

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213994Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

## Table of Contents

Executive Summary.....	3
Drug Substance.....	11
Drug Substance addendum.....	23
Drug Product.....	26
Environmental.....	61
Labeling.....	64
Process/Manufacturing.....	75
Biopharmaceutics.....	97
Microbiology.....	105

## RECOMMENDATION

<input checked="" type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input type="checkbox"/> Complete Response

## NDA 213994 Assessment 1

<b>Drug Product Name</b>	Ephedrine Sulfate Injection
<b>Dosage Form</b>	Solution for intravenous injection
<b>Strength</b>	5 mg/mL
<b>Route of Administration</b>	Intravenous injection
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Nevakar, Inc.
<b>US agent, if applicable</b>	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document #1; eCTD 0001	18 Dec 2019	All, original submission
Supporting document #3; eCTD 0003	3 Apr 20	Microbiology
Supporting document #5; eCTD 0005	20 May 20	Drug product
Supporting document #6; eCTD 0006	3 Jun 20	Process and manufacturing
Supporting document #7; eCTD 0007	5 Jun 20	biopharm
Supporting document #10; eCTD 0010	21 Aug 20	Drug product
Supporting document #11; eCTD 0011	26 Aug 20	Drug product
Supporting document #12; eCTD 0012	31 Aug 20	Drug product
Supporting document #13; eCTD 0013	8 Sep 20	Drug substance

### QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
<b>Drug Substance</b>	Sharon Kelly	Donna Christner

<b>Drug Product</b>	Jizhou Wang	Julia Pinto
<b>Manufacturing</b>	Cassandra Abellard	Joanna Wang
<b>Microbiology</b>	Bethanie Lee	Jesse Wells
<b>Biopharmaceutics</b>	Jia Yin	Hansong Chin
<b>Regulatory Business Process Manager</b>	Anika Lalmansingh	
<b>Application Technical Lead</b>	Valerie Amspacher	
<b>Laboratory (OTR)</b>	N/A	N/A
<b>Environmental</b>	Jizhou Wang	Julia Pinto

## EXECUTIVE SUMMARY

### I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

All CMC disciplines recommend approval.

A shelf-life of 24 months is acceptable when stored at the recommended storage condition of 20°–25° (68°–77° F). Excursions permitted to 15°C to 30°C (59°F to 86°F).

### II. SUMMARY OF QUALITY ASSESSMENTS

#### A. Product Overview

Ephedrine Sulfate Injection, USP is a clear, colorless, sterile solution filled into 10 mL glass vials for intravenous administration in the proposed 5 mg/mL strength. Each vial will be packed in a carton.

A shelf-life of 24 months is acceptable when stored at the recommended storage condition of 20°–25° (68°–77° F). Excursions permitted to 15°C to 30°C (59°F to 86°F).

<b>Proposed Indication(s) including Intended Patient Population</b>	treatment of clinically important hypotension occurring in the setting of anesthesia
<b>Duration of Treatment</b>	acute
<b>Maximum Daily Dose</b>	50 mg
<b>Alternative Methods of Administration</b>	N/A

#### B. Quality Assessment Overview

**Drug Substance: Adequate**

Ephedrine sulfate is manufactured (b) (4) (Adequate, CMC Review #1). The API is the subject of a USP monograph. The supplier specification meets the monograph requirements. Additional testing by (b) (4) includes residual solvents (b) (4) and elemental impurities. They have provided the sponsor with an Elemental Risk Assessment which supports elimination of this testing. The specification includes a test for enantiomeric purity (NLT (b) (4)%) because the ephedrine sulfate manufactured by (b) (4) is predominantly the (-)-ephedrine sulfate. The non-USP methods were fully validated by (b) (4) and they have provided the reports to (b) (4), the drug product manufacturer. (b) (4) performed method verification which includes: system suitability, specificity, method precision, and results comparison to (b) (4) Certificate of Analysis. Representative batch analysis data is provided for the two batches used for registration and stability of the drug product. The data conforms to specification (assay NLT (b) (4)%. Total impurities NMT (b) (4)%, Chiral purity NLT (b) (4)%). The holder of DMF (b) (4) has established a (b) (4) month retest date for the drug substance based on currently available stability results included in the DMF.

**Drug Product: Adequate**

The sponsor has manufactured three (3) registration batches of drug product. All the excipients (Sodium chloride, sodium hydroxide and/or acetic acid) are USP grade. The quality of the drug product has been adequately controlled as per official USP monograph, USP General Chapters, ICH guidelines and internal data trends. The long term (25 ± 2°C/60 ± 5% RH) and accelerated (40 ± 2°C / 75 ± 5% RH) stability storage conditions as well as the photo stability and Freeze/Thaw stress stability studies justified a shelf-life of 24 months when the drug product is stored at the recommended storage condition of 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F). The sponsor has performed adequate extractables and leachables studies to demonstrate the suitability of the primary packaging system.

**Labeling: Adequate**

**Manufacturing: Adequate**

The manufacturing process consists of (b) (4)

(b) (4). The drug product is supplied in a 10 mL USP (b) (4) clear glass vial with a (b) (4) stopper and an aluminum seal. The drug product manufacturer is acceptable after PAI. All other facilities are acceptable.

**Biopharmaceutics:** Adequate

In this NDA submission, Nevakar submitted the information based on Agency’s response dated August 1, 2018, to support a biowaiver request for the proposed product. Biopharmaceutics assessment is focused on the biowaiver request.

The formulation of the proposed drug product and the post-dilution LD is similar, except a small difference in the amount of sodium chloride, which is not expected to affect the bioavailability of the proposed drug product. The provided physicochemical comparison data showed similarity in pH and osmolality between the post-dilution LD and the proposed drug product. Per CFR 320.24(b)(6), A biobridge between the LD (Akovaz, N 208289) and proposed drug product has been established.

**Microbiology (if applicable):** Adequate

The integrity of the proposed container closure system was adequately validated. (b) (4)

The release specifications contain adequate controls to assure microbiological control of the subject drug product.

**C. Risk Assessment**

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

Sterility	Formulation Container Closure Process Parameters Scale/ Equipment Site	H	Controlled according to appropriate manufacturin g procedures	Acceptable	
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/ equipment Site	M	Controlled according to appropriate manufacturin g procedures	Acceptable	
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/ Equipment Site	L	Controlled by specification	Acceptable	
Uniformity of Dose – Fill/delivera ble Volume	Formulation Container Closure Process Parameters Scale/ equipment site	L	Controlled by specification	Acceptable	
Osmolality	Formulation Raw materials Process parameters Scale/ Equipment Site	L	Controlled by specification	Acceptable	
pH	Formulation Container Closure Raw materials Process parameters Scale/	L	Controlled by specification	Acceptable	

	Equipment Site				
Particulate Matter	Formulation Container Closure Raw materials Process parameters Scale/ equipment Site	M	Controlled by specification	Acceptable	
Leachable Extractables	Formulation Container Closure Raw materials Process parameters Scale/ equipment Site	L	Found acceptable during review	Adequate	
Appearance	Formulation Raw materials Process Parameters Scale/ Equipment Site	L	Controlled by specification	Acceptable	

**D. List of Deficiencies for Complete Response**

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

## QUALITY ASSESSMENT DATA SHEET

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Ephedrine sulfate	1	18 Jul 20 with addendum 14 Sep 20	
	V		Sterile processing facility	1	4 Feb 20	
	III		Glass vial	4		
	V		stopper	4		
	III		stopper	4		

Action codes for DMF Table:

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

**B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA**

Document	Application Number	Description
NDA	208289	Akovaz

**2. CONSULTS**

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

**Screenshot of inspection view in Panorama taken 14 Sep 20**

**Inspection View - Overall**

Planned Completion: Oct 18, 2020 | Status: Current | Condition: On Target | Percent Complete: 98.89%

Task Number	Task Name	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
<b>Parent: Manufacturing Facility Inspection (2)</b>								
14	Enter Application Specific Inspection Criteria		Anika Laimansingh	12/22/19	12/20/19	Complete	Go to Form	
142	Overall Manufacturing Inspection Recommendation		Cassandra Abellard	8/28/20	4/24/20	Complete	Go to Form Approve	



Valerie  
Amspacher

Digitally signed by Valerie Amspacher  
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# CHAPTER I: DRUG SUBSTANCE

