CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213407Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☐ Approval
☒ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213407
Assessment 1

Drug Product Name	Ephedrine Sulfate (b) (4) Injection
Dosage Form	Parenteral
Strength	50 mg/ 10 mL, (5 mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Nexus Pharmaceuticals Inc
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
NDA213407: SDN 1; eCTD 0000	06/03/2019	OPQ
IR Response: SDN 7; eCTD 0006	08/15/2019	OPMA
IR Response: SDN 8; eCTD 0007	09/26/2019	ONDP
IR Response: SDN 10; eCTD 0009	10/07/2019	ONDP
IR Response: SDN 11; eCTD 0010	11/13/2019	ONDP, OPMA
IR Response: SDN 12; eCTD 0011	11/25/2019	ONDP
IR Response: SDN 13; eCTD 0012	12/13/2019	ONDP
IR Response: SDN 14; eCTD 0013	12/17/2019	OPMA
IR Response: SDN 15; eCTD 0014	12/23/2019	ONDP
IR Response: SDN 17; eCTD 0017	01/14/2020	ONDP
IR Response: SDN 18; eCTD 0018	01/23/2020	ONDP

IR Response: SDN 19; eCTD 0019	02/07/2020	ONDP
IR Response: SDN 20; eCTD 0020	02/13/2020	ONDP
IR Response: SDN 21; eCTD 0021	02/27/2020	ONDP
IR Response: SDN 24; eCTD 0024	03/09/2020	ONDP
IR Response: SDN 25; eCTD 0025	03/12/2020	ONDP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Lawrence Perez	Donna Christner
Drug Product	Valerie Amspacher	Julia Pinto
Manufacturing	Yeung Chan	Ubrani Venkataram
Microbiology	Aditi Das	Neal Sweeney
Biopharmaceutics	Sarah Ibrahim	Kelly Kitchens
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Lawrence Perez	
Laboratory (OTR)	N/A	N/A
Environmental	Valerie Amspacher	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Based on the assessments of the submitted information and responses to the Information Requests, approval of this application is recommended. The following Postmarketing Commitment (PMC) will be sent to the NDA applicant: To provide assurance on the presence and levels of leachables in the drug product, perform leachables testing on the first commercial stability batch manufactured starting at release and each stability timepoint through to expiry.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product, Ephedrine Sulfate Injection, 5 mg/mL, is a sterile solution with sodium chloride in (b) (4) water packaged in a (b) (4) glass vial, a 20 mm (b) (4) closure (b) (4) and a 20 mm aluminum seal with a flip-off cap. Drug Substance and Drug Product specifications are adequate to support the safety and efficacy of commercial drug product.

We agree with the sponsor's proposed shelf-life of 24-months when stored at 25ºC (77ºF) with excursions permitted to 15ºC to 30ºC.

Proposed Indication(s) including Intended Patient Population	Ephedrine sulfate (b) (4) is an α- and β-adrenergic agonist and a norepinephrine-releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.
Duration of Treatment	Acute
Maximum Daily Dose	50 mg (one vial)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance Ephedrine sulfate is (b) (4) being developed by Nexus Pharmaceuticals Inc. in the form of Ephedrine Sulfate (b) (4) Injection for the treatment of clinically important hypotension occurring in the setting of anesthesia. Ephedrine sulfate is a compendial drug substance. For this NDA the drug substance

specification complies with the current USP monograph and ICH Q6A guidance. The information on the manufacturer, method of manufacturing, characterization, specification, packaging and stability of ephedrine sulfate is detailed in DMF (b) (4). Nexus Pharmaceuticals has established a retest period of (b) (4) for the drug substance Ephedrine sulfate when stored at (b) (4) which can be granted, based on data in DMF (b) (4) which supports an expiration date of (b) (4).

