CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215875Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215875		
Applicant Name	PAR Sterile Products, LLC		
Drug Product Name	Epinephrine in Sodium Chloride Injection		
Dosage Form.	Injection		
Proposed Strength(s)	8 mcg/mL, 16 mcg/mL, 20 mcg/mL, 32 mcg/mL, and 40 mcg/mL		
Route of Administration	Intravenous		
Maximum Daily Dose	12 mg (See clinical review)		
Rx/OTC Dispensed	Rx		
Proposed Indication	Increase mean arterial blood pressure in adult patients with hypotension associated with septic shock		
Drug Product Description	250 mL single-dose infusion bags (non-PVC with single-funciton connector port) containing 250 mL of a sterile, clear, colorless solution in 250 mL 0.9% sodium chloride. Product is contained in an aluminum foil pouch with oxygen scavenger.		
Co-packaged product information	N/A		
Device information:	Infusion bag with Single Function Connector Port and Cap		
Storage Temperature/ Conditions	20° to 25°C (68° to 77°F) [*See USP Controlled Room Temperature*]. Epinephrine is light sensitive. Protect from light and freezing.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Ben Zhang OPQ/ONDP/DNDAPI/NDB 3	Zhengfu Wang OPQ/ONDP/DNDAPI/NDB 3
	Drug Product/ Labeling	Akm Khairuzzaman OPQ/ONDP/DNDPIII/NDP B5	Theodore Carver OPQ/ONDP/DNDPIII/NDP B5

	Manufacturing	Suresh Dadiboyena OPQ/OPMA/DPMAIII/PMB9	Kamal Tiwari OPQ/OPMA/DPMAIII/PMB9
	Biopharmaceutics	Huong Moldthan OPQ/ONDP/DB/BB3	Haritha Mandula OPQ/ONDP/DB/BB3
	Microbiology	BreOnna DeLaine-Elias OPQ/OPMA/DMAI/MAB2	Neal J. Sweeney OPQ/OPMA/DMAI/MAB2
	Other (specify):	N/A	
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 24 months is granted when the drug product is stored 20° to 25°C (68° to 77°F)

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

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1) Background

The Applicant, Nevakar Injectables, Inc. has submitted NDA 215875 for marketing approval of five new pre-diluted strengths of epinephrine in 0.9% saline solution, as a treatment to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. This 505(b)(2) NDA relies on FDA's previous findings of safety and effectiveness for the listed drug, ADRENALIN® (epinephrine injection) 1 mg/mL, approved under NDA 204200 (Par Pharmaceutical, Inc.). The Epinephrine in 0.9% Sodium Chloride Injection product is a drug-device

combination product presented as a ready-to-use sterile solution in 250 mL IV infusion bags, with five strengths containing concentrations of 8 mcg/mL, 16 mcg/mL, 20 mcg/mL, 32 mcg/mL, and 40 mcg/mL epinephrine base.

2) Drug Substance (Epinephrine)

The drug substance is the R-enantiomer of epinephrine base consistently manufactured in a single crystalline form. The applicant referenced all CMC information on the drug substance to DMF (b) (4) This DMF has been reviewed and found adequate to support other applications. There have been no quality related amendments since the DMF was found adequate in the last review cycle, and DMF (b) (4) is adequate to support the current NDA. The specification from the drug product manufacturer is consistent with the specification from DMF (b) (4) and the USP monograph, and the NDA includes CoAs from both the drug substance and drug product manufacturer for 2 drug substance batches.

3) Drug Product (Epinephrine in sodium chloride)

The drug product is a 250 mL ready-to-use single-dose sterile solution in infusion bags. The inactive ingredients are sodium chloride, hydrochloric acid and/or sodium hydroxide, disodium edetate dihydrate (EDTA), L (+) – tartaric acid, and (b) (4) All excipients are at acceptable levels; notably the formulation does not contain an antioxidant; however, it is packaged in an opaque aluminum pouch containing an oxygen scavenger, which protect the drug product from oxidation and light degradation. No other infusion devices are co-packaged with the drug product. Extractable/leachable studies support compatibility of the infusion bags with the epinephrine solution. The tests and acceptance criteria are appropriate to support drug product quality.12 months long-term and 6 months accelerated stability data support a shelf life of 24 months for the drug product when stored at the recommended storage condition. The batch release and stability data support stability of epinephrine with respect to oxidative degradation and S-isomer formation through the proposed shelf life. In-use ability data were provided to support use of the drug product for up to (b) (4) hours after removal from the foil pouch.