<b>Drug Substance Name</b>	Ephedrine Sulfate
<b>NDA Number</b>	213994
<b>Assessment Cycle Number</b>	1
<b>DMF Number</b>	(b) (4)
<b>DMF Status</b>	<b>Adequate</b>
<b>Applicant Name</b>	Nevakar Inc.
<b>DMF Holder</b>	(b) (4)

## **Assessment Recommendation: Adequate**

### **Assessment Summary:**

Ephedrine sulfate is manufactured (b) (4) (Adequate, CMC Review #1). The API is the subject of a USP monograph. The supplier specification meets the monograph requirements. Additional testing by (b) (4) includes residual solvents (b) (4) and elemental impurities. They have provided the sponsor with an Elemental Risk Assessment which supports elimination of this testing. The specification includes a test for enantiomeric purity (NLT (b) (4)%) because the ephedrine sulfate manufactured by (b) (4) is predominantly the (-)-ephedrine sulfate. The non-USP methods were fully validated by (b) (4) and they have provided the reports to (b) (4) the drug product manufacturer. (b) (4) performed method verification which includes: system suitability, specificity, method precision, and results comparison to (b) (4) Certificate of Analysis. Representative batch analysis data is provided for the two batches used for registration and stability of the drug product. The data conforms to specification (assay NLT (b) (4)%. Total impurities NMT (b) (4)%, Chiral purity NLT (b) (4)%). The holder of DMF (b) (4) has established a (b) (4) month retest date for the drug substance based on currently available stability results included in the DMF.

### **List Submissions being assessed:**

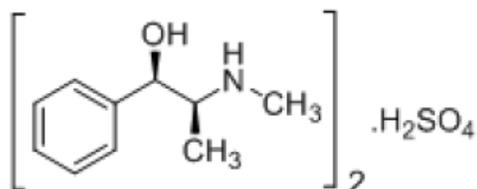
<b>Document(s) Assessed</b>	<b>Date Received</b>
Original SDN #01	December 18, 2019

**Highlight Key Issues from Last Cycle and Their Resolution: N.A.**

**Concise Description of Outstanding Issues: N.A.**

## S.1 GENERAL INFORMATION

Structure



Molecular Formula  $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$  Relative Molecular Mass 428.54

Ephedrine sulfate has two chiral centers and there are four possible isomers. The ephedrine sulfate manufactured by the DMF Holder (b) (4) is predominantly the (-)-ephedrine sulfate as indicated in the structural formula above.

Nomenclature:

rINN: Ephedrine sulfate

Chemical Name: Benzenemethanol,  $\alpha$ -[1-(methylamino) ethyl]-, [R-(R\*, S\*)]-, sulfate (2,1)(salt)

IUPAC: (1R,2S)-2-(Methylamino)-1-phenyl-1-propanol sulfate (2:1)

CAS: 134-72-5

### General Properties of Ephedrine Sulfate, USP

Physical/Chemical Properties	Description
Physical Description	Fine, white, odorless crystals or powder
Bulk Density	About 0.5 g/mL
Solubility <sup>a</sup>	Freely soluble in water, sparingly soluble in alcohol
Melting Point	245°C
Optical Rotation <sup>a</sup>	-30.5° to -32.5°
pKa <sup>b</sup>	13.89 and 9.52
Log p <sup>b</sup>	1.32
Polymorphism	Potential for forming polymorphs is not known for ephedrine sulfate manufactured at (b) (4). This has been studied by XRD and DSC.
Hygroscopicity	Not hygroscopic in nature (0.05% increase in mass at 25°C, 80% RH for 24 hours).
Isomerism	Ephedrine sulfate has two chiral centers and four possible isomers. The API manufactured by the DMF supplier is the <i>l</i> -isomer and is controlled (b) (4). The three other potential isomers are impurities; they are <i>d</i> -ephedrine sulfate, <i>l</i> -pseudoephedrine sulfate, and <i>d</i> -pseudoephedrine sulfate.

a Per USP definitions: Freely soluble 1-10 part solvent for 1 part solute; sparingly soluble 30 parts solvent for 1 part solute

b Reference: <https://www.drugbank.ca/salts/DBSALT001503>

**Assessment: Adequate**

For additional information regarding this section, reference is made to Type II DMF (b) (4). The sponsor has sufficient knowledge of the general properties and how they may impact the manufacture of the drug product.

**S.2 MANUFACTURE**



(b) (4)

**Assessment: Adequate**

For further details, reference DMF for this section of the NDA.

**S.3 CHARACTERIZATION**

Full details on confirmation of structure, scientific data for structure elucidation and characterization for ephedrine sulfate, USP have been provided in DMF (b) (4).

**Assessment: Adequate- Reference DMF (b) (4)**



(b) (4)

3 7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

## S.6 CONTAINER CLOSURE

(b) (4)

### **Assessment: Adequate**

Reference DMF (b) (4) for additional information on the packaging material.

## S.7 STABILITY

(b) (4) has established a (b) (4) month retest date for the drug substance based on currently available stability results included in the DMF.

### **Assessment: Adequate**

Reference DMF (b) (4) for this section of the NDA.

## R REGIONAL INFORMATION

Not Applicable: Comparability Protocols, Post-Approval Commitments,  
Lifecycle Management Considerations

## DRUG SUBSTANCE LIST OF DEFICIENCIES

None

*Primary Drug Substance Assessor Name and Date:*

Sharon Kelly, Ph.D. July 17, 2020

*Secondary Assessor Name and Date:*

Donna Christner, Ph.D. July 17, 2020

Branch Chief

DNDAPI Branch 2



Sharon  
Kelly

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Donna  
Christner

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# CHAPTER I: DRUG SUBSTANCE

<b>Drug Substance Name</b>	Ephedrine Sulfate
<b>NDA Number</b>	213994
<b>Assessment Cycle Number</b>	1
<b>DMF Number</b>	(b) (4)
<b>DMF Status</b>	<b>Adequate</b>
<b>Applicant Name</b>	Nevakar Inc.
<b>DMF Holder</b>	(b) (4)

Updated Specifications were provided on 08-SEPT-2020 in response to an IR request 03-SEPT-2020 from the clinical division. The API Specification is reproduced below. The acceptance criterion for enantiomeric purity is tightened.  
*Adequate.*

(b) (4) Acceptance Criteria for Ephedrine Sulfate, USP

Test Parameter	Acceptance Criteria	Analytical Method Reference
Description (Visual)	(b) (4)	NA
Solubility	(b) (4)	STA-ATX-0129
Identification tests	(b) (4)	
Infrared absorption	(b) (4)	USP monograph for Ephedrine Sulfate and USP<197K>
Sulfate	(b) (4)	USP monograph for Ephedrine Sulfate and USP<191>
Specific optical rotation	(b) (4)	USP monograph for Ephedrine Sulfate and USP<781S>
Acidity or alkalinity	(b) (4)	USP monograph for Ephedrine Sulfate
Loss on drying	(b) (4)	USP monograph for Ephedrine Sulfate and USP<731>
Residue on ignition	(b) (4)	USP monograph for Ephedrine Sulfate and USP<281>
Chloride	(b) (4)	USP monograph for Ephedrine Sulfate and USP<221>
Ordinary impurities	(b) (4)	USP monograph for Ephedrine Sulfate and USP<466>

Related Substances by HPLC	
(b) (4)	(b) (4)
Any unidentified impurity	STA-ATX-0129
Total Impurities	
Assay by HPLC (on anhydrous basis)	
Enantiomeric purity by HPLC	
Residual solvents by HSGC	
(b) (4)	(b) (4)
Endotoxin	TM.05239
Total aerobic microbial count	USP<85>
Total combined mods and yeast count	USP<61>

Sources: STA-ATX-0129; TM.05239

NA = not applicable; NMT = no more than; NLT = no less than

*Primary Drug Substance Assessor Name and Date:*

Sharon Kelly, Ph.D. Sept. 14, 2020

*Secondary Assessor Name and Date:*

Donna Christner, Ph.D. Sept. 14, 2020

Branch Chief

DNDAPI Branch 2



Sharon  
Kelly

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Donna  
Christner

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## CHAPTER II: DRUG PRODUCT

### [IQA NDA Assessment Guide Reference](#)

<b>Product Information</b>	
<b>NDA Number</b>	213994
<b>Assessment Cycle Number</b>	1
<b>Drug Product (DP) Name / Strength</b>	Ephedrine Sulfate Injection, USP 5 mg/mL
<b>Route of Administration</b>	intravenous administration
<b>Drug Product Manufacturer</b>	Nevakar, Inc. (Nevakar)
<b>RLD Information (Brand Name of Product, Applicant)</b>	Akovaz™ (ephedrine sulfate injection, USP)
<b>RLD/RS Number</b>	NDA208289
<b>Proposed Indication</b>	The treatment of clinically important hypotension occurring in the setting of anesthesia

#### **Assessment Recommendation: Adequate**

**Assessment Summary:** The drug product, Ephedrine Sulfate Injection, USP, 5 mg/mL, is a clear, colorless, sterile solution ready for intravenous administration. Each mL contains ephedrine sulfate USP 5 mg (equivalent to 3.8 mg ephedrine base), sodium chloride 9 mg, and sodium hydroxide and/or acetic acid for pH adjustment, if necessary. The pH range is 4.5 to 7.0. The product is filled into 10 mL glass vials with a (b) (4) Gray stopper and a 20 mm, aluminum, flip off seal.

