CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 211880

Name: Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials

Sponsor: International Medication Systems, Ltd.

Approval Date: April 24, 2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211880

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211880

APPROVAL LETTER

ANDA 211880

ANDA APPROVAL

International Medication Systems, Limited
1886 Santa Anita Avenue
South El Monte, CA 91733
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 20, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials.

Reference is also made to the complete response letter issued by this office on January 23, 2020, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Adrenalin Injection, 30 mg/30 mL (1 mg/mL), of Par Sterile Products, LLC (Par).

We note that International Medication Systems, Limited (IMS) was granted a Competitive Generic Therapy (CGT) designation for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL) Multiple-Dose Vials. However, as noted in the October 19, 2018 CGT Designation – Grant Letter, your drug product is not eligible for CGT exclusivity under section 505(j)(5)(B)(v) of the FD&C Act because there were unexpired patents or exclusivities listed in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book) for the RLD at the time of submission of your ANDA.

The RLD upon which you have based your ANDA, Par's Adrenalin Injection, 30 mg/30 mL (1 mg/mL), is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
9,119,876 (the '876 patent)	March 13, 2035
9,295,657 (the '657 patent)	March 13, 2035
10,130,592 (the '592 patent)	March 13, 2035

Your ANDA contains paragraph IV certifications to each of the patents[1] under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials, under this ANDA. You have notified the Agency that IMS complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that no action for infringement was brought against IMS within the statutory 45-day period.

With respect to 180-day generic drug exclusivity, we note that IMS was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials. Therefore, with this approval, IMS is eligible for 180 days of generic drug exclusivity for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials. FDA notes that after issuance of this approval letter, eligibility for 180-day exclusivity is subject to future events that may result in forfeiture of exclusivity under section 505(j)(5)(D) of the FD&C Act. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the FD&C Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not

be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[2] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees

must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
CAPT, USPHS
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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[1] The Agency notes that the '592 patent was submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to this patent would not create a statutory stay of approval.

[2] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

John Ibrahim

Digitally signed by John Ibrahim
Date: 4/24/2020 11:10:38AM
GUID: 542af06d0124375c12e8c1d9fc86e87c

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211880

LABELING

Barcode 3 of 9

6990610H

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPINEPHRINE INJECTION, safely and effectively. See full prescribing information for EPINEPHRINE INJECTION.

EPINEPHRINE injection 1 mg/mL, for intramuscular, subcutaneous, and intravenous use
Initial U.S. Approval: 1939

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	01/2019
Dosage and Administration (2.3)	01/2019
Warnings and Precautions (5.3, 5.4. 5.5, 5.6, 5.7)	01/2019

----------INDICATIONS AND USAGE----------

Epinephrine Injection, USP is a non-selective alpha and beta adrenergic agonist indicated for:
- Emergency treatment of allergic reactions (Type 1), including anaphylaxis (1.1)
- To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Anaphylaxis:
  - *Adults and Children 30 kg (66 lbs) or more:* 0.3 to 0.5 mg (0.3 mL to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2.2)
  - *Children 30 kg (66 lbs) or less:* 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2.2)
- Hypotension associated with septic shock:
  - Dilute epinephrine in dextrose solution prior to infusion (2.3)
  - Infuse epinephrine into a large vein (2.3)
  - Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure (2.3)
  - Wean gradually (2.3)
  - See Full Prescribing Information for instructions on dilution and administration of the injection.

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 30 mg/30 mL (1 mg/mL) multiple dose vial (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Do not inject into buttocks, digits, hands, or feet (5.1)
- Avoid extravasation into tissues, which can cause local necrosis (5.3)
- May aggravate angina pectoris or produce ventricular arrhythmias (5.7)

----------ADVERSE REACTIONS----------

Common adverse reactions to systemically administered epinephrine include anxiety, tremor, weakness, dizziness, sweating, palpitations and pallor (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amphastar Pharmaceuticals, Inc. at 1-800-423-4136 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Drugs that counter the pressor effects of epinephrine include alpha blockers, vasodilators such as nitrates, diuretics, antihypertensives and ergot alkaloids. (7.1)
- Drugs that potentiate the effects of epinephrine include sympathomimetics, beta blockers, tricyclic antidepressants, MAO inhibitors, COMT inhibitors, clonidine, doxapram, oxytocin, levothyroxine sodium, quinidine and certain antihistamines. (7.2)
- Drugs that increase the arrhythmogenic potential of epinephrine include beta blockers, cyclopropane and halogenated hydrocarbon anesthetics, antihistamines, exogenous thyroid hormones, diuretics, and cardiac glycosides. Observe for development of cardiac arrhythmias. (7.3)
- Potassium-depleting drugs, including corticosteroids, diuretics, and theophylline, potentiate the hypokalemic effects of epinephrine. (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Elderly patients and pregnant women may be at greater risk of developing adverse reactions when epinephrine is administered parenterally (8.1, 8.5)
- Pregnancy: May cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Anaphylaxis

Emergency treatment of allergic reactions (Type I), including anaphylaxis, which may result from insect stings or bites, foods, drugs, sera, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

1.2 Hypotension associated with Septic Shock

Epinephrine Injection, USP is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Inspect visually for particulate matter and discoloration prior to administration; solution should be clear and colorless. Do not use if the solution is colored or cloudy, or if it contains particulate matter.

2.2 Anaphylaxis

Inject Epinephrine Injection, USP intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. When administering to a child, to minimize the risk of injection related injury, hold the leg firmly in place and limit movement prior to and during an injection. The injection may be repeated every 5 to 10 minutes as necessary. For intramuscular administration, use a needle long enough (at least 1/2 inch) to ensure the injection is administered into the muscle. Monitor the patient clinically for the severity of the allergic reaction and potential cardiac effects of the drug, and repeat as needed. Do not administer repeated injections at the same site, as the resulting vasoconstriction may cause tissue necrosis.

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) of undiluted Epinephrine Injection, USP administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, up to a maximum of 0.5 mg (0.5 mL) per injection, repeated every 5 to 10 minutes as necessary. Monitor clinically for reaction severity and cardiac effects.

Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) of undiluted Epinephrine Injection USP, administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, up to a maximum of 0.3 mg (0.3 mL) per injection, repeated every 5 to 10 minutes as necessary. Monitor clinically for reaction severity and cardiac effects.

2.3 Hypotension associated with Septic Shock

Dilute 1 mL (1 mg) of epinephrine from its vial to 1,000 mL of a 5 percent dextrose or 5 percent dextrose and sodium chloride solution to produce a 1 mcg per mL dilution. Administration in saline solution alone is not recommended. If indicated, administer whole blood or plasma separately.

Whenever possible, give infusions of epinephrine into a large vein. Avoid using a catheter tie-in technique, because the obstruction to blood flow around the tubing may cause stasis and increased local concentration of the drug. Avoid the veins of the leg in elderly patients or in those suffering from occlusive vascular diseases.

To provide hemodynamic support in septic shock associated hypotension in adult patients, the suggested dosing infusion rate of intravenously administered epinephrine is 0.05 to 2 mcg/kg/min, and is titrated to achieve a desired mean arterial pressure (MAP). The dosage may be adjusted periodically, such as every 10 - 15 minutes, in increments of 0.05 to 0.2 mcg/kg/min, to achieve the desired blood pressure goal.

After hemodynamic stabilization, wean incrementally over time, such as by decreasing doses of epinephrine every 10 minutes to determine if the patient can tolerate gradual withdrawal. Epinephrine Injection, USP diluted in 5 percent dextrose solutions or 5 percent dextrose and sodium chloride solutions are stable for 4 hours at room temperature or 24 hours under refrigerated conditions.

3 DOSAGE FORMS AND STRENGTHS

Epinephrine Injection, USP: clear, colorless solution supplied as 30 mg/30 mL (1 mg/mL) in a multiple dose amber glass vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Incorrect Locations of Injection for Anaphylaxis

Injection into the anterolateral aspect of the thigh (vastus lateralis muscle) is the most appropriate location for administration because of its location, size, and available blood flow. Injection into (or near) smaller muscles, such as in the deltoid, is not recommended.

Do not administer repeated injections of epinephrine at the same site, as the resulting vasoconstriction may cause tissue necrosis.

Do not inject into buttock. Injection into the buttock may not provide effective treatment of anaphylaxis and has been associated with the development of Clostridial infections (gas gangrene).

Do not inject into digits, hands, or feet. Epinephrine is a strong vasoconstrictor. Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area and tissue necrosis.

5.2 Serious Infections at the Injection Site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

5.3 Extravasation and Tissue Necrosis with Intravenous Infusion

Avoid extravasation of epinephrine into the tissues, to prevent local necrosis. When Epinephrine Injection, USP is administered intravenously, check the infusion site frequently for free flow. Blanching along the course of the infused vein, sometimes without obvious extravasation, may be attributed to vasa vasorum constriction with increased permeability of the vein wall, permitting some leakage. This also may progress on rare occasions to superficial slough. Hence, if blanching occurs, consider changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

There is potential for gangrene in a lower extremity when infusions of catecholamine are given in an ankle vein.

Antidote for Extravasation Ischemia: To prevent sloughing and necrosis in areas in which extravasation has taken place, infiltrate the area with 10 mL to 15 mL of saline solution containing from 5 mg to 10 mg of **phentolamine**, an adrenergic blocking agent. Use a syringe with a fine hypodermic needle, with the solution being infiltrated liberally throughout the area, which is easily identified by its cold, hard, and pallid appearance. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours.

5.4 Hypertension

Because individual response to epinephrine may vary significantly, monitor blood pressure frequently and titrate to avoid excessive increases in blood pressure.

Patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types may experience severe, prolonged hypertension when given epinephrine.

5.5 Pulmonary Edema

Epinephrine increases cardiac output and causes peripheral vasoconstriction, which may result in pulmonary edema.

5.6 Renal Impairment

Epinephrine constricts renal blood vessels, which may result in oliguria or renal impairment.

5.7 Cardiac Arrhythmias and Ischemia

Epinephrine may induce cardiac arrhythmias and myocardial ischemia in patients, especially patients suffering from coronary artery disease, or cardiomyopathy.

5.8 Allergic Reactions Associated with Sulfite

Epinephrine Injection, USP contains sodium bisulfite which may cause mild to severe allergic reactions including anaphylaxis or asthmatic episodes in susceptible individuals. However, the presence of bisulfite in this product should not preclude its use for the treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive, as the alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

6 ADVERSE REACTIONS

Common adverse reactions to systemically administered epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with heart disease, hypertension, or hyperthyroidism *[see Warnings and Precautions (5.7)]*.

The true incidence of adverse reactions associated with the systemic use of epinephrine is difficult to determine. Adverse reactions reported in observational trials, case reports, and studies are listed below by body system:

Cardiovascular: angina, arrhythmias, hypertension, pallor, palpitations, tachyarrhythmia, tachycardia, vasoconstriction, ventricular ectopy and stress cardiomyopathy.

Rapid rises in blood pressure associated with epinephrine use have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease *[see Warnings and Precautions (5.7)]*.

Neurological: disorientation, impaired memory, panic, psychomotor agitation, sleepiness, tingling.

Psychiatric: anxiety, apprehensiveness, restlessness.

Other:
Patients with Parkinson's disease may experience psychomotor agitation or a temporary worsening of symptoms *[see Warnings and Precautions (5.7)]*.

Diabetic patients may experience transient increases in blood sugar.

Injection into the buttock has resulted in cases of gas gangrene *[see Warnings and Precautions (5.1)]*.

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported following epinephrine injection in the thigh *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 Drugs Antagonizing Pressor Effects of Epinephrine

- α-blockers, such as phentolamine
- Vasodilators, such as nitrates
- Diuretics
- Antihypertensives

- Ergot a a o t
- Phenoth az ne ant p ychot c

7.2 Drugs Po en ia ing Pressor Effec s of Epinephrine t

- Sympathomimet c
- β-b oc er , uch a proprano o
- Tr cyc c ant - epre ant
- Monoam ne ox a e (MAO) nh b tor
- Catecho -O-methy tran fera e (COMT) nh b tor , uch a entacapone t
- C on ne
- Doxapram
- Oxytoc n

7.3 Drugs Po en ia ing Arrhy hmogenic Effec s of Epinephrine t

Car ac arrhythm a are more common among pat ent rece v ng any of the fo ow ng rug *[see Warnings and Precautions (5.7) and Adverse Reactions (6)]*.

- β-b oc er , uch a proprano o t
- Cyc opropane or ha ogenate hy rocarbon ane thet c , uch a ha othane
- Ant h tam ne
- Thyro hormone
- D uret c
- Car ac g yco e , uch a g ta g yco e
- Qu n ne

7.4 Drugs Po en ia ing Hypokalemic Effec s of Epinephrine t

- Pota um ep et ng uret c
- Cort co tero
- Theophy ne

8 USE IN SPECIFIC POPULATIONS t

8.1 Pregnancy

R Summary t

Pro onge exper ence w th ep nephr ne u e n pregnant women over evera eca e , ba e on pub he terature, o not ent fy a rug a oc ate r of major b rth efect , mi carr age or a ver e materna or feta outcome . However, there are r to the mother an fetu a oc ate w th ep nephr ne u e ur ng abor or e very *(see Clinical Considerations)*. In an ma repro uct on tu e , ep nephr ne a m n tere by the ubcutaneou route to pregnant rabb t , m ce, an ham ster , ur ng the per o of organogene , re u te n a ver e eve opmenta effect (nc u ng ga tro ch , an embryon c etha ty, an e aye e eta o ficat on) at o e approx mate y 2 t me the max mum recommen e a y ntramu cu ar, ubcutaneou , or ntravenou o e *(see Data)*.

The e t mate bac groun r of major b rth efect an m i carr age for the n cate popu at on un nown. A pregnanc e have a bac groun r of btrth efect, o , or other a ver e outcome . In the Un te State genera popu at on, the e t mate bac groun r of major b rth efect an m i carr age n c n ca y recogn ze pregnanc e 2-4% an 15-20%, re pect ve y.

C n ca Con erat ont

Disease-associated maternal and/or embryo/fetal risk t
Dur ng pregnancy, anaphy ax can be cata troph c an can ea to hypox c- chem c encepha opathy an permanent centra t nervou y tem amage or eath n the mother an , more common y, n the fetu or neonate. The preva ence of anaphy ax occurr ng ur ng pregnancy reporte to be approx mate y 3 ca e per 100,000 e ver e .

Management of anaphy ax ur ng pregnancy m iar to management n the genera popu at on. Ep nephr ne the fir t ne-me cat on of cho ce for treatment of anaphy ax ; t hou be u e n the ame manner n pregnant an non-pregnant pat ent . In conjunct on w th the a m n trat on of ep nephr ne, the pat ent hou ee mme ate me ca or ho p ta care.

Hypoten on a oc ate w th ept c hoc a me ca emergency n pregnancy wh ch can be fata f eft untreate . De ay ng treatment n pregnant women w th hypoten on a oc ate w th ept c hoc may ncrea e the r of materna an feta t morb ty an morta ty. L fe- u ta n ng therapy for the pregnant woman hou not be w thhe ue to potent a concern t regar ng the effect of ep nephr ne on the fetu . t

Labor or Delivery t

Ep nephr ne u ua y nh b t pontaneou or oxytoc n n uce contract on of the pregnant human uteru an may e ay the econ tage of abor. Avo ep nephr ne ur ng the econ tage of abor. In o age uffic ent to re uce uter ne contract on , the rug may cau e a pro onge per o of uter ne atony w th hemorrhage. Avo ep nephr ne n ob tetr c when materna t b oo pre ure excee 130/80 mmHg. t

A though ep nephr ne may mprove materna hypoten on a oc ate w th ept c hoc an anaphy ax , t may re u t n t uter ne va ocon tr ct on, ecrea e uter ne b oo flow, an feta anox a. t

Data t

Animal Data

In an embryofeta eve opment tu y w th pregnant rabb t o e ur ng the per o of organogene (on ay 3 to 5, 6 to 7 or 7 to 9 of ge tat on), ep nephr ne cau e teratogen c effect (nc u ng ga tro ch) at o e approx mate y 15 t me the max mum recommen e ntramu cu ar, ubcutaneou , or ntravenou o e (on a mg/m^2 ba at a materna ubcutaneou t o e of 1.2 mg/ g/ ay for two to three ay). An ma treate on ay 6 to 7 ha ecrea e number of mp antat on .

In an embryofeta eve opment tu y, pregnant m ce were a m n tere ep nephr ne (0.1 to 10 mg/ g/ ay) on Ge tat on Day 6 to 15. Teratogen c effect , embryon c etha ty, an e ay n e eta o ficat on were ob erve at approx mate y 3 t me the max mum recommen e ntramu cu ar, ubcutaneou , or ntravenou o e (on a mg/m^2 ba at materna ubcutaneou o e of 1 mg/ g/ ay for 10 ay). The e effect were not een n m ce at approx mate y 2 t me the max mum recommen e a y ntramu cu ar or ubcutaneou o e (on a mg/m^2 ba at a ubcutaneou materna o e of 0.5 mg/ g/ ay for 10 ay).

In an embryofeta eve opment tu y w th pregnant ham ster o e ur ng the per o of organogene from ge tat on ay 7 to 10, ep nephr ne pro uce re uct on n tter ze an e aye e eta o ficat on at o e approx mate y 2 t me the t max mum recommen e ntramu cu ar, ubcutaneou , or ntravenou o e (on a mg/m^2 ba at a materna ubcutaneou t o e of 0.5 mg/ g/ ay).

8.2 Lac a ion t

R Summary t

There no nformat on regar ng the pre ence of ep nephr ne n human mi or the effect of ep nephr ne on the brea tfe nfant or on mi pro uct on. However, ue to t poor ora b oava ab ty an hort ha f- fe, ep nephr ne expo ure expecte to be very ow n the brea tfe nfant.

Ep nephr ne the fir t- ne me cat on of cho ce for treatment of anaphy ax ; t hou be u e n the ame manner for t anaphy ax n brea tfee ng an non-brea tfee ng pat ent . t

8.4 Pedia ric Use t

C n ca u e ata upport we ght-ba e o ng for treatment of anaphy ax n pe atr c pat ent , an other reporte c n ca exper ence w th the u e of ep nephr ne ugge t that the a ver e react on een n ch ren are m iar n nature an extent to tho e both expecte an reporte n a u t . t

Safety an effect vene of ep nephr ne n pe atr c pat ent w th ept c hoc have not been e tab he . t

8.5 Geria ric Use t

C n ca tu e for the treatment of anaphy ax have not been performe n ubject age 65 an over to eterm ne whether they re pon fferent y from younger ubject . However, other reporte c n ca exper ence w th u e of ep nephr ne for the treatment of anaphy ax ha ent fie that ger atr c pat ent may be part cu ar y en t ve to the effect of ep nephr ne. t Therefore, for the treatment of anaphy ax , con er tart ng w th a ower o e to ta e nto account potent a concom tant ea e or other rug therapy.

C n ca tu e of ep nephr ne for the treatment of hypoten on a oc ate w th ept c hoc not nc u e uffic ent t number of ubject age 65 an over to eterm ne whether they re pon fferent y from younger ubject . Other reporte c n ca exper ence ha not ent fie fference n re pon e between the e er y an younger pat ent . In genera , o e ect on for an e er y pat ent hou be caut ou , u ua y tart ng at the ow en of the o ng range, reflect ng the greater frequency of ecrea e hepat c, rena , or car ac funct on, an of concom tant ea e or other rug therapy.

10 OVERDOSAGE t

Over o age of ep nephr ne may pro uce extreme y e evate arter a pre ure, wh ch may re u t n cerebrova cu ar hemorrhage, part cu ar y n e er y pat ent . Over o age may a o re u t n pu monary e ema becau e of per phera va cu ar con tr ct on together w th car ac t mu at on. Ep nephr ne over o age can a o cau e tran ent bra ycar a fo owe by tachycar a an the e may be accompan e by potent a y fata car ac arrhythm a . Premature ventr cu ar contract on may appear w th n one m nute after nject on an may be fo owe by mu t foca ventr cu ar tachycar a (prefib at on rhythm). Sub ence of the ventr cu ar effect may be fo owe by atr a tachycar a an occa ona y by atr oventr cu ar b oc . Myocar a chem a an nfarct on, car omyopathy, extreme pa or an co ne of the n, metabo c ac o ue to e evate b oo act c ac eve , an rena n uffic ency have a o been reporte .

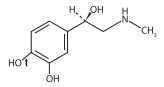
Ep nephr ne rap y nact vate n the bo y an treatment fo ow ng over o e w th ep nephr ne pr mar y upport ve. Treatment of pu monary e ema con t of a rap y act ng a pha-a renerg c b oc ng rug (uch a phento am ne me y ate) an re p ratory upport. Treatment of arrhythm a con t of a m n trat on of a beta-a renerg c b oc ng rug (uch a t proprano o). If nece ary, pre or effect may be counteracte by rap y act ng va o ator or α-a renerg c b oc ng rug . If t pro onge hypoten on fo ow uch mea ure , t may be nece ary to a m n ter another pre or rug.

11 DESC I TION t

Ep nephr ne Inject on, USP a c ear, co or e , ter e o ut on conta n ng 1 mg/mL ep nephr ne, pac age a 30 mL of o ut on n a mu t p e o e amber g a v a . In the 30 mL v a , each 1 mL of Ep nephr ne Inject on, USP o ut on conta n 1 mg ep nephr ne, 9 mg o um ch or e, 1.5 mg o um metab u fite, hy roch or c ac to a ju t pH, 5.4 mg ch orobutano a a pre ervat ve an water for nject on. The pH range 2.2-5.0.

Ep nephr ne a ympathomimet c catecho am ne. The chem ca name of ep nephr ne : 1,2-Benzene o , 4-[(1R)-1-hy roxy-2-(methy am no)ethy]-, or (-)-3,4-D hy roxy-α-[2-(methy am no)ethy]benzy a coho .

The chem ca tructure of ep nephr ne : t



The mo ecu ar we ght of ep nephr ne 183.2. t

Ep nephr ne o ut on eter orate rap y on expo ure to a r or ght, turn ng p n from ox at on to a renochrome an brown from the format on of me an n.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Ac ion

Ep nephr ne act on both a pha an beta-a renerg c receptor . The mechan m of the r e n b oo pre ure 3-fo : a rect myocar a t mu at on that ncrea e the trength of ventr cu ar contract on (po t ve notrop c act on), an ncrea e heart rate t (po t ve chronotrop c act on), an per phera va ocon tr ct on.

12.2 Pharmacodynamics

Ep nephr ne ncrea e g ycogeno y , re uce g uco e up ta e by t ue , an nh b t n u n re ea e n the pancrea , re u t ng n hyperg ycem a an ncrea e b oo act c ac .

Intramu cu ar an ubcutaneou u e for anaphy ax

Through t act on on a pha-a renerg c receptor , ep nephr ne e en the va o at on an ncrea e va cu ar permeab ty that occur ur ng anaphy ax , wh ch can ea to o of ntrava cu ar flu vo ume an hypoten on.

Through t act on on beta-a renerg c receptor , ep nephr ne cau e bronch a mooth mu c e re axat on an he p a ev ate broncho pa m, wheez ng an y pnea that may occur ur ng anaphy ax .

Ep nephr ne a o a ev ate prur tu , urt car a, an ang oe ema an may re eve ga tro nte t na an gen tour nary ymptom s a oc ate w th anaphy ax becau e of t re axer effect on the mooth mu c e of the tomach, nte t ne, uteru an ur nary b a er.

Intravenou u e for hypoten on a oc ate w th ept c hoc

When a m n tere parentera y, ep nephr ne ha a rap on et an hort urat on of act on.

Fo ow ng ntravenou a m n trat on of ep nephr ne, ncrea e n y to c b oo pre ure an heart rate are ob erve . Decrea e n y tem c va cu ar re tance an a to c b oo pre ure are ob erve at ow o e of ep nephr ne becau e of β2-me ate va o at on, but are overta en by α1-me ate me pher phera va ocon tr ct on at h gher o e ea ng to ncrea e n a to c b oo pre ure. The on et of b oo pre ure ncrea e fo ow ng an ntravenou o e of ep nephr ne < 5 m nute an the t me to off et b oo pre ure re pon e occur w th n 15 m nute . Mo t va cu ar be are con tr cte nc u ng rena , p anchn c, muco a an n.

Ep nephr ne cau e my r a when a m n tere parentera y.

12.3 Pharmacokine ics

Fo ow ng ntravenou nject on, ep nephr ne rap y c eare from the p a ma w th an effect ve ha f- fe of < 5 m nute . A pharmaco net c tea y tate fo ow ng cont nuou ntravenou nfu on ach eve w th n 10-15 m nute . In pat ent w th ept c hoc , ep nephr ne p ay o e-proport ona pharmaco net c n the nfu on o e range of 0.03 to 1.7 mcg/ g/m n.

Ep nephr ne exten ve y metabo ze w th on y a ma amount excrete unchange .

Ep nephr ne rap y egra e to van y man e c ac , an nact ve metabo te, by monoam ne ox a e an catecho -O-methy tran fera e that are abun ant y expre e n the ver, ney an other extraneurona t ue . The t ue w th the h ghe t contr but on to remova of c rcu at ng exogenou ep nephr ne are the ver (32%), ney (25%), e eta mu c e (20%), an me enter c organ (12%).

Spec fic Popu at on

Elderly

In a pharmaco net c tu y of 45-m nute ep nephr ne nfu on g ven to hea thy men age 20 to 25 year an hea thy men age 60 to 65 year , the mean p a ma metabo c c earance rate of ep nephr ne at tea y tate wa greater among the o er men (144.8 ver u 78 mL/ g/m n for a 0.0143 mcg/ g/m n nfu on).

Body Weight

Bo y we ght ha been foun to nfluence ep nephr ne pharmaco net c . H gher bo y we ght wa a oc ate w th a h gher p a ma ep nephr ne c earance an a ower concentrat on p ateau.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mu agenesis, Impairmen of Fer ili y

Long-term tu e to eva uate the carc nogen c potent a of ep nephr ne have not been con ucte .

Ep nephr ne an other catecho am ne have been hown to have mutagen c potent a *in vitro*. Ep nephr ne wa po t ve n the *Salmonella* bacter a rever e mutat on a ay, po t ve n the mou e ymphoma a ay, an negat ve n the *in vivo* m cronuc eu a ay. Ep nephr ne an ox at ve mutagen ba e on the *E. coli* WP2 Mutox te t bacter a rever e mutat on a ay. Th hou not prevent the u e of ep nephr ne un er the con t on note un er *Indications and Usage (1)*.

The potent a for ep nephr ne to mpa r repro uct ve performance ha not been eva uate , but ep nephr ne ha been hown to ecrea e mp antat on n fema e rabb t o e ubcutaneou y w th 1.2 mg/ g/ ay (15-fo the h ghe t human ntramu cu ar or t ubcutaneou a y o e) ur ng ge tat on ay 3 to 9.

16 HOW SUPPLIED/STORAGE AND HANDLING

Epinephrine Injec ion, USP 30 mL Mul i-Dose Vials:

Each carton conta n 1 mu t p e o e v a conta n ng 30 mg/30 mL (1 mg/mL) ep nephr ne nject on, USP o ut on n an amber g a v a .

NDC 76329-9060-0 t 30 mL v a Stoc No. 9061

V a an content mu t be car e 30 ay after n t a u e.

Store between 20°C to 25°C (68°F to 77°F) *[See USP Controlled Room Temperature]*. Ep nephr ne ght en t ve. Protect from ght an freez ng.

In pect v ua y for part cu ate matter an co orat on pr or to a m n trat on. Do not u e the o ut on f t co ore or c ou y, or f t conta n part cu ate matter. t

17 PATIENT COUNSELING INFORMATION

A v e pat ent or the r careg ver about common a ver e react on a oc ate w th the u e of ep nephr ne nc u ng an ncrea e n heart rate, the en at on of a more forcefu heartbeat, pa p tat on , weat ng, nau ea an vom t ng, ffic ty breath ng, pa or, zz ne , wea ne or ha ne , hea ache, apprehen on, nervou ne , or anx ety. The e ymptom san gn u ua y ub e rap y, e pec a y w th re t, qu et an recumbent po t on ng.

Warn pat ent w th a goo re pon e to n t a treatment about the po b ty of recurrence of ymptom san n truct pat ent to obta n proper me ca attent on f ymptom sreturn.

Warn pat ent w th abete that they may eve op ncrea e b oo g uco e eve fo ow ng ep nephr ne a m n trat on.

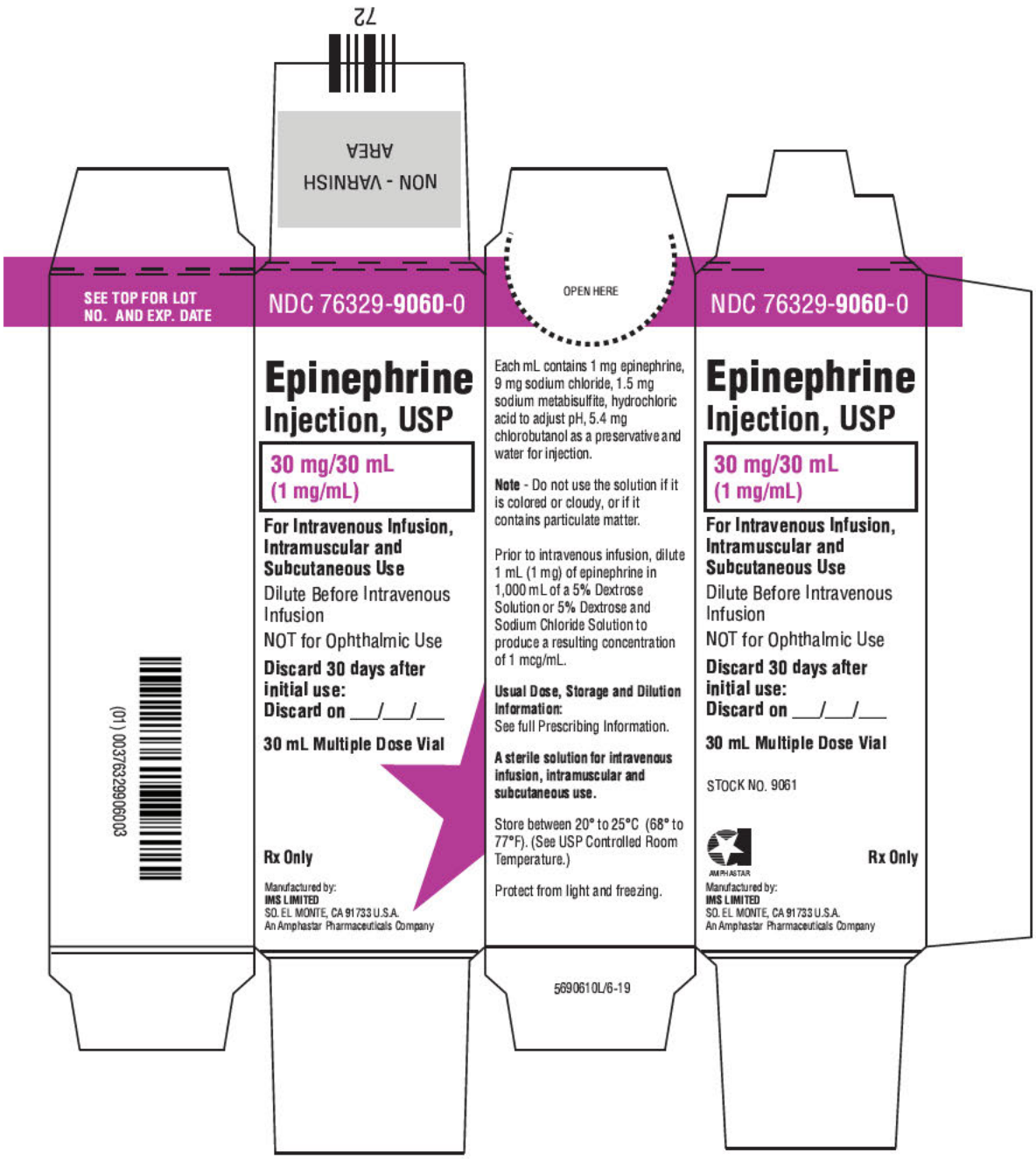
Rare ca e of er ou n an oft t ue nfect on , nc u ng necrot z ng fa c t an myonecro cau e by C o tr a (ga gangrene), have been reporte at the nject on te fo ow ng ep nephr ne nject on for anaphy ax . A v e pat ent to ee me ca care f they eve op gn or ymptom sof nfect on, uch a per tent re ne , warmth, we ng, or ten erne , at the ep nephr ne nject on te *[see Warnings and Precautions (5.2)]*.

Rx On y

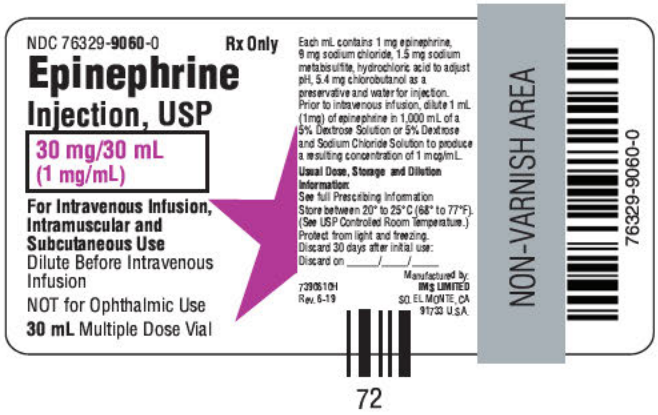
INTERNATIONAL MEDICATION SYSTEMS, LIMITED
SO. EL MONTE, CA 91733, U.S.A.
An Ampha tar Pharmaceut ca Company

REV. 06-19

CC File No.: t 6990610H/6-19
Date: 6/5/19
Product: Epinephrine Injection, USP
Flat size: 11" x 16"
Folded Size: t 2 ¾ x 1"
Colors: Black text
Barcode: t 3 of 9 t


72
NON - VARNISH AREA
SEE TOP FOR LOT NO. AND EXP. DATE
NDC 76329-9060-0
OPEN HERE
NDC 76329-9060-0
Epinephrine Injection, USP
30 mg/30 mL (1 mg/mL)
For Intravenous Infusion, Intramuscular and Subcutaneous Use
Dilute Before Intravenous Infusion
NOT for Ophthalmic Use
Discard 30 days after initial use:
Discard on ___/___/___
30 mL Multiple Dose Vial
Rx Only
Manufactured by:
IMS LIMITED
SO. EL MONTE, CA 91733 U.S.A.
An Amphastar Pharmaceuticals Company
(01) 00376329906003
Each mL contains 1 mg epinephrine, 9 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection.
Note - Do not use the solution if it is colored or cloudy, or if it contains particulate matter.
Prior to intravenous infusion, dilute 1 mL (1 mg) of epinephrine in 1,000 mL of a 5% Dextrose Solution or 5% Dextrose and Sodium Chloride Solution to produce a resulting concentration of 1 mcg/mL.
Usual Dose, Storage and Dilution Information:
See full Prescribing Information.
A sterile solution for intravenous infusion, intramuscular and subcutaneous use.
Store between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)
Protect from light and freezing.
5690610L/6-19
Epinephrine Injection, USP
30 mg/30 mL (1 mg/mL)
For Intravenous Infusion, Intramuscular and Subcutaneous Use
Dilute Before Intravenous Infusion
NOT for Ophthalmic Use
Discard 30 days after initial use:
Discard on ___/___/___
30 mL Multiple Dose Vial
STOCK NO. 9061
AMPHASTAR
Rx Only
Manufactured by:
IMS LIMITED
SO. EL MONTE, CA 91733 U.S.A.
An Amphastar Pharmaceuticals Company

(b) (4)


NDC 76329-9060-0
Rx Only
Epinephrine
Injection, USP
30 mg/30 mL
(1 mg/mL)
For Intravenous Infusion, Intramuscular and Subcutaneous Use
Dilute Before Intravenous Infusion
NOT for Ophthalmic Use
30 mL Multiple Dose Vial
Each mL contains 1 mg epinephrine, 9 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection.
Prior to intravenous infusion, dilute 1 mL (1mg) of epinephrine in 1,000 mL of a 5% Dextrose Solution or 5% Dextrose and Sodium Chloride Solution to produce a resulting concentration of 1 mcg/mL.
Usual Dose, Storage and Dilution Information:
See full Prescribing Information
Store between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)
Protect from light and freezing.
Discard 30 days after initial use:
Discard on _____/_____/_____
7390610H
Rev. 6-19
Manufactured by:
IMS LIMITED
SO. EL MONTE, CA
91733 U.S.A.
NON-VARNISH AREA
76329-9060-0

72

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211880

LABELING REVIEW(s)

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	July 12, 2019
ANDA Number(s)	211880
Review Number	3
Applicant Name	International Medication Systems, Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials
Proposed Proprietary Name	None
Submission Received Date	June 14, 2019 (CR Resubmission)
Primary Labeling Reviewer	Wan Lee, PharmD
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☒ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) received (add date):

1. GENERAL COMMENTS
   Comment

2. CONTAINER LABEL
   a. Comment
   b. Comment

3. CARTON LABELING
4. PRESCRIBING INFORMATION
   a. Comment
   b. Subheading
      i. Comment
      ii. Comment
5. MEDICATION GUIDE
6. STRUCTURED PRODUCT LABELING (SPL)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with Choose an item. all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission July 12, 2019 received June 14, 2019.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

The below comments are from the labeling review C2 based on the submissions dated February 13 and March 13, 2019. Brief regulatory history: a CR was issued on May 30, 2019, for Pharmaceutical Quality deficiencies. Our C2 comments were included on this CR letter.