Drug Product: Adequate

The drug product is Ephedrine sulfate 5 mg/mL in solution with sodium chloride in (b) (4) water. Packaged in a (b) (4) glass vial, a 20mm (b) (4) closure (b) (4) and a 20 mm aluminum seal with a flip-off cap. A 24-month expiration date is requested and is supported by the stability data. The drug product specification is adequate to assure the identity, strength, quality, purity, and potency of the drug product. The regulatory analytical procedures are appropriate for the intended use, including method validation.

An adequate leachables study with testing of at least 3 timepoints has not been provided. The following PMC will be sent: To provide assurance on the presence and levels of leachables in the drug product, perform leachables testing on the first commercial stability batch manufactured starting at release and each stability timepoint through to expiry.

Labeling: Adequate

The Prescribing Information complies with all statutory/regulatory requirements and is consistent with guidance recommendations from a product quality perspective. The issues highlighted in Chapter IV: Labeling will be resolved during labeling discussions with the sponsor.

Manufacturing: Adequate

The drug product manufacturing process operations include (b) (4)

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 213407 are found to be acceptable.

Biopharmaceutics: Adequate

The Ephedrine Sulfate (b) (4) Injection was developed by Nexus Pharmaceuticals. Nexus Pharmaceuticals is seeking Agency's approval of the proposed drug product by relying on the Agency's finding of safety and effectiveness of Akovaz® (Ephedrine Sulfate) Injection NDA 208289 held by Avadel Legacy Pharmaceuticals, (b) (4) The application is based on a biowaiver for the proposed product. The proposed formulation includes the same active ingredient (b) (4) sodium chloride.

The Applicant provided adequate justification for the differences in the physiochemical properties between the proposed and the listed drug product. Consistent with 21 CFR 320.24 (b)(6), FDA deemed the information supporting the relative bioavailability of the proposed drug product to the listed drug to be adequate, and a biobridge has been established to the Agency's finding of safety and effectiveness for the Listed Drug (LD). Thus, an in vivo bioavailability (BA)/bioequivalence (BE) bridging study is not needed.

Microbiology (if applicable): Adequate

The submission is recommended for approval on the basis of sterility assurance. No deficiencies were identified.

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 Considerations / Comments**
Sterility	Formulation/ Container Closure Process/Scale/ Equipment/Site	High	Drug product release specification includes sterility (USP <71>) and bacterial endotoxin (USP <85>) testing. Container closure integrity studies indicate that the	Acceptable	Given that the product sterility is the high risk attribute, any proposed changes in (b) (4) manufacturing process or microbiological

			container closure system remains integral and therefore can maintain the sterility of the product.		testing-related product specification may need to be carefully evaluated.
Endotoxin (b) (4)	Formulation/ Container Closure Process/Scale/ Equipment/Site	Medium	The proposed endotoxin limit of NMT (b) (4) (USP <85>) is adequate.	Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels will need to be evaluated based on the MDD.
Assay (API)	Raw Materials/ Formulation/ Container Closure Process/Scale/ Equipment/Site	Low	In-process controls for drug substance (b) (4)	Acceptable	
Physical Stability	Raw Materials/ Formulation/ Container Closure Process/Scale/ Equipment/Site	Low	Stability of API and drug product, and suitability of commercial container closure system have been well demonstrated. Manufacturing process is reasonably well-controlled.	Acceptable	
Uniformity of Dose (Fill/ Deliverable Volume)	Formulation Container Closure Process/Scale/ Equipment/Site	Low	Controlled by end product “Volume in Container” testing per specification	Acceptable	
Osmolality	Formulation/Raw materials/ Container closure Process/Scale/ Equipment/Site	Low	Osmolality is monitored on release per in house method with acceptance limits of (b) (4) mOsm/kg.	Acceptable	
pH	Formulation/Raw materials/ Container closure Process/Scale/ Equipment/Site	Low	The pH is monitored per USP <791> on release with acceptance limits of 4.5 - 7.0.	Acceptable	
Particulate Matter	Formulation/Raw materials/ Container closure Process/Scale/ Equipment/Site	Low	Particulate matter (b) (4) is monitored on release per USP <788>.	Acceptable	