In this NDA submission, Ephedrine Sulfate Injection, USP, 5 mg/mL is developed as a ready-to-use solution of ephedrine sulfate and is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia, same as the innovator Reference Listed Drug (RLD) Akovaz™ (ephedrine sulfate Injection, USP 50 mg/mL, NDA208289], which is diluted to a concentration of 5 mg/mL with normal saline or 5% dextrose solution prior to administration. Reducing this critical time in the preparation of the drug product can potentially reduce the stress on the health professionals by decreasing the possibility of dosing errors and the potential microbial contamination.

The sponsor has manufactured three (3) registration batches of drug product. All the excipients (Sodium chloride, sodium hydroxide and/or acetic acid) are USP grade. The quality of the drug product has been adequately controlled as per official USP monograph, USP General Chapters, ICH guidelines and internal data trends. The long term (25 ± 2°C/60 ± 5% RH) and accelerated (40 ± 2°C / 75 ± 5% RH) stability storage conditions as well as the photo stability and Freeze/Thaw stress stability studies justified a shelf-life of 24 months when the drug product is stored at the recommended storage condition of 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F).

The sponsor has performed adequate extractables and leachables studies to demonstrate the suitability of the primary packaging system.

In a word, the quality of the drug product Ephedrine Sulfate Injection, USP, 5 mg/mL in this NDA submission is acceptable from CMC perspectives.

**Comments:**

From the CMC perspective, the osmolality range for this product seems adequate. However, the PharmTox reviewer noted that the specification for osmolality differs from that of the B2 reference product (Akovaz). The Sponsor's response to Pharmtox's IR addressing the osmolality differences seems to have created a reliance on other products to which they didn't refer/bridge/patent certify as supporting a B2 application (T-con dated 08/25/2020) (*See details in PharmTox review*).

**List Submissions being assessment (table):**

<b>Document(s) Assessed</b>	<b>Date Received</b>
Original submission	12/18/2020
Responses to IR	05/01/2020
Responses to IR	08/21/2020
Responses to IR	08/25/2020
Responses to IR	08/27/2020

**Highlight Key Issues from Last Cycle and Their Resolution:**

N/A

**Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed):**

N/A

## P.1 DESCRIPTION AND COMPOSITION

### Component/Composition

The drug product, Ephedrine Sulfate Injection, USP is a clear, colorless, sterile solution filled into 10 mL glass vials for intravenous administration in the proposed 5 mg/mL strength. The composition of Ephedrine Sulfate Injection, USP 5 mg/mL is presented in the **Table 1** below.

*Start of applicant's materials*

**Table 1: Unit Composition of Ephedrine Sulfate Injection, USP 5 mg/mL**

Ingredient	% w/v	Quantity/mL	Quantity/vial (10 mL)	Pharmaceutical Function
Ephedrine sulfate, USP	0.5	5.0 mg	50.0 mg (equivalent to 38 mg of ephedrine base)	Active
Sodium chloride, USP	0.9	9.0 mg	90.0 mg	(b) (4)
(b) (4) Glacial acetic acid, USP	q.s. to adjust to pH 4.7	q.s. to adjust to pH 4.7	q.s. to adjust to pH 4.7	pH adjuster(s)
Sodium hydroxide, NF				(b) (4)
Water for Injection, USP	q.s. to 1.0 mL	q.s.	q.s. to 10 mL	Vehicle
<b>Total volume</b>	NA	1 mL	10.0 mL	NA

q.s. = quantity sufficient; NA = not applicable; NF = National Formulary; USP = United States Pharmacopoeia

*End of applicant's materials*

The primary container closure system for the proposed drug product is a 10 mL, USP, (b) (4) glass vial, with a (b) (4) stopper and a 20 mm, aluminum, flip off seal (*Section 3.2.P.7.*)

#### **Assessment: Adequate**

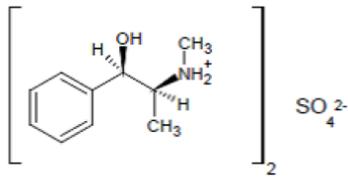
- The Sponsor has provided adequate information of the composition and the container closure system for the drug product.

• (b) (4)  
As per Agency's request dated August 21, 2020, the Sponsor has agreed to revise the name in the 08/25/2020 response.

## P.2 PHARMACEUTICAL DEVELOPMENT

### Overview

Ephedrine sulfate is an alpha and beta-adrenergic agonist and a norepinephrine releasing agent. The chemical name of ephedrine sulfate is benzene methanol,  $\alpha$ -[1-(methylamino)ethyl]-, [*R*-(*R*<sup>\*</sup>, *S*<sup>\*</sup>)]-, sulfate (2:1) (salt) and the molecular weight is 428.54 g/mol. It has the following structural formula:



The reference listed drug (RLD), Akovaz™ (NDA # 208289) is a clear, colorless, sterile solution for intravenous injection. Each mL contains ephedrine sulfate, 50 mg (equivalent to 38 mg ephedrine base) in water for injection. The pH is adjusted with sodium hydroxide and/or glacial acetic acid if necessary. The pH range is 4.5 to 7.0. To administer a bolus IV injection, it has to be diluted to a concentration of 5 mg/mL using 0.9% sodium chloride solution or 5% dextrose solution before administration.

In this NDA submission, Ephedrine Sulfate Injection, USP, 5 mg/mL is developed as a ready-to-use solution of ephedrine sulfate and is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia, same as the RLD. Reducing this critical time in the preparation of the drug product can potentially reduce the stress on the health professionals by decreasing the possibility of dosing errors and the potential microbial contamination.

The drug product is supplied in a 10 mL USP (b) (4) clear glass vial with a (b) (4) stopper and an aluminum seal (**Note:** (b) (4)

(b) (4) *As per Agency's request dated August 21, 2020, the Sponsor has agreed to revise the name in the 08/25/2020 response*). The recommended storage condition for the drug product is at 20°C to 25°C (68°F to 77°F), protected from light.

### 1.1.1. Development Summary

Development studies for Ephedrine Sulfate Injection, USP were carried out by Nevakar Inc., (Bridgewater, NJ). The drug substance for all the development activities was obtained from (b) (4)





**Assessment: Adequate**

- a. The primary container closure system for the proposed drug product is a 10 mL, USP, (b) (4) glass vial, with a (b) (4) Gray stopper and a 20 mm, aluminum, flip off seal. The secondary packaging system is the carton.
- b. (b) (4) *As per Agency's request dated August 21, 2020, the Sponsor has agreed to revise the name in the 08/25/2020 response.*
- c. Integrity testing Results indicate that the vial, stopper, and seal combination are qualified for use based on passing all specifications for integrity parameters.
- d. The Sponsor has performed photostability tests as per ICH Q1B to demonstrate the suitability of the primary and secondary packaging.
- e. The sponsor has performed adequate Extractables studies and Leachables studies for the (b) (4) Grey rubbery stopper, which has been used in many FDA approved products:
  - It is acceptable that the sponsor has only run extractables studies for the (b) (4) Gray rubber stopper since (b) (4) glass vial is chemically stable and the risk for leachables at neutral and acidic condition is very low.
  - The EXTRACTABLES STUDIES are acceptable in terms of the **pH range and polarity of the solvents** (b) (4) (b) (4) (b) (4) ).
  - The LEACHABLE STUDIES are adequate in terms of **AET** (considering SCT, MDD and 50% uncertainty factor), the **batch selection** (3 registration batches), the **time points** [0, 3, 6, 12, 18 (24 and 36 on going) at the long-term storage conditions of 25°C/60% RH and for 6 months at the accelerated storage conditions of 40°C/75%RH], **verified methods** with adequate *system suitability, Method precision / accuracy /repeatability, Range, Specificity and sufficient sensitivity (LOD/LOQ < AET).*

