CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204640Orig1s002

Trade Name:	ADREALIN
Generic or Proper Name:	Epinephrine, EQ 30 MG Base/30 ML, solution
Sponsor:	PH Health
Approval Date:	December 23, 2015
Indication:	Emergency treatment of allergic reactions (Type I), including anaphylaxis Induction and maintenance of mydriasis during intraocular surgery

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204640Orig1s002

APPROVAL LETTER

NDA 204640/S-002

APPROVAL LETTER

Par Sterile Products, LLC
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Attention: Carla English
Manager, Regulatory Affairs

Dear Ms. English:

Please refer to your Supplemental New Drug Application (sNDA) dated March 31, 2015, received March 31, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adrenalin® (epinephrine injection, USP) 1 mg/mL, 30 mL vial.

We acknowledge receipt of your amendment dated September 3, 2015, which constituted a complete response to our July 31, 2015, action letter.

This prior approval supplemental new drug application proposes a change in formulation for the Adrenalin 30 mL vial presentation.

We have completed our review of this supplemental new drug application, as amended. This supplement is approved for use as recommended in the enclosed, agreed-upon labeling text.

We note that your December 10, 2015, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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 http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate-container labels submitted on September 3, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204640/S-002**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REPORTING REQUIREMENTS

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Lydia Gilbert-McClain, M.D.
Deputy Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Approved package insert, immediate container, and carton labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204640Orig1s002

LABELING

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

ADRENALIN (epinephrine injection) 1 mg/mL (1:1000)
1mL vial: for intramuscular, subcutaneous, and intraocular use
30 mL vial: for intramuscular and subcutaneous use
Initial U.S. Approval: 1939

----------INDICATIONS AND USAGE----------
Adrenalin® is a non-selective alpha and beta adrenergic agonist indicated for:
- Emergency treatment of allergic reactions (Type 1), including anaphylaxis (Adrenalin® 1 mL and 30 mL vials) (1.1)
- Induction and maintenance of mydriasis during intraocular surgery (Adrenalin® 1 mL vial only) (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Anaphylaxis (Adrenalin® 1 mL and 30 mL vials):
  - *Adults and Children 30 kg (66 lbs) or more*: 0.3 to 0.5 mg (0.3 to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2.1)
  - *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 (2.1)
- Intraocular surgery (Adrenalin® 1 mL vial only): Dilute 1 mL with 100 to 1000 mL of an ophthalmic irrigation fluid, for ophthalmic irrigation or intracameral injection (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 1 mg/mL (1:1000), 1 mL single-use vials and 30 mL multiple-dose vials (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Do not use 30 mL vial for ophthalmic indication (5.1)
- Undiluted ophthalmic administration: associated with corneal endothelial damage (5.2)
- Do not inject into buttocks, digits, hands, or feet (5.3)
- May aggravate angina pectoris or produce ventricular arrhythmias, particularly in patients with underlying heart disease, administer with caution when used intramuscularly or subcutaneously (5.4)
- Patients with hyperthyroidism, Parkinson's disease, diabetes, and pheochromocytoma are at greater risk of having adverse reactions when used intramuscularly or subcutaneously (5.4)
- Presence of sulfite in this product should not deter use for anaphylaxis (5.5)

----------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. Arrhythmias, including fatal ventricular fibrillation, rapid rises in blood pressure producing cerebral hemorrhage, and angina have occurred (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical, Inc. at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Sympathomimetic agents: possible additive effects (7)
- Cardiac glycosides, halogenated hydrocarbon anesthetics, or diuretics: observe for development of cardiac arrhythmias (7)
- Tricyclic antidepressants, MAO inhibitors, levothyroxine sodium, and certain antihistamines: potentiate effects of epinephrine (7)
- Beta-adrenergic blocking drugs: antagonize the cardiostimulating and bronchodilating effects of epinephrine (7)
- Alpha-adrenergic blocking drugs: antagonize the vasoconstricting and hypertensive effects of epinephrine (7)
- Ergot alkaloids may reverse the pressor response to epinephrine (7)

----------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)

See 17 for PATIENT COUNSELING INFORMATION

Revised: December 2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Adrenalin® is available as a single-use 1 mL vial and a multiple-use 30 mL vial. The 1 mL vial is for intramuscular, subcutaneous, and intraocular use. The 30 mL vial is for intramuscular and subcutaneous use only, and is NOT FOR OPHTHALMIC USE.

1.1 Anaphylaxis (Adrenalin® 1 mL single-use and 30 mL multiple-dose vials)

Emergency treatment of allergic reactions (Type I), including anaphylaxis, which may result from allergic reactions to insect stings, biting insects, foods, drugs, sera, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. The signs and symptoms associated with anaphylaxis include flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with hypotension, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, airway swelling, laryngospasm, bronchospasm, pruritus, urticaria or angioedema, swelling of the eyelids, lips, and tongue.

1.2 Induction and Maintenance of Mydriasis during Intraocular Surgery (Adrenalin® 1 mL single-use vial only)

Induction and maintenance of mydriasis during intraocular surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Anaphylaxis (Adrenalin® 1 mL single-use and 30 mL multiple-dose vials)

Inject Adrenalin® intramuscularly or subcutaneously into the anterolateral aspect of the thigh. 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 5/8 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, with repeat doses titrated to effect. Do not administer repeated injections at the same site, as the resulting vasoconstriction may cause tissue necrosis.

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

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL to 0.5 mL) of undiluted Adrenalin® 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 Adrenalin® 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.

2.2 Induction and Maintenance of Mydriasis during Intraocular Surgery (Adrenalin® 1 mL single-use vial only)

Adrenalin® must be diluted prior to intraocular use. Dilute 1 mL of Adrenalin® 1 mg/mL (1:1000) in 100 to 1000 mL of an ophthalmic irrigation fluid to create an epinephrine concentration of 1:100,000 to 1:1,000,000 (10 mcg/mL to 1 mcg/mL). Use the irrigating solution as needed for the surgical procedure.

After dilution in an ophthalmic irrigating fluid, Adrenalin® may also be injected intracamerally as a bolus dose of 0.1 mL at a dilution of 1:100,000 to 1:400,000 (10 mcg/mL to 2.5 mcg/mL).

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

Note: The Adrenalin® 30 mL multiple-dose vial is not for ophthalmic use. USE ONLY THE ADRENALIN 1 ML SINGLE-USE VIAL FOR OPHTHALMIC USE.

3 DOSAGE FORMS AND STRENGTHS

Adrenalin® 1 mg/mL (1:1000) epinephrine injection, 1 mL solution in a single-use clear glass vial and 30 mL solution in a multiple-dose amber glass vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Ophthalmic Injury from Adrenalin® 30 mL multiple-dose vial

The Adrenalin® 30 mL multiple-dose vial is not for ophthalmic use because it contains chlorobutanol which may be harmful to the corneal endothelium.

5.2 Injury with Undiluted Intraocular Solution

The Adrenalin® 1 mL single-use vial, while it does not contain chlorobutanol, **must** be diluted before intraocular use. Epinephrine containing sodium bisulfite has been associated with corneal endothelial damage when used in the eye at undiluted concentrations (1 mg/mL) [*see Dosage and Administration (2.2)*].

5.3 Incorrect Locations of Injection

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 due to possible differences in absorption associated with this use.

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 gas gangrene. Cleansing with alcohol does not kill bacterial spores, and therefore, does not lower this risk.

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 has been associated with tissue necrosis.

5.4 Disease Interactions

Some patients may be at greater risk for developing adverse reactions after systemic epinephrine administration. Despite these concerns, the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.

Patients with Heart Disease

Epinephrine should be administered with caution in patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, cerebrovascular disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. [*see Drug Interactions (7) and Adverse Reactions (6.1)*]

Other Patients and Diseases

Epinephrine should be administered with caution to patients with hyperthyroidism, Parkinson's disease, diabetes mellitus, pheochromocytoma, elderly individuals, and pregnant women. Patients with Parkinson's disease may experience psychomotor agitation or notice a temporary worsening of symptoms. Diabetic patients may experience transient increases in blood sugar.

5.5 Allergic Reactions Associated with Sulfite

Adrenalin® 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

6.1 Adverse Reactions Associated with Intramuscular/Subcutaneous Use (for Anaphylaxis)

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 (5.4)*].

Due to the lack of randomized, controlled clinical trials of epinephrine for the treatment of anaphylaxis, 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, and ventricular ectopy.

Angina may occur in patients with coronary artery disease [*see Warnings and Precautions (5.4)*].

Arrhythmias, including fatal ventricular fibrillation, have occurred, particularly in patients with underlying organic heart disease or patients receiving drugs that sensitize the heart to arrhythmias [*see Warnings and Precautions (5.4)*].

Rapid rises in blood pressure associated with epinephrine use have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see Warnings and Precautions (5.4)*].

Respiratory: respiratory difficulties.

Neurological: dizziness, disorientation, excitability, headache, impaired memory, lightheadedness, nervousness, panic, psychomotor agitation, sleepiness, tingling, tremor, and weakness.

