CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211363Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	211363 (Resubmission, Sequence 18, SDN 19)		
Applicant Name	International Medication Systems, Ltd.		
Drug Product Name	Epinephrine Injection		
Dosage Form.	Injection		
Proposed Strength(s)	(b) (4) mg/mL (0.1 mg/mL)		
Route of Administration	Intravenous		
Maximum Daily Dose	(b) (4) mg per day (per clinical estimate)		
Rx/OTC Dispensed	Rx		
Proposed Indication	To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.		
Drug Product Description	The drug product is a 10 mL solution of 0.1 mg/mL epinephrine contained in (b) (4) glass container within a Luer-Jet® prefilled syringe system. Prior to use, the contents of the syringe are added to 1000 mL of 5% Dextrose Injection USP or 5% Dextrose and Sodium Chloride solution.		
Co-packaged product information	None		
Device information:	The drug product is a single-dose prefilled syringe.		
Storage Temperature/ Conditions	Store at 20°C to 25°C; protect from light; do not freeze or refrigerate.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Ben Zhang ONDP/DNDAPI/NDB3	Zhengfu Wang ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Rao Kambhampati ONDP/DNDPII/NDPB5	Theodore Carver ONDP/DNDPII/NDPB5
	Manufacturing	Allison Aldridge OPMA/DPMAIV/PMB12	Sateesh Sathigari OPMA/DPMAIV/PMB12

	Biopharmaceutics	Rajesh Savkur ONDP/DB/BB3	Haritha Mandula ONDP/DB/BB3
	Microbiology	Jianli Xue OPMA/DMAI/MAB2	Nandini Bhattacharya OPMA/DMAI/MAB2
	Other (specify):	See CDRH consult below	
	RBPM	Grafton Adams OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver ONDP/DNDPII/NDPB5	
Consults	CDRH Consult Review for syringe device constituent: Primary Reviewer: Rong Guo, OPEQ/OHT3/DHT3C Secondary Reviewer: Courtney Evans, OPEQ/OHT3/DHT3C Conclusion: Adequate.		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

An expiration dating period of 20 months is granted when the drug product is stored at 20°C to 25°C.

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 211363 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 it purports the drug product to have. As such, OPQ recommends approval of this NDA from a quality perspective.

2.) **Background:**
The Applicant, International Medication Systems Ltd., resubmitted NDA 211363 on February 16, 2022. For the original NDA 211363 submission,

FDA issued a Complete Response based on a major deficiency identified in the OPQ integrated quality review dated 12/1/2018. (b) (4) (b) (4) (b) (4) The Applicant subsequently reformulated the drug product to optimize it (b) (4), prior to resubmitting the NDA with the new drug product composition. This NDA resubmission is the subject of this integrated quality review.

2) **Summary of the response to the previously identified drug product deficiency and the drug product review:**

To address the major deficiency identified in the previous review, the Applicant reformulated the drug product (b) (4) (b) (4) (b) (4) The Applicant provided release and stability testing data for three batches of the drug product manufactured using the new formulation (b) (4). These batches met specification at release and through the assigned shelf life. In addition, the acceptance criteria for impurities in the drug product specification were revised to appropriate limits (b) (4) The assigned drug product shelf life of 20 months is based on 24 months of long-term stability data for three batches of the reformulated drug product. The Applicant has satisfactorily addressed the deficiency identified in the previous Complete Response letter dated 12/12/2018.

3) **Summary of reviews for other disciplines.**

No significant changes to information provided for the drug substance, manufacturing, microbiology, and device information were reported. The updated information was reviewed and found to be adequate. The biopharmaceutics review concluded that the scientific bridge between the listed drug and the reformulated epinephrine injection drug product remains adequate and that therefore, no additional in vivo bioequivalence (BE) study is needed. Minor required labeling revisions have been communicated to the

Applicant and will be addressed in the final labeling. The NDA is adequate and recommended for approval from the OPQ perspective.

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
NDA 211363 Resubmission Review

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The following changes to the US Prescribing Information (USPI) document are recommended:

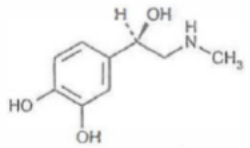
1) **Currently in the Description Section of the US Physician Information (USPI) document, the drug product was described first and then followed by drug substance. Per current USPI practice, the drug substance should be described first and then followed by the drug product.**

2) **Presently in the Description Section, inactive ingredients were not listed in the alphabetical order (b) (4). Therefore, it should be changed to as follows: Each mL of the solution contains epinephrine (0.1 mg) as the active ingredient and the following inactive ingredients: citric acid monohydrate (3.3 mg), edetate disodium dihydrate (0.004 mg), sodium citrate dihydrate (1.5 mg), sodium chloride (8.2 mg) (b) (4) and Water for Injection. Hydrochloric acid solution is added to dissolve the active ingredient. Sodium hydroxide solution is added to adjust the pH. Nitrogen is used for blanketing protection.**

3) **Pharmacologic/Therapeutic class information should be changed from (b) (4) (b) (4) to "Epinephrine is a non-selective alpha- and beta-adrenergic agonist".**

4) **Chemical name, structural formula, molecular weight, and structural formula information should be changed to as follows:**

   The chemical name of epinephrine is (*R*)-4-(1-Hydroxy-2-(methylamino)ethyl)benzene-1,2-diol. It has a molecular formula of $C_9H_{13}NO_3$ and molecular weight of 183.20 and the following structural formula:



   Epinephrine is practically insoluble in water and ethanol.

5) **Per USP Monograph, the following current statement "Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin." should be changed to as follows: Epinephrine injection should not be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate. Epinephrine solution deteriorates rapidly on exposure to air or light therefore it should be preserved in light-resistant containers.**

6) **In the How Supplied/Storage and Handling Section, the current statement should be changed to as follows for clarity: Each prefilled syringe is packaged in a carton. 10 individual cartons are shrink wrapped as a group of 10.**

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION (PI)

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	EPINEPHRINE INJECTION USP
Route(s) of administration	Adequate	Intravenous use
Dosage Forms and Strengths Heading in Highlight		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Injection: 1 mg/10 mL (0.1 mg/mL) single-dose prefilled syringe
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Single-dose prefilled syringe

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is colored or cloudy, or if it contains particulate matter. Discard any unused portion.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling	Adequate	

requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

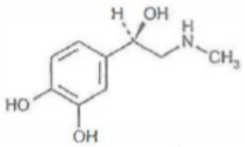
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Prefilled syringe containing epinephrine as the hydrochloride in a sterile solution.
Strength(s) in metric system	Adequate	10 mL single-dose prefilled syringe containing 1 mg/10 mL (0.1 mg/mL) epinephrine as the hydrochloride in a sterile solution.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	Single-dose prefilled syringe

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		Note: Currently in the description section, drug product was described first and then followed by drug substance. Per current USPI practice, the drug substance should be described first and then followed by the drug product.
Proprietary and established name(s)	Adequate	Epinephrine Injection USP. No proprietary name was proposed by the applicant.
Dosage form(s) and route(s) of administration	Adequate	Injection. Intravenous.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	Presently in the Description Section, inactive ingredients were not listed in the alphabetical order (b) (4) (b) (4). Therefore, it should be changed to as follows: Each mL of the solution contains epinephrine (0.1 mg) as the active ingredient and the following inactive ingredients: citric acid monohydrate (3.3 mg), edetate disodium dihydrate (0.004 mg), sodium citrate dihydrate (1.5 mg), sodium chloride (8.2 mg) (b) (4) (b) (4), and Water for Injection. Hydrochloric acid solution is added to dissolve the active ingredient. Sodium hydroxide solution is added to adjust the pH. Nitrogen is used for blanketing protection.

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.	Inadequate	See immediate above comment.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	Sterile aqueous solution.
Pharmacological/Therapeutic class	Inadequate	Presently it was stated as (b) (4) (b) (4) (b) (4) but it should be changed to "Epinephrine is a non-selective alpha- and beta-adrenergic agonist".
Chemical name, structural formula, molecular weight	Inadequate	Presently no molecular formula was included. The current information should be changed to as follows: The chemical name of epinephrine is (*R*)-4-(1-Hydroxy-2-(methylamino)ethyl)benzene-1,2-diol. It has a molecular formula of $C_9H_{13}NO_3$ and molecular weight of 183.20 and the following structural formula:  Epinephrine is practically insoluble in water and ethanol.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	pH 2.2-5.0

Section 11 (DESCRIPTION) Continued

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	Inadequate	Presently the following statement was included: Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. It should be changed to the following statement per USP monograph and current labeling: Epinephrine injection should not be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate. Epinephrine solution deteriorates rapidly on exposure to air or light therefore if should be preserved in light-resistant containers.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL) is available in a single-dose Luer-Jet™ Luer-Lock prefilled syringe
Strength(s) in metric system	Adequate	1 mg/10 mL (0.1 mg/mL)
Available units (e.g., bottles of 100 tablets)	Inadequate	Available units statement should be changed to as follows for clarity: Each prefilled syringe is packaged in a carton. 10 individual cartons are shrink wrapped as a group of 10.
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Single-dose prefilled syringe

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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Epinephrine is light sensitive. Protect from light until ready to use. Do not refrigerate. Protect from freezing. (b) (4)

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

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store at room temperature, between 20°C to 25°C (68°F to 77°F). (See USP Controlled Room Temperature.)
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling: Not applicable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Marketed by: International Medication Systems, Limited So. El Monte, CA 91733, U.S.A. An Amphastar Pharmaceuticals Company

2.0 PATIENT LABELING:

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides): Not applicable

3.0 CONTAINER AND CARTON LABELING

3.1 Container (Prefilled Syringe) Label

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Item	Items Proposed in Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	EPINEPHRINE INJECTION, USP
Strength(s) in metric system	Adequate	1 mg/10 mL (0.1 mg/ mL)
Route(s) of administration	Inadequate	Change from "FOR I.V. USE" to "For Intravenous Use"
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	1 mg/10 mL (0.1 mg/ mL)
"Rx only" displayed on the principal display	Adequate	Rx only
NDC	Adequate	NDC 76329-3318-1
Lot number and expiration date	Adequate	Yes, space was included for lot number and expiration date printing.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Due to lack of adequate space, storage conditions were not included on the prefilled pen label.
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, and these products require a "Not for direct infusion" statement.	N/A	Single-Dose (b) (4)
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	Due to lack of adequate space, ingredients information was not included on the container label.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Included

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items Proposed in Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	IMS LIMITED So. EL Monte, CA 91733, U.S.A.
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	Do not use if solution is colored or cloudy or contains particulate.
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.	Adequate	
And others, if space is available.	N/A	

3.2 Carton Labeling:

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Item	Items Proposed in Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Inadequate	Change "EPINEPHRINE Inj. USP" to EPINEPHRINE Injection USP
Strength(s) in metric system	Adequate	1 mg/10 mL (0.1 mg/mL)
Route(s) of administration	Adequate	For Intravenous Use
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	1 mg/10 mL
"Rx only" displayed on the principal display	Adequate	Rx Only
NDC	Adequate	NDC 76329-3318-1
Lot number and expiration date	Adequate	Space was included on the prefilled pen label for printing lot number and expiration date, therefore, it was not included on the carton label.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Store at 20°C to 25°C [68°F to 77°F] [See USP controlled room temperature].
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, and these products require a "Not for direct infusion" statement.	Adequate	Single-dose (b) (4)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	The current information should be changed to as follows: Each mL of the solution contains epinephrine (0.1 mg) as the active ingredient and the following inactive ingredients: citric acid monohydrate (3.3 mg), edetate disodium dihydrate (0.004 mg), sodium citrate dihydrate (1.5 mg), sodium chloride (8.2 mg) for adjustment of tonicity, and Water for Injection. Hydrochloric acid solution is added to dissolve the active ingredient. Sodium hydroxide solution is added to adjust the pH. Nitrogen is used for blanketing protection.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Included

Item	Items Proposed in Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	International Medication Systems, Limited So. El Monte, CA 91733, U.S.A. An Amphastar Pharmaceuticals Company
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	Protect from light by retaining product in carton until ready to use. Do not use if the solution is colored or cloudy or contains particulate matter. Caution: Handle glass with care. Inspect for damage prior to assembly.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Container and Carton Labeling: The container and carton labels will be adequate if the following suggested changes are incorporated in the revised documents.