- No organic leachables above AET were detected, and thus E/L correlation cannot be established. (b) (4) were reportable at several time points and conditions. None of the elements listed in the USP General Chapter <232> were reportable.
- The stopper vendor (b) (4) certified that Sponsor that PAHs, nitrosamines, and 2-mercaptobenzothiazole **have not been intentionally** added to the process. The sponsor claimed that the analytical methods are sensitive enough to detect PAHs, nitrosamines, and 2-mercaptobenzothiazole and these high risky leachables are not present in the drug product (STUQL20AA0510-2) (Response dated May 1, 2020). *PharmTox reviewer Dr. Newton Woo has confirmed that the AETs/SCTs for PAHs, nitrosamines, and 2-mercaptobenzothiazole are acceptable (Email dated August 27, 2020).*

## P.8 STABILITY

### 1.1. Routine Stability Studies:

**Latest specification** being assessed: Submitted in eCTD #010 dated 21082020

Test	Acceptance Criteria	Method
Appearance	Clear, colorless solution essentially free of visible particles	Visual
pH of solution	4.5 – 7.0	USP <791>
Assay of Ephedrine Sulfate	(b) (4)	HPLC-UV
Related Substances	(b) (4)	HPLC-UV
	Any Individual Impurity	
	Total Impurities	
Particulate Matter (Sub visible)	≥ 10µm	USP <788>
	≥ 25µm	
Osmolality	(b) (4)	USP <785>
Sterility	(b) (4)	USP <71>
Bacterial Endotoxins	(b) (4)	USP <85>

(b) (4)

NMT = not more than; NA = not applicable; USP = United States Pharmacopoeia; HPLC = High Performance Liquid Chromatography; IR = infrared

### Protocol and batch selection

Registration Batch #	Orientation	Condition
NEA001	invert and upright	<ul style="list-style-type: none"> <li>Accelerated storage condition 40°C ± 2°C, 25 % RH at 0, 1, 3 and 6 months</li> <li>Long-term storage condition: 25°C ± 2°C, 40 % ± 5 % RH at 0, 3, 6, 9, 12, 18, 24 and 36 months</li> </ul>
NEA002		
NEA003		

## 1.2. One-Time Stability Studies

A Photostability Study (Protocol # (b) (4)-PRT-2548), Shipping Study (Protocol # TP-14129-00-090619-PD01), and Freeze Thaw Study (Thermal Cycling) (Protocol # (b) (4)-PRT-2550) Stability Study were performed as one-time supporting studies for their respective purpose.

## 1.3. Proposed Shelf Life Period at Labeled Storage Condition

The available stability data the long term ( $25 \pm 2^{\circ}\text{C} / 60 \pm 5\% \text{RH}$ ) and accelerated ( $40 \pm 2^{\circ}\text{C} / 75 \pm 5\% \text{RH}$ ) stability storage conditions support the proposed storage statement in the draft label for a **24-month** shelf life.

## 1.4. Stability Data Discussion

**Route stability studies** for the three registration batches stored in *inverted and upright* orientations conform to all specifications through 12-month storage at  $25 \pm 2^{\circ}\text{C} / 60 \pm 5\% \text{RH}$  and 6-month storage at  $40 \pm 2^{\circ}\text{C} / 75 \pm 5\% \text{RH}$ . No significant detectable changes were observed at any of the storage conditions for assay and/or impurity profile of the batches tested up to the respective timepoints at either storage condition. Stability samples are randomly pulled from a batch. The proposed acceptance range is the standard acceptance range for injectables based on USP <788>.

The batches undergoing the additional testing for chiral impurities at the 9-month and 12-month timepoints have shown **no changes in chirality**.

The data in **Table 3 to 14** in P.8.3 were summarized by reviewer in the following table below for better visualization.

**Summary of the stability results (Table 3 to Table 14) by Reviewer:**

Test	Specification	Batch # NEA001				Batch # NEA002				Batch # NEA003			
		Accelerated 0, 1, 3 & 6 M		Long term 0, 3, 6, 9 & 12 M		Accelerated 0, 1, 3 & 6 M		Long term 0, 3, 6, 9 & 12 M		Accelerated 0, 1, 3 & 6 M		Long term 0, 3, 6, 9 & 12 M	
		Inverted	Upright	Inverted	Upright	Inverted	Upright	Inverted	Upright	Inverted	Upright	Inverted	Upright
<b>Orientation</b>													
<b>Appearance</b>	Clear, colorless solution essentially free from visible particles	meet	meet	meet	meet	meet	meet	meet	meet	meet	meet	meet	meet
<b>pH</b>	4.5 to 7.0	5.1-5.4	5.1-5.4	4.9-5.1	5.0-5.1	4.9-5.1	4.9-5.2	4.9-5.0	4.9-5.2	4.9-5.2	4.9-5.3	4.9-5.2	4.9-5.1
<b>Osmolality</b>	(b) (4)	313-314	313	313-316	312-321	311-315	311-314	313-314	312-314	312-314	313-314	312-314	313-314
<b>Assay by HPLC</b>		100.2-100.9	100.0-100.9	100.0-101.0	103.0-101.1	100.6-101.1	100.3-100.7	97.9-101.0	97.9-100.8	100.3-100.6	100.3-100.8	99.3-100.7	98.5-100.7
<b>Related Substance By HPLC</b>		0.0	0.0	0-ND	0-ND	0	0	0-ND	0-ND	0	0	0	0-ND
		ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
		ND	ND	ND	ND	ND	ND	ND	ND	ND	0-ND	ND	ND
		0-ND	0-ND	0-ND	0-ND	0-ND	0-ND	0-ND	0-ND	0-ND	0-ND	0-ND	0-ND
	<b>Total Impurities: Report results</b>	0	0	0-ND	0-ND	0	0	0-ND	0-ND	0	0-ND	0-ND	0-ND
<b>Particulate matter</b>	NMT (b) (4) per container: ≥ 10µm	12-732	13-732	8-732	4-732	8-96	9-96	8-96	2-96	8-331	54-331	8-331	1-331
	NMT (b) (4) per container: ≥ 25µm	0-2	0-3	0-2	0-2	0	0-1	0	0-1	0-1	0-1	0-1	0-1
<b>Sterility</b>	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
<b>Bacterial Endotoxins</b>	(b) (4)	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6	<0.6
<b>Chiral Assay (HPLC)</b>	d-Ephedrine: Report results			0.0% - <LOQ <sup>a</sup>	0.0% - <LOQ <sup>a</sup>			0.0% - <LOQ <sup>a</sup>	0.0% - <LOQ <sup>a</sup>			0.0% - <LOQ <sup>a</sup>	0.0% - <LOQ <sup>a</sup>
	l-Pseudoephedrine: Report results			<LOQ <sup>a</sup>	0.0% - <LOQ <sup>a</sup>			<LOQ <sup>a</sup>	<LOQ <sup>a</sup>			ND- <LOQ <sup>a</sup>	ND- <LOQ <sup>a</sup>
	d-Pseudoephedrine: Report results			<LOQ <sup>a</sup>	0.0% - <LOQ <sup>a</sup>			<LOQ <sup>a</sup>	<LOQ <sup>a</sup>			ND- <LOQ <sup>a</sup>	ND- <LOQ <sup>a</sup>

**Summary of Photo stability studies (Table 15, 16 and 17) by reviewer:**

Test	Specification	NEA001			NEA002			NEA003		
		Fully Exposed Sample	Dark Control Sample	Commercial Packaging Condition	Fully Exposed Sample	Dark Control Sample	Commercial Packaging Condition	Fully Exposed Sample	Dark Control Sample	Commercial Packaging Condition
Appearance	Clear, colorless solution essentially free from visible particles									
pH	4.5 to 7.0	5.0	5.1	5.1	5.0	4.9	5.1	5.1	5.0	5.1
Assay by HPLC	(b) (4)									
Related Substance By HPLC		100.3	103.7	101.8	100.5	101.8	101.8	100.3	101.1	103.3
		0	0	0	0	0	0	0	0	0
		ND	ND	ND	ND	ND	ND	ND	ND	ND
		ND	ND	ND	ND	ND	ND	ND	ND	ND
		0	0	0	0	0	0	0	0	0
	<b>Total Impurities:</b> Report results	0	0	0	0	0	0	0	0	0
Particulate matter	NMT (b) (4) per container: $\geq 10\mu\text{m}$	8	11	11	16	0	4	1	1	6
	NMT (b) (4) per container: $\geq 25\mu\text{m}$	0	0	0	13	0	0	0	0	0

## One-time stress tests: Photostability and Freeze Thaw studies

Photostability and Freeze/Thaw Testing for NEA001/NEA002/NEA003 Samples) show the drug product in the immediate pack vials can be stored at the proposed long-term storage condition protected from light.

