CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214628Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	214628		
Applicant Name	Nevakar Injectables, Inc.		
Drug Product Name	Norepinephrine in Sodium Chloride Injection		
Dosage Form.	Injection		
Proposed Strength(s)	4 mg per 250 mL (16 mcg/mL), 8 mg per 250 mL(32 mcg/mL), and 16 mg per 250 mL (64 mcg/mL)		
Route of Administration	Intravenous		
Maximum Daily Dose	(b) (4) mg/mL		
Rx/OTC Dispensed	Rx		
Proposed Indication	Norepinephrine is a catecholamine indicated for restoration of blood pressure in adult patients with acute hypotensive states.		
Drug Product Description	Norepinephrine in Sodium Chloride Injection (norepinephrine bitartrate) is supplied as a clear, colorless sterile solution in a 250 mL non-PVC infusion bag with single function connector system consisting of a port and cap, packaged individually in an aluminum foil pouch with an oxygen scavenger.		
Co-packaged product information	N/A		
Device information:	This product is classified as a combination product because it is packaged in an infusion bag with single function connector system consisting of a port and cap.		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhengfu Wang ONDP/DNDAPI/NDB3	N/A
	Drug Product/ Labeling	Akm Khairuzzaman ONDP/DNDPIII/NDPB5	Theodore Carver ONDP/DNDPIII/NDPB5

	Manufacturing	Krishna Ghosh OPMA/DPMAIV/PMB12	Sateesh Kuma Sathigari OPMA/DPMAIV/PMB12
	Biopharmaceutics	N/A	N/A
	Microbiology	Julia Marre OPMA/DMAI/MAB2	N/A
	Other (specify):	None	
	RBPM	Grafton Adams CDER/OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver CDER/OPQ/ONDP/DNDPIII/NDPB5	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

An expiry dating period of 24 months is granted for Norepinephrine Bitartrate in Sodium Chloride Injection when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

]**b. Additional Comments for Action**
None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Conclusion
The Office of Pharmaceutical Quality Review team has assessed NDA 214628 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that the drug product purports to have. As such, OPQ recommends approval of this NDA from a quality perspective.

2.) Background:

The Applicant developed the proposed drug product, Norepinephrine Bitartrate in Sodium Chloride Injection, as ready-to-use sterile injectable solutions in non-PVC infusion bags, for intravenous infusion. Each mL contains 16 mcg/mL, 32 mcg/mL, or 64 mcg/mL of norepinephrine supplied as 31.90 or 63.80 or 127.6 micrograms per mL of norepinephrine bitartrate monohydrate. This application is a 505(b)(2) NDA that relies on previous findings of safety and efficacy for the listed drug, Levophed, 4mg/4mL. This application is seeking approval for the same clinical indication, route of administration, dose, and dosing regimen as those of the listed drug.

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3.) Summary of the resolution of deficiencies and the review for each OPQ discipline.

Manufacturing Process - Several comments related to the manufacturing process were sent to the Applicant in the complete response letter issued in the previous cycle (6/14/2021). The Applicant (b) (4) [redacted] (b) (4) In summary, the Applicant adequately addressed all process-related comments and deficiencies in this NDA resubmission.

Manufacturing Facilities - The drug product manufacturing facility (b) (4) [redacted] was previously given a withhold recommendation after a pre-approval inspection, resulting in a facility deficiency in the Complete Response letter issued the previous review cycle (6/14/2021). During review of this NDA resubmission (amendment 18, 04/22/2022), an inspection was conducted from (b) (4) [redacted] (b) (4), which covered all items developed by the firm to address the deficiencies identified in the last review cycle. Based on the PAI re-inspection, collected corrective action documents and data submitted in the

application from the scaled-up batches, the manufacturing site is acceptable for final drug product manufacturing for NDA 214628. Therefore, all facilities for NDA 214628 were found to be acceptable, as summarized in the table below.

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)		Manufacturing; In-process control testing; Release testing; Stability testing, Packaging of Drug Product	Approve - Based on PAI
		(b) (4) testing (Norepinephrine Bitartrate) |	Approve - Based on Previous History
		Manufacturing, testing, packing, stability and releasing facility of API || DMF: (b) (4)	Approve - Based on Previous History

Recommendation for other disciplines - See also CDTL review from previous review cycle (June 9th, 2021).
The drug product aspects, including composition, product development, container closure, and stability data, were previously reviewed and found to be adequate. The current resubmission includes an additional specified impurity, (b) (4) and the addition of release and shelf-life acceptance criteria of (b) (4)% for this impurity in the revised drug product specification, which was reviewed in consultation with the nonclinical review team. The drug product review concluded that the updated specification is adequate.

The drug substance information in Module 3 of this NDA and DMF (b) (4) were previously reviewed in the last review cycle and found to be adequate (04/23/2021). The drug substance information in this NDA resubmission were unchanged except for addition of additional batch data, which were reviewed and found to be adequate. Therefore, the drug substance remains adequate.

With regards to biopharmaceutics aspects, the scientific bridge based on physicochemical comparison of the proposed and listed drug products remains adequate, and no further review was required for this resubmission. With respect to microbiological aspects, there are no changes in the current

resubmission other than additional stability data for the drug product, which are adequate. Therefore, the NDA remains adequate with respect to the microbiology review. With respect to quality aspects of the labeling, these aspects were previously reviewed and found to be adequate (see IQA labeling review), and the final labeling will be assessed prior to approval.

In summary, the reviews for all OPQ disciplines conclude that NDA 214628 is recommended for approval.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes.

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None.

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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

Items	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	NOREPINEPHRINE (b) (4) IN SODIUM CHLORIDE INJECTION	Acceptable
Established name(s)	NOREPINEPHRINE (b) (4) IN SODIUM CHLORIDE INJECTION	Acceptable
Route(s) of administration	IV infusion	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Not Acceptable (b) (4)
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.	Acceptable
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the	Do not use if the solution is discolored (on the container label)	Acceptable

reconstituted or diluted product)		
Available dosage form(s)	IV injection	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Follows approved USP product for the LD	Equivalence statement should be next to strengths
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	Acceptable

1.2.3 Section 11 (DESCRIPTION)

Items	**Information Provided in the NDA**	**Assessor's Comments**
DESCRIPTION section		
Proprietary and established name(s)	NOREPINEPHRINE (b) (4) IN SODIUM CHLORIDE INJECTION	Acceptable
Dosage form(s) and route(s) of administration	IV injection, IV route	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Follows approved USP product for the LD	Acceptable
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided	Acceptable
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.	FDA recommended to use equivalence statement of "as follows: "Each mL contains the equivalent of 16 or 32 or 64 micrograms of norepinephrine base supplied as 31.90 or 63.80 or 127.6	Acceptable

	micrograms per mL of norepinephrine bitartrate monohydrate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	Acceptable
Statement of being sterile (if applicable)	Yes	Acceptable
Pharmacological/ therapeutic class	Yes	Acceptable
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	Not Applicable	Acceptable
Other important chemical or physical properties (such as pKa or pH)	pH 3.5 – 4.5	Acceptable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity	None present	Acceptable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Items	**Information Provided in the NDA**	**Assessor's Comments**
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	IV Injection	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
Available units (e.g., bottles of 100 tablets)		Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose,	(b) (4)	Acceptable

multiple-dose, single-patient use). Other package terms include pharmacy bulk package and imaging bulk package.		
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.)	Protect from light. (b) (4) [redacted]	Acceptable
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature [20° to 25°C (68° to 77°F)], excursions permitted to 15° to 30°C (59° to 86°F)	Acceptable
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."	Not Applicable	Acceptable
Include information about child-resistant packaging	Not Acceptable	Acceptable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Items	**Information Provided in the NDA**	**Assessor's Comments**
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Par Pharmaceutical (b) (4) [redacted]	Manufacturer's name and address is not provided.