1. CONTAINER LABEL
   To prevent cluttering of the PDP, decrease the size of the half star. To increase contrast, consider using a white background with black letters. In addition, [redacted] (b) (4) for boxing the strength statement and for the half star. Please refer to the color scheme in your carton labeling.

   Response:

   The following changes have been made to the principal display panel of the container label:

   - The size of the half star has been decreased;
   - The background color has been changed *from* [redacted] (b) (4) *to* white with black letters to increase contrast;
   - The color scheme has been revised to make the expression of strength and the half star pink, consistent with the carton labeling.

   Per Comment 3a below, the following additional changes were made to provide for the new indication and route of administration, per NDA 204640/S-009 approved on January 29, 2019:

   - "Intravenous Infusion" has been added in front of "Intramuscular and Subcutaneous Use";
   - The statement "Dilute Before Intravenous Infusion" has been added above "NOT for Ophthalmic Use";
   - Information on dilution prior to intravenous infusion has been added to the side panel.

   This is acceptable.

2. CARTON LABELING
   We acknowledge your modifications on the net quantity statement. However, we recommend increasing the prominence of the expression of strength (e.g., boxing, highlighting, etc.).

Response:

The prominence of the expression of strength was increased as recommended by changing the font color *from* (b) (4) *to* pink, and adding bold black boxing.

Per Comment 3a below, the following additional changes were made to provide for the new indication and route of administration, per NDA 204640/S-009 approved on January 29, 2019:

- "Intravenous Infusion" has been added in front of "Intramuscular and Subcutaneous Use" to all three occurrences where the Use statement appears;
- The statement "Dilute Before Intravenous Infusion" has been added to the primary and rear panels;
- Information on dilution prior to intravenous infusion has been added to the side panel.

This is acceptable.

3. PRESCRIBING INFORMATION
   a. We note that in our DRL letter dated January 30, 2019 and via an email correspondence in February, we stated that the most current model labeling approved for your proposed drug product is not being used according to 21 CFR 314.94 (8)(iv). Refer to Drugs@FDA: FDA Approved Drug Products, NDA 204640/S-009 approved on January 29, 2019, and revise accordingly. Since the new indication "to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock" does not contain protected patents or exclusivities, please retain this information in your labeling.

   Response:

   Per the FDA's suggestion, IMS submits this amendment to retain the new indication of "to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock," which, as the FDA suggested, does not contain protected patents or exclusivities. Additionally, per FDA's suggestion, IMS revised its label accordingly to include intravenous infusion as an additional route of administration to match the RLD's label provided in NDA 204640/S-009 approved January 29, 2019.

   As requested, IMS has revised its proposed draft prescribing information, as well as the container and carton labels as discussed in the response to Comments 1 and 2 above, to retain the new indication and route of administration, per NDA 204640/S-009, approved on January 29, 2019. The revised Labeling Statement is provided in **Section 1.14.3.1**.

   This is acceptable.

   b. To be consistent with the RLD, please note that sections or subsections of labeling that are identified as containing recent major changes (RMC) must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text. We refer you to 21 CFR 201.57(d)(9). In addition, change the dates in the RMC to "01/2019". Please refer to the RLD.

Response:
As requested, the package insert has been revised to be consistent with the RLD to include vertical lines on the left edge of text that contains recent major changes and the date has been changed to 01/2019.

This is acceptable.

c. DOSAGE FORMS AND STRENGTHS: Include "glass" to read "…dose amber glass vial." to be consistent with the RLD and in the HOW SUPPLIED section.

Response:
In the Microsoft Word version of the prescribing information, "glass" was added and the statement in the DOSAGE FORMS AND STRENGTHS has been revised to read "…dose amber glass vial" as requested.

We note that this revision was made in the PDF version of the PI, not the Microsoft Word version. This is acceptable as this will be the version used for our review.

d. HOW SUPPLED/STORAGE AND HANDLING: Remove (b) (4).

Response:
In the Microsoft Word version of the prescribing information, (b) (4) (b) (4) of the HOW SUPPLIED/STORAGE AND HANDLING section as requested.

This is acceptable.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:
See section 2.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

1. Drug Facts: Discussion about label carve-out between DLR and OGDP: NDA decided to remove the mydriasis indication due to lack of safety data for tartaric acid use intraocularly. NDA submitted a citizen petition requesting FDA to refrain from approving any generic drug products that does not contain the same inactive ingredients. The CP was denied.

This is not applicable to this proposed NDA as they are only proposing the multiple dose vial, 30 mL, indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis.

Discussions pertaining to USP General Chapter <7> Labeling that single-entity drug products that can be expressed as a ratio (i.e., epinephrine, neostigmine and isoproterenol injections), shall be labeled only in terms of strength/mL. A ratio expression such as 1:1000 is an unacceptable format for single-entity drug products.

Justification for approving ANDAs for single entity injection products epinephrine, neostigmine, isoproterenol without ration expression of strength if the RLD still labels its products with the ratio of strength.

2. Considerations during this review of this application: (memo uploaded in Drug Facts on 5/15/2019)

a. The Applicant proposed the original formulation which is not Q1/Q2 the same as the reformulated RLD NDA 204640, Adrenalin®. Which PI should the ANDA use as their model labeling?

b. The Prior Approval Supplement-009 was approved on January 29, 2019, which provided for a new indication, to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. Should this new indication applicable to the original formulation of epinephrine injection?

Recommendations:

a. Before the approval of S-009, the differences from the original PI and S-008 are the inactive ingredients (reformulation of both NDA 204200 (1 mL SDV) and NDA 204640 (30 mL MDV)) and the safety labeling changes (SLCs). These SLCs included revisions of the USPI that addressed (b) (4) , and addition of myocardial ischemia and infarction and cardiomyopathy. The SLC after the reformulation of NDA 204200 (1 mL SDV) and with the removal of the indication for mydriasis, revisions were made to the container labels and carton labeling of the SDV and MDV. We felt that these SLC updates are applicable to the drug product and not the inactive ingredients.

In addition, the Applicant proposed the original formulation that is not Q1/Q2 the same as the reformulated RLD but is Q1/Q2 the same as the original RLD. The Applicant has requested a waiver under 21 CFR 314.99(b) requesting that the Agency waive the requirements found at 21 CFR 314.94(a)(9)(iii) to permit approval of the proposed test product, which is Q1/Q2 different from the currently approved RLD. The Applicant indicated that the differences in the formulation do not affect the safety or efficacy of the proposed drug product. The biowaiver was granted.

b. The PAS for Supplement-009 for NDA 204200 (S-009) and NDA 204640 (S-009) proposes the addition of a new indication "to increase mean arterial blood pressure in adult patients with hypotension associated with

septic shock". The Applicant has not conducted any nonclinical/clinical studies and relied soley on published clinical studies. We have consulted the Division of Cardiovascular and Renal Products (DCRP) and stated:

The NDA supplements we just approved were labeling supplements to add a new indication to each of the two Adrenalin NDAs. These were 505(b)(2) submissions based on published literature. Other than product labeling, there was no change whatsoever in either of the two Adrenalin drug products (1 mL and 30 mL vials, each containing 1 mg epinephrine/mL). From a clinical standpoint, and without regard to any applicable exclusivity or patents, I think that an ANDA for an epinephrine drug product that claims Adrenalin as the listed drug and satisfies the requirements for a successful ANDA should result in indications similar to the current indications of Adrenalin.

We were referred to the Biopharmaceutics' review for NDAs 204200 and 204640:

It was communicated to the Applicant that biowaiver request per 21 CFR 320.22(b)(1) is not appropriate because for increasing mean arterial blood pressure in patients with hypotension associated with septic shock by IV route Adrenalin® does not contain the same inactive ingredients as the products used in the published studies. It was also communicated that for the new indication, Adrenalin® can be bridged to formulations in the published literature under 21 CFR 3420.24(b)(6) based on (1) the comparison between the two with respect to qualitative and quantitative formulation, and physicochemical properties (e.g., pH, osmolality, etc.), and (2) justification that differences if any do not impact the disposition, efficacy, and safety of Adrenalin® for the new indication.

The comparable pH and osmolality data on Adrenalin® and formulations used in the published clinical studies (Adrenaline Aguettant, and Adrenaline Injection BP 1/1000) with and without dilution is indicative of the absence of the impact of qualitative (e.g., (b) (4) *and quantitative (e.g.,* (b) (4) *) difference if any with regards to excipients. Further, all above formulations are qualitatively similar with respect to* (b) (4) *. The absence of the physicochemical characteristic on Adrenaline Renaudin due to its unavailability commercially is not of a concern since (1) Adrenaline Renaudin is qualitatively very similar to Adrenaline Aguettant; and (2) Adrenalin is adequately bridged to Adrenaline Aguettant.*

Table 5. Side-by-side Comparison of Composition for Formulations Used in Published Studies vs Adrenalin® (NDA 204200 and 204640)[14]

Ingredient	Function	IIG limit for iv use* (%)	Concentration (mg/mL)				
			Adrenalin[5] (1-mL vial)	Adrenalin[5] (30-mL vial)	ADRENALINE AGUETTANT[6]	ADRENALINE RENAUDIN[4]	Adrenaline Injection BP 1/1000 (1 mg/mL); Antigen Pharmaceuticals Ltd.[4]
Epinephrine	Active	(b) (4)	1.0 mg/mL*	1.0 mg/mL*	1.0 mg/mL	1.0 mg/mL	1.0 mg/mL
(b) (4)	(b) (4)		(b) (4)				(b) (4)
Sodium chloride							
Sodium metabisulfite							
Hydrochloric acid	pH adjusting agent						
(b) (4)	(b) (4)						
Chlorobutanol (b) (4)	Preservative						
Water for Injection	(b) (4)						
(b) (4)							

Based on the qualitative formulation information (Table 5), it is noted that Adrenalin® differs with respect to (b) (4)

Specifically, (b) (4)

With the information from DCRP and the biopharmaceutics' review, the inactive ingredients of the original formulation of epinephrine is similar to the European Adrenaline products studied in the published literature. We find it acceptable that the new indication in S-009 is applicable to the proposed ANDA, the original formulation of epinephrine.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain.

Policy Issue Affecting Multiple Drug Products	FDA-2017-P-3352	Multiple: epinephrine injection products	Multiple: epinephrine auto-injectors containing sulfites	Requests FDA amend the sulfite warning requirement in 21 C.F.R. 201.22 for sulfite-containing epinephrine for injection for use in emergency situations, in order to remove misleading information and acknowledge the current availability of approved epinephrine products that do not contain sulfite.	Multiple
No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Filing or Labeling			5/26/2017	Geeta Daniel

Not applicable to the subject ANDA as this CP pertains only to auto-injectors.

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): NDA 204640/S-009**

Supplement Approval Date: January 29, 2019

Proprietary Name: Adrenalin®

Established Name: Epinephrine Injection, USP

Description of Supplement:

These Prior Approval supplemental new drug applications provide for the use of Adrenalin (epinephrine injection, USP) to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

**As stated in C1 and C2, the subject ANDA used the original formulation and model labeling prior to the reformulation; therefore, the proposed ANDA is not Q1/Q2 to the most current approved model labeling (S-009). As determined (see section 2.2), the most current approved labeling, S-009, will be used as safety updates and a new indication have been added since the original NDA submission.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

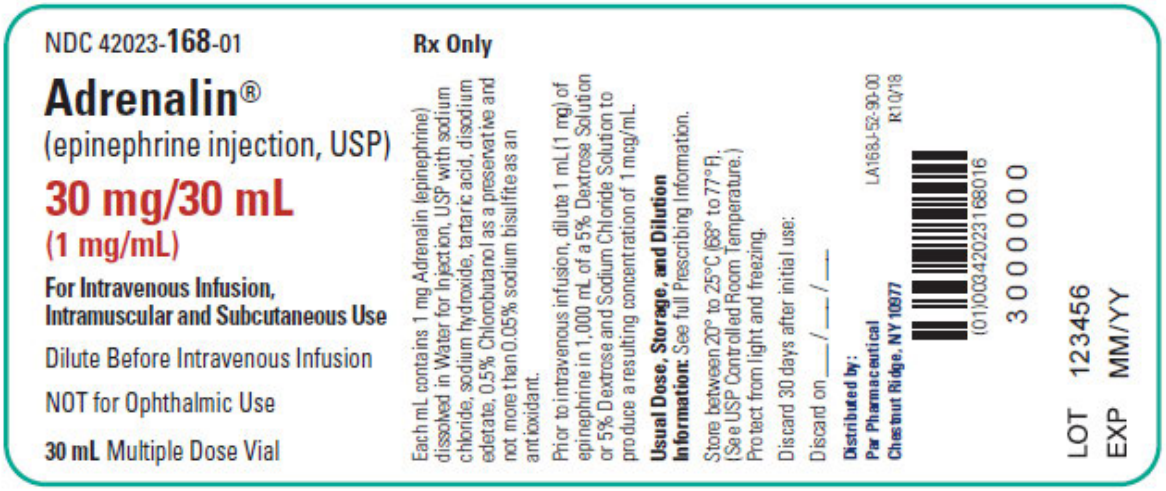
Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

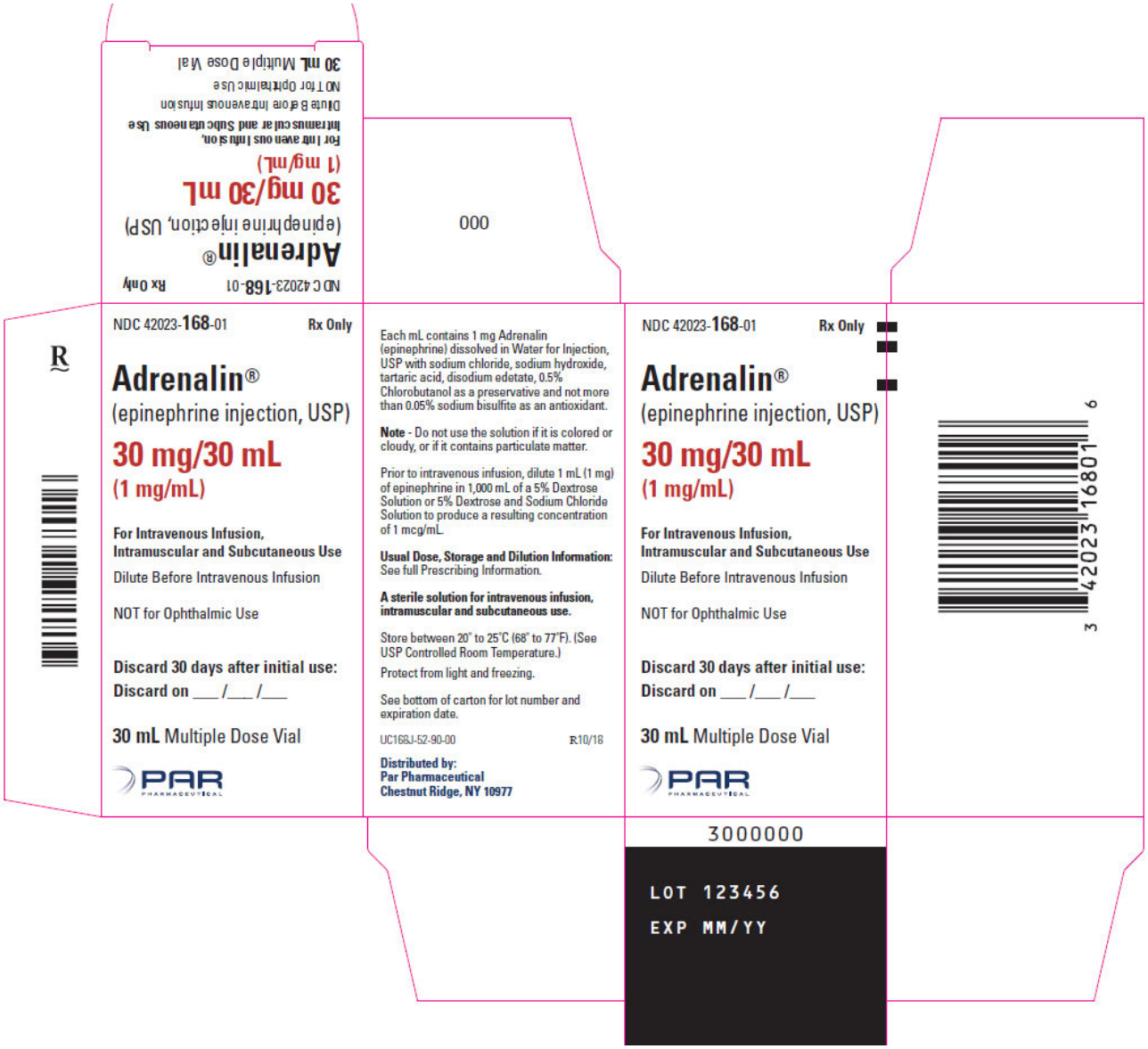
Reviewer Comments:

None

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS S-009 Approval on January 29, 2019]





3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 7/12/2019.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	**Date**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
Currently Official	YES	[redacted]	Epinephrine Injection	Packaging and storage— Preserve in single-dose or multiple-dose, light-resistant containers, preferably of Type I glass. Labeling— (b) (4) [redacted]
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

We note in accordance with the USP, the statement "Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter." is present on the labeling.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/12/2019.

Table 3 provides Orange Book patents for the Model Labeling NDA 204640 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact (enter Carve-out or None)**
9119876	2035-03-13			IV	6/14/2019* 6/14/2018	None
10130592	2035-03-13			IV	6/14/2019* 6/14/2018	None
9295657	2035-03-13	U-1829	EMERGENCY TREATMENT OF ALLERGIC REACTIONS (TYPE I), INCLUDING ANAPHYLAXIS	IV	6/14/2019* 6/14/2018	None
*Patent Re-Certification						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

We note in the OB, the new indication "to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock" is not associated with a patent at this time.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

None

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.	Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.	**Acceptable:** No changes made

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Epinephrine Injection, USP 30 mL Multi-Dose Vials: Each carton contains 1 multiple dose vial containing 30 mg/30 mL (1 mg/mL) epinephrine injection, USP solution 1 in an amber glass vial. NDC 76329-9060-0 30 mL vial Stock No. 9061 Vial and contents must be discarded 30 days after initial use. Store between 20°C to 25°C (68°F to 77°F) *[See USP Controlled Room Temperature]*. Epinephrine is light sensitive. Protect from light and freezing. Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.	**Epinephrine Injection, USP 30 mL Multi-Dose Vials:** Each carton contains 1 multiple dose vial containing 30 mg/30 mL (1 mg/mL) epinephrine injection, USP solution in an amber glass vial. NDC 76329-9060-0 30 mL vial Stock No. 9061 Vial and contents must be discarded 30 days after initial use. Store between 20°C to 25°C (68°F to 77°F) *[See USP Controlled Room Temperature]*. Epinephrine is light sensitive. Protect from light and freezing. Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.	**Acceptable:** No changes made

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
INTERNATIONAL MEDICATION SYSTEMS, LIMITED SO. EL MONTE, CA 91733, U.S.A. An Amphastar Pharmaceuticals Company	INTERNATIONAL MEDICATION SYSTEMS, LIMITED SO. EL MONTE, CA 91733, U.S.A. An Amphastar Pharmaceuticals Company	**Acceptable:** No changes made

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:
None

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	Multiple Dose Vial: 30 mL vial (1 mg/mL)	June 14, 2019	Satisfactory
Blister	NA			
Carton	Final	1 x 30 mL Vial (MDV)	June 14, 2019	Satisfactory
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission**	**Recommendation**

			Received Date	
Prescribing Information	Draft	June 2019	June 14, 2019	Satisfactory
Medication Guide	NA			
Patient Information	NA			
SPL Data Elements		June 2019	June 14, 2019	Satisfactory

Wan Lee

Digitally signed by Wan Lee
Date: 7/12/2019 01:53:40PM
GUID: 582a2cfa001b51dba58dfaf180bcd09a

Betty Turner

Digitally signed by Betty Turner
Date: 7/15/2019 06:02:40PM
GUID: 508da70600028acef381be737f7836a9

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	March 13, 2019
ANDA Number(s)	211880
Review Number	2
Applicant Name	International Medication Systems, Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials
Proposed Proprietary Name	None
Submission Received Date	March 13, 2019 February 13, 2019 (response to DRL)
Primary Labeling Reviewer	Wan Lee, PharmD
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☒ Yes ☐ No

Combined Insert/Outsert ☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on March 13, 2019 based on your submission received February 13, 2019:

1. CONTAINER LABEL
   To prevent cluttering of the PDP, decrease the size of the half star. To increase contrast, consider using a white background with black letters. In addition, (b) (4) for boxing the strength statement and for the half star. Please refer to the color scheme in your carton labeling.

2. CARTON LABELING
   We acknowledge your modifications on the net quantity statement. However, we recommend increasing the prominence of the expression of strength (e.g., boxing, highlighting, etc.).

3. PRESCRIBING INFORMATION
   a. We note that in our DRL letter dated January 30, 2019 and via an email correspondence in February, we stated that the most current model labeling approved for your proposed drug product is not being used according to 21 CFR 314.94 (8)(iv). Refer to Drugs@FDA: FDA Approved Drug Products, NDA 204640/S-009 approved on January 29, 2019, and revise accordingly. Since the new indication "to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock" does not contain protected patents or exclusivities, please retain this information in your labeling.
   b. To be consistent with the RLD, please note that sections or subsections of labeling that are identified as containing recent major changes (RMC) must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text. We refer you to 21 CFR 201.57(d)(9). In addition, change the dates in the RMC to "01/2019". Please refer to the RLD.
   c. DOSAGE FORMS AND STRENGTHS: Include "glass" to read "…dose amber glass vial." to be consistent with the RLD and in the HOW SUPPLIED section.
   d. HOW SUPPLED/STORAGE AND HANDLING: Remove (b) (4).

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

N/A

1.1 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
None

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Email correspondence from the Applicant on February 5, 2019.

We are reviewing the labeling comments provided in the Discipline Review Letter for ANDA 211880 for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials. Comment 4a states to refer to Drugs@FDA for NDA 204640/S-008 approved on August 9, 2017, and revise IMS' prescribing information accordingly.

In referencing Drugs@FDA, we note a subsequent approval for the RLD: NDA 204640/S-009 approved on January 29, 2019 providing for a new indication, Hypotension associated with septic shock.

The Discipline Review letter for ANDA 211880 is dated January 30, 2019, so I thought it would be best to double check which RLD labeling version we should indeed reference for the prescribing information, S-008 or S-009?

Additionally, because S-008 also provides for updated vial and carton labels, can you please confirm whether these are the correct reference for IMS' vial and carton labels for the side-by-side comparisons?

Labeling's response:

I want to acknowledge that after the Discipline Review Letter was sent, RLD NDA 204640/S-009 was approved on January 29, 2019. Supplement-009 should be used as the reference for the prescribing information. In addition, new carton and container labels were approved with S-009 and those labels should be used for your side-by-side comparison. These revisions included the display of the strength per total volume as the primary and prominent expression on the PDP of the label, followed in close proximity by strength/mL enclosed by parenthesis. Please refer to the Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf

Reviewer Comments:

The below comments are from the labeling review C1 based on the submissions dated June 14 and August 20, 2018.

1. GENERAL COMMENTS
   a. The Orange Book has been updated with a new patent. Address patent number 10130592.

Response:

Patent information for U.S. Patent Number 10130592 ("the '592 Patent") listed under NDA 204640 is provided in **Section 1.3.5.1**. In the opinion of IMS, the '592 Patent is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of IMS's Epinephrine Injection, USP, 1 mg/mL 30 mL, for which this ANDA is submitted. The corresponding Paragraph IV Certification is provided in **Section 1.3.5.2** and an updated Exclusivity Statement is provided in **Section 1.3.5.3**.

With submission of this amendment and in accordance with 21 CFR 314.95(d)(1), IMS is concurrently sending notice of its Paragraph IV Certification to each owner of U.S. Patent no. 10130592 or the representative(s) designated by the owner to receive the notice identified under 21 CFR 314.95(a).

This is acceptable.

   b. Revise the alpha symbol, "α" throughout the labeling.

Response:

The "α" symbol has been revised throughout the labeling as requested.

This is acceptable.

2. CONTAINER LABEL
   a. Relocate "Rx Only" from the side panel to the bottom main panel and the NDC number to the top of the main panel.

Response:

"Rx Only" has been relocated to the top of the main panel next to the NDC number, to align with the RLD container label. The NDC number has been relocated to the top of the main panel as well.

It is acceptable that the "Rx Only" statement is relocated to the top of the main panel next to the NDC as this aligns with the RLD. However, since space is limited on the PDP, we will recommend decreasing the size of the half star and changing their color scheme (i.e. similar to their carton labeling).

   b. Please change (b) (4) to read "Usual Dosage".

Response:

" (b) (4) has been modified to read "Usual Dosage" as requested.

The Applicant modified to read "Usual Dose, Storage and Dilution Information:" which is acceptable as it aligns with the RLD.

c. Revise "9.0 mg sodium chloride," to read "9 mg sodium chloride" (delete trailing "0"). For consistency, please revise in the PRESCRIBING INFORMATION as well.

Response:

"9.0 mg sodium chloride" has been revised to read "9 mg sodium chloride" on the Container Label, Carton Label and the Insert as requested.

This is acceptable.

d. Add one of the qualifying statement on the labeling, ("Manufactured by ___", "Marketed by___", "Distributed by___"). Please refer to 21 CFR 201.1(h)(5).

Response:

The qualifying statement "Manufactured by" has been added to the Container Label and Carton Label.

We note that qualifying statement is not added to the PI. This is acceptable.

e. Comment as to whether or not text appears on your cap/ferrule overseal. USP standard prohibits the use of certain statements on the cap/ferrule overseal. We refer you to the following address for additional information and guidance: https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

Response:

There is no text on the cap/ferrule overseal of this proposed injectable product.

This is acceptable.

3. CARTON LABELING

a. See container label comments.

Response:

The comments noted for the Container Label have also been applied to the Carton Label. Please see responses to Comments 2c and 2d above.

This is acceptable.

b. To align with the RLD, add on the primary display panels the recommended statement, "Discard 30 days after initial use: Discard after __/__/__".

Response:

The statement "Discard 30 days after initial use: Discard on __/__/__" was added to the Carton to be consistent with the RLD.

This is acceptable.

c. Add on the side panel above Dosage, "Note – Do not use the solution if it is colored or cloudy, or if it contains particulate matter."

Response:

The following statement has been added to the side panel of the Carton as requested: "**Note** – Do not use the solution if it is colored or cloudy, or if it contains particulate matter".

This is acceptable.

d. Please relocate the "Rx Only" statement to appear opposite of the NDC on the same line or at the bottom of the principal display panel. Please refer to the reference listed drug labeling. Please ensure that the NDC and Rx statement appear on the second and fourth panel.

Response:

The "Rx Only" statement has been relocated toward the bottom of the principal display panel as well as the back panel. The NDC number has been added to the top of the back panel.

This is acceptable.

e. The expression of strength and established name should be the most prominent (e.g., bolding, boxing, highlighting, etc.). Decrease the prominence of the net quantity statement by deleting the color. Relocate closer to the bottom of the panel using black font.

Response:

The net quantity statement on both the principal display panel and back panel have been relocated from the top of the panels to the lower half of the panels and the associated color was removed and replaced with black text.

The color of the net quantity statement is deleted as requested. (b) (4)

f. We recommend decreasing the size of the purple half star image to avoid interference with the other text on the panel.

Response:

The purple star was reduced in size to avoid interference with the text as requested.

This is acceptable.

4. PRESCRIBING INFORMATION

a. We note that the most current model labeling approved for your proposed drug product is not being used according to 21 CFR 314.94 (8)(iv). Refer to Drugs@FDA:

FDA Approved Drug Products, NDA 204640/S-008 approved on August 9, 2017, and revise accordingly.

Response:

As confirmed by Juliette Larmie-Gyamfi, Pharm.D., Labeling Project Manager via email on February 7, 2019, the insert has been modified by following NDA 204640/S-009 as the Reference Listed Drug source, which was approved on January 29, 2019 by FDA. Please note that the formulation being used for this ANDA utilizes and reflects the original formulation for Adrenalin® NDA 204640, approved on December 18, 2013.

2/13/2019 submission (SDN 6):

*We note that the Word version is not consistent with the PDF version in this submission. The Word version contains text that is retained from supplement 8 that should be omitted in the last approved NDA supplement 9 (i.e. sections 1 and 12.2). It has been verified that the PDF version contains the correct text when compared to the RLD NDA supplement 9.

3/13/2019 submission (SDN 8; Module 1.14.1): See Labeling History chart below:

SUBMISSION TYPE/ DATE	LABELING CHANGES	DATE OF LABELING	COMMENTS / EXPLANATION FOR PROPOSED CHANGES
Response to Information Request – Amendment Verification Statement **Sequence 0007** 13 March 2019	(b) (4)	**March 2019:** • **30 mL Multiple-dose Vial Label** (7390610G/3-19) • **Unit Carton** (5690610K/3-19) • **Package Insert** (6990610G/3-19)	(b) (4) Electronic (eCTD) submission providing draft vial label and draft carton label in Adobe PDF format and draft package insert in Adobe pdf and MS Word formats.
Response to Discipline Review Letter - Labeling **Sequence 0005** 13 February 2019	Revised per FDA comments in the Discipline Review Letter - Labeling dated Jan. 30, 2019 and per RLD Adrenalin® labeling, S-009 approved Jan. 29, 2019. Annotated comparisons to the RLD are provided in Sections **1.14.1.2** and **1.14.3.1**.	**January 2019:** • **30 mL Multiple-dose Vial Label** (7390610F/1-19) • **Unit Carton** (5690610J/1-19) • **Package Insert** (6990610F/1-19)	Changes made per **Discipline Review Letter - Labeling** dated January 30, 2019. Electronic (eCTD) submission providing draft vial label, draft carton label and draft package insert in Adobe pdf and MS Word formats.
Original ANDA ANDA #211880 **Sequence 0000** 14 June 2018	Proposed labels and labeling submitted in draft	**February 2018:** • **Vial Label** (7390610E/2-18) • **Unit Carton** (5690610H/2-18) • **Package Insert** (6990610E/2-18)	Original application for Epinephrine Injection USP. Electronic (eCTD) submission providing proposed labels and labeling in MS Word, Adobe pdf and Structured Product Labeling (SPL) formats.

We will request that the Applicant (b) (4) .

b. HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise the limitation statement and title to read as follows:

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPINEPHRINE INJECTION, safely and effectively. See full prescribing information for EPINEPHRINE INJECTION.

EPINEPRINE injection, for intramuscular and subcutaneous use
Initial U.S. Approval: 1939

Response:

As requested, the insert has been modified to reflect the limitation statement and title as follows:

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPINEPHRINE INJECTION, safely and effectively. See full prescribing information for EPINEPHRINE INJECTION.

EPINEPRHINE injection 1 mg/mL, for intramuscular, subcutaneous, and intravenous use
Initial U.S. Approval: 1939

We note that the Applicant kept the strength under the limitation title. We will not comment as it is the "same as" the RLD.

c. FULL PRESCRIBING INFORMATION:
3 DOSAGE FORMS AND STRENGTHS should read: "Epinephrine Injection, USP 1 mg/mL, 30 mL solution in a multiple-dose amber glass vial." Please revise.

Response:

The Dosage Forms and Strengths section has been modified to reflect the statement "Epinephrine Injection, USP: clear, colorless solution supplied as 30 mg/30 mL (1 mg/mL) in a multiple dose amber glass vial." This statement follows the RLD Adrenalin® labeling approved on January 29, 2019 (NDA 204640/S-009).

This is acceptable.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:
See section 2.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

1. Drug Facts: Discussion about label carve-out between DLR and OGDP: NDA decided to remove the mydriasis indication due to lack of safety data for tartaric acid use intraocularly. NDA submitted a citizen petition requesting FDA to refrain from approving any generic drug products that does not contain the same inactive ingredients. The CP was denied.

This is not applicable to this proposed NDA as they are only proposing the multiple dose vial, 30 mL, indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis.

Discussions pertaining to USP General Chapter <7> Labeling that single-entity drug products that can be expressed as a ratio (i.e., epinephrine, neostigmine and isoproterenol injections), shall be labeled only in terms of strength/mL. A ratio expression such as 1:1000 is an unacceptable format for single-entity drug products.

Justification for approving ANDAs for single entity injection products epinephrine, neostigmine, isoproterenol without ration expression of strength if the RLD still labels its products with the ratio of strength.

2. Considerations during this review of this application:

a. The Applicant proposed the original formulation which is not Q1/Q2 the same as the reformulated RLD NDA 204640, Adrenalin®. Which PI should the ANDA use as their model labeling?

b. The Prior Approval Supplement-009 was approved on January 29, 2019, which provided for a new indication, to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. Should this new indication applicable to the original formulation of epinephrine injection?

Recommendations:

a. Before the approval of S-009, the differences from the original PI and S-008 are the inactive ingredients (reformulation of both NDA 204200 (1 mL SDV) and NDA 204640 (30 mL MDV)) and the safety labeling changes (SLCs). These SLCs included revisions of the USPI that addressed the (b) (4) and addition of myocardial ischemia and infarction and cardiomyopathy. The SLC after the reformulation of NDA 204200 (1 mL SDV) and with the removal of the indication for mydriasis, revisions were made to the container labels and carton labeling of the SDV and MDV. We felt that these SLC updates are applicable to the drug product and not the inactive ingredients.

In addition, the Applicant proposed the original formulation that is not Q1/Q2 the same as the reformulated RLD but is Q1/Q2 the same as the original RLD. The Applicant has requested a waiver under 21 CFR 314.99(b) requesting that the Agency waive the requirements found at 21 CFR 314.94(a)(9)(iii) to permit approval of the proposed test product, which is Q1/Q2 different from the currently approved RLD. The Applicant indicated that the differences in the formulation do not affect the safety or efficacy of the proposed drug product. The biowaiver was granted.

b. The PAS for Supplement-009 for NDA 204200 (S-009) and NDA 204640 (S-009) proposes the addition of a new indication "to increase mean arterial blood pressure in adult patients with hypotension associated with

septic shock". The Applicant has not conducted any nonclinical/clinical studies and relied soley on published clinical studies. We have consulted the Division of Cardiovascular and Renal Products (DCRP) and stated:

The NDA supplements we just approved were labeling supplements to add a new indication to each of the two Adrenalin NDAs. These were 505(b)(2) submissions based on published literature. Other than product labeling, there was no change whatsoever in either of the two Adrenalin drug products (1 mL and 30 mL vials, each containing 1 mg epinephrine/mL). From a clinical standpoint, and without regard to any applicable exclusivity or patents, I think that an ANDA for an epinephrine drug product that claims Adrenalin as the listed drug and satisfies the requirements for a successful ANDA should result in indications similar to the current indications of Adrenalin.