Psychiatric: anxiety, apprehensiveness, restlessness.

Gastrointestinal: nausea, vomiting.

Other:

Patients with Parkinson's disease may experience psychomotor agitation or a temporary worsening of symptoms [*see Warnings and Precautions (5.4)*].

Diabetic patients may experience transient increases in blood sugar [*see Warnings and Precautions (5.4)*].

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area [*see Warnings and Precautions (5.3)*]. Adverse events experienced as a result of an injection into these areas include increased heart rate, local reactions including injection site pallor, coldness, hypoesthesia, and tissue loss, or injury at the injection site resulting in bruising, bleeding, discoloration, erythema, and skeletal injury.

Injection into the buttock has resulted in cases of gas gangrene [*see Warnings and Precautions (5.3)*].

Skin: sweating.

6.2 Adverse Reactions Associated with Intraocular Use (for Mydriasis)

Epinephrine containing sodium bisulfite has been associated with corneal endothelial damage when used in the eye at undiluted concentrations (1 mg/mL).

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical, Inc. at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

7 DRUG INTERACTIONS

Epinephrine should be administered cautiously to patients taking other sympathomimetic agents because of the possibility of additive effects.

Patients who are concomitantly receiving cardiac glycosides, digitalis, diuretics, quinidine, and other antiarrhythmics should be observed carefully for the development of cardiac arrhythmias [*see Warnings and Precautions (5.4) and Adverse Reactions (6.1)*].

Administer epinephrine cautiously to patients receiving halogenated hydrocarbon general anesthetics, such as halothane, as coadministration may result in arrhythmias.

The effects of epinephrine may be potentiated by tricyclic antidepressants such as imipramine, monoamine oxidase inhibitors (MAOI), levothyroxine sodium, and certain antihistamines, notably diphenhydramine, tripelannamine, and dexchlorpheniramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol.

The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs, such as phentolamine.

Ergot alkaloids may reverse the pressor effects of epinephrine.

Epinephrine should not be used to counteract circulatory collapse or hypotension caused by phenothiazines, as a reversal of the pressor effects of epinephrine may result in further lowering of blood pressure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (fetal anoxia, spontaneous abortion, or both). Epinephrine is teratogenic in rabbits, mice and hamsters dosed during organogenesis.

Epinephrine has been shown to have teratogenic effects (including gastroschisis and embryonic lethality) when administered subcutaneous in rabbits at approximately 15 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at a maternal subcutaneous dose of 1.2 mg/kg/day for two to three days).

In mice, teratogenic effects (including embryonic lethality) were observed at approximately 3 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at maternal subcutaneous dose of 1 mg/kg/day for 10 days). These effects were not seen in mice at approximately 2 times the maximum recommended daily intramuscular or subcutaneous dose (on a mg/m^2 basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

In hamsters, teratogenic effects were observed at approximately 2 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 mg/kg/day for 4 days).

8.2 Labor and Delivery

Use with caution during labor and delivery. Although epinephrine improves maternal hypotension associated with anaphylaxis, it may result in uterine vasoconstriction, decreased uterine blood flow, and fetal anoxia.

8.3 Nursing Mothers

It is not known whether epinephrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when epinephrine is administered to a nursing woman.

8.4 Pediatric Use

Clinical use data support weight-based dosing for treatment of anaphylaxis in pediatric patients, and other reported clinical experience with the use of epinephrine suggests that the adverse reactions seen in children are similar in nature and extent to those both expected and reported in adults.

The safety and effectiveness of epinephrine (at a dilution of 1:100,000 to 1:400,000) for induction and maintenance of mydriasis during intraocular surgery have been established in pediatric patients. Use of Adrenalin® for induction and maintenance of mydriasis during intraocular surgery in pediatric patients is supported by adequate and well controlled studies in adults and uncontrolled studies in pediatric patients.

8.5 Geriatric Use

Clinical studies for the treatment of anaphylaxis have not been performed in subjects aged 65 and over to determine whether they respond differently from younger subjects. However, other reported clinical experience with use of epinephrine for the treatment of anaphylaxis has identified that geriatric patients may be particularly sensitive to the effects of epinephrine. Therefore, for the treatment of anaphylaxis, consider starting with a lower dose to take into account potential concomitant disease or other drug therapy.

For induction and maintenance of mydriasis during intraocular surgery, no overall differences have been observed between elderly and other patients.

10 OVERDOSAGE

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients. Overdosage may also result in pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Treatment consists of a rapidly acting α-adrenergic blocking drug and respiratory support.

Epinephrine is rapidly inactivated in the body and treatment following overdose with epinephrine is primarily supportive. If necessary, pressor effects may be counteracted by rapidly acting vasodilators or α-adrenergic blocking drugs. If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug.

Epinephrine overdosage can also cause transient bradycardia followed by tachycardia and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be

followed by multifocal ventricular tachycardia (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug such as propranolol.

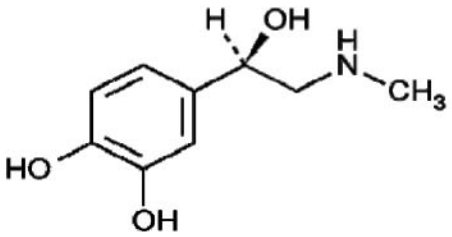
Overdosage sometimes results in extreme pallor and coldness of the skin, metabolic acidosis due to elevated blood lactic acid levels, and kidney failure. Suitable corrective measures must be taken in such situations.

11 DESCRIPTION

Adrenalin® (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL (1:1000) 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, 9.0 mg sodium chloride, 1.0 mg 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, 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.

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.

The chemical structure of epinephrine is:



The molecular weight of epinephrine is 183.2.

Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epinephrine acts on both alpha and beta-adrenergic receptors.

12.2 Pharmacodynamics

Through its action on alpha-adrenergic receptors, epinephrine lessens the vasodilation and increased vascular permeability that occurs during anaphylaxis, which can lead to loss of intravascular fluid volume and hypotension.

Through its action on beta-adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation and helps alleviate bronchospasm, wheezing and dyspnea that may occur during anaphylaxis.

Epinephrine also alleviates pruritus, urticaria, and angioedema and may relieve gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus and urinary bladder.

Epinephrine increases glycogenolysis, reduces glucose up take by tissues, and inhibits insulin release in the pancreas, resulting in hyperglycemia and increased blood lactic acid [*see Warnings and Precautions (5.4)*].

Epinephrine causes mydriasis when administered intraocularly or parenterally.

12.3 Pharmacokinetics

When administered parenterally or intraocularly, epinephrine has a rapid onset and short duration of action.

The extent of human systemic exposure at the labeled intraocular dose has not been evaluated, however, significant systemic concentrations or plasma exposure of epinephrine are not expected when administered intraocularly.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long- term studies to evaluate the carcinogenic potential of epinephrine have not been conducted.

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro*. Epinephrine was positive in the *Salmonella* bacterial reverse mutation assay, positive in the mouse lymphoma assay, and negative in the *in vivo* micronucleus assay. Epinephrine is an oxidative mutagen based on the *E. coli* WP2 Mutoxitest bacterial reverse mutation assay. This should not prevent the use of epinephrine under the conditions noted under *Indications and Usage (1).*

The potential for epinephrine to impair reproductive performance has not been evaluated, but epinephrine has been shown to decrease implantation in female rabbits dosed subcutaneously with 1.2 mg/kg/day (15-fold the highest human intramuscular or subcutaneous daily dose) during gestation days 3 to 9.

14 CLINICAL STUDIES

14.1 Induction and Maintenance of Mydriasis during Intraocular Surgery

In randomized, controlled studies, patients undergoing routine cataract extraction were evaluated after receiving intraocular irrigation with or without epinephrine diluted up to 1:1,666,666 (0.6 mcg/mL). Patients have also been evaluated after receiving bolus intracameral injections of epinephrine diluted between 1:25,000 (40 mcg/mL) and 1:400,000 (2.5 mcg/mL).

In patients with similar pupil diameters at baseline, with or without the use of preoperative mydriatic agents, mydriasis was maintained better in the eyes receiving epinephrine by an average of one to two millimeters in pupil diameter. Pupil constriction to 5mm or less occurred more often in the patients not receiving epinephrine.

Mean pulse rate and blood pressure showed no significant difference between patients receiving epinephrine and controls and there was no increased incidence of ventricular dysrhythmias in patients receiving epinephrine.

16 HOW SUPPLIED/STORAGE AND HANDLING

Adrenalin® 1 mL Single-Use Vials:

Each carton contains 25 single-use vials containing 1 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL (1:1000) in a 3 mL clear glass vial.

NDC 42023-159-25 1 mL vial

Adrenalin® 30 mL Multi-Dose Vials:

Each carton contains either 1 multiple-dose vial or 10 multiple-dose vials containing 30 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL (1:1000) in a 36 mL amber glass vial.

NDC 42023-168-01 30 mL vial, pack of 1

NDC 42023-168-10 30 mL vial, pack of 10

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.