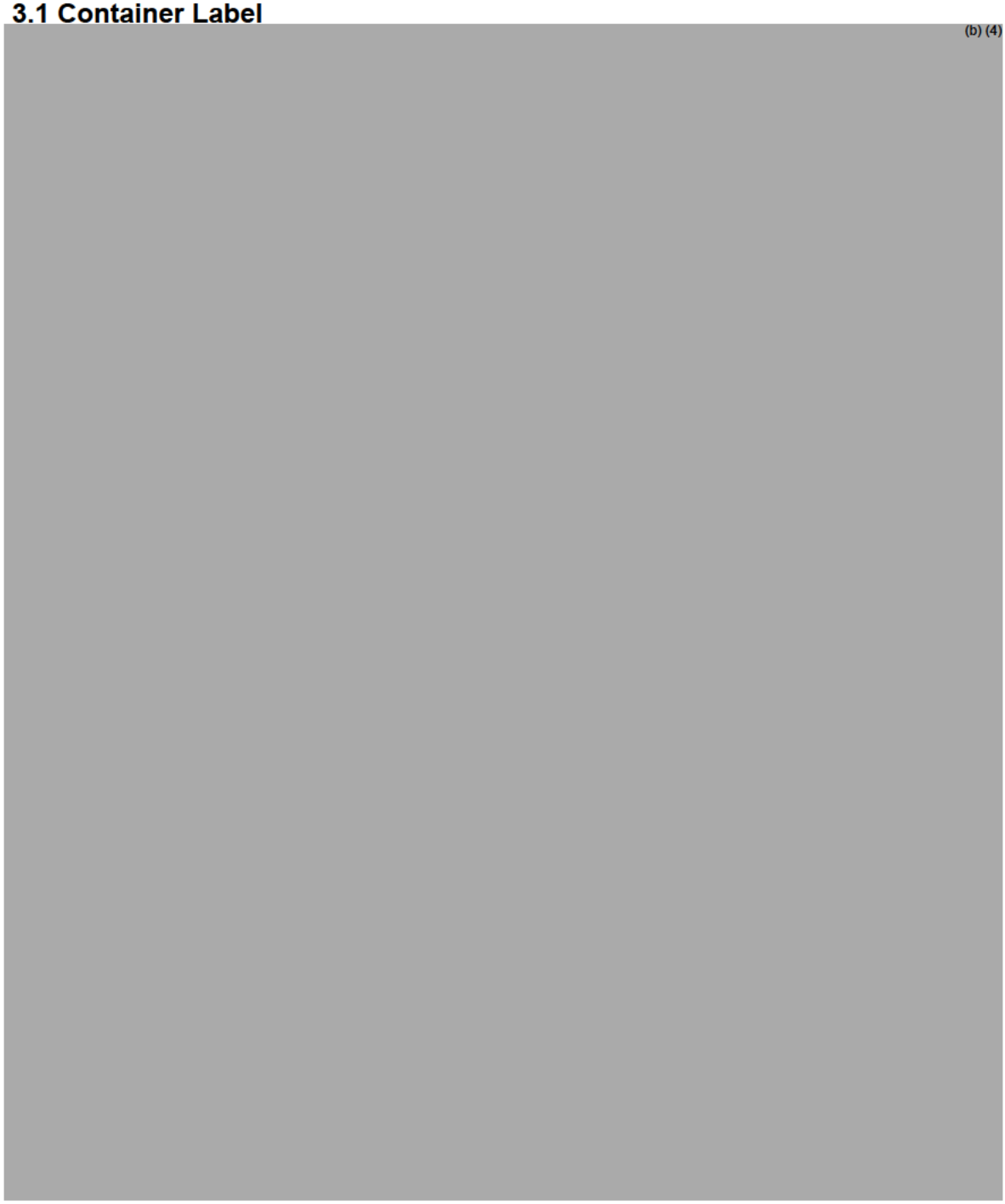
2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Not applicable

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)



Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	Norepinephrine (b) (4) in Sodium Chloride Injection	0.9% should be included before Sodium Chloride in the name of the product on the container labeling.
Dosage strength	4 mg / 250mL, 8 mg / 250mL, and 16 mg/250 mL	Acceptable
Route of administration	Intravenous Infusion	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Follows approved USP product for the LD	Acceptable
Net contents (e.g. tablet count)	250 ml per infusion bag	Acceptable
"Rx only" displayed on the principal display	yes	Acceptable
NDC number	yes	Acceptable
Lot number and expiration date	yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature [20° to 25°C (68° to 77°F)]	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use)	Single dose	Acceptable
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Not applicable	Acceptable
If alcohol is present, must provide the amount of	Not Acceptable	Acceptable

alcohol in terms of percent volume of absolute alcohol		
Items	**Information Provided in the NDA**	**Assessor's Comments**
Name of manufacturer/distributor	Distributed by: Par Pharmaceutical (b) (4)	Manufacturer's name and address is not provided.
Medication Guide (if applicable)	Not Applicable	Acceptable
No text on Ferrule and Cap Overseal	Not Applicable	Acceptable
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.	Follows approved USP product for the LD.	Acceptable

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

1. In the dosage form and strength section of the package insert, FDA recommended to use "single dose container". (This has been inserted by FDA on the PI)
2. In the description section of the package insert, FDA recommended to use equivalence statement of "31.90 or 63.80 or 127.6 micrograms per ml of norepinephrine bitartrate monohydrate" on the labeling. (This has been inserted by FDA on the PI).
3. Please include "0.9%" before Sodium Chloride in the name of the product on the container labeling. (This will be communicated to the Applicant)

Overall Assessment and Recommendation: Adequate after the above deficiencies are fulfilled.

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 11/30/2020.

Secondary Assessor Name and Date (and Secondary Summary, as needed): David Claffey, Ph.D., 11/30/2020.