We were referred to the Biopharmaceutic's review for NDAs 204200 and 204640:

It was communicated to the Applicant that biowaiver request per 21 CFR 320.22(b)(1) is not appropriate because for increasing mean arterial blood pressure in patients with hypotension associated with septic shock by IV route Adrenalin® does not contain the same inactive ingredients as the products used in the published studies. It was also communicated that for the new indication, Adrenalin® can be bridged to formulations in the published literature under 21 CFR 3420.24(b)(6) based on (1) the comparison between the two with respect to qualitative and quantitative formulation, and physicochemical properties (e.g., pH, osmolality, etc.), and (2) justification that differences if any do not impact the disposition, efficacy, and safety of Adrenalin® for the new indication.

The comparable pH and osmolality data on Adrenalin® and formulations used in the published clinical studies (Adrenaline Aguettant, and Adrenaline Injection BP 1/1000) with and without dilution is indicative of the absence of the impact of qualitative (e.g., (b) (4) (b) (4) *) and quantitative (e.g.,* (b) (4) *difference if any with regards to excipients. Further, all above formulations are qualitatively similar with respect to* (b) (4) ((b) (4) *The absence of the physicochemical characteristic on Adrenaline Renaudin due to its unavailability commercially is not of a concern since (1) Adrenaline Renaudin is qualitatively very similar to Adrenaline Aguettant; and (2) Adrenalin is adequately bridged to Adrenaline Aguettant.*

Table 5. Side-by-side Comparison of Composition for Formulations Used in Published Studies vs Adrenalin® (NDA 204200 and 204640)[14]

Ingredient	Function	IIG limit for iv use* (%)	Concentration (mg/mL)				
			Adrenalin[5] (1-mL vial)	Adrenalin[5] (30-mL vial)	ADRENALINE AGUETTANT[5]	ADRENALINE RENAUDIN[6]	Adrenaline Injection BP 1/1000 (1 mg/mL); Antigen Pharmaceuticals Ltd.[4]
Epinephrine	Active		1.0 mg/mL*	1.0 mg/mL*	1.0 mg/mL	1.0 mg/mL	1.0 mg/mL
Sodium chloride							
Sodium metabisulfite							
Hydrochloric acid	pH adjusting agent						
Chlorobutanol	Preservative						
Water for Injection							

(b) (4)

Based on the qualitative formulation information (Table 5), it is noted that Adrenalin® differs with respect to (b) (4) *pH adjusting agent (Hydrochloric acid), and preservative (Chlorobutanol, 30mL vial only). Specifically,* (b) (4) *and chlorobutanol are not present in the formulations used in the published clinical studies. Whereas,* (b) (4) *is absent in Renaudin formulation and* (b) (4) *is absent in both Aguettant and Renaduin formulations. With regards to* (b) (4) *pH adjusting components, the comparable pH data (Table 6) of Adrenalin® vs Adrenaline Aguettant, and Adrenaline Injection BP 1/1000 formulations pre- and post- dilution (with 5% dextrose or with 5% dextrose and saline) indicates the absence of the impact of qualitative [e.g.,* (b) (4) *), hydrochloric acid (* (b) (4) *Adrenaline injection BP)] difference if any.*

With the information from DCRP and the biopharmaceutic's review, the inactive ingredients of the original formulation of epinephrine is similar to the European Adrenaline products studied in the published literature. We find it acceptable that the new indication in S-009 is applicable to the proposed ANDA, the original formulation of epinephrine.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? Choose an item. If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain.

CP	FDA-2017-P-3252	Multiple epinephrine injection products	Multiple epinephrine auto-injectors containing sulfites	Requests FDA amend the sulfite warning requirement in 21 C.F.R. 201.22 for sulfite-containing epinephrine for injection for use in emergency situations. In order to remove misleading information and acknowledge the current availability of approved epinephrine products that do not contain sulfite.	Multiple	No Approval Actions (APTA) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead. No COMMENTS for Filing or Labeling

Not applicable to the subject ANDA as this CP pertains only to auto-injectors.

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page**?** NO

3.2 MODEL LABELING

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): NDA 204640/S-009**

Supplement Approval Date: January 29, 2019

Proprietary Name: Adrenalin®

Established Name: Epinephrine Injection, USP

Description of Supplement:

These Prior Approval supplemental new drug applications provide for the use of Adrenalin (epinephrine injection, USP) to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

**As stated in C1, the subject ANDA used the original formulation and model labeling prior to the reformulation; therefore, the proposed ANDA is not Q1/Q2 to the most current approved model labeling (S-009). As determined (see section 2.2), the most current approved labeling, S-009, will be used as safety updates and a new indication have been added since the original NDA submission.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

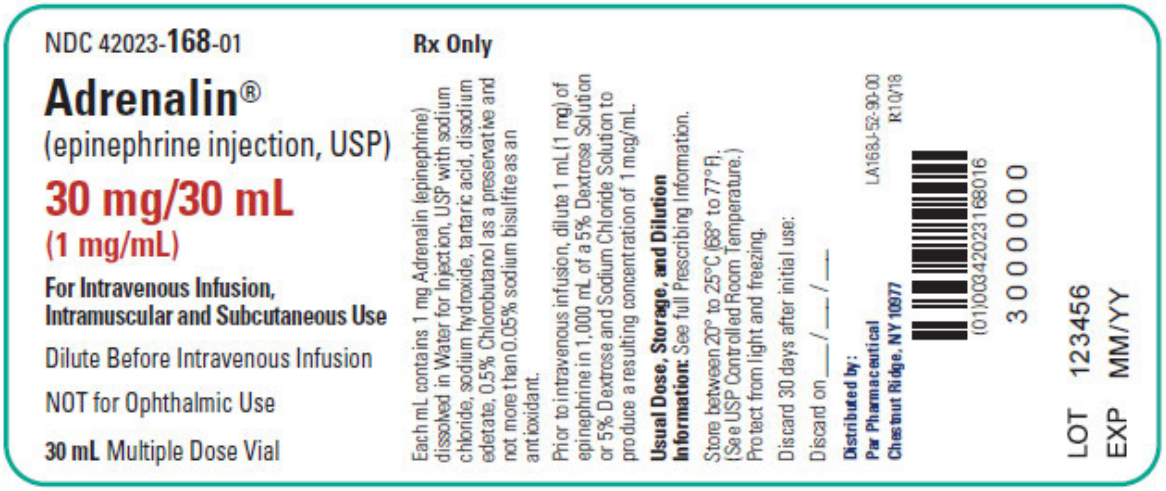
Reviewer Comments:

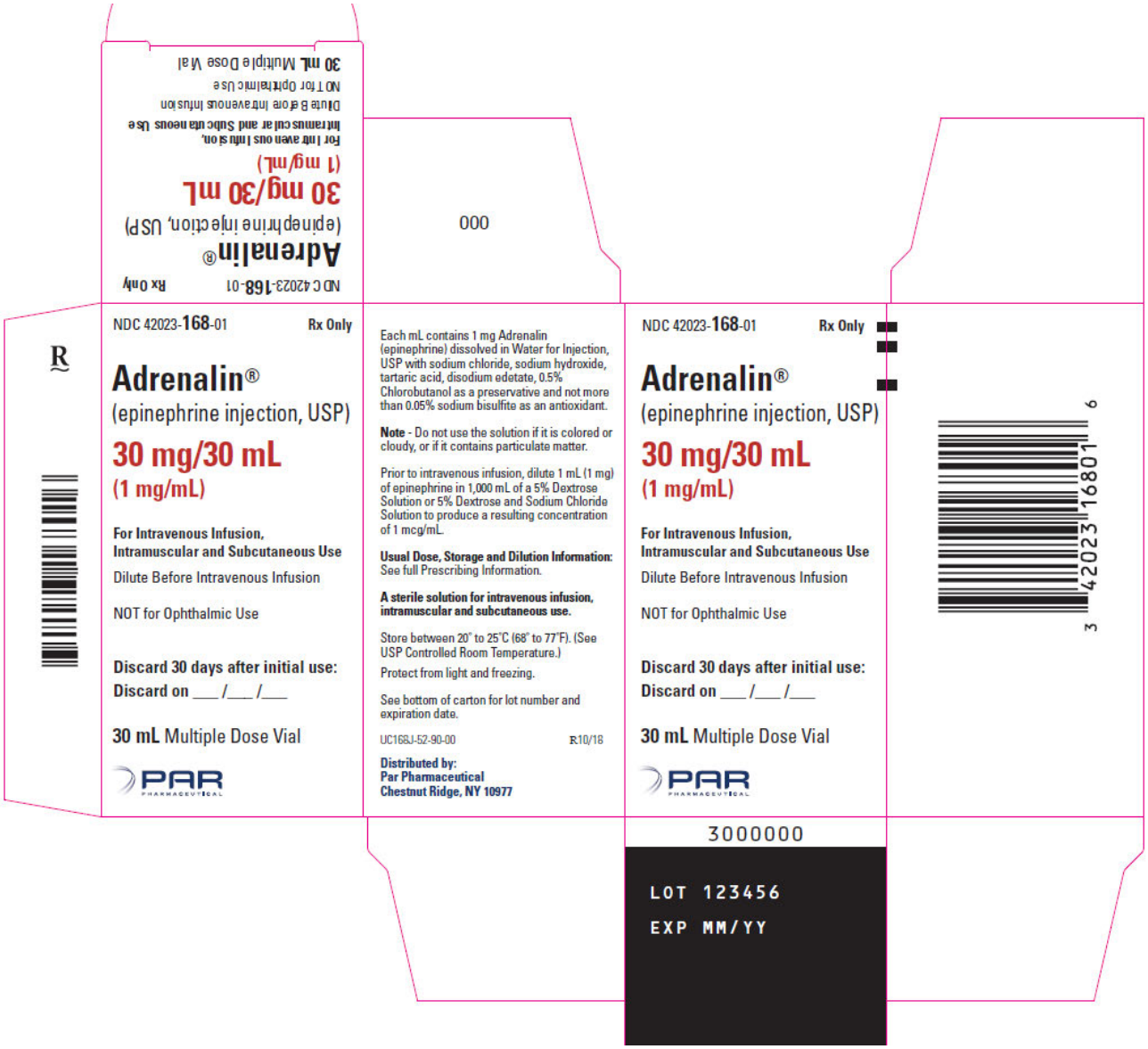
a. The Applicant [redacted] (b) (4) .

b. The Model Labeling has combined insert labeling for two different injection sizes, NDAs 204200 (SDV) 1 mg/mL and NDA 204640 (MDV) 30 mg/30 mL.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS S/009 Approval on January 29, 2019]





3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 3/13/2019.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	YES	[redacted]	Epinephrine Injection	Packaging and storage— Preserve in single-dose or multiple-dose, light-resistant containers, preferably of Type I glass. Labeling— (b) (4) [redacted]
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 3/13/2019.

Table 3 provides Orange Book patents for the Model Labeling NDA 204640 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
10130592	3/13/2035			IV	6/14/2018	None
9119876	3/13/2035			IV	6/14/2018	None
9295657	3/13/2035	U-1829	EMERGENCY TREATMENT OF ALLERGIC REACTIONS (TYPE I), INCLUDING ANAPHYLAXIS	IV	2/13/2019	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

None

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.	Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.	**Acceptable:** No changes made.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment
Epinephrine Injection, USP 30 mL Multi-Dose Vials: Each carton contains 1 multiple-dose vial containing 30 mL epinephrine injection, USP solution 1 mg/mL in an amber glass vial. NDC 76329-9061-0 30 mL vial Stock No. 9061 Vial and contents must be discarded 30 days after initial use. Store between 20°C to 25°C (68°F to 77°F) (See USP Controlled Room Temperature). Epinephrine is light sensitive. Protect from light and freezing. Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.	**Epinephrine Injection, USP 30 mL Multi-Dose Vials:** Each carton contains 1 multiple dose vial containing 30 mg/30 mL (1 mg/mL) epinephrine injection, USP solution 1 in an amber glass vial. NDC 76329-9060-0 30 mL vial Stock No. 9061 Vial and contents must be discarded 30 days after initial use. Store between 20°C to 25°C (68°F to 77°F) *[See USP Controlled Room Temperature]*. Epinephrine is light sensitive. Protect from light and freezing. Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.	**Acceptable:** No changes made.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment

Table 7: Manufacturer/Distributor/Packer Statements		
IMS LIMITED SO. EL MONTE, CA 91733 U.S.A. An Amphastar Pharmaceuticals Company	Manufactured by: **IMS LIMITED** SO. EL MONTE, CA 91733 U.S.A. An Amphastar Pharmaceuticals Company	**Acceptable:** Changes made as requested.

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:
None

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	Multiple Dose Vial: 30 mL vial (1 mg/mL)	February 13, 2019	Revise
Blister	NA			
Carton	Final	Multiple Dose Vial: 30 mL vial (1 mg/mL)	February 13, 2019	Revise
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	January 2019	February 13, 2019	Revise
Medication Guide	NA			
Patient Information	NA			
SPL Data Elements		June 2018	June 14, 2018	Satisfactory*
*Submission was satisfactory from the June submission (C1).				

Wan Lee

Digitally signed by Wan Lee
Date: 4/01/2019 01:12:07PM
GUID: 582a2cfa001b51dba58dfaf180bcd09a

Betty Turner

Digitally signed by Betty Turner
Date: 4/01/2019 01:41:33PM
GUID: 508da70600028acef381be737f7836a9

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	November 20, 2018
ANDA Number(s)	211880
Review Number	1
Applicant Name	International Medication Systems, Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials
Proposed Proprietary Name	None
Submission Received Date	August 20, 2018 (Resubmission after RTR) June 14, 2018 (Original)
Primary Labeling Reviewer	Wan Lee, PharmD
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Acceptable for Filing	☒ Yes	☐ No

Combined Insert/Outsert	☐ Yes	☒ No	(If yes, indicate ANDA number)

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on November 20, 2018, based on your submission(s) received August 20, 2018 and June 14, 2018:

1. GENERAL COMMENTS
    a. The Orange Book has been updated with a new patent. Address patent number 10130592.
    b. Revise the alpha symbol, "α" throughout the labeling.

2. CONTAINER LABEL
    a. Relocate "Rx Only" from the side panel to the bottom main panel and the NDC number to the top of the main panel.
    b. Please change (b) (4) to read "Usual Dosage".
    c. Revise "9.0 mg sodium chloride," to read "9 mg sodium chloride" (delete trailing "0"). For consistency, please revise in the PRESCRIBING INFORMATION as well.
    d. Add one of the qualifying statement on the labeling, ("Manufactured by ___", "Marketed by___", "Distributed by___"). Please refer to 21 CFR 201.1(h)(5).
    e. Comment as to whether or not text appears on your cap/ferrule overseal. USP standard prohibits the use of certain statements on the cap/ferrule overseal. We refer you to the following address for additional information and guidance: https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

3. CARTON LABELING
    a. See container label comments.
    b. To align with the RLD, add on the primary display panels the recommended statement, "Discard 30 days after initial use: Discard after __/__/__".
    c. Add on the side panel above Dosage, "Note – Do not use the solution if it is colored or cloudy, or if it contains particulate matter."
    d. Please relocate the "Rx Only" statement to appear opposite of the NDC on the same line or at the bottom of the principal display panel. Please refer to the reference listed drug labeling. Please ensure that the NDC and Rx statement appear on the second and fourth panel.
    e. The expression of strength and established name should be the most prominent (e.g., bolding, boxing, highlighting, etc.). Decrease the prominence of the net quantity statement by deleting the color. Relocate closer to the bottom of the panel using black font.
    f. We recommend decreasing the size of the purple half star image to avoid interference with the other text on the panel.

4. PRESCRIBING INFORMATION
    a. We note that the most current model labeling approved for your proposed drug product is not being used according to 21 CFR 314.94 (8)(iv). Refer to Drugs@FDA: FDA Approved Drug Products, NDA 204640/S-008 approved on August 9, 2017, and revise accordingly.

b. HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise the limitation statement and title to read as follows:

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPINEPHRINE INJECTION, safely and effectively. See full prescribing information for EPINEPHRINE INJECTION.

EPINEPRINE injection, for intramuscular and subcutaneous use
Initial U.S. Approval: 1939

c. FULL PRESCRIBING INFORMATION:
3 DOSAGE FORMS AND STRENGTHS should read: "Epinephrine Injection, USP 1 mg/mL, 30 mL solution in a multiple-dose amber glass vial." Please revise.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

NA

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
None

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES

If YES, please explain.

Discussion about label carve-out between DLR and OGDP: NDA decided to remove the mydriasis indication due to lack of safety data for tartaric acid use intraocularly. NDA submitted a citizen petition requesting FDA to refrain from approving any generic drug products that does not contain the same inactive ingredients. The CP was denied.

This is not applicable to this proposed NDA as they are only proposing the multiple dose vial, 30 mL, indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis.

Discussions pertaining to USP General Chapter <7> Labeling that single-entity drug products that can be expressed as a ratio (i.e., epinephrine, neostigmine and isoproterenol injections), shall be labeled only in terms of strength/mL. A ratio expression such as 1:1000 is an unacceptable format for single-entity drug products.

Justification for approving ANDAs for single entity injection products epinephrine, neostigmine, isoproterenol without ration expression of strength if the RLD still labels its products with the ratio of strength.

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES

If YES, please explain.

S/E Determination	Internal	Adrenalin	epinephrine solution	Determine whether NDA 204640 was withdrawn for reasons of safety or effectiveness.	204640	No Approval Actions (AP/TA) can be taken prior to final S/E Determination	All disciplines can continue communications (CRL, IR/DRL); CC should contact Policy if related to CP
CP	FDA-2017-P-3352	Multiple: epinephrine injection products	Multiple: epinephrine auto-injectors containing sulfites	Requests FDA amend the sulfite warning requirement in 21 C.F.R. 201.22 for sulfite-containing epinephrine for injection for use in emergency situations, in order to remove misleading information and acknowledge the current availability of approved epinephrine products that do not contain sulfite.	Multiple	No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Filing or Labeling

The proposed drug product contains sodium metabisulfite.

Is the drug product listed in the Susceptibility Test Interpretive Criteria web page? NO

Is there a mid-review cycle meeting (MRCM) task in Platform? NO

If **YES**, what is the proposed agenda from DLR for MRCM?

Click here to enter text.

Is there a Product Development or Pre-ANDA Submission Project under the ANDA Program? NO

If **YES**, review the meeting minutes and state the labeling impact, if any.

Click here to enter text.

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION/DRUG FACTS LABELING (OTC)

Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC) (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA 204640/S-008**

Supplement Approval Date: August 9, 2017

Proprietary Name: Adrenalin®

Established Name: Epinephrine Injection, USP

Description of Supplement: These supplemental new drugs applications (sNDA) included new safety information that should be included in the labeling for Adrenalin (epinephrine injection, USP) 1 mg/mL. This information pertains to the serious risk of confusion between the previous Adrenalin product that was indicated for mydriasis (ophthalmic route of administration) and the reformulated Adrenalin product that is not indicated for mydriasis.

These supplemental new drug applications provide for revisions to the labeling for Adrenalin (epinephrine injection, USP) 1 mg/mL consistent with our June 28, 2017, correspondence and with our July 20, 2017, revisions to the package insert, including the addition of stress cardiomyopathy in the Adverse Reactions section of the package insert.

**The subject ANDA used the original formulation and model labeling prior to the reformulation; therefore, the proposed ANDA is not Q1/Q2 to the most current approved model labeling (S-008). For the purpose of this review, the most current approved labeling, S-008, will be used as safety updates have been added since the original NDA submission. We will request the Applicant to revise their labeling according to the last approved labeling.

Other important information:

Supplement 9: (Pending)

This supplemental application proposes to add the following new indication for Adrenalin®:

- To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

Supplement 2: Approved 12/23/2015 (approval of change in formulation)

Submission:

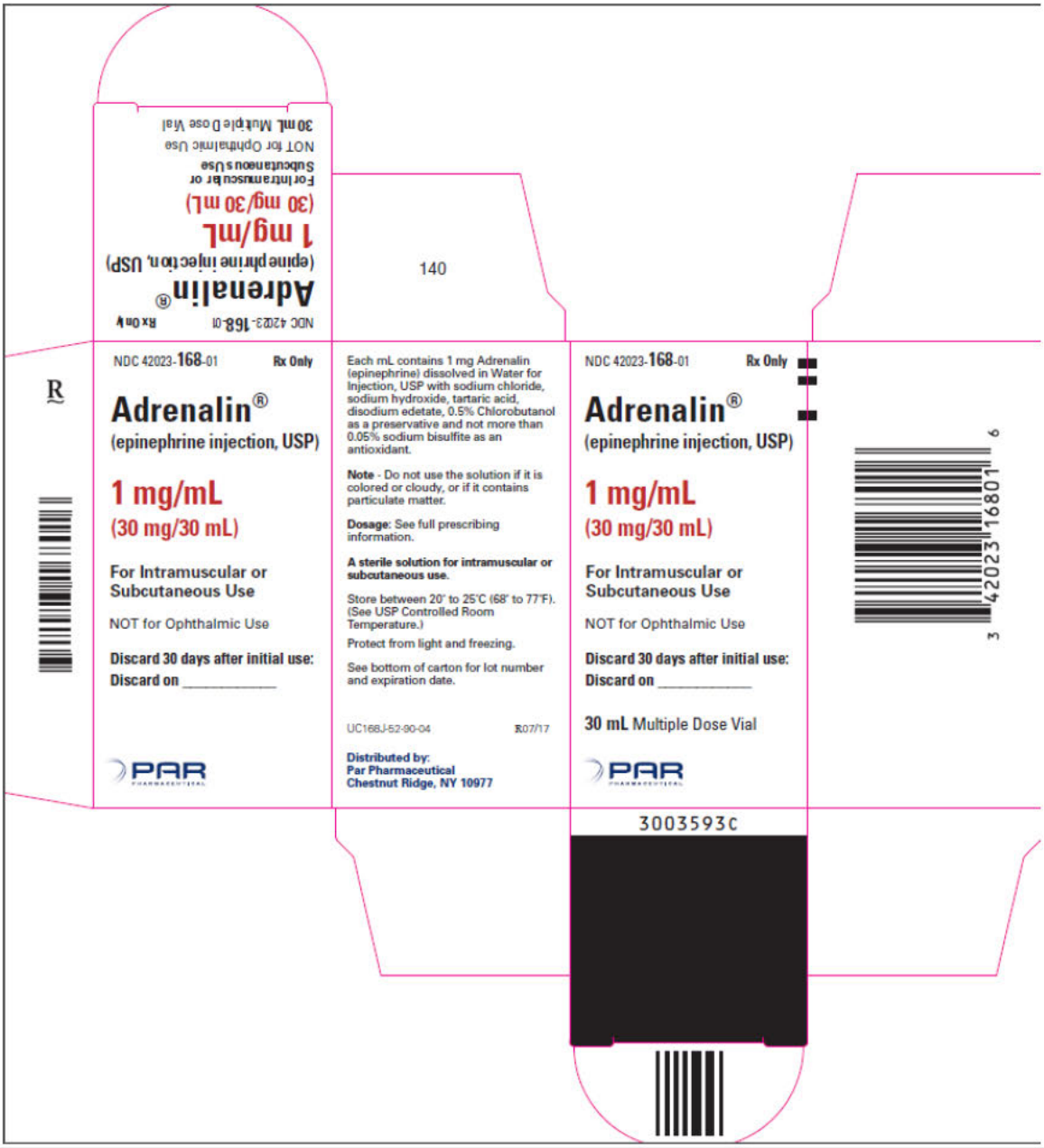
As outlined in on our Post Marketing Commitment (1977-1), Par agreed to evaluate formulation and process improvements to reduce the levels of impurities in Adrenalin. (b) (4) (b) (4) (b) (4) These studies were reported to the Agency according to agreed schedule during 2013 and 2014.

At this time, Par submits a Prior Approval Supplement seeking approval for a change in formulation to provide for a more stable product. The new formulation differs from the current approved formulation of Adrenalin 30 mL in terms of (b) (4) and sodium hydroxide) and (b) (4). In addition, concentrations of sodium chloride and (b) (4) have also been changed.

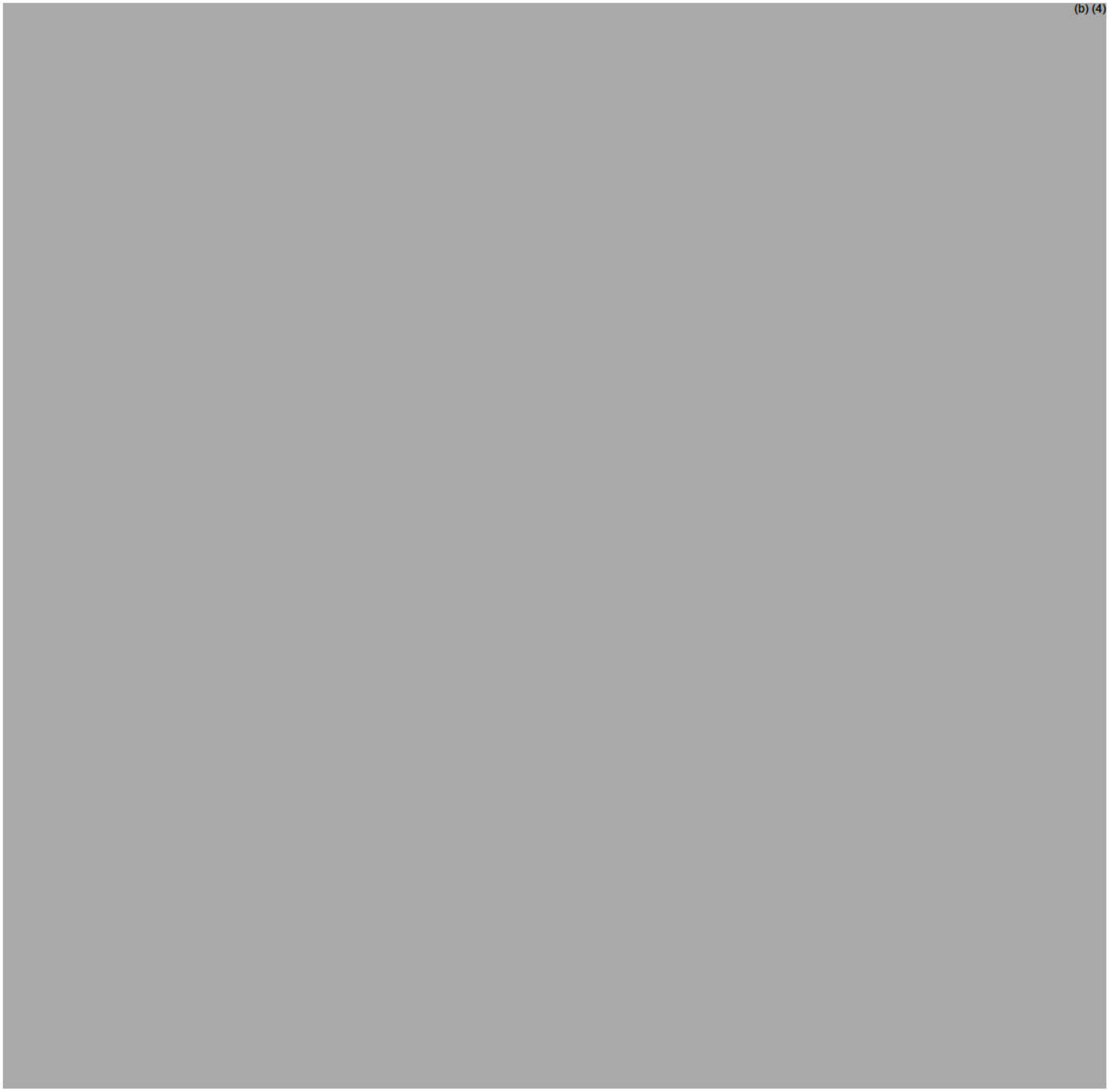
Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC) (Check the box used as the Model Labeling)
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):**

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: DARRTS AR-4, submitted 2/14/2018 (new formulation))



Model container/carton/blister labels (Source: DARRTS ANRPT-1; February 12, 2015 (SDN 33); (USPI in the same submission indicating old formulation).


(b) (4)

(b) (4)

2.3 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 11/20/2018.

Table 2: USP				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	YES		Epinephrine Injection	**Packaging and storage**—Preserve in single-dose or multiple-dose, light-resistant containers, preferably of Type I glass. **Labeling**—The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.
Not Yet Official	NO		NA	

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 11/20/2018.

Table 3 provides Orange Book patents for the Model Labeling (NDA 204640) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
9119876	3/13/2035			IV	6/14/2018	None
9295657	3/13/2035	U-1829	EMERGENCY TREATMENT OF ALLERGIC REACTIONS (TYPE I), INCLUDING ANAPHYLAXIS	IV	6/14/2018	None
10130592†	3/13/2035			TBD	11/26/2018	
† A new patent was added to the Orange Book.						

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NA					

2.5 MANUFACTURING FACILITY

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of ANDA Manufacturer/Distributor/Packer (Module 3.2.P.3)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
Name: International Medication Systems, Ltd. An Amphastar Company Address: (b) (4) Responsibilities: (b) (4)	**IMS LIMITED** SO. EL MONTE, CA 91733 U.S.A.	INTERNATIONAL MEDICATION SYSTEMS, LIMITED SO. EL MONTE, CA 91733, U.S.A. An Amphastar Pharmaceuticals Company

3. ASSESSMENT OF ANDA LABELING AND LABELS

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT.)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Is the established name the same as the USP monograph title appearing in section 2.3? **YES**
Is the established name the same as the RLD's nonproprietary name? **YES**
If YES is answered to both questions, then continue with review.
If NO is answered to EITHER questions, then advise firm to revise to the USP name (if applicable) and include justification language under Reviewer Comments.
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **YES**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer statement acceptable? **NO**
Is there a Pregnancy Registry for the NDA RLD? **NA** (If YES, determine if it is required for the ANDA and provide assessment under Reviewer Comments.)
For antiretroviral applications, did the applicant state its intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval? **NA**

Reviewer Comments:

a. We note that the subject ANDA is seeking approval of the original formulation of the RLD which is not Q1 and Q2 from the currently approved RLD formulation. It has been determined that the original formulation was not reformulated due to safety or efficacy reasons (see final meeting notes between DLR and OGDP in SharePoint), but rather Par's response to a post-marketing commitment (PMC 1977-1) that was requested by the Agency at the time of approval of the 1 mL vial (NDA 204200) in December 2012. The PMC was to reduce the levels of impurities with Adrenalin (epinephrine injection).

   Reference is made to a Policy meeting held on June 15, 2017, that discussed pending Policy decisions on CPs regarding the sulfite warnings, S/E determination, and the use of the original formulation. It was decided that the labeling should be the same as the RLD regardless of the formulation it is based on. This ANDA is for the 1 mL single dose vial which is different from the subject ANDA.

   We note that the SLCs (6/28/2017, 3/23/2016, and 2/5/2016) addresses both NDAs (204200 and 204640) on their letters and are applicable to the drug product regardless of formulation. We will request that the Applicant use the most current approved RLD labeling for their proposed drug product, at Drugs@FDA: FDA Approved Drug Products, NDA 204640/S-008 approved on August 9, 2017, and revise accordingly.

   We also note that there is a pending supplement, supplement 9, (refer to section 2.2) in house where the RLD will be revised.

b. NDA 204200 1 mg/mL (SDV) and NDA 204640 30 ml (MDV). The 1 mL SDV (original formulation) was indicated for emergency allergic reactions and mydriasis and the 30 mL MDV only for emergency allergic reactions. NDA 204200/S-004 on September 12, 2016, the 1 mL SDV was reformulated and the mydriasis indication was removed. NDA 204640/S-002 on December 23, 2015, the 30 mL MDV was reformulated.

c. Please refer to Section 3.1.4 RX: Container Label

3.1.1.1 RX: DESCRIPTION

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Adrenalin® (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 1 mL of solution in a single-use clear glass vial or 30 mL of solution in a multiple-dose amber glass vial. In the 1 mL vial, each 1 mL of Adrenalin® solution contains 1 mg epinephrine, 7.3 mg sodium chloride, 0.457 mg sodium metabisulfite, 1 mg sodium hydroxide, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, hydrochloric acid to adjust pH, and water for injection. In the 30 mL vial, each 1 mL of Adrenalin® solution contains 1 mg epinephrine, 6.15 mg sodium chloride, 0.457 mg sodium metabisulfite, 0.920 mg sodium hydroxide, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, hydrochloric acid to adjust pH, 5.25 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0. Labeling for the original formulation: Original submission approved December 18, 2013 sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. In the 30 mL vial, each 1 mL of Adrenalin® solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.
ANDA Labeling	Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

Reviewer Assessment:

Are the inactive ingredients accurate? **PENDING CHEMISTRY REVIEW**
For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NO**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **YES**
Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **NA**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:

a. We note that the RLD, NDA 204640, labeling markets both multiple-dose vials and single-dose vials. The subject ANDA is proposing multiple-dose vials and have omitted the information specific to the single-dose vials from their proposed labeling. This is consistent with the labeling for other approved and pending ANDAs for this drug product.
b. The Applicant used the RLD submission on December 16, 2013 (SDN 15) with the old formulation as their model labeling. They have requested a bioequivalence waiver:

IMS is seeking approval of a previously approved formulation of the RLD and for which the Agency has not made a determination that the formulation was not withdrawn for reasons of safety or effectiveness. A request for waiver of formulation sameness requirements per 21 CFR 314.94(a)(9)(iii) to permit approval of the proposed formulation, which is qualitatively (Q1) and quantitatively (Q2) different from the currently approved RLD formulation is provided in **Section 1.12.5**. Supporting information that identifies and characterizes the differences in formulation between IMS' proposed product and the currently approved formulation of the RLD ("Current RLD"), and which demonstrates that the differences do not affect the safety or efficacy of the proposed drug product, is also provided.

Table 1. Comparison of Proposed IMS Formulation to the RLD Formulations

#	Ingredients	Concentration, mg/mL			Use of Ingredient
		IMS Generic ANDA 211880	Original RLD NDA 204640	Current RLD NDA 204640	
1	Epinephrine	1	1	1	API
2	(b) (4)	-	-	(b) (4)	
3	(b) (4)	-	-	(b) (4)	
4	Sodium Metabisulfite	1.5	1.5	0.457	(b) (4)
5	(b) (4)	-	-	(b) (4)	
6	Chlorobutanol (b) (4)	5.4	5.4	5.25	preservative
7	Sodium Chloride	9	9	6.15	(b) (4)
8	pH Adjusted by Hydrochloride Acid	pH = 2.2 -5.0	pH = 2.2 -5.0	pH = 2.2 -5.0	to adjust pH

c. Per the Bioequivalence review, the Division of Bioequivalence grants the BE waiver:

The proposed test product, Epinephrine Injection USP, 1 mg Base/mL (30 mL Fill) is an aqueous solution that is administered via intravenous injection route. The route of administration and dosage form of the test product are same as that of the RLD product.

The RLD was reformulated and approved on December 23, 2015. The test product is not Q1/Q2 the same as the reformulated RLD but is Q1/Q2 the same as the original RLD. Based on a Citizen's petition response for a different configuration (single dose-1mL fill volume) of the same product, "*When an ANDA applicant seeks approval for a parenteral formulation that is the same as the previously marketed formulation of the RLD, but not the same as the currently marketed formulation of the RLD, FDA has determined that, in appropriate circumstances, under § 314.99(b), it may waive the requirement in the regulation that the inactive ingredients in a parenteral drug product approved under an ANDA be the same as those in the RLD (except for preservatives, buffers, and antioxidants), as long as the statutory requirement regarding the safety of inactive ingredients has been met*".[1]

The CP response also states that the formulation of Adrenalin® 1 mg/mL single dose product was not withdrawn for safety or effectiveness reasons. For both single dose and multidose products, the RLD sponsor stated the products were reformulated to improve stability.[2,3] Therefore, per 21 CFR § 314.99 (b), the waiver of the requirements under 21 CFR § 314.94(a)(9)(iii) can be waived for the current test product.