4) Manufacturing

Process: The drug product us manufactured (b) (4) (b) (4) Exhibit batches were manufactured at (b) (4) and (b) (4) (intended commercial) scales using equipment of the same design and operating principles as for the commercial process. The in-process controls and compatibility studies for

product contact equipment were found to be adequate. The manufacturing process overall is adequate.
Facilities: All manufacturing facilities were reviewed and overall approval recommended based on previous inspection history and manufacturing experience (see Table 2 on page 2 of the Manufacturing review).

5) Biopharmaceutics
The proposed drug is a ready-to-use diluted solution of epinephrine for intravenous use; therefore, the biopharmaceutics review concerned the biowaiver request and physiochemical comparison to the diluted listed drug. The review concluded that the physicochemical comparison supports the bridge between the listed drug and the proposed drug product and that and additional *in vivo* bioequivalence (BE) study is not required. The NDA is recommended for approval from the biopharmaceutics perspective.

6) Microbiology
The microbiology review covered aspects of the drug product manufacturing including the (b) (4) process and validation, the container-closure system, the microbiological controls including release and stability test, data, and specifications, environmental monitoring, labeling, and other microbiological aspects. No deficiencies were identified, and the NDA is recommended for approval from the microbiology perspective.

7) Quality Labeling
The quality labeling review identified several edits to be recommended in the prescribing information and container labeling. The labeling is recommended for approval after these revisions have been implemented.

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): Choose Yes or No.

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None

Comparability Protocols (PACMP): No
Comments: None

Additional Lifecycle Comments:

The drug product is very sensitive to minor changes in pH, temperature, and light. Any future manufacturing changes with respect to these critical attributes should be considered as a prior approval change. Additionally, note that this product has a stability issue. Therefore, any prior approval supplement (PAS) regarding extension of expiry date need be carefully reviewed.

Theodore Carver

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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	None	Acceptable
Established name(s)	EPINEPHRINE 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.	Injection: 250 mL single-dose infusion bags: – 2 mg (b) (4) epinephrine (8 mcg/mL) in 0.9% sodium chloride – 4 mg (b) (4) epinephrine (16 mcg/mL) in 0.9% sodium chloride – 5 mg (b) (4) epinephrine (20 mcg/mL) in 0.9% sodium chloride – 8 mg (b) (4) epinephrine (32 mcg/mL) in 0.9% sodium chloride – 10 mg (b) (4) epinephrine (40 mcg/mL) in 0.9% sodium chloride	(b) (4) (b) (4) because epinephrine used in the formulation is a base
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-	Single dose.	Acceptable

use). Other package terms include pharmacy bulk package and imaging bulk package.		
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)	None	Acceptable
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	Active ingredient is not a salt, it's a base	Acceptable
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)	EPINEPHRINE 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.	Active ingredient is not a salt, it's a base	Acceptable
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided in a tabular format	Acceptable

Reference ID: 5142498

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.	Provided in a tabular format	Acceptable
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)	Section 11 says, *"It has a pH range of* (b) (4)	The pH is corrected in the PI as "3.7-4.3" because pH is revised in the DP specification. It is now 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)	Not applicable	Acceptable
Identification of dosage forms, e.g., shape, color,	Provided	Acceptable