Akm Khairuzzaman

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Date: 11/30/2020 08:45:52AM
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David Claffey

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NDA 214628
Norepinephrine Bitartrate in Sodium Chloride Injection
Integrated Quality Review

Recommendation: Complete Response
Review 1

Drug Name/Dosage Form	Norepinephrine Bitartrate in Sodium Chloride Injection
Strength	4 mg / 250mL, 8 mg / 250mL & 16 mg / 250 mL
Route of Administration	Parenteral (IV infusion)
Rx/OTC Dispensed	Rx
Applicant	Nevakar Inc.
Submissions (s) Reviewed	NDA 214628, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	ONDP/DNDAPI/NDB3
Drug Product/Environmental Assessment (EA)	Akm Khairuzzaman	ONDP/DNDPIII/NDPB5
Process and Facility	Krishna Ghosh	OPMA/DPMAIV/PMB12
Biopharmaceutics	Zhuojun Zhao	ONDP/DB/BB3
Microbiology	Karthik Krishnan	OPMA/DMAI/MAB3
RBPM	Grafton Adams	OPRO/ DRBPMI
Application Technical Lead (ATL)	Akm Khairuzzaman	ONDP/DNDPIII/NDPB5

Quality Review Data Sheet

DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	COMMENTS
(b) (4)	Type II	(b) (4)		Adequate	DMF reviewed on 4/2/2021
	Type III			Adequate	*
	Type III			Adequate	*
	Type III			Adequate	*
	Type III			Adequate	*
	Type III			Adequate	*

*Adequate information provided in the NDA. Assessment on the item referenced item can be found in the NDA review.

Other Documents: *Pre-IND # 135595 meeting written response dated 1/2/2019 & 04/29/2020.*

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality (OPQ) recommends a **complete response (CR)** action due to deficiencies related to process and facilities (specifically related to [redacted] (b) (4) the drug product manufacturing facility).

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Background, and Quality Assessment Summary

The applicant, Nevakar Inc., has sought U.S. marketing approval for Norepinephrine Bitartrate in Sodium Chloride Injection, 4 mg / 250mL, 8 mg / 250mL & 16 mg / 250 mL for intravenous infusion in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Norepinephrine is a sympathomimetic catecholamine that is indicated for blood pressure control in certain acute hypotensive states. It is also indicated as an adjunct in the treatment of cardiac arrest and profound hypotension. The proposed Norepinephrine Bitartrate in Sodium Chloride Injection is supplied as a ready-to-use, sterile solution in single-dose 250 ml infusion bag. This NDA for Norepinephrine Bitartrate in Sodium Chloride Injection relies for approval, in part, on the FDA's findings of efficacy and safety for the Listed Drug (LD), Levophed 4mg/4ml (NDA 007513). The listed drug product is a concentrate in a vial that requires dilution with 5% dextrose in an infusion bag prior to use. The proposed infusion rate is 8 mcg to 12 mcg norepinephrine per minute (followed by a maintenance dose of 2-4 micrograms per minute). The Listed Drug Product also has the same infusion rate after reconstitution. The scientific bridge between the LD and the proposed drug product was established as per the 21 CFR 320.24(b)(6) through comparisons of formulation and physiochemical data, demonstrating that the differences will not impact the in vivo performance of the proposed drug product. From a quality perspective, the proposed control strategies are adequate to ensure consistent product quality regarding identity, strength, purity, sterility, potency, and stability. Stability studies revealed that the drug product is stable up to 24 months and the out of pouch in use stability data indicated that the product is stable for 24 hours. The proposed 24-month shelf life is based on their statistical analysis and found to be acceptable. Among all the listed manufacturing facilities, the drug product manufacturing facility is recommended as " Withhold" due to several GMP issue. The review evaluation on the drug product fracturing is concluded as "Inadequate" due to several manufacturing process related issue.

A. Drug Substance (Norepinephrine) Quality Summary

Norepinephrine bitartrate is a compendial (USP & Ph. Eur.) drug substance that exist as norepinephrine bitartrate monohydrate. It is a chiral compound with one chiral center in norepinephrine base and the isomer of R-configuration is used in the drug product. All CMC information, including structural characterization, impurities, physicochemical properties,

manufacturing, specification, batch analysis and stability data have been cross-referenced to DMF (b) (4), held by (b) (4). Dr. Martin Haber's review concluded that the CMC information provided in the NDA and DMF is adequate and there are no drug substance related deficiencies that need to be reported to the applicant. The drug substance is controlled for its identity using three different methods as per the USP monograph. It is also controlled for its assay, enantiomeric impurity (D-norepinephrine) and the impurities that are process related and/or degradation products, including residual solvents. Other attributes that are tested at release include appearance, solubility, melting point, optical rotation, residue on ignition, water determination, bacterial endotoxins, and microbial bioburden. The analytical procedures used to perform the testing conform (for the most part) to the analytical procedures in the recently established USP Monograph for norepinephrine bitartrate. The combined data provide adequate information about API identification, purity, and impurity. The proposed drug substance specification is adequate. (b) (4) A (b) (4) retest period has been established by the DMF holder.

B.1. Product Design, and Release Specification:

Norepinephrine Bitartrate in Sodium Chloride Injection is a ready-to-use parenteral infusion solution intended for the use as a sympathomimetic catecholamine in patients for blood pressure control. Each mL contains the equivalent of 16 or 32 or 64 micrograms base of norepinephrine supplied as 31.90 or 63.80 or 127.6 micrograms per ml of norepinephrine bitartrate monohydrate and the following inactive ingredients: 9 mg/ml sodium chloride, 10 microgram/ml of edetate disodium dihydrate, (b) (4). The recommended clinical dose and infusion rate for the proposed Norepinephrine Bitartrate in Sodium Chloride Injection is identical to the LD. (b) (4) All proposed excipients are compendial grade. No novel or human/animal origin excipients were proposed. All the inactive ingredients are below the levels provided in Inactive Ingredients Database (IID) maintained by FDA. Critical material attributes of the excipients employed in the formulation are controlled as per the relevant USP/NF monographs. The material attributes of the excipients do not directly impact the quality attributes of the finished product. Dr. Akm Khairuzzaman reviewed the drug product information including drug product composition, drug product specification including assay and limits proposed for impurities, excipient information, analytical methods, container closure system, compatibility information, and stability data, and environmental assessment (EA). Dr. Khairuzzaman' s review concluded that the product release specification, involving testing of product critical quality attributes such as appearance, identity, assay for L-norepinephrine, enantiomeric impurity (D-norepinephrine), related substance, (b) (4) pH, osmolality, particulate matter, sterility, container content for injections, weight loss, and bacterial endotoxins, is adequate. The analytical procedures have been adequately validated. The drug product reviewer also performed a risk assessment for critical attributes and concluded that the final risk is low for the proposed product.

B.2. Manufacturing: Dr. Krishnakali Ghosh reviewed the manufacturing process and its controls information including manufacturing facilities. The manufacturing process utilizes (b) (4) (b) (4). The process steps used to manufacture the drug product include (b) (4)

(b) (4) appropriate control is in place during the production. These controls include manufacturing process control (e.g.) and appropriate in-process tests . According to Dr. Krishnakali Ghosh's review, the applicant has not demonstrated that the drug product batches can be manufactured with consistent quality. Dr. Krishnakali Ghosh's review concluded the following outstanding issue with respect manufacturing process: inadequate . Dr. Krishnakali Ghosh's review recommended "Inadequate" for this NDA from manufacturing process and facility perspective.