Based on the information provided, the Division of Bioequivalence (DB) grants the waiver of in vivo BE study requirements for Epinephrine Injection USP, EQ 1 mg Base/mL (30 mL Fill), per Section 21 CFR § 320.24 (b) (6).

d. We will have the Applicant to revise the alpha symbol, "α" throughout the labeling.

e. Full Prescribing Information:

3 DOSAGE FORMS AND STRENGTHS should read: "Epinephrine Injection, USP 1 mg/mL, 30 mL solution in a multiple-dose amber glass vial."

f. In accordance with 21 CFR 201.57 and 201.100(d), we confirm that the correct warning statements were added to the WARNINGS section of the insert labeling for use in emergency situations:

5.5 Allergic Reactions Associated with Sulfite

Epinephrine Injection, USP contains sodium bisulfite which may cause mild to severe allergic reactions including anaphylaxis or asthmatic episodes in susceptible individuals. However, the presence of bisulfite in this product should not preclude its use for the treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive, as the alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

This is acceptable.

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

Table 7: Comparison of Model Labeling to ANDA Labeling

Model Labeling	**Adrenalin® 1 mL Single-Use Vials:** Each carton contains 25 single-use vials containing 1 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL in a 3 mL clear glass vial. NDC 42023-159-25 1 mL vial **Adrenalin® 30 mL Multi-Dose Vials:** Each carton contains 1 multiple-dose vial containing 30 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL in a 36 mL amber glass vial. NDC 42023-168-01 30 mL vial Vial and contents must be discarded 30 days after initial use. Store between 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Epinephrine is light sensitive. Protect from light and freezing. Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.
ANDA Labeling	**Epinephrine Injection, USP 30 mL Multi-Dose Vials:** Each carton contains 1 multiple-dose vial containing 30 mL epinephrine injection, USP solution 1 mg/mL in an amber glass vial. NDC 76329-9061-0 30 mL vial Stock No. 9061 Vial and contents must be discarded 30 days after initial use. Store between 20°C to 25°C (68°F to 77°F) (See USP Controlled Room Temperature). Epinephrine is light sensitive. Protect from light and freezing. Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.

Reviewer Assessment:

Are all of the submitted labels and labeling reflected in the How Supplied section? **NO**
Is the description (e.g., scoring, color, imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **PENDING CHEMISTRY REVIEW**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**

If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **YES**

Reviewer Comments:
See sections 3.1.4 and 3.1.6.

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **NO**
Is the Medication Guide same as the model labeling, except for allowable differences? **NA**
Has the Applicant committed to provide a sufficient number of medication guides? **NA**
Is the phonetic spelling of the proprietary or established name present? **NA**
Is FDA 1-800-FDA-1088 phone number included? **NA**

Reviewer Comments:
Click here to enter text.

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **NO**
Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments:
Click here to enter text.

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**
(For BLISTER labels go to section 3.1.5.)

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **YES**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
If the container label is too small to contain all required information, does it meet the "too small" exemption found in 21 CFR 201.10(i)? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**
Is the following information properly displayed?
- Net quantity statement: **YES**
- Route(s) of administration (other than oral): **YES**
- Warnings (if any) or cautionary statements (if any): **NA**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **NA**
- Controlled substance symbol: **NA**
- Usual Dosage statement: **NO**

Product strength equivalency statement: **NA**
NDC: **YES**
Bar code per 21 CFR 201.25(c)(2): **YES**
Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the USP recommendations and/or differences in test methods (e.g., organic impurities, assay) reflected on the label(s)? **NA**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **NO**
Does any inactive ingredient require special warnings, precautions, or labeling statements? ****YES**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Are requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100)? **YES**

Reviewer Comments:

a. Please change (b) (4) to read "Usual Dosage".
b. We will have the Applicant add one of the qualifying statement on the labeling, (manufactured by, marketed by, distributed by…).
c. Due to space limitations, the statement "Do not use the solution if it is colored or cloudy, or if it contains particulate matter" is not on the container label. However, it is noted that the RLD container label does not contain this statement either. We will request that this statement is added on the carton label to be in line with the RLD. See comment 3.1.6 (b).

** See section 3.1.1.1 (f).

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling **NO**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **YES**

Reviewer Comments:

a. Per the USP General Chapters <7> Labeling, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength/mL enclosed by parentheses. We note that the expression of strength for the subject ANDA does not follow the USP; however, the expression of strength is the same as the RLD. There is a pending consult (expedited review) with OLDP. When the RLD revises their labels, we will request the proposed ANDA to make the revisions.

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable (other than Pharmacy Bulk Package)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**

Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:
Click here to enter text.

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **NA**
Does the container label include graduation marks? **NA**
Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:
Click here to enter text.

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **NA**

Reviewer Comments:
Click here to enter text.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **YES** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NO**
If country of origin is not on Container, does it appear on outer packaging labeling? **NA**

Reviewer Comments:
To align with the RLD, we will ask the Applicant to:

a. Add on the primary display panels, "Discard 30 days after initial use: Discard after __/__/__".
b. See comment 3.1.4 (b). We will ask the Applicant to add on the side panel above Dosage, "Note – Do not use the solution if it is colored or cloudy, or if it contains particulate matter."
c. Relocate the "Rx Only" statement to the principle display panel.

d. Per 21 CFR 201.1(h)(5), we will have the Applicant add one of the qualifying statement on the labeling, (manufactured by, marketed by, distributed by…).

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **CLICK HERE**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **CLICK HERE**
Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**
Is the applicant's "patent carve out" acceptable? **CLICK HERE**
Is the applicant's "exclusivity carve out" acceptable? **CLICK HERE**
Is the established name for this ANDA acceptable? **CLICK HERE**
Is title case used in expressing the established name? **CLICK HERE**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **CLICK HERE**
Is the following information properly displayed?

- Pharmacological category: **CLICK HERE**
- Net quantity statement: **CLICK HERE**
- Route(s) of administration (other than oral): **CLICK HERE**
- Warnings (if any) or cautionary statements (if any): **CLICK HERE**
- NDC: **CLICK HERE**
- Bar code per 21 CFR 201.25(c)(2): **CLICK HERE**

Is the Manufacturer/Distributor/Packager statement acceptable? **CLICK HERE**
For foreign manufacturers, does the labeling have the country of origin? **CLICK HERE**
Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **CLICK HERE**
Is the storage statement acceptable? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
Are multiple strengths differentiated by use of different color or other acceptable means? **CLICK HERE**
Are the labels of related products differentiated to avoid selection errors? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Click here to enter text.
ANDA Labeling	Click here to enter text.

Reviewer Assessment:

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **CLICK HERE**
Are the inactive ingredients listed in alphabetical order? **CLICK HERE**

For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **CLICK HERE** Has the statement been verified by chemistry? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.
ANDA	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**
Is the storage statement acceptable as compared to the Model Labeling? **NA**
Is the storage statement acceptable as compared to USP? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.2 OTC: PATIENT LABELING

Is patient labeling required? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was patient labeling submitted? **CLICK HERE**
Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.3 CONTAINER/CLOSURE

Reviewer Assessment:

(b) (4)

[redacted]

3.4 CALCULATIONS FOR CONTENTS AND VERIFICATION OF ALUMINUM CONTENT

Is calculation of ingredient(s) or verification of aluminum content required? **NO**

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**

Table 10: Ingredients		
Click here to enter text.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the stated contents in the table above acceptable? **CLICK HERE**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the chemistry reviewer verify the aluminum content? **CLICK HERE**
Are the labeling requirements met per 21 CFR 201.323? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

Table 11: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	ANDA Tablet/Capsule Size (mm) and imprint code from SPL	ANDA Tablet/Capsule Size (mm) and imprint code (Cite source: e.g., Chemistry Review, Product Specification in 3.2.P.5.1, and Commercial Batch Record in 3.2.P.3.3)
NA		

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **NA**
Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments:
None

4. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:
11/29/18 (email): The USP working group have pending consults with OLDP for NDA 204200 (single-dose vial) to (b) (4) and to revise the expression of strength for NDA 204640 (multiple-dose vial).

5. SPECIAL CONSIDERATIONS

Since this is the first proposed generic for the 30 mL multiple-dose vial, a memo will be placed into SharePoint to summarize this application.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation

Container	Final	Multiple Dose Vial: 30 mL vial (1 mg/mL)	June 14, 2018	Revise
Blister	NA			
Carton	Final	Multiple Dose Vial: 30 mL vial (1 mg/mL)	June 14, 2018	Revise
(Other – specify)	NA			

Table 13 Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	February 2018	June 14, 2018	Revise
Medication Guide	NA			
Patient Information	NA			
SPL Data Elements	NA	June 2018	June 14, 2018	Satisfactory

Wan Lee

Digitally signed by Wan Lee
Date: 1/11/2019 11:23:29AM
GUID: 582a2cfa001b51dba58dfaf180bcd09a

Betty Turner

Digitally signed by Betty Turner
Date: 1/11/2019 11:50:50AM
GUID: 508da70600028acef381be737f7836a9

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211880

CHEMISTRY REVIEW(s)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Complete Response-Minor
☐ Complete Response-Major
☐ Complete Response-Major-Facilities Only

U.S. FOOD & DRUG ADMINISTRATION

ANDA 211880
Assessment 4

Drug Product Name	Epinephrine Injection USP
Dosage Form	Injection
Strength	1 mg (base)/mL
Route of Administration	Intramuscular, Intravenous, subcutaneous
Rx/OTC Dispensed	Rx
Applicant	International Medication Systems, Limited 1886 Santa Anita Avenue South El Monte, CA 91733
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission	06/14/2018	All
Resubmission after Refuse to Receive	08/20/2018	All
Amendment-Quality/ Response to Information Request	11/15/2018	Process
Amendment-Response to Labeling Discipline Review Letter	02/13/2019	Labeling
Amendment-Labeling/Response to Information Request	03/13/2019	Labeling
Amendment-Quality/Response to Discipline Review Letter	03/14/2019	Drug Substance, Drug Product, Process, and Microbiology
Amendment-Resubmission after Action-Complete Response	06/14/2019	Drug Substance and Drug Product
Amendment-Quality/ Response to Information Request	08/22/2019	Drug Product
Amendment-Resubmission after Action-Complete Response	01/27/2020	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Yichuan Xu	Yun (Jenny) Wang
Drug Product	Raman Murali	Kai Kwok
Manufacturing	Process: Brian Rogers Facility: Rose Xu	Yong Hu

Microbiology	Julia Marre	Denise Miller
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Suzan Ghodasara	
Application Technical Lead	Raman Murali	
Laboratory (OTR)	N/A	
Environmental	N/A	

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESMENT DATA SHEET

IQA ANDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Epinephrine USP	Adequate	Review #6: 1/8/2020	Reviewed by Y.Xu
	Type III		(b) (4)	Adequate	1/18/2017	Reviewed by B. Stevens
	Type III			Adequate	8/29/2017	Reviewed by L.Qi
	Type IV			Adequate	11/14/2016	Reviewed by V. Amspacher

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 204640	Adrenalin® by Par Pharmaceuticals, 30 mL (MDV)
ANDA	ANDA 207568	Epinephrine Injection, USP, 1mg/1mL, 1 mL **Note:** RLD NDA 204200 - Adrenalin® by Par Pharmaceuticals, 1 mL) (SDV)

2. CONSULTS

N/A

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

EXECUTIVE SUMMARY (APPROVALS ONLY)

IQA ANDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The application is recommended for approval. Drug product quality, facility, and Microbiology reviews are adequate. OPQ recommends approval of ANDA.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis, and Hypotension associated with septic shock.
Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-) -3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol. Epinephrine is white or off-white crystalline substance. (b) (4) [redacted]

Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.
Dosage:
Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) of undiluted Epinephrine Injection, USP administered intramuscularly or

subcutaneously in the anterolateral aspect of the thigh, every 5 to 10 minutes as necessary.
Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) up to a maximum of 0.3 mg (0.3 mL) administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, per injection, repeated every 5 to 10 minutes as necessary.
How Supplied:
Epinephrine Injection, USP 30 mL Multi-Dose Vials:
Each carton contains 1 multiple-dose vial containing 30 mL epinephrine injection, USP solution 1 mg/mL in an amber glass vial.
Vial and contents must be discarded 30 days after initial use.
Storage and Handling
Store between 20°C to 25°C (68°F to 77°F) (See USP Controlled Room Temperature). Epinephrine is light sensitive. Protect from light and freezing.

Final recommended dissolution method/specification acknowledged by Firm?	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	☒ Yes ☐ No *(see comments) ☐ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	☒ Yes ☐ No *(see comments) ☐ N/A

Proposed Indication(s) including Intended Patient Population	*Anaphylaxis:* Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary Children 30 kg (66 lbs) or less: 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary *Hypotension associated with septic shock:* 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

Duration of Treatment	Duration of treatment varies with indication and use. Refer to labeling.
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview (Please note: ATLs should check the most recent policy alert list)

ANDA 211880 is ready for Approval.

Policy Alert
Citizen Petition pending. The RPM will contact the policy lead on the CP.

CP	FDA-2019-P-6044	Adrenaline	epinephine injection	Par requests that FDA expedite its review of Par's pending Prior Approval Supplements ("PASes") that seek to eliminate an overage of the active ingredient in Adrenalin® and to make attendant changes to the product's shelf life. Until the Agency takes final action on each PAS, Par asks that it refrain from approving any ANDA submitted under Section 505(j) of the FDCA for an epinephrine injection product that cites Par's Adrenalin® as the reference listed drug ("RLD").

C. Risk Assessment

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #4	Comments*
(b) (4)	Medium	(b) (4)	Low	Adequate PD information provided
	Medium		Low	Adequate
	Medium		Low	Adequate specification controls
	Medium		Low	Provided additional information
	Medium		Low	Provided additional information

Application Technical Lead Name and Date: Raman Murali, PhD, 3/26/2020

Raman Murali

Digitally signed by Raman Murali
Date: 3/30/2020 10:43:17AM
GUID: 508da701000286d1f02ed0090280bc19

Quality Review Data Sheet

ANDA# 211880
Drug Product: Epinephrine Injection, USP, 1mg/1mL, 30 mL
Review # 4

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	ype II	(b) (4)	Epinephrine USP	Adequate	Review #6: 1/8/2020	Reviewed by Y.Xu
	ype III		(b) (4)	Adequate	1/18/2017	Reviewed by B. Stevens
	ype III			Adequate	8/29/2017	Reviewed by L.Qi
	ype IV			Adequate	11/14/2016	Reviewed by V. Amspacher

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 204640	Adrenalin® by Par Pharmaceuticals, 30 mL (MDV)
ANDA	ANDA 207568	Epinephrine Injection, USP, 1mg/1mL, 1 mL **Note:** RLD NDA 204200 - Adrenalin® by Par Pharmaceuticals, 1 mL) (SDV)

2. CONSULTS: N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

DRUG SUBSTANCE

IQA Review Guide Reference

Product Background

Drug Product Category (or Mechanism of Action):

Indication: Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis

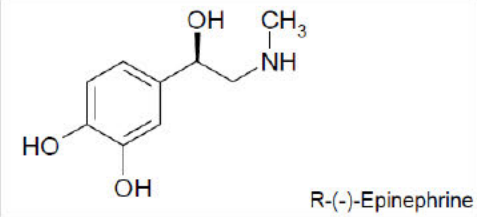
ANDA (review cycle number): 211880 Review # 4

Chemical Name and Structure:

1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-; (-)-3 ,4-Dihydroxy-α-[(methyl amino)methyl]benzyl alcohol

OR

(-)-3 ,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol



R-(-)-Epinephrine

DMF # (if applicable): (b) (4)

ANDA Applicant Name: International Medication Systems, Limited (IMS)

DMF Holder: (b) (4)

Review Recommendation: **Adequate**
DMF review #6 is adequate on 1/8/2020 by Y. Xu.

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:
The DS section of the ANDA is adequate.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment (SD#16) (Quality)	1/27/2020
Amendment (SD#15) (Bioequivalence/Quality)	9/23/2019
Amendment (SD#14) (Quality)	8/22/2019
Amendment (SD#11) (Quality)	6/14/2019
Amendment (SD#10)(Labeling)	4/10/2019
Amendment (SD#9) (Quality)	3/14/2019
Amendment (SD#8)(Labeling)	3/13/2019
Amendment (SD#6)(Labeling)	2/13/2019
Amendment (SD#4)	11/15/2018
Amendment (SD#2)	8/20/2018
Original submission (SD#1)	6/14/2018

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): None

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DRUG PRODUCT

IQA Review Guide Reference

Product Background

Drug Product Category (or Mechanism of Action): Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist

Indication: for emergency treatment of allergic reactions (Type 1), including anaphylaxis

ANDA (review cycle number): ANDA# 211880
Review # 4

Drug Product Name / Strength: Drug Product: Epinephrine Injection, USP, 1mg/1mL, 30 mL

Route of Administration: Intramuscular or subcutaneous injection

Applicant Name: International Medication Systems, Limited (IMS)

Review Recommendation: **Adequate**

(b) (4)

[redacted]

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

- **RLD and Reference Standard:** NDA 204640 Adrenalin® by Par Pharmaceuticals

- **Description of the Drug Substance(s) and Drug Product(s) and from Package Insert**

Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol.
Epinephrine is white or off-white crystalline substance. (b) (4)

Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

- **Brief Description of the Manufacturing Process:** Unit Steps are:

(b) (4)

- **Description of How the Drug Product is Intended to be Used (for In-Use Stability Studies) from Package Insert**

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) of undiluted Epinephrine Injection, USP administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, every 5 to 10 minutes as necessary.

Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) up to a maximum of 0.3 mg (0.3 mL) administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, per injection, repeated every 5 to 10 minutes as necessary.

- **How Supplied:**

Epinephrine Injection, USP 30 mL Multi-Dose Vials:

Each carton contains 1 multiple-dose vial containing 30 mL epinephrine injection, USP solution 1 mg/mL in an amber glass vial.

NDC 76329-9061-0 30 mL vial Stock No. 9061

Vial and contents must be discarded 30 days after initial use.

Storage and Handling

Store between 20°C to 25°C (68°F to 77°F) (See USP Controlled Room Temperature). Epinephrine is light sensitive. Protect from light and freezing.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment (SD#16) (Quality)	1/27/2020
Amendment (SD#15) (Bioequivalence/Quality)	9/23/2019
Amendment (SD#14) (Quality)	8/22/2019
Amendment (SD#11) (Quality)	6/14/2019
Amendment (SD#10)(Labeling)	4/10/2019
Amendment (SD#9) (Quality)	3/14/2019
Amendment (SD#8)(Labeling)	3/13/2019
Amendment (SD#6)(Labeling)	2/13/2019
Amendment (SD#4)	11/15/2018
Amendment (SD#2)	8/20/2018
Original submission (SD#1)	6/14/2018

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining:
None

List Number of Comparability Protocols (ANDA only): None

P.1 Description and Composition

Component/composition table

Revised in response to BE deficiency (see review of SD15):

Table 1: Components and Composition of Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials – *Commercial Batch Size* (b) (4) Liters)

Inactive Ingredients	Formulation		Specific Amount Added (g)	Calculation of Specific Amount for Commercial Batch Size: (b) (4)
	RLD[a] (JHP Pharmaceuticals)	IMS Proposed Product		
Sodium Chloride	9.0 mg/mL	9.0 mg/mL		(b) (4)
Sodium Metabisulfite	1.5 mg/mL	1.5 mg/mL		
Chlorobutanol[b]	5.4 mg/mL	5.4 mg/mL		
Hydrochloric acid	(to adjust pH)	(to adjust pH)		
Water for Injection (WFI)				
				(b) (4)

Components and Composition of Epinephrine Injection USP provided in the original submission:

Materials	Function	Quality Standard	Amount per Unit Vial (30 mL)	% w/w
Epinephrine USP	Active ingredient	USP	(b) (4)	
Hydrochloric Acid NF	(b) (4) adjust pH	NF	pH adjustment (b) (4)	

Materials	Function	Quality Standard	Amount per Unit Vial (30 mL)	% w/w
Sodium Chloride USP	(b) (4)	USP	(b) (4)	0.90
Chlorobutanol (b) (4) NF	Preservative	NF		0.54
Sodium Metabisulfite NF	(b) (4)	NF		0.15
Water for Injection, USP	(b) (4) (b) (4)	USP	(b) (4)	
(b) (4)				

Unit Dose Composition – Comparison between the Exhibit Batch Formulation and the Commercial Batch Formulation of Epinephrine Injection USP, 1 mg/mL, 30 mL MDV

Materials	Function	Quality Standard	Amount per mL	Exhibit Batch Formulati	Commerci al Formulati
Epinephrine USP	Active ingredient	USP	1.13 mg		(b) (4)
(b) (4) Hydrochloric Acid NF	(b) (4)	NF	(b) (4)		
Sodium Chloride USP	(b) (4)	NF	9.0 mg		
Chlorobutanol (b) (4) NF	Preservative	USP	5.4 mg		
Sodium Metabisulfite NF	(b) (4)	NF	1.5 mg		
Water for Injection USP	(b) (4) (b) (4)	USP	(b) (4)		
					(b) (4)

Reviewer's Assessment: ***{adequate}***

(b) (4)

(b) (4)

RLD FORMULATION COMPARISION NOT TO BE RELEASED UNDER FOIA

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(b) (4)

R Regional Information

Environmental

Reviewer's Assessment: *{Adequate }*
Applicant claimed categorical exclusion cited in 21 CFR 25.31(b).

Methods Verification Package

Reviewer's Assessment: *{Adequate }*

Comparability Protocols

Reviewer's Assessment: *{Adequate }*

None provided

Lifecycle Management Considerations

N/A

Drug Product: List of Deficiencies

None

Primary Drug Product Reviewer Name and Date: Raman Murali; 1/25/2019; 1/31/2019; 4/30/2019; 5/9/2019; 8/1/2019; 8/14/2019; 11/15/2019; 12/12/2019; 3/3/2020

Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019; CR#1: 5/13/2019; CR#2: 8/6/2019; CR#3: 12/11/2019; CR#4: 3/5/2020 (No quality amendment for the DP, only for the DS)

LABELING

IQA Review Guide Reference

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No

For DRL, the applicant will be asked to include visual color and clarity in the DP specifications.

If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☒ No ☐ N/A If "No," explain. The firm will be asked to provide in use stability data to support stability of the DP up to 30 days after initial use per proposed PI.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None

List of Deficiencies:

None

Primary Drug Product Reviewer Name and Date: Raman Murali, 1/25/2019 ***Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019***

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – ANDA

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #4	Comments*
(b) (4)	Medium	(b) (4)	Low	Adequate PD information provided
	Medium		Low	Adequate
	Medium		Low	Adequate specification controls
	Medium		Low	Provided additional information
	Medium		Low	Provided additional information

Raman Murali

Digitally signed by Raman Murali
Date: 3/06/2020 10:21:52AM
GUID: 508da701000286d1f02ed0090280bc19

Kai Kwok

Digitally signed by Kai Kwok
Date: 3/05/2020 05:46:19PM
GUID: 531543b00000571ac408640b9cf905cb

PROCESS

Product Background:	**RLD NDA 204640 Adrenalin®**
ANDA:	**211880**
Drug Product Name / Strength:	**Epinephrine Injection USP / 1 mg (base)/mL**
Route of Administration:	**Injection**
Applicant Name:	**International Medication Systems, Limited**

Review Recommendation:	***Adequate from a process perspective***
Theme:	**N/A**
Justification:	***N/A***

Review Summary: Epinephrine is a white or almost white crystalline powder very slightly soluble in water and in alcohol. Epinephrine HCl is created (b) (4) and is very soluble in water.

The proposed drug product is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0. The proposed product is formulated with (b) (4) The drug product is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis.

Submission Under Review:	**Amendment**	**SDN 8**	**03/14/2019**
Submissions Previously Reviewed	**Amendment**	**SDN 4**	**11/15/2018**
	Amendment	**SDN 2**	**08/20/2018**
	Original	**SDN 1**	**06/14/2018**

Highlight Key Outstanding Issues from Last Cycle: **NA**

Concise Description Outstanding Issues Remaining: No issues remain

List Number of Comparability Protocols: No comparability protocols related to drug product manufacturing were submitted.

P.3 Manufacture

Batch Formula

Table 32P32-1 Batch Compositions of the Proposed Drug Product, Epinephrine Injection USP, 1 mg/mL, 30 mL (CCD-5)

Product Strength	Epinephrine Injection USP, 1 mg/mL, 30 mL	
Batch Size	Stability Lot Size: (b) (4)	Proposed Initial Commercial (b) (4)
	Amount per Batch	Amount per Batch
Active Ingredient		
Epinephrine USP*	(b) (4)	
Inactive Ingredients:		
Hydrochloric Acid NF*	(b) (4)	
	pH adjustment	pH adjustment
Sodium Chloride USP	(b) (4)	
Chlorobutanol (b) (4) NF		
Sodium Metabisulfite NF		
Water for Injection, USP		
(b) (4)		
(b) (4)		

(b) (4)

(b) (4)

[redacted]

Summary of Process Validation Studies Conducted

Reviewer's Assessment: The applicant has provided process validation studies related to the (b) (4) process. These will be reviewed by the micro reviewer.

Assessment of Microbiological Controls

Reviewer's Assessment: N/A

Comparability Protocols

Reviewer's Assessment: No comparability protocols related to manufacturing were submitted.

Lifecycle Management Considerations

N/A

List of Deficiencies Sent in 02/11/2019 DRL:

(b) (4)

[redacted]

(b) (4)

.

Review #1

Primary Process Reviewer Name and Date: ***Brian Rogers 01/31/2019***

Secondary Reviewer Name and Date: ***Yong Hu 02/01/2019***

Review #2

Primary Process Reviewer Name and Date: ***Brian Rogers 03/18/2019***

Secondary Reviewer Name and Date: ***Yong Hu 04/10/2019***

Brian Rogers

Digitally signed by Brian Rogers
Date: 4/11/2019 01:24:52PM
GUID: 508da7210002a054552cbf1a8fc2e128

Yong Hu

Digitally signed by Yong Hu
Date: 4/11/2019 02:58:28PM
GUID: 508da7220002a14416588a81227bc049

FACILITIES

IQA Review Guide Reference

Product Background:

Epinephrine Injection, USP, 1mg/1mL is used for emergency treatment of allergic reactions (Type I) including anaphylaxis and allergic reaction.

ANDA: ANDA 211880

Drug Product Name / Strength: Epinephrine Injection, USP, 1mg/1mL, 30 mL

Route of Administration: Injection

Applicant Name: International Medication Systems, Limited

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:

(b) (4) . The firm is acceptable for (b) (4) based on its compliance history and its manufacturing capability.

International Medication Systems, Limited (IMS) (FEI 2016148) (b) (4) The firm is acceptable based on the previous inspections and the manufacturing capability.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Original	8/20/2018
Quality Amendment SD 4	11/15/2018
Quality Amendment SD 9	3/14/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): N/A

3.2.S.2 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)				

Reviewer's Assessment: ***Adequate***

(b) (4)

(b) (4)

3.2.P.3 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
International Medication Systems, Limited (IMS)	2016148	(b) (4)		• Acceptable based on previous inspection history and manufacture capability

Reviewer's Assessment: ***Adequate***

(b) (4)

(b) (4)

Comparability Protocols: N/A

Lifecycle Management Considerations: N/A

List of Deficiencies: N/A

Primary Facilities Reviewer Name and Date: Rose Xu, 5/2/2019

Secondary Reviewer Name and Date: Yong Hu, Ph.D., 5/15/2019

Rose Xu

Digitally signed by Rose Xu
Date: 5/15/2019 09:31:18AM
GUID: 5277e72900088dc65127c01f0d78be60

Yong Hu

Digitally signed by Yong Hu
Date: 5/15/2019 09:46:34AM
GUID: 508da7220002a14416588a81227bc049

MICROBIOLOGY

Product Background: Epinephrine Injection USP, 1 mg/mL is a clear, colorless, sterile solution packaged as 30 mL of solution in a multiple-dose, amber, glass vial. This drug is indicated for emergency treatment of allergic reactions (type I), including anaphylaxis.

ANDA: 211-880

Drug Product Name / Strength: Epinephrine Injection USP; 1 mg/mL (30 mL-fill, multiple-dose solution)

Route of Administration: Intramuscular/subcutaneous

Applicant Name: International Medication Systems, Limited

Manufacturing Site:

International Medication Systems, Ltd. (an Amphastar Company)

(b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Review Summary: This drug product is (b) (4). The applicant has provided adequate information and studies to support the sterility assurance of the drug product through the integrity of the container closure system, the effectiveness of the (b) (4) the sterilization of equipment, the endotoxin release specification, the method suitability for endotoxin and sterility testing, and the stability testing of the drug product.

List Submissions Being Reviewed:

Submit	Received	Assigned to Reviewer
13 June 2018	14 June 2018	18 July 2018
17 August 2018	20 August 2018	04 September 2018
15 November 2018	15 November 2018	-
13 March 2019	13 March 2019	-

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks: The Agency refused to receive the original submission of ANDA 211880. The resubmission of ANDA 211880 only includes information responding to deficiencies the Agency described in the refuse to receive letter to the ANDA 211880 applicant dated 09 September 2018. Therefore, this microbiology review reviews documents from the original and resubmission ANDA 211880.
The process reviewer sent IRs to the applicant in the TCIR asking the applicant to provide tables of in-process tests and limits, hold times, and equipment used during manufacture. This microbiology review includes information from the applicant's response to the TCIR.

Concise Description Outstanding Issues Remaining: NA

Supporting Documents: NA

List Number of Comparability Protocols (ANDA only): NA

S Drug Substance: (b) (4), a quality microbiology review is not needed.

Reviewer note: Epinephrine is sensitive to light. Specification for drug substance is NMT 357 EU/mg bacterial endotoxins, (b) (4)

P Drug Product

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The drug product is a sterile, clear/colorless solution in an amber glass vial with a (b) (4) flip off seal. The drug product is multiple-dose and is provided as 30 mL/vial (1 mg/mL Epinephrine solution).

- **Drug product composition –** The composition of the drug product is copied from submission *Section 3.2.P.1 Description of Composition of Drug Product:*

Table 32P12-1 Unit Dose Compositions (Per Unit and Per mL) of Epinephrine Injection USP, 1 mg/mL, 30 mL

Product Strength	Epinephrine Injection USP, 1 mg/mL, 30 mL	
API:	Amount per mL	Amount Per Unit (30 mL Vial)
Epinephrine USP*	(b) (4)	(b) (4)
Inactive Ingredients:		
Hydrochloric Acid NF		
	pH adjustment	
Sodium Chloride USP	9.0 mg	
Chlorobutano (b) (4) NF	5.4 mg	
Sodium Metabisulfite NF	1.5 mg	
Water for Injection, USP		
(b) (4)	(b) (4)	
(b) (4)		

- **Description of container closure system –** (b) (4)

(b) (4)

Reviewer's Assessment: ***Adequate***

The composition of the drug product and the container closure system were adequately described.

P.2 Pharmaceutical Development

(b) (4)

23 pages have been withheld as b4 (CCI/TS) immediately following this page

(b) (4)

A Appendices: NA

R Regional Information

Executed Batch Records

Executed batch records were provided for lots 081117A, 081617A, and 081817A. These were the lots placed on stability.

Reviewer's Assessment: ***Adequate***

Executed batch records were provided by the applicant.

Comparability Protocols: NA

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

2.A. Package Insert: Epinephrine injection, USP at 1 mg/mL, 30 mL multiple-dose vial. Vial must be discarded 30 days after initial use. Store between 20 – 25°C. Protect from light and freezing.

Post-dilution/constitution hold time: NA; the drug product is administered undiluted.

Reviewer's Assessment: ***Adequate***
Storage conditions were listed on the drug product label. The drug is administered undiluted so there is no need for post-dilution/constitution hold time studies.

Post-Approval Commitments: NA

List of Deficiencies: NA

Primary Microbiology Reviewer Name and Date: Julia Marré, PhD, Microbiologist, 03/15/2019

Secondary Reviewer Name and Date: Denise Miller, Sr. Microbiologist, 03/15/2019

Julia Marre

Digitally signed by Julia Marre
Date: 3/22/2019 03:03:02PM
GUID: 5ac654d90075eaa6b93887b3adda09f0

Denise Miller

Digitally signed by Denise Miller
Date: 3/25/2019 09:03:19AM
GUID: 508da7280002a5d546459b998253d1aa

Raman Murali

Digitally signed by Raman Murali
Date: 3/30/2020 12:12:30PM
GUID: 508da701000286d1f02ed0090280bc19

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☒ Complete Response-Minor
☐ Complete Response-Major
☐ Complete Response-Major-Facilities Only

ANDA 211880
Assessment 3

Drug Product Name	Epinephrine Injection USP
Dosage Form	Injection
Strength	1 mg (base)/mL
Route of Administration	Intramuscular, Intravenous, subcutaneous
Rx/OTC Dispensed	Rx
Applicant	International Medication Systems, Limited 1886 Santa Anita Avenue South El Monte, CA 91733
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission	06/14/2018	All
Resubmission after Refuse to Receive	08/20/2018	All
Amendment-Quality/ Response to Information Request	11/15/2018	Process
Amendment-Response to Labeling Discipline Review Letter	02/13/2019	Labeling
Amendment-Labeling/Response to Information Request	03/13/2019	Labeling
Amendment-Quality/Response to Discipline Review Letter	03/14/2019	Drug Substance, Drug Product, Process, and Microbiology
Amendment-Resubmission after Action-Complete Response	06/14/2019	Drug Substance and Drug Product
Amendment-Quality/ Response to Information Request	08/22/2019	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Yichuan Xu	Yun (Jenny) Wang
Drug Product	Raman Murali	Kai Kwok
Manufacturing	Process: Brian Rogers Facility: Rose Xu	Yong Hu
Microbiology	Julia Marre	Denise Miller
Biopharmaceutics	N/A	

Regulatory Business Process Manager	Suzan Ghodasara
Application Technical Lead	Raman Murali
Laboratory (OTR)	N/A
Environmental	N/A

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESMENT DATA SHEET

IQA ANDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Epinephrine USP	Adequate	Review #5: 12/3/2019	Reviewed by Y.Xu
	Type III		(b) (4)	Adequate	1/18/2017	Reviewed by B. Stevens
	Type III			Adequate	8/29/2017	Reviewed by L.Qi
	Type IV			Adequate	11/14/2016	Reviewed by V. Amspacher

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 204640	Adrenalin® by Par Pharmaceuticals, 30 mL (MDV)
ANDA	ANDA 207568	Epinephrine Injection, USP, 1mg/1mL, 1 mL **Note:** RLD NDA 204200 - Adrenalin® by Par Pharmaceuticals, 1 mL) (SDV)

2. CONSULTS: N/A

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

U.S. FOOD & DRUG ADMINISTRATION

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

IQA ANDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Minor

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – Minor.

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance: Inadequate-Minor

1. Primary Justification:

A revised USP monograph for Epinephrine became official on December 1, 2019. The DMF holder has updated the DS specification to comply with the revised USP monograph that became official in 12/1/2019. The applicant will be asked to revise the drug substance specification, organic impurities and analytical methods, along with the method verification/equivalency studies, as appropriate, to comply with the revised USP monograph. See deficiency below.

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

A revised USP monograph for Epinephrine became official on December 1, 2019. Please revise the drug substance specification, list of organic impurities and analytical methods, along with the method verification/equivalency studies, as appropriate, to comply with the revised USP monograph. Please consult with their DMF holder, if necessary. To show compliance with the monograph, it is recommended to use/footnote the USP listed impurity names in the drug substance specification.

Drug Product: Adequate

1. Primary Justification:

Drug product review is adequate

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

Drug Product review is adequate.