Leachable Extracts	Formulation/Raw materials/ Container closure Process/Scale/ Equipment/Site	Low	The extractables and leachables studies indicate no product quality risk from container closure system used to package the drug product	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)

Application Technical Lead Name and Date:
Lawrence B. Perez, Ph.D.
CMC Review Chemist
25-Mar-2020

U.S. FOOD & DRUG ADMINISTRATION

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	Adequate	Reviewed by Lawrence Perez on 25-Jul-2019	LOA: 20-Mar-2019
	III		(b) (4)	N/A	Not reviewed, Information provided in NDA	LOA: 1-Apr-2019
	III			N/A	Not reviewed, Information provided in NDA	LOA: 11-Dec-2015
	V			N/A	Not reviewed, Information provided in NDA	LOA: 11-May-2005

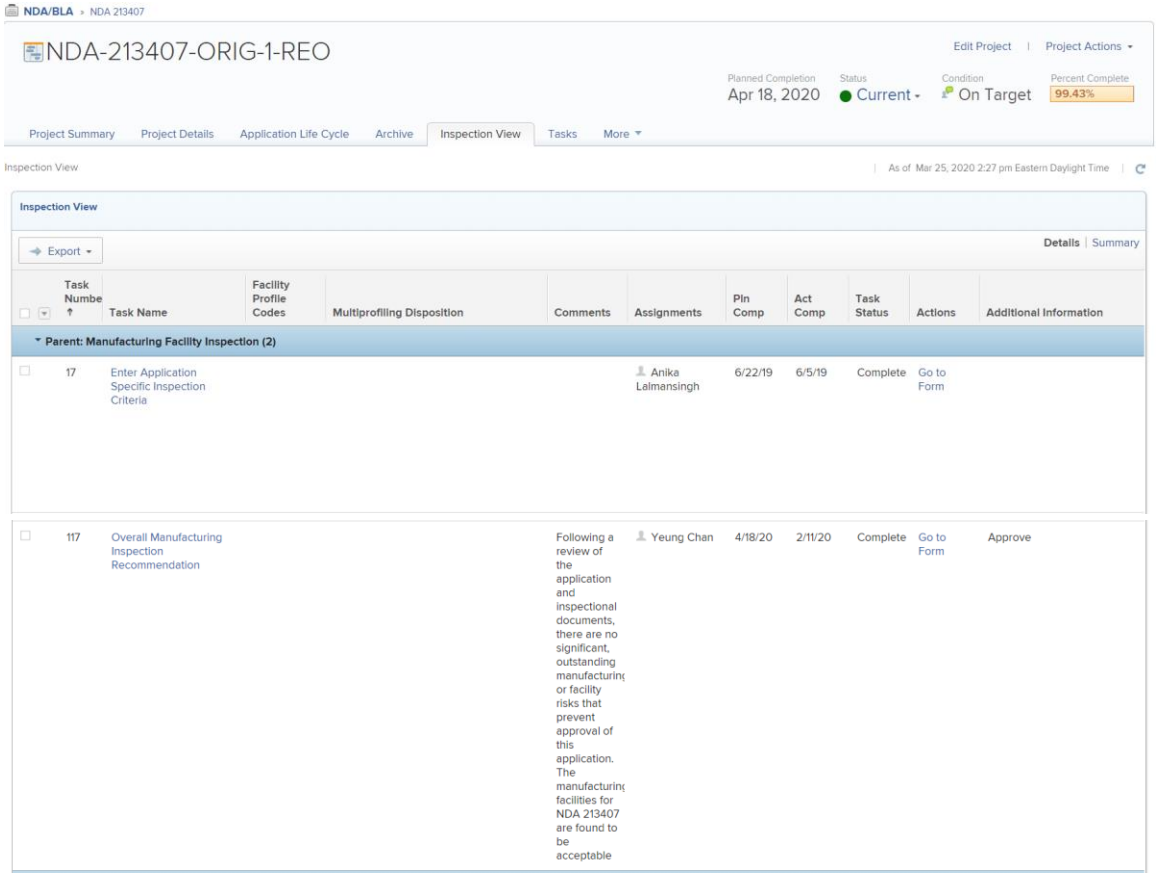
B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	208289	Reference Listed Drug (RLD): Akovaz (Ephedrine Sulfate)