### a. Photostability( (b) (4)-PRT-2548):

The photostability exposure was performed by (b) (4). All three lots (NEA001, NEA002, and NEA003) were exposed using ICH guidelines for the photostability study. The samples were exposed in a photostability chamber to light providing an overall illumination of NLT (b) (4) lux hours and an integrated near ultraviolet energy of NLT (b) (4) watt-hours/square meter. (b) (4) photostability radiant exposure report is attached to this report as Attachment A. Refer to Table below for sample conditions.

Lot Numbers	Fully Exposed Condition	Dark Control (Aluminum Foil)	Marketing Pack Condition
NEA001	20 vials	20 vials	20 vials
NEA002	20 vials	20 vials	20 vials
NEA003	20 vials	20 vials	20 vials

Ephedrine Sulfate Injection (5 mg/mL, 10 mL) will be exposed in a photostability chamber to light providing an overall illumination of NLT (b) (4) lux hours and an integrated near ultraviolet energy of NLT (b) (4) watt hours/square meter.

### Results:

The photostability data were provided in **Table 15, 16 and 17** in P.8.3 and were summarized by reviewer in the table above for better visualization. The results show that the drug product is not sensitive to light in terms of assay, impurities, pH and Particulate Matter.

### Conclusion:

The results show that the drug product in the immediate pack vials can be stored at the proposed long-term storage condition protected from light.

### b. Freeze/Thaw Stressing

The samples were placed in a freezer (-20°C) for 24 hours followed by thawing at 40°C for 24 hours (this is considered one cycle of temperature excursion). Three cycles of freeze-thaw were performed. Refer to the table below for sample conditions.

Cycle	Lower Temperature Extreme	Higher Temperature Extreme
First Cycle	24 H @ -20°C	24 H @ 40°C
Second Cycle	24 H @ -20°C	24 H @ 40°C
Third Cycle	24 H @ -20°C	24 H @ 40°C

c. The results in the **table18** below show that the Freeze/Thaw Stressing has no impacts on the attributes for the drug product in terms of assay, impurities,

pH and Particulate Matter.

Start of applicant's materials

**Table 18: NEA002 Freeze Thaw Results**

Test	Specification	Freeze Thaw Sample	Control Sample
Appearance	Clear, colorless solution essentially free from visible particles	Clear, colorless solution essentially free from visible particles	Clear, colorless solution essentially free from visible particles
pH	4.5 to 7.0	5.0	4.9
Ephedrine Sulfate Assay	(b) (4)	102.4%	101.8%
(b) (4)	Report results	0.0%	0.0%
(b) (4)	Report results	ND	ND
(b) (4)	Report results	ND	ND
Any Unspecified Impurities	NMT (b) (4) % each	0.0%	0.0%
Total Impurities	Report results	0.0%	0.0%
Particulate Matter	NMT (b) (4) per container: $\geq 10 \mu\text{m}$	5	0
	NMT (b) (4) per container: $\geq 25 \mu\text{m}$	0	0

End of applicant's materials

**Assessment: Adequate**

- The stability specifications are in line with the release specification in appearance, assay, related substances, pH, particulate matter, sterility and bacterial endotoxins.
- Three (3) registration batches with both *inverted and upright* orientations have been selected for Stability studies as per ICH guidelines under long-term [ $25^\circ \pm 2^\circ\text{C}/60\% \pm 5\% \text{RH}$ ] and accelerated conditions [ $40^\circ \pm 2^\circ\text{C}/75\% \pm 5\% \text{RH}$ ]. The results of 6 months accelerate stability studies and 12 months long term stability studies met the pre-determined specification, and thus the proposed 24 month of shelf life is justified.
- The sponsor has performed one-time stressed tests including Photostability and Freeze Thaw studies. The results show the drug product in the immediate pack vials can be stored at the proposed long-term storage condition protected from light.
- *The sponsor has committed to including 'Container Content for Injections' test per USP <697> in the stability program to ensure that there isn't any evaporation of the solution during stability in the response dated August 27, 2020. See postapproval commitments below.*

- *There are OOTs for the Particulate Matter.* (b) (4)  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

*Response to Agency's request dated August 26, 2020, the Sponsor has committed to investigate the root cause of the variability of the particulate matter in the response dated*

August 27, 2020. See postapproval commitments below.

## Post-Approval Stability Protocol and Commitment

The sponsor, Nevakar, Inc., hereby commits:

- a. that the first three (3) commercial batches of Ephedrine Sulfate Injection, USP will be placed on stability and tested accordingly to the stability protocol provided in Section 3.2.P.8.1.
- b. to place one lot of Ephedrine Sulfate Injection, USP in the commercial package into stability every year. Stability studies will be reported as they become available (e.g. in Annual Report) or as specified by the Agency.
- c. If any lots are found outside the approved specifications in post approval stability studies, the out of specification will be communicated as appropriate to FDA under 21 CFR 314.81(b) (1)(ii). Deviations that do not affect the safety and efficacy of the product will be promptly discussed between the applicant and reviewing division and reported to the FDA. The Agency will be immediately informed if there are any significant problems identified to the extent that the shelf life would be affected.

In addition, in the response to Agency's request dated August 27, 2020, the Sponsor has committed to:

- a. evaluating the existing method design and qualification for the method for testing the particulate matter. If method modification is required to ensure consistency of data, Nevakar commits to supplemental verification/validation activities, as warranted. If the existing methodology and qualification are deemed sufficient without additional work, an appropriate justification will be provided.
- b. including 'Container Content for Injections' test per USP <697> in the stability program to ensure that there isn't any evaporation of the solution during stability.

### Assessment: Adequate

- Sponsor adequately provided Post-Approval Stability Protocol and Stability Commitment.

## R REGIONAL INFORMATION

### Environmental

The anticipated amount of Ephedrine Sulfate drug substance used in the fifth year of marketing for manufacture of drug product for human use will be about (b) (4) corresponding to an Expected Introduction Concentration (EIC) into the aquatic environment as follows:

(b) (4)

This level is about two orders of magnitude below the threshold level of 1 ppb established in

21CFR §25.31(b). In accordance with §25.15(a), the applicant hereby states compliance with the categorical exclusion criteria as noted in the previous bullet and is not aware of any extraordinary circumstances that exist with the use of his drug product in the context of this submission.

**Assessment: Adequate**

The sponsor has demonstrated that EIC into the aquatic environment is two orders of magnitude below the threshold level of 1 ppb established in 21CFR §25.31(b), which justifies the compliance with the categorical exclusion criteria.

**Methods Validation or Verification Package**

**Assessment: Adequate**

**Comparability Protocols**

N/A

**Assessment: N/A**

**Post-Approval Commitments**

**Assessment: Adequate**

**Lifecycle Management Considerations**

N/A

**DRUG PRODUCT LIST OF DEFICIENCIES**

N/A

*Primary Drug Product Assessor Name and Date: Jizhou Wang, PhD, 8/23/2020*

*Secondary Assessor Name and Date (and Secondary Summary, as needed):  
Julia Pinto, PhD, 08/28/2020*

# CHAPTER III: ENVIRONMENTAL

[IQA NDA Assessment Guide Reference](#)

## R REGIONAL INFORMATION

Environmental

**Assessment: {Adequate/Inadequate}**

*Primary Environmental Assessor Name and Date:*

*Secondary Assessor Name and Date (and Secondary Summary, as needed):*

# CHAPTER IV: LABELING

## [IQA NDA Assessment Guide Reference](#)

### 1.0 PRESCRIBING INFORMATION

#### Assessment of Product Quality Related Aspects of the Prescribing Information:

#### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
<b>Product Title in Highlights</b>		
Proprietary name	<b>Not provided</b>	<b>Not provided</b>
Established name(s)	EPHEDRINE SULFATE INJECTION	Adequate
Route(s) of administration	<b>intravenous</b>	
<b>Dosage Forms and Strengths Heading in Highlights</b>		
Summary of the dosage form(s) and strength(s) in metric system.	5 mg/mL ephedrine sulfate in a ready-to-use, single-dose, 10 mL vial (50 mg/10 mL)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	single-dose	Adequate