B.3. Microbiological Aspects: Microbiology reviewer, Dr. Karthik Krishnan reviewed the microbiological controls information including drug product specification. The drug product specification includes test for sterility (USP <71>) and bacterial endotoxin (USP<85>). Dr. Karthik Krishnan's review concluded that the manufacturing of the drug product is adequately controlled for microbiological attributes at various stages of the process. The solution is controlled with a bio burden test. . Process validation is found to be acceptable. . The drug product is tested for sterility and is controlled for endotoxins against an acceptable limit of NMT EU/mg of Norepinephrine for all strengths. The in-use hold time of 24 hours after opening from the overwrap is also supported by the microbiological data. Dr. Karthik Krishnan's review recommended approval of the NDA.

B.4. Biopharmaceutics Aspects: The proposed to-be-marketed drug product, Norepinephrine Bitartrate in Sodium Chloride Injection is not quantitatively and qualitatively the same as the Levophed 4mg/4ml (NDA 007513). The Listed Drug is a concentrate in a vial and requires dilution with 5% dextrose prior to use, whereas the test product is a ready to use intravenous infusion. The recommended clinical dose and rate of infusion for the proposed Norepinephrine Bitartrate in Sodium Chloride Injection is identical to the LD. The difference in sodium chloride amount, the absence of Sodium Metabisulfite and the presence of Edetate Disodium Dihydrate in the proposed Norepinephrine in Sodium Chloride Injection is found unlikely to affect the in vivo disposition of Norepinephrine in human. Because there is no bioequivalence study, data from comparative *in vitro* physicochemical characteristics (e.g. pH and osmolality) have been provided to establish the scientific bridge to the LD as per the 21 CFR 320.24(b)(6). Dr. Zhuojun Joan Zhao's review concluded that the totality of data and information provided in the application, support that the formulation differences between the LD and the proposed drug product are not expected to demonstrate differences in the *in vivo* drug performance. Therefore, a scientific "bridge" between the proposed drug product and the LD has been established to support the 505(b)(2) application and the reliance on FDA's determination of safety and efficacy of the LD. In summary, biopharmaceutics information provided is adequate.

B.5. Container Closure System: The drug product is packaged in a 250 mL [redacted] non-PVC infusion bag. The infusion bag is not co-packaged with the catheter, needle, and the infusion rate controller. Based on study of leachables and extractables, and pharmaceutical development studies, the applicant has demonstrated compatibility with the active ingredient, excipients, container and closure components, and dosing components. The product stability data also indicate suitability of the proposed container closure system for the intended use.
The applicant has demonstrated the container closure package integrity of Norepinephrine Bitartrate in [redacted] Injection. USP physicochemical [<661>] and biological testing [<87>, <88>, <661.2>], and elemental impurity testing (USP <232> <233>) are appropriately performed. Based on the toxicological safety assessment of the available chemical and biological data, negligible risk of adverse effects in humans would be expected under the proposed conditions of manufacturing and storage and clinical use with the [redacted] infusion bag.

B.6. Product Stability, Expiration Date & Storage Conditions. The applicant provided data from stability studies from seven (7) registration batches stored in the intended commercial packaging under long-term conditions (25°C ± 2°C/40% RH ± 5% RH) for up to 12 months, intermediate condition (30°C ± 2°C/35% RH ± 5% RH) for up to 12 months, and accelerated conditions (40°C ± 2°C/25% RH ± 5% RH) for 6 months. Data reveal that the drug product is sensitive to temperature and pH with respect to isomerization to D-isomer (enantiomeric impurity). There is a downward trending in assay over time at all stability storage condition. However, based on the applicant's statistical analysis on the data using the 95% one-sided confidence, the predicted storage time at 25°C for L-norepinephrine to reach a 90% specification is more than 24 months. Therefore, the stability data and statistical analysis support an expiration dating period of 24 months for the drug product stored in the proposed container closure system at 20 – 25ºC (68 – 77ºF). The product excursions to 15 – 30ºC (59 – 86ºF) are acceptable. Photostability of the proposed product has been demonstrated. Study of product stability under temperature cycling conditions does not show any significant change with respect to all evaluated parameters. The out of pouch in use stability data indicated that the product is stable for 24 hours.

C. Assessment of Manufacturing Facilities:
Dr. Krishnakali Ghosh reviewed the process/facility information. The proposed commercial batch size is [redacted] corresponding to approximately [redacted] scale up from the registration batches (3 batches with a theoretical batch size of [redacted]). The composition of the drug product, the drug product manufacturing process, and the packaging system used to manufacture the drug product used in formal registration stability batches are the same as that proposed for commercial. The manufacturing process involves [redacted]. No overage or reprocessing will be employed in the manufacture of this drug product. The [redacted] solution [redacted] is tested for pH, appearance, assay of active, and bioburden. During [redacted], the following tests are also performed: bioburden, [redacted] volume and leak test. After that, secondary packaging tests are also performed for integrity/leak of the container closure system.
A pre-approval inspection was conducted at the drug product manufacturing site, [redacted]. Dr. Krishnakali Ghosh's evaluation of all unit manufacturing processes and review of FDA 483 observations from the pre-approval inspection concluded that the firm is not ready to manufacture commercial batches of Norepinephrine in Sodium Chloride Injection in 250 ml 0.9% Sodium Chloride due to lack of commercial manufacturing equipment installed and qualified, inadequate process controls for bag