2. CONSULTSs

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

C. **Facilities approval screenshot for NDA213407 as of 25-Mar-2020**



NDA/BLA › NDA 213407

NDA-213407-ORIG-1-REO

Edit Project | Project Actions

Planned Completion: Apr 18, 2020 | Status: Current | Condition: On Target | Percent Complete: 99.43%

Project Summary | Project Details | Application Life Cycle | Archive | Inspection View | Tasks | More

Inspection View

As of Mar 25, 2020 2:27 pm Eastern Daylight Time

Inspection View

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Details | Summary

Task Number	Task Name	Facility Profile Codes	Multiprofiling Disposition	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
Parent: Manufacturing Facility Inspection (2)										
17	Enter Application Specific Inspection Criteria				Anika Lalmansingh	6/22/19	6/5/19	Complete	Go to Form	
117	Overall Manufacturing Inspection Recommendation			Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 213407 are found to be acceptable	Yeung Chan	4/18/20	2/11/20	Complete	Go to Form	Approve

Lawrence Perez

Digitally signed by Lawrence Perez
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DRUG PRODUCT LIST OF DEFICIENCIES

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate.

The PI complies with all statutory/regulatory requirements and is consistent with guidance recommendations from a product quality perspective. The issues highlighted below will be resolved during labeling discussions with the sponsor.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	N/A	
Established name(s)	Yes	Ephedrine Sulfate *injection* (b) (4) for intravenous use.
Route(s) of administration	Yes	IV use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	(b) (4) *injection* (b) (4) *50 mg /10 mL (equivalent to 38 mg /10 mL ephedrine base)* 5 mg/mL, (equivalent to 3.8 mg/ *mL* ephedrine base) (b) (4)

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.	Yes	Phrase, "(b) (4) " needs to be removed from Section 16 Phrase "(b) (4) single dose" needs to be added.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
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)	N/A	Sponsor states, (b) (4) "

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	Ephedrine sulfate *injection* (b) (4)
Strength(s) in metric system	Yes	Need to add "*contains 50 mg /10 mL, equivalent to 38 mg ephedrine base,"* 5 mg/mL ephedrine sulfate, equivalent to 3.8 mg ephedrine base
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Salt policy does not apply because ephedrine sulfate injection has a USP monograph
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	No	Need to add color and clarity Need to add "contains *50 mg /10 mL, equivalent to 38 mg ephedrine base,"* 5 mg/mL ephedrine sulfate, equivalent to 3.8 mg ephedrine base
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.	No	Phrase "single dose" needs to be added.

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	Ephedrine sulfate *injection* (b) (4)
Dosage form(s) and route(s) of administration	Yes	Solution for intravenous injection
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	Salt policy does not apply because ephedrine sulfate injection has a USP monograph
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
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.	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Yes	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

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

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	Vials and cartons
Strength(s) in metric system	Yes	Ephedrine sulfate *injection* (b) (4) Need to add "*contains 50 mg /10 mL, equivalent to 38 mg ephedrine base*," 5 mg/mL ephedrine sulfate, equivalent to 3.8 mg ephedrine base
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	No	Need to add clear, colorless
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.	Yes	Phrase, (b) (4)" needs to be removed from Section 16 Phrase "(b) (4) single dose" needs to be added.