Overall Assessment and Recommendation: Adequate with the following proposed changes to the and container and carton labels:

1) **On the container label make the following change: Change "FOR I.V. USE" to "For Intravenous Use".**

2) **On the carton label make the following changes:**

   a) **Change "EPINEPHRINE Inj. USP" to "EPINEPHRINE Injection USP".**

b) The current information regarding active ingredient and inactive ingredients should be changed to as follows: Each mL of the solution contains epinephrine (0.1 mg) as the active ingredient and the following inactive ingredients: citric acid monohydrate (3.3 mg), edetate disodium dihydrate (0.004 mg), sodium citrate dihydrate (1.5 mg), sodium chloride (8.2 mg) for adjustment of tonicity, and Water for Injection. Hydrochloric acid solution is added to dissolve the active ingredient. Sodium hydroxide solution is added to adjust the pH. Nitrogen is used for blanketing protection.

Primary Labeling Assessor Name and Date: Rao V Kambhampati, Ph.D. 6/4/2022

Rao Kambhampati

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BIOPHARMACEUTICS

Product Background:
NDA/ANDA: NDA-211363-ORIG-1-RESUB-19

Drug Product Name / Strength: Epinephrine injection, 0.1 mg/mL, 10 mL Pre-filled Syringe

Route of Administration: Intravenous injection

Applicant Name: International Medication Systems Ltd.

Executive Summary:
The Applicant proposed a new formulation of the 0.1 mg/mL strength of a 10 mL-Pre-filled Syringe Epinephrine injection that is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. The proposed product (10 mL) is directed to be diluted to 1000 mL in either 5% Dextrose solution or 5% Dextrose + Sodium chloride solution so as to achieve a final concentration of (b) (4) mg/mL of the Epinephrine API prior to administration. The proposed drug-device combination product is based on the Listed Drug (LD) product – Epinephrine injection, 1 mg/mL that is available in a 2 mL-single-dose ampule that was developed by Belcher Pharmaceuticals LLC. The LD product was approved under NDA 205029 on 7/29/2014. The LD product (1 mL) is directed to be diluted to 1000 mL in either 5% Dextrose solution or 5% Dextrose + Sodium chloride solution so as to achieve a final concentration of 0.001 mg/mL of the Epinephrine API prior to administration. The LD product is indicated for administration as an intravenous infusion, or as an injection via intramuscular, subcutaneous or intraocular routes of administration. The proposed product is developed for the same indication, dose and route of administration (intravenous infusion at 0.05–2 µg/kg/min) as the LD product. Each mL of the diluted products contains 1 µg of the Epinephrine API. This NDA (NDA-211363-ORIG-1) was submitted to the Division of Cardiovascular and Renal Products on 2/14/2018 under section 505 (b)(2). The submission was resubmitted as RESUB-19 (NDA-211363-ORIG-1-RESUB-13) on 2/16/2022 upon addressing the deficiency comments communicated by the Drug Product assessor in the Complete Response (CR) Letter dated 12/12/2018.

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 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-211363-ORIG-1-RESUB-19 for Epinephrine injection, 0.1 mg/mL, 10 mL Pre-filled Syringe is adequate and is **RECOMMENDED** for approval.

List Submissions being assessed:

2/14/2018	NDA-211363-ORIG-1 (Sequence 0000)
2/16/2022	NDA-211363-ORIG-1-RESUB-19 (Sequence 0018)
3/16/2022	Response to Information Request/Quality (Sequence 0022)

BIOPHARMACEUTICS ASSESSMENT

Bridging of proposed product to the LD product:

The Listed Drug (LD) product is available in a 1 mg/mL, 2 mL-single-dose ampule. The LD product (1 mL) is directed to be diluted to 1000 mL in either 5% Dextrose solution or 5% Dextrose + (b) (4) Sodium chloride solution so as to achieve a final concentration of 0.001 mg/mL of the Epinephrine API prior to administration. Dilution and administration in a saline solution alone is not recommended. The LD product is indicated for administration as an intravenous infusion, or as an injection via intramuscular, subcutaneous or intraocular routes of administration[1]. Each mL of the diluted product contains 1 µg of the Epinephrine API.

The proposed product is a 0.1 mg/mL, 10 mL single-dose pre-filled syringe developed for the same dose, indication and route of administration (intravenous infusion) as the LD product. The proposed product (10 mL) is directed to be diluted to 1000 mL in either 5% Dextrose solution or 5% Dextrose + (b) (4) Sodium chloride solution so as to achieve a final concentration of 0.001 mg/mL of the Epinephrine API prior to administration. Each mL of the diluted product contains 1 µg of the Epinephrine API.

In the RESUB-19 submission (sequence 0018), the Applicant requested a biowaiver for the proposed product based on 21 CFR 320.22(b). Subsequent to the Biopharmaceutics IR response (sequence 0022), the Applicant submitted data in support of a bridge between the proposed product and the LD via 21 CFR 320.24(b)(6). Based on the submitted information, the Applicant requested a waiver of the *in vivo* bioavailability studies. The details of the IR, Applicant's response and the Reviewer's assessment are provided in Appendix 1, and the details of the information in support of the bridge are presented in the Link to information to support a bridge between the LD and proposed product.

Reviewer's Assessment:

***Formulation differences between the proposed and the LD product*:**

[1] Link to labeling information of the LD product

The proposed product – Epinephrine injection for the IV infusion contains the same active ingredient as the LD product. In response to the deficiency comments communicated by the DP assessor in the Complete Response (CR) Letter dated 12/12/2018[2], the Applicant reformulated the proposed drug product, and resubmitted the submission as RESUB-19 (NDA-211363-ORIG-1-RESUB-19; sequence 0018) on 2/16/2022[3]. The composition of the LD and the proposed product (b) (4) before and after dilution are shown below in Tables 1A and 1B.

Table 1A: Composition of LD and proposed product before dilution

	Listed Drug Product		IMS Newly Formulated Product	
Ingredients	Amount/mL	Amount/Container	Amount/mL	Amount/Container
Epinephrine	1 mg	1 mg	0.1 mg	1 mg
Sodium Chloride	8.6 mg	8.6 mg	8.2 mg	82 mg
Hydrochloric Acid[1,2]				(b) (4)
Sodium Hydroxide	N/A	N/A		(b) (4)
Citric Acid Monohydrate	N/A	N/A	3.3 mg	33 mg
Sodium Citrate Dihydrate	N/A	N/A	1.5 mg	15 mg
Sodium Metabisulfite	N/A	N/A	0.075 mg	0.75 mg
Edetate Disodium Dihydrate (EDTA)	N/A	N/A	0.004 mg	0.04 mg
Water for Injection	QS AD	QS AD	QS AD	QS AD
Administered volume - *Hypotension associated with Septic Shock*	For administration, epinephrine from its container is diluted to **1 mcg of epinephrine** in dextrose solution prior to infusion.			

Table 1B: Composition of LD and proposed product after dilution

	Listed Drug Product	IMS Newly Formulated Product
Ingredients	Amount/mL[3]	Amount/mL[3]
Epinephrine	1 mcg	1 mcg
Sodium Chloride	8.6 mcg	82 mcg
Hydrochloric Acid[1,2]		(b) (4)
Sodium Hydroxide	N/A	(b) (4)
Citric Acid Monohydrate	N/A	33 mcg
Sodium Citrate Dihydrate	N/A	15 mcg
Sodium Metabisulfite	N/A	0.75 mcg
Edetate Disodium Dihydrate (EDTA)	N/A	0.04 mcg
Water for Injection	QS AD	QS AD
Administered volume - *Hypotension associated with Septic Shock*	Deliver **0.05 mcg/kg/min to 2 mcg/kg/min** of the 1 mcg epinephrine dilution to achieve a desired mean arterial pressure.	

The LD product (1 mL of 1 mg/mL Epinephrine), when diluted with 1000 mL of either diluent, yields 1001 mL of the product with the API at a final concentration of 1 µg/mL. The proposed product (10 mL of 0.1 mg/mL Epinephrine), when diluted with 1000 mL of either diluent, yields 1010 mL of the product with the API at a final concentration of (b) (4) g/mL.

- The final concentration of the Epinephrine API in the proposed product is present in the same final concentration as the LD product (1 µg/mL).
- The excipients (highlighted in yellow) are not qualitatively/quantitatively (Q1/Q2) same.
- The LD contains HCl and NaCl.
- The proposed product contains HCl, Citric acid monohydrate, Sodium citrate dihydrate and NaCl, however, the concentration of NaCl in the proposed product differs from the LD. The proposed product also contains Disodium EDTA and Sodium metabisulfite.

The excipients in the LD product – HCl as the pH adjuster and NaCl as the tonicity adjuster – contribute towards the pH and osmolality of the LD, respectively.

[2] Link to deficiency comments in Complete Response (CR) Letter
[3] Link to Applicant's response to DP assessor's deficiency comments in CR Letter

The excipients in the proposed product – Citric acid monohydrate, Sodium citrate dihydrate (b) (4) (b) (4) and NaCl as the tonicity adjuster – (b) (4) (b) (4) respectively. Disodium EDTA (b) (4) (b) (4) Sodium metabisulfite is included as an antioxidant. HCl acid is also included as the pH adjuster.

***Comparison of physicochemical characteristics between the diluted LD and the diluted proposed products*:**

A comparison of the physicochemical characteristics of three lots of the diluted LD (L#s 20390, 20394 and 20395) and three lots of the diluted proposed product (L#s 082920A, 082920B and 082920c) is shown below in Tables 2A and 2B:

Table 2A: pH of LD and proposed product (diluted in 5% w/v Dextrose or 5% w/v Dextrose + (b) (4) NaCl)

		Before Dilution		After Dilution			
				5% Dextrose Solution[1]		5% Dextrose and Sodium Chloride Solution[2]	
Manufacturer	Lot#	Test Results	Average / SD	Test Results	Average / SD	Test Results	Average / SD
IMS	082920A	3.8 3.8 3.8	Average: 3.8 SD: 0.01	4.4 4.4 4.4	Average: 4.4 SD: 0.02	4.2 4.1 4.1	Average: 4.1 SD: 0.03
	082920B	3.8 3.8 3.8		4.4 4.4 4.4		4.1 4.1 4.1	
	082920C	3.8 3.8 3.8		4.4 4.3 4.3		4.2 4.2 4.2	
LD Product	20390	3.3 3.3 3.3	Average: 3.3 SD: 0.01	4.7 4.7 4.7	Average: 4.7 SD: 0.01	4.5 4.5 4.5	Average: 4.5 SD: 0.01
	20394	3.3 3.3 3.3		4.8 4.8 4.8		4.5 4.5 4.5	
	20395	3.3 3.3 3.3		4.8 4.8 4.8		4.5 4.5 4.5	

Table 2B: Osmolality of LD and proposed product (diluted in 5% w/v Dextrose or 5% w/v Dextrose + (b) (4) NaCl)

		Before Dilution		After Dilution			
				5% Dextrose Solution[1]		5% Dextrose and Sodium Chloride Solution[2]	
Manufacturer	Lot#	Test Results	Average / SD	Test Results	Average / SD	Test Results	Average / SD
IMS	082920A	306 306 307	Average: 307 SD: 0.50	259 259 259	Average: 260 SD: 1.0	547 546 548	Average: 548 SD: 0.73
	082920B	307 306 307		260 259 260		548 548 548	
	082920C	307 307 307		259 262 259		547 548 548	
LD Product	20390	286 286 286	Average: 286 SD: 0.50	259 259 259	Average: 259 SD: 0.33	550 551 550	Average: 550 SD: 1.2
	20394	285 287 286		259 259 259		548 548 550	
	20395	286 286 286		258 259 259		551 550 551	

Based on the information submitted in Table 2A, the mean pH of the three batches of the LD diluted in 5% Dextrose is 4.7. The mean pH of the proposed product diluted in 5% Dextrose is 4.4. The mean pH of the three batches of the LD diluted in 5% Dextrose + (b) (4) NaCl is 4.5. The mean

[4] https://www.researchgate.net/publication/259757323_Excipient_Selection_In_Parenteral_Formulation_Development

pH of the proposed product diluted in 5% Dextrose + (b) (4) NaCl is 4.1. The difference in pH between the diluted-proposed product and the diluted-LD is not expected to influence the bioavailability of the drug *in vivo* or pose a safety issue.

Based on the information submitted in Table 2B, the mean osmolality of the three batches of the LD diluted in 5% Dextrose is 259. The mean osmolality of the proposed product diluted in 5% Dextrose is 260. The mean osmolality of the three batches of the LD diluted in 5% Dextrose + (b) (4) NaCl is 550. The mean pH of the proposed product diluted in 5% Dextrose + (b) (4) NaCl is 548. The difference in osmolality between the diluted-proposed product and the diluted-LD is within (b) (4) %, and is not expected to influence the bioavailability of the drug *in vivo* or pose a safety issue.