Reference ID: 5142498

coating, scoring, imprinting, NDC number		
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 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.)	The following statement is provided: *"Epinephrine is light sensitive. Protect from light and freezing.* (b) (4) [redacted] *"Keep in foil overwrap until ready to use. Discard after 24 hours of opening overwrap"*	The statement in the PI has been edited to read as follows: "*"Epinephrine is light sensitive. Protect from light and freezing."* *"Keep in foil overwrap until ready to use. Discard after 24 hours of opening overwrap"* This is now acceptable.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store between 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].	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 (b) (4) [redacted]	Not Acceptable	Acceptable

1.2.6 Manufacturing Information After Section 17 (for drug products)

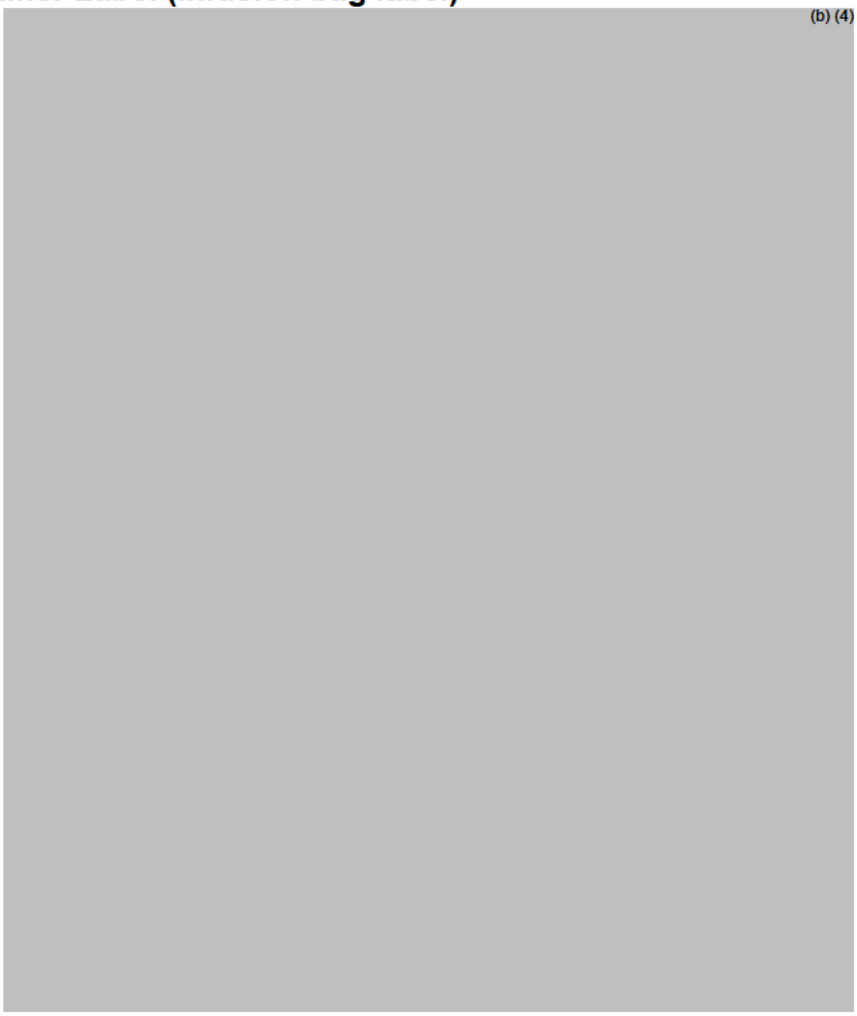
Items	Information Provided in the NDA	Assessor's Comments
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Par Pharmaceutical Cranbury, NJ 08512	Acceptable

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 (infusion bag label)



Note: All other strengths have identical information except for strength and NDC number.

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Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	Epenephrine in 0.9% Sodium Chloride Injection	Acceptable
Dosage strength	Provided	Acceptable
Route of administration	Intravenous Infusion	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not a salt	Acceptable
Net contents	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 between 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].	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 alcohol in terms of percent volume of absolute alcohol	Not Acceptable	Acceptable
Name of manufacturer/distributor	Distributed by: Parr Pharmaceutical Chestnut ridge, NY 10977	Acceptable
Medication Guide (if applicable)	Not Applicable	Acceptable
No text on Ferrule and Cap	Not Applicable	Acceptable

Overseal		
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: The following container/ closure labeling comment has been sent out to the Applicant.

