep out of reach of children" (optional for Rx, required for OTC)	Not applicable for Rx drugs	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	For subcutaneous use only	Acceptable

Conclusion: Acceptable for 0.1 mg/mL (b) (4)

Jizhou Wang

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Julia Pinto

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MICROBIOLOGY

Product Background:

NDA: 212909

Drug Product Name / Strength: Phenylephrine Hydrochloride Injection USP, 0.1 mg/ml (b) (4)

Route of Administration: Intravenous injection

Applicant Name: Sintetica SA

Manufacturing Site(s):
Sintetica SA
Via Penate, 5
Mendrisio, Ticino, Switzerland 6850

Method of Sterilization: The drug product is (b) (4) (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): N/A

Justification (ANDA only): N/A

Review Summary: The drug product is (b) (4) (b) (4)

List Submissions Being Reviewed: 12/21/2018, 02/28/2019, 05/15/2019, 06/28/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The drug product is supplied as a (b) (4) 0.1 mg/ml sterile, single-use, injectable solution in (b) (4) 5 ml (5 ml fill) glass ampoules, respectively.

Concise Description Outstanding Issues Remaining: None.

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

The drug substance, Phenylephrine Hydrochloride, is supplied by (b) (4) (b) (4) The applicant established microbiological limit for the drug substance is (b) (4) EU/mg for endotoxins, conducted per USP<85>; however, as the drug substance is not (b) (4) (b) (4) t will not be reviewed further.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Phenylephrine Hydrochloride Injection USP, is supplied as (b) (4) 0.1 mg/ml sterile, single-use, clear, and colorless injectable solution in (b) (4) 5 ml (5 ml fill) glass ampoules, respectively.

- **Drug product composition** – The drug product composition, as derived from Section 3.2.P.3.2, Batch Formula, is as follows:

	0.1 mg/ml (b) (4)	
Component	**mg/ml**	**Function**
Phenylephrine HCl, USP	0.100	API
Sodium Chloride, USP	9.000	(b) (4)
Hydrochloric Acid (b) (4) USP	to pH (b) (4)	pH Adjustment
Water for Injection, USP (b) (4)	(b) (4)	(b) (4)
	NA	

- **Description of container closure system** – The drug product is supplied in (b) (4) (b) (4) 5 ml glass ampoule. The ampoules are supplied as (b) (4) A summary of the drug product container closure system components is as follows (*from Section 3.2.P.7, Container Closure System (Phenylephrine hydrochloride, Injection), pg. 2*):

Component	Description	Manufacturer/Supplier	DMF #
Ampoule	Type (b) (4) (USP) clear colorless glass (b) (4) 5 ml ampoules	(b) (4)	

Reviewer's Assessment: Adequate

The applicant provided an adequate description of the drug product composition and container/closure system.

(b) (4)

[redacted]

P.7 Container Closure

Summary table of the container closure system proposed

Reviewer's Assessment: See section P.1.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(Section 3.2.P.8, Stability Summary and Conclusion (Phenylephrine hydrochloride, Injection))

The proposed expiry is 36 months at 20-25ºC.

Reviewer's Assessment: Adequate

The applicant's proposed 36-month expiry is acceptable from the standpoint of microbiological product quality based on the provided microbial test data.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The product stability specification includes the following microbiological tests:

Test	Acceptance Criteria	Method
Bacterial Endotoxins	(b) (4) EU/mg	USP<85>
Sterility	No bacterial and mycotic growth after 14 days	USP<71>

Post-approval long-term stability conditions will be 25±2°C. The testing schedule in the post-approval protocol is as follows:

Test Schedule for Initial Commercial Stability Batches				
Long Term, 25±2°C				
Interval (Month)	0	12	24	36
Bacterial Endotoxins	X	-	-	X
Sterility	X	-	-	X
CCIT	X	-	-	X

The applicant stated that one commercial batch per year will be subject to long term stability testing. Post-approval stability testing results will be reported as they become available in either periodic reports or as specified by the Agency. Non-conforming batches will be withdrawn from the market.

Reviewer's Assessment: Adequate

The applicant has met regulatory expectations regarding the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life.

P.8.3 Stability Data

The applicant provided bacterial endotoxins and sterility data up to 48 months (long-term and accelerated).

Reviewer's Assessment: Adequate

The applicant provided acceptable microbiology stability data.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not Applicable

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not Applicable

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not Applicable

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not Applicable

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not Applicable

R Regional Information

Executed Batch Records

Executed batches: 14251, 15015, and 15263

On March 4, 2019 and April 30, 2019, the following Microbiology information request was forwarded to the applicant by the CDER project manager. The manufacturing batch records in Section 3.2.R, 3.2.R.1.P (b) (4) are acknowledged.

(b) (4)

Reviewer's Assessment: Adequate

The applicant provided an acceptable response to the microbiology deficiency.

Comparability Protocols

Reviewer's Assessment: ***Not Applicable***

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

(*Section 1.14.1.3, PHE Sintetica_01_mg/mL_PI proposed, and Section 1.14.1.3, PHE Sintetica_10_mg/mL_PI proposed*)

The storage temperature of the drug product is 20-25ºC, and it is a sterile solution for intravenous injection (b) (4) as a ready-to-use 0.1 mg/ml formulation. Each ampoule is single-use, (b) (4)

On March 4, 2019 and April 30, 2019, the following Microbiology information request was forwarded to the applicant by the CDER project manager. The drug product storage, preparation, and route of administration information in Section 1.14.1.3, (b) (4) is acknowledged; however, no information was provided regarding the (b) (4)

(b) (4)

[redacted]

Post-Approval Commitments: See P.8.2

Reviewer's Assessment: ***Not Applicable***

List of Deficiencies: **None.**

Primary Microbiology Reviewer Name and Date:

Jason K. Morgan, Ph.D., 01/31/2019

David Bateman, Ph.D., 07/03/2019

Secondary Reviewer Name and Date: John W. Metcalfe, Ph.D., 07/05/2019

John Metcalfe

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Comments: I concur with the primary reviewer's assessment.