Labeling: Adequate

B. Manufacturing: Adequate

1. Primary Justification:
2. Secondary Justification (if necessary)
3. Tertiary Justification (if necessary):
4. Insert additional justification below (if necessary)

C. Biopharmaceutics: Adequate

1. Primary Justification:
2. Secondary Justification (if necessary):
3. Tertiary Justification (if necessary):
4. Insert additional justification below (if necessary)

D. Microbiology: Adequate

1. Primary Justification:

2. Secondary Justification (if necessary):

3. Tertiary Justification (if necessary):

4. Insert additional justification below (if necessary)

E. List of Deficiencies for Complete Response

1. **Overall Quality Deficiencies - Optional (Deficiencies that affect multiple sub-disciplines)**
   None

2. **Drug Substance Deficiencies**
   A revised USP monograph for Epinephrine became official on December 1, 2019. Please revise the drug substance specification, list of organic impurities and analytical methods, along with the method verification/equivalency studies, as appropriate, to comply with the revised USP monograph. Please consult with their DMF holder, if necessary. To show compliance with the monograph, it is recommended to use/footnote the USP listed impurity names in the drug substance specification.

3. **Drug Product Deficiencies**
   None

4. **Labeling Deficiencies (Please contact OGD if you identify any Labeling deficiencies with your comments)**
   None

5. **Manufacturing Deficiencies**
   None

6. **Biopharmaceutics Deficiencies**
   None

7. **Microbiology Deficiencies**
   None

8. **Other Deficiencies (Specify discipline, such as Environmental)**
   N/A

Application Technical Lead Name and Date: Raman Murali, PhD., 1/2/202

Raman Murali

Digitally signed by Raman Murali
Date: 1/03/2020 03:28:52PM
GUID: 508da701000286d1f02ed0090280bc19

Quality Review Data Sheet

ANDA# 211880
Drug Product: Epinephrine Injection, USP, 1mg/1mL, 30 mL
Review # 3

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Epinephrine USP (b) (4)	Adequate	Review #5: 12/3/2019	Reviewed by Y.Xu
	Type III			Adequate	1/18/2017	Reviewed by B. Stevens
	Type III			Adequate	8/29/2017	Reviewed by L.Qi
	Type IV			Adequate	11/14/2016	Reviewed by V. Amspacher

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 204640	Adrenalin® by Par Pharmaceuticals, 30 mL (MDV)
ANDA	ANDA 207568	Epinephrine Injection, USP, 1mg/1mL, 1 mL **Note:** RLD NDA 204200 - Adrenalin® by Par Pharmaceuticals, 1 mL) (SDV)

2. CONSULTS: N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				

Clinical				
Other				

DRUG SUBSTANCE

IQA Review Guide Reference

Product Background

Drug Product Category (or Mechanism of Action):

Indication: Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis

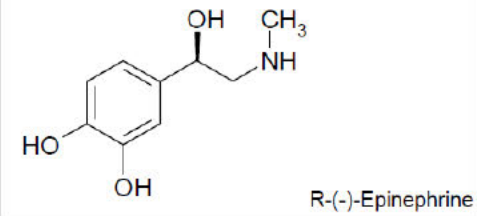
ANDA (review cycle number): 211880 Review #3

Chemical Name and Structure:

1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-; (-)-3 ,4-Dihydroxy-α-[(methyl amino)methyl]benzyl alcohol

OR

(-)-3 ,4-Dihydroxy-α-[(methylamino)methyl]benzylalcohol



R-(-)-Epinephrine

DMF # (if applicable): (b) (4)

ANDA Applicant Name: International Medication Systems, Limited (IMS)

DMF Holder: (b) (4)

Review Recommendation: **Inadequate - Minor**
DMF review #5 is adequate on 12/3/2019 by Y. Xu.

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

The ANDA is not approvable.
A revised USP monograph for Epinephrine that became official on December 1, 2019. The DMF holder has updated the DS specification to comply with the revised USP monograph that became official in 12/1/2019. The applicant will be asked to revise the

drug substance specification, organic impurities and analytical methods, along with the method verification/equivalency studies, as appropriate, to comply with the revised USP monograph.
See deficiency below.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment (SD#15) (Bioequivalence/Quality)	9/23/2019
Amendment (SD#14) (Quality)	8/22/2019
Amendment (SD#11) (Quality)	6/14/2019
Amendment (SD#10)(Labeling)	4/10/2019
Amendment (SD#9) (Quality)	3/14/2019
Amendment (SD#8)(Labeling)	3/13/2019
Amendment (SD#6)(Labeling)	2/13/2019
Amendment (SD#4)	11/15/2018
Amendment (SD#2)	8/20/2018
Original submission (SD#1)	6/14/2018

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining:
ANDA is approvable. The drug substance specifications do not comply with the revised USP monograph for Epinephrine that became official on December 1, 2019.

List Number of Comparability Protocols (ANDA only): None

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DRUG PRODUCT

IQA Review Guide Reference

Product Background

Drug Product Category (or Mechanism of Action): Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist

Indication: for emergency treatment of allergic reactions (Type 1), including anaphylaxis

ANDA (review cycle number): ANDA# 211880
Review # 3

Drug Product Name / Strength: Drug Product: Epinephrine Injection, USP, 1mg/1mL, 30 mL

Route of Administration: Intramuscular or subcutaneous injection

Applicant Name: International Medication Systems, Limited (IMS)

Review Recommendation: **Adequate**

(b) (4)

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

- **RLD and Reference Standard:** NDA 204640 Adrenalin® by Par Pharmaceuticals

- **Description of the Drug Substance(s) and Drug Product(s) and from Package Insert**

Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol.
Epinephrine is white or off-white crystalline substance. (b) (4)

Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

- **Brief Description of the Manufacturing Process:** Unit Steps are:

(b) (4)

- **Description of How the Drug Product is Intended to be Used (for In-Use Stability Studies) from Package Insert**

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) of undiluted Epinephrine Injection, USP administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, every 5 to 10 minutes as necessary.

Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) up to a maximum of 0.3 mg (0.3 mL) administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, per injection, repeated every 5 to 10 minutes as necessary.

- **How Supplied:**

Epinephrine Injection, USP 30 mL Multi-Dose Vials:

Each carton contains 1 multiple-dose vial containing 30 mL epinephrine injection, USP solution 1 mg/mL in an amber glass vial.

NDC 76329-9061-0 30 mL vial Stock No. 9061

Vial and contents must be discarded 30 days after initial use.

Storage and Handling
Store between 20°C to 25°C (68°F to 77°F) (See USP Controlled Room Temperature). Epinephrine is light sensitive. Protect from light and freezing.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment (SD#14) (Quality)	8/22/2019
Amendment (SD#11) (Quality)	6/14/2019
Amendment (SD#10)(Labeling)	4/10/2019
Amendment (SD#9) (Quality)	3/14/2019
Amendment (SD#8)(Labeling)	3/13/2019
Amendment (SD#6)(Labeling)	2/13/2019
Amendment (SD#4)	11/15/2018
Amendment (SD#2)	8/20/2018
Original submission (SD#1)	6/14/2018

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining:
None

List Number of Comparability Protocols (ANDA only): None

P.1 Description and Composition

Component/composition table

Revised in response to BE deficiency (see review of SD15):

Table 1: Components and Composition of Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials – *Commercial Batch Size* (b) (4) Liters)

Inactive Ingredients	Formulation		Specific Amount Added (g)	Calculation of Specific Amount for Commercial Batch Size:
	RLD[a] (JHP Pharmaceuticals)	IMS Proposed Product		
Sodium Chloride	9.0 mg/mL	9.0 mg/mL	(b) (4)	(b) (4)
Sodium Metabisulfite	1.5 mg/mL	1.5 mg/mL		
Chlorobutanol[b]	5.4 mg/mL	5.4 mg/mL		
Hydrochloric acid	(to adjust pH)	(to adjust pH)		
Water for Injection (WFI)	(b) (4)	(b) (4)		

Components and Composition of Epinephrine Injection USP provided in the original submission:

Materials	Function	Quality Standard	Amount per Unit Vial (30 mL)	% w/w
Epinephrine USP	Active ingredient	USP	(b) (4)	
Hydrochloric Acid NF	(b) (4) adjust pH	NF		
Sodium Chloride USP	(b) (4)	USP		

Materials	Function	Quality Standard	Amount per Unit Vial (30 mL)	% w/w
Chlorobutanol (b) (4) NF	Preservative	NF	(b) (4)	
Sodium Metabisulfite NF	(b) (4)	NF		
Water for Injection, USP	(b) (4) (b) (4)	USP		
(b) (4)				

Unit Dose Composition – Comparison between the Exhibit Batch Formulation and the Commercial Batch Formulation of Epinephrine Injection USP, 1 mg/mL, 30 mL MDV

Materials	Function	Quality Standard	Amount per mL	Exhibit Batch Formulati	Commerci al Formulati
Epinephrine USP	Active ingredient	USP		(b) (4)	
(b) (4) Hydrochloric Acid NF	(b) (4)	NF			
Sodium Chloride USP	(b) (4)	NF	9.0 mg	(b) (4)	
Chlorobutanol (b) (4) NF	Preservative	USP	5.4 mg		
Sodium Metabisulfite NF	(b) (4)	NF	1.5 mg		
Water for Injection USP	(b) (4) (b) (4)	USP	(b) (4)	(b) (4)	
(b) (4)					

Reviewer's Assessment: ***{adequate}***

See also review of SD15: RLD sponsor specifically stated (b) (4)

(b) (4)

RLD FORMULATION COMPARISION NOT TO BE RELEASED UNDER FOIA

46 pages have been withheld as b4 (CCI/TS) immediately following this page

(b) (4)

R Regional Information

Environmental

Reviewer's Assessment: *{Adequate }*
Applicant claimed categorical exclusion cited in 21 CFR 25.31(b).

Methods Verification Package

Reviewer's Assessment: *{Adequate }*

Comparability Protocols

Reviewer's Assessment: *{Adequate }*

None provided

Lifecycle Management Considerations

N/A

Drug Product: List of Deficiencies

None

Primary Drug Product Reviewer Name and Date: Raman Murali; 1/25/2019; 1/31/2019; 4/30/2019; 5/9/2019; 8/1/2019; 8/14/2019; 11/15/2019; 12/12/2019

Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019; CR#1: 5/13/2019; CR#2: 8/6/2019; CR#3: 12/11/2019

LABELING

IQA Review Guide Reference

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No

For DRL, the applicant will be asked to include visual color and clarity in the DP specifications.

If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☒ No ☐ N/A If "No," explain. The firm will be asked to provide in use stability data to support stability of the DP up to 30 days after initial use per proposed PI.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None

List of Deficiencies:

None

Primary Drug Product Reviewer Name and Date: Raman Murali, 1/25/2019 ***Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019***

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – ANDA

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2	Comments*
(b) (4)	Medium	(b) (4)	Low	Adequate PD information provided
	Medium		Low	Adequate
	Medium		Low	Adequate specification controls
	Medium		Low	Provided additional information
	Medium		Low	Provided additional information

Kai Kwok

Digitally signed by Kai Kwok
Date: 12/13/2019 05:53:51PM
GUID: 531543b00000571ac408640b9cf905cb

Raman Murali

Digitally signed by Raman Murali
Date: 12/16/2019 11:59:48AM
GUID: 508da701000286d1f02ed0090280bc19

Recommendation: Approval

ANDA 211880
Review 2

Drug Name/Dosage Form	Epinephrine Injection USP
Strength	1 mg (base)/mL
Route of Administration	Intramuscular, Intravenous, subcutaneous
Rx/OTC Dispensed	Rx
Applicant	International Medication Systems, Limited 1886 Santa Anita Avenue South El Monte, CA 91733
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	*06/14/2018*	*All*
Resubmission after Refuse to Receive	*08/20/2018*	*All*
Amendment-Quality/ Response to Information Request	*11/15/2018*	*Process*
Amendment-Response to Labeling Discipline Review Letter	*02/13/2019*	*Labeling*
Amendment-Labeling/Response to Information Request	*03/13/2019*	*Labeling*
Amendment-Quality/Response to Discipline Review Letter	*03/14/2019*	*Drug Substance, Drug Product, Process, and Microbiology*
Amendment-Resubmission after Action-Complete Response	*06/14/2019*	*Drug Substance and Drug Product*

Amendment-Quality/ Response to Information Request	*08/22/2019*	*Drug Product*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Yichuan Xu	Yun (Jenny) Wang
Drug Product	Raman Murali	Kai Kwok
Process	Brian Rogers	Yong Hu
Microbiology	Julia Marre	Denise Miller
Facility	Rose Xu	Yong Hu
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Suzan Ghodasara	
Application Technical Lead	Raman Murali	
Laboratory (OTR)	N/A	N/A
ORA Lead	Michael Tollon	N/A
Environmental	N/A	N/A

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Epinephrine USP	Adequate	8/21/2019	Reviewed by Y.Xu Adequate with additional comments
	Type III		(b) (4)	Adequate	1/18/2017	Reviewed by B. Stevens
	Type III			Adequate	8/29/2017	Reviewed by L.Qi

(b) (4)	Type IV	(b) (4)	Adequate	11/14/2016	Reviewed by V. Amspacher

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 204640	Adrenalin® by Par Pharmaceuticals, 30 mL (MDV)
ANDA	ANDA 207568	Epinephrine Injection, USP, 1mg/1mL, 1 mL **Note:** RLD NDA 204200 - Adrenalin® by Par Pharmaceuticals, 1 mL) (SDV)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

ANDA 211880 is recommended for Approval. Drug product quality, process, facility, and Microbiology reviews are adequate. OPQ recommends approval of ANDA.

II. Summary of Quality Assessments

A. Product Overview

Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis. Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol. Epinephrine is white or off-white crystalline substance. (b) (4)

.

Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

Dosage:

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) of undiluted Epinephrine Injection, USP administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, every 5 to 10 minutes as necessary.

Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) up to a maximum of 0.3 mg (0.3 mL) administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, per injection, repeated every 5 to 10 minutes as necessary.

How Supplied:

Epinephrine Injection, USP 30 mL Multi-Dose Vials:

Each carton contains 1 multiple-dose vial containing 30 mL epinephrine injection, USP solution 1 mg/mL in an amber glass vial.

Vial and contents must be discarded 30 days after initial use.

Storage and Handling

Store between 20°C to 25°C (68°F to 77°F) (See USP Controlled Room Temperature). Epinephrine is light sensitive. Protect from light and freezing.

Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee	☒ Yes ☐ No *(see comments) ☐ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	DD, BC or designee	☒ Yes ☐ No *(see comments) ☐ N/A

Proposed Indication(s) including Intended Patient Population	Anaphylaxis: *Adults and Children 30 kg (66 lbs) or more:* 0.3 to 0.5 mg (0.3 mL to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary *Children 30 kg (66 lbs) or less:* 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary Hypotension associated with septic shock: 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
Duration of Treatment	Duration of treatment varies with indication and use. Refer to labeling.
Maximum Daily Dose	(b) (4) day
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

ANDA 211880 is ready for Approval.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2A	Comments
(b) (4)	Medium	(b) (4)	Low	Adequate PD information provided
	Medium		Low	Adequate
	Medium		Low	Adequate specification controls
	Medium		Low	Provided additional information
	Medium		Low	Provided additional information

Raman Murali

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Date: 8/27/2019 03:10:44PM
GUID: 508da701000286d1f02ed0090280bc19

Quality Review Data Sheet

ANDA# 211880
Drug Product: Epinephrine Injection, USP, 1mg/1mL, 30 mL
Review # 2

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Epinephrine USP	Adequate	8/21/2019	Reviewed by Y.Xu Adequate with additional comments
	Type III		(b) (4)	Adequate	1/18/2017	Reviewed by B. Stevens
	Type III			Adequate	8/29/2017	Reviewed by L.Qi
	Type IV			Adequate	11/14/2016	Reviewed by V. Amspacher

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 204640	Adrenalin® by Par Pharmaceuticals, 30 mL (MDV)
ANDA	ANDA 207568	Epinephrine Injection, USP, 1mg/1mL, 1 mL **Note:** RLD NDA 204200 - Adrenalin® by Par Pharmaceuticals, 1 mL) (SDV)

2. CONSULTS: N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				

CDRH				
Clinical				
Other				

DRUG SUBSTANCE

IQA Review Guide Reference

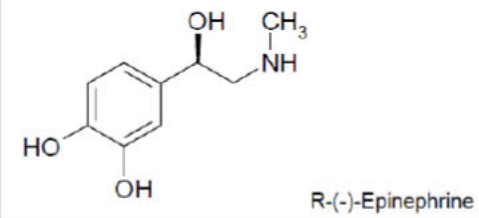
Product Background

Drug Product Category (or Mechanism of Action):

Indication: Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis

ANDA (review cycle number): 211880 Review #2

Chemical Name and Structure:
1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-; (-)-3 ,4-Dihydroxy-α-[(methyl amino)methyl]benzyl alcohol
OR
(-)-3 ,4-Dihydroxy-α-[(methylamino)methyl]benzylalcohol



R-(-)-Epinephrine

DMF # (if applicable): (b) (4)

ANDA Applicant Name: International Medication Systems, Limited (IMS)

DMF Holder: (b) (4)

Review Recommendation: **Adequate**
DMF review #4 is adequate with additional comments on 8/21/2019 by Y. Xu

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:
The ANDA is approvable. DMF review #4 is adequate with additional comments.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment (SD#14) (Quality)	8/22/2019
Amendment (SD#11) (Quality)	6/14/2019
Amendment (SD#10)(Labeling)	4/10/2019
Amendment (SD#9) (Quality)	3/14/2019
Amendment (SD#8)(Labeling)	3/13/2019
Amendment (SD#6)(Labeling)	2/13/2019
Amendment (SD#4)	11/15/2018
Amendment (SD#2)	8/20/2018
Original submission (SD#1)	6/14/2018

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining:
None. ANDA is approvable.

List Number of Comparability Protocols (ANDA only): None

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Primary Drug Substance Reviewer Name and Date: Raman Murali, 1/25/2019; 1/31/2019; 4/30/2019; 5/9/2019; 8/1/2019; 8/14/2019, 8/22/2019; 8/26/2019

Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019; CR#1: 5/13/2019; IR#2: 8/6/2019; 8/22/2019 (updated per DMF Review #4); CR#2A: 8/26/2019

DRUG PRODUCT

IQA Review Guide Reference

Product Background
Drug Product Category (or Mechanism of Action): Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist

Indication: for emergency treatment of allergic reactions (Type 1), including anaphylaxis

ANDA (review cycle number): ANDA# 211880
Review # 2

Drug Product Name / Strength: Drug Product: Epinephrine Injection, USP, 1mg/1mL, 30 mL

Route of Administration: Intramuscular or subcutaneous injection

Applicant Name: International Medication Systems, Limited (IMS)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

- **RLD and Reference Standard:** NDA 204640 Adrenalin® by Par Pharmaceuticals

- **Description of the Drug Substance(s) and Drug Product(s) and from Package Insert**

Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol.

Epinephrine is white or off-white crystalline substance. (b) (4)

Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

- (b) (4)

- **Description of How the Drug Product is Intended to be Used (for In-Use Stability Studies) from Package Insert**

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) of undiluted Epinephrine Injection, USP administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, every 5 to 10 minutes as necessary.

Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) up to a maximum of 0.3 mg (0.3 mL) administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, per injection, repeated every 5 to 10 minutes as necessary.

- **How Supplied:**

Epinephrine Injection, USP 30 mL Multi-Dose Vials:

Each carton contains 1 multiple-dose vial containing 30 mL epinephrine injection, USP solution 1 mg/mL in an amber glass vial.

NDC 76329-9061-0 30 mL vial Stock No. 9061

Vial and contents must be discarded 30 days after initial use.

Storage and Handling
Store between 20°C to 25°C (68°F to 77°F) (See USP Controlled Room Temperature). Epinephrine is light sensitive. Protect from light and freezing.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment (SD#14) (Quality)	8/22/2019
Amendment (SD#11) (Quality)	6/14/2019
Amendment (SD#10)(Labeling)	4/10/2019
Amendment (SD#9) (Quality)	3/14/2019
Amendment (SD#8)(Labeling)	3/13/2019
Amendment (SD#6)(Labeling)	2/13/2019
Amendment (SD#4)	11/15/2018
Amendment (SD#2)	8/20/2018
Original submission (SD#1)	6/14/2018

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining:
None

List Number of Comparability Protocols (ANDA only): None

P.1 Description and Composition

Component/composition table

Materials	Function	Quality Standard	Amount per Unit Vial (30 mL)	% w/w
Epinephrine USP	Active ingredient	USP	(b) (4)	
Hydrochloric Acid NF	(b) (4) adjust pH	NF		
Sodium Chloride USP	(b) (4)	USP		
Chlorobutanol (b) (4) NF	Preservative	NF		
Sodium Metabisulfite NF	(b) (4)	NF		
Water for Injection, USP	(b) (4) (b) (4)	USP		
	(b) (4)			

Unit Dose Composition – Comparison between the Exhibit Batch Formulation and the Commercial Batch Formulation of Epinephrine Injection USP, 1 mg/mL, 30 mL MDV

Materials	Function	Quality Standard	Amount per mL	Exhibit Batch Formulati	Commercial Formulati
Epinephrine USP	Active ingredient	USP	(b) (4)	(b) (4)	
(b) (4) Hydrochloric Acid NF	(b) (4)	NF			
Sodium Chloride USP	(b) (4)	NF			
Chlorobutanol (b) (4) NF	Preservative	USP			
Sodium Metabisulfite NF	(b) (4)	NF			
Water for Injection USP	(b) (4) (b) (4)	USP	(b) (4)		
	(b) (4)				
	(b) (4)				

Reviewer's Assessment: *{adequate}*
The proposed formulation is Q1/Q2 to RLD, Par Sterile Products, LLC's Adrenalin® (NDA 204640), original formulation approved on December 18, 2013 (see Filing

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(b) (4)

R Regional Information

Environmental

Reviewer's Assessment: *{Adequate }* Applicant claimed categorical exclusion cited in 21 CFR 25.31(b).

Methods Verification Package

Reviewer's Assessment: *{Adequate }*

Comparability Protocols

Reviewer's Assessment: *{Adequate }* **None provided**

Lifecycle Management Considerations

N/A

Drug Product: List of Deficiencies

None

Primary Drug Product Reviewer Name and Date: Raman Murali; 1/25/2019; 1/31/2019; 4/30/2019; 5/9/2019; 8/1/2019; 8/14/2019

Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019; CR#1: 5/13/2019; CR#2: 8/6/2019; CR#2A: 8/26/2019

LABELING

IQA Review Guide Reference

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No

For DRL, the applicant will be asked to include visual color and clarity in the DP specifications.

If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☒ No ☐ N/A If "No," explain. The firm will be asked to provide in use stability data to support stability of the DP up to 30 days after initial use per proposed PI.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None

List of Deficiencies:

None

Primary Drug Product Reviewer Name and Date: Raman Murali, 1/25/2019 ***Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019***

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – ANDA

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2A	Comments*
(b) (4)	Medium	(b) (4)	Low	Adequate PD information provided
	Medium		Low	Adequate
	Medium		Low	Adequate specification controls
	Medium		Low	Provided additional information
	Medium		Low	Provided additional information

Kai Kwok

Digitally signed by Kai Kwok
Date: 8/26/2019 01:44:57PM
GUID: 531543b00000571ac408640b9cf905cb

Raman Murali

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Date: 8/26/2019 01:48:00PM
GUID: 508da701000286d1f02ed0090280bc19

PROCESS

Product Background:	**RLD NDA 204640 Adrenalin®**
ANDA:	**211880**
Drug Product Name / Strength:	**Epinephrine Injection USP / 1 mg (base)/mL**
Route of Administration:	**Injection**
Applicant Name:	**International Medication Systems, Limited**

Review Recommendation:	***Adequate from a process perspective***
Theme:	**N/A**
Justification:	***N/A***

Review Summary: Epinephrine is a white or almost white crystalline powder very slightly soluble in water and in alcohol. Epinephrine HCl is created (b) (4) and is very soluble in water.

The proposed drug product is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0. The proposed product is formulated with (b) (4) The drug product is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis.

Submission Under Review:	**Amendment**	**SDN 8**	**03/14/2019**
Submissions Previously Reviewed	**Amendment**	**SDN 4**	**11/15/2018**
	Amendment	**SDN 2**	**08/20/2018**
	Original	**SDN 1**	**06/14/2018**

Highlight Key Outstanding Issues from Last Cycle: **NA**

Concise Description Outstanding Issues Remaining: No issues remain

List Number of Comparability Protocols: No comparability protocols related to drug product manufacturing were submitted.

P.3 Manufacture

Batch Formula

Table 32P32-1 Batch Compositions of the Proposed Drug Product, Epinephrine Injection USP, 1 mg/mL, 30 mL (CCD-5)

Product Strength	Epinephrine Injection USP, 1 mg/mL, 30 mL	
Batch Size	Stability Lot Size: (b) (4)	Proposed Initial Commercial
	Amount per Batch	Amount per Batch
Active Ingredient		
Epinephrine USP*	(b) (4)	
Inactive Ingredients:		
Hydrochloric Acid NF*	(b) (4)	
	pH adjustment	pH adjustment
Sodium Chloride USP	(b) (4)	
Chlorobutanol (b) (4) NF		
Sodium Metabisulfite NF		
Water for Injection, USP		
(b) (4)		
(b) (4)		

(b) (4)

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(b) (4)

Summary of Process Validation Studies Conducted

Reviewer's Assessment: The applicant has provided process validation studies related to the (b) (4) process. These will be reviewed by the micro reviewer.

Assessment of Microbiological Controls

Reviewer's Assessment: N/A

Comparability Protocols

Reviewer's Assessment: No comparability protocols related to manufacturing were submitted.

Lifecycle Management Considerations

N/A

List of Deficiencies Sent in 02/11/2019 DRL:

(b) (4)

(b) (4)

.

Review #1

Primary Process Reviewer Name and Date: ***Brian Rogers 01/31/2019***

Secondary Reviewer Name and Date: ***Yong Hu 02/01/2019***

Review #2

Primary Process Reviewer Name and Date: ***Brian Rogers 03/18/2019***

Secondary Reviewer Name and Date: ***Yong Hu 04/10/2019***

Brian Rogers

Digitally signed by Brian Rogers
Date: 4/11/2019 01:24:52PM
GUID: 508da7210002a054552cbf1a8fc2e128

Yong Hu

Digitally signed by Yong Hu
Date: 4/11/2019 02:58:28PM
GUID: 508da7220002a14416588a81227bc049

FACILITIES

IQA Review Guide Reference

Product Background:

Epinephrine Injection, USP, 1mg/1mL is used for emergency treatment of allergic reactions (Type I) including anaphylaxis and allergic reaction.

ANDA: ANDA 211880

Drug Product Name / Strength: Epinephrine Injection, USP, 1mg/1mL, 30 mL

Route of Administration: Injection

Applicant Name: International Medication Systems, Limited

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:

(b) (4) . The firm is acceptable for (b) (4) based on its compliance history and its manufacturing capability.

International Medication Systems, Limited (IMS) (FEI 2016148) (b) (4) The firm is acceptable based on the previous inspections and the manufacturing capability.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Original	8/20/2018
Quality Amendment SD 4	11/15/2018
Quality Amendment SD 9	3/14/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): N/A

3.2.S.2 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)			• Low	• Acceptable based on previous inspection history and manufacture capability

Reviewer's Assessment: ***Adequate***

(b) (4)

(b) (4)

3.2.P.3 Manufacture

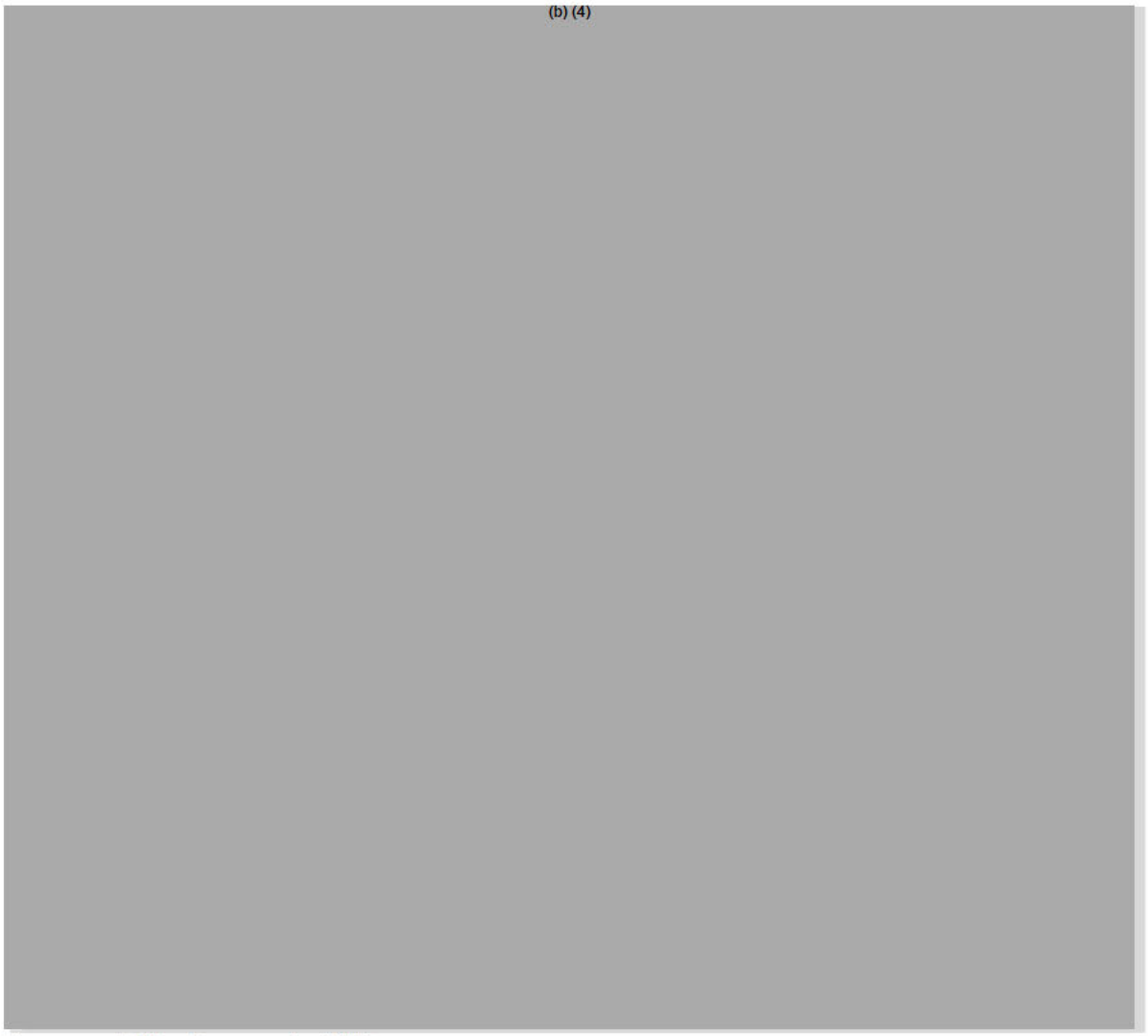
Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
International Medication Systems, Limited (IMS)	2016148	(b) (4)		• Acceptable based on previous inspection history and manufacture capability

Reviewer's Assessment: ***Adequate***

(b) (4)

(b) (4)



Comparability Protocols: N/A

Lifecycle Management Considerations: N/A

List of Deficiencies: N/A

Primary Facilities Reviewer Name and Date: Rose Xu, 5/2/2019

Secondary Reviewer Name and Date: Yong Hu, Ph.D., 5/15/2019

Rose Xu

Digitally signed by Rose Xu
Date: 5/15/2019 09:31:18AM
GUID: 5277e72900088dc65127c01f0d78be60

Yong Hu

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Date: 5/15/2019 09:46:34AM
GUID: 508da7220002a14416588a81227bc049

MICROBIOLOGY

Product Background: Epinephrine Injection USP, 1 mg/mL is a clear, colorless, sterile solution packaged as 30 mL of solution in a multiple-dose, amber, glass vial. This drug is indicated for emergency treatment of allergic reactions (type I), including anaphylaxis.

ANDA: 211-880

Drug Product Name / Strength: Epinephrine Injection USP; 1 mg/mL (30 mL-fill, multiple-dose solution)

Route of Administration: Intramuscular/subcutaneous

Applicant Name: International Medication Systems, Limited

Manufacturing Site:

International Medication Systems, Ltd. (an Amphastar Company)

(b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Review Summary: This drug product is (b) (4). The applicant has provided adequate information and studies to support the sterility assurance of the drug product through the integrity of the container closure system, the effectiveness of (b) (4), the sterilization of equipment, the endotoxin release specification, the method suitability for endotoxin and sterility testing, and the stability testing of the drug product.

List Submissions Being Reviewed:

Submit	Received	Assigned to Reviewer
13 June 2018	14 June 2018	18 July 2018
17 August 2018	20 August 2018	04 September 2018
15 November 2018	15 November 2018	-
13 March 2019	13 March 2019	-

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks: The Agency refused to receive the original submission of ANDA 211880. The resubmission of ANDA 211880 only includes information responding to deficiencies the Agency described in the refuse to receive letter to the ANDA 211880 applicant dated 09 September 2018. Therefore, this microbiology review reviews documents from the original and resubmission ANDA 211880.
The process reviewer sent IRs to the applicant in the TCIR asking the applicant to provide tables of in-process tests and limits, hold times, and equipment used during manufacture. This microbiology review includes information from the applicant's response to the TCIR.

Concise Description Outstanding Issues Remaining: NA

Supporting Documents: NA

List Number of Comparability Protocols (ANDA only): NA

S Drug Substance: Drug substance is not sterile and, therefore, a quality microbiology review is not needed.

Reviewer note: Epinephrine is sensitive to light. Specification for drug substance is NMT 357 EU/mg bacterial endotoxins, (b) (4)

P Drug Product

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The drug product is a sterile, clear/colorless solution in an amber glass vial with a (b) (4) flip off seal. The drug product is multiple-dose and is provided as 30 mL/vial (1 mg/mL Epinephrine solution).

- **Drug product composition –** The composition of the drug product is copied from submission *Section 3.2.P.1 Description of Composition of Drug Product:*

Table 32P12-1 Unit Dose Compositions (Per Unit and Per mL) of Epinephrine Injection USP, 1 mg/mL, 30 mL

Product Strength	Epinephrine Injection USP, 1 mg/mL, 30 mL	
API:	Amount per mL	Amount Per Unit (30 mL Vial)
Epinephrine USP*	(b) (4)	
Inactive Ingredients:		
Hydrochloric Acid NF	(b) (4)	
	pH adjustment	(b) (4)
Sodium Chloride USP	9.0 mg	
(b) (4) Chlorobutano NF	5.4 mg	
Sodium Metabisulfite NF	1.5 mg	
Water for Injection, USP	(b) (4)	
	(b) (4)	

- **Description of container closure system –** (b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment: ***Adequate***

The composition of the drug product and the container closure system were adequately described.

P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

A Appendices: NA

R Regional Information

Executed Batch Records

Executed batch records were provided for lots 081117A, 081617A, and 081817A. These were the lots placed on stability.

Reviewer's Assessment: ***Adequate***

Executed batch records were provided by the applicant.

Comparability Protocols: NA

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

2.A. Package Insert: Epinephrine injection, USP at 1 mg/mL, 30 mL multiple-dose vial. Vial must be discarded 30 days after initial use. Store between 20 – 25°C. Protect from light and freezing.

Post-dilution/constitution hold time: NA; the drug product is administered undiluted.

Reviewer's Assessment: ***Adequate***
Storage conditions were listed on the drug product label. The drug is administered undiluted so there is no need for post-dilution/constitution hold time studies.