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.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
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.”	N/A	
Include information about child-resistant packaging	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
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Yes	

2.0 PATIENT LABELING

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

(b) (4)

Item	Information Provided in the NDA (container / carton)	Assessor's Comments about Container / Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes / Yes	Ephedrine Sulfate *injection* (b) (4)
Dosage strength	Yes / Yes	*Need to add "equivalent to 38 mg ephedrine base*
Route of administration	Yes / Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A – USP monograph for ephedrine sulfate injection	*Need to add "equivalent to 38 mg ephedrine base*
Net contents (e.g. tablet count)	Yes / Yes	
"Rx only" displayed on the principal display	Yes / Yes	
NDC number	Yes / Yes	
Lot number and expiration date	Yes / Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes / Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	No / No	Phrase " (b) (4) single dose" needs to be added. Should the (b) (4) " be on the container label?
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes / Yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes / Yes	
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	Yes / 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	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate
The immediate container label(s) comply with all statutory/regulatory requirements and are consistent with guidance recommendations from a Quality perspective. The carton labeling complies with all regulatory requirements from a Quality perspective. The issues highlighted below will be resolved during labeling discussions with the sponsor.

Valerie Amspacher

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Julia Pinto

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	Ephedrine Sulfate (b) (4) Injection
NDA Number	NDA 213407
Assessment Cycle Number	1
Drug Product Name/ Strength	Ephedrine sulfate (b) (4) injection, 5 mg/mL, (equivalent to 3.8 mg ephedrine base) (b) (4) 5 to 10 mg as needed, not to exceed 50 mg.
Route of Administration	Intravenous
Applicant Name	Nexus Pharmaceuticals Inc
Therapeutic Classification/ OND Division	Miscellaneous Anesthetics /DAAAP
Proposed Indication	For the treatment of clinically important hypotension occurring in the setting of anesthesia.

Assessment Recommendation: **Adequate**

The Ephedrine Sulfate (b) (4) Injection was developed by Nexus Pharmaceuticals. Nexus Pharmaceuticals is seeking Agency's approval of the proposed drug product by relying on the Agency's finding of safety and effectiveness of Akovaz® (Ephedrine Sulfate) Injection NDA 208289 held by Avadel Legacy Pharmaceuticals, (b) (4) . The application is based on a biowaiver for the proposed product. The proposed formulation includes the same active ingredient and (b) (4) sodium chloride.

The Applicant provided adequate justification for the differences in the physiochemical properties between the proposed and the listed drug product. Consistent with 21 CFR 320.24 (b)(6), FDA deemed the information supporting the relative bioavailability of the proposed drug product to the listed drug to be adequate, and a ***biobridge*** has been established to the Agency's finding of safety and effectiveness for the Listed Drug (LD). Thus, an in vivo bioavailability (BA)/bioequivalence (BE) bridging study is not needed.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original	June 3, 2019
S009	October 7, 2019

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): None

B. Background

Ephedrine Sulfate Injection 5 mg/mL, 10 mL Fill/ 10 mL Vial, (b) (4) (b) (4) does not need any further dilution. Unlike the LD, Nexus's proposed drug product does not need dilution before administration as an intravenous bolus to achieve the desired concentration. It contains 0.9% Sodium Chloride, mimicking dilution with normal saline. It contains no bacteriostatic agent or other preservative and is supplied in an Ephedrine Sulfate Injection, 5 mg/mL, 10 mL Fill/ 10 mL Vial.

The Applicant proposed to rely on the Agency's previous findings of safety and efficacy of the listed drug Akovaz® (Ephedrine Sulfate) Injection NDA 208289 as well as published literature and data generated by the Sponsor, to satisfy the 505(b)(2) regulatory requirements. No clinical safety and efficacy or pharmacokinetic studies were conducted in support of this 505(b)(2) application. The establishment of adequate bridging to the listed drug serves as a clinical surrogate for NDA approvability decision making.

The Applicant claims that as Ephedrine Sulfate Injection and the LD are in aqueous solutions, containing the same amount of active ingredient and both are injected intravenously, bioavailability of parenteral solution is self-evident. Therefore, the biobridge between the proposed drug and the LD can be adequately established.