1. *Include the following information on your infusion bag and overwrap label:*
   (a) quantitative amount of all inactive ingredient
   (b) pH

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation: *Overall, the labeling is acceptable. Some CMC edits were made directly in the PI document, uploaded into the SharePoint. Additional comment on Carton and Container Labeling were communicated to the Applicant. Once the Applicant accept them and revise their Carton and Container Labeling, it should be acceptable.*

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 1/30/2023.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Theodore Carver, Ph.D., 1/30/2023

Reference ID: 5142498

Akm Khairuzzaman

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BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	Epinephrine in 0.9% Sodium Chloride Injection
NDA Number	215875
Assessment Cycle Number	Original-1
Drug Product Name/ Strength	Epinephrine in 0.9% Sodium Chloride Injection / 8, 16, 20, 32, and 40 mcg/mL
Route of Administration	Intravenous
Applicant Name	Nevakar Injectables, Inc.
Therapeutic Classification/ OND Division	CDER/OND/OII/DPACC
LD Number	NDA-204200 (Adrenalin®)
Proposed Indication	Indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

Assessment Recommendation: **Adequate**

Assessment Summary:

Nevakar Injectables, Inc. (The Sponsor) is seeking approval of Epinephrine in 0.9% Sodium Chloride Injection / 8, 16, 20, 32, and 40 mcg/mL, originally submitted on 06/22/2022 under NDA-215875 via the 505(b)(2) pathway using Adrenalin®) as the listed drug (LD).

The current marketed product, Adrenalin is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 1 mL of solution in a single dose clear glass vial. Adrenalin treatment for hypotension associated with septic shock requires to dilute 1 mL (1 mg) of epinephrine from its vial to 1,000 mL of a 5% dextrose or 5% percent dextrose and sodium chloride solution to produce a 1 µg per mL dilution[1]. Each mL of the diluted product contains 1 µg of the Epinephrine API.

The proposed drug, Epinephrine in 0.9% Sodium Chloride Injection is a sterile (b) (4) solution of epinephrine filled into 250-mL non-PVC infusion bags for intravenous (IV) administration and is available in five strengths containing epinephrine base equivalent to 8 mcg/mL, 16 mcg/mL, 20 mcg/mL, 32 mcg/mL, and 40 mcg/mL. Nevakar' s Epinephrine in 0.9% Sodium Chloride Injection is presented in a ready-to-use formulation that does not require further dilution as in LD (Adrenaline which requires further dilution prior to administration).

[1] \\CDSESUB1\EVSPROD\nda215875\0001\m1\us\114-labeling\listed-drug\approved\adrenalin-pi-2019.pdf

Features	List Drug (LD)	Proposed Drug Product
Route	Injection: 1 mg/mL single dose vial and 30 mg/30 mL (1 mg/mL) multiple dose vial (3)	Epinephrine in 0.9% sodium chloride injection is ready to use. No further dilution prior to infusion.
Mode of administration	Adrenalin can be injected intramuscularly (IM) or subcutaneously (SC) into the anterolateral aspect of the thigh, through clothing if necessary.	For intravenous infusion only. Product presentation does not support IM or SC use.

1. Biowaiver: Requested in Module 1.12.15

Since the excipients in the proposed product quantitatively and qualitatively (Q1/Q2) differ from the LD product, the Applicant has intended to bridge the proposed product to the LD product via 21 CFR 320.24(b)(6) and has requested a waiver of the *in vivo* bioavailability studies. The Biopharmaceutics assessment focuses on the information submitted to bridge the two products. As part of the bridging strategy, the Applicant submitted comparative physicochemical data to demonstrate that the pH and osmolality of the proposed product are similar to the LD. Based on the submitted information, this Reviewer concludes that the presence of the excipients unique to the proposed product, the exclusion of the excipients from the LD product, or the differences in the concentration of the excipients between the proposed product and the LD are not expected to alter the *in vivo* PK profile of Epinephrine following an intravenous route of administration. The Applicant has submitted adequate information and justification in support of the bridge between the LD and the proposed product. Consistent with 21 CFR 320.24 (b)(6), this Reviewer deems the information supporting the relative bioavailability of the proposed drug product to the LD to be adequate, and a ***scientific bridge*** has been established to the Agency's finding of safety and effectiveness for the Listed Drug for the approval of the proposed drug product per 505 (b)(2) application pathway. Thus, an additional *in vivo* bioequivalence (BE) bridging study is not required.