### 1.2 FULL PRESCRIBING INFORMATION

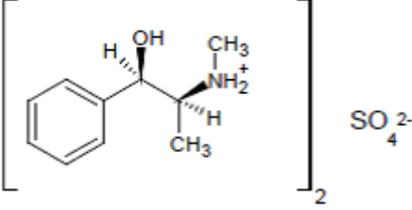
#### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
<b>DOSAGE AND ADMINISTRATION section</b>		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	ready-to-use	Adequate

### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
<b>DOSAGE FORMS AND STRENGTHS section</b>		
Available dosage form(s)	Injection	Adequate
Strength(s) in metric system	5 mg/mL ephedrine sulfate	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not applicable. The salt name follows RLD	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	5 mg/mL ephedrine sulfate in a ready-to-use, single-dose, 10 mL vial (50 mg/10 mL). Bolus intravenous injection: 5 to 10 mg (equivalent to 3.8 to 7.6 mg ephedrine base) as needed, not to exceed 50 mg.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate

### 1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
<b>DESCRIPTION section</b>		
Proprietary and established name(s)	Ephedrine sulfate	Adequate
Dosage form(s) and route(s) of administration	a clear, colorless, sterile, ready-to-use solution for intravenous injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not applicable. The salt name follows RLD	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	sodium chloride, and sodium hydroxide and/or acetic acid for pH adjustment, if necessary	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Each mL contains ephedrine sulfate USP 5 mg (equivalent to 3.8 mg ephedrine base), sodium chloride 9 mg, and sodium hydroxide and/or acetic acid for pH adjustment, if necessary. The pH range is 4.5 to 7.0	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	Yes	Adequate
Pharmacological/therapeutic class	an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent	Adequate
Chemical name, structural formula, molecular weight	 <p>(1R,2S)-(-)-2-methylamine-1-phenylpropan-1-ol sulfate, Molecular weight: 428.5 g/mol.</p>	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	The pH range is 4.5 to 7.0.	Adequate

**Section 11 (DESCRIPTION) Continued**

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	N/A

#### 1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
<b>HOW SUPPLIED/STORAGE AND HANDLING section</b>		
Available dosage form(s)	Injection	Adequate
Strength(s) in metric system	5 mg/mL	Adequate
Available units (e.g., bottles of 100 tablets)	10 mL clear glass vial; for single use (supplied in packages of 50)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single use	Adequate

#### Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store in carton until time of use. For single use only. Discard unused portion.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and	N/A	Adequate

desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store Ephedrine Sulfate Injection, USP 5 mg/mL at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in carton until time of use	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Vial stoppers are not manufactured with natural rubber latex	Adequate
Include information about child-resistant packaging	N/A	N/A

### 1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

### 1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
<b>Manufacturing Information After Section 17</b>		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Par Pharmaceutical Companies, Inc. Chestnut Ridge, NY 10977	Adequate

## 2.0 PATIENT LABELING

**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):**

***Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."***

### **3.0 CARTON AND CONTAINER LABELING**

#### **3.1 Container Label**

*(Copy/paste or refer to a representative example of a proposed container)*



#### **3.2 Carton Labeling**

*(Copy/paste or refer to a representative example of a proposed carton labeling)*

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS)  
immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	EPHEDRINE SULFATE INJECTION	Adequate
Dosage strength	5 mg/mL	Adequate
Route of administration	Intravenous injection	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not provided	Inadequate
Net contents (e.g. tablet count)	Provided (10 single vial)	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Yes	Adequate
Lot number and expiration date	Yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Yes (single-dose)	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	Adequate
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap over seal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	N/A	N/A

**Assessment of Carton and Container Labeling: *Inadequate***

***Any deficiencies should be listed at the end in the “ITEMS FOR ADDITIONAL ASSESSMENT.”***

**ITEMS FOR ADDITIONAL ASSESSMENT**

- a. Delete USP from the name on the labels of the container and carton;
- b. Include the salt equivalency statement on the side of the labels of the container and carton;
- c. “Ephedrine Sulfate” should be on one line on the labels of the container and carton for prominence.

**Overall Assessment and Recommendation:**

*Primary Labeling Assessor Name and Date:*

*Secondary Assessor Name and Date (and Secondary Summary, as needed)*

APPEARS THIS WAY ON ORIGINAL



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Wang

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Julia  
Pinto

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## MANUFACTURING INTEGRATED ASSESSMENT

<b>Application ID</b>	NDA 213994
<b>Drug Product Name</b>	Ephedrine Sulfate Injection, USP
<b>Strengths</b>	5 mg/mL
<b>Dosage Form</b>	Injection
<b>Administration Route</b>	intravenous
<b>Indication</b>	Treatment of clinically important hypotension occurring in the setting of anesthesia
<b>Applicant Name</b>	Nevakar, Inc.

### I. Manufacturing Summary

**Facility Assessment Recommendation: Adequate**

**Process Assessment Recommendation: Adequate**

**Assessment Summary:** The drug product, Ephedrine Sulfate Injection, USP is a clear, colorless, sterile solution filled into 10 mL glass vials for intravenous (IV) administration. The manufacturing process consists of (b) (4)

. The drug product is supplied in a 10 mL USP (b) (4) clear glass vial with a (b) (4) stopper and an aluminum seal. The recommended storage condition for the drug product is at 20°C to 25°C (68°F to 77°F), protected from light. The drug product manufacturer is acceptable after PAI. All other facilities are acceptable.

**List Submissions being assessed (Table):**

Document Description (SD #)	Date Received
0001	12/23/2016- New NDA
0004	01/17/2020- Resubmission after RTR
0006	06/03/20- Quality/Response to IR

**Highlight Key Issues from Last Cycle and Their Resolution: N/A- First Review**

**Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None**

#### 1. Post-Approval Commitments and Lifecycle Management Considerations

<b>Postmarketing commitments (PMC)?</b>	No
<b>Post-approval inspection?</b>	No
<b>Lifecycle considerations</b>	No

**V. List of Outstanding Information Request/Deficiencies:**

Outstanding Deficiencies Collation Table
N/A

**VI. Signature Block**

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	C. Abellard	J. Wang	5/5/2020	IR	TBD
2	C. Abellard	J. Wang	6/3/2020	Adequate	Approve
Choose an item.			Click to enter a date.	Choose an item.	Choose an item.



Joanne  
Wang

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Cassandra  
Abellard

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**BIOPHARMACEUTICS ASSESSMENT**

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**Application No.:** NDA 213994**Submission Type:** 505(b)(2)**PDUFA Goal Date:** 10/18/2020**Drug Product Name / Strength:** Ephedrine sulfate Injection, USP/ 5 mg/mL**Dosage Form:** Injection**Route of Administration:** Intravenous Injection**Indication:** The treatment of clinically important hypotension in the setting of anesthesia**Applicant:** Nevakar, Inc**Conclusion/Recommendation:** Adequate

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**REVIEW SUMMARY**

The Listed Drug (LD) for this NDA is Akovaz<sup>®</sup> (ephedrine sulfate injection, USP) under NDA 208289 (approved in April 2016). Akovaz<sup>®</sup> is approved as a 50 mg/mL solution in a 1 mL glass vial and must be diluted to a final concentration of 5 mg/mL in either 0.9% sodium chloride or 5% dextrose before administration. Nevakar's ephedrine sulfate injection USP, 5 mg/mL is a ready-to-use formulation that does not require pre-dilution before administration. The concentration of Nevakar's product is the same as the final concentration (after dilution) of the LD product, Akovaz<sup>®</sup>. The comparison of the LD product and Nevakar's proposed drug product is shown in **Table 1**.

In the pre-IND (PIND) 138870 meeting package dated May 30, 2018 and the Agency's response dated August 1, 2018, the plan for the waiver of in vivo bioequivalent (BE) study for the proposed drug product was discussed. The Agency determined that the a biowaiver request per CFR 320.22(b)(1) may be possible, provided following information was submitted: 1) side-by-side comparative table of the proposed drug product formulation and the reference drug product formulation (undiluted and diluted); 2) scientific justification that the different formulation (if this is the case) will not change the bioavailability of the drug compared to the reference product; 3) comparative physiochemical property data, such as pH and osmolarity of the proposed drug product formulation and the reference drug product formulation (after dilution).<sup>1</sup> In this NDA submission, Nevakar submitted the information based on Agency's response dated August 1, 2018, to support a biowaiver request for the proposed product. Biopharmaceutics assessment is focused on the biowaiver request.