Post-Approval Commitments: NA

List of Deficiencies: NA

Primary Microbiology Reviewer Name and Date: Julia Marré, PhD, Microbiologist, 03/15/2019

Secondary Reviewer Name and Date: Denise Miller, Sr. Microbiologist, 03/15/2019

Julia Marre

Digitally signed by Julia Marre
Date: 3/22/2019 03:03:02PM
GUID: 5ac654d90075eaa6b93887b3adda09f0

Denise Miller

Digitally signed by Denise Miller
Date: 3/25/2019 09:03:19AM
GUID: 508da7280002a5d546459b998253d1aa

Raman Murali

Digitally signed by Raman Murali
Date: 8/27/2019 03:34:38PM
GUID: 508da701000286d1f02ed0090280bc19

Recommendation: Approval

ANDA 211880
Review 2

Drug Name/Dosage Form	Epinephrine Injection USP
Strength	1 mg (base)/mL
Route of Administration	Intramuscular, Intravenous, subcutaneous
Rx/OTC Dispensed	Rx
Applicant	International Medication Systems, Limited 1886 Santa Anita Avenue South El Monte, CA 91733
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	*06/14/2018*	*All*
Resubmission after Refuse to Receive	*08/20/2018*	*All*
Amendment-Quality/ Response to Information Request	*11/15/2018*	*Process*
Amendment-Response to Labeling Discipline Review Letter	*02/13/2019*	*Labeling*
Amendment-Labeling/Response to Information Request	*03/13/2019*	*Labeling*
Amendment-Quality/Response to Discipline Review Letter	*03/14/2019*	*Drug Substance, Drug Product, Process, and Microbiology*
Amendment-Resubmission after Action-Complete Response	*06/14/2019*	*Drug Substance and Drug Product*

Amendment-Quality/ Response to Information Request	*08/22/2019*	*Drug Product*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Yichuan Xu	Yun (Jenny) Wang
Drug Product	Raman Murali	Kai Kwok
Process	Brian Rogers	Yong Hu
Microbiology	Julia Marre	Denise Miller
Facility	Rose Xu	Yong Hu
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Suzan Ghodasara	
Application Technical Lead	Raman Murali	
Laboratory (OTR)	N/A	N/A
ORA Lead	Michael Tollon	N/A
Environmental	N/A	N/A

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Epinephrine USP	Adequate	8/21/2019	Reviewed by Y.Xu Adequate with additional comments
	Type III		(b) (4)	Adequate	1/18/2017	Reviewed by B. Stevens
	Type III			Adequate	8/29/2017	Reviewed by L.Qi

(b) (4)	Type IV	(b) (4)	Adequate	11/14/2016	Reviewed by V. Amspacher

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 204640	Adrenalin® by Par Pharmaceuticals, 30 mL (MDV)
ANDA	ANDA 207568	Epinephrine Injection, USP, 1mg/1mL, 1 mL **Note:** RLD NDA 204200 - Adrenalin® by Par Pharmaceuticals, 1 mL) (SDV)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

ANDA 211880 is recommended for Approval. Drug product quality, process, facility, and Microbiology reviews are adequate. OPQ recommends approval of ANDA.

II. Summary of Quality Assessments

A. Product Overview

Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis. Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol. Epinephrine is white or off-white crystalline substance. (b) (4)

.

Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

Dosage:

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) of undiluted Epinephrine Injection, USP administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, every 5 to 10 minutes as necessary.

Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) up to a maximum of 0.3 mg (0.3 mL) administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, per injection, repeated every 5 to 10 minutes as necessary.

How Supplied:

Epinephrine Injection, USP 30 mL Multi-Dose Vials:

Each carton contains 1 multiple-dose vial containing 30 mL epinephrine injection, USP solution 1 mg/mL in an amber glass vial.

Vial and contents must be discarded 30 days after initial use.

Storage and Handling

Store between 20°C to 25°C (68°F to 77°F) (See USP Controlled Room Temperature). Epinephrine is light sensitive. Protect from light and freezing.

Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee	☒ Yes ☐ No *(see comments) ☐ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	DD, BC or designee	☒ Yes ☐ No *(see comments) ☐ N/A

Proposed Indication(s) including Intended Patient Population	Anaphylaxis: *Adults and Children 30 kg (66 lbs) or more:* 0.3 to 0.5 mg (0.3 mL to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary *Children 30 kg (66 lbs) or less:* 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary Hypotension associated with septic shock: 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
Duration of Treatment	Duration of treatment varies with indication and use. Refer to labeling.
Maximum Daily Dose	(b) (4) day
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

ANDA 211880 is ready for Approval.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2A	Comments
(b) (4)	Medium	(b) (4)	Low	Adequate PD information provided
	Medium		Low	Adequate
	Medium		Low	Adequate specification controls
	Medium		Low	Provided additional information
	Medium		Low	Provided additional information

Raman Murali

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Date: 8/27/2019 03:10:44PM
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Quality Review Data Sheet

ANDA# 211880
Drug Product: Epinephrine Injection, USP, 1mg/1mL, 30 mL
Review # 2

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Epinephrine USP	Adequate	8/21/2019	Reviewed by Y.Xu Adequate with additional comments
	Type III		(b) (4)	Adequate	1/18/2017	Reviewed by B. Stevens
	Type III			Adequate	8/29/2017	Reviewed by L.Qi
	Type IV			Adequate	11/14/2016	Reviewed by V. Amspacher

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 204640	Adrenalin® by Par Pharmaceuticals, 30 mL (MDV)
ANDA	ANDA 207568	Epinephrine Injection, USP, 1mg/1mL, 1 mL **Note:** RLD NDA 204200 - Adrenalin® by Par Pharmaceuticals, 1 mL) (SDV)

2. CONSULTS: N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				

CDRH				
Clinical				
Other				

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DRUG SUBSTANCE

IQA Review Guide Reference

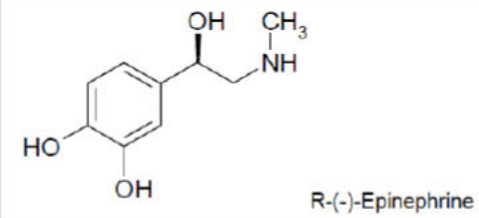
Product Background

Drug Product Category (or Mechanism of Action):

Indication: Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis

ANDA (review cycle number): 211880 Review #2

Chemical Name and Structure:
1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-; (-)-3 ,4-Dihydroxy-α-[(methyl amino)methyl]benzyl alcohol
OR
(-)-3 ,4-Dihydroxy-α-[(methylamino)methyl]benzylalcohol



R-(-)-Epinephrine

DMF # (if applicable) (b) (4)

ANDA Applicant Name: International Medication Systems, Limited (IMS)

DMF Holder: (b) (4)

Review Recommendation: **Adequate**
DMF review #4 is adequate with additional comments on 8/21/2019 by Y. Xu

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:
The ANDA is approvable. DMF review #4 is adequate with additional comments.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment (SD#14) (Quality)	8/22/2019
Amendment (SD#11) (Quality)	6/14/2019
Amendment (SD#10)(Labeling)	4/10/2019
Amendment (SD#9) (Quality)	3/14/2019
Amendment (SD#8)(Labeling)	3/13/2019
Amendment (SD#6)(Labeling)	2/13/2019
Amendment (SD#4)	11/15/2018
Amendment (SD#2)	8/20/2018
Original submission (SD#1)	6/14/2018

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining:
None. ANDA is approvable.

List Number of Comparability Protocols (ANDA only): None

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(b) (4)

[redacted]

Drug Substance: List of Deficiencies:

None

Primary Drug Substance Reviewer Name and Date: Raman Murali, 1/25/2019; 1/31/2019; 4/30/2019; 5/9/2019; 8/1/2019; 8/14/2019, 8/22/2019; 8/26/2019

Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019; CR#1: 5/13/2019; IR#2: 8/6/2019; 8/22/2019 (updated per DMF Review #4); CR#2A: 8/26/2019

DRUG PRODUCT

IQA Review Guide Reference

Product Background
Drug Product Category (or Mechanism of Action): Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist

Indication: for emergency treatment of allergic reactions (Type 1), including anaphylaxis

ANDA (review cycle number): ANDA# 211880
Review # 2

Drug Product Name / Strength: Drug Product: Epinephrine Injection, USP, 1mg/1mL, 30 mL

Route of Administration: Intramuscular or subcutaneous injection

Applicant Name: International Medication Systems, Limited (IMS)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

- **RLD and Reference Standard:** NDA 204640 Adrenalin® by Par Pharmaceuticals

- **Description of the Drug Substance(s) and Drug Product(s) and from Package Insert**

Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol.

Epinephrine is white or off-white crystalline substance. The molecule is optically active and is not known to exhibit polymorphism. Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin.
Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

- **Brief Description of the Manufacturing Process:** Unit Steps are:

(b) (4)

- **Description of How the Drug Product is Intended to be Used (for In-Use Stability Studies) from Package Insert**

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) of undiluted Epinephrine Injection, USP administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, every 5 to 10 minutes as necessary.

Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) up to a maximum of 0.3 mg (0.3 mL) administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, per injection, repeated every 5 to 10 minutes as necessary.

- **How Supplied:**

Epinephrine Injection, USP 30 mL Multi-Dose Vials:

Each carton contains 1 multiple-dose vial containing 30 mL epinephrine injection, USP solution 1 mg/mL in an amber glass vial.

NDC 76329-9061-0 30 mL vial Stock No. 9061

Vial and contents must be discarded 30 days after initial use.

Storage and Handling
Store between 20°C to 25°C (68°F to 77°F) (See USP Controlled Room Temperature). Epinephrine is light sensitive. Protect from light and freezing.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment (SD#14) (Quality)	8/22/2019
Amendment (SD#11) (Quality)	6/14/2019
Amendment (SD#10)(Labeling)	4/10/2019
Amendment (SD#9) (Quality)	3/14/2019
Amendment (SD#8)(Labeling)	3/13/2019
Amendment (SD#6)(Labeling)	2/13/2019
Amendment (SD#4)	11/15/2018
Amendment (SD#2)	8/20/2018
Original submission (SD#1)	6/14/2018

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining:
None

List Number of Comparability Protocols (ANDA only): None

P.1 Description and Composition

Component/composition table

Materials	Function	Quality Standard	Amount per Unit Vial (30 mL)	% w/w
Epinephrine USP	Active ingredient	USP	(b) (4)	
Hydrochloric Acid NF	(b) (4) adjust pH	NF		
Sodium Chloride USP	(b) (4)	USP		
Chlorobutanol (b) (4) NF	Preservative	NF		
Sodium Metabisulfite NF	(b) (4)	NF		
Water for Injection, USP	(b) (4) (b) (4)	USP		

(b) (4)

Unit Dose Composition – Comparison between the Exhibit Batch Formulation and the Commercial Batch Formulation of Epinephrine Injection USP, 1 mg/mL, 30 mL MDV

Materials	Function	Quality Standard	Amount per mL	Exhibit Batch Formulati	Commercial Formulati
Epinephrine USP	Active ingredient	USP	(b) (4)	(b) (4)	
(b) (4) Hydrochloric Acid NF	(b) (4)	NF			
Sodium Chloride USP	(b) (4)	NF	9.0 mg		
Chlorobutanol (b) (4)	Preservative	USP	5.4 mg		
Sodium Metabisulfite NF	(b) (4)	NF	1.5 mg		
Water for Injection USP	(b) (4) (b) (4)	USP	(b) (4)		

(b) (4)

Reviewer's Assessment: ***{adequate}***
The proposed formulation is Q1/Q2 to RLD, Par Sterile Products, LLC's Adrenalin® (NDA 204640), original formulation approved on December 18, 2013 (see Filing

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Deficiency:
Please provide retest schedule for the components of your container/closure system.

P.8 Stability

For ANDAs – Most current drug product stability specification with date of update

(SD#11; 6/14/2019)

In line with USP 42 Monograph of the DP

In line with Micro Review #1 Recommendation for Endotoxin and Sterility

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(b) (4)

R Regional Information

Environmental

Reviewer's Assessment: *{Adequate }*
Applicant claimed categorical exclusion cited in 21 CFR 25.31(b).

Methods Verification Package

Reviewer's Assessment: *{Adequate }*

Comparability Protocols

Reviewer's Assessment: *{Adequate }*

None provided

Lifecycle Management Considerations

N/A

Drug Product: List of Deficiencies

None

Primary Drug Product Reviewer Name and Date: Raman Murali; 1/25/2019; 1/31/2019; 4/30/2019; 5/9/2019; 8/1/2019; 8/14/2019

Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019; CR#1: 5/13/2019; CR#2: 8/6/2019; CR#2A: 8/26/2019

LABELING

IQA Review Guide Reference

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No

For DRL, the applicant will be asked to include visual color and clarity in the DP specifications.

If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☒ No ☐ N/A If "No," explain. The firm will be asked to provide in use stability data to support stability of the DP up to 30 days after initial use per proposed PI.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None

List of Deficiencies:

None

Primary Drug Product Reviewer Name and Date: Raman Murali, 1/25/2019 ***Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019***

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – ANDA

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2A	Comments*
(b) (4)	Medium	(b) (4)	Low	Adequate PD information provided
	Medium		Low	Adequate
	Medium		Low	Adequate specification controls
	Medium		Low	Provided additional information
	Medium		Low	Provided additional information

Kai Kwok

Digitally signed by Kai Kwok
Date: 8/26/2019 01:44:57PM
GUID: 531543b00000571ac408640b9cf905cb

Raman Murali

Digitally signed by Raman Murali
Date: 8/26/2019 01:48:00PM
GUID: 508da701000286d1f02ed0090280bc19

Recommendation: Complete Response - Minor

A/NDA 211880
Review 01

Drug Name/Dosage Form	Epinephrine Injection USP
Strength	1 mg(base)/mL
Route of Administration	Intramuscular; subcutaneous
Rx/OTC Dispensed	Rx
Applicant	International Medication Systems, Limited 1886 Santa Anita Avenue South El Monte, CA 91733
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	*06/14/2018*	*All*
Resubmission after Refuse to Receive	*8/20/2018*	*All*
Amendment-Quality Response to Information Request	*11/15/2018*	*Process*
Amendment-Response to Labeling Discipline Review Letter	*2/13/2019*	*Labeling*
Amendment-Labeling Response to Information Request	*3/13/2019*	*Labeling*
Amendment-Quality Response to Information Request	*3/14/2019*	*DS, DP, Process, Micro*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Yichuan Xu	Yun (Jenny) Wang

Drug Product	Raman Murali	Kai Kwok
Process	Brian Rogers	Yong Hu
Microbiology	Julia Marre	Denise Miller
Facility	Rose Xu	Yong Hu
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Suzan Ghodasara	
Application Technical Lead	Raman Murali	
Laboratory (OTR)	N/A	N/A
ORA Lead	Michael Tollon	N/A
Environmental	Raman Murali	Kai Kwok

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Epinephrine USP	Inadequate	4/24/2019	Reviewed by Y.Xu
	Type III		(b) (4)	Adequate	1/18/2017	Reviewed by B. Stevens
	Type III			Adequate	8/29/2017	Reviewed by L.Qi
	Type IV			Adequate	11/14/2016	Reviewed by V. Amspacher

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 204640	Adrenalin® by Par Pharmaceuticals, 30 mL (MDV)
ANDA	ANDA 207568	Epinephrine Injection, USP, 1mg/1mL, 1 mL **Note:** RLD NDA 204200 - Adrenalin® by Par Pharmaceuticals, 1 mL) (SDV)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER

Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Abbreviated Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – **Minor**.

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Minor

Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis.

Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol.

Epinephrine is white or off-white crystalline substance. (b) (4)

The DMF (b) (4) for Epinephrine holder is (b) (4). The DMF review dated 4/24/2019 by Y. Xu is inadequate.

Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

No labeling issue was found.

B. Process: Adequate

The manufacturing process involves (b) (4)

(b) (4)

Process review is adequate.

C. Facility: Adequate

The manufacturing facilities for ANDA 211880 are found acceptable.

D. Biopharmaceutics:
N/A

E. Microbiology (if applicable): Adequate
Microbiology review is adequate.

List of Deficiencies for Complete Response

I. Drug Substance Deficiencies

1) DMF# (b) (4) for epinephrine has been reviewed and found inadequate. The DMF holder, (b) (4) was notified of the deficiencies on April 26, 2019. Please consult with your DMF holder, and provide the updated relevant drug substance sections. Do not respond to this ANDA CR letter until you have confirmed that the DMF holder has responded to the DMF CR letter cited above or your amendment will not be considered a complete response.

II. Drug Product Deficiencies

1) (b) (4)

2)

III. Environmental Deficiencies

1) None

IV. Labeling Deficiencies

1) None

V. Process Deficiencies

1) None

VI. Facilities Deficiencies

1) None

VII. Biopharmaceutics Deficiencies

1) None

VIII. Microbiology Deficiencies

1) None

IX. Other Deficiencies (specify discipline)

1) None

Application Technical Lead Name and Date: Raman Murali, Ph.D., 5/17/2019

Raman Murali

Digitally signed by Raman Murali
Date: 5/17/2019 03:12:21PM
GUID: 508da701000286d1f02ed0090280bc19

FACILITIES

IQA Review Guide Reference

Product Background:

Epinephrine Injection, USP, 1mg/1mL is used for emergency treatment of allergic reactions (Type I) including anaphylaxis and allergic reaction.

ANDA: ANDA 211880

Drug Product Name / Strength: Epinephrine Injection, USP, 1mg/1mL, 30 mL

Route of Administration: Injection

Applicant Name: International Medication Systems, Limited

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:

(b) (4) The firm is acceptable (b) (4) based on its compliance history and its manufacturing capability.

International Medication Systems, Limited (IMS) (FEI 2016148) (b) (4) The firm is acceptable based on the previous inspections and the manufacturing capability.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Original	8/20/2018
Quality Amendment SD 4	11/15/2018
Quality Amendment SD 9	3/14/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): N/A

3.2.S.2 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)			• Low	• Acceptable based on previous inspection history and manufacture capability

Reviewer's Assessment: ***Adequate***

(b) (4)

(b) (4)

3.2.P.3 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
International Medication Systems, Limited (IMS)	2016148	(b) (4)		• Acceptable based on previous inspection history and manufacture capability

Reviewer's Assessment: ***Adequate***

(b) (4)

Comparability Protocols: N/A

Lifecycle Management Considerations: N/A

List of Deficiencies: N/A

Primary Facilities Reviewer Name and Date: Rose Xu, 5/2/2019

Secondary Reviewer Name and Date: Yong Hu, Ph.D., 5/15/2019

Rose Xu

Digitally signed by Rose Xu
Date: 5/15/2019 09:31:18AM
GUID: 5277e72900088dc65127c01f0d78be60

Yong Hu

Digitally signed by Yong Hu
Date: 5/15/2019 09:46:34AM
GUID: 508da7220002a14416588a81227bc049

Quality Review Data Sheet

ANDA# 211880
Drug Product: Epinephrine Injection, USP, 1mg/1mL, 30 mL
Review # 1a

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Epinephrine USP	Inadequate	4/24/2019	Reviewed by Y.Xu
	Type III		(b) (4)	Adequate	1/18/2017	Reviewed by B. Stevens
	Type III			Adequate	8/29/2017	Reviewed by L.Qi
	Type IV			Adequate	11/14/2016	Reviewed by V. Amspacher

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 204640	Adrenalin® by Par Pharmaceuticals, 30 mL (MDV)
ANDA	ANDA 207568	Epinephrine Injection, USP, 1mg/1mL, 1 mL **Note:** RLD NDA 204200 - Adrenalin® by Par Pharmaceuticals, 1 mL) (SDV)

2. CONSULTS: N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				

Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Drug Product: List of Deficiencies

(b) (4)

Primary Drug Product Reviewer Name and Date: Raman Murali; 1/25/2019; 1/31/2019; 4/30/2019; 5/9/2019

Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019; CR#1: 5/13/2019

LABELING

IQA Review Guide Reference

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No

For DRL, the applicant will be asked to include visual color and clarity in the DP specifications.

If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☒ No ☐ N/A If "No," explain. The firm will be asked to provide in use stability data to support stability of the DP up to 30 days after initial use per proposed PI.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None

List of Deficiencies:

None

Primary Drug Product Reviewer Name and Date: Raman Murali, 1/25/2019 ***Secondary Reviewer Name and Date: Kai Kwok, 2/1/2019***

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – ANDA

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1a	Comments*
(b) (4)	Medium	(b) (4)	Low	Adequate PD information provided
	Medium		Medium	(b) (4)
	Medium		Low	Adequate specification controls
	Medium		Medium	Provided additional information
	Medium		Low	Provided additional information

Kai Kwok

Digitally signed by Kai Kwok
Date: 5/13/2019 11:16:13AM
GUID: 531543b00000571ac408640b9cf905cb

Raman Murali

Digitally signed by Raman Murali
Date: 5/13/2019 12:59:50PM
GUID: 508da701000286d1f02ed0090280bc19

PROCESS

Product Background:	**RLD NDA 204640 Adrenalin®**
ANDA:	**211880**
Drug Product Name / Strength:	**Epinephrine Injection USP / 1 mg (base)/mL**
Route of Administration:	**Injection**
Applicant Name:	**International Medication Systems, Limited**

Review Recommendation:	***Adequate from a process perspective***
Theme:	**N/A**
Justification:	***N/A***

Review Summary: Epinephrine is a white or almost white crystalline powder very slightly soluble in water and in alcohol. Epinephrine HCl is created (b) (4) and is very soluble in water.

The proposed drug product is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0. The proposed product is formulated (b) (4) The drug product is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis.

Submission Under Review:	**Amendment**	**SDN 8**	**03/14/2019**
Submissions Previously Reviewed	**Amendment**	**SDN 4**	**11/15/2018**
	Amendment	**SDN 2**	**08/20/2018**
	Original	**SDN 1**	**06/14/2018**

Highlight Key Outstanding Issues from Last Cycle: **NA**

Concise Description Outstanding Issues Remaining: No issues remain

List Number of Comparability Protocols: No comparability protocols related to drug product manufacturing were submitted.

P.3 Manufacture

Batch Formula

Table 32P32-1 Batch Compositions of the Proposed Drug Product, Epinephrine Injection USP, 1 mg/mL, 30 mL (CCD-5)

Product Strength	Epinephrine Injection USP, 1 mg/mL, 30 mL	
Batch Size	**Stability Lot Size:**	**Proposed Initial Commercial**
	(b) (4)	
	Amount per Batch	Amount per Batch
Active Ingredient		
Epinephrine USP*	(b) (4)	
Inactive Ingredients:		
Hydrochloric Acid NF*	(b) (4)	
	pH adjustment (b) (4)	pH adjustment (b) (4)
Sodium Chloride USP	(b) (4)	
Chlorobutanol (b) (4) NF		
Sodium Metabisulfite NF		
Water for Injection, USP		
(b) (4)		
(b) (4)		

(b) (4)

(b) (4)

List of Deficiencies Sent in 02/11/2019 DRL:

(b) (4)

(b) (4)

Review #1

Primary Process Reviewer Name and Date: ***Brian Rogers 01/31/2019***

Secondary Reviewer Name and Date: ***Yong Hu 02/01/2019***

Review #2

Primary Process Reviewer Name and Date: ***Brian Rogers 03/18/2019***

Secondary Reviewer Name and Date: ***Yong Hu 04/10/2019***

Brian Rogers

Digitally signed by Brian Rogers
Date: 4/11/2019 01:24:52PM
GUID: 508da7210002a054552cbf1a8fc2e128

Yong Hu

Digitally signed by Yong Hu
Date: 4/11/2019 02:58:28PM
GUID: 508da7220002a14416588a81227bc049

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-NAI

ANDA#: 211880

Drug Product: EPINEPHRINE INJECTION

DMF#: (b) (4)

DMF Subject (API name): EPINEPHRINE

1. Does the Type II API DMF list any manufacturing facilities, critical intermediate facilities, or testing facilities for routine release or stability testing that are not listed in the facility profile and/or on the 356h form for the referencing ANDA? ☐Yes ☒No

If yes, include the information identifying each facility and its function below:

Facility Name and Address	Function*	FEI/DUNS#

* CSN: Non-Sterile API by Chemical Synthesis
CSS: Sterile API by Chemical Synthesis
CSP: Chemical Sterilization
CTL: Control Testing Laboratories
CTB: Control Testing Laboratories "Also"
CTX: Control Testing Laboratories "Also" (Drugs)
CXA: Plant/Animal Extraction Purified API
CFN: Non –Sterile API by Fermentation
CFS: Sterile API by Fermentation

Note: *Add "-Critical Intermediate" to the appropriate manufacturing code if the site manufactures a critical intermediate.*

RBPM to include the following comment in the early-IR sent to the applicant:

"Please note that there are [manufacturing facilities] [manufacturing facility (critical intermediate)] [and/or] [testing facilities performing routine release or stability testing] that are included in DMF [DMF#] for [API name] that were not included on your form 356h. Please contact your DMF holder to resolve any discrepancies and clarify which DMF related facilities support your application. Please note that a revised 356h form will be required to add any new facilities to your application. The addition of a new facility or

new facilities may result in an extension of the performance goal date for your submission."

If a critical intermediate facility is identified, please select justification(s) from the following:

☐ The intermediate is only X number of steps prior to the final API and the risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.

☐ The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.

☐ The drug substance is very complex and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.

2. Does the DMF include any data (e.g. Ames study or cited literature studies) that requires a pharm/tox consult?
☐Yes ☒No

If yes, prepare the consult and send to DCR in Panorama and enter date sent below.

Consult form date:

3. After examining the labelling for the drug product:

Is a DCR consult required to establish the Maximum Daily Dose (MDD)? ☐Yes ☒No

Is a DCR consult required to establish the product use (i.e. duration and frequency of use, patient population)? ☐Yes ☒No

The following question applies to drug products indicated for the treatment of cancer.

Is a consult required to determine if the drug product is indicated for the treatment of advanced cancer in the context of ICH S9? ☐Yes ☒No

Is a DCR consult required to determine that the drug substance is carcinogenic? ☐Yes ☒No

If yes to any of the above prepare the appropriate consult and send to DCR in Panorama and enter date sent below.

Consult form date:

Benjamin Lim

Digitally signed by Benjamin Lim
Date: 9/10/2018 08:15:16PM
GUID: 508da7040002892a7c056659385f70e2

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-NAI

ANDA#: 211880

Drug Product: EPINEPHRINE INJECTION

DMF#: (b) (4)

DMF Subject (API name): EPINEPHRINE

1. Does the Type II API DMF list any manufacturing facilities, critical intermediate facilities, or testing facilities for routine release or stability testing that are not listed in the facility profile and/or on the 356h form for the referencing ANDA? ☐Yes ☒No

If yes, include the information identifying each facility and its function below:

Facility Name and Address	Function*	FEI/DUNS#

* CSN: Non-Sterile API by Chemical Synthesis
CSS: Sterile API by Chemical Synthesis
CSP: Chemical Sterilization
CTL: Control Testing Laboratories
CTB: Control Testing Laboratories "Also"
CTX: Control Testing Laboratories "Also" (Drugs)
CXA: Plant/Animal Extraction Purified API
CFN: Non –Sterile API by Fermentation
CFS: Sterile API by Fermentation

Note: *Add "-Critical Intermediate" to the appropriate manufacturing code if the site manufactures a critical intermediate.*

RBPM to include the following comment in the early-IR sent to the applicant:

"Please note that there are [manufacturing facilities] [manufacturing facility (critical intermediate)] [and/or] [testing facilities performing routine release or stability testing] that are included in DMF [DMF#] for [API name] that were not included on your form 356h. Please contact your DMF holder to resolve any discrepancies and clarify which DMF related facilities support your application. Please note that a revised 356h form will be required to add any new facilities to your application. The addition of a new facility or

new facilities may result in an extension of the performance goal date for your submission."

If a critical intermediate facility is identified, please select justification(s) from the following:

☐ The intermediate is only X number of steps prior to the final API and the risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.

☐ The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.

☐ The drug substance is very complex and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.

2. Does the DMF include any data (e.g. Ames study or cited literature studies) that requires a pharm/tox consult?
☐Yes ☒No

If yes, prepare the consult and send to DCR in Panorama and enter date sent below.

Consult form date:

3. After examining the labelling for the drug product:

Is a DCR consult required to establish the Maximum Daily Dose (MDD)? ☐Yes ☒No

Is a DCR consult required to establish the product use (i.e. duration and frequency of use, patient population)? ☐Yes ☒No

The following question applies to drug products indicated for the treatment of cancer.

Is a consult required to determine if the drug product is indicated for the treatment of advanced cancer in the context of ICH S9? ☐Yes ☒No

Is a DCR consult required to determine that the drug substance is carcinogenic? ☐Yes ☒No

If yes to any of the above prepare the appropriate consult and send to DCR in Panorama and enter date sent below.

Consult form date:

Benjamin Lim

Digitally signed by Benjamin Lim
Date: 6/26/2018 06:44:46PM
GUID: 508da7040002892a7c056659385f70e2

ANDA: 211880
Company: International Medication Systems, Ltd.
Drug Product: Epinephrine Injection USP, 1 mg/ ml(30 ml multi dose vial)
RLD: NDA 204640, Adrenalin (Epinephrine Injection), Par Pharmaceutical
Indication: Epinephrine Injection USP is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis
Risk Profile Performed By: Raman Murali, Ph.D.

PRODUCT PROPERTY/CQAS	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	COMMENTS
Chemical Stability (All CQAs)	4	3	3	36 Moderate	(b) (4)
Meeting USP <1> Requirement	3	4	3	36 Moderate	

Risk ranking criteria:

- Product properties or CQAs that fall under a RPN of 25 are considered as low risk.
- Product properties or CQAs at or above RPN 25 but below 60 are considered as moderate risk.
- Product properties or CQAs at or above an RPN 60 are considered as high risk.

(b) (5)

Following Table can be copied in the IQA Template under Risk Assessment Section:

Product Property/ CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Cycle #	Comments
Chemical Stability (All CQAs)	Low Low Low Low (b) (4)	(b) (4)		

	Low	(b) (4)		
	Low	(b) (4)		
	Moderate			
	Moderate			
	Low			
	Moderate			

		(b) (4)		
Meeting USP <1> Requirement	Moderate			
Reconstitution time (For Powder for Injections only)				

Risk ranking criteria:

- Product properties or CQAs that fall under a RPN of 25 are considered as low risk.
- Product properties or CQAs at or above RPN 25 but below 60 are considered as moderate risk.
- Product properties or CQAs at or above an RPN 60 are considered as high risk.

(b) (4)


(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211880

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	211880		
Drug Product Name	Epinephrine Injection USP		
Strength(s)	EQ 1 mg Base/mL (30 mL Fill)		
Applicant Name	International Medication Systems, Limited		
Applicant Address	1886 Santa Anita Avenue South El Monte, CA 91733		
Applicant's Telephone Number	(b) (6)		
Applicant's Fax Number	(626) 459-5592		
Original Submission Date(s)	08/20/2018 (Resubmission after RTR)		
Submission Date(s) of Amendment(s) Under Review	09/23/2019		
Primary Reviewer	Rukia Mchumo, Ph.D.		
Secondary Reviewer	Eunjung Park, Ph.D.		
Tertiary Reviewer	N/A		
First Generic	Yes		
Waiver/Deem Bioequivalent	**☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A**		
Formulation	**☒ Adequate ☐ Inadequate**		
Will Response to CR Result in a Reformulation?	**☐ Possibly ☐ No ☒ N/A**		
Deficiency Classification	**☐ Major** **☐ Minor/IR** **☒ N/A (Review is Adequate)**		
Major Deficiency Theme	**N/A**		
Justification for Major Designation	**N/A**		
Overall Review Result	**☒ Adequate ☐ Inadequate**		
Product Specific Guidance (PSG) Referenced in Review	**☐ Recommended/Latest Revision Date: _____** **RLD Number: _____** **☒ N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	**☐ YES ☒ NO**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**

1, 2, 15	**Waiver/Deem Bioequivalent**	**EQ 1 mg Base/mL (30 mL Fill)**	**☒ Adequate ☐ Inadequate**

1 EXECUTIVE SUMMARY

This is an amendment assessment for a waiver of in vivo bioequivalence (BE) testing of International Medication Systems Limited's test product, Epinephrine Injection USP, EQ 1 mg Base/mL (30 mL Fill), under Section 21 CFR § 320.22 (b) (1). The Reference Listed Drug (RLD) product is Par Sterile Products' ADRENALIN® (epinephrine) Injection (EQ 1 mg Base/mL (EQ 30 mg Base /30 mL), approved on Dec 18, 2013 under NDA 204640.

The BE assessment of the original submission (8/20/2018) was initially deemed adequate[1]. In the original submission, the applicant indicated that (b) (4) of hydrochloric acid (HCl) as a pH adjuster was used in the test formulation. In contrast, the RLD sponsor specifically stated (b) (4) of HCl was used in the RLD formulation. In the original BE assessment, the amount of HCl was not considered for Q1/Q2 assessment (see justification in the original BE assessment). (b) (4) Consequently, the waiver request could not be granted, and the BE assessment was deemed inadequate. Therefore, a Complete Response Letter (CRL)[6] was sent to the applicant to request for complete test formulation composition specifically actual amounts used for all excipients (b) (4)

In the current amendment, the applicant provided a revised test formulation composition table indicating the (b) (4) , which is (b) (4) allowable limit for Q1/Q2 sameness.

[1] GDRP, ANDA-211880-ORIG-1-RESUB-2, Bioequivalence Review, A211880N000DB-Review01-N08202018.pdf (http://panorama.fda.gov/task/view?ID=5b7ce05b0017ae910a1aadc137168026)

[2] (b) (4)

[3] (b) (4)

(http://panorama.fda.gov/task/view?ID=58e1e1a60002d058ac69f19b86163828)

[5] GDRP, ANDA-211880-ORIG-1-AMEND-11, Bioequivalence Review, A211880N000DB-Review01-Add08202018 (http://panorama.fda.gov/task/view?ID=5d09459f00162e1106b715d9a8330f1a)

[6] GDRP, ANDA-211880-ORIG-1-AMEND-11, Final Decision, A211880N000DPM-CompleteResonse02.docx (http://panorama.fda.gov/task/view?ID=5d09459f001630d80362be947c0dfe03)

Therefore, the proposed test product, Epinephrine Injection USP, EQ 1 mg Base/mL (30 mL Fill) is Q1/Q2 the same as the **original RLD product**, ADRENALIN® (epinephrine) Injection, (EQ 1 mg Base/mL (EQ 30 mg Base /30 mL); which is the basis of submission.

As discussed in the original assessment[1], the RLD was reformulated and the test product is not Q1/Q2 the same as the reformulated RLD due to the differences in the amounts of (b) (4) . However, the applicant requested a waiver under 21 CFR 314.99(b) for the Agency to waive the requirements found at 21 CFR 314.94(a)(9)(iii), which allows an applicant to seek approval of a parenteral product if it differs from the RLD only in preservative, buffer or antioxidant. The applicant also compared the test product and current RLD formulation and stated that the differences in the formulation do not affect the safety or efficacy of the proposed drug product (see details in original BE review). Additionally, an internal evaluation by the Agency concluded that the original RLD was not withdrawn for safety and efficacy reasons[7]. Therefore, per 21 CFR § 314.99 (b), the waiver of the requirements under 21 CFR §314.94(a)(9)(iii) can be waived for the current test product and the bio waiver can be evaluated based on the test product's Q1/Q2 sameness to the original RLD.

Based on the above information, DB grants the waiver of in vivo BE study requirements for the test product, Epinephrine Injection USP, EQ 1 mg Base/mL (30 mL Fill) pursuant to **21 CFR 320.24(b)(6)**.

The application is adequate with no deficiencies.

[7] DARRTS, FRM-ADMIN-01 (Memorandum to File), dated 1/30/2019 (https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804d7e1b&_afrRedirect=4698807132654926)

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3 SUBMISSION SUMMARY

3.1 Review of Current Submission

3.1.1 DB's Deficiency

We have potential concerns about the qualitative and quantitative (Q1/Q2) sameness of your product to the reference listed drug (RLD) with respect to inactive ingredients. Please provide an updated Components and Composition table for your test product listing the specific amount of each inactive ingredient added, including for those excipients, (b) (4) If the proposed amount of any ingredient in your formulation has a range, then it is recommended that you provide the proposed mean amount as well as upper and lower limits. In addition to the updated Components and Composition table, please provide information and documentation to indicate how you calculated the specific amounts of each inactive ingredient added to your formulation and how you determined the function of each excipient.