***Effect of excipients unique to the proposed product*:**

(i) *Citric acid monohydrate and Sodium citrate dihydrate* (b) (4) (b) (4) (b) (4) The Applicant stated that these (b) (4) components are commonly used and have no impact on the in vivo PK profile of the product. This Reviewer finds the Applicant's justification acceptable.

(ii) *Sodium metabisulfite*: Sodium metabisulfite functions as a reducing agent to prevent the drug from oxidation by being preferentially oxidized over Epinephrine. The Applicant stated that the concentration of Sodium metabisulfite in the final diluted drug product is 0.75 µg/mL, and would not impact the safety or efficacy of the product. In addition, the Clinical Pharmacology assessor does not expect Sodium metabisulfite at the final concentration in the proposed product to affect the PK of Epinephrine following an IV route of administration.

(iii) *Edetate disodium dihydrate (EDTA)*: (b) (4) (b) (4). The Applicant stated that the concentration of EDTA in the final diluted drug product is (b) (4) µg/mL, and would not impact the safety or efficacy of the product. In addition, the Clinical Pharmacology assessor does not expect EDTA at the final concentration in the proposed product to affect the PK of Epinephrine following an IV route of administration.

***Effect of changes in the concentration of excipients in the proposed and LD products*:**

(i) *Hydrochloric acid (HCl)*: (b) (4) (b) (4) (b) (4) The difference in the concentration of HCl between the LD and proposed product is not expected to affect the PK of Epinephrine when administered intravenously.

(ii) *Sodium chloride*: Sodium chloride is used as a tonicity adjusting aid in the proposed product and in the LD. Although the concentration (%w/v) of NaCl in the proposed product is ~10× higher compared to the LD, the difference in osmolality between the two diluted products (in either diluent) is within (b) (4)% of each other. This difference in osmolality is not expected to influence the bioavailability of the proposed drug product *in vivo* or pose a safety issue following an IV route of administration.

Based on the above assessment, this Reviewer concludes that the presence of the excipients unique to the proposed 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.

APPENDIX 1
IR comments, Applicant's Response to IR and Reviewer's assessment

On 3/2/2022, the following Information Request (IR1) comments were communicated to the Applicant. On 3/16/2022, the Applicant responded to the Agency's IR (IR1) comments (Sequence 0022). The Agency's IR comments, the Applicant's response to the IR, and the Reviewer's assessment are included below:

Information Request 1 (IR1):

Item 1:

Please note that since your newly formulated product does not contain the same active and inactive ingredients in the same concentration as the Listed Drug (LD) product, your request for a biowaiver cannot be granted based on 21 CFR 320.22(b). However, a scientific bridge (bioavailability/bioequivalence) may be established on the basis of 21 CFR 320.24(b)(6) if you can provide a justification that the changes in formulation of your proposed product will not affect the PK and the *in vivo* performance of the LD product.

In support of establishing a "bridge" based on 21 CFR 320.24(b)(6), submit a side-by-side comparison on three batches of the newly formulated product and the LD product before and after dilution into the recommended diluents (5% dextrose solution and 5% dextrose with sodium chloride solution). Please provide the following information:

(i) A side-by-side comparison table of the formulation (qualitative and quantitative composition) before and after reconstitution/dilution, administered volume, etc. for the newly formulated product and the LD product.

(ii) Comparative physicochemical data (pH, osmolality, etc.,) before and after reconstitution and dilution. The measurements should be performed in triplicate for each lot tested.

(iii)Include a justification for any differences in the formulation and dosing of the proposed product relative to the LD product including the physicochemical properties of the newly formulated product relative to the LD product. Your justification for any differences between the two formulations should demonstrate that the difference for each active and/or inactive ingredient would not affect the pharmacokinetic performance towards any difference in clinical safety and/or efficacy outcome. You may include literature data and/or your study reports to support your biowaiver request.

Applicant's response to Item 1:

The Applicant stated that a side-by-side comparison table of the formulation before and after reconstitution/dilution and in the administered volume for Listed Drug (LD) product and proposed newly formulated product has been provided. The details are provided in the Link to Applicant's response to IR1 Item 1.

Reviewer's assessment:

The Applicant submitted the comparative formulation and physicochemical properties on three batch of the newly formulated proposed product and three batches of the LD. Measurement of the physicochemical properties have been performed in triplicate.

The Applicant's response to IR1 Item 1 is adequate and acceptable.

Rajesh Savkur

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Date: 5/04/2022 11:11:02AM
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Haritha Mandula

Digitally signed by Haritha Mandula
Date: 5/04/2022 01:12:30PM
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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	211363
Assessment Cycle Number	MR02
Drug Product Name/ Strength	Epinephrine Injection USP, 0.1 mg/ml, 10 ml
Route of Administration	Intravenous
Applicant Name	International Medicine Systems, Limited
Therapeutic Classification/ OND Division	CDER/OND/OCHEN/DCN
Manufacturing Site	International Medication Systems, Ltd. (IMS) 1886 Santa Anita Ave., South El Monte, CA 91733
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original submission	2/16/2022
IR response	6/17/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: The resubmission provided response to CR letter sent on 12/12/2018. A new formulation was proposed in this resubmission (b) (4) the drug product release specification (BET) has been revised.

Concise Description of Outstanding Issues: None

Supporting Documents: Microbiology review N211363MR01.pdf (adequate) dated 9/5/2018 for information regarding building and facility, overall manufacturing operation, EM, sterilization/depyrogenation validation, (b) (4), sterility test validation.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Sterile, clear, colorless solution supplied in 10 ml single-dose glass vial, co-packaged with pre-filled syringe
- **Drug product composition –**

Product Strength	Epinephrine injection USP, 0.1 mg/mL, 10 mL		
Material	Amount per mL	Amount Per Unit (PFS)	% w/v
API:			
Epinephrine USP*	0.1 mg	1 mg	0.01%
Inactive Ingredients**:			
Sodium Citrate Dihydrate USP	1.5 mg	15 mg	0.15%
Citric Acid Monohydrate USP	3.3 mg	33 mg	0.33%
Sodium Chloride USP	8.2 mg	82 mg	0.82%
Sodium Metabisulfite NF	0.075 mg	0.75 mg	0.0075%
Edetate Disodium Dihydrate USP	0.004 mg	0.04 mg	0.0004%
Hydrochloric Acid NF	PRN to dissolve the API	PRN to dissolve the API	PRN to dissolve the API
Sodium Hydroxide NF	PRN for pH adjustment	PRN for pH adjustment	PRN for pH adjustment
Water for Injection USP	QS Ad	QS Ad	QS Ad

* Calculated based on actual potency availability (as is) for Epinephrine injection. (b) (4) (b) (4).

** Nitrogen is used as (b) (4) blanketing protection, (b) (4)

- **Description of container closure system –**

Component	Medication Container (Primary)	Rubber Stopper Closure (Primary)	Medication Vial Cap	Co-packaged Prefilled Syringe
Description	10 mL (b) (4) glass container	10 mL (b) (4) (b) (4) stoppers	10 mL vial cap, (b) (4)	10 mL Luer-Jet® Syringe, (b) (4)
Manufacturer	(b) (4)		IMS	IMS
IMS' Part No.			4811108 or 4811101	3624101

Note: The rubber stopper has been changed (b) (4) (b) (4) (b) (4) N211363MR01.pdf dated 9/5/2018 indicated that the drug product never comes in contact with the vial cap.

Exhibit batches # 082920A, 082920B and 082920C: (b) (4) units
Proposed commercial batch (b) (4) units

Assessment: ***Adequate***

The sponsor provided an adequate description of the drug product's composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

13 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Assessment: ***Adequate***

The sponsor provided adequate data for the finished drug product stability testing.

R REGIONAL INFORMATION

Executed Batch Records

Executed batch record was provided for batch# 082920A, 082920B and 082920C for the drug product.

Assessment: ***Adequate***

The provided executed batch record is acceptable.

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

2.A. Prescribing Information
Storage: 20-25°C (68-77°F). The proposed drug product is single-dose pre-filled syringe and the label contains "Discard any unused portion".

(b) (4)

The package insert does not contain any instruction for post dilution storage.

Assessment: ***Adequate***

The application provided an adequate description of the finished drug product package insert.

Primary Microbiology Assessor Name and Date:
Jianli Xue, Ph.D.
CDER/OPQ/OPMA/DMA I/BII
6/17/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Nandini Bhattacharya
CDER/OPQ/OPMA/DMA I/BII
6/17/2022

Jianli Xue

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Date: 6/17/2022 01:34:29PM
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Nandini Bhattacharya

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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	6/7/2022		
To:	Adams Grafton		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division**	Choose an item.
From	Rong Guo OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Choose an item. OPEQ/OHT3/DHT3C		
Subject	NDA211363, Epinephrine ICC2200331 ICCR# 00839559		
Recommendation	Approval for the Device Constituent Parts of the Combination Product. A post approval inspection to International Medication Systems, Ltd. (IMS) (FEI: 2016148) is recommended.		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA211363
Sponsor	INTERNATIONAL MEDICATION SYSTEMS LTD
Drug/Biologic	Epinephrine
Indications for Use	To increase mean arterial blood pressure (MAP) in adult patients with hypotension associated with septic shock
Device Constituent	Pre-Filled Syringe
Files reviewed	NDA211363 resubmission, eCTD sequence 18, receive date 2/16/2022 \\CDSESUB1\evsprod\NDA211363\0018

2. PURPOSE/BACKGROUND

2.1. Scope

INTERNATIONAL MEDICATION SYSTEMS LTD is requesting approval of Epinephrine. The device constituent of the combination product is a Pre-Filled Syringe.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

Please review the device constituent, ensure that there is no new information that needs to be reviewed.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- ☐ Device performance
- ☐ Biocompatibility of the patient contacting components
- ☐ Sterility
- ☐ Stability – device performance on stability
- ☐ Essential Performance Requirements (EPR) Control strategy
- ☐ Quality Systems Assessment

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors (deferred to DMEPA)

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. Indications for Use

Combination Product	Indications for Use
Epinephrine	To increase mean arterial blood pressure (MAP) in adult patients with hypotension associated with septic shock
Pre-Filled Syringe	Delivery of the Drug Product

3. DEVICE DESCRIPTION

3.1. Device Description

Table 32P7-1 Packaging System for Epinephrine Injection USP, 0.1 mg/mL, 10 mL (CCD-6)

Component	Description	IMS Part No.	Manufacturer
CONTAINER	10 mL (b) (4) glass container	(b) (4)	(b) (4)
CLOSURE	10 mL (b) (4): (b) (4) stoppers		
	10 mL vial cap (b) (4) (b) (4)	4811108 or 4811101	IMS
INJECTOR	Luer-Jet® injector (Luer tip, 10 mL, (b) (4) cap)	3624101	IMS

(b) (4)

3.2. Facilities & Quality Systems Triage Inspection Recommendation Information

CDRH completed a review of the Facilities	☑ Yes ☐ No ☐ N/A
Inspection Recommendation	☐ Pre-Approval Inspection (PAI) ☑ Post-Approval Inspection ☑ Routine Surveillance ☐ No Inspection Needed ☐ N/A

CDRH completed a review of the Quality Systems	☑ Yes ☐ No ☐ N/A

In 3.2.P.3 Manufacturer, sponsor confirmed compliance to 21 CFR 210 and 211, and 21 CFR 820 for the device where applicable. Device quality system regulation compliance (specified in 21 CFR 820 and not covered in 21 CFR 210 and 211): management responsibility, design controls, purchasing controls, and corrective and preventive actions are located in 3.2.R. Information on components.

Table 32P31-1 Manufacturer of Drug Product
(Epinephrine Injection USP, 0.1 mg/mL, 10 mL; CCD-6)

Name / Address	Responsibilities	Contact Information
International Medication Systems, Ltd. (IMS) 1886 Santa Anita Ave., South El Monte, CA 91733 FEI: 2016148 DUNS No.: 055750020	Manufacturing, packaging, labeling and control operations, distribution, as well as release and stability testing of drug product	Gisela Sharp, Associate Director, Regulatory Affairs International Medication Systems, Ltd., 1886 Santa Anita Ave., South El Monte, CA 91733 Phone: (626) 459-5253 Alt: (909) 942-4176 Fax: (626) 459-5592 Email: GiselaS@ims-limited.com
Amphastar Pharmaceuticals, Inc. (Headquarters of IMS) FEI No.: 3002936358 DUNS No.: 024736733	Elemental impurities testing / risk evaluation	Gisela Sharp, Associate Director, Regulatory Affairs Amphastar Pharmaceuticals, Inc. 11570 6th Street, Rancho Cucamonga, CA 91730 Phone: 909-980-9484, ext. 2016 Fax: 909-980-6422 Email: GiselaS@Amphastar.com

An inspection on July 21, 2015 to August 10, 2015 at International Medication Systems, Limited, located at 1886 Santa Anita Ave., South El Monte, California 91733-3414 resulted a warning letter as the firm was not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820. However, the most recent inspection (b) (4) (D) (4) (b) (4) resulted NAI. A post approval inspection to International Medication Systems, Ltd. (IMS) (FEI: 2016148) is recommended.