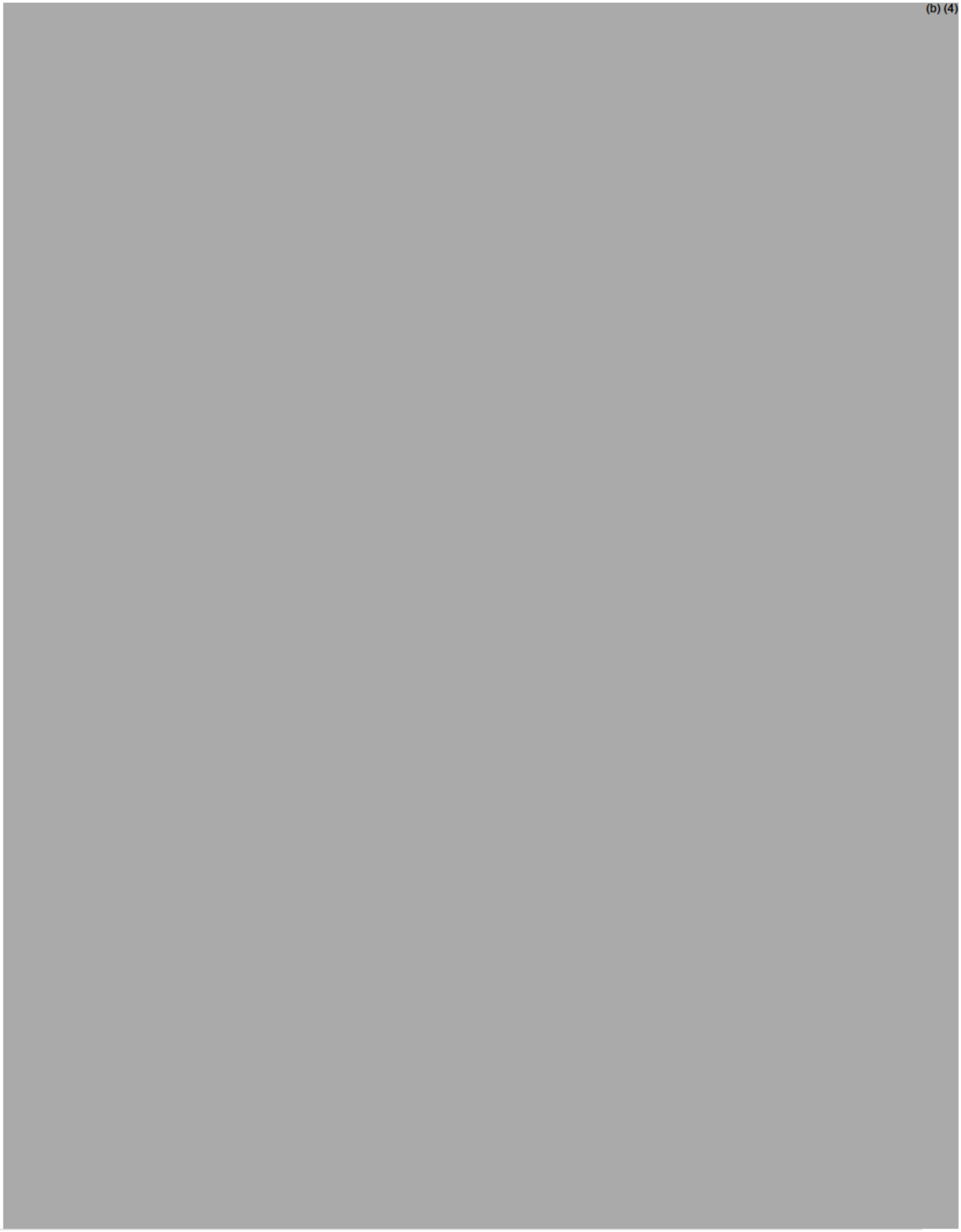
over-pouching, inadequate microbiological controls and environmental monitoring practices along with lack of GMP controls (i.e. failure investigations, stability studies program, maintenance and calibration, laboratory controls) observed during the pre-approval inspection related to manufacturing and testing of the drug product. Therefore, the overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA is **withhold** approval. The Panorama screen shot of the facility assessment recorded on 6/3/2021 is shown below. For additional details, please refer to Dr. Krishnakali Ghosh's facility review in Panorama dated 6/3/2021.

Manufacturing facility related deficiencies to be communicated in the CR letter:

1. During a recent inspection of the (b) (4) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility that were conveyed to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

Additional deficiencies related to manufacturing process:

(b) (4)



(b) (4)

[redacted]

D. The applicant has claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) on the basis that no extraordinary circumstances exists under 21 CFR 25.15(d) that would warrant preparation of an environmental assessment. The applicant's claim of categorical exclusion is acceptable.

E. OPQ's all labeling recommendations are reflected in the most recent version of the product labeling

F. Life Cycle Knowledge Information: The drug product (b) (4) [redacted]. Any future manufacturing changes with respect to these two critical attributes should be considered as a prior approval change.

OVERALL ASSESSMENT AND SIGNATURES

Application Technical Lead (ATL) Assessment and Signature:

At present, there are no outstanding deficiencies related to the drug substance, drug product, biopharmaceutics, and microbiology sections of the NDA. However, due to outstanding manufacturing process and facility related deficiencies, the OPQ's overall recommendation for NDA 214628 is ***complete response (CR)***.

Akm Khairuzzaman, Ph.D.
Application Technical Lead (ATL)
ONDP/DNDPIII/NDPB5

Akm Khairuzzaman -S

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Life Cycle Knowledge Management

NDA 214628 (Norepinephrine Bitartrate in Sodium Chloride Injection)

Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H (High)**	(b) (4)	Acceptable	Given that the product sterility is the high-risk attribute, any proposed changes in (b) (4) or microbiological testing-related product specification may need to be carefully evaluated.
Bacterial Endotoxin	Formulation Container Closure Process Parameters Scale/equipment/ Site	**H (High)**		Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels will need to be evaluated based on the maximum total daily dose.
Norepinephrine Assay	Temperature and pH	**M (Medium)**		Acceptable	Any change on sterilization process and pH of the formulation will need to be carefully evaluated
Enantiomeric Purity	pH and Temperature	**M (Moderate)**		Acceptable	Any change on sterilization process and pH of the formulation will need to be carefully evaluated

(Continued, Next Page)

QUALITY ASSESSMENT

Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evaluation	Comments
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low)	(b) (4)	Acceptable	
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	**M** **(Moderate)**		Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	**M** **(Moderate)**		Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)		Acceptable	

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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

Items	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	NOREPINEPHRINE (b) (4) IN SODIUM CHLORIDE INJECTION	Acceptable
Established name(s)	NOREPINEPHRINE (b) (4) IN SODIUM CHLORIDE INJECTION	Acceptable
Route(s) of administration	IV infusion	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Not Acceptable (b) (4)
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.	Acceptable
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the	Do not use if the solution is discolored (on the container label)	Acceptable

reconstituted or diluted product)		
Available dosage form(s)	IV injection	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Follows approved USP product for the LD	Equivalence statement should be next to strengths
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	Acceptable

1.2.3 Section 11 (DESCRIPTION)

Items	**Information Provided in the NDA**	**Assessor's Comments**
DESCRIPTION section		
Proprietary and established name(s)	NOREPINEPHRINE (b) (4) IN SODIUM CHLORIDE INJECTION	Acceptable
Dosage form(s) and route(s) of administration	IV injection, IV route	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Follows approved USP product for the LD	Acceptable
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided	Acceptable
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.	FDA recommended to use equivalence statement of "as follows: "Each mL contains the equivalent of 16 or 32 or 64 micrograms of norepinephrine base supplied as 31.90 or 63.80 or 127.6	Acceptable

	micrograms per mL of norepinephrine bitartrate monohydrate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	Acceptable
Statement of being sterile (if applicable)	Yes	Acceptable
Pharmacological/ therapeutic class	Yes	Acceptable
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	Not Applicable	Acceptable
Other important chemical or physical properties (such as pKa or pH)	pH 3.5 – 4.5	Acceptable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity	None present	Acceptable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Items	**Information Provided in the NDA**	**Assessor's Comments**
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	IV Injection	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
Available units (e.g., bottles of 100 tablets)		Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose,	(b) (4)	Acceptable

multiple-dose, single-patient use). Other package terms include pharmacy bulk package and imaging bulk package.		
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.)	Protect from light. (b) (4) [redacted]	Acceptable
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature [20° to 25°C (68° to 77°F)], excursions permitted to 15° to 30°C (59° to 86°F)	Acceptable
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."	Not Applicable	Acceptable
Include information about child-resistant packaging	Not Acceptable	Acceptable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Items	Information Provided in the NDA	Assessor's Comments
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Par Pharmaceutical (b) (4) [redacted]	Manufacturer's name and address is not provided.