From a Biopharmaceutics perspective, NDA 215875-ORIG-1 for Epinephrine injection 0.9% Sodium Chloride Injection / 8, 16, 20, 32, and 40 mcg/mL is adequate and is **RECOMMENDED** for approval.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0000 (1): original submission **0005: Quality / Response**	**06/22/2022** **11/08/2022**

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

B.1 BCS DESIGNATION

Assessment: The submission does not contain a request for BCS Designation.

Solubility: The solubility of epinephrine in water is dependent on pH. The minimal solubility has been reported at pH 9.4 due to presence of unionized species. The physical form or particle size of the drug substance is not likely to influence the drug product characteristics as the drug product is formulated as a solution.

Permeability: Not provided.

Dissolution: Drug product is solution, so dissolution information is not applied.

B.2 BRIDGING OF PROPOSED DRUG PRODUCT TO THE LD PRODUCT

In pre-IND meeting, it was agreed that that due to drug concentration differences and qualitative and quantitative differences in inactive ingredients, the proposed product and the LD can be bridged under 21 CFR 320.24(b)(6).

The Applicant submitted a side-by-side comparison of the composition of the proposed product and the LD is presented in Table 2. The major differences being a lower concentration of epinephrine (ready-to-use for the proposed product vs to-be-diluted for Adrenalin®), low concentration of edetate sodium (EDTA) in the proposed product (0.01 mg/mL) than in Adrenalin (0.20 mg/mL) and the absence of sodium metabisulfite in proposed product. The reviewer calculated the final concentration of the LD after dilution per instruction. (i.e., The concentrated solution is diluted using 5% dextrose injection or 5% dextrose and sodium chloride solution to achieve the final concentration of 1mcg/mL for administration via intravenous infusion (IV).

The proposed drug product, Epinephrine in 0.9% Sodium Chloride Injection is a sterile [redacted]^(b) (4) solution of epinephrine filled into 250-mL non-PVC infusion bags for intravenous (IV) administration and is available in five strengths containing epinephrine base equivalent to 8 mcg/mL, 16 mcg/mL, 20 mcg/mL, 32 mcg/mL, and 40 mcg/mL.
The proposed drug product and the LD share the same IV route of administration, and IV dosing regimen and dosing recommendation, with the only exception being the administered volumes (i.e., infusion flow rate in mL/min) which differ for the two products.

Further, physicochemical analysis of the proposed product and the LD (both diluted in 5% Dextrose and undiluted) shows that the two products have similar osmolality. However, the osmolarity of the LD is diluted in 5% Dextrose and 0.9% Sodium Chloride Injection) and pH (Table 3[2]) is significantly high for all tested lots. The applicant was asked to provide physicochemical characterization, including pH and osmolarity of LD that is diluted in 0.9% Sodium Chloride only. The IR was sent dated 10/25/2002

[2] \\CDSESUB1\EVSPROD\nda215875\0001\m2\27-clin-sum\summary-biopharm.pdf

requesting comparison of physicochemical properties (i.e., pH and osmolarity) data (n = 3) of proposed drug product and Listed Drug (LD) when the LD is diluted in 0.9% Sodium Chloride. The IR response was received on 11/08/2022 and the Applicant adequately addressed the IR (Please refer to Appendix for additional details).