17 PATIENT COUNSELING INFORMATION

Advise patients or their caregivers about common adverse reactions associated with the use of epinephrine including an increase in heart rate, the sensation of a more forceful heartbeat, palpitations, sweating, nausea and vomiting, difficulty breathing, pallor, dizziness, weakness or shakiness, headache, apprehension, nervousness, or anxiety. These symptoms and signs usually subside rapidly, especially with rest, quiet and recumbent positioning.

Warn patients with a good response to initial treatment about the possibility of recurrence of symptoms and instruct patients to obtain proper medical attention if symptoms return.

Warn patients with diabetes that they may develop increased blood glucose levels following epinephrine administration.

Distributed by:
Par Pharmaceutical Companies, Inc.
Chestnut Ridge, NY 10977

Adrenalin® is a registered trademark of Par Sterile Products, LLC (Chestnut Ridge, NY).
Registered Trademark No 53,934

R12/15 OS159J-01-90-02
3003592B

NDC 42023-168-01

Adrenalin®
(epinephrine injection, USP)

1 mg/mL
(30 mg/30 mL)
1:1000

For Intramuscular or Subcutaneous Use

Not for Ophthalmic Use

30 mL Multiple Dose Vial

Each mL contains 1 mg Adrenalin
ephrine) dissolved in Water for
tion, USP with sodium chloride,
m hydroxide, tartaric acid, disodium
ta, 0.5% Chlorobutanol as a
rvative and not more than 0.05%
m bisulfite as an antioxidant.

Rx Only

ge*
ful prescribing information.
between 2°F to 25°C (68° to 77°F).
USP Controlled Room Temperature)
ct from light and freezing.
rd 30 days after initial use:
d on_____

ibuted by:
Par Pharmaceutical Cos., Inc.
Chestnut Ridge, NY 10977

ICP/15 LA1 681-52-90-01

(01)00342023168016

3003591

LOT
EXP

NDC 42023-168-10

Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000

For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
30 mL Multiple Dose Vial

Rx Only

Each mL contains 1 mg Adrenalin (epinephrine) dissolved in Water for Injection, USP with sodium chloride, sodium hydroxide, tartaric acid, disodium edetate, 0.5% Chlorobutanol as a preservative and not more than 0.05% sodium bisulfite as an antioxidant.

...ge:
...ull prescribing information.

... between 20° to 25°C (68° to 77°F).
...USP Controlled Room Temperature)
...ct from light and freezing.

...rd 30 days after initial use:

...rd on_____

...ibuted by:
...Pharmaceutical Cos., Inc.
Chestnut Ridge, NY 10977

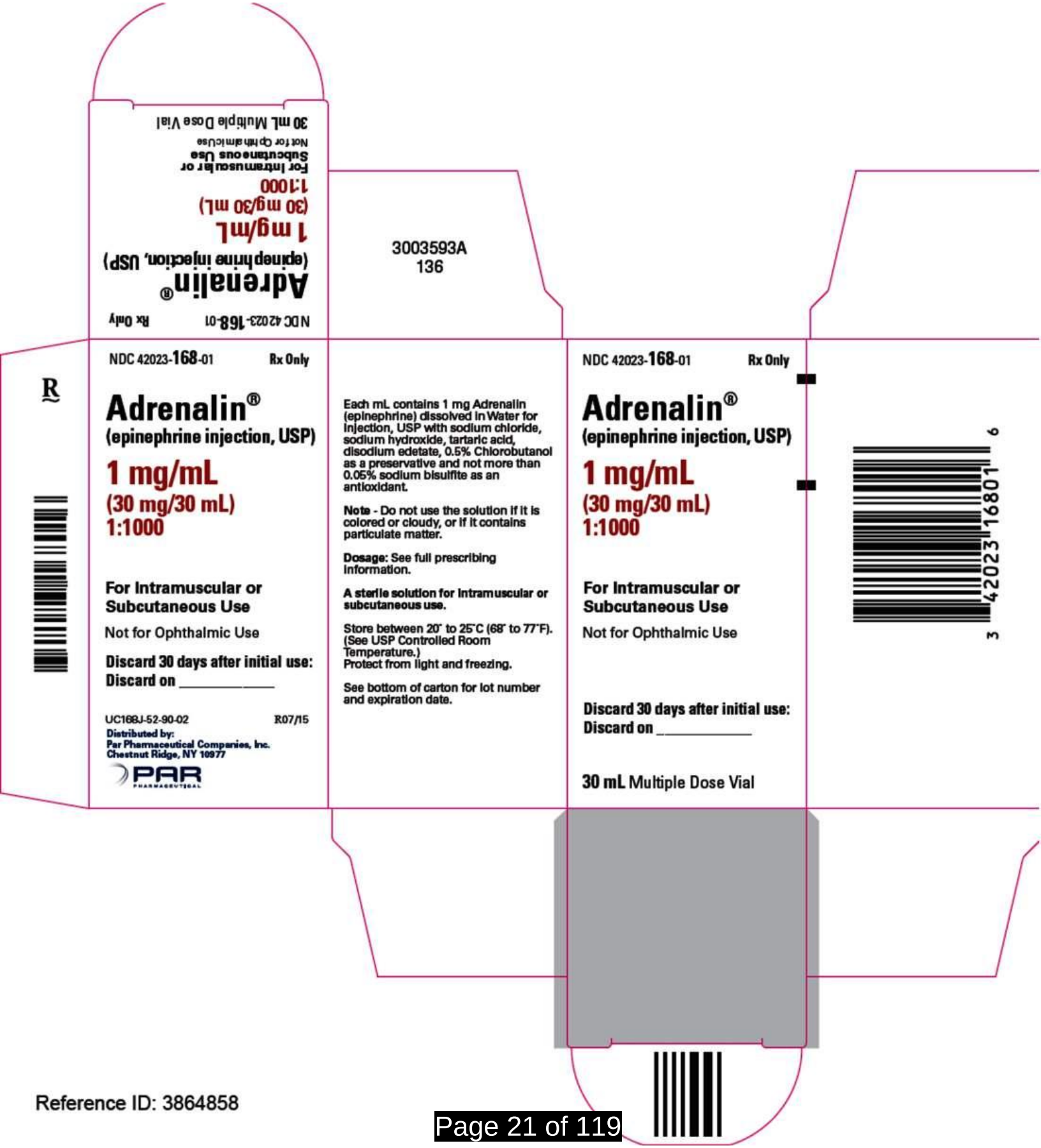
107/15

LA168J-10-90-01

(01)00342023168108

3003589

LOT
EXP



NDC 42023-168-01 Rx Only

Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000
For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
30 mL Multiple Dose Vial

3003593A
136

NDC 42023-168-01 Rx Only

Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000
For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
Discard 30 days after initial use:
Discard on _____
UC168J-52-90-02 R07/15
Distributed by:
Par Pharmaceutical Companies, Inc.
Chestnut Ridge, NY 10977
PAR PHARMACEUTICAL

Each mL contains 1 mg Adrenalin (epinephrine) dissolved in Water for Injection, USP with sodium chloride, sodium hydroxide, tartaric acid, disodium edetate, 0.5% Chlorobutanol as a preservative and not more than 0.05% sodium bisulfite as an antioxidant.

Note - Do not use the solution if it is colored or cloudy, or if it contains particulate matter.

Dosage: See full prescribing information.

A sterile solution for intramuscular or subcutaneous use.

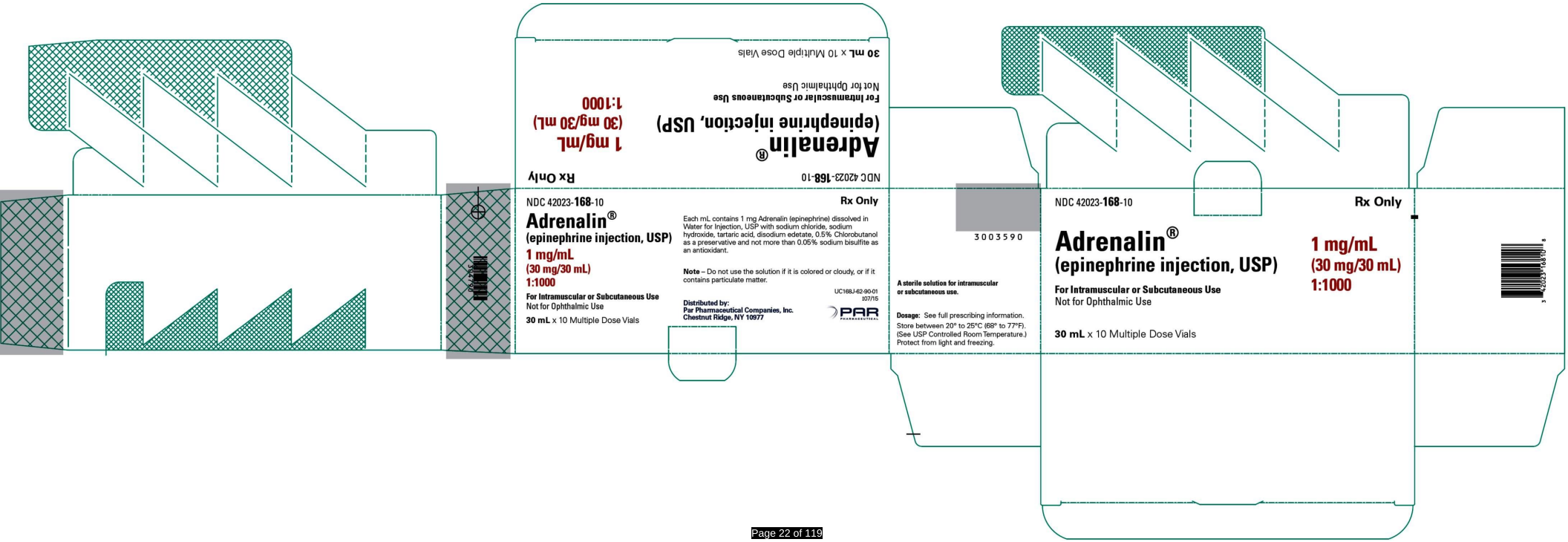
Store between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)
Protect from light and freezing.