4. DEVICE PERFORMANCE REVIEW

4.1. Design Verification/Validation

4.1.1. Device Specification Standards and Guidance Documents

Syringe	Data Adequate		
	Yes	No	N/A

Pre-filled Syringe	ISO 11040-8, Prefilled syringes – Part 8: Requirements and test methods for prefilled syringes	☐	☐	☑
Co-packaged Syringe	ISO 7886-1, Sterile Hypodermic Syringes for Single Use—Part 1: Syringes for Manual Use	☑	☐	☐
Insulin Syringe	ISO 8537, Sterile single-use syringes, with or without needle, for insulin	☐	☐	☑
Needle/Sharps		**Data Adequate**		
		Yes	**No**	**N/A**
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use	☐	☐	☑
Needle	ISO 9626, Stainless steel needle tubing for the manufacture of medical devices	☑	☐	☐
Needle	ISO 6009, Hypodermic needles for single use – Color coding for identification	☐	☐	☑
Sharps Injury Prevention Feature	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	☐	☐	☑
Luer Lock		**Data Adequate**		
		Yes	**No**	**N/A**
Connection	(b) (4)	☑	☐	☐
Other		**Data Adequate**		
		Yes	**No**	**N/A**
[Other]	[Other]	☐	☐	☑

Sponsor provided design verification for dose accuracy, break loose force / glide force, and connectivity in 3.2.P.7 functional perform assess injector epi inj.

7.1. Part I

- Key Dimensions
- Seal Integrity Testing
- Dose Accuracy per USP <697> (Container Content for Injections)
- Dead Space per ISO 7886-1
- Connectivity (b) (4)
- Tip Cap (Cover) Removal Force
- (b) (4)
- Validation of Graduation Markings (Equal to or Greater than Half Nominal Capacity)
- Validation of Graduation Markings (Less than Half Nominal Capacity)
- Validation of Graduation Markings (Graduation Marking Scale Length, Interval and Numbered Volume Increments)
- Liquid Leakage at Syringe Piston Under Compression
- Break Force / Glide Force

7.2. Part II

- Separation Force
- Unscrewing Torque
- Ease of Assembly

7.3. Part III

- Liquid Leakage
- Air Leakage
- Resistance to Overriding
- Stress Cracking

4.1.2. Device Performance Evaluation

Essential Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	(b) (4)	Y	Y	Y	
Break loose Force		Y	Y	Y	
Glide Force		Y	Y	Y	
Cap Removal Force		Y	n/a	n/a	n/a
Luer connection		Y	n/a	n/a	n/a

Reviewer Comment
All testing are acceptable and meet acceptance criteria.

Luer connectivity testing was performed per ISO (b) (4) This is acceptable as FDA removed the initial deadline to switch (b) (4) (b) (4) and set a new compliance date of December 23, 2023.

4.1.3. Biocompatibility Evaluation

☑ Biocompatibility was **evaluated** [e.g. co-packaged syringes, co-packaged components outside of primary container closure]
☐ Biocompatibility was not evaluated because the syringe is part of the primary container closure. Defer to CDER.

Biocompatibility of the injector was provided in 3.2.P.7 container closure system. Per 2016 FDA biocompatibility guidance, the injector has indirect blood path with limited contact duration. Cytotoxicity, sensitization, irritation, acute systemic toxicity, material mediated pyrogenicity was provided. All testing are acceptable and meet acceptance criteria per ISO 10993 series.

4.1.4. Sterility Evaluation

☐ Sterility **Evaluated** (e.g. co-packaged syringes, co-packaged components outside of primary container closure)
☑ Sterility not evaluated (syringe, including needle are part of primary container closure, sterility evaluation is under the purview of CDER)

5. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	On lot release and stability program	Y
Break loose Force	On lot release and stability program	Y
Glide Force	On lot release and stability program	Y
Cap Removal Force	Design verification	Y
Luer connection	Design verification	Y

Reviewer Comments
The essential performance requirements are on lot release and on stability program. The control strategy is adequate.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

<<END OF REVIEW>>

Theodore Carver

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/s/

THEODORE E CARVER
06/30/2022 11:36:06 PM

NDA 211363: Epinephrine Injection USP (Luer-Jet™ Luer-Lock Prefilled Syringe)

Integrated Quality Review

Recommendation: A Complete Response (CR)

Drug Name/Dosage Form	Epinephrine Injection, USP (Luer-Jet™ Luer-Lock Prefilled Syringe)
Strength	0.1 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	International Medication Systems, Limited
Submissions (s) Reviewed	NDA 211363, DMFs, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sharon Kelly	ONDP/DNDPI/NDPBI
Drug Product & Environmental Assessment (EA)	Rao Kambhampati	ONDP/DNDPI/NDPBI
Process & Facility	Peter Guerrieri	OPQ/OPF/DPAI/PABI
Biopharmaceutics	Qi Zhang	ONDP/DB/BBI
Microbiology	Samata Tiwari	OPQ/OPF/DMA/MABII
Regulatory Business Process Manager	Grafton Adams	OPRO DRBPMI/RBPMBI
Device Constituent	Rong Guo	CDRH/ODE/DAGRID/GHDB
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

RELATED/SUPPORTING DOCUMENTS

Document	Application Number	Description
Type II DMFs	(b) (4)	The DMFs (b) (4) have been reviewed in the context of the current submission, and found adequate.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 211363 (Epinephrine Injection, USP) is **not** recommended for approval.

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

Not applicable.

II. Summary of Quality Assessments

The applicant, International Medication Systems (IMS), Limited, has sought U.S. marketing approval for the combination product, Epinephrine Injection, USP Luer-Jet™ Luer-Lock Prefilled Syringe, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. IMS has marketed this drug product since the early 1970's without an approved NDA or ANDA. This 505(b)(2) NDA submission has been made pursuant to FDA's Compliance Policy Guide Section 440.100 in order to voluntarily demonstrate the safety and efficacy of the drug product. For the approval of this NDA, the applicant relies on FDA's previous finding of safety and efficacy for the listed drug (LD) i.e., Belcher Pharmaceuticals' Epinephrine Injection USP, 1 mg/mL, in a (b) (4) ampule (reference NDA 205029). The proposed product, which will be provided as a 10 mL sterile solution for injection in a prefilled syringe configuration, is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock, This proposed indication is the same as currently approved for Belcher Pharmaceuticals, LLC's NDA 205029 for Epinephrine Injection, USP (approved on July 29, 2014). (b) (4) (b) (4) (b) (4) From product quality perspective, the proposed formulation design and product development are not adequately optimized, (b) (4) (b) (4) which is unacceptable as per ICH Guidance for Industry -Q8(R2) Pharmaceutical Development (2009).

A. Drug Substance (Epinephrine) Quality Summary

Epinephrine, a well-established compendial drug substance, is the subject of a USP monograph. The CMC details concerning the drug substance such as structural characterization, impurity profile, manufacturing, and stability have been cross-referenced to Type II DMFs # (b) (4) (b) (4). DMF # (b) (4) has been previously reviewed and found adequate. DMF # (b) (4) and DMF (b) (4) have been reviewed in the context of the current submission and found adequate (refer to DMF reviews by S. Kelly, dated 10/09/2018, and 10/09/2018,

respectively). Based on review of information provided in this NDA, batches of epinephrine drug substance from [redacted] as well as the two newly proposed

alternative suppliers, [redacted] are comparable when analyzed by the applicant using the identical analytical methods. The release specifications and acceptance criteria are set to conform to the Epinephrine USP monograph requirements, USP general requirements, and/or ICH guidelines Q3A and Q3C. Specifically, the critical quality attributes (CQAs) such as description, assay, identification, optical rotation, impurity levels, [redacted] residue on ignition, levels for adrenalone and norepinephrine, residual solvents, and levels of microbial and bacterial endotoxins are tested on release. The methods for epinephrine drug substance assay (by titration), and residual solvent (by GC analysis) have been validated. Based on adequate stability data, the API manufacturer, [redacted], has set a retest period of [redacted] for the drug substance.

B. Drug Product Quality Summary

The proposed drug product (Epinephrine Injection USP, 0.1 mg/mL, 10 mL) is a sterile, injectable solution of epinephrine. The finished product consists of a drug product filled and labeled 10 mL vial, which has been stoppered and capped. The drug product is co-packaged with a sterile Luer-Jet® injector system. This prefilled syringe device is a [redacted] dispenser delivering a unit dose of the active ingredient (1 mg total dose of epinephrine solution) intended for dilution prior to administration by intravenous infusion. Each unit dose contains 10 mL of 0.1mg/mL medication. [redacted] All the excipients are compendial and are not of human or animal origin. Unlike the listed drug, the proposed formulation involves the use of different inactive ingredients i.e., [redacted] sodium bisulfite [redacted] and sodium citrate dehydrate and citric acid monohydrate, [redacted]. The inactive ingredient sodium bisulfite is tested and qualified to meet USP standards. The quantities of the excipients used in the formulation are lower than the other FDA approved injectable solution products. The excipients compatibility has been established. [redacted]

The control strategy mainly consists of in-process controls and product release specification. The revised product specification that includes testing for all critical quality attributes, including the sterility, is acceptable. Specifications for inactive ingredients are adequate. Risk assessment for drug product elemental impurities has been conducted in compliance with the USP <232>/<233> and ICH Q3D. The levels of identified degradation products i.e., norepinephrine (EPB), adrenalone [redacted]), benzylepinephrine [redacted], and [redacted] have been justified as per ICH Q3B. The other identified degradants i.e., [redacted] have been justified per ICH M7 (QSAR). Regarding product stability, 24-month long-term stability data have been provided for three drug product batches [redacted] but since one of the batches failed at the 24-month time point for Impurity [redacted] content, the applicant has requested [redacted]-month expiration dating period when the drug product vials are stored at controlled room temperature (25^{0}C). However, the relevance of these data for assessing the product stability is very limited given that no product stability data have been generated for batches manufactured [redacted]

Container-Closure System: The packaging components of the drug product include 10 mL (b) (4) glass container (primary), rubber stopper closure (primary), a vial cap, and co-packaged prefilled syringe (10 mL Luer-Jet Syringe, (b) (4). Regarding compatibility, the applicant has demonstrated that the drug product bulk solution is compatible with (b) (4) (b) (4) (b) (4) under tested conditions. All extractable and leachable compounds have been shown to be well below the permitted limits.

Luer-Jet™ Injector: Based on CDRH review of Luer-JetTM Injector, the dose accuracy for delivered dose, and the break loose force and glide force verification have been adequately demonstrated. The product release specification includes testing for break/glide force. The biocompatibility evaluation appropriately complies with the FDA biocompatibility guidance and corresponding ISO standard. Hazard/risk analysis related to the usage of Epinephrine injection is acceptable. Luer-Jet injectors are (b) (4) Container-closure integrity of the proposed product configuration is demonstrated through the finished product sterility test results obtained during release testing. Functionality test results have demonstrated suitability of Luer-Jet for intended use. The data provided demonstrate suitability-for-intended-use expectations with respect to protection, safety, compatibility, and performance per the FDA guidance. In addition, the applicant has provided a summary of the validation testing/closure integrity challenge studies performed to demonstrate the sterility assurance of the 3 mL, 5mL, 10 mL, and 50 mL Luer-Jet® Injector system.

Manufacturing: The manufacturing process, (b) (4), is adequately described. (b) (4) The applicant has demonstrated consistent capability of meeting the in-process specification, and adequate method precision. (b) (4) (b) (4). Adequate controls are in place from particulate, leachable, and process stability perspectives. The batch formula accurately reflects the proposed composition for commercial manufacturing. The risk mitigating factors i.e., in-process controls for pH, clarity and adherence to USP <788> for particulates, are adequate.