Based on the above assessment, this Reviewer concludes that the presence of the excipients unique to the proposed product, the exclusion of the excipients from the LD product, or the differences in the concentration of the excipients between the proposed product and the LD are not expected to alter the *in vivo* PK profile of Epinephrine following an IV route of administration. The Applicant has submitted adequate information and justification in support of the bridge between the LD and the proposed product. Consistent with 21 CFR 320.24 (b)(6), this Reviewer deems the information supporting the relative bioavailability of the proposed drug product to the LD to be adequate, and a ***scientific bridge*** has been established to the Agency's finding of safety and effectiveness for the Listed Drug. Thus, an additional *in vivo* bioequivalence (BE) bridging study is not required.

Table 2. Composition of Epinephrine in 0.9% Sodium Chloride Injection and the LD, Adrenalin (NDA 204200)

Ingredient	Epinephrine in 0.9% Sodium Chloride Injection					Adrenalin (NDA 204200)	Adrenaline diluted (Calculated by Reviewer)
Epinephrine base, USP	8 mcg/mL	16 mcg/mL	20 mcg/mL	32 mcg/mL	40 mcg/mL	1 mg/mL	1 mcg/mL
Sodium chloride, USP	9 mg/mL					7.3 mg/mL	0.0073 mg/mL
Sodium Metabisulfite	Not Present					0.457 mg/mL	457 mcg/mL
Edetate Disodium Dihydrate, USP	0.01 mg/mL					0.20 mg/mL	0.002 mg/mL
L (+)-Tartaric Acid, NF	6.6 mcg/mL	13.1 mcg/mL	16.4 mcg/mL	26.2 mcg/mL	32.8 mcg/mL	2.25 mg/mL	2.25 mcg/mL
Hydrochloric acid, NF	Q. S. to adjust pH to 4.0					Q. S.	Q. S.
Sodium Hydroxide, NF	Q.S. to adjust pH to 4.0					1 mg/mL	1 mcg/mL
						(b) (4)	

NF = National Formulary; q.s. = quantity sufficient; USP = United States Pharmacopeia
Source: Notebook: 15268, 13480
1 Expiry Date – December 2021
2 Expiry Date – June 2021
3 Expiry Date – January 2022
4 Expiry Date – March 2022

Table 3. Physicochemical Property Data Comparison for Epinephrine in 0.9% Sodium Chloride Injection versus Listed Drug

Product		Adrenalin® (Epinephrine Injection, 1mg/mL)								
		Undiluted			Diluted to 1 mcg/mL with 5% Dextrose Injection			Diluted to 1 mcg/mL with 5% Dextrose and 0.9% Sodium Chloride Injection		
Test	Sample Number	Lot # 344613[1]	Lot # 336476[2]	Lot # 345632[3]	Lot # 344613[1]	Lot # 336476[2]	Lot # 345632[3]	Lot # 344613[1]	Lot # 347784[4]	Lot # 345632[3]
pH	Vial 1	4.17	4.16	4.11	4.53	4 5	4.33	4.31	4.3	4.32
	Vial 2	4.17	4.15	4.11	4.53	4.49	4.35	4 3	4.34	4.33
	Vial 3	4.18	4.12	4.1	4.59	4 53	4.36	4.32	4.31	4.32

Osmolality (mOsm/kg)	**Vial 1**	288	288	288	261	263	263	553	552	552	
	Vial 2	288	287	286	262	263	263	553	552	551	
	Vial 3	287	288	286	262	263	263	552	553	553	
Product		**Epinephrine in 0.9% Sodium Chloride Injection**									
Concentration		**8 mcg/mL**			**16 mcg/mL**			**20 mcg/mL**	**32 mcg/mL**	**40 mcg/mL**	
Test		**Batch: 2080023**	**Batch: 2080024**	**Batch: 2080031**	**Batch: 2080021**	**Batch: 2080022**	**Batch: 2080027**	**Batch: 2080028**	**Batch: 2080029**	**Batch: 2080025**	**Batch: 2080026**	**Batch: 2080032**
pH		4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Osmolality (mOsm/kg)		292	312	297	287	293	309	286	288	290	301	311