- The focus of the biopharmaceutics review was the assessment of adequate bridging of the proposed drug product to the listed drug and the following **information request in the 74 day letter** was conveyed to the Applicant:

Per the requirements of 21 CFR 320.24(b)(6), a bridge (bioavailability/bioequivalence) between the listed and the proposed drug product may be established with supporting data/information to include:

- Comparison of the physiochemical characteristics (i.e. pH and osmolality) between your proposed drug product and the listed drug products;
- Your justification for any differences between the two formulations and to demonstrate that the difference for each active and/or inactive ingredient would not affect the pharmacokinetic performance towards any difference in clinical safety and/or efficacy outcome.

In the response dated October 7, 2019, the Applicant provided the following table comparing the proposed product and the reference product:

	Listed Drug	**Proposed Drug Product**

Product Name	Akovaz® (Ephedrine Sulfate) injection	Ephedrine Sulfate (b) (4) (b) (4) Injection
Conditions of Use	Akovaz ® is indicated for the following: Ephedrine sulfate injection is an alpha- and beta- adrenergic agonist and a\norepinephrine releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.	Ephedrine Sulfate Injection is indicated for the following: Ephedrine sulfate (b) (4) (b) (4) injection is an alpha- and beta- adrenergic agonist and a norepinephrine releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of
Active Ingredient	Ephedrine Sulfate	Ephedrine Sulfate, USP
Inactive Ingredients	Water for Injection	Sodium Chloride, USP Water for Injection, USP
Route of Administration	Intravenous	Intravenous
Dosage Form	Injectable	Injectable
Strength	50 mg/mL, 1 mL/vial	5 mg/mL, 50 mg /10 mL vial

A side-by-side comparison of the physiochemical characteristics between Nexus's proposed drug product and LD is shown below:

Test	**RLD** **AKOVAZ®, Ephedrine Sulfate Injection, USP (50 mg/mL), 1 mL Fill/Vial, from Avadel Legacy Pharmaceuticals, LLC**	**Proposed Drug Product** **Ephedrine Sulfate Injection, 5 mg/mL, 10 mL Fill**		
	Lot: 839069	**Exhibit Batch V017A17**	**Exhibit Batch**	**Exhibit Batch**
Appearance	Clear colorless	Clear colorless	Clear colorless	Clear colorless
	No visible particulates	solution, No visible particulates	solution, No visible particulates	solution, No visible particulates
pH	50 mg/mL solution:	N/A	N/A	N/A

	5 mg/mL in 0.9% Sodium Chloride (NaCl) solution*: 5.7	5.8	5.5	5.8
Osmolality (mOsm/kg)	5 mg/mL in 0.9% NaCl solution*: 284	316	314	319
Assay	102.3%	101.1%	101.0%	101.4%
Any Unspecified Impurity	Not Detected (ND)	< Limit of Quantitation (LOQ)	<LOQ	<LOQ
Total Impurities	ND	<LOQ	<LOQ	<LOQ
Enantiomeric Purity: (+) 1S, 2R Ephedrine	ND	ND	ND	ND

*Sample preparation: Take 1 mL of RLD in a 10 mL volumetric flask and dilute to volume with 0.9% NaCl Solution.

Taking into account the Applicant's response and other information provided in the submission, overall biopharmaceutics information of this submission is summarized below:

- There are no inactive ingredients in the proposed drug product other than sodium chloride (b) (4).
- The pH, calculated ionic strength as well as measured osmolality of the proposed drug product are similar to those of the listed drug.
- The viscosity of both formulations was not presented; however, the composition as listed supports that the viscosity is expected to be similar.
- The addition of sodium chloride as an excipient in the proposed drug product would not affect the disposition of the proposed drug product.

B. BIOWAIVER REQUEST
Assessment: *{Adequate}*

- The Applicant provided adequate justification that the differences in the formulation between its product and reference product do not affect the pharmacokinetic performance of the proposed product compared to that of the reference product
- The biobrdige between the LD and proposed drug product has been established. Thus, anin vivo BA/BE bridging study is not needed.Overall, NDA 213407 for Ephedrine Sulfate (b) (4) Injection is acceptable from a Biopharmaceutics perspective.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor:
Sarah Ibrahim, Ph.D.
Secondary Biopharmaceutics Assessor:
Hansong Chen, Ph.D.