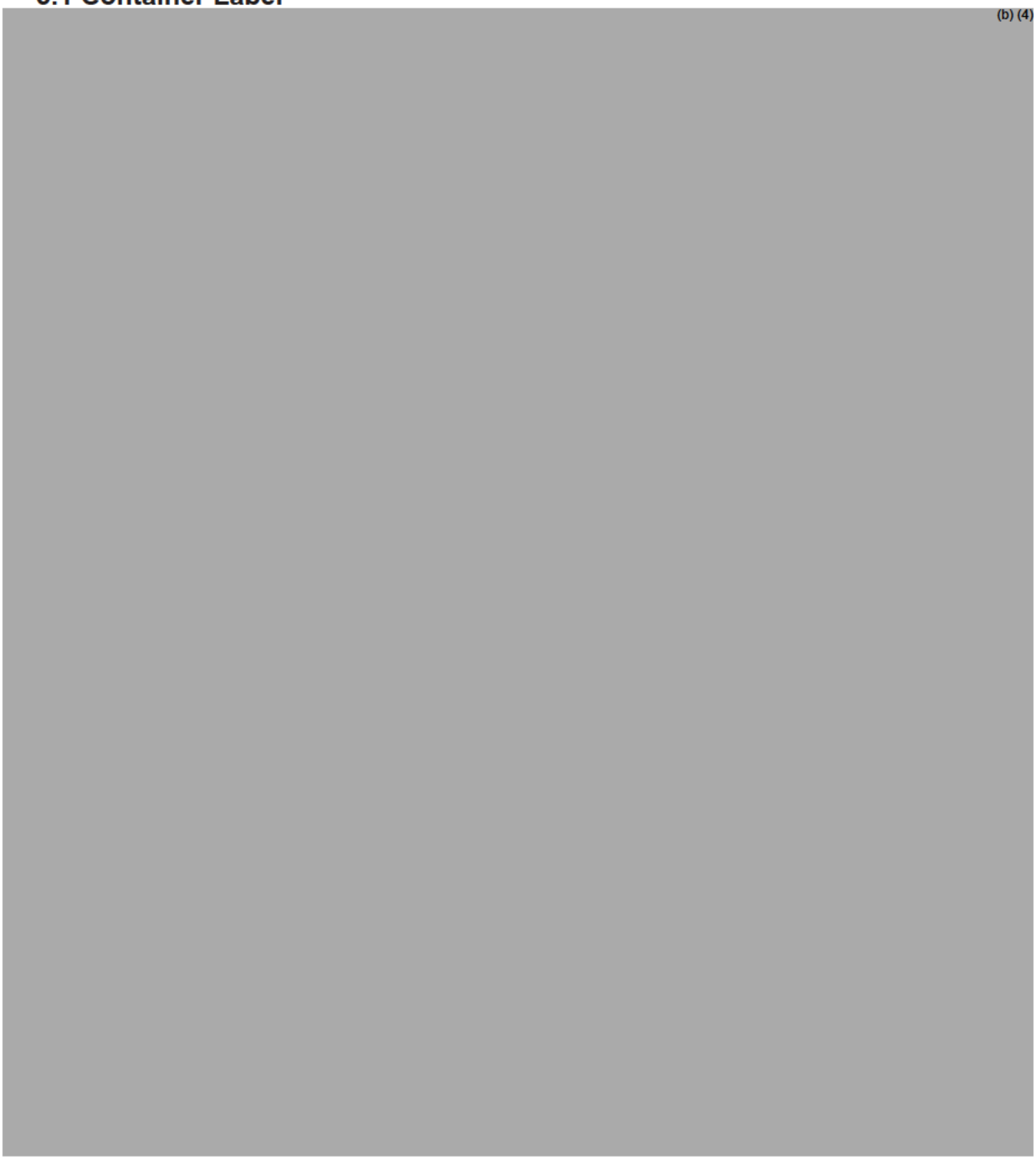
2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Not applicable

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)



Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	Norepinephrine (b) (4) in Sodium Chloride Injection	0.9% should be included before Sodium Chloride in the name of the product on the container labeling.
Dosage strength	4 mg / 250mL, 8 mg / 250mL, and 16 mg/250 mL	Acceptable
Route of administration	Intravenous Infusion	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Follows approved USP product for the LD	Acceptable
Net contents (e.g. tablet count)	250 ml per infusion bag	Acceptable
"Rx only" displayed on the principal display	yes	Acceptable
NDC number	yes	Acceptable
Lot number and expiration date	yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature [20° to 25°C (68° to 77°F)]	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use)	Single dose	Acceptable
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Not applicable	Acceptable
If alcohol is present, must provide the amount of	Not Acceptable	Acceptable

alcohol in terms of percent volume of absolute alcohol		
Items	**Information Provided in the NDA**	**Assessor's Comments**
Name of manufacturer/distributor	Distributed by: Par Pharmaceutical [redacted] (b) (4)	Manufacturer's name and address is not provided.
Medication Guide (if applicable)	Not Applicable	Acceptable
No text on Ferrule and Cap Overseal	Not Applicable	Acceptable
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.	Follows approved USP product for the LD.	Acceptable

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

1. In the dosage form and strength section of the package insert, FDA recommended to use "single dose container". (This has been inserted by FDA on the PI)
2. In the description section of the package insert, FDA recommended to use equivalence statement of "31.90 or 63.80 or 127.6 micrograms per ml of norepinephrine bitartrate monohydrate" on the labeling. (This has been inserted by FDA on the PI).
3. Please include "0.9%" before Sodium Chloride in the name of the product on the container labeling. (This will be communicated to the Applicant)

Overall Assessment and Recommendation: Adequate after the above deficiencies are fulfilled.

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 11/30/2020.

Secondary Assessor Name and Date (and Secondary Summary, as needed): David Claffey, Ph.D., 11/30/2020.

Akm Khairuzzaman

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David Claffey

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CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	214628
Assessment Cycle Number	# 1
Drug Product Name/ Strength	Norepinephrine in Sodium Chloride Injection/16, 32 and 64 µg/mL
Route of Administration	Intravenous Injection
Applicant Name	Nevakar, Inc.
Therapeutic Classification/OND Division	Agents used in Hypotension and Shock/ Division of Cardiology and Nephrology (DCN)
LD Number	NDA 007513, LEVOPHED® (Norepinephrine Bitartrate) Injection, USP
Proposed Indication	To raise blood pressure in adult patients with severe, acute hypotension
Primary Assessors	*Zhuojun Joan Zhao, Ph.D.*
Secondary Assessors	*Poonam Delvadia, Ph.D.*
Assessment	**Adequate**
Recommendation	Based on the assessment of the overall information, from a Biopharmaceutics perspective, NDA 214628 Norepinephrine in Sodium Chloride Injection, 16, 32 and 64 µg/mL, is recommended for **APPROVAL**.