Source: Notebook: 15268, 13480

[1] Expiry Date – December 2021

[2] Expiry Date – June 2021

[3] Expiry Date – January 2022

[4] Expiry Date – March 2022

APPENDIX

BIOPHARMACEUTICS LIST OF DEFICIENCIES

(Dated 10/25/2022)

It is noted that the tonicity of the solution is significantly low in all tested lots for your proposed product, Epinephrine in 0.9% Sodium Chloride Injection in comparison to diluted listed drug (LD) in 5% dextrose and 0.9% Sodium Chloride. For ease of comparison, provide the comparative physicochemical properties (i.e., pH and osmolarity) data (n = 3) when the (List Drug (LD) is diluted in 0.9% Sodium Chloride.

Applicant's Response dated 11/08/2022

The Applicant provided the comparison of pH and osmolarity of two lots of the LD (Adrenalin®) when diluted in 0.9% sodium chloride injection (Table 4). Also, data for pH and osmolality for the 11 registration batches of Epinephrine in 0.9% Sodium Chloride injection are presented in Table 5.

Table 4: pH and Osmolality of Adrenalin®, diluted in 0.9% Sodium Chloride Injection, USP

Adrenalin® (Epinephrine Injection 1mg/mL diluted in 0.9% Sodium Chloride Injection, USP (Final concentration: 1 mcg/mL)								
Tests		Lot # 55323 Expiry Date – Mar 2024 Date of analysis: 01-Nov-2022			Lot # 56450 Expiry Date: Apr 2024 Date of analysis: 01-Nov-2022			
		Sample 1	Sample 2	Sample 3	Sample 1	Sample 2	Sample 3	
Appearance		CCS	CCS	CCS	CCS	CCS	CCS	
pH		4.88	4.74	4.84	4.80	4.79	4.84	
Osmolality (mOsm/kg)		290	292	287	286	286	286	
Color	L*	100	100	100	100	100	100	
	a*	0.0	0.0	0.0	0.0	0.0	0.0	
	b*	-0.1	0.0	0.1	0.1	0.0	0.1	

CCS - Clear colorless solution
Notebook: DOC16056

Table 5: pH and Osmolality at Release for Registration Batches of Epinephrine in 0.9% Sodium Chloride Injection

Strength	8 mcg/mL			16 mcg/mL			20 mcg/mL	32 mcg/mL	40 mcg/mL		
Batch Number	2080023	2080024	2080031	2080021	2080022	2080027	2080028	2080029	2080025	2080026	2080032
pH	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Osmolality (mOsm/Kg)	292	312	297	287	293	309	286	288	290	301	311

Review Assessment:

Based on submitted data, there is no significant difference observed between osmolality values for the LD diluted in 0.9% sodium chloride injection and Epinephrine in 0.9% Sodium Chloride Injection. Therefore, the Applicant's response is satisfactory.

Primary Biopharmaceutics Assessor's Name and Date: Huong Moldthan, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Haritha Mandula, Ph.D.

Huong Moldthan

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Date: 2/22/2023 03:04:09PM
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Haritha Mandula

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Date: 2/22/2023 04:01:23PM
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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Epinephrine in 0.9% Sodium Chloride Injection is indicated as a treatment to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.
NDA Number	215875
Assessment Cycle Number	01
Drug Product Name/ Strength	ADRENALIN®; Epinephrine in 0.9% Sodium Chloride Injection 8, 16, 20, 32, and 40 mcg/mL
Route of Administration	Intravenous Injection
Applicant Name	Par Sterile Products, LLC (formerly owned by Nevakar Injectables, Inc.) 300 Tice Blvd, Suite 230 Woodcliff Lake, NJ 07677
Therapeutic Classification/ OND Division	Division of Cardiology and Nephrology
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary**:** The submission **is recommended** for approval on the basis of sterility assurance.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
SN 0001 (original submission)	June 22, 2022
SN 0006 (updated batch records)	December 13, 2022
SN 0010 (transfer of ownership)	January 31, 2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A. This is a first cycle review.