Microbiological Aspects: The product sterility is the key critical quality attribute of the proposed product. Routine microbiology tests, i.e. sterility, and bioburden testing are performed as part of the release testing of each batch of finished product. IMS also performs the microbiological monitoring/testing for supporting sterile injection product manufacturing, which includes bioburden monitoring (b) (4) (b) (4) per IMS' SOP. In addition, IMS monitors microbiological quality (b) (4) on routine basis. (b) (4). The container-closure integrity of Epinephrine

Injection has been demonstrated via process validation, which demonstrates that the container-closure integrity system is capable of acting as an effective barrier against microbial ingress and adequately prevents product leakage. Container-closure integrity of the proposed product configuration is also demonstrated through the finished product sterility test results obtained during release testing. The information regarding the overall manufacturing process to assure the microbiological quality of the drug product is adequate. The environmental monitoring program, proposed hold time, sterilization/depyrogenation of containers, closures, equipment and components, and the validation data (b) (4) are adequate. The depyrogenation of the proposed production vials (b) (4) of the subject drug product have been successfully validated. Furthermore, the product release specification includes appropriate tests and acceptance criteria to support the microbiological quality of the drug product. Specifically, the drug product release specification includes sterility (USP <71>), and bacterial endotoxins (USP <85>) testing.

Biopharmaceutics Aspects: The original submission included a request for biowaiver of *in vivo* bioavailability/bioequivalence (BA/BE) study for the proposed product under the provision of 21 CFR 320.22(b)(1). However, the applicant's biowaiver request per 21 CFR § 320.22(b)(1) is not feasible, because the formulation of the proposed to-be-marketed parenteral drug product is not qualitatively and quantitatively (Q1/Q2) the same as that of the listed drug (LD) due to the presence of (b) (4) (sodium bisulfite, (b) (4) Nevertheless, a scientific bridge can be established between the proposed drug product and the LD based on 21 CFR 320.24(b)(6). Based on the side-by-side comparison, the proposed product and the LD are similar in terms of indication, dosage form, and dosage and administration route, concentration, infusion volume and rate at the point of patient contact. In addition, the proposed and the LD products are sterile, non-pyrogenic, and colorless solutions with comparable pH, osmolality, viscosity, and specific gravity. The addition of sodium bisulfite (b) (4), and sodium citrate dihydrate and citric acid monohydrate (b) (4) is not anticipated to alter the systemic bioavailability, efficacy, and safety of the proposed drug product. Overall, per 21 CFR 320.24(b)(6), the applicant's proposed drug product has been adequately bridged to the LD. Hence, an in-vivo bioavailability study, comparing the LD with the proposed drug product, is not needed, and the request for biowaiver by the applicant for the proposed product is appropriately justified.

Expiration Date & Storage Conditions: Given that the applicant has not provided any stability data for the stability lots of Epinephrine Injection USP, 0.1 mg/mL (b) (4) no product expiration date can be assigned at this stage.

C. Assessment of Manufacturing Facilities: The office of Process and Facilities has recommended an overall approval for all the currently listed manufacturing facilities concerning this NDA. Specifically, the drug substance is proposed to be manufactured by (b) (4) manufacturers. Originally, (b) (4) was listed as the DS manufacturer. However, based on the LOA provided, the site would no longer manufacture the drug substance after (b) (4) and a finite supply of material is available. In response to the Information Request, the applicant provided two additional sites for DS manufacturing, (b) (4) (b) (4) which are assessed to be acceptable and expected to supply future commercial batches. Since a complete supply chain for commercial availability is now in place, the drug substance facilities are deemed acceptable.

D. Biopharmaceutics Considerations:

- BCS Designation: The proposed drug product is an injectable solution, and the applicant has not request an official BCS designation.
- Biowaivers/Biostudies: The applicant's biowaiver request under 21 CFR 320.24(b)(6) is acceptable.
- IVIVC: N/A.

III. Summary of Drug Product and Intended Use

Proprietary Name of the Drug Product	Not applicable
Non-Proprietary Name of the Drug Product	Epinephrine Injection, USP
Active ingredient	Epinephrine
Route of Administration	Intravenous (infusion)
Strength(s)	0.1 mg/mL (1 mg/10 mL)
Proposed Indication(s)	Epinephrine is a non-selective alpha and beta adrenergic agonist indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.
Maximum Daily Dose/ Duration of Treatment	(b) (4)
Alternative Methods of Administration	N/A

IV. List of Deficiencies:

A. Drug Product:

1. (b) (4)

2. Given that you have not provided stability data for the lots of Epinephrine Injection USP, 0.1 mg/mL manufactured as per the proposed commercial process (b) (4) an accurate determination of product expiration date is not possible at this stage.

   To address the above-listed deficiencies, we recommend you provide: a) batch analysis data for the lots of Epinephrine Injection USP, 0.1 mg/mL, manufactured as per the proposed commercial process (b) (4) and b) long-term and accelerated stability data for product stability batches, (b) (4)

B. Quality Labeling:

Given that the term "single-use" is a retired term, replace the term "single-use" with the term "single-dose" throughout the label and labeling.

Life Cycle Knowledge Information/Final Risk Assessment

(Please see the other page)

Final Risk Assessment

NDA 211363: Epinephrine Injection USP (Luer-Jet™ Luer-Lock Prefilled Syringe)

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	(b) (4)
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M** **(Moderate)**		Acceptable	
Assay (API), Product Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)		Not acceptable. Basis for a CR recommend ation.	
Assay (b) (4)	Formulation Raw materials Process parameters Scale/equipment/ site				
Uniformity of Dose – Fill/ Deliverable Volume	Formulation Container-Closure Process Parameters Scale/equipment/ site	L (Low))		Acceptable	

Final Risk Assessment (continued)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	(b) (4)	Acceptable	
pH (b) (4)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		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	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 211363: Epinephrine Injection USP (Luer-Jet™ Luer-Lock Prefilled Syringe) is **not** recommended for an approval.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products (Actg)
ONDP/DNDPI/NDPBI

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LABELING

Review of NDA 211363

R Regional Information

1.14 Labeling

Immediate Container Label

Syringe Label:

(b) (4)

[redacted]

Reviewer's Assessment: Adequate from CMC review stand point but this NDA will be a CR

(b) (4)

Carton Labeling

(b) (4)

[redacted]

Reviewer's Assessment: Adequate from CMC review stand point but this NDA will be CR (b) (4).

List of Deficiencies: None.

QUALITY ASSESSMENT

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 10/4/18

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Wendy Wilson-Lee, Ph.D. 10/4/18

Rao Kambhampati

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

NDA: 211363
Submission Type: 505(b)(2) Type 7-Drug Already Marketed Without Approved NDA
Drug Product Name/Strength: Epinephrine Injection USP, 1 mg/10 ml (0.1 mg/ml) Luer-Jet™ Luer-Lock Prefilled Syringe
Dosage Form: Injection
Route of Administration: Intravenous (IV)
Applicant Name: International Medication Systems (IMS), Limited
Intended Use: Treatment of hypotension associated with septic shock
Listed Drug (LD): Epinephrine Injection USP 1 mg/ml [NDA 205029, Belcher Pharmaceuticals, approved 7/29/2014]

REVIEW SUMMARY

This 505(b)(2) NDA for Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL in a 10 mL Luer-Jet™ Luer-Lock Prefilled Syringe), relies for approval on FDA's findings of safety and effectiveness of the Listed Drug (LD), Epinephrine Injection USP, 1 mg/mL in a 1 mL single-use Ample (NDA 205029; Belcher Pharmaceuticals, LLC).

The Biopharmaceutics review evaluates information and data supporting the Applicant's biowaiver request.

The Applicant's biowaiver request per 21 CFR § 320.22(b)(1) is not feasible, because the formulation of the proposed to-be-marketed parenteral drug product (DP) is not qualitatively and quantitatively (Q1/Q2) the same as that of the LD, due to the presence of (b) (4) (sodium bisulfite, (b) (4) and differences in (b) (4)

However, a scientific bridge can be established between the proposed DP and the LD, based on 21 CFR 320.24(b)(6). Based on the side-by-side comparison between the proposed and the LD products provided by the Applicant and the information available in the labeling of the LD, the proposed and the LD are same in terms of indication, dosage form, and dosage and administration route, concentration and infusion volume and rate at the point of patient contact. The proposed and the LD products are both sterile, non-pyrogenic, and colorless solutions with comparable pH, osmolality, viscosity, and specific gravity. The addition of sodium bisulfite (b) (4) (b) (4) and sodium citrate dihydrate and citric acid monohydrate (b) (4) to the formulation of the proposed DP, is not anticipated to alter the systemic bioavailability, efficacy and safety of the proposed drug product.

Overall, per 21 CFR 320.24(b)(6), the Applicant's proposed drug product has been adequately bridged to the LD; therefore, an in-vivo bioavailability study, comparing the LD with the proposed drug product, is not needed.

RECOMMENDATION: ADEQUATE

From the Biopharmaceutics perspective, NDA 211363, for Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL) Luer-Jet™ Luer-Lock Prefilled Syringe, is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Qi Zhang, PhD **9/28/2018**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Jing Li, PhD **9/28/2018**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

List of Submissions Being Reviewed:

eCTD # (SND #)	Received date	Document
0000 (1)	2/14/2018	Original submission
0005 (6)	6/4/2018	Quality/Response to information request dated 4/23/2018

Biowaiver Request:

This 505(b)(2) NDA relies for approval on FDA's findings of safety and effectiveness of the Listed Drug (LD), Epinephrine Injection USP, 1 mg/mL in a 1 mL single-use Ample (NDA 205029; Belcher Pharmaceuticals, LLC; approved 7/29/2014). Unlike the LD, the proposed drug product (DP) is packaged in a single use 10 mL Luer-Jet™ Luer-Lock Prefilled Syringe with a lower drug concentration (1 mg/10 mL [0.1 mg/mL] vs. 1 mg/mL), and is formulated to contain (b) (4) (i.e. sodium bisulfite (b) (4) sodium citrate dehydrate (b) (4) and citric acid monohydrate (b) (4)). The Applicant has marketed the un-approved same drug product indicated for use in cardiac resuscitation since the early 1970's, using the same active ingredient, formulation, and dosage form.

For a parenteral injection product, under 21 CFR 320.22(b)(1), bioequivalence of the drug product may be self-evident when both Q1/Q2 requirements are met, namely when the test product contains the same active and inactive ingredients in the same concentration as the LD. The proposed drug product does not meet the Q1/Q2 criteria for a waiver of the requirement to submit evidence of in vivo bioavailability or bioequivalence under 21 CFR 320.22(b)(1), because the formulation of the proposed injectable product is Q1/Q2 different from the LD, due to the presence of three additional inactive ingredients, i.e. sodium bisulfite, sodium citrate dihydrate and citric acid monohydrate. In an Information Request from the NDA Filing Communication Letter dated 4/23/2017, FDA notified the Applicant that their biowaiver request per 21 CFR § 320.22(b)(1) is not feasible. However, the "bridge" between the proposed drug product and the LD could be based on 21 CFR 320.24(b)(6).

For this purpose, the Applicant had provided the side-by-side comparison information/data for the differences in the qualitative/quantitative compositions between the proposed and the approved drug products containing same active ingredient epinephrine, including Belcher's NDA 205029 (LD). (See **Appendix** for Table 1.12.15-1.) In addition, upon request, the Applicant has provided the comparative physiochemical data generated from 3 proposed drug product lots and 3 LD lots, to establish the bridge between the proposed drug product and the LD.

Information to Support Bridging:

Indication

The only indication for which the Applicant seeks approval for this NDA submission is "to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock", which is the same as the LD, Belcher's NDA 205029. Per the Meeting Request – Written Responses letter dated September 18, 2017, FDA informed the Applicant that their reliance on NDA 205029 for the FDA's previous finding of safety and effectiveness for Epinephrine Injection to support the proposed indication is acceptable.

Strength

A lower 0.1 mg/mL [1 mg/10 mL] strength of epinephrine is proposed compared to 1 mg/mL strength approved for the LD. However, considering that the same total drug amount (1 mg; 1: 100 dilution for the proposed vs. 1: 1000 dilution for the LD product)) is introduced into the injection site, the difference in strength is not expected to impact the bioavailability of the drug.

Dosage and Administration

Regardless of the proposed lower strength, 0.1 mg/mL, the proposed DP and the LD are same in terms of dosage and administration route (for IV infusion). The concentration (1 µg/mL) after the dilution, infusion volume (1000 mL) and rate (0.05 µg/kg/min to 2 µg/kg/min) are the same at the point of patient contact.