See bottom of carton for lot number and expiration date.

NDC 42023-168-01 Rx Only

Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000
For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
Discard 30 days after initial use:
Discard on _____
30 mL Multiple Dose Vial

3 42023 16801 6


NDC 42023-168-10
Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000
For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
30 mL x 10 Multiple Dose Vials
Rx Only
Each mL contains 1 mg Adrenalin (epinephrine) dissolved in Water for Injection, USP with sodium chloride, sodium hydroxide, tartaric acid, disodium edetate, 0.5% Chlorobutanol as a preservative and not more than 0.05% sodium bisulfite as an antioxidant.
Note – Do not use the solution if it is colored or cloudy, or if it contains particulate matter.
UC168J-62-90-01
107/15
Distributed by:
Par Pharmaceutical Companies, Inc.
Chestnut Ridge, NY 10977
PAR PHARMACEUTICAL
3003590
A sterile solution for intramuscular or subcutaneous use.
Dosage: See full prescribing information.
Store between 20° to 25°C (68° to 77°F).
(See USP Controlled Room Temperature.)
Protect from light and freezing.
NDC 42023-168-10
Rx Only
Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000
For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
30 mL x 10 Multiple Dose Vials

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/s/

LYDIA I GILBERT MCCLAIN
12/23/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204640Orig1s002

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

APPLICATION:	NDA 204640, S-002	**TRADE NAME:**	Adrenalin®
APPLICANT/SPONSOR:	PAR Sterile Products	**USAN NAME:**	Epinephrine injection, USP 1 mg/mL, 30 mL vial
MEDICAL OFFICER:	Peter Starke, MD	**CATEGORY:**	Alpha and beta adrenergic
TEAM LEADER:	Janet Maynard, MD		
DATE:	July 10, 2015	**ROUTE:**	Subcutaneous or Intramuscular

SUBMISSIONS REVIEWED IN THIS DOCUMENT / OTHER RELEVANT DOCUMENTS

Document Date	CDER Stamp Date	Submission	Comments
March 31, 2015	March 31, 2015	S-002	CMC supplement

REVIEW SUMMARY:

This is a prior approval CMC supplement submitted by PAR Sterile Products to change (b) (4) the formulation of Adrenalin (epinephrine injection, USP) 1 mg/mL (1:1000), 30 mL vials. There are no changes proposed for the 1 mL vial presentation (NDA 204200). Changes to the formulation for the 30 mL vial presentation include (b) (4) . With these changes, PAR proposes to (b) (4) At the same time, PAR has also proposed some editorial changes and corrections to the PI, all of which are acceptable from a clinical perspective.

OUTSTANDING ISSUES:

(b) (4)

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: ____ **APPROVAL** __X__ **COMPLETE RESPONSE**

OTHER ACTION: ____

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/s/

PETER R STARKE
07/10/2015

JANET W MAYNARD
07/10/2015

MEDICAL OFFICER REVIEW

Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

APPLICATION:	NDA 204640, S-002	**TRADE NAME:**	Adrenalin®
APPLICANT/SPONSOR:	Par Sterile Products	**USAN NAME:**	Epinephrine injection, USP 1 mg/mL, 30 mL vial
MEDICAL OFFICER:	Peter Starke, MD	**CATEGORY:**	Alpha and beta adrenergic
TEAM LEADER:	Janet Maynard, MD		
DATE:	July 30, 2015	**ROUTE:**	Subcutaneous or Intramuscular

SUBMISSIONS REVIEWED IN THIS DOCUMENT / OTHER RELEVANT DOCUMENTS

Document Date	CDER Stamp Date	Submission	Comments
March 31, 2015	March 31, 2015	S-002, SD-41	CMC supplement
July 22, 2015	July 22, 2015	SD-49	Quality Response to teleconference of July 10, 2015

REVIEW SUMMARY:

This is summary review of a prior approval CMC supplement submitted by PAR Sterile Products to change (b) (4) the formulation of Adrenalin (epinephrine injection, USP) 1 mg/mL (1:1000), 30 mL vials. The supplement is being handled by OND, and the PDUFA date for this supplement is July 31, 2015.

The main issue for consideration with this supplement wa (b) (4) , I provided an initial review that recommended a complete response action. However, Par responded on July 22, 2015, after which ONDQA reconsidered and (b) (4) Therefore, it was determined that a CMC prior approval supplement would be appropriate and acceptable. This decision is consistent with other decisions regarding similar naming situations for other drugs across the Agency.

While the appropriate regulatory path is a CMC PAS, the supplement is being managed by OND, given the need for a pharm-tox review of the excipients and impurities. After review, there remain CMC and labeling deficiencies for the supplement that must be addressed prior to taking an Approval action. Therefore, the recommendation from ONDQA for this supplement remains a Complete Response action, and the clinical team concurs.

OUTSTANDING ISSUES:

See review for details.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: ____ **APPROVAL** X **COMPLETE RESPONSE**

OTHER ACTION: X **COMMENTS TO THE APPLICANT**

Executive Summary

This is summary review of a prior approval CMC supplement submitted by PAR Sterile Products to change (b) (4) the formulation of Adrenalin (epinephrine injection, USP) 1 mg/mL (1:1000), 30 mL vials. The supplement is being handled by OND, and the PDUFA date for this supplement is July 31, 2015.

The main issue for consideration with this supplement was (b) (4) . The initial call from ONDQA was that this would be the case, and this was communicated to Par on July 10, 2015. Based on this consideration, I provided an initial review that recommended a complete response action. However, Par responded on July 22, 2015, after which ONDQA reconsidered and made a determination that (b) (4) (see explanation below). Therefore, it was determined that a CMC prior approval supplement would be appropriate and acceptable. This decision is consistent with other decisions regarding similar naming situations for other drugs across the Agency.

While the appropriate regulatory path is a CMC PAS, the supplement is being managed by OND, given the need for a pharm-tox review of the excipients and impurities. After review, there remain CMC and labeling deficiencies for the supplement that must be addressed prior to taking an Approval action. Therefore, the recommendation from ONDQA for this supplement remains a Complete Response action, and the clinical team concurs.

The proposed labeling that accompanies the supplement is appended to the end of this review. The proposed changes to the prescribing information (PI) are acceptable. However, there remains the need for changes to the carton and container labeling to match the description of the product in the Description section (Section 11) of the PI.

Summary of the Review Issues

Changes to the formulation for the 30 mL vial presentation include addition of tartaric acid and disodium edetate (EDTA), and (b) (4) With these changes, Par proposes to (b) (4)

The addition of tartaric acid to the solution (b) (4) The initial call from ONDQA was that this would be the case, and this was communicated to Par on July 10, 2015. Par responded on July 22, 2015, after which ONDQA reconsidered and made a determination that this would (b) (4) (see explanation below). Therefore, a CMC prior approval supplement would be appropriate and acceptable. This decision is consistent with other decisions regarding similar naming situations for other drugs across the Agency.

In their response, Par noted that the active ingredient (API) in the drug product, which is epinephrine base, has not changed. Steps to making the formulation include (b) (4) o create the final formulation. (b) (4) What has changed is (b) (4) While theoretically (b) (4)

(b) (4)

With this supplement, Par has also proposed some minor editorial changes and corrections to the PI, all of which are acceptable. However, (b) (4) which both differs from what is in the currently approved PI and is incorrect. (b) (4) Par is aware that they will need to send in carton/container labeling that corrects this, and the Orange Book staff has also been notified. However, the revised carton/container labeling has not yet been submitted.

There are no changes proposed for the 1 mL vial presentation (NDA 204200). Par proposes to submit a supplement for similar changes to the 1mL vial presentation once this supplement is approved. This is acceptable.

During the review, consults were obtained from Pharmacology/Toxicology with regard to levels of excipients and impurities, and from the Division of Medication Errors and Prevention Assessment (DMEPA) with regard to changes to the labeling. Both found the changes acceptable.