Remarks: This NDA application relies on the Agency's previous findings of safety and effectiveness for the listed drug, ADRENALIN® (epinephrine injection) 1 mg/mL, approved under NDA 204200 (Par Pharmaceutical, Inc.).

ADRENALIN® is approved as 1 mg/mL single dose vials (NDA 204200). This application is seeking approval for the same clinical indication, route of administration, dose, and dosing regimen as those of the listed drug. Where ADRENALIN® must be diluted before administration, the proposed drug product is a drug-device combination product presented as a ready-to-use sterile solution in 250 mL IV infusion bags.

The applicant submitted a pre-IND meeting requestion (PIND 148210) requesting feedback regarding the proposed manufacturing process, including sterility assurance. The agency's written response, dated 7/22/2022, included a statement that the applicant microbial control strategy appeared reasonable and a recommendation to (b) (4)

It should also be noted that the ownership/applicant transferred from Nevakar Injectables, Inc. (NJ Center of Excellence, 1019 US Highway 202/206, Building K, Bridgewater, NJ 08807) to Par Sterile Products, LLC in SN 0010 dated January 31, 2023.

Concise Description of Outstanding Issues: None.

Supporting Documents:

- Microbiology review N (b) (4) MR01.pfd, dated 01/07/2021 and deemed adequate covers the manufacturing of (b) (4) (b) (4) This review covers the same container closure system and manufacturing equipment at the subject manufacturing site, (b) (4)

Select Number of Approved Comparability Protocols: 00

Product Quality Microbiology Assessment

S DRUG SUBSTANCE

The drug substance is not sterile; therefore, the API information is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** The drug product, Epinephrine in 0.9% Sodium Chloride Injection, is a clear, colorless, sterile solution in 250 mL 0.9% sodium chloride presented in five strengths, as summarize below.
  - 2 mg equivalent of epinephrine (8 mcg/mL) in 0.9% sodium chloride
  - 4 mg equivalent of epinephrine (16 mcg/mL) in 0.9% sodium chloride
  - 5 mg equivalent of epinephrine (20 mcg/mL) in 0.9% sodium chloride
  - 8 mg equivalent of epinephrine (32 mcg/mL) in 0.9% sodium chloride
  - 10 mg equivalent of epinephrine (40 mcg/mL) in 0.9% sodium chloride

- **Drug product composition –**

Ingredient, Quality Standard	Function	Quantity / mL				
		8 mcg/mL	16 mcg/mL	20 mcg/mL	32 mcg/mL	40 mcg/mL
Epinephrine base	API	8 mcg	16 mcg	20 mcg	32 mcg	40 mcg
Sodium Chloride	(b) (4)	9 mg	9 mg	9 mg	9 mg	9 mg
Disodium Edetate Dihydrate (EDTA)		10 mcg	10 mcg	10 mcg	10 mcg	10 mcg
L (+) – Tartaric acid		6.6 mcg	13.1 mcg	16.4 mcg	26.2 mcg	32.8 mcg
Hydrochloric acid	pH adjusting agent	q.s. for pH adjustment to 4.0				
Sodium hydroxide	pH adjusting agent	q.s. for pH adjustment to 4.0				
(b) (4)	(b) (4)	q.s.				

- **Description of container closure system –** The proposed container closure system is a 250-mL (b) (4) non-PVC infusion bag with a single function connector (SFC) system consisting of an SFC port and an SFC cap assembled with an SFC (b) (4) disc, packaged individually in (b) (4) aluminum foil (b) (4) with an oxygen scavenger.
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Component	Description	Supplier / Reference DMF
250 mL (b) (4) Bag (b) (4)	(b) (4)	(b) (4)
(b) (4) (b) (4) Bag and Port		

Images of the CCS are provided below for reference (3.2.P.7 pages 5,11 of 23).

Figure 2: Materials of Construction

(b) (4)

Assessment: *Adequate*

The information provided in the application adequately describes the drug product and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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/s/

THEODORE E CARVER
03/15/2023 10:03:29 PM