Presence of Sodium Bisulfite (b) (4)

- Because the IV administered drug product is introduced directly into systemic circulation, the addition of sodium bisulfite (b) (4) to the Applicant's product is not anticipated to alter the systemic bioavailability of epinephrine.
- Per Section 2.2 (Dosage and Administration) of the proposed labeling, the maximum amount per single time use of this drug product in adults is approximately 10 mL which contains 1 mg epinephrine and (b) (4) sodium bisulfite. Of note, the total cumulative dose cannot be predicted; continuous epinephrine infusion is generally required over several hours or days until the patient's hemodynamic status improves.
- Section 5 (b) (4) (Warnings and Precautions) describes the allergic-type reactions (including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people) associated with the use of sodium bisulfite.
- To support the safety of the sodium bisulfite content (b) (4) in the proposed drug product, the Applicant provided two additional approved drug products: Adrenaclick®(Epinephrine) Injection, 1 mg/mL, [NDA 020800] and AUVI-Q® (Epinephrine) Injection, 1 mg/mL [NDA 201739], both of which contain higher concentrations of sodium bisulfite (1.5 mg/ml or 1.67 mg/ ml). However, it is noted that these two referenced injections are for intramuscular or subcutaneous use, but not for IV use. In addition, the maximum amount of sodium bisulfite delivered per unit dose is 0.3 mL * 1.5 mg/mL = 0.5 mg for NDA 020800, or 0.3 mL * 1.67 mg/mL = 0.57 mg for NDA 201739.

- Sodium bisulfite is listed in the Inactive Ingredients (IIG) Database. This Reviewer identified one drug product approved for IV administration, Methyldopate HCl Injection, 50 mg/mL [ANDA 071279, approved on 12/02/1987] containing 3.2 mg/mL Sodium Bisulfite. The maximum dose of 4 g methyldopate HCl per day (1 g every six hours per labelling of ANDA 071279) for adults delivers 256 mg sodium bisulfite via IV route, which is 25.6 times of the amount of sodium bisulfate delivered by single use of the proposed DP.

Overall, the addition of sodium bisulfite (b) (4) to the proposed DP, is not anticipated to alter the efficacy of epinephrine without posing additional safety concern.

Presence of Sodium Citrate Dihydrate (b) (4) *and Citric Acid Monohydrate* (b) (4) (b) (4)

Though sodium citrate dihydrate and citric acid monohydrate do not exist in any of the reference products for epinephrine (see **Appendix** for Table 1.12.15-1.), these common (b) (4) agents have been extensively used in the approved injection solutions for IV use, per IIG database. The maximum potency per unit dose for sodium citrate dehydrate (trisodium citrate dihydrate) is up to 24.75 mg/mL (Dexamethasone Sodium Phosphate Injection, EQ 10 mg phosphate/mL, ANDA 207442), and the maximum potency per unit dose for citric acid monohydrate is up to 2.2 mg/mL (Hydromorphone HCl Injection, 2 mg/mL, ANDA 202159)

Comparative Physicochemical Properties:

The pH data confirmed that there is no difference in pH before dilution; the pH for all 6 lots for both products is 3.3 before dilution (**Table 1**). After dilution, the pH of the proposed product is consistently the same (pH=4.2) whether it is diluted with 5% dextrose solution or 5% dextrose and sodium chloride solution; however, the pH of the LD are 5.5 or 5.7. The observed difference in pH after dilution is due to different dilution factors (1: 100 vs. 1: 1000) (b) (4) The proposed injection contains (b) (4) components (sodium citrate dihydrate, citric acid monohydrate, and sodium bisulfite), whereas the LD does not contain any. The difference in pH attribute between the final diluted proposed and LD product is not anticipated to impact the efficacy and safety of the proposed drug product.

The osmolality for the proposed and LD products before dilution are approximately 226 mOsm/Kg and 285 mOsm/Kg respectively, and such difference is expected due to the different concentrations of dissolved solids (0.1 mg/mL vs. 1 mg/mL). The final osmolality of the diluted injection solution for the proposed and LD products are similar (about (b) (4) mOsm/Kg with dilution of 5% dextrose, respectively, and about 556 and 560 mOsm/Kg with dilution of 5% dextrose and sodium chloride solution, respectively.) (**Table 2**)

There are no significant differences in viscosity and specific gravity between the LD and the proposed product either before or after drug product dilution.

Table 1: Comparison of pH Results for The LD and Proposed Drug Product

Manufacturer	Lot #	Before Dilution		After Dilution			
				5% Dextrose Solution[1]		5% Dextrose and Sodium Chloride Solution[2]	
		Test Result	Average (n=3)	Test Result	Average (n=3)	Test Result	Average (n=3)
IMS	SI043A8	(b) (4)					
	SI044B8						
	SI045B8						
RLD	17307						
	17310						
	17311						

[1] *pH of 5% dextrose solution diluent is 5.8*
[2] *pH of 5% dextrose and sodium chloride solution diluent is 6.1*

Table 2: Comparison of Osmolality Results for The LD and Proposed Drug Product

Manufacturer	Lot #	Before Dilution		After Dilution			
				5% Dextrose Solution[1]		5% Dextrose and Sodium Chloride Solution[2]	
		Test Result	Average (n=3)	Test Result	Average (n=3)	Test Result	Average (n=3)
IMS	SI043A8	(b) (4)					
	SI044B8						
	SI045B8						
RLD	17307						
	17310						
	17311						

[1] *Osmolality of 5% dextrose solution diluent is 264*
[2] *Osmolality of 5% dextrose and sodium chloride solution diluent is 560*

In conclusion, both the proposed and the reference products are sterile, non-pyrogenic and colorless solutions with comparable pH, osmolality, viscosity, and specific gravity.

Reviewer's Assessment: ADEQUATE

The scientific bridge to the LD was established pursuant to 21 CFR 320.24(b)(6), based on the side-by-side comparison in formulation and physicochemical properties between the proposed and listed products, and information available in the labeling of the LD; therefore, an in-vivo bioavailability study, comparing the LD with the proposed drug product, is not needed.

From the Biopharmaceutics perspective, NDA 211363, for Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL) Luer-Jet™ Luer-Lock Prefilled Syringe, is **ADEQUATE** and recommended for **APPROVAL**.

Refer to the Drug Substance and Drug Product Reviews for additional CMC information. Refer to the FDA recommended labeling to ensure safe and effective use of the proposed drug product.

LIST OF BIOPHARMACEUTICS INFORMATION REQUESTS

IR dated 4/23/2018:

The formulation of the proposed drug product is not qualitatively and quantitatively the same as the formulation of the listed drug product (Belcher's Epinephrine Injection USP 1 mg/mL; NDA 205029), for example, with respect to the presence/absence of antioxidant (b) (4) Therefore, a biowaiver under regulation 21 CFR 320.22(b)(1) is not feasible for your proposed drug product. However, the "bridge" between the proposed and the listed drug product may be supported by required information, based on 21 CFR 320.24(b)(6), that justifies the differences in drug products would not contribute to differences in the in vivo performance. We acknowledge that you have provided a summary side-by-side comparison for the differences in the qualitative/quantitative compositions between the proposed product and the listed drug products to support the bridging of the formulation between the proposed and the listed drug. Please submit the following additional information in support of the bridge under 21 CFR 320.24(b)(6):

Comparative physicochemical data (such as pH, osmolality, viscosity, specific gravity, color and clarity) before and after dilution (per labeling instructions) for at least 3 production lots of the proposed drug product and 3 lots of the listed drug product. The measurements should be done in triplicate for each lot tested. Include justification for why you believe that any observed differences in the physicochemical properties of the test and reference drug products would not impact the efficacy and safety of the proposed drug product.

APPENDIX

Table 1.12.15-1 Comparison of Proposed and Reference Products – Conditions of Use, Formulation and Other Particulars

DRUG PRODUCT	Proposed	Reference							
Manufacturer Application number Approval date	IMS NDA 211363	Belcher NDA 205029 7/29/14	JHP (Par) NDA 204640 12/18/13	 10/7/12	PAR NDA 204200 9/16/16	 	Mylan NDA 019430 12/22/87	Impax NDA 20800 5/30/03	Kaleo NDA 201739 8/10/12
Conditions of Use (Indication)	To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.	To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.	Emergency treatment of allergic reactions (Type 1), including anaphylaxis		Emergency treatment of allergic reactions (Type 1), including anaphylaxis		Emergency treatment of allergic reactions (Type 1), including anaphylaxis	Emergency treatment of allergic reactions (Type 1), including anaphylaxis	Emergency treatment of allergic reactions (Type 1), including anaphylaxis
	---	For induction and maintenance of mydriasis during intraocular surgery	---	For induction and maint-enance of mydriasis during intraocular surgery	---	---	---	---	---
Route of Administration	Intravenous (infusion)	IV (infusion), IM, SC, Intra-ocular	IM, SC	IM, SC, Intra-ocular	IM, SC	IM, SC	IM, SC	IM, SC	IM, SC
Active Ingredient	Epinephrine, USP	Epinephrine	Epinephrine		Epinephrine		Epinephrine	Epinephrine	Epinephrine
Strength (mg/mL)	0.1	1	1	1	1	1	1/0.5	1	1
Volume (mL)	10	1	30	1	30	1	0.3/0.3	0.3/0.15	0.3/0.15
Container	Prefilled syringe	Ampule	Multi Dose Vial	Vial	Multi Dose Vial	Vial	Auto Injector	Auto Injector	Auto Injector

DRUG PRODUCT		Proposed	Reference							
Formulation (mg/mL)										
API	Epinephrine, claimed as	0.1	1	1	1	1	1	1/0.5	1	1
(b) (4)	Sodium chloride	(b) (4)	9	9	9	6.15	7.3	6	8.67	7.67
	Sodium metabisulfite		---	1.5	1	0.457	0.457	1.67	---	---
	Sodium bisulfite		---	---	---	-	---	---	1.5	1.67
	Chlorobutanol	---	---	5.4	---	5.25	---	---	< 5	---
	Disodium edetate dihydrate	---	---	---	---	0.2	0.2	---	---	---
	Tartaric acid	---	---	---	---	2.25	2.25	---	---	---
	Sodium hydroxide	---	---	---	---	0.92	1	---	Yes	---
	Sodium citrate dihydrate	(b) (4)	---	---	---	---	---	---	---	---
	Citric acid monohydrate		---	---	---	---	---	---	---	---
	Citric acid anhydrous	---	---	---	---	---	---	---	---	---
	Hydrochloric acid	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed

Table 1.12.15-2 Comparison of Reference Products – Basis of Approval for Indication

DRUG PRODUCT	Reference							
Manufacturer Application number Approval date	Belcher NDA 205029 7/29/14	JHP (Par) NDA 204640 12/18/13	 10/7/12	PAR NDA 204200 9/16/16	 	Mylan NDA 019430 12/22/87	Impax NDA 20800 5/30/03	Kaleo NDA 201739 8/10/12
Basis of Approval for Indication	Literature summary	Literature summary	Literature summary	Lit. sum-mary	Lit. sum-mary	Unknown clinical information	Literature summary	Bio-equivalence Study

Qi Zhang

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Date: 9/28/2018 11:29:08AM
GUID: 547e178000007695c91eb10380b07939

Jing Li

Digitally signed by Jing Li
Date: 9/28/2018 03:05:14PM
GUID: 508da7420002bb05ac913303b23c39bb

MICROBIOLOGY

NDA: 211363

Drug Product Name / Strength: Epinephrine Injection USP, 0.1 mg/mL, 10 mL

Route of Administration: Sterile solution for injection, intravenous (Infusion)

Applicant Name: International Medication Systems, Limited

Manufacturing Site: International Medication Systems, Ltd., 1886 Santa Anita Ave., South El Monte, CA 91733

Method of Sterilization: (b) (4)

Review Summary: The submission is recommended for approval on the basis of sterility assurance

List Submissions being reviewed: 02/14/2018, 05/15/2018 and 07/09/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: A Microbiology Information Request was issued to the applicant on June 21, 2018, and the applicant forwarded responses on July 09, 2018.

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents:

- Microbiology reviews 203449.doc, dated 7/26/2012 and associated amendment 203449a1.doc, dated 11/5/2012 for information regarding container/closure sterilization, initial validation study of (b) (4) initial validation study of (b) (4)
- DMF (b) (4) and associated Microbiology Review (b) (4) MR01.doc (adequate), dated 7/18/2016 regarding the sterile finished products and (b) (4) processing operations at (b) (4)

Remarks Section: None

S Drug Substance

The drug substance is not the focus of this review [redacted]

P.1 Description of the Composition of the Drug Product

Description of drug product – The subject drug product (Epinephrine Injection USP, 0.1 mg/mL, 10 mL) is a sterile, injectable solution of epinephrine. The finished product consists of 1) a drug product filled and labeled 10 mL vial which has been stoppered and capped, and 2) [redacted] injector (Luer-Jet®). [redacted]

Drug product composition –
[3.2.P.1 Description and Composition of the Drug Product (Epinephrine Injection USP, injection, solution. pdf)]

Unit Dose Compositions (Per Unit and Per mL) of Epinephrine Injection USP, 0.1 mg/mL, 10 mL is provided in the table below:

Chemical Material	Used As	Amount per mL	Amount Per Unit (PFS)
Epinephrine USP*	Active ingredient	[redacted]	[redacted]
Hydrochloric Acid NF	To dissolve API [redacted]	NA	NA
Citric Acid Monohydrate USP	[redacted]	[redacted]	[redacted]
Sodium Citrate Dihydrate USP			
Sodium Chloride USP	Tonicity agent	[redacted]	[redacted]
Sodium Bisulfite [redacted]	[redacted]		
Water for Injection USP			
Nitrogen NF	[redacted]	NA	NA

*Active ingredient: [redacted]

- **Description of container closure system** –
[3.2.P.7-summary of container/closure-system (Epinephrine Injection USP, injection, solution. Pdf)]

The following table summarizes the unit configuration and components, which make up the container/closure system for the proposed Epinephrine Injection USP, 0.1 mg/mL, 10 mL.

Epinephrine Injection USP, 0.1 mg/mL, 10 mL

Component	Description	IMS Part No.	Manufacturer
CONTAINER	10 mL (b) (4) glass container	1210010	(b) (4)
CLOSURE	10 mL (b) (4) rubber stopper	3722010	IMS
	10 mL vial cap (b) (4) (color may be changed)	3811100	IMS
INJECTOR	Luer-Jet® Injector (Luer Tip, 10 mL, (b) (4) (b) (4) cap)	3624101	IMS

The drug product is filled and sealed in the glass vial and rubber stoppered as indicated in the table above. The applicant stated that the drug product never comes in contact with the vial cap (see diagram below). The DP is co-packaged with a sterile Luer-Jet® injector system, which is to be assembled by the user prior administration of the DP.

Figure 1 – Configuration of Luer-Jet® Prefilled Syringe Injector component

(b) (4)

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

Acceptable

(b) (4)

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(b) (4)

Acceptable

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not applicable.

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not applicable.

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not applicable.

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not applicable.

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not applicable.

R Regional Information

Executed Batch Records

Executed batch records were provided for batches SI077F5, SI026E3 and SI098E2.

The batch records confirm that validated sterilization/depyrogenation (b) (4) manufacturing processes were used for the manufacture of the exhibit batch.

Reviewer's Assessment:

Acceptable

Comparability Protocols

No CP was included in the application.

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

2.A. Package Insert

The subject drug product is a [redacted] (b) (4) sterile solution for injection. It is supplied in a 10 mL [redacted] (b) (4) single dose vial (the package contains a 10-mL, [redacted] (b) (4) Luer-jet injector for use during the time of drug product administration by the user). The subject drug product is stored at room temperature 20-25°C (68-77°F). The vials are for single use only. Any unused product in the ampule must be discarded.

For Hypotension associated with Septic Shock, the drug product is administered by continuous infusion after diluting it with 5 percent dextrose solution or 5 percent dextrose and sodium chloride solution. The entire contents of epinephrine prefilled syringe will be added to [redacted] (b) (4) mL of a 5 percent dextrose containing solution. The package insert does not contain any instruction for post dilution storage. Each mL of this dilution contains 1 mcg of epinephrine.

Reviewer's Assessment:

Acceptable

Post-Approval Commitments: Not applicable.

Lifecycle Management Considerations: Not applicable.

List of Deficiencies:

None Identified

Primary Microbiology Reviewer Name and Date:

Samata Tiwari, Ph.D. (09/05/2018)
Microbiologist
CDER/OPQ/OPF/DMA/BII

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Neal Sweeney, Ph.D. (09/05/2018)
Senior Microbiologist
CDER/OPQ/OPF/DMA/BII

Samata Tiwari

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Neal Sweeney

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OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Device Constituent Review: CDER NDA 211363 CDRH ICC1800188

Date	September 25, 2018
To	Grafton Adams
Requesting Division	CDER/OPQ/OPRO/DRBPMI/RBPMBI
From	Rong Guo CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Carolyn Dorgan CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for NDA 211363 Epinephrine
Recommendation	CDRH recommends **Approval** based on review of the device constituent part of the combination product.

Digital Signature Concurrence Table	
Reviewer	
Team Lead	
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2018-02449
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=2667
ICC tracking # (Lead)	ICC1800188
Submission Number	NDA211363
Sponsor	International Medication Systems
Drug	Epinephrine Injection USP, 0.1 mg/mL
Indications for Use	To increase mean arterial blood pressure (MAP) in adult patients with hypotension associated with septic shock.
Device Constituent	Luer-Jet Prefilled Syringe
Related Files	NDA211363 eCTD Sequence0000 (SDN1) submitted on 02/14/2018

2. PURPOSE/BACKGROUND

2.1. Scope

The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the device constituent parts of the subject combination product. This evaluation covered the intended design and design control information for the subject device constituent part.

The review of submission documentation by CDRH/ODE found that the design requirements of the device components are acceptable, and that essential performance of the final finished device can be assured with a reasonable degree of certainty. Essential performance elements of the device under review by the consultant were considered to be:

- Dose accuracy
- Break loose and gliding force
- Biocompatibility of non-primary closure components

This review did not cover the following content

- Review of drug product
- Review of primary container closure-drug product interaction, sterility, or toxicology
- Manufacturing of the drug product
- Manufacturing of the device constituent part of the combination product

2.2. Background

Epinephrine is an alpha and beta adrenergic agonist indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

Dosage and Administration

10 mL prefilled syringe containing 1 mg/10 mL epinephrine as the hydrochloride in a sterile, (b) (4) solution, marked Epinephrine Injection USP, 1 mg/ 10mL (0.1 mg/mL).

- Dilute epinephrine in dextrose solution prior to infusion.
- Infuse epinephrine into a large vein.
- Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure
- Wean gradually.

Storage
Protect from light until ready to use.
Do not refrigerate. Protect from freezing.
Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature].
Protect from alkalis and oxidizing agents.
(b) (4)
(b) (4)

3. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

Epinephrine Injection, USP 1: 10,000 (0.1 mg/ml) is packaged with the Luer-Jet® Prefilled Injector System which includes a vial containing the medication and an injector with a needleless Luer connector tip that connects to other Luer connecting devices.

(b) (4)

The same injector was reviewed in ANDA203449 Sodium bicarbonate injection USP, Approved 09/19/2017

4. DESIGN CONTROL REVIEW

The design considerations for functional performance (from Design History File of Epinephrine Injection) are provided in Suitability for use evaluation report located in Section 3.2.P.2.5, focusing on functional performance tests. The Sponsor claimed that the Design Control activity has already been completed previously and the specific Design Output for these Design Requirements are addressed in the Design History File for this product filed on site at IMS, Limited.

5. DESIGN VERIFICATION AND VALIDATION REVIEW

5.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing		X	

To-be-marketed device was used in the pivotal clinical trial			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry	X		
Traceability demonstrated for specifications to performance data		X	

Reviewer's note:
The subject drug product is currently marketed by the same Sponsor without an approved abbreviated/new drug application. IMS has marketed the subject drug product since the early 1970's using the same active ingredient formulation, and dosage form, indicated for use in cardiac resuscitation. This 505(b)(2) NDA submission is made pursuant to FDA's Compliance Policy Guide Section 440.100 in order to voluntarily demonstrate the safety and efficacy of the drug product.

Discipline Specific Design Verification / Validation*						
	Consult Needed			**Consultant**	**Attributes Acceptable**	
	Yes	**No**	**N/A**		**Yes**	**No**
Engineering (Materials, Mechanical, General)		no			yes	
Biocompatibility		no			yes	
Sterility				Deferred to OPF sterility reviewer		
Software / Cybersecurity			n/a			
Electrical Safety / EMC			n/a			
Human Factors			n/a			

The following verifications are taken from Suitability for use evaluation report located in Section 3.2.P.2.5, except biocompatibility (taken from Component 4-Injectors located in Section 3.2.P.2.7).

Table 4: Part I Methods and Acceptance Criteria

#	Method	Reference	Acceptance Criteria
1	Dead Space (Dose Delivery)	USP <1>	The volume of dispensed medication must be NLT 10mL for Epinephrine Injection. Reliability based on Tolerance Interval K_{Target} must be ≤ K_{Actual} per ISO 11608-1.
2	Dead Space	ISO 7886-1	The volume of water left in pre-filled injector unit must be NMT (b) (4) for 10mL Luer-Jet Injectors.
3	Tip Cap (Cover) Removal Force	Guidance for Industry and FDA Staff: Glass Syringes for Delivering Drug and Biological Products	Determinations of the force required to open the injector tip cap (cover) of the injector tip must be made.
4	Validation of Graduation Markings (Equal or Greater than Half Nominal Capacity)	ISO 7886-1	Tolerance on the graduated capacity must be within (b) (4)% of the expelled volume.
5	Validation of Graduation Markings (Less than Half Nominal Capacity)	ISO 7886-1	Tolerance on the graduated capacity must be within ± (b) (4)% of 10mL + (b) (4)% of expelled/target volume).
6	Validation of Graduation Markings (Graduation Marking Scale Length, Interval and Numbered Volume Increments)	ISO 7886-1	Graduation scale length must be at least (b) (4)mm, resolution of graduation mark scale interval must be at least (b) (4)mL and resolution of volume increment between numbered lines on graduation marking scale must be at least (b) (4)mL.
7	Break Force / Glide Force	Guidance for Industry and FDA Staff: Glass Syringes for Delivering Drug and Biological Products	The overall force required to initiate movement of the plunger (Break Force) and the mean force (Glide Force) must be NMT (b) (4)N. This shows that any value of force obtained below (b) (4)N indicates normal operation of the unit (injector and vial) and any value of force above (b) (4)N may indicate an abnormal unit (jams or holdups). Reliability based on Tolerance Interval K_{Target} must be ≤ K_{Actual} per ISO 11608-1.
8	Liquid Leakage at Syringe Piston Under Compression	ISO 7886-1	There shall be no signs of water leakage past the piston seals (stopper rings).

5.2. Dose accuracy

For Dead Space Study per USP <1> (Dose Delivery); one specimen each from three lots were evaluated for dose delivery, 25 units from 25 different lots at initial product release and 16 units from 11 different stability lots at 18 months and 24 months past expiration were evaluated for Dose Delivery reliability throughout product shelf life. For Dead Space Study per ISO 7886-1, thirty (30) 10ml injectors were used.

Dose accuracy for delivered dose was evaluated per USP <1> Injections/General Requirements (Dose Delivery) by assessing the fill volume of the vial. The contents of one vial from three different lots were dispensed into separate beakers and weighed. Using the density of the medication, the volume of the dispensed medication was determined. The volume of dispensed medication must be NLT 10 ml for Epinephrine Injection Table 7). In addition, units at initial finished product release (Table 8) also show the results from delivered dose evaluation.

Table 7: Volume in Container Summary (Dose Delivery of Stability Lots) Summary

Lot Tested	SI089L1	SI094D2	SI099F2
Specification	NLT (b) (4)		
Volume in Injector (mL)	(b) (4)		
Results (Pass/Fail)	PASS	PASS	PASS

Table 8: Volume in Container (Dose Delivery at Initial Finished Product Release) Summary

Lot Tested	SI009G6, SI010I6, SI011I6, SI012J6, SI013K6, SI015A7, SI016A7, SI018B7, SI019B7, SI020B7, SI021B7, SI022B7, SI023D7, SI024D7, SI025F7, SI026F7, SI027F7, SI028G7, SI029H7, SI030I7, SI031I7, SI032I7,SI033I7, SI034J7, SI035J7
Units Tested	25
Maximum Volume in Container (mL)	(b) (4)
Minimum Volume in Container (mL)	
Mean Volume in Container (mL)	
Standard Deviation	
K_{Target} (Tolerance Interval Factor per ISO 11608-1)	
K_{Actual} (Tolerance Interval per ISO 11608-1)	
Results (Pass/Fail)	PASS

Reviewer comment: *The dose accuracy for delivered dose is appropriate and acceptable. All tests were performed with the actual drug product. According to USP <905>, content uniformity requires separately measuring 10 samples, and calculating mean, standard deviation, and Acceptance Value (AV). There is no additional test for outliers if standard deviation is less than 6.25 for 10 samples.*

The dead space of the complete 10ml pre-filled injector unit (injector and vial) was evaluated per ISO 7886-1 Sterile Hypodermic Syringes for Single Use by assessing the leftover liquid (water) when the nominal amount is completely dispensed. The mass of a dry pre-filled injector unit was obtained before drawing in water to the nominal capacity. Then the entire volume was completely dispensed, and the pre-filled injector unit is wiped dry on the outside surface before the unit is weighed again. Since the density of water is 1.000 g/ml, the difference in mass of the pre-filled injector unit before and after the test indicates the amount of water retained in the unit which in turns indicates the dead space within the unit. Per ISO 7886-1, the specification for water retained is NMT (b) (4) ml for the 10ml Luer-jet Injector.

Table 10: Volume Retained in Container Summary

Specification	NMT (b) (4)
Maximum Volume Retained in Injector (mL)	(b) (4)
Results (Pass/Fail)	PASS

5.3. Break loose and glide force

For Break Force and Glide Force testing, a total of 250 specimens from different lots were evaluated initially to develop the routine release criterion of NMT (b) (4) N. Additionally, 3081 units from 25 different lots were evaluated at initial finished product release to demonstrate acceptable maximum Break/Glide Force.

Table 14: Break Force / Glide Force Studies for Finished Product Release Criterion Development

Lot Tested	SI180A1, SI179A1, SI178A1, SI176L0	SI179A1, SI172L0, SI175L0, SI176L0, SI177A1
Type of Test	Break Force (Unit Only)	Break Force (Unit Connected to Smallbore Extension Set)
Mean (N)	15.76	16.93
Standard Deviation	3.88	3.31
Maximum (N)	29.39	26.82
Minimum (N)	9.51	10.70
Units Tested	125	125
Type of Test	Glide Force (Unit Only)	Glide Force (Unit Connected to Smallbore Extension Set)
Mean (N)	7.43	8.82
Standard Deviation	1.21	1.33
Maximum (N)	10.77	14.72
Minimum (N)	5.39	6.80
Units Tested	125	125
Recommended Release Criteria	Force NMT (b) (4) (testing with unit only)	

Table 15: Break Force / Glide Force at Initial Product Release

# of Samples Tested	Release Criterion (N)	Minimum (N)	Maximum (N)	Mean (N)	Standard Deviation	K_{Target} (Tolerance Interval Factor per ISO 11608-1)	K_{Actual} (Tolerance Interval per ISO 11608-1)	Result (Pass/Fail)
3081	Break Force (N)							
	(b) (4)	3.89	25.39	10.32	2.15	3.805	11.48	PASS
	Glide Force (N)							
	(b) (4)	7.05	24.07	14.13	1.57	3.805	13.29	PASS

Reviewer comment: *The break loose force and glide force verification is appropriate and acceptable.*

5.4. Tip cap removal force

Thirty (30) units of injectors from 10 lots (i.e., 300 Units total) were used to perform the Tip Cap (Cover) Removal Force study. The results from this study reveals the mean of 300 injectors tested to be 19.2 N with a standard deviation of 6.2. At 99.7% confidence level (i.e., 3 times standard deviation), the Tip Cap Removal Force range of acceptance criteria must be no less than (b) (4) N) and no more than (b) (4) (N).

Table 3: Summary of Tip Cap Removal Force for 10 mL Luer-Jet Injector

Sample Tested	Mean	Standard Deviation
300	19.2	6.2

Reviewer comment: *The tip cap removal force verification is acceptable.*

5.5. Compatibility of the system

The following performance testing per ISO (b) (4) were provided to show that the injector is compatible with the commonly available Luer connectors representing actual in-field use. All testing passed acceptance criteria.

Table 5: Part II Methods and Acceptance Criteria

#	Method	Reference	Acceptance Criteria
1	Separation Force	ISO (b) (4)	The Luer-Jet injector shall remain attached to the Luer connector.
2	Unscrewing Torque	ISO	The Luer-Jet injector shall remain attached to the Luer connector.
3	Ease of Assembly	ISO	A satisfactory fit shall be achieved by applying an axial force not exceeding (b) (4) N while applying a torque not exceeding (b) (4) N-m.

Table 6: Part III Methods and Acceptance Criteria

#	Method	Reference	Acceptance Criteria
1	Liquid Leakage	ISO (b) (4)	There shall be no leakage sufficient to form a falling drop.
2	Air Leakage	ISO	There shall be no signs of continued formation of air bubbles. Bubbles formed during the first 5 seconds shall be disregarded.
3	Resistance to Overriding	ISO	The Luer connectors shall not override the threads of the injector under test.
4	Stress Cracking	ISO	There shall be no evidence of Stress Cracking.

5.6. Biocompatibility

Based on the device description and its indications for use, the Luer-Jet® injector is considered as an externally communicating device, blood path, indirect. Per the FDA guidance Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process (2016), cytotoxicity, sensitization, irritation, acute systemic toxicity, material-mediated pyrogenicity and hemocompatibility endpoints are recommended. The following test reports are provided in "Component 4-Injectors" located in Section 3.2.P.7. Tests were done by (b) (4)

- In vitro cytotoxicity MEM elution test based on ISO 10993 Biological evaluation of medical devices, Part 5 Test for in vitro cytotoxicity;
- Irritation testing intracutaneous reactivity test in New Zealand white rabbits based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;
- Maximization test for delayed-type hypersensitivity in guinea pigs based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;
- Acute systemic toxicity testing in CD-1 Mice based on ISO 10993 Biological evaluation of medical device, Part 11 Tests for systemic toxicity;
- Hemocompatibility testing (direct and extraction methods) based on ISO 10993 Biological evaluation of medical devices, Part 4 Selection of tests for interactions with blood;
- Material-mediated pyrogen test in New Zealand white rabbits based on ISO 10993 Biological evaluation of medical device, Part 11 Tests for systemic toxicity.

Reviewer comment*: The provided testing complies with the FDA biocompatibility guidance and corresponding ISO standard. The biocompatibility evaluation is acceptable.*

5.7. Stability

The proposed shelf life is (b) (4) months. Stability data were obtained from stability study under long-term normal storage condition (25 ± 2 ºC) studies for the stability lots of Epinephrine Injection USP, 0.1 mg/mL, 10 mL. 240 units from 11 different stability lots at 18 months and 24 months past expiration demonstrated acceptable dose accuracy and Break/Glide Force reliability throughout product shelf life.

Table 9: Volume in Container (Dose Delivery After Expiration) Summary

Lot Tested	SI054E4, SI051B4, SI048B4(S), SI077F5, SI026E3, SI048B4(B), SI042L3, SI037J3, SI018A3, SI016L2, SI098E2
Units Tested	16
Maximum Volume in Container (mL)	(b) (4)
Minimum Volume in Container (mL)	
Mean Volume in Container (mL)	
Standard Deviation	
K_{Target} (Tolerance Interval Factor per ISO 11608-1)	
K_{Actual} (Tolerance Interval per ISO 11608-1)	
Results (Pass/Fail)	PASS

Table 16: Break Force / Glide Force After Expiration

# of Samples Tested	Release Criterion (N)	Minimum (N)	Maximum (N)	Mean (N)	Standard Deviation	K_{Target} (Tolerance Interval Factor per ISO 11608-1)	K_{Actual} (Tolerance Interval per ISO 11608-1)	Result (Pass/Fail)
240	Break Force (N)							
	(b) (4)	6.58	27.40	10.89	2.41	4.043	14.94	PASS
	Glide Force (N)							
	(b) (4)	4.93	29.50	7.36	1.85	4.043	10.00	PASS

Reviewer comment: *The stability data is acceptable. Volume in container was tested by dispensing the contents of vials into separate beakers and weigh the dispensed contents. This test measures the delivered dose from the syringe.*

6. RISK ANALYSIS

6.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities			x

6.2. Summary of Risk Analysis

Hazard/risk factors related to the usage of Epinephrine injection are identified and listed in the following table. The severity rating and probability rating of the risks with the risk mitigations and controls in place are evaluated.

Table 1: Identification, Evaluation and Mitigation of Hazards/Risks Related to the Usage of Epinephrine Injection

	Item/Process Steps	Failure Description	Reason of Failure	Effect on Procedure / Patient	SR	PR	Risk Mitigation (RM) / Controls (b) (4)	PR after RM
1	Medication administration (dosage)	Inaccurate dosage	Inaccurate graduation marks design	Partial dose, overdosage, treatment not fully effective, adverse effect	3	2		1
2	Medication administration (assembly)	Unable to assemble product	Force vial into injector without proper torque	Unusable device	2	2		1
3	Medication administration (dosage)	Adverse reaction during administration of medication	Incorrect rate of administration	Adverse reactions such as cerebrovascular hemorrhage, precordial distress, vomiting, headache, dyspnea	3	2		1
4	Medication administration (dosing instructions)	Administration made at incorrect location / route	User does not administer medication correctly	Partial dose, treatment not fully effective, adverse effect	3	2		1
5	Medication administration (assembly)	Loss of sterility due to user action	User touches injector tip during assembly	Non-sterile medication	3	2		1
6	Shipping/ Storage	Damage during shipping Improper user storage	Damage to product during shipping/storage process	Unusable device, loss of sterility	3	2		1

The Sponsor summarized that with the current risk mitigation and controls in place, the risks related to the use of Epinephrine all fall into the "Acceptable Risk" portions of the grid and ongoing monitoring of customer complaints are continually performed through the Management Review Program. All risks in relation to the usage of Epinephrine Injection are identified and evaluated to be acceptable and sufficiently mitigated.

Reviewer comment*: The provided risk analysis is acceptable.*

7. LABELING

Draft syringe label:

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

(b) (4)

8. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

Table 32P51-1 Finished Product Specifications for Epinephrine Injection USP, 0.1 mg/mL, 10 mL

Test Required	Method No.	Specifications
Color and Clarity	LTM-19-130	The solution is not pinkish and it contains no precipitate. If any yellow color is observed, the absorbance of the *Test Solution* does not exceed that of the *Standard Solution*.
Identification A. B.	LTM-19-130	A. (b) (4) B. Retention time of sample corresponds to standard
pH	LTM-19-130	2.2 - 5.0
Total Acidity	LTM-19-130	NMT (b) (4) mL of 0.01 N NaOH
Assays: Epinephrine	LTM-19-130	(b) (4)
Sodium Chloride	LTM-19-130	
Sulfur Dioxide from Sodium Bisulfite	LTM-19-130	
Container Content	LTM-19-130	(b) (4) 10.0 mL
Sterility Test	SOP-04-099	No growth observed
Bacterial Endotoxin Test	SOP-05-011	NMT (b) USP EU/mg
Particulate Matter	SOP-04-087	(b) (4)
Elemental Impurities*, USP<232><233>	SOP-E-2164	Meets USP<232> Drug Product Analysis Option
Other Requirements	It meets the requirements under *Injections and Implanted Drug Products* <1>	

*Risk assessment for drug product elemental impurities contamination and development of an adequate control strategy was conducted and met the requirements of Amphastar SOP-E-2164 in compliance with the USP <232>/<233> and ICH Q3D.

Testing method of Container Content:

Container Content ⟨697⟩: Ref. Current USP. Use the vial injector packaged with the medication, where applicable. Select 3 containers if the volume is 10 mL. If necessary, fit the containers with the accessories required for their use (needle, piston, syringe) and transfer the entire contents of each container without emptying the needle into a dry tared beaker by slowly and constantly depressing the piston. Determine the volume, in mL, calculated as the mass, in g, divided by the density.
The volume measured for each of the containers is NLT the nominal volume.
Density for 0.1 mg/mL Injection = 1.006 g/mL

***Reviewer Comment**: The spec "container content" measures the delivered volume by the injector, which reflects the dose accuracy requirement of the injector. Syringe functionality (break loose force and glide force) is not in the DP lot release spec. The reviewer thinks not including break loose force and glide force in the DP release is acceptable since the Sponsor showed the ability to control the syringe functionality. A total of 250 specimens from different lots were evaluated to develop the routine release criterion of NMT (b) (4) N; Additionally, 3081 units from 25 different lots were evaluated at initial finished product release to demonstrate acceptable maximum break loose force and glide force; 150 Units sampled from the IMS stability program at 18 months and 90 Units at 24 months were tested at 18 months and 24 months. All tested units verified and tested meet the established criteria of NMT (b) (4) N, at expiry (b) (4) months) and after expiration (24 months). The Sponsor demonstrated that syringe functionality is controlled throughout product shelf life. The provided specifications are acceptable.*

9. INTERACTIVE REVIEW

No information request with the Sponsor.

10. RECOMMENDATION

The device constituent of the combination product is approval.

Mohan Sapru

Digitally signed by Mohan Sapru
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