(b) (4) . Therefore, ONDQA has determined that the stability data do not support (b) (4) Additionally, there are (b) (4) noted with this formulation, both of which were reviewed and found acceptable by the Pharm/Tox reviewers. Given the deficiencies with the submitted CMC data, Dr. Kim recommends a complete response action. Please see his review for details of the deficiencies.

During the review period, it was noted that biopharm must consider (b) (4) . However, with the supplement, Par did not submit a request for granting a biowaiver along with a justification for why the formulation changes could be allowed without the need for biopharm data. Par will need to do so. While a final determination will be made by the Agency once Par has submitted their biowaver request and justification, a justification could include the following considerations:

1. (b) (4)
2. (b) (4)

(b) (4)

3.

4.

5.

6.

Deficiencies

Several CMC and labeling deficiencies were identified in this supplement submission. These may be briefly summarized as a lack of adequate stability data, the need for revised carton/container labeling, and the need for the applicant to submit a request for a biowaiver with accompanying justification. Therefore, ONDQA recommends a Complete Response action to this supplement, and the DPARP concurs.

Comments to Applicant

Note that CMC comments are forthcoming from ONDQA, so the comments below are not the final comments to be sent.

1. CMC deficiencies (see CMC review).
2. Submit a request for a biowaiver along with appropriate justification.

15 Pages have been held in full as draft labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER R STARKE
07/30/2015

JANET W MAYNARD
07/30/2015

MEDICAL OFFICER REVIEW

Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

APPLICATION:	NDA 204-640, S-002	**TRADE NAME:**	Adrenalin®
APPLICANT/SPONSOR:	Par Sterile Products	**USAN NAME:**	Epinephrine injection, USP 1 mg/mL, 30 mL vial
MEDICAL OFFICER:	Peter Starke, MD	**CATEGORY:**	Alpha and beta adrenergic agonist
TEAM LEADER:	Janet Maynard, MD		
DATE:	December 16, 2015	**ROUTE:**	Subcutaneous or Intramuscular

SUBMISSIONS REVIEWED IN THIS DOCUMENT / OTHER RELEVANT DOCUMENTS

Document Date	CDER Stamp Date	Submission	Comments
July 31, 2015			*Cycle 1 Complete Response letter*
September 3, 2015	September 3, 2015	SD-52	Complete Response submission
November 22, 2015	November 22, 2015	SD-54	Annotated labeling
December 10, 2015	December 10, 2015	SD-56	Final package insert labeling

REVIEW SUMMARY:

This is summary review of a Complete Response (Cycle 2) to a prior approval CMC supplement submitted by Par Sterile Products to change [redacted] (b) (6) the formulation of Adrenalin (epinephrine injection, USP) 1 mg/mL (1:1000), 30 mL vials. The supplement was first submitted on March 31, 2015, a Complete Response action was taken on July 30, 2015, because of CMC and labeling deficiencies, and Par sponsor responded on September 3, 2015. The PDUFA date for this supplement is January 3, 2016. All review teams have found the responses acceptable, and the recommendation for this supplement is Approval. The final Prescribing Information (aka Package Insert), submitted on December 10, 2015, is attached to this review.

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: X **APPROVAL** ____ **COMPLETE RESPONSE**

OTHER ACTION: ____ **COMMENTS TO THE APPLICANT**

Executive Summary

This is summary review of a Complete Response (Cycle 2) to a prior approval CMC supplement submitted by Par Sterile Products to change (b) (4) the formulation of Adrenalin (epinephrine injection, USP) 1 mg/mL (1:1000), 30 mL vials. The supplement also includes some minor editorial changes to the labeling. The supplement was first submitted on March 31, 2015, a Complete Response action was taken on July 30, 2015, because of CMC and labeling deficiencies, and Par sponsor responded on September 3, 2015. The PDUFA date for this supplement is January 3, 2016. All review teams have found the responses acceptable, and the recommendation for this supplement is Approval.

In the first cycle, the supplement was managed by OND, given the proposed changes to the labeling and the need for a pharm-tox review of the excipients and impurities. As a result, OND has continued to manage the supplement in Cycle 2.

The proposed labeling that accompanies the supplement is appended to the end of this review. The proposed changes to the prescribing information (PI) and carton/container labels were reviewed by the clinical and CMC teams as well as by the Division of Medication Error Prevention and Analysis (DMEPA), and are acceptable.

Summary of the Review Issues

Changes to the formulation for the 30 mL vial presentation include addition of tartaric acid and disodium edetate (EDTA), and (b) (4) With these changes, Par proposes (b) (4) .

The addition of tartaric acid to the solution (b) (4) . However, after consideration, (b) (4) so a CMC supplement is appropriate.

The reasoning is (b) (4)

With this supplement, Par has also proposed some minor editorial changes and corrections to the PI, all of which are acceptable. (b) (4) The Orange Book staff previously picked up on this, and currently lists Adrenalin as epinephrine hydrochloride. Comments were sent as part of the Complete Response action in the first cycle, and Par has now responded with new carton/container labeling that addresses this issue.

There are no changes proposed for the 1 mL vial presentation (NDA 204-200). (b) (4) . This is acceptable.

During the first review cycle, consults were obtained from Pharmacology/Toxicology with regard to levels of excipients and impurities, and from the Division of Medication Errors and Prevention Assessment (DMEPA) with regard to changes to the labeling. Both found the changes acceptable. As a result, DMEPA was not re-consulted in this review cycle.

(b) (4) With this response, Par submitted the requested data, which ONDQA has reviewed and found acceptable.

During the first review period, it was noted that biopharm must consider whether the addition of tartaric acid and EDTA to the formulation changes the product in such a manner that the two products are not bioequivalent. However, Par did not submit a request for a biowaiver with the supplement, nor did they submit a justification for why the formulation changes could be allowed without the need for biopharm data. With this response, Par has submitted a request for a biowaiver with justification. The biopharm reviewer has found this acceptable.

Deficiencies

There are no remaining deficiencies with this supplement. Therefore, ONDQA recommends an approval action, and the DPARP concurs.

Comments to Applicant

None.

Revised Carton and Container Labeling

Figure 1. Revised Carton Label

Figure 2. Revised Carton: 10-pack

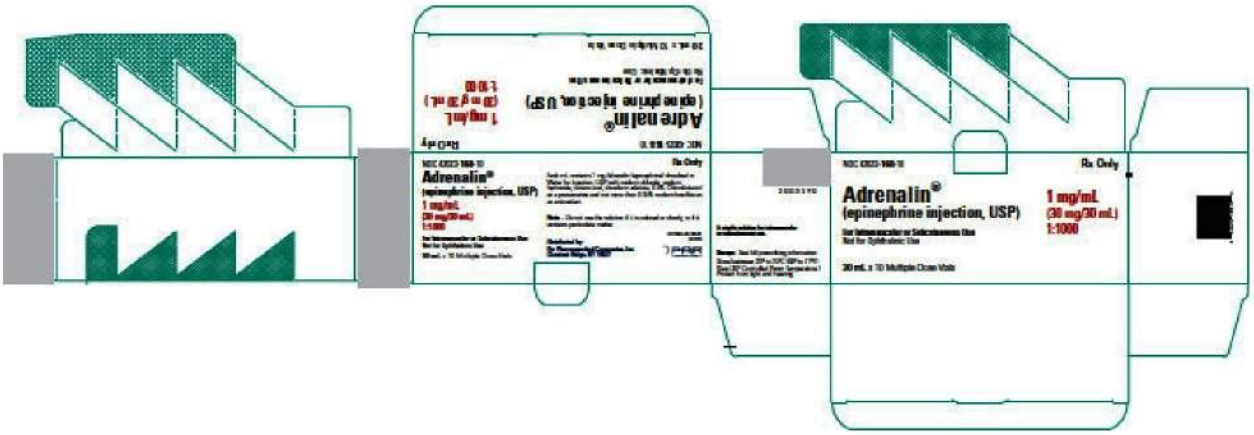

Figure 3. Revised Vial

Edits to the Prescribing Information

The edits that will be made to the prescribing information with this supplement are shown on the following pages. Additions are underlined in blue font and deletions in ~~strikeout~~ in red font.