Background

This 505 (b)(2) application seeks approval for Norepinephrine in Sodium Chloride Injection, 16, 32 and 64 µg/mL for intravenous (IV) administration, which is indicated to raise blood pressure in adult patients with severe, acute hypotension. The Listed Drug (LD) is Hospira's LEVOPHED® (Norepinephrine Bitartrate) injection, EQ 4 mg base/4 mL, NDA 007513.

Assessment Summary:

This Biopharmaceutics Review evaluated the overall data supporting the bridge between the proposed drug product and the LD.

The Nevakar's proposed Norepinephrine in Sodium Chloride Injection is intended for the same indications and has the same active ingredient, dosage form, dose, dosing regimen, and route of administration as the LD, but is different in concentration, excipients and flow rate of the infusion. Due to the difference, a biowaiver under 21 CFR 320.22(b)(1) is not feasible. However, a bridge between the proposed drug product and the listed drug product can be established based on 21 CFR 320.24 (b)(6).

The difference in sodium chloride amount, the absence of Sodium Metabisulfite and the presence of Edetate Disodium Dihydrate in the proposed Norepinephrine in Sodium Chloride Injection is found unlikely to affect the in vivo disposition of Norepinephrine in human. The

Applicant also provided comparative physicochemical data, which showed comparable pH and osmolality between the proposed and the LD products.

The Applicant has provided sufficient information to support the bridge between the proposed Norepinephrine in Sodium Chloride Injection and the listed drug, LEVOPHED® (Norepinephrine Bitartrate) injection under 21CFR 320.24 (b) (6).

List Submissions being assessed:

Document(s) Assessed	Date Received
0001 (1) Original Submission	August 15, 2020

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues): None

B.1 DRUG SUBSTANCE

The drug substance is Norepinephrine Bitartrate USP, same as the API in the LD product LEVOPHED® (Norepinephrine Bitartrate) injection. The Applicant found that Norepinephrine Bitartrate is freely soluble in (b) (4) water.

B.2 DRUG PRODUCT

The composition of the proposed Norepinephrine in Sodium Chloride Injection is shown in Table 1.

Table 1: Quantitative and Qualitative Composition of the Proposed Norepinephrine in Sodium Chloride Injection

Ingredient	Grade	Quantity/bag (250 mL)			Quantity/mL		
		16 mcg/mL	32 mcg/mL	64 mcg/mL	16 mcg/mL	32 mcg/mL	64 mcg/mL
Norepinephrine (as norepinephrine bitartrate)	USP	4 mg	8 mg	16 mg	16 mcg	32 mcg	64 mcg
Sodium chloride	USP	(b) (4)			9.0 mg	9.0 mg	9.0 mg
Edetate disodium dihydrate	USP				10 mcg	10 mcg	10 mcg
(b) (4)	NF						(b) (4)
	NF						
	USP						
	NF						
					(b) (4)		

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

B.3 BRIDGE BETWEEN THE PROPOSED DRUG PRODUCT AND THE LISTED DRUG PRODUCT

The following information is evaluated in support of the bridging between the proposed drug product and the listed drug product:

1. Formulation, dosage form, and administered volume
2. Comparative physicochemical data

1) Formulation, dosage form and administered volume

The quantitative composition between the proposed Norepinephrine in Sodium Chloride Injection and LEVOPHED® are shown in Table 2.

Table 2: Comparative table of Comparative Composition of the proposed drug product and LD LEDVOPHED®

Ingredient	Quantity/mL							
	Levophed					Norepinephrine in Sodium Chloride Injection		
	Undiluted	Diluted to 4 mcg/mL[a]	Diluted to 16 mcg/mL[a]	Diluted to 32 mcg/mL[a]	Diluted to 64 mcg/mL[a]	16 mcg/mL	32 mcg/mL	64 mcg/mL
Norepinephrine, USP	1 mg	4 mcg	16 mcg	32 mcg	64 mcg	16 mcg	32 mcg	64 mcg
Sodium Chloride, USP	q.s. for isotonicity	(b) (4)				9.0 mg	9.0 mg	9.0 mg
Edetate Disodium Dihydrate, USP	--					0.01 mg	0.01 mg	0.01 mg
Sodium metabisulfite, USP	(b) (4)					--	--	--
								(b) (4)

Reviewer's Assessment:

Based on the proposed label, Nevakar's Norepinephrine in Sodium Chloride Injection is a ready to use intravenous injection solution, whereas LEVOPHED® is presented as a concentrated solution (4 mg/4 mL) to be diluted with 5% dextrose or sodium chloride injection solution with 5% dextrose to a final concentration of 4 µg/mL prior to administration. Higher concentration solutions might be used in patients requiring fluid restriction per LEVOPHED® label. Based on the flexibility in preparation of the final concentration for intravenous infusion, the proposed concentrations 16, 32 and 64 µg/mL of Nevakar's Norepinephrine in Sodium Chloride Injection is deemed acceptable from Biopharmaceutics perspective, as the same dose could be given by adjusting the infusion flow rates shown in Table 3.

Table 3: Dosing of Norepinephrine in Sodium Chloride Injection Compared to LEVOPHED®

Presentation (mg/mL)	Concentration (mcg/mL)	Initial Dose		Maintenance Dose	
		Dose per Minute (mcg/min)	Flow Rate (mL/min)	Dose per Minute (mcg/min)	Flow Rate (mL/min)
Levophed (4 mg in 1000 mL)	4	8-12	(b) (4)	2-4	(b) (4)
Norepinephrine in Sodium Chloride Injection 16 mcg/mL (4 mg in 250 mL)	16				
Norepinephrine in Sodium Chloride Injection 32 mcg/mL (8 mg in 250 mL)	32				
Norepinephrine in Sodium Chloride Injection 64 mcg/mL (16 mg in 250 mL)	64				

The amount of sodium chloride at the point of patient contact from Nevakar's Norepinephrine in Sodium Chloride Injection and the diluted LD product are similar (shown in Table 2), while the main difference between the two formulations are the absence of Sodium Metabisulfite and the presence of Edetate Disodium (EDTA) Dihydrate in the proposed Norepinephrine in Sodium Chloride Injection.

- Sodium Metabisulfite is used as (b) (4) (antioxidant) in the LD product. The absence of Sodium Metabisulfite in Nevakar's Norepinephrine in Sodium Chloride Injection is not likely to affect the in vivo disposition of Norepinephrine.

- The Applicant added EDTA (10 µg/mL) as chelating (b) (4) agent the in the proposed Norepinephrine in Sodium Chloride Injection, as norepinephrine is (b) (4) .
  The Applicant conducted literature search for the effects of EDTA on the pharmacokinetics and/or pharmacodynamics in human for norepinephrine, catecholamines, epinephrine and dopamine and provided the following justification for the presence of EDTA in Nevakar's Norepinephrine in Sodium Chloride Injection[1]:

  1. EDTA is unlikely to affect norepinephrine's mechanism of action in humans based on different mechanism of action of EDTA and norepinephrine. EDTA is a chelating agent, (b) (4) , while Norepinephrine functions as a peripheral vasoconstrictor (alpha-adrenergic action) and an inotropic stimulator of the heart and dilator of coronary arteries (beta-adrenergic action)[2].
  2. Norepinephrine is metabolized in the liver and other tissues by a combination of reactions involving the enzymes catechol-O-methyltransferase (COMT) and MAO[2], while EDTA formed chelate is excreted in the urine with 50% in 1 hour and over 95% in 24 hours[3].