David Bateman

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BIOPHARMACEUTICS

Product Background: Sintetica SA is developing (b) (4) Phenylephrine Hydrochloride Injection USP, 0.1 mg/mL (b) (4) referencing Vazculep® (phenylephrine hydrochloride) injection, USP, 10 mg/mL, NDA 204300. The reference product is available as 10mg/mL, a concentrated Solution which needs to be diluted prior to use. The proposed phenylephrine hydrochloride injection strength, 0.1 mg/mL, is intended to offer a simpler approach to use and can be given via IV bolus injection without dilution. However, Phenylephrine hydrochloride 10 mg/mL, a concentrated solution, needs dilution prior to use. Phenylephrine hydrochloride Injections USP, 0.1 mg/mL (b) (4) is indicated for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.

NDA: 204300

Drug Product Name / Strength: Phenylephrine Hydrochloride Injection USP, 0.1 mg/mL (b) (4) (b) (4)

Route of Administration: Intravenous

Applicant Name: Sintetica SA

Review Recommendation: **Adequate**

Review Summary:
The applicant claimed that the differences in formulations between their proposed product and the reference product, Vazculep®, do not affect the safety or efficacy of the proposed drug product. The Applicant provided adequate justification for the differences in the inactive ingredients and provided comparative physiochemical property data between the proposed and listed drug products. Consistent with 21 CFR 320.24 (b)(6), the information supporting the ***biobridge*** of the Applicant's proposed drug product to the listed drug is adequate. Thus, an additional in vivo bioequivalence (BE) bridging study is not needed. Therefore, NDA 212909 for Phenylephrine Hydrochloride Injection USP, 0.1 mg/ml (b) (4) is **recommended for approval.**

List Submissions being reviewed:

Submission Date	Purpose of Submission
12/21/2018	Original
05/15/2019	Amendment – Information Request

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Biowaiver Request

Reviewer's Assessment: ***Adequate***

In the original submission, the Applicant requested a [redacted]

Table 1: Formulation comparison of Vazculep® (reference product) and [redacted] Phenylephrine hydrochloride [redacted] 0.1 mg/mL

Material	Function	Strength (mg/ml)	[redacted]	
		Vazculep® RLD		**Phenylephrine hydrochloride Injection USP, 0.1 mg/ml**
Phenylephrine HCl	Drug substance	10.0 mg		0.1 mg
Sodium Chloride	[redacted]	3.5 mg		9.0 mg
[redacted] Sodium Citrate Dihydrate		4.0 mg		--
Citric Acid monohydrate		1.0 mg		--
Sodium metabisulfite		2.0 mg		--
Sodium Hydroxide		[redacted]		--
Hydrochloric Acid		[redacted]		Up to pH 3.0-5.0*
Water for injections		[redacted]		[redacted]
[redacted]		-		NA

In the response to the Information Request (IR), the applicant provided the following justification to demonstrate that the test products do not differ from the reference product in any way that can influence the physiological disposition, affect efficacy and safety:

- The proposed products, Phenylephrine hydrochloride [redacted] 0.1 mg/mL are preservative and sulphite free when compared with the reference product. The purpose of excipient selection is to simplify the formulation and to exclude any risk for the patient.

To improve safety of the proposed products, (b) (4)

(b) (4)

- According to 21 CFR 314.94.(a)(9)(iii)-

"Generally, a drug product intended for parenteral use must contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a) (3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in (b) (4) (b) (4) provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product".

(b) (4)

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Environmental
NDA 212909 Phenylephrine Hydrochloride Injection USP

The proposed drug product is intended to replace the use of similar drug products that are already approved and on the market; therefore, no additional risk is likely to occur to the environment from the use the proposed drug product.

Thus, the applicant claims a Categorical Exclusion from the requirement to prepare an Environmental Assessment for the drug product in compliance with the categorical exclusion criteria 21 CFR Part 25.31(a). The applicant also claims that to the best of their knowledge the drug product causes no extraordinary circumstances that may significantly affect the quality of the human environment (21 CFR 25.15 (d)).

Reviewer's Comment: The applicant's environmental assessment statements are satisfactory.

Reviewer/Review Date: Sukhamaya (Sam) Bain, PhD/05-SEP-2019

Sukhamaya Bain

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ATTACHMENT I: Final Risk Assessments

Final Risk Assessment – NDA 212909 Phenylephrine Hydrochloride Injection USP

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach** (b) (4)	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Appearance	• Components • Container closure • Container closure integrity	Low		Acceptable	Appearance test in the shelf-life specification of the DP
Identity	• No drug • Incorrect drug	Low		Acceptable	Identification tests in the release specification of the DP
Assay/Purity	• Input purity of the API • Formulation (b) (4)	Low		Acceptable	Assay test in the shelf-life specification of the DP
Microbial Limits	• Aqueous formulation	Low		Acceptable	N/A
Sterility	• Formulation • Container depyrogenation • Sterilization of the DP	Low		Acceptable	Sterility test in the shelf-life specification of the DP
Bacterial Endotoxins	• Formulation • Container depyrogenation, • Sterilization of the DP	Low		Acceptable	Bacterial Endotoxins test in the shelf-life specification

Sukhamaya Bain

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