11 Pages have been held in full as draft labeling

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/s/

PETER R STARKE
12/16/2015

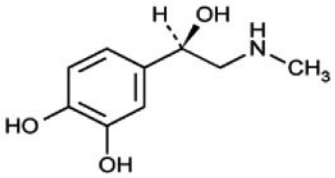
JANET W MAYNARD
12/16/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204640Orig1s002

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW *Review #2*	1. ORGANIZATION Branch 1/PMAD1/OLDP/OPQ	2. NDA NUMBERS 204640
3. NAME AND ADDRESS OF APPLICANT Par Sterile Products, LLC One Upper Pond Road Parsippany, NJ 07054 Tel: [redacted] (b) (6), Fax: 973-658-3585 Ms Carla English Manager Regulatory Affairs e-mail: regulatory.psp@parpharm.com		4. AF NUMBER 5. SUPPLEMENT(S) NUMBER(S) & DATES(S) **SCM-002[AC]; PAS; SDN 052** Letter Date: 9/3/15 Stamp Date: 9/3/15 **Due Date: 1/3//15**
6. NAME OF DRUG Adrenalin®	7. NONPROPRIETARY NAME epinephrine injection, USP	
8. SUPPLEMENT PROVIDES FOR: Complete response resubmission to FDA's complete response letter dated July 31, 2015 for PAS/S-002.		
9. PHARMACOLOGICAL CATEGORY Emergency treatment of allergic reactions (Type 1), including anaphylaxis.	10. HOW DISPENSED RX x_ OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) Injection	13. POTENCY 1 mg/mL (1:1000)	
14. CHEMICAL NAME AND STRUCTURE 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2 (methylamino)ethyl]benzyl alcohol  Molecular Weight: 183.2		15. RECORDS AND REPORTS CURRENT YES_NO REVIEWED YES_NO
15. COMMENTS: All remaining issues were resolved satisfactorily.		
17. CONCLUSION AND RECOMMENDATION Chemist recommends approval of this supplement.		
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE On file	DATE COMPLETED November 20, 2015

Background

This is applicant's response to the CR Letter dated July 31, 2015.

Review

The resubmission is reviewed as follows:

Deficiency #1

(b) (4)

Response #1

(b) (4)

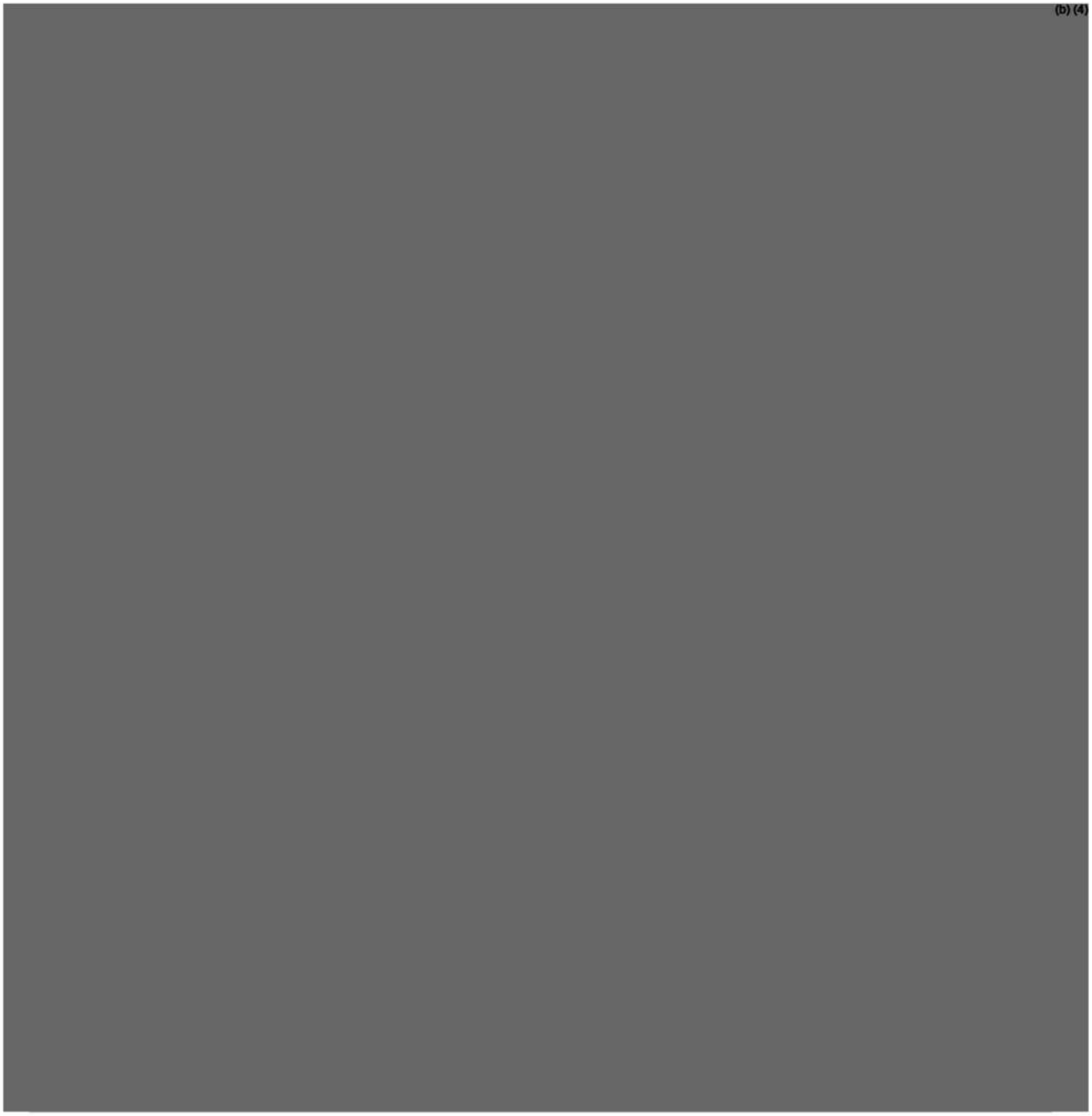
Evaluation: *Acceptable*
Provided data are adequate.

Deficiency #2

(b) (4)

Response #2

(b) (4)



Evaluation: *Acceptable*
Provided data are adequate.

Biopharmaceutics

Deficiency #1
Submit a biowaiver request for your proposed drug formulation with justification that your proposed formulation changes of inactive ingredients/excipients will not affect the overall drug product performance, including bioavailability/safety/efficacy of your product compared to the currently approved drug product.

Response #1
As requested, a copy of our biowaiver request for the proposed drug formulation is provided in Module 1, Section 1.12.15.

1.12.15 Request for Waiver of In-Vivo Study

Par Sterile Products, LLC requests a waiver of in vivo bioequivalence studies under 21 CFR §320.22(b)(1) based on the following:

(i) Adrenalin® (epinephrine injection, USP) is a parenteral solution intended solely for administration by injection; and
(ii) it contains the same active ingredients in the same concentration

In support of our request for biowaiver, we are providing the following information:

1. The table below summarizes the formulation comparison between the proposed drug product and the reference listed drug.

Table 1: Comparison of New Adrenalin 30 mL Formulation to Current Adrenalin 30 mL Formulation

Ingredient	Grade	Function	New Formulation Adrenalin 30 mL Vial (mg/mL)	Current Formulation Adrenalin 30 mL Vial (mg/mL)
Epinephrine	USP	Active	(b) (4)	(b) (4)
Sodium Chloride	USP	(b) (4)	6.15 mg	9.0 mg
Chlorobutanol (b) (4) (b) (4)	NF		(b) (4)	5.14 mg
Sodium Metabisulfite (b) (4)	NF		(b) (4)	1.64 mg
Tartaric Acid	NF		2.25 mg	(b) (4)
Sodium Hydroxide	NF		0.920 mg	
Disodium Edetate (EDTA)	USP		0.20 mg	
(b) (4)				(b) (4)

2. Conditions of Use: The conditions of use, prescribed, recommended or suggested in the labeling proposed for Epinephrine Injection have been previously approved as part of this NDA.

3. Active Ingredients: The active pharmaceutical ingredient (API) of the proposed drug product is Epinephrine which is the same active ingredient as that of the current formulation.

4. Inactive Ingredients: In addition to the currently used inactive ingredients, additional inactive ingredients consist of (b) (4). Specifically, Tartaric Acid and Sodium Hydroxide (b) (4), Disodium Edetate (EDTA) (b) (4) and Hydrochloric Acid was added for adjusting pH if necessary.

5. Route of Administration, Dosage Form and Strength: The route of administration, dosage form and strength of the proposed formulation is the same as that of the current formulation. The proposed drug product is a sterile solution intended for intramuscular and subcutaneous injection.

6. The drug product is a reformulated product that is identical, except for (b) (4) that could not affect the bioavailability of the reformulated product, to the current drug product for which the same manufacturer has obtained approval and the following conditions are met:

   (i) The bioavailability of the currently approved formulation has been waived by the FDA during the review of the original submission; and
   (ii) Both formulations meet appropriate in vitro tests such as potency and purity approved by FDA. Specifically. In addition, physicochemical properties such as pH, Color and Clarity, Osmolality (mOsm/kg) and Specific Gravity have been tested and found to be comparable (refer to Table 1 of our response).

Evaluation: ***See comment below.***

Our preliminary assessment is that the responses and justification for Product Quality Response #2, especially Osmolality, are acceptable from Biopharm viewpoint.

The biowaiver request (for Biopharmaceutics Response #1) is acceptable from Biopharm viewpoint. (Dr. Mei Ou)

Labeling

Deficiency #1

Remove the statement (b) (4) " from the carton and package labeling (to be consistent with the package insert labeling).

Response #1

The carton and package labeling (vial label) have been revised to remove the statement (b) (4) to be consistent with the package insert labeling. A copy of the revised labeling and side-by-side labeling comparison are provided in Module 1, Section 1.14.1.