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<sup>1</sup> <\\cdsesub1\evsprod\nda213994\0001\m1\us\16-meetings\pind-type-b-fda-written-response-ref-id-4300176-01-aug-2018.pdf>

**Table 1.** Comparison of composition of the LD product Akovaz<sup>®</sup> (before and after dilution) and Nevakar’s proposed drug product

Ingredient	Quantity (mg/mL)		
	Akovaz (Undiluted)	Akovaz Diluted to 5 mg/mL with 0.9% Sodium Chloride Injection <sup>a</sup>	Nevakar’s Ephedrine Sulfate Injection, USP 5 mg/mL
Ephedrine Sulfate, USP	50.0	5.0	5.0
Sodium Chloride, USP	--	~8.1 <sup>b</sup>	9.0
Glacial Acetic Acid, USP	q.s. to pH 4.5-7.0	q.s. <sup>c</sup>	q.s. to pH 4.7
Sodium Hydroxide, NF	q.s. to pH 4.5-7.0	q.s.c	q.s. to pH 4.7
Water for Injection, USP	q.s.	q.s.	q.s.

NF = National Formulary; q.s. = quantity sufficient; USP = United States Pharmacopeia

<sup>a</sup> Akovaz may also be diluted with 5% Dextrose Injection.

<sup>b</sup> Calculated based on dosage and administration instructions for Akovaz for the preparation of a 5 mg/mL solution for bolus intravenous administration, which state: withdraw 50 mg (1 mL of 50 mg/mL) of AKOVAZ (ephedrine sulfate injection) and dilute with 9 mL of 0.9% Sodium Chloride Injection (Akovaz PI, August 2018). Each 100 mL of 0.9% Sodium Chloride Injection, USP contains 900 mg sodium chloride in water for injection.

<sup>c</sup> Controlled to pH 4.5-7.0 prior to dilution step.

**Biowaiver Request**

The formulation of the proposed drug product and the post-dilution LD is similar, except a small difference in the amount of sodium chloride, which is not expected to affect the bioavailability of the proposed drug product. The provided physicochemical comparison data showed similarity in pH and osmolality between the post-dilution LD and the proposed drug product. Per CFR 320.24(b)(6), A biobridge between the LD (Akovaz, N 208289) and proposed drug product has been established.

**Biopharmaceutics Review Recommendation: Adequate**

From a biopharmaceutics perspective, NDA 213394 is recommended for APPROVAL.

**Signatures**

**Primary Biopharmaceutics Reviewer**

Jia Yin, Ph.D.  
 Division of Biopharmaceutics  
 Office of New Drug Products, OPQ

**Secondary Biopharmaceutics Reviewer**

Hansong Chen, PharmD, Ph.D.  
 Division of Biopharmaceutics  
 Office of New Drug Products, OPQ

APPEARS THIS WAY ON ORIGINAL

**BIOPHARMACEUTICS ASSESSMENT**

**List Submissions Being Reviewed**

Received Date	Submission
12/18/2019	Original submission
6/5/2020	Response to Biopharmaceutics IR

**Biowaiver Request**

**Reviewer’s Assessment:**

The proposed drug product is a parental solution intended for intravenous injection. The main difference between the proposed drug product and the LD is the concentration of the API (ephedrine sulfate), as the LD (50 mg/mL) requires dilution before administration while the proposed drug product (5 mg/mL) is ready to use. Based on the Agency’s response to the meeting package submitted on 5/30/2018 regarding the biowaiver plan, the Applicant submitted data to show that the formulation of the proposed drug product and the post-dilution LD is similar, except a small difference in the amount of sodium chloride, which is not expected to affect the bioavailability of the proposed drug product. The Applicant also provided physicochemical comparison between the post-dilution LD (3 commercial lots) and the proposed drug product (3 exhibit lots). The data showed similar pH and osmolality between the proposed product and the post-dilution LD. The biowaiver request can be granted.

Following the Agency’s response (dated August 1, 2018) to the meeting package submitted on May 30, 2018, Nevakar submitted a biowaiver request and the supporting data. The side-by-side comparison of formulation between the LD and the proposed drug product is shown in **Table 1**. As shown, the formulation of the proposed product and the post-dilution LD is similar, except slightly different amount of sodium chloride. According to the Applicant, the inactive ingredients such as sodium chloride, sodium hydroxide, and glacial acetic acid are only for controlling tonicity and pH. Therefore, the Applicant does not anticipate that the small differences in these excipients have significant effect on the bioavailability of its drug product .

The Applicant also submitted comparative physicochemical property data (pH and osmolality) for the proposed drug product and the LD (after dilution) (**Table 2**). However, according to the Agency’s response (dated August 1, 2018) to the meeting package submitted on May 30, 2018, the Applicant was recommended to submit comparative physicochemical data using at least 3 product lots of the proposed drug product and 3 commercial lots of the LD. As shown in **Table 2**, data from only 2 commercial lots of the LD were provided. The Applicant was requested to submit physicochemical property data for one more commercial lot of the LD for comparison in an Information Request (IR)

dated 5/8/2020 (**Appendix 1**). In addition, since the LD can be diluted in both 0.9% sodium chloride and 5% dextrose before administration, the Applicant was also asked to provide comparative physicochemical data (pH and osmolality) of the proposed drug product and the reference drug product after dilution in 5% dextrose.

**Table 2.** Physicochemical comparison (pH and osmolality) for the proposed product (Ephedrine Sulfate Injection, USP 5 mg/mL) and the LD Akovaz<sup>®</sup> (after dilution)

Test <sup>a</sup>	Specification for Ephedrine Sulfate Injection, USP 5 mg/mL	Ephedrine Sulfate Injection, USP 5 mg/mL			Akovaz (Diluted to 5 mg/mL with Saline)	
		NEA001	NEA002	NEA003	Lot 833055	Lot 00084A
pH	4.5-7.0	5.1-5.2	4.9-5.0	4.8-4.9	5.21-5.32	5.31-5.35
Osmolality (mOsm/kg)	(b) (4)	312-314	313-315	313-314	303-304	302-304

Source: [Module 3.2.P.5.4, Table 2](#) (data for Ephedrine Sulfate Injection USP, 5 mg/mL); [Ephedrine Sulfate Injection, USP 5 mg/mL Pharmaceutical Development Report, Table 10](#) (data for Akovaz)

<sup>a</sup> Tests performed in triplicate. Results reported as range.

In response to the IR dated 5/8/2020, the Applicant provided the requested data (**Table 3**). As shown, the pH of the LD after dilution ranges from 5.1 to 6.0 (pH after dilution in 0.9% sodium chloride 5.2 – 6.0; pH after dilution in 5% dextrose 5.1 – 5.2). In comparison, the pH of the proposed drug product ranges from 4.8 – 5.2. The pH of the proposed product and post-dilution LD is considered similar.

The osmolality of the post-dilution LD ranges from 266 to 304 mOsm/kg (osmolality after dilution in 0.9% sodium chloride 285 – 304 mOsm/kg; osmolality after dilution in 5% dextrose 266 – 270 mOsm/kg). In comparison, the osmolality of the proposed drug product ranges from 312 – 315 mOsm/kg. As the proposed drug product is manufactured in sodium chloride solution for ready-to-use, the comparison of osmolality between the proposed drug and LD diluted with 0.9% sodium chloride is more relevant. Although the proposed drug has slightly higher osmolality than the diluted LD, the difference is not expected to bring any additional safety issue.

Overall, the physicochemical properties of the proposed drug product and the post-dilution LD (in sodium chloride) are comparable.