3. Also, refer to the Pharmacology/Toxicology review for the evaluation of the safety of the proposed amount of EDTA in Norepinephrine in Sodium Chloride Injection.

Therefore, information listed in labels and literature support that the presence of EDTA (10 µg/mL) in Nevakar's Norepinephrine in Sodium Chloride Injection is not likely to affect the in vivo disposition kinetics of Norepinephrine in human.

2) **Comparative Physicochemical Data**

The Applicant provided physicochemical property data of the proposed Norepinephrine in Sodium Chloride injection and LD product.

Table 4: Physicochemical Property Data for the Proposed Norepinephrine in Sodium Chloride Injection versus LD Product

	Levophed								
	No Dilution			Diluted to 4 mcg/mL with 5% Dextrose Injection			Diluted to 4 mcg/mL with 5% Dextrose and Sodium Chloride Injection		
Test	Lot: 080953A Expiry: 01 Feb 2021	Lot: 050203A Expiry: 01 Nov 2020	Lot: 050303A Expiry: 01 Nov 2020	Lot: 080953A Expiry: 01 Feb 2021	Lot: 050203A Expiry: 01 Nov 2020	Lot: 050303A Expiry: 01 Nov 2020	Lot: 080953A Expiry: 01 Feb 2021	Lot: 050203A Expiry: 01 Nov 2020	Lot: 050303A Expiry: 01 Nov 2020
pH	3.47	3.40	3.41	4.33	4.24	4.30	4.03	4.10	4.07
	3.44	3.40	3.41	4.30	4.23	4.29	4.02	4.10	4.07
	3.44	3.39	3.41	4.29	4.22	4.28	4.02	4.09	4.07
Osmolality (mOsm/kg)	262	263	258	260	266	262	551	556	572
	266	259	263	263	263	258	560	560	565
	261	260	267	259	261	266	557	568	569
	Norepinephrine in Sodium Chloride Injection								
		16 µg/mL			32 µg/mL		64 µg/mL		
	Time Point	Batch: 1980008	Batch: 1980009	Batch: 1980010	Batch: 1980007		Batch: 1980005	Batch: 1980006	Batch: 1980012
pH	Initial	4.1	4.0	4.0	4.0		3.9	3.9	4.0
	6 Month	4.1	4.1	4.1	4.2		4.0	4.0	4.1
	12 Month	4.1	4.0	4.1	4.1		4.0	4.1	4.0
Osmolality (mOsm/kg)	Initial	279	281	280	280		282	278	279
	6 Month	278	280	283	295		283	281	289
	12 Month	287	289	288	284		288	288	283

Reviewer's Assessment:

As shown in Table 4, Nevakar's Norepinephrine in Sodium Chloride Injection, 16, 32 and 64 µg/mL has similar pH (3.9-4.1) and osmolality (278 to 289 mOsm/Kg) comparable to those of the LD product, LEVOPHED® without dilution (pH 3.39-3.47; osmolality 258-267 mOsm/kg) and with dilution (pH 4.02-4.33; osmolality 258-572 mOsm/kg).

[1] \\CDSESUB1\evsprod\nda214628\0001\m1\us\112-other-correspondence\request-for-waiver-for-in-vivo-bioavailability-studies.pdf

[2] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c4de72a8-2a75-4984-ce90-e4870226dc12

[3] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=290c3e9c-c0c6-440a-1a9c-46e3e2b07a77

Poonam Delvadia

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Zhuojun Zhao

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214628
Assessment Cycle Number	01
Drug Product Name/ Strength	Norepinephrine in Sodium Chloride Injection / 16 mcg/mL, 32 mcg/mL, and 64 mcg/mL
Route of Administration	Intravenous
Applicant Name	Nevakar, Inc.
Therapeutic Classification/ OND Division	CDER/OND/ODEI/DCRP
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD seq #0001	08/17/2020
eCTD seq #0003	10/02/2020
eCTD seq #0006	12/01/2020
eCTD seq #0009	12/22/2020

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

Remarks: The drug product is indicated to raise blood pressure in adult patients with severe acute hypotension and references the listed drug Levophed 4mg/4ml (NDA 007513). The drug product is presented in 250-mL (b) (4) non-PVC infusion bag in three strengths (16 mcg/mL, 32 mcg/mL, and 64 mcg/mL) for single use intravenous administration at 8-12 mcg/min (followed by a maintenance dose of 2-4 mcg/min). This review includes information requests sent on 11/17/2020 and 12/11/2020, as well as responses received on 12/01/2020 and 12/22/2020.

Concise Description of Outstanding Issues: None

Supporting Documents: None

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Section 3.2.P.1, pg. 1/3 in "description-and-composition.pdf"

Norepinephrine in Sodium Chloride injection is a clear, colorless, sterile solution presented in three strengths: 16 mcg/mL, 32 mcg/mL, and 64 mcg/mL. All three presentations are in 250 mL volume filled into a 250 mL (b) (4) non-PVC infusion bag for single use intravenous administration.

Composition

Section 3.2.P.1, pg. 2/3 in "description-and-composition.pdf"

Ingredient	Quantity per mL	Function
Norepinephrine bitartrate, USP	16 mcg, 32 mcg, or 64 mcg	Active Ingredient
Sodium Chloride USP	9 mg	Tonicity modifier
Edetate disodium dihydrate, USP	10 mcg	Chelating agent
(b) (4)		

Container closure system

Section 3.2.P.1, pg. 3/3 in "description-and-composition.pdf"

Primary container: 250 mL (b) (4) non-PVC infusion bag (b) (4)

Component	Description	Manufacturer
(b) (4)		

The bag and closure system drawing provided (*Section 3.2.P.1, pg. 1/1 in* (b) (4)) is replicated below with the relevant format highlighted in yellow:

Secondary packaging: The infusion bag is packaged individually in a (b) (4) aluminum foil pouch (b) (4) with an oxygen scavenger (b) (4).

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Assessment: *Adequate*
The firm provided an adequate description of the drug product's composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

[redacted]

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MICROBIOLOGY LIST OF DEFICIENCIES

None

Primary Microbiology Assessor Name and Date:
Karthik Mosur Krishnan, Ph.D., 01/07/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Yeissa Chabrier Rosello, Ph.D., 01/07/2021

Karthik Krishnan

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Date: 1/07/2021 02:55:16PM
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Yeissa Chabrier Rosello

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Date: 1/15/2021 10:41:25AM
GUID: 5317ea990000ce969cecabfa83284493

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/s/

AKM KHAIRUZZAMAN
06/04/2021 08:47:49 AM
A Complete Response (CR) is recommended from OPQ due to drug product manufacturing facility related issues.