Review:

1.14 Labeling

1.14.1 Draft Labeling

- Carton – 10 Pack: *Acceptable*
- Carton – 1 Pack: *Acceptable*
- Vial Label – Single Pack: *Acceptable*
- Vial Label – 10 Pack: *Acceptable*

1.14.1.2 Annotated Draft Labeling Text

SIDE-BY-SIDE COMPARISON - CONTAINER AND CARTON LABELING

Comparison of previously submitted labeling from original supplement filed March 31, 2015 to the revised labeling updated according to FDA's July 31, 2015 Complete Response Letter.

EXPLANATION OF DIFFERENCES

Item #	Description of Difference
1.	Remove the statement [redacted] (b) (4) from carton and package labeling (vial label) to be consistent with the package insert labeling.
2.	Updated company address from [redacted] (b) (4). Refer to notification submitted to NDA on July 16, 2015.
3.	Updated revision date and component code.

Evaluation: ***Acceptable***

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

[redacted] (b) (4)

3.2.P.8.3 Stability Data

4 Pages have been withheld in full as b4

(b) (4)

[redacted]

CON CLUSION AND RECOMMENDATION

Remaining issues are resolved satisfactorily.
Chemist recommends approval of this supplement.

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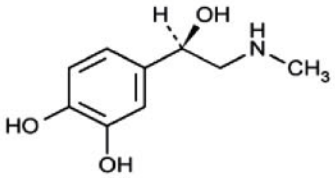
/s/

CHONG HO KIM
12/02/2015

RAMESH RAGHAVACHARI
12/04/2015

CHEMIST'S REVIEW *Review #2*	1. ORGANIZATION Branch 1/PMAD1/OLDP/OPQ	2. NDA NUMBERS 204640
3. NAME AND ADDRESS OF APPLICANT Par Sterile Products, LLC One Upper Pond Road Parsippany, NJ 07054 Tel: (b) (6), Fax: 973-658-3585 Ms Carla English Manager Regulatory Affairs e-mail: regulatory.psp@parpharm.com		4. AF NUMBER 5. SUPPLEMENT(S) NUMBER(S) & DATES(S) **SCM-002[AC]; PAS; SDN 052** Letter Date: 9/3/15 Stamp Date: 9/3/15 **Due Date: 1/3//15**
6. NAME OF DRUG Adrenalin®	7. NONPROPRIETARY NAME epinephrine injection, USP	
8. SUPPLEMENT PROVIDES FOR: Complete response resubmission to FDA's complete response letter dated July 31, 2015 for PAS/S-002.		
9. PHARMACOLOGICAL CATEGORY Emergency treatment of allergic reactions (Type 1), including anaphylaxis.	10. HOW DISPENSED RX x_ OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) Injection	13. POTENCY 1 mg/mL (1:1000)	
14. CHEMICAL NAME AND STRUCTURE 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol  Molecular Weight: 183.2		15. RECORDS AND REPORTS CURRENT YES_NO REVIEWED YES_NO
15. COMMENTS: All remaining issues were resolved satisfactorily.		
17. CONCLUSION AND RECOMMENDATION Chemist recommends approval of this supplement.		
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE On file	DATE COMPLETED November 20, 2015

Background

This is applicant's response to the CR Letter dated July 31, 2015.

Review

The resubmission is reviewed as follows:

Deficiency #1

(b) (4)

Response #1

(b) (4)

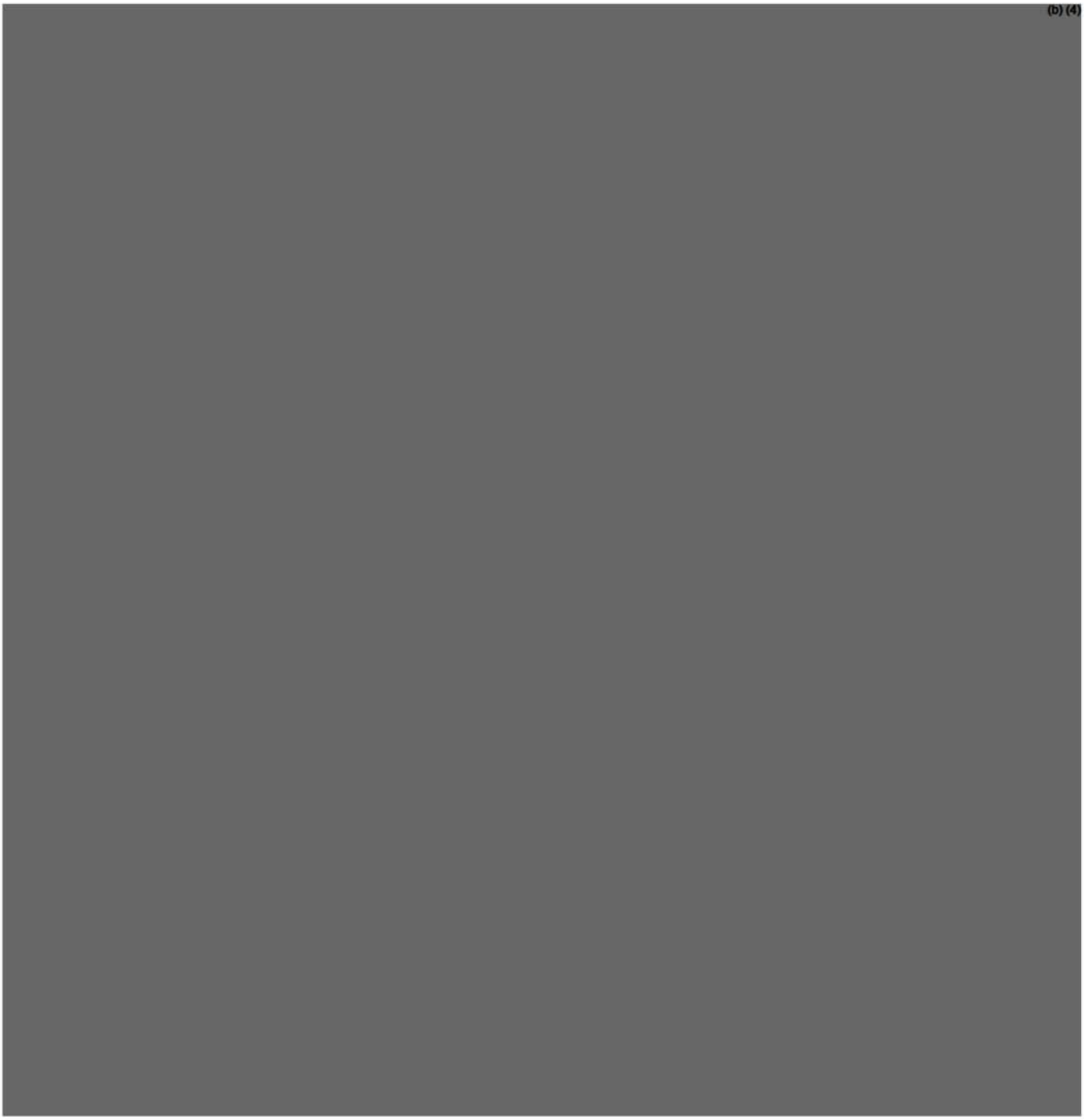
Evaluation: *Acceptable*
Provided data are adequate.

Deficiency #2

(b) (4)

Response #2

(b) (4)



Evaluation: *Acceptable*
Provided data are adequate.

Biopharmaceutics

Deficiency #1
Submit a biowaiver request for your proposed drug formulation with justification that your proposed formulation changes of inactive ingredients/excipients will not affect the overall drug product performance, including bioavailability/safety/efficacy of your product compared to the currently approved drug product.

Response #1
As requested, a copy of our biowaiver request for the proposed drug formulation is provided in Module 1, Section 1.12.15.

1.12.15 Request for Waiver of In-Vivo Study

Par Sterile Products, LLC requests a waiver of in vivo bioequivalence studies under 21 CFR §320.22(b)(1) based on the following:

(i) Adrenalin® (epinephrine injection, USP) is a parenteral solution intended solely for administration by injection; and
(ii) it contains the same active ingredients in the same concentration

In support of our request for biowaiver, we are providing the following information:

1. The table below summarizes the formulation comparison between the proposed drug product and the reference listed drug.

Table 1: Comparison of New Adrenalin 30 mL Formulation to Current Adrenalin 30 mL Formulation

Ingredient	Grade	Function	New Formulation Adrenalin 30 mL Vial (mg/mL)	Current Formulation Adrenalin 30 mL Vial (mg/mL)
Epinephrine	USP	Active	(b) (4)	(b) (4)
Sodium Chloride	USP	(b) (4)	6.15 mg	9.0 mg
Chlorobutanol (b) (4) (b) (4)	NF		(b) (4) g	5.14 mg
Sodium Metabisulfite (b) (4)	NF		(b) (4)	1.64 mg
Tartaric Acid	NF		2.25 mg	(b) (4)
Sodium Hydroxide	NF		0.920 mg	
Disodium Edetate (EDTA)	USP		0.20 mg	

2. Conditions of Use: The conditions of use, prescribed, recommended or suggested in the labeling proposed for Epinephrine Injection have been previously approved as part of this NDA.