**Table 3.** Physicochemical property comparison (pH and osmolality) for the proposed drug product (Ephedrine Sulfate Injection, USP 5 mg/mL) and the LD Akovaz<sup>®</sup> (after dilution)

Akovaz <sup>™</sup> , Ephedrine Sulfate Injection, 50 mg/mL Manufacturer: Avadel Legacy Pharmaceuticals, LLC					
Sample	Test	Lot: 833055 Expiry: 08/2020	Lot: 00084A Expiry: 01/2021	Lot: 943014 Expiry: 10/2022	
Akovaz <sup>™</sup> (No Dilution)	pH	5.90	5.67	5.78	
		NT	NT		5.84
					5.83
	Osmolality (mOsm/kg)	314	312	316	
		315	312	315	
		319	311	316	
Akovaz <sup>™</sup> diluted to 5 mg/mL with 5% Dextrose	pH	5.1	5.2	5.1	
		5.1	5.2	5.1	
		5.0	5.2	5.1	
	Osmolality (mOsm/kg)	269	268	269	
		266	268	269	
		268	270	269	
Akovaz <sup>™</sup> diluted to 5 mg/mL with 0.9 % Sodium Chloride Injection	pH	5.2	5.3	6.0	
		5.3	5.3	5.9	
		5.3	5.3	6.0	
	Osmolality (mOsm/kg)	303	304	285	
		304	302	285	
		304	303	286	
Nevakar's Ephedrine Sulfate Injection USP, 5 mg/mL					
Sample	Test	Lot # NEA001	Lot # NEA002	Lot # NEA003	
Nevakar's Ephedrine Sulfate Injection USP, 5 mg/mL	pH	Beginning	5.1	4.9	4.9
		Middle	5.2	5.0	4.9
		End	5.1	4.9	4.8
	Osmolality (mOsm/kg)	Beginning	312	315	313
		Middle	314	313	313
		End	312	314	314
NT- Not Tested References: : ATR-P2770-TPML-19-970 and -971, ATR-P2770-TPML-20-970 & 971, 20-453-1, ATR-P2770-TPML-20-453-1, and Section 3.2.P.5.4 (Original NDA 213994)					

**Conclusion**

A biobridge between the LD (Akovaz, N 208289) and proposed drug product has been established under 21 CFR 320.24(b)(6) due to the following reasons:

- 1) Both the LD and proposed drug product are for intravenous injection.
- 2) The proposed drug product contains the same concentration of active ingredient as the diluted LD. Although the diluted LD and proposed drug product have slightly different concentrations of inactive ingredient, the disposition of the drug following intravenous injection of solution is not expected to be affected by this difference.
- 3) The proposed drug product and LD have comparable physicochemical properties including osmolality and pH.

**APPENDIX 1**  
**Biopharmaceutics Information Requests (IRs)**

**IR dated 5/8/2020 and Response received 6/5/2020<sup>2</sup>**

**IR**

1. We acknowledge that you have provided comparative physicochemical property data (pH and osmolarity) of 3 registration batches of the proposed drug product and 2 commercial batches of the reference drug product (after dilution in saline). As the reference product can be diluted in either 0.9% sodium chloride or 5% dextrose before administration, please provide comparative physicochemical property data (pH and osmolarity) of the proposed drug product and the reference drug product after dilution in 5% dextrose. Also, please refer to Agency's response to pre-IND (PIND) 138870 meeting package dated May 30, 2018 and provide physicochemical property data for one more commercial batch of the reference drug product for comparison.

**The Applicant's response**

The Applicant's response was summarized in the review.

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<sup>2</sup> <\\cdsesub1\evsprod\nda213994\0007\m1\us\111-information-amendment\0007-response-to-information-request-cmc-only-dated-08-may-2.pdf>



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# CHAPTER VII: MICROBIOLOGY

## [IQA NDA Assessment Guide Reference](#)

<b>Product Information</b>	
<b>NDA Number</b>	213994
<b>Assessment Cycle Number</b>	1
<b>Drug Product Name/ Strength</b>	Ephedrine Sulfate Injection, USP 5 mg/mL
<b>Route of Administration</b>	IV
<b>Applicant Name</b>	Nevakar, Inc.
<b>Therapeutic Classification/ OND Division</b>	Division of Anesthesiology, Addiction and Pain Medicine (DAAP)
<b>Manufacturing Site</b>	(b) (4)
<b>Method of Sterilization</b>	

**Assessment Recommendation: Adequate**

**Assessment Summary: Recommended**

**List Submissions being assessed (table):**

Document(s) Assessed	Date Received
0001 (1) ORIG-1	12/18/2019
0003 (3) Amendment/IR response	04/03/2020

**Highlight Key Issues from Last Cycle and Their Resolution: N/A**

**Remarks: N/A**

**Concise Description of Outstanding Issues**

**(List bullet points with key information and update as needed): N/A**

**Supporting Documents:**

- DMF (b) (4) for facility description and floor plans
  - (b) (4).docx dated 01/30/2020 (adequate)
- DMF (b) (4) depyrogenation
  - (b) (4).doc dated 02/03/2017 (adequate)

## S DRUG SUBSTANCE – N/A

### P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of the drug product** – Ephedrine Sulfate Injection, USP 5 mg/mL is a clear, colorless, sterile solution filled into 10 mL glass vials closed with 20 mm stoppers sealed with 20 mm flip-off caps.
- **Drug product composition** –

Ingredient, Quality	Function	% w/v	Quantity/mL	Quantity/vial
Ephedrine sulfate, USP	API	0.5	5.0 mg	50.0 mg
Sodium chloride, USP	(b) (4)	0.9	9.0 mg	90.0 mg
(b) (4) Glacial acetic acid, USP	pH adjusters (b) (4)	q.s. to pH 4.7		
(b) (4) Sodium hydroxide, NF	(b) (4)			
WFI, USP	vehicle	q.s to 1.0 mL	q.s	q.s. to 10 mL

- **Description of container closure system** –

Component	Description	Manufacturer
Vial	10 mL (b) (4) glass vials (b) (4)	(b) (4)
Stopper	20 mm (b) (4) grey rubber stoppers	
Cap	20 mm aluminum flip-off, (b) (4)	

#### **Assessment: Adequate**

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

### P.2 PHARMACEUTICAL DEVELOPMENT



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## P.8 STABILITY

### P.8.1 STABILITY SUMMARY AND CONCLUSION

Accelerated ( $40\pm 2^{\circ}\text{C}$  /  $75\pm 5\%$  RH) and long-term ( $25\pm 2^{\circ}\text{C}$  /  $60 \pm 5\%$  RH) storage studies for the three registration batches of drug product (NEA001, NEA002, NEA003) are underway. Results from 6 months of the accelerated study and 12 months of the long-term study are included in the 12/18/2019 submission and comply with specifications, which are the same as those for release.

The microbiological testing schedule is as follows:

Accelerated BET/Sterility: 0, 3, 6 months

Long-term BET/Sterility: 0, 3, 6, 12, 18, 24, 36 months

Proposed expiry: 24 months

**Assessment: Adequate**

The applicant has proposed an acceptable expiration period for the subject drug product.

## P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

The proposed product stability specifications include the following microbiological test:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP <85>	(b) (4)
Sterility	USP <71>	(b) (4)

Following approval of the subject ANDA, long-term stability studies on commercial batches will be initiated. The first three commercial batches of drug product will be placed on stability and testing will be done according to the protocol detailed in Section P.8.1. In addition, one commercial batch of each presentation of the product manufactured in each subsequent year will be added to the stability program.

### **Assessment: Adequate**

The post-approval stability protocol and stability commitment are adequate to assure the maintenance of microbiological quality over the proposed shelf-life of the subject drug product.

## P.8.3 STABILITY DATA

Stability studies for all three registration batches are underway and comply with specifications up through 6 months at accelerated and through 12 months at long-term conditions. Data are provided for NEA001, NEA002, and NEA003.

### **Assessment: Adequate**

The stability data provided support the maintenance of microbiological quality through 6 months at accelerated conditions and through 12 months at long-term storage conditions.

## R REGIONAL INFORMATION

### **Executed Batch Records**

Executed batches: NEA001, NEA002, NEA003

### **Assessment: Adequate**

Completed batch records indicated that validated (b) (4) manufacturing processes were used for the product of registration/exhibit batches.

**Comparability Protocols** – No CP was included in the application.

## **2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1**

### **2.A. Prescribing Information**

(Section 1.14.1.3 Ephedrine Sulfate – Prescribing Information (PDF))

Route of administration: IV

Container: Single-use vial, ready to use

Storage: 25°C with excursions permitted to 15-30°C. Store in carton until time of use, single use only, discard any unused portion

#### **Assessment: Adequate**

The package insert and drug product labels provide adequate instructions for storage and use of the subject drug product to assure microbiological quality during administration.

*Primary Microbiology Assessor Name and Date: Bethanie L. Lee, Ph.D. 04/07/2020*

*Secondary Assessor Name and Date: Jesse Wells, Ph.D. 04/07/2020*



Jesse  
Wells

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Bethanie  
Lee

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Valerie  
Amspacher

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/s/  
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