3.1.2 Applicant's Response:

As requested by the Agency, the following items:

- an updated Components and Composition table for test product listing each inactive ingredient,
- information and documentation to indicate how the specific amounts of each inactive ingredient is determined calculated, and
- how the function of each excipient is determined are responded and provided below:

(1) Components and Composition Table

Table 1 summarizes the updated Components and Composition tables for IMS Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials for the proposed Commercial Batch Size ((b) (4)), listing the specific amount of each inactive ingredient added, including for those excipients, which IMS (b) (4)

Table 1: Components and Composition of Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials – *Commercial Batch Size* ((b) (4))

Inactive Ingredients	Formulation		Specific Amount Added (g)
	RLD[a] (JHP Pharmaceuticals)	IMS Proposed Product	
Sodium Chloride	(b) (4)	9.0 mg/mL	(b) (4)
Sodium Metabisulfite		1.5 mg/mL	
Chlorobutanol[b]		5.4 mg/mL	
Hydrochloric acid	(to adjust pH)	(b) (4) (to adjust pH)	
Water for Injection (WFI)			

(b) (4)

(i) Hydrochloric Acid

As shown above, hydrochloric acid was added (b) (4) estimate based on expected quantity required to neutralize epinephrine base and adjust pH to range (b) (4) . Therefore, to target pH (b) (4) of (b) (4) HCl is needed. As recommended by the Agency, for commercial batch size, IMS proposed a mean amount of (b) (4) hydrochloric acid with (b) (4) and (b) (4) t of (b) (4) and (b) (4) respectively, to adjust pH to the range. It should be noted the RLD also adds hydrochloric acid *estimate based on expected quantity required to* (b) (4) *adjust pH to range*[8].

(ii) Water for Injection (WFI)

Additionally, WFI was added (b) (4)

(2) Information and documentation on specific amount of each inactive ingredient

As the Agency requested, please refer to **Table 1** for information and documentation on

[8] 1Center for Drug Evaluation and Research Application number: 204640Orig1s000 Clinical Pharmacology and Biopharmaceutics Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204640Orig1s000ClinPharmR.pdf

specific amount of each inactive ingredient calculation for Commercial Batch Size, including hydrochloric acid (b) (4)

Please note *Water for Injection* is (b) (4) satisfied with the IMS current (b) (4) procedure of Epinephrine Injection USP.

(3) Function of each excipient

There are five (5) excipients added in IMS proposed drug product formulation as follows:

- Sodium Chloride
- Sodium Metabisulfite
- Chlorobutanol
- Hydrochloric Acid
- Water for Injection

Details of how the function of each excipient was determined are described in **Table 2**:

Table 2: Determination of Excipient Functions

#	Excipient	Function	Determination of Function*
1	Sodium Chloride	(b) (4)	(b) (4)
2	Sodium Metabisulfite		
3	Chlorobutanol	preservative	
4	Hydrochloric Acid	pH adjustment	
5	Water for Injection	(b) (4)	

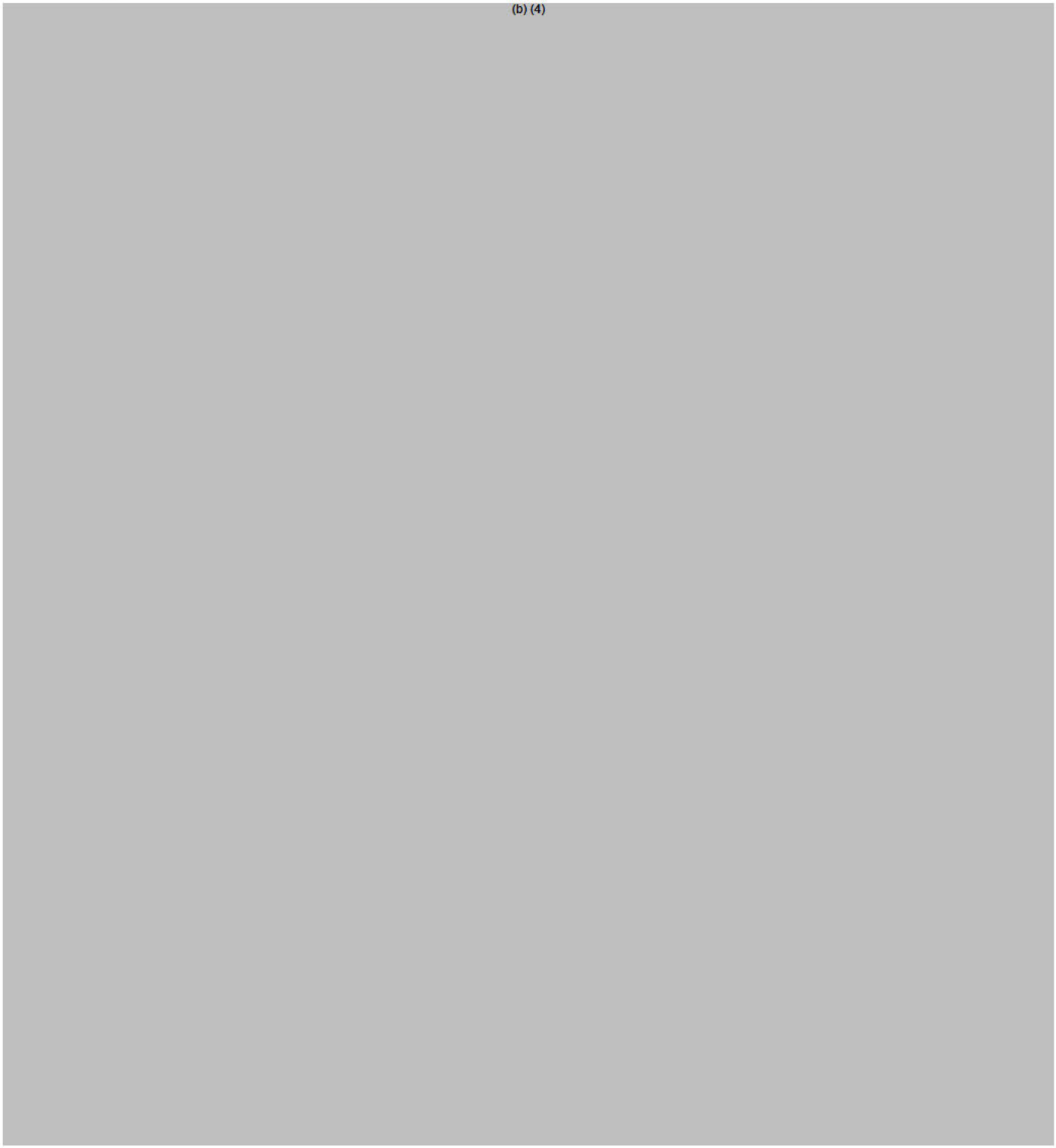
*Reference: ANDA 211880, Sequence 0001, Section 1.12.5 Request for Waiver of Formulation Sameness Requirements per 21 CFR 314.94(a)(9)(iii)

3.1.3 Assessor's Comments

Assessor calculated % HCl difference between Test and RLD Formulations

Original RLD Formulation[9], **(NOT TO BE RELEASED UNDER FOIA)**

(b) (4)




(b) (4)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	211880
APPLICANT:	International Medication Systems, Limited
DRUG PRODUCT:	Epinephrine Injection, EQ 1 mg Base/mL (30 mL Fill)

The Division of Bioequivalence has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Hongling Zhang, Ph.D.
Acting Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Outcome Page

Completed Assignment for 211880 ID: 40323

Reviewer: Mchumo, Rukia **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Epinephrine Injection, EQ 1 mg Base/mL (30 mL Fill)

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
40323	9/23/2019	BIO	ANDA Amendment [1]	1	1
40323	9/23/2019	Parallel	Waiver Injectable (Per application) [1]	1	1
				Total:	2

DIVISION OF BIOEQUIVALENCE ASSESSMENT

ADDENDUM

ANDA No.	211880
Drug Product Name	Epinephrine Injection USP
Strength(s)	EQ 1 mg Base/mL (30 mL Fill)
Applicant Name	International Medication Systems, Limited
Applicant Address	1886 Santa Anita Avenue South El Monte, CA 91733
Applicant's Telephone Number	(b) (4)
Applicant's Fax Number	(626) 459-5592
Original Submission Date(s)	06/14/2018
Submission Date(s) of Amendment(s) Under Review	08/20/2018 (Resubmission after RTR)
Primary Reviewer	Rukia Mchumo, Ph.D.
Secondary Reviewer	Xiaojian Jiang, Ph.D.
Tertiary Reviewer	N/A
First Generic	Yes
Waiver/Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**
Formulation	☐ **Adequate** ☒ **Inadequate**
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☒ **No** ☐ **N/A**
Deficiency Classification	☐ **Major** ☒ **Minor/IR** ☐ **N/A (Review is Adequate)**
Major Deficiency Theme	**N/A**
Justification for Major Designation	**N/A**
Overall Review Result	☐ **Adequate** ☒ **Inadequate**
Product Specific Guidance (PSG) Referenced in Review	☐ **Recommended/Latest Revision Date: _____** **RLD Number: _____** ☒ **N/A (no PSG available at time of review)**
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**

Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1, 2	Waiver/Deem Bioequivalent	EQ 1 mg Base/mL (30 mL Fill)	☐ Adequate ☒ Inadequate

1 EXECUTIVE SUMMARY

This is an addendum to the previous bioequivalence (BE) assessment[1] for International Medication Systems, Limited's test product, Epinephrine Injection USP, EQ 1 mg Base/mL (30 mL Fill). The applicant requested a waiver of in vivo bioequivalence (BE) testing for its test product under Section 21 CFR § 320.22 (b) (1). The Reference Listed Drug (RLD) product referenced in this application is Par Sterile Products' ADRENALIN® (epinephrine) Injection, (EQ 1 mg Base/mL (EQ 30 mg Base /30 mL), manufactured by Par Sterile Products LLC (N204640; approved on Dec 18, 2013). The purpose of this addendum is to change the previous BE outcome from Adequate to Inadequate. The letter to the applicant in this review supersedes the letter in the previous BE assessment.

Per 21 CFR 314.94(a)(9)(iii) and 21 CFR 314.127(a)(8)(ii)(B), a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration (i.e., be qualitatively (Q1) and quantitatively (Q2) the same) as the RLD. However, an applicant may seek approval of a parenteral product if it differs from the RLD in preservative, buffer, or antioxidant (exception excipients) provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

The RLD was reformulated and approved on December 23, 2015 for the revised formulation. In the original BE review, based on the information submitted, the test product was deemed Q1/Q2 the same as the original RLD, but not Q1/Q2 the same as the reformulated RLD. The test product differs from the reformulated RLD due to the amounts of (b) (4)

The applicant requested a waiver under 21 CFR 314.99(b), where the Agency can waive the requirements found at 21 CFR 314.94(a)(9)(iii), which allows an applicant to seek approval of a parenteral product if it differs from the RLD only in preservative, buffer or antioxidant. The applicant also compared the test product and current RLD formulation and stated that the differences in the formulation do not affect the safety or efficacy of the proposed drug product. On the other hand, the Agency through the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) conducted an internal evaluation on whether the original formulation of ADRENALIN® (epinephrine) Injection, (EQ 1 mg

[1] http://panorama.fda.gov/task/view?ID=5b7ce05b0017ae910a1aadc137168026

Base/mL (EQ 30 mg Base /30 mL) was withdrawn for safety and efficacy reasons. Per the DPARP assessment, the original RLD formulation was not withdrawn for safety and efficacy reasons, but to improve stability from (b) (4) to twenty-four months[2]. Therefore, per 21 CFR § 314.99 (b), the waiver of the requirements under 21 CFR §314.94(a)(9)(iii) can be waived for the current test product. Hence, the original assessment of the current ANDA was deemed adequate (See the original BE assessment for details)[1].

It is noted that for pH adjuster hydrochloric acid (HCl), the test formulation (b) (4)

Similar to (b) (4) and approved ANDA 207568[7] for the same product, in the original BE assessment of the current ANDA, the assessor considered the calculation of the difference in the amount of HCl between the test and RLD product not necessary for Q1/Q2 determination (please see detailed justification in the original BE assessment)[1].

(b) (4)

The Q1/Q2 assessment will be evaluated upon receipt of this information.

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[2] DARRTS, FRM-ADMIN-01 (Memorandum to File), dated 1/30/2019 (https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804d7e1b&_afrRedirect=4698807132654926)

(b) (4)

[7] GDRP, ANDA-207568-ORIG-1-AMEND-4, Bioequivalence Discipline Review, Bioequivalence Primary Review, A207568N000DB_NA06042015.doc ver 6, dated 9/2/2015 (http://panorama.fda.gov/task/view?ID=5575cc74006d951a73421a812ac182be)

Consequently, International Medication Systems, Limited's waiver of in vivo BE study requirements for the test product, Epinephrine Injection USP, EQ 1 mg Base/mL (30 mL Fill) **cannot** be granted at this time due to incomplete formulation information.

The application is **incomplete**.

2 APPENDIX

2.1 Formulation Data

2.1.1 Test Formulation

The proposed drug product, Epinephrine Injection, USP, is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

The proposed product is formulated with (b) (4) .

Table 32P12-1 Unit Dose Compositions (Per Unit and Per mL) of Epinephrine Injection USP, 1 mg/mL, 30 mL

Product Strength	Epinephrine Injection USP, 1 mg/mL, 30 mL	
API:	**Amount per mL**	**Amount Per Unit (30 mL Vial)**
Epinephrine USP*	(b) (4)	
Inactive Ingredients:		
Hydrochloric Acid NF	pH adjustment (b) (4)	pH adjustment (b) (4)
Sodium Chloride USP	9.0 mg	(b) (4)
Chlorobutanol (b) (4) NF	5.4 mg	
Sodium Metabisulfite NF	1.5 mg	
Water for Injection, USP	(b) (4)	
(b) (4)		(b) (4)
*Active ingredient	(b) (4)	

(b) (4)

Test Batch Record[8]

[8] GS Review, ANDA 211880, submission date: 6/14/2018. Module 3.2.P.3.3-MPR for Intended Commercial Batch (\\cdsesub1\evsprod\anda211880\0000\m3\32-body-data\32p-drug-prod\epinephrine-injection-usp\32p3-manuf\mpr-for-intended-commercial-batch.pdf)

[redacted] (b) (4)

2.1.2 Original RLD Composition

Adrenalin® (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 1 mL of solution in a single-use clear glass vial or 30 mL of solution in a multiple-dose amber glass vial.

In the 30 mL vial, each 1 mL of Adrenalin® solution contains 1 mg epinephrine, [redacted] (b) (4) sodium chloride, [redacted] (b) (4) sodium metabisulfite, [redacted] (b) (4), hydrochloric acid to adjust pH, [redacted] (b) (4) chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

The [redacted] (b) (4).

Original RLD Formulation[9], **(NOT TO BE RELEASED UNDER FOIA)**

[9] [redacted] (b) (4)

3 pages have been withheld as b4 (CCI/TS) immediately following this page

NOTES TO THE REGULATORY PROJECT MANAGER (RPM):
The deficiency letter in the current review SUPERSEDES the comments letter in the original bioequivalence (BE) review [GDRP: ANDA-211880-ORIG-1-RESUB-2, A211880N000DB-Review01-N08202018.docx, 5/21/2019.

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA:	211880
APPLICANT:	International Medication Systems, Limited
DRUG PRODUCT:	Epinephrine Injection, EQ 1 mg Base/mL (30 mL Fill)

The Division of Bioequivalence has completed its review and has identified the following deficiency:

We have potential concerns about the qualitative and quantitative (Q1/Q2) sameness of your product to the reference listed drug (RLD) with respect to inactive ingredients. Please provide an updated Components and Composition table for your test product listing the specific amount of each inactive ingredient added, including for those excipients, which (b) (4). If the proposed amount of any ingredient in your formulation has a range, then it is recommended that you provide the proposed mean amount as well as upper and lower limits. In addition to the updated Components and Composition table, please provide information and documentation to indicate how you calculated the specific amounts of each inactive ingredient added to your formulation and how you determined the function of each excipient.

Sincerely yours,

{See appended electronic signature page}

Hongling Zhang, Ph.D.
Acting Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

3 *Completed Assignment for 211880 ID: 39941*

Reviewer: Mchumo, Rukia **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Epinephrine Injection, EQ 1 mg Base/mL (30 mL Fill)

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
39941	8/20/2019	BIO	Addendum [1]	1	1
39941	8/20/2019	Parallel	Addendum (not for Clarification or Error Correction) [1]	1	1
				Total:	2

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	211880
Drug Product Name	Epinephrine Injection USP
Strength(s)	EQ 1 mg Base/mL (30 mL Fill)
Applicant Name	International Medication Systems, Limited
Applicant Address	1886 Santa Anita Avenue South El Monte, CA 91733
Applicant's Telephone Number	(b) (6)
Applicant's Fax Number	(626) 459-5592
Original Submission Date(s)	06/14/2018
Submission Date(s) of Amendment(s) Under Review	08/20/2018 (Resubmission after RTR)
Primary Reviewer	Rukia Mchumo, Ph.D.
Secondary Reviewer	Dongmei Lu, Ph.D.
Tertiary Reviewer	N/A
First Generic	Yes
Waiver/Deem Bioequivalent	☒ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☐ **N/A**
Formulation	☒ **Adequate** ☐ **Inadequate**
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**
Deficiency Classification	☐ **Major** ☐ **Minor/IR** ☒ **N/A (Review is Adequate)**
Major Deficiency Theme	**N/A**
Justification for Major Designation	**N/A**
Overall Review Result	☒ **Adequate** ☐ **Inadequate**
Product Specific Guidance (PSG) Referenced in Review	☐ **Recommended/Latest Revision Date: _____** **RLD Number: _____** ☒ **N/A (no PSG available at time of review)**
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**

Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**

1, 2	**Waiver/Deem Bioequivalent**	**EQ 1 mg Base/mL (30 mL Fill)**	**☒ Adequate ☐ Inadequate**

1 EXECUTIVE SUMMARY

International Medication Systems, Limited, requested a waiver of in vivo bioequivalence (BE) testing for its test product, Epinephrine Injection USP, EQ 1 mg Base/mL (30 mL Fill), under Section 21 CFR § 32.22(b)(1). The Reference Listed Drug (RLD) product referenced in this application is Par Sterile Products' ADRENALIN® (epinephrine) Injection, (EQ 1 mg Base/mL (EQ 30 mg Base /30 mL), manufactured by Par Sterile Products LLC (N204640; approved on Dec 18, 2013).

The proposed test product, Epinephrine Injection USP, 1 mg Base/mL (30 mL Fill) is an aqueous solution that is administered via intramuscular and subcutaneous injection routes. The route of administration and dosage form of the test product are same as that of the RLD product.

Per 21 CFR 314.94(a)(9)(iii) and 21 CFR 314.127(a)(8)(ii)(B), a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration (i.e., be qualitatively (Q1) and quantitatively (Q2) the same) as the RLD. However, an applicant may seek approval of a parenteral product if it differs from the RLD in preservative, buffer, or antioxidant (exception excipients) provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

The RLD was reformulated and approved on December 23, 2015 for the revised formulation. Based on the information submitted, the test product is Q1/Q2 the same as the original RLD, but not Q1/Q2 the same as the reformulated RLD. The test product differs from the reformulated RLD due to the amounts of (b) (4) .

The applicant has requested a waiver under 21 CFR 314.99(b) requesting that the Agency waive the requirements found at 21 CFR 314.94(a)(9)(iii) to permit approval of the proposed test product, which is Q1/Q2 different from the currently approved RLD. The applicant also compared the test product and current RLD formulation and indicated that the differences in the formulation do not affect the safety or efficacy of the proposed drug product (See reviewer's comments in section 4.1 for details)

The Agency through the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) conducted an internal evaluation on whether the original formulation of ADRENALIN® (epinephrine) Injection, (EQ 1 mg Base/mL (EQ 30 mg Base /30 mL) was withdrawn for safety and efficacy reasons. Per the DPARP review, the original RLD

formulation was not withdrawn for safety and efficacy reasons, but to improve stability from (b) (4) to twenty-four months[1].

Per 21 CFR § 314.99 (b), the waiver of the requirements under 21 CFR §314.94(a)(9)(iii) can be waived for the current test product.

Based on the information provided, the Division of Bioequivalence (DB) grants the waiver of in vivo BE study requirements for the test product, Epinephrine Injection USP, EQ 1 mg Base/mL (30 mL Fill) pursuant to 21 CFR 320.24(b)(6).

The application is adequate with no deficiencies.

[1]DARRTS, FRM-ADMIN-01 (Memorandum to File), dated 1/30/2019 (https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804d7e1b&_afrRedirect=46988 07132654926)

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strength(s)	Epinephrine Injection USP, EQ 1 mg Base/mL (30 mL Fill)*
Reference Standard (RS) and Strength(s)	ADRENALIN® (epinephrine) Injection, EQ 30MG BASE/30ML (EQ 1MG BASE/ML)
RS Holder; NDA/ANDA Number; Approval Date[2]	PAR STERILE PRODUCTS LLC; N204640; Dec 18, 2013
Reference Listed Drug (RLD) and Strength(s)	ADRENALIN® (epinephrine) Injection, EQ 30MG BASE/30ML (EQ 1MG BASE/ML)
RLD Holder; NDA/ANDA Number; Approval Date[3]	PAR STERILE PRODUCTS LLC; N204640; Dec 18, 2013

*For the rest of the review, the product strength will be referred to as 1mg/mL

Reviewer's Note: The RLD is also available in EQ 1 mg/mL single dose (NDA 204200). The applicant is requesting waiver only for the 1 mg/mL (30 mL Fill) multi-dose product. The difference between the single and multidose formulations of the RLD is the absence of the preservative (Chlorobutanol) in the single-dose configuration in the unit formula[4].

3.2 PK/PD Information[5,6]

Most recent RLD label (provide embedded document)	 204200Orig1s007,2 04640Orig1s008lbl.p
Indication	Adrenalin® is a non-selective alpha and beta adrenergic agonist indicated for: • Emergency treatment of allergic reactions (Type 1), including anaphylaxis
Boxed warning	N/A
Bioavailability	When administered parenterally, epinephrine has a rapid onset and short duration of action. (b) (4)

[2] Per Orange Book, search word: Adrenalin
[3] Per Orange Book, search word: Adrenalin
[4] GSR, submission date: 03/07/2012. Module 3.2.P.1. Description and Composition of the Drug Product (\\cdsesub1\evsprod\nda204200\0000\m3\32-body-data\32p-drug-prod\adrenalin-inj-all-strengths\32p1-desc-comp\desc-and-comp.pdf)
[5] RLD Label from Drugs@FDA, search word: Adrenalin. Action date: 08/09/2017-SUPPL-8
[6] http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=223&sec=monphar&t=0

	(b) (4)
Food Effect	
Tmax	
Metabolism	
Excretion	
Half-life	
Maximum Daily Dose	

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	N/A	
Summary of OGD or DB History	Approved ANDAs:	None for the 30 mL fill volume
	Pending ANDAs:	Only current application

	Controls:	Yes. CC 8398810[7] submitted by applicant as Amphastar Pharmaceuticals CC 10337274[8] CC 13070403[9] CC 1429438[10] Please see table below for details
	Protocols:	None

[7] GDRP, 8398810, Controlled Correspondence: Proposed Formulation for a Generic Adrenalin. Primary Review (http://panorama.fda.gov/task/view?ID=5756bbec002546f6b2e69d6338bbd042)
[8] GDRP, 10337274 (http://panorama.fda.gov/document/view?ID=5821ff660049b62676b5bfa8f7c400ef)
[9] GDRP, 13070403, Controlled Correspondence: Epinephrine Injection USP, 1 mg/mL (30 mg/30 mL) RLD N204640-Request for Formulation Guidance, OGD Review, C13070403DFR_RVW (http://panorama.fda.gov/task/view?ID=589c7721008cddbfe13b6102d8d29c76)
[10] GDRP, 14294384, Controlled Correspondence: Epinephrine Injection USP, 1 mg/mL (30 mg/30 mL) RLD N204640-Request for Formulation Guidance, Primary Review (http://panorama.fda.gov/task/view?ID=58ebb8e5000b5f5bad7146885e351a5d)

	Pending Citizen Petitions and other legal and regulatory issues:[11] If yes, please comment.	☒ Yes ☐ No Docket # FDA-2017-P-3352, which requests FDA to amend the sulfite warning requirement in 21 C.F.R. 201.22 for sulfite-containing epinephrine for injection for use in emergency situations, in order to remove misleading information and acknowledge the current availability of approved epinephrine products that do not contain sulfite. No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Filing or Labeling Internal S/E determination for epinephrine solution referencing NDA204640[12] No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead All disciplines can continue communications (CRL, IR/DRL); CC should contact Policy if related to CP

[11] http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx

Applicant's Controlled Correspondence History

CC #	Date Submitted	Request	RLD Comparison	Outcome
8398810	6/6/2016	Q1/Q2	New Formulation	Inadequate (Not Q2)
10337274	09/23/16	Q1/Q2	New Formulation	Inadequate (Not Q1/Q2)
13070403	2/8/2017	Q1/Q2	New and Original	Inadequate (New RLD) Adequate* (Original RLD)
14294384	4/7/2017	(b) (4)	New and Original	Adequate

*The CC reviewer also reconsidered and reevaluated the applicant's formulation in CC10337274 and determined that the formulation was Q1/Q2 the same to the original RLD formulation. The applicant was notified of this outcome along with the response to CC 13070403.

Reviewer's Note: The RLD formulation was updated (Submission date: 03/31/2015) and approved on December 23, 2015[13]. Therefore, the Q1/Q2 sameness of the applicant's test product in CCs was determined based on the current RLD composition.

Other Controlled Correspondence and Citizen Petitions

Ref #	CC/CP	Request	Outcome/Comment
11707726[14]*	CC	Request to confirm if it is acceptable to submit ANDA that references the original RLD (Adrenalin®) and not the reformulated RLD	Acceptable with applicant advised to resubmit ANDA citing 314.99 (b)
FDA-2017-1573*	CP	Pleases see details under reviewer's comments in section 4.1	

*The CC and CP reference Adrenalin, EQ 1 mg Base/mL (1 mL single dose product)

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--

[12] Policy Alert List as of 01/14/2019 (http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/OGDPAL/SitePages/Home.aspx)
[13] DARRTS, NDA 204640, 12/23/2015 COR-SNDAACTION-05 (Approval)
[14] GDRP, 11707726, Controlled Correspondence: epinephrine Injection 1 mg/mL RLD 204200-RLD Evaluation (http://panorama.fda.gov/task/view?ID=5845eded007f55d1ad7706d15eef05e7)

In vitro dissolution	No	--
Waiver requests	YES	1
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

3.5 Formulation

Location in appendix	Section 4.1
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	--

3.6 Waiver Request (s)

Strengths for which waivers are requested	1 mg/mL (30 mg/30 mL)
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**WAIVER GRANTED**
If not then why?	--

3.7 Comments for Other OGD Disciplines

Discipline	Comment
NA	None

4 APPENDIX

4.1 Formulation Data

4.1.1 Test Formulation

The proposed drug product, Epinephrine Injection, USP, is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial. In the 30 mL vial, each 1 mL of Epinephrine Injection, USP solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, 5.4 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

The proposed product is formulated with (b) (4) .

Table 32P12-1 Unit Dose Compositions (Per Unit and Per mL) of Epinephrine Injection USP, 1 mg/mL, 30 mL

Product Strength	Epinephrine Injection USP, 1 mg/mL, 30 mL	
API:	**Amount per mL**	**Amount Per Unit (30 mL Vial)**
Epinephrine USP*	(b) (4)	(b) (4)
Inactive Ingredients:		
Hydrochloric Acid NF	pH adjustment (b) (4)	pH adjustment (b) (4)
Sodium Chloride USP	9.0 mg	(b) (4)
Chlorobutanol (b) (4) NF	5.4 mg	(b) (4)
Sodium Metabisulfite NF	1.5 mg	(b) (4)
Water for Injection, USP	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
*Active ingredient	(b) (4)	

(b) (4)

4.1.2 RLD Composition

Adrenalin® (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple-dose amber glass vial.

In the 30 mL vial, each 1 mL of Adrenalin® solution contains 1 mg epinephrine, (b) (4) mg sodium chloride, (b) (4) mg sodium metabisulfite, (b) (4) hydrochloric acid to adjust pH, (b) (4) mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

(b) (4)

Current RLD Formulation[15] **(NOT TO BE RELEASED UNDER FOIA)**

(b) (4)

Original RLD Formulation[16] **(NOT TO BE RELEASED UNDER FOIA)**

[15] EDR, NDA 204640, submission date: 06/21/2017. Module 3.2.P.3.2. Batch Formula. Accessed 07/17/2018
[16] EDR, NDA 204640, submission date: 08/15/2013. Module 3.2.P.1 Description and Composition of the Drug Product. Accessed 07/17/2018

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(b) (4)

Reviewer's Comments

- The RLD, Adrenalin® (epinephrine)Injection is available in a 1 mL single—use (N204200) and 30 mL multi-use configurations (N204640). The applicant is only requesting a waiver of the 30 mL multi-dose configuration (RLD is N204640).
- The original RLD formulation was approved on Dec 18, 2013. However, the RLD sponsor updated its formulation, which was approved on December 23, 2015. The original and current RLD formulations are not the same, therefore a comparison of the test formulation was conducted with original and current formulations of the RLD, respectively.

(b) (4)

- The applicant requested a waiver request under 21 CFR § 32.22(b)(1) for the test product, Epinephrine Injection, EQ 1 mg Base/mL (30 mL Fill). The applicant also requested a 314.99(b) waiver request for requirements of 21 CFR 314.94(a)(9)(iii)[21].

Comparison of Test Formulation to Original RLD Formulation

- The amount of active ingredient (Epinephrine) in the test product is equivalent to that in the original reference product. Route of administration, dosage form and strength of the test product are also the same as those of the reference product.
- The RLD contains (b) (4) while the test product contains (b) (4) Based on the comparable assay results for test and RLD, and the USP Assay specification of (b) (4) % which is the same for the test product and RLD, the (b) (4) for the test product is acceptable.
- The applicant used Hydrochloric Acid (HCl) as the pH adjuster ((b) (4) (b) (4) The RLD sponsor uses (b) (4) HCl solution as pH adjuster. The reviewer considers the differences in amounts of HCL as pH adjuster is not necessary due to the following reasons:
    - The CMC review of the original RLD formulation was evaluated by not considering the actual amount of HCl used in the batch but (b) (4) the quantity ((b) (4) mg) was listed in the composition[22].
    - In response to the CR letter regarding the reformulated product for the 30 mL fill RLD, the sponsor provided a formulation comparison table between the current and original RLD, (b) (4) The CMC review was adequate, and formulation was recommended for approval.[23].

[21] GSR, ANDA 211880, submission date: 8/20/2018. Module 1.12.5 (\\cdsesub1\evsprod\anda211880\0001\m1\us\request-for-waiver-of-formulation-sameness.pdf)

[22] DARRTS, NDA 204640. Dated 12/11/2013-REV-QUALITY-21 (Primary Review). Accessed 07/19/2018

[23] DARRTS, NDA 204640. Dated 12/04/2015-REV-QUALITY-21 (Primary Review). Accessed 07/19/2018

Ingredient	Adrenalin® 1mL Vial (mg/mL)	Adrenalin® 30 mL Vial (mg/mL)	EpiPen® Auto-injector (mg/mL)
Epinephrine	1:1000	1:1000	(b) (4)
Sodium Metabisulfite	1	1.5	
Sodium Chloride	9	9	
Chlorobutanol	(b) (4)	5.4 (b) (4)	
Hydrochloric Acid			
Water for Injection			

Evaluation: Adequate

The composition of this drug product is similar to other currently approved epinephrine drug products. It is noted that 1 mL package has lower sodium metabisulfite than the 30 mL package. Also note that the Twinject Epinephrine product does contain (b) (4)

- The reviewer also checked previously reviewed ANDAs for the same product and noted that the BE review for a recently approved ANDA 207568[24] was deemed adequate without consideration of the difference in the amount of HCl for Q1/Q2 determination; the formulation composition in this ANDA listed HCl as (b) (4) [25]. Similarly, BE review of (b) (4) was deemed acceptable with amount of HCl listed (b) (4), and the amount of HCl was not considered for the Q1/Q2 determination[26].
- The RLD label lists the pH specification of 2.5-5.0, which is the same as the applicant's. The applicant's measured pH value for each of the three exhibit batches is 3.6, which is within the RLD specification. The applicant did not provide pH measurements from RLD characterization studies. However, based on the RLD sponsor, the pH results are 3.6, 3.5, and 3.5 for lot's 173138, 173141, and 173142, respectively[27], which are comparable to the test.

Comparison of Test Formulation to Current RLD Formulation

- As stated earlier in the review, the RLD sponsor reformulated its product and the test product **is not** Q1/Q2 the same as the reformulated RLD. The applicant submitted three different Controlled Correspondences (Please refer to section 3.3 for details) requesting Agency's confirmation on Q1/Q2 sameness of the test product to the RLD. In all three CCs, the applicant's formulation was deemed not Q1/Q2 when compared to the reformulated RLD and the applicant was advised that if an ANDA were to be submitted it would be refused for filing. However, in CC 13070403, the applicant specifically requested for Agency's advice regarding

[24] DARRTS, ANDA 207568, dated 07/06/2018, COR-ANDAACTION-02 (Full Approval).
[25] GDRP, ANDA-207568-ORIG-1-AMEND-4, Bioequivalence Discipline Review, Bioequivalence Primary Review, A207568N000DB_NA06042015.doc ver 6, dated 9/2/2015 (http://panorama.fda.gov/task/view?ID=5575cc74006d951a73421a812ac182be)
[26] (b) (4) (http://panorama.fda.gov/task/view?ID=58e1e1a60002d058ac69f19b86163828)
[27] GSR, NDA 204640, dated 08/15/2013. Module 3.2.P.5.4 Batch Analyses.

Q1/Q2 sameness of the test product in comparison to the original RLD formulation. Therefore, in response to the CC, the applicant's formulation submitted in previous CC 10337274 was reconsidered and the applicant was notified that the test formulation is Q1/Q2 the same as original RLD and that an ANDA application will likely be accepted for filing.

- The test product differs from the reformulated RLD due to the amounts of (b) (4) (refer to section 4.1.3). The applicant compared the test product and current RLD formulation and provided stability data of up to 6 months showing the pH of the formulation, which meets the current and original RLD's shelf life specification of 2.2-5.0. This indicates that the absence of (b) (4) in the test formulation did not affect the pH of the formulation. Additionally, the applicant also discussed the differences in the amounts of other exception excipients and concluded that they are within the FDA IIG database, and therefore do not affect the safety or efficacy of the test product.
- Based on the RLD sponsor, the pH of the current RLD formulation is approximately 4.0, which is slightly higher than the original RLD and the test product, but still within the shelf-life specification of 2.5-5.0.

Per 21 CFR § 314.122 (a), *"An abbreviated new drug application that refers to, or a petition under section 505(j)(2)(C) of the act and 314.93 that relies on, a listed drug that has been voluntarily withdrawn from sale in the United States must be accompanied by a petition seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons. The petition must be submitted under 10.25(a) and 10.30 of this chapter and must contain all evidence available to the petitioner concerning the reasons for the withdrawal from sale."* Per 21 CFR § 314.161 (a) (1), *"A determination whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons may be made by the agency at any time after the drug has been voluntarily withdrawn from sale, but must be made"*

The current applicant did not submit a request for safety and efficacy determination. However, the Division of Bioequivalence II (DB II), through the Office of Regulatory Policy (ORP) submitted a consult to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to request determination of whether the original formulation of the RLD, Adrenalin (epinephrine) Injection, 1 mg/mL (30 ml fill volume) was voluntarily withdrawn or withheld from sale for safety and effectiveness reasons. Per the DPARP reviewer[28], "*The original formulation of Adrenalin 30 mL (NDA 204640) was not reformulated for safety or effectiveness reasons. This product would be considered safe*

[28]DARRTS, NDA 204640, FRM-ADMIN-01 (Memorandum to File), dated 1/30/2019(https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804d7e1b&_afrRedirect=4698807132654926)

and effective if it were reintroduced to the market today." The reviewer further states "based on the clinical review, there are no safety concerns with the post marketing commitment for leachables. I also looked at the approval of supplement 2 where the formulation was changed to add tartaric acid (b) (4) *of this product. I do not believe this change was due to any safety issues of the old formulation but rather to extend the shelf life from* (b) (4) *to 24 months."*

Per 21 CFR § 314.99 (b), *"An applicant may ask FDA to waive under this section any requirement that applies to the applicant under 314.92 through 314.99. The applicant must comply with the requirements for a waiver under 314.90. If FDA grants the applicant's waiver request with respect to a requirement under 314.92 through 314.99, the waived requirement will not constitute a basis for refusal to approve an ANDA under 314.127"*.