3. Active Ingredients: The active pharmaceutical ingredient (API) of the proposed drug product is Epinephrine which is the same active ingredient as that of the current formulation.

4. Inactive Ingredients: In addition to the currently used inactive ingredients, additional inactive ingredients consist of (b) (4). Specifically, Tartaric Acid and Sodium Hydroxide were added (b) (4), Disodium Edetate (EDTA) was added (b) (4) and Hydrochloric Acid was added (b) (4).

5. Route of Administration, Dosage Form and Strength: The route of administration, dosage form and strength of the proposed formulation is the same as that of the current formulation. The proposed drug product is a sterile solution intended for intramuscular and subcutaneous injection.

6. The drug product is a reformulated product that is identical, except for a different buffer, pH adjuster and preservative that could not affect the bioavailability of the reformulated product, to the current drug product for which the same manufacturer has obtained approval and the following conditions are met:

   (i) The bioavailability of the currently approved formulation has been waived by the FDA during the review of the original submission; and
   (ii) Both formulations meet appropriate in vitro tests such as potency and purity approved by FDA. Specifically. In addition, physicochemical properties such as pH, Color and Clarity, Osmolality (mOsm/kg) and Specific Gravity have been tested and found to be comparable (refer to Table 1 of our response).

Evaluation: ***See comment below.***

Our preliminary assessment is that the responses and justification for Product Quality Response #2, especially Osmolality, are acceptable from Biopharm viewpoint.

The biowaiver request (for Biopharmaceutics Response #1) is acceptable from Biopharm viewpoint. (Dr. Mei Ou)

Labeling

Deficiency #1

Remove the statement "(b) (4)" from the carton and package labeling (to be consistent with the package insert labeling).

Response #1

The carton and package labeling (vial label) have been revised to remove the statement (b) (4) to be consistent with the package insert labeling. A copy of the revised labeling and side-by-side labeling comparison are provided in Module 1, Section 1.14.1.

Review:

1.14 Labeling

1.14.1 Draft Labeling

- Carton – 10 Pack: *Acceptable*
- Carton – 1 Pack: *Acceptable*
- Vial Label – Single Pack: *Acceptable*
- Vial Label – 10 Pack: *Acceptable*

1.14.1.2 Annotated Draft Labeling Text

SIDE-BY-SIDE COMPARISON - CONTAINER AND CARTON LABELING

Comparison of previously submitted labeling from original supplement filed March 31, 2015 to the revised labeling updated according to FDA's July 31, 2015 Complete Response Letter.

EXPLANATION OF DIFFERENCES

Item #	Description of Difference
1.	Remove the statement [redacted (b) (4)]" from carton and package labeling (vial label) to be consistent with the package insert labeling.
2.	Updated company address from [redacted (b) (4)]. Refer to notification submitted to NDA on July 16, 2015.
3.	Updated revision date and component code.

Evaluation: ***Acceptable***

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

[redacted (b) (4)]

3.2.P.8.3 Stability Data

[redacted 4 Pages have been held in full as b4]

(b) (4)

[redacted]

CON CLUSION AND RECOMMENDATION

Remaining issues are resolved satisfactorily.
Chemist recommends approval of this supplement.

Chongho Kim -S

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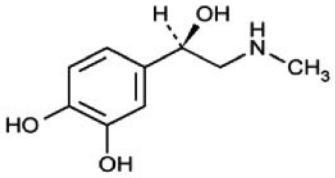
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chongho Kim -S, 0.9.2342.19200300.100.1.1=1300085235
Date: 2015.11.24 07:29:40 -05'00'

Ramesh Raghavachari -S

Digitally signed by Ramesh Raghavachari -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300211793, cn=Ramesh Raghavachari -S
Date: 2015.11.24 16:48:07 -05'00'

CHEMIST'S REVIEW *Review #1*	1. ORGANIZATION Branch 1/PMAD1/OLDP/OPQ	2. NDA NUMBERS 204640
3. NAME AND ADDRESS OF APPLICANT Par Sterile Products, LLC One Upper Pond Road Parsippany, NJ 07054 Tel: (b) (6), Fax: 973-658-3585 Ms Carla English Manager Regulatory Affairs e-mail: regulatory.psp@parpharm.com		4. AF NUMBER 5. SUPPLEMENT(S) NUMBER(S) & DATES(S) **SCM-002; PAS; SDN 041** Letter Date: 3/31/15 Stamp Date: 3/31/15 **SCM-002[BC]; SDN 050** Letter Date: 7/27/15 Stamp Date:7/27/15 **Due Date: 7/31/15**
6. NAME OF DRUG Adrenalin®	7. NONPROPRIETARY NAME epinephrine injection, USP	
8. SUPPLEMENT PROVIDES FOR: a new formulation of Adrenalin Injection, 30mL presentation		
9. PHARMACOLOGICAL CATEGORY Emergency treatment of allergic reactions (Type 1), including anaphylaxis.	10. HOW DISPENSED RX x OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) Injection	13. POTENCY 1 mg/mL (1:1000)	
14. CHEMICAL NAME AND STRUCTURE 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol  Molecular Weight: 183.2		15. RECORDS AND REPORTS CURRENT YES_NO REVIEWED YES_NO
15. COMMENTS: See Deficiency Comments (attached)		
17. CONCLUSION AND RECOMMENDATION Chemist recommends CR action for this supplement.		
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE On file	DATE COMPLETED July 30, 2015

Background

Par agreed to evaluate formulation and process improvements to [redacted]. Several studies were conducted to evaluate formulation changes [redacted], particularly for Adrenalin 30 mL, [redacted]. 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 [redacted]. The new formulation differs from the current approved formulation of Adrenalin 30 mL in terms of [redacted] (tartaric acid and sodium hydroxide) and disodium edetate. In addition, [redacted] have also been changed.

The following information is included in support of this supplement:

- Revised Labeling
- Batch Analysis of Drug Substance Lots Used
- Description and Composition of the Drug Product
- Pharmaceutical Development
- Excipient Specifications, Analytical Methods and Data
- Drug Product Manufacturing Process and Controls
- Drug Product Specification, Analytical Methods and Data
- Stability Data
- Executed Batch Records

Par confirms that there were no changes to the following areas as approved in the NDA:

- No change in the approved drug substance specifications or analytical methods
- No change in the container/closure system
- No change in the drug product stability program

[redacted]

Review:

CMC review is focused on the following issues:

- *Manufacturing process and controls for the new formulation*
- *Development history of the new formulation*

- *Compatibility with the container closure system*
- *Bioequivalent issue*
- *Stability data to support the proposed expiration dating period*
- *Safety and toxicity of new impurities*

1. 1.14.3 Listed Drug Labeling

1.14.3.1 – insert-comparison

Approved Package Insert (12/2013)	Proposed Package Insert (3/2015)
11 DESCRIPTION Adrenalin® (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL (1:1000) 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, 9.0 mg sodium chloride, 1.0 mg 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.	**11 DESCRIPTION** Adrenalin® (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL (1:1000) 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, 9.0 mg sodium chloride, 1.0 mg 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, **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.

Evaluation: ***Acceptable***

PI labeling looks fine. However, carton and package labeling need to be changed: ***Remove the statement*** [redacted] (b) (4)

3.2.S Drug Substance

No change in the approved drug substance specifications or analytical methods is made.

3.2.S.4.4 Batch Analysis

(b) (4) certificate of analyses for Epinephrine, USP API lots used in the manufacture of the drug product batches RC3208, RC3210, and RC3211 are enclosed in this section. **All test results meet the proposed acceptance criteria.**

Sample Name	Manufacturer	Manufacturer's Lot #	Par's Receiving Lot #	Drug Product Batch #
(b) (4)				

CERTIFICATE OF ANALYSIS- RAW MATERIALS CHEMISTRY

(b) (4)

TEST	ANALYTICAL PROCEDURE (Type, #)	ACCEPTANCE CRITERIA	RESULT
Description	(b) (4)	White to practically white, microcrystalline powder or granules	Satisfactory (b) (4)
(b) (4)			

(b) (4)

Notes: N/A

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3.2.P Adrenalin® Injection – Par Sterile Products

3.2.P.1 DESCRIPTION AND COMPOSITON

Adrenalin® Injection is currently marketed by Par Sterile Products (formally JHP Pharmaceuticals) and is currently manufactured at [redacted].

Description

The description of this product has not been changed from that which is currently filed.

Composition

The composition of the new formulation Adrenalin® Injection is provided in the table below.

Ingredient	Grade	Function	Batch Quantity	Unit Formula
Epinephrine	USP	Active	[redacted]	[redacted]
Sodium Chloride	USP	[redacted]		6.15 mg
Chlorobutanol [redacted]	NF			5.25 mg [redacted]
Sodium Metabisulfite[2] [redacted]	NF			0.457 mg [redacted]
Tartaric Acid	NF			2.25 mg