Hansong Chen

Digitally signed by Hansong Chen
Date: 3/24/2020 02:53:27PM
GUID: 525d7d660003845a197a2e1682433d0d

Sarah Ibrahim

Digitally signed by Sarah Ibrahim
Date: 3/24/2020 04:48:35PM
GUID: 546b898a000820c3599fd87d16af9641

U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	
ANDA Number	213407
Assessment Cycle Number	1
Drug Product Name / Strength	Ephedrine Sulfate (b) (4) Injection, 50 mg/ 10 mL (5 mg/mL)
Route of Administration	Intravenous
Applicant Name	Nexus Pharmaceuticals Inc
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A

Assessment Summary:

- The submission is recommended for approval on the basis of sterility assurance.
- No deficiencies were identified.

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
06/03/2019	06/03/2019	N/A	08/15/2019

12/13/2019	12/13/2019	N/A	12/16/2019
01/23/2020	01/23/2020	N/A	01/23/2020

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

Remarks: An information request (IR) was conveyed on 11/26/2019 and a response was received from the applicant on 12/13/2019. A second IR was conveyed on 01/13/2020 and a response was received from the applicant on 01/23/2020. The responses to both the IRs are covered in this review.

Concise Description of Outstanding Issues: None

Supporting Documents:
DMF # (b) (4), regarding the (b) (4) stopper and associated microbiology review D18370M15R01.doc (adequate), dated 03/04/2019.

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

Assessment: ***The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance is not necessary.***

P DRUG PRODUCT

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product – The drug product is a non-preserved, sterile aqueous solution for injection containing Ephedrine Sulfate Injection (5 mg/mL) and is supplied as10 mL fill in 10 mL (b) (4) vials.

- **Drug product composition** –
  (3.2.P.1, Description and composition)

Ingredient	Quantity per mL	Function
Ephedrine Sulfate, USP	5.0 mg	Active Ingredient
Sodium chloride, USP	(b) (4)	
Water for Injection, USP		

Exhibit batch size: (b) (4)
Proposed Commercial Batch size: (b) (4)

Note to reviewer: Based on the current projected market demand and facility capacity, future Exhibit batch size is indicated to be (b) (4) of manufacturing process description and batch record (b) (4).pdf under the updated section 3.2.P.3.)

- **Description of container closure system** –
  (3.2.P.1., Description and composition; 3.2.P.7. Container-closure-system)

Component	Description	Manufacturer
Vial (container)	(b) (4)	
Stopper (closure)		

Assessment: An adequate description of the drug product composition and container closure system was provided.

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Ephedrine sulfate (b) (4) injection is supplied as a colorless, sterile, non-pyrogenic, preservative-free single-dose vial, packaged in a 10 mL glass vial at a concentration of 50 mg/vial (5 mg/mL) ephedrine sulfate, equivalent to 3.8 mg ephedrine base. Storage instructions are as follows: store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] and discard unused portion. Do not dilute before administration.
Note to reviewer: For bolus intravenous administration, solution of 5 mg/mL of Ephedrine sulfate (b) (4) injection (b) (4) does not require prior dilution.

Assessment:

Adequate

MICROBIOLOGY LIST OF DEFICIENCIES: None

Primary Microbiology Assessor Name and Date:
Aditi Das, Ph.D., 1/27/2020

Secondary Assessor Name and Date:
Neal Sweeney, Ph.D., 1/27/2020

Aditi Das

Digitally signed by Aditi Das
Date: 3/25/2020 11:54:24AM
GUID: 59ce55a8001021f51621534263276c8f

Neal Sweeney

Digitally signed by Neal Sweeney
Date: 3/25/2020 01:01:22PM
GUID: 508da70c00028f5119acd77351f33159

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04/15/2020 02:27:48 PM

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KIMBERLY A COMPTON
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