CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211363Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	August 15, 2022
From	Mohan Sapru, M.S., Ph.D. Branch Chief, New Drug Products Division III, Branch V Office of New Drug Products/OPQ
Through	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiology and Nephrology
Submission Type	NDA Resubmission
Type of Application	505(b)(2)
Applicant	International Medication Systems, Ltd.
Date of Receipt	February 16, 2022
PDUFA Goal Date	August 16, 2022
Established/Proper Name	Epinephrine Injection
Strength	1 mg/mL (0.1 mg/mL)
Route of Administration	Intravenous (IV)
Maximum Daily Dose	12 mg
Proposed Indication(s)	Hypotension Associated with Septic Shock
Regulatory Action	**Approval**

This CDTL review is based on the primary reviews, memos, and documented review input, as listed below:

Material Reviewed/Consulted	Review Team
OPQ's Integrated Quality Review (DARRTS, dated June 30, 2022)	Zhengfu Wang, Rao Kambhampati, Allison Aldridge, and Theodore Carver
DMEPA Review (DARRTS, dated May 27, 2022, and July 26, 2022)	Hina Mehta

OPQ: Office of Pharmaceutical Quality; DMEPA: Division of Medication Error Prevention and Analysis.

1. Background

In accordance with Section 505(b)(2) of the FD&C Act, the Applicant submitted the original NDA 211363 on February 14, 2018. FDA issued a Complete Response Letter, on December 12, 2018, mainly because the Applicant had proposed to manufacture the prefilled syringe drug product using (b) (4) (b) (4). Specifically, the original Integrated Quality Review concluded that from product quality perspective, the proposed formulation design and product development was not adequately optimized, (b) (4)

(b) (4) absent an adequate justification, was deemed unacceptable as per ICH Guidance for Industry-Q8(R2) Pharmaceutical Development (for details refer to OPQ's Integrated Quality Assessment, dated November 29, 2018, and CDTL Review, dated December 6, 2018).

2. Product Quality

In the current NDA resubmission, the Applicant addressed the quality deficiency identified in the original NDA review by reformulating the drug product to optimize it (b) (4) (b) (4) This formulation improvement was achieved by optimizing the formulation (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 shelf life of 20 months is based on 24 months of long-term stability data for three batches of the reformulated drug product. In conclusion, the Applicant has satisfactorily addressed the deficiency listed in the Complete Response Letter, dated December 12, 2018.

3. Manufacturing Facilities

All the facilities are acceptable.

4. Non-Clinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology

N/A

6. Statistical-Evaluation

N/A

7. Clinical Studies, and Financial Certification Disclosure

No clinical studies were performed in support of this 505(b)(2) NDA. Financial certifications (Form FDA 3454 and Form FDA 3455) are not applicable to this application because no bioavailability/bioequivalence studies were performed for the proposed product.

8. Advisory Committee Meeting

N/A

9. Pediatrics, and Other Relevant Regulatory Issues

None of the PREA criteria apply to this application. Hence, the Applicant is exempt from this requirement.

10. Labeling

Per the finalized product label and labeling, the Applicant has incorporated Agency's all labeling recommendations and edits.

11. Risk Benefit Assessment

The current NDA has relied on FDA's previous finding of safety and efficacy for the Listed Drug (LD) i.e., Belcher Pharmaceuticals' Epinephrine Injection USP, 1 mg/mL (reference NDA 205029). The Applicant's proposed product is essentially similar to the LD, as it has the same active moiety and delivers the same amount of drug to the patient. The proposed indication is the same as currently approved for the LD. Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for the currently marketed LD.

12. Recommended Regulatory Action

All the reviews of this application recommended approval, and I concur with the review teams. Based on the OPQ's Integrated Quality Review (DARRTS, dated June 30, 2022), an expiry period of 20 months for the proposed product, stored at controlled room temperature (20°C – 25°C; 68°F – 77°F) in the proposed commercial container closure system, is granted.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MOHAN K SAPRU
08/15/2022 10:38:54 AM

NORMAN L STOCKBRIDGE
08/15/2022 10:55:12 AM

Cross-Discipline Team Leader Review: NDA 211363

Date	03-December-2018
From	Mohan Sapru, M.S., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	Epinephrine Injection, USP (Luer-Jet™ Luer-Lock Prefilled Syringe)
Type of Application	505(b)(2)
Applicant	International Medication Systems, Limited
Date of Receipt	14-February-2018
PDUFA Goal Date	14-December-2018
Established/Proper Name	Epinephrine Injection, USP
Dosage forms; Strength	Parenteral; 1 mg/10 mL (0.1 mg/mL)
Route of Administration	Intravenous Infusion
Recommendation	**A Complete Response**

This secondary review is based on the primary reviews, memos and documented review input, as listed below:

Material Reviewed/Consulted	**Review Team**
Integrated Quality Assessment (PANORAMA, dated 29-November, 2018)	OPQ: Sharon Kelly, Rao Kambhampati, Peter Guerrieri, Qi Zhang, Samata Tiwari, and Mohan Sapru
Delivery Device (Luer-Jet® Prefilled Injector System) Inter-Center Consult Review (dated 25-September, 2018)	Rong Guo, Office of Device Evaluation (CDRH)
DMEPA Labeling Reviews (DARRTS, dated 12-October, 2018, and 31-October, 2018)	Maximilian Straka; Division of Medication Error Prevention and Analysis (DMEPA)

1. Background

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 submission has been made voluntarily pursuant to FDA's Compliance Policy Guide Section 440.100 in order to 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 1 mL 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).