Based on the above information, and as per 21 CFR § 314.99 (b), the waiver of the requirements under 21 CFR § 314.94(a)(9)(iii) is granted to the test product that is not Q1/Q2 the same as the reformulated RLD, but the same as the original RLD; which is the case for the current test product.

Therefore, the test product meets the criteria for waiver of in vivo BE study requirements and the waiver request is granted per 21 CFR 320.24(b)(6).

4.2 Consult Reviews

N/A

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	211880
APPLICANT:	International Medication Systems, Limited
DRUG PRODUCT:	Epinephrine Injection, EQ 1 mg Base/mL (30 mL Fill)

The Division of Bioequivalence has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies,or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Ethan Stier, Ph.D.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.3 Outcome Page

ANDA 211880

Reviewer:	Mchumo, Rukia	**Date Completed:**
Verifier:	,	**Date Verified:**
Division:	Division of Bioequivalence	
Description:	Epinephrine Injection, EQ 1 mg Base/mL (30 mL Fill)	

Items:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Score***	***Subtotal***
37827	8/20/2018	BIO	ANDA Original [1]	1	1
37827	8/20/2018	Parallel	Waiver Injectable (Per application) [1]	1	1
37827	8/20/2018	Parallel	Pre-Screening [0.25]	0.25	0.25
37827	8 20/2018	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
				Total:	3.25

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211880

MICROBIOLOGY REVIEW(s)

MICROBIOLOGY

Product Background: Epinephrine Injection USP, 1 mg/mL is a clear, colorless, sterile solution packaged as 30 mL of solution in a multiple-dose, amber, glass vial. This drug is indicated for emergency treatment of allergic reactions (type I), including anaphylaxis.

ANDA: 211-880

Drug Product Name / Strength: Epinephrine Injection USP; 1 mg/mL (30 mL-fill, multiple-dose solution)

Route of Administration: Intramuscular/subcutaneous

Applicant Name: International Medication Systems, Limited

Manufacturing Site:

International Medication Systems, Ltd. (an Amphastar Company)

(b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Review Summary: This drug product is (b) (4). The applicant has provided adequate information and studies (b) (4)

List Submissions Being Reviewed:

Submit	Received	Assigned to Reviewer
13 June 2018	14 June 2018	18 July 2018
17 August 2018	20 August 2018	04 September 2018
15 November 2018	15 November 2018	-
13 March 2019	13 March 2019	-

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks: The Agency refused to receive the original submission of ANDA 211880. The resubmission of ANDA 211880 only includes information responding to deficiencies the Agency described in the refuse to receive letter to the ANDA 211880 applicant dated 09 September 2018. Therefore, this microbiology review reviews documents from the original and resubmission ANDA 211880.
The process reviewer sent IRs to the applicant in the TCIR asking the applicant to provide tables of in-process tests and limits, hold times, and equipment used during manufacture. This microbiology review includes information from the applicant's response to the TCIR.

Concise Description Outstanding Issues Remaining: NA

Supporting Documents: NA

List Number of Comparability Protocols (ANDA only): NA

S Drug Substance:

(b) (4), a quality microbiology review is not needed.

Reviewer note: Epinephrine is sensitive to light. Specification for drug substance is NMT 357 EU/mg bacterial endotoxins, (b) (4)

P Drug Product

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The drug product is a sterile, clear/colorless solution in an amber glass vial with a (b) (4) flip off seal. The drug product is multiple-dose and is provided as 30 mL/vial (1 mg/mL Epinephrine solution).

- **Drug product composition –** The composition of the drug product is copied from submission *Section 3.2.P.1 Description of Composition of Drug Product:*

Table 32P12-1 Unit Dose Compositions (Per Unit and Per mL) of Epinephrine Injection USP, 1 mg/mL, 30 mL

Product Strength	Epinephrine Injection USP, 1 mg/mL, 30 mL	
API:	Amount per mL	Amount Per Unit (30 mL Vial)
Epinephrine USP*	(b)	(b) (4)
Inactive Ingredients:		
Hydrochloric Acid NF	(b) (4)	
	pH adjustment (b) (4)	
Sodium Chloride USP	9.0 mg	
Chlorobutano (b) (4) NF	5.4 mg	
Sodium Metabisulfite NF	1.5 mg	
Water for Injection, USP	3	
(b) (4)	(b) (4)	
	(b) (4)	

- **Description of container closure system** (b) (4)

(b) (4)

Reviewer's Assessment: ***Adequate***

The composition of the drug product and the container closure system were adequately described.

P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

Post-Approval Commitments: NA

List of Deficiencies: NA

Primary Microbiology Reviewer Name and Date: Julia Marré, PhD, Microbiologist, 03/15/2019

Secondary Reviewer Name and Date: Denise Miller, Sr. Microbiologist, 03/15/2019

Julia Marre

Digitally signed by Julia Marre
Date: 3/22/2019 03:03:02PM
GUID: 5ac654d90075eaa6b93887b3adda09f0

Denise Miller

Digitally signed by Denise Miller
Date: 3/25/2019 09:03:19AM
GUID: 508da7280002a5d546459b998253d1aa

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211880

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ANDA 211880

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

International Medication Systems, Limited
1886 Santa Anita Ave
South El Monte, CA 91733
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Madam:

This is in reference to your amendment received on January 27, 2020, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is April 26, 2020.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Parth Soni, Regulatory Project Manager, at (301) 796 - 7673.

Sincerely,

{See appended electronic signature page}

For Parth Soni
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Lakeeta Carr

Digitally signed by Lakeeta Carr
Date: 1/31/2020 09:17:11AM
GUID: 55c368af001e64633843f8960e43a933

ANDA 211880

COMPLETE RESPONSE

International Medication Systems, Limited
1886 Santa Anita Ave
South El Monte, CA 91733
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on August 20, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials.

We acknowledge receipt of the September 23, 2019 submission, which constituted a complete response to our September 13, 2019 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Substance

A revised USP monograph for Epinephrine became official on December 1, 2019. To comply with the revised USP monograph, please revise the drug substance specification, list of organic impurities and analytical methods, along with the method verification/equivalency studies, as appropriate. Please consult with the DMF holder, if necessary. To show compliance with the monograph, it is recommended to use/footnote the USP listed impurity names in the drug substance specification.

DRUG PRODUCT / PROCESS / MICROBIOLOGY / FACILITY INSPECTION / BIOEQUIVALENCE / LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the

compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure that your ANDA addresses all listed patents and exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

On December 20, 2019, Latham & Watkins LLP, on behalf of Par Sterile Products, LLC, submitted a citizen petition to FDA (Docket No. FDA-2019-P-6044) regarding Adrenalin approved under New Drug Applications (NDA) 204200 and 204640 and applications that reference Adrenalin as a reference listed drug (RLD). The issues raised by this petition are currently under review by the Agency, and FDA has not made a final decision on the issues the petition raises. The comments included in this communication reflect only our current thinking, and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petition.

The resubmission to this CR letter will be considered to represent a **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Parth Soni, PharmD, Regulatory Project Manager, Division of Project Management, at (301) 796-7673.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Mandy Kwong

Digitally signed by Mandy Kwong
Date: 1/23/2020 12:05:45PM
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ANDA 211880

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

International Medication Systems, Limited
1886 Santa Anita Avenue
South El Monte, CA 91733
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Madam:

This is in reference to an amendment to the Drug Master File (DMF) [redacted] (b) (4) received on October 25, 2019, which is referenced in your abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is January 24, 2020.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Parth Soni, PharmD, Regulatory Project Manager, at (301) 796-7673.

Sincerely,

{See appended electronic signature page}

Parth Soni, PharmD
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Parth Soni

Digitally signed by Parth Soni
Date: 11/04/2019 04:51:05PM
GUID: 5aa056d80038df3ddee2bdb6593c87c4

ANDA 211880

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

International Medication Systems, Limited
1886 Santa Anita Avenue
South El Monte, CA 91733
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Madam:

This is in reference to your amendment received on September 23, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is December 22, 2019.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Parth Soni, Regulatory Project Manager, at (301) 796-7673.

Sincerely,

{See appended electronic signature page}

Parth Soni, PharmD
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Parth Soni

Digitally signed by Parth Soni
Date: 9/24/2019 10:44:03AM
GUID: 5aa056d80038df3ddee2bdb6593c87c4

ANDA 211880

COMPLETE RESPONSE

International Medication Systems, Limited
1886 Santa Anita Avenue
South El Monte, CA 91733
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on August 20, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials.

We acknowledge receipt of the June 14, 2019 submission, which constituted a complete response to our May 30, 2019 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

BIOEQUIVALENCE

We have potential concerns about the qualitative and quantitative (Q1/Q2) sameness of your product to the reference listed drug (RLD) with respect to inactive ingredients. Please provide an updated Components and Composition table for your test product listing the specific amount of each inactive ingredient added, including for those excipients, which (b) (4). If the proposed amount of any ingredient in your formulation has a range, then it is recommended that you provide the proposed mean amount as well as upper and lower limits. In addition to the updated Components and Composition table, please provide information and documentation to indicate how you calculated the specific amounts of each inactive ingredient added to your formulation and how you determined the function of each excipient.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address:

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

DRUG SUBSTANCE / DRUG PRODUCT / PROCESS / MICROBIOLOGY / FACILITY INSPECTION / LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure that your ANDA addresses all listed patents and exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
BIOEQUIVALENCE

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial

response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Parth Soni, Regulatory Project Manager, Division of Project Management, at (301) 796-7673.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Mandy Kwong

Digitally signed by Mandy Kwong
Date: 9/13/2019 09:43:46AM
GUID: 529372550000cc96a0a98e57d06862e5

ANDA 211880

INFORMATION REQUEST

International Medication System Limited
1886 Santa Anita Avenue
South El Monte, CA 91733
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 20, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Epinephrine Injection USP, 1 mg (base)/mL.

We also refer to your June 14, 2019 submission, containing your response to our complete response letter.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than August 26, 2019, in order to continue our evaluation of your ANDA.

Comments and information requests:

A. Drug Product

1. A revised USP monograph for Epinephrine will become official on December 1, 2019. Please acknowledge that you will update the drug substance specification and analytical methods, along with their method verification/equivalency studies, as appropriate, to comply with the revised USP monograph once it becomes official.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Suzan Ghodasara, Regulatory Business Process Manager, at (301) 796 - 7164.

Sincerely,

{See appended electronic signature page}

Suzan Ghodasara
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Suzan Ghodasara

Digitally signed by Suzan Ghodasara
Date: 8/22/2019 02:53:50PM
GUID: 5a85f77e000ee9ee78ef5d8694ea04bb

ANDA 211880

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

International Medication System Limited
1886 Santa Anita Avenue
South El Monte, CA 91733
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Madam:

This is in reference to your amendment received on June 14, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. The GDUFA goal date for review of this priority minor amendment is September 13, 2019.

If you have any questions, contact Parth Soni, Regulatory Project Manager, at (301) 796-7673.

Sincerely,

{See appended electronic signature page}

Parth Soni, PharmD
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Parth Soni

Digitally signed by Parth Soni
Date: 6/19/2019 12:05:17PM
GUID: 5aa056d80038df3ddee2bdb6593c87c4

U.S. FOOD & DRUG ADMINISTRATION

ANDA 211880

COMPLETE RESPONSE

International Medication Systems, Limited
11570 6th Street
Rancho Cucamonga, CA 91730
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on August 20, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Substance

1. The Drug Master File (DMF) # (b) (4) for Epinephrine has been reviewed and found inadequate. The DMF holder, (b) (4), was notified of the deficiencies on April 26, 2019. Please consult with your DMF holder and provide the updated relevant drug substance sections. Do not respond to this ANDA CR letter until you have confirmed that the DMF holder has responded to the DMF CR letter cited above or your amendment will not be considered a complete response.

Drug Product

2. (b) (4)

3.

LABELING

1. CONTAINER LABEL

   To prevent cluttering of the PDP, decrease the size of the half star. To increase contrast, consider using a white background with black letters. In addition, (b) (4) for boxing the strength statement and for the half star. Please refer to the color scheme in your carton labeling.

2. CARTON LABELING

   We acknowledge your modifications on the net quantity statement. However, we recommend increasing the prominence of the expression of strength (e.g., boxing, highlighting, etc.).

3. PRESCRIBING INFORMATION

   a. We stated in our DRL letter dated January 30, 2019, and via an email correspondence on February 7, 2019, that the most current model labeling approved for your proposed drug product is not being used according to 21 CFR 314.94 (8)(iv). Refer to Drugs@FDA: FDA Approved Drug Products, NDA 204640/S-009 approved on January 29, 2019, and revise accordingly. Since the new indication "to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock" does not contain protected patents or exclusivities, please retain this information in your labeling.

   b. To be consistent with the RLD, please note that sections or subsections of labeling that are identified as containing recent major changes (RMC) must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text. We refer you to 21 CFR 201.57(d)(9). In addition, change the dates in the RMC to "01/2019". Please refer to the RLD.

   c. DOSAGE FORMS AND STRENGTHS: Include "glass" to read "…dose amber glass vial." to be consistent with the RLD and in the HOW SUPPLIED section.

   d. HOW SUPPLED/STORAGE AND HANDLING: Remove (b) (4).

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

PROCESS/MICROBIOLOGY/FACILITY INSPECTION/BIOEQUIVALENCE

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR320.24(a)), please continue to monitor for the availability of new and revised product specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/LABELING

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Lauren Moulder, Regulatory Project Manager, Division of Project Management, at (301) 796-0212.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 5/30/2019 10:31:56AM
GUID: 5277df670008860f7e1231f730a8684c

ANDA 211880

DISCIPLINE REVIEW LETTER

International Medication Systems, Limited
1886 Santa Anita Avenue
South El Monte, CA 91733

Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Ms. Sharp:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 20, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Epinephrine Injection USP, 30 mg/30 mL (1mg/mL) multiple-dose vials.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have concluded the Quality review of this ANDA and have identified the following initial deficiencies:

A. Drug substance

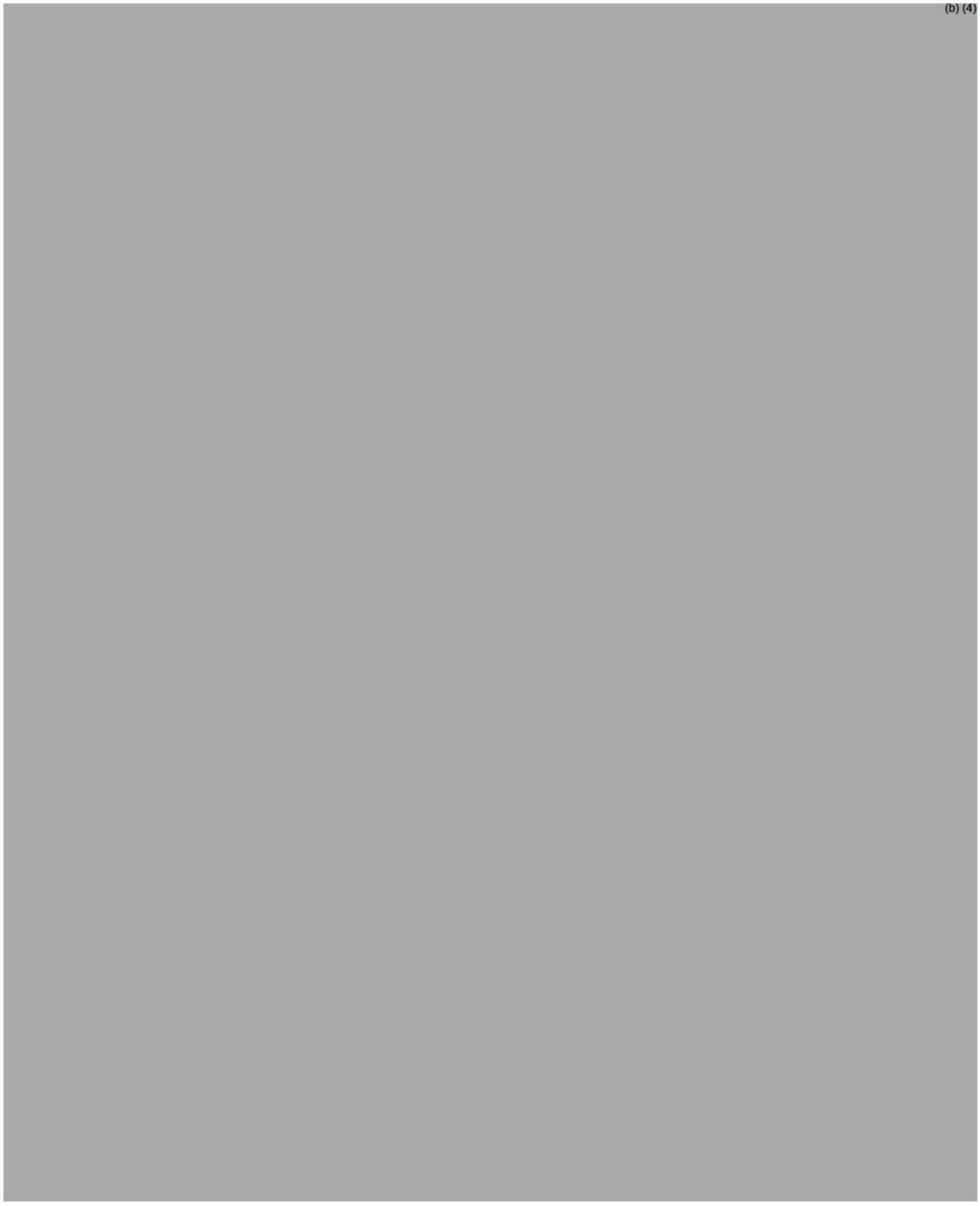
1. DMF# (b) (4) for epinephrine has been reviewed and found inadequate. The DMF holder, (b) (4) has been notified of any deficiencies. Please work with your DMF holder to resolve any issues with the DMF in a timely manner. Please be aware that the quality review of the ANDA cannot be fully completed until all DMF deficiencies are adequately resolved. Please consult with your DMF holder and provide the updated relevant drug substance sections (e.g., specification, method validation/verification) for further Agency evaluation.
2. (b) (4)

(b) (4)

B. Drug Product

(b) (4)

(b) (4)



U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

(b) (4)

C. Process

(b) (4)

D. Microbiology

(b) (4)

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(b) (4)

If you would like to respond to these initial deficiencies before the end of this review-cycle, we request a complete written response to this discipline review letter within 30 days. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
QUALITY

If you do not submit a complete written response within 30 days, these initial deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Suzan Ghodasara, Regulatory Business Process Manager, at suzan.ghodasara@fda.hhs.gov or (301) 796-7164.

Sincerely,

{See appended electronic signature page}

Suzan Ghodasara
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Suzan Ghodasara

Digitally signed by Suzan Ghodasara
Date: 2/11/2019 09:36:49AM
GUID: 5a85f77e000ee9ee78ef5d8694ea04bb

ANDA 211880

DISCIPLINE REVIEW LETTER
No Comments

International Medication Systems, Limited
11570 6th Street
Rancho Cucamonga, CA 91730
Attention: Gisela Sharp

Dear Gisela Sharp:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 20, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Epinephrine Injection USP, 30 mg/30 mL (1mg/mL) multiple-dose vials.

We have completed the bioequivalence review of this ANDA and have not identified any possible deficiencies at this time.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the GDUFA II Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Eva Chan, Bioequivalence Project Manager, at Eva.Chan@fda.hhs.gov or 240-402-9648.

Sincerely,

{See appended electronic signature page}

[1] The term "GDUFA II Commitment Letter" refers to the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Eva Chan, Pharm.D.
OFFICE OF BIOEQUIVALENCE
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Eva Chan

Digitally signed by Eva Chan
Date: 2/01/2019 12:58:32PM
GUID: 5501aef7000701abf42f6a9736a5c4cd

U.S. FOOD & DRUG ADMINISTRATION

ANDA 211880

DISCIPLINE REVIEW LETTER

International Medication Systems, Limited
1886 Santa Anita Avenue
South El Monte, CA 91733

Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Ms. Sharp:

This communication is in reference to your abbreviated new drug application (ANDA) dated June 14, 2018, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL), Multiple-Dose Vials.

We have completed the Labeling review of this ANDA and have the following preliminary thoughts on possible deficiencies:

LABELING DEFICIENCIES:

Labeling Deficiencies determined on November 20, 2018, based on your submission(s) received August 20, 2018 and June 14, 2018:

1. GENERAL COMMENTS
   a. The Orange Book has been updated with a new patent. Address patent number 10130592.
   b. Revise the alpha symbol, "α" throughout the labeling.

2. CONTAINER LABEL
   a. Relocate "Rx Only" from the side panel to the bottom main panel and the NDC number to the top of the main panel.
   b. Please change [redacted] (b) (4) to read "Usual Dosage".
   c. Revise "9.0 mg sodium chloride," to read "9 mg sodium chloride" (delete trailing "0"). For consistency, please revise in the PRESCRIBING INFORMATION as well.
   d. Add one of the qualifying statement on the labeling, ("Manufactured by ___", "Marketed by___", "Distributed by___"). Please refer to 21 CFR 201.1(h)(5).

e. Comment as to whether or not text appears on your cap/ferrule overseal. USP standard prohibits the use of certain statements on the cap/ferrule overseal. We refer you to the following address for additional information and guidance: https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

3. CARTON LABELING
   a. See container label comments.
   b. To align with the RLD, add on the primary display panels the recommended statement, "Discard 30 days after initial use: Discard after __/__/__".
   c. Add on the side panel above Dosage, "Note – Do not use the solution if it is colored or cloudy, or if it contains particulate matter."
   d. Please relocate the "Rx Only" statement to appear opposite of the NDC on the same line or at the bottom of the principal display panel. Please refer to the reference listed drug labeling. Please ensure that the NDC and Rx statement appear on the second and fourth panel.
   e. The expression of strength and established name should be the most prominent (e.g., bolding, boxing, highlighting, etc.). Decrease the prominence of the net quantity statement by deleting the color. Relocate closer to the bottom of the panel using black font.
   f. We recommend decreasing the size of the purple half star image to avoid interference with the other text on the panel.

4. PRESCRIBING INFORMATION
   a. We note that the most current model labeling approved for your proposed drug product is not being used according to 21 CFR 314.94 (8)(iv). Refer to Drugs@FDA: FDA Approved Drug Products, NDA 204640/S-008 approved on August 9, 2017, and revise accordingly.

   b. HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise the limitation statement and title to read as follows:

      HIGHLIGHTS OF PRESCRIBING INFORMATION
      These highlights do not include all the information needed to use EPINEPHRINE INJECTION, safely and effectively. See full prescribing information for EPINEPHRINE INJECTION.

      EPINEPRINE injection, for intramuscular and subcutaneous use
      Initial U.S. Approval: 1939

   c. FULL PRESCRIBING INFORMATION:

3 DOSAGE FORMS AND STRENGTHS should read: “Epinephrine Injection, USP 1 mg/mL, 30 mL solution in a multiple-dose amber glass vial.” Please revise.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review-cycle, we request a complete written response no later than February 13, 2019. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

If you do not submit a complete written response by February 13, 2019, these possible deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the GDUFA II Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your

[1] The term “GDUFA II Commitment Letter” refers to the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Juliette Larmie-Gyamfi, Labeling Project Manager, at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely,

Juliette N. Larmie-gyamfi -A

Digitally signed by Juliette N. Larmie-gyamfi -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001695466, cn=Juliette N. Larmie-gyamfi -A
Date: 2019.01.30 14:52:49 -05'00'

Juliette Larmie-Gyamfi, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 211880

INFORMATION REQUEST / TCIR

International Medication Systems, Limited
ATTENTION: Gisela Sharp
Senior Manager, Regulatory Affairs
11570 6th Street
Rancho Cucamonga, CA 91730

Dear Madam:

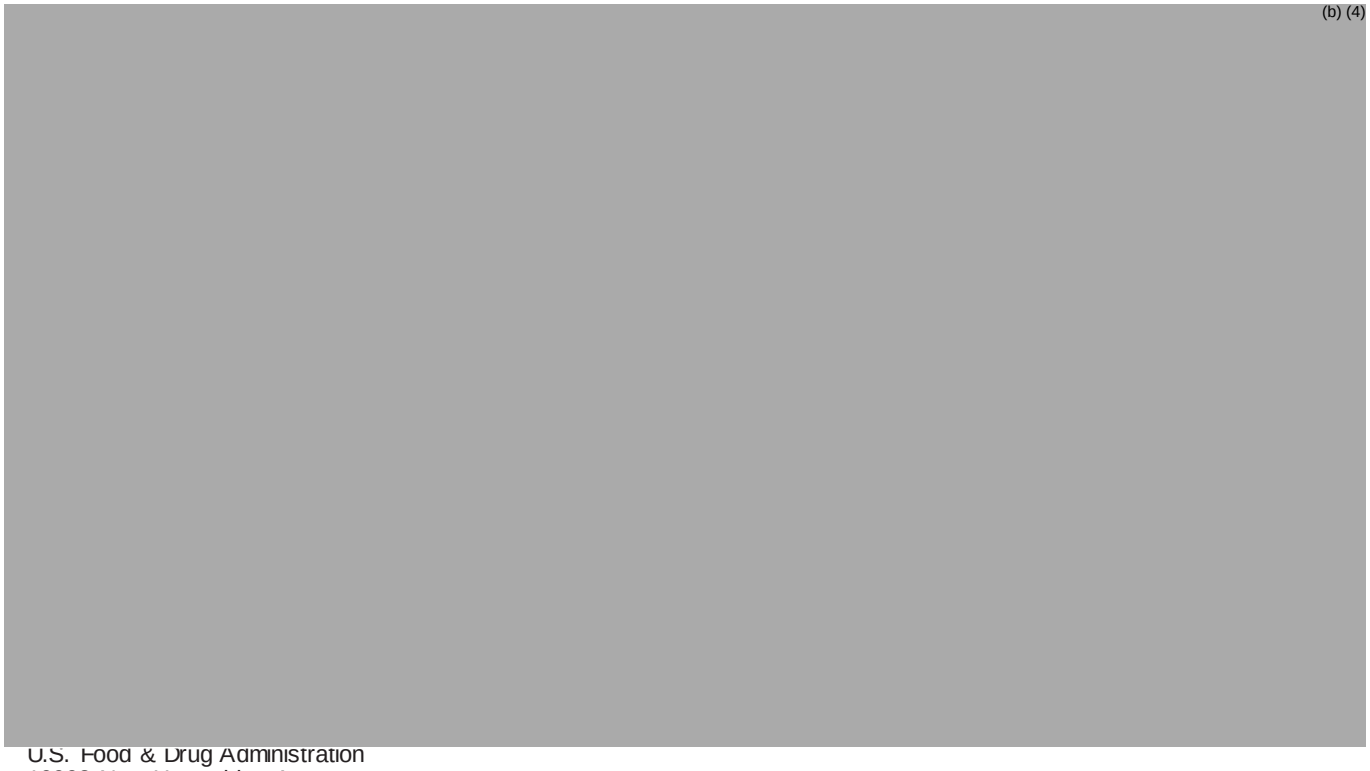
Please refer to your Abbreviated New Drug Application (ANDA) dated June 14, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection USP, 1 mg (base)/mL.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 30 days, in order to continue our evaluation of your ANDA.

Comments and information requests:

A. Process

(b) (4)



U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

(b) (4)

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Suzan Ghodasara, Regulatory Business Process Manager, at (301) 796-7164.

Sincerely,

{See appended electronic signature page}

Suzan Ghodasara
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Suzan Ghodasara

Digitally signed by Suzan Ghodasara
Date: 10/23/2018 10:45:17AM
GUID: 5a85f77e000ee9ee78ef5d8694ea04bb

U.S. FOOD & DRUG ADMINISTRATION

ANDA 211880

GRANT—
COMPETITIVE GENERIC THERAPY DESIGNATION

International Medication Systems, Limited
1886 Santa Anita Avenue
South El Monte, CA 91733
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) resubmitted on August 20, 2018, in response to a Refuse to Receive letter issued by the Agency on August 9, 2018, under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Epinephrine Injection USP, 30 mg/30 mL (1 mg/mL) multiple-dose vials.

We acknowledge that you have requested that the drug product under your ANDA be designated as a Competitive Generic Therapy (CGT) pursuant to section 506H(b) of the FD&C Act and that your request was made concurrently with the resubmission of ANDA 211880.

We have reviewed your request and have determined that the drug product under your ANDA meets the criteria for designation as a CGT pursuant to section 506H(b) of the FD&C Act. Therefore, we are granting your request to designate the drug product under your ANDA as a CGT. While the drug product under your ANDA qualifies for CGT designation under section 506H, we note that there are unexpired patents or exclusivities listed in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book) for the reference listed drug, Adrenalin, under new drug application (NDA) 204640 at the time of the resubmission of our ANDA. Therefore, pursuant to section 505(j)(5)(B)(v)(III)(aa) of the FD&C Act, your drug product is not eligible for CGT exclusivity under section 505(j)(5)(B)(v).

If you have concerns regarding the content of this letter, you should contact the Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov[1].

Sincerely,

Rinku Patel -S4

Digitally signed by Rinku Patel -S4
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rinku Patel -S4, 0.9.2342.19200300.100.1.1=2000401187
Date: 2018.10.19 14:52:37 -04'00'

For Martin Shimer, R.Ph.
Deputy Director
Division of Legal and Regulatory Support
Office of Generic Drug Policy
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

ANDA 211880

REFUSE-TO-RECEIVE

International Medication Systems Ltd
11570 6th Street
Rancho Cucamonga, CA 91730
Attention: Gisela Sharp

Dear Gisela Sharp:

This is in reference to your abbreviated new drug application (ANDA) dated June 13, 2018 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Epinephrine Injection USP, 30 mg/30 mL (1mg/mL) multiple-dose vials.

We refuse-to-receive this ANDA under 21 CFR 314.101 for the following reasons:

Major deficiencies:

1. You have failed to provide a drug product that is qualitatively and quantitatively the same as the reference listed drug (RLD). Pursuant to 21 CFR 314.94(a)(9)(iii), a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the RLD. However, an applicant may seek approval of a parenteral product if it differs from the RLD only in preservative, buffer, or antioxidant.

   We acknowledge that your drug product is qualitatively and quantitatively the same as the original reference listed drug (RLD). However, from the information provided in your cover letter and basis of submission statement, it does not appear that you wish to seek approval of a previously approved formulation of the RLD and for which the Agency has not made a determination that the formulation was not withdrawn for reasons of safety or effectiveness. Therefore, you must submit the following additional information in order for the ANDA to be sufficiently complete to permit a substantive review:

   - A request under 21 CFR 314.99(b) asking that the Agency waive the requirements found at 21 CFR 314.94(a)(9)(iii) to permit approval of your proposed formulation, which is qualitatively(Q1) and quantitatively(Q2) different from the currently approved RLD formulation.

   - Consistent with the requirements for a waiver under 21 CFR 314.90 and 21 CFR 314.99, you should also submit supporting documentation for the waiver request, including information that identifies and characterizes the differences in formulation between your proposed product and the currently approved formulation of the RLD, and which demonstrates that the differences do not affect the safety or efficacy of the proposed drug product.

2. The stability data provided in your submission is incomplete. (b) (4) [redacted]. However, in accordance with the guidances for industry on *ANDA Submissions – Refuse-to-Receive Standards* (December 2016, Rev. 2) and *ANDAs: Stability Testing of Drugs Substances and Products, Questions and Answers* (May 2014), if accelerated data show a significant change or failure of any attribute in one or more batches, an applicant should submit intermediate data for all three batches.

In addition, please address the following minor deficiencies:

1. In module 1.3.5, provide an exclusivity statement to indicate your marketing intentions.

2. In module 3.2.P.3.1, ensure the contact person address and phone number listed for your drug product manufacturer correlates with the information listed in FDA Form 356h.

3. In module 3.2.P.5.3, provide the Sample Statement of Availability and Identification for the drug product. Ensure to include the drug product name.

4. Documents submitted electronically should follow all published eCTD specifications and FDA guidances including those on the CDER eCTD web page, which is located at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm. There are documents within your submission that do not conform to the standards outlined in the specifications or guidance recommendations that affect the display and/or reviewability of the ANDA. The highlighted examples do not comprise an exhaustive list. It is incumbent upon the applicant to ensure that all documents conform to the listed standards, which includes utilizing the appropriate **operation attribute** in managing each individual file (e.g., not creating duplicate files) in a submission. **Any questions regarding the technical component of the electronic submission and preparing your corrective submission should be directed to CDER ESUB at esub@fda.hhs.gov.** The following issues regarding eCTD specifications and guidances were found:

    a. **There are issues where documents do not contain adequate, descriptive bookmarks and/or hypertext links.** A table of contents (TOC), hypertext links and bookmarks provide essential navigation through PDF documents. Include a hypertext linked TOC and bookmarks in documents 5 pages or longer. The document TOC helps the reviewer navigate to the information of interest within the document that is not provided in the submission table of contents. For documents with a table of contents, provide bookmarks and hypertext links for each item listed in the table of contents including tables, figures, publications, references, and associated appendices that are essential for navigation through documents. Make the bookmark hierarchy identical to the table of contents; up to four levels deep in the hierarchy. Furthermore, when creating bookmarks and hypertext links, choose the **magnification setting "Inherit Zoom"** so that the destination page displays at the same magnification level that the reviewer is using for the rest of the document. Hypertext links that open a file or document should be set to open the file or document in a **new window**. See the document

entitled *Portable Document Format (PDF) Specifications* (at pg. 5-6), located at, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf, and the technical specification document, *M2 eCTD: Electronic Common Technical Document Specification* (at pg. 7-4) located at: http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. **An example of such issue is:**

i. Module 1.14.3.1, "Annotated Side-by-Side Package Insert Comparison"

In response to this refuse-to-receive letter, you may either: 1) withdraw your ANDA under 21 CFR 314.99, 2) correct the deficiencies and resubmit the ANDA using the same ANDA number, or 3) take no action, in which case FDA may consider the ANDA withdrawn after one year. See 21 CFR 314.101(b)(3).

For more information, please refer to the guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards* (Rev. 2, December 2016) and the related refuse-to-receive guidances available on FDA's website at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.[1] In accordance with section 744B(a)(3)(D) of the FD&C Act, you are eligible to receive a refund of 75% of the filing fee for this application. To initiate the refund, please e-mail the Division of User Fee Management and Budget Formulation at CDERcollections@fda.hhs.gov with your Tax ID number (required for all domestic companies) or DUNS number (required for all foreign companies), and the address where the refund is to be sent. Please note that the Tax ID number or the DUNS number is required, and FDA cannot process a refund without it. If no refund is requested, FDA will process the refund in a timely manner as long as all required information is available.

Submission of a response to the refuse-to-receive letter will be subject to the same filing fee as a new ANDA, under section 744B(a)(3)(E) of the FD&C Act. We will not process and review a partial response. If you submit a partial response to this refuse-to-receive letter that does not address all deficiencies listed herein, we will refuse-to-receive any amended application at the time of the partial response.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you elect to correct the deficiencies and resubmit the ANDA and wish to discuss payment options, or have user fee payment inquiries, e-mail CDERcollections@fda.hhs.gov for assistance. If you have concerns regarding the content of this letter, you should contact the Division of Filing Review via e-mail at DFRsupervisor@fda.hhs.gov[2] within **seven** calendar days of the date of this letter and before you submit a response that addresses any deficiencies

noted in this correspondence. We also recommend that you sign up for Generic Drug e-mail updates,[3] which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

for Johnny Young, M.A.
Director
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[2] A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.
[3] http://go.fda.gov/subscriptionmanagement

Ilinca Duveau

Digitally signed by Ilinca Duveau
Date: 8/09/2018 09:51:46AM
GUID: 53b44d7d000131fd11df4744f93d2705