- **Proposed Use of the Drug Product**

Non-Proprietary Name of the Drug Product	Epinephrine Injection, USP
Active ingredient	Epinephrine
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	For dosage and administration: • Add the entire contents of epinephrine prefilled syringe to (b) (4) mL of a 5 percent dextrose containing solution. • Each mL of this dilution contains 1 mcg of epinephrine. 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. • Continuous epinephrine infusion is generally required over several hours or days until the patient's hemodynamic status improves.
Alternative Methods of Administration	N/A

2. Quality/Chemistry, Manufacturing and Controls (CMC)

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 similar 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) 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.

Drug Substance (Epinephrine): 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, which have either been previously reviewed and found adequate or have been reviewed in the context of the current submission and found adequate. The drug substance 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, loss on drying, residue on ignition, levels for adrenalone and norepinephrine, residual solvents, and levels of microbial and bacterial endotoxins are tested on release. Based on adequate stability data, the drug substance manufacturer, Boehringer Ingelheim, has demonstrated stability for a period of (b) (4) for the drug substance.

Drug Product: 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 the 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. The prefilled syringe device is a (b) (4) 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. 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., (b) (4) sodium bisulfite (b) (4) and sodium citrate dehydrate and citric acid monohydrate, (b) (4) 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. (b) (4) 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 (b) (4) have been justified as per ICH Q3B. The other identified degradants (b) (4) have been justified per ICH M7 (QSAR). Regarding product stability, 24-month long-term stability data have been provided for three drug product batches (b) (4) but since one of the batches failed at the 24-month time point for Impurity (b) (4) (b) (4) content, the applicant has requested (b) (4) expiration dating period when the drug product vials are stored at controlled room temperature (25^0C). However, the validity of the stability data generated for a formulation, which is inadequately optimized, (b) (4) is very limited. For seeking approval via NDA resubmission, the applicant will need to manufacture the drug product batches (using the proposed commercial manufacturing process) (b) (4) and provide stability data for such batches in order to support a commercially viable expiration period for the to be marketed product.

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, sterilized). Regarding compatibility, the applicant has demonstrated that the drug product bulk solution is compatible (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. The 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. Specifically, 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, which is a (b) (4), is adequately described. Specifically, it involves (b) (4). The pH range for the in-process testing is acceptable. The applicant has demonstrated consistent capability of meeting the in-process specification, and adequate method precision. (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). In addition, IMS monitors microbiological quality (b) (4). The container-closure integrity of Epinephrine Injection has been demonstrated via process validation, which demonstrates that the container-closure integrity system can act 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 for product (b) (4) are adequate. The depyrogenation of the proposed production vials (b) (4) (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.

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 manufactured (b) (4) no product expiration date can be assigned at this stage.

Assessment of Manufacturing Facilities: The drug substance is proposed to be manufactured by three different manufacturers. The office of Process and Facilities has recommended an overall approval for all the currently listed manufacturing facilities concerning this NDA.

3. Non-Clinical Pharmacology/Toxicology

N/A

4. Clinical Pharmacology

N/A

5. Statistical-Evaluation:

N/A

6. Safety

N/A

7. Advisory Committee Meeting

N/A

8. Pediatrics

N/A

9. Other Relevant Regulatory Issues

N/A

10. Labeling

A detailed labeling review has not been undertaken for this NDA. Accordingly, the applicant was informed that the identified deficiencies preclude a discussion of labeling and post-marketing requirements/commitments at this time. Briefly, based on DMEPA's labeling review, the revised syringe container label and the carton labeling for Epinephrine Injection USP, Luer-Jet Luer-Lock prefilled syringe are acceptable from a medication error perspective. In addition, DMEPA determined that a human factors validation study is not needed at this time because: a) the product has over 40 years of marketing history b) the healthcare providers have familiarity with the product, and c) the applicant continues to monitor all customer complaints through the Management Review Program. The applicant has agreed to change the strength presentation to “Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL)” in accordance with USP General Chapter <7>. It is recommended that the term "single-use" be replaced with the term "single-dose" throughout the label and labeling.

11. Risk Benefit Assessment/ Recommendations

- **Risk Benefit Assessment**

The current NDA is a 505(b)(2) application that 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 1 mL ampule (reference NDA 205029). The applicant's proposed product is essentially similar to the LD, as it has the same active moiety and delivers the same amount of drug to the patient. Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for the currently marketed LD.

- **Recommended Regulatory Action**

(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). Hence, I concur with the OPQ review team's recommendation for a Complete Response for this NDA.

12. List of Deficiencies:

A. Drug Product:

1. (b) (4) (b) (4) We note that from the 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).

2. Please note that the validity of the stability data generated for a formulation, which is inadequately optimized, (b) (4) is very limited.

   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, manufactured (as per the proposed commercial process) (b) (4) (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.

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/s/

MOHAN K SAPRU
12/05/2018

NORMAN L STOCKBRIDGE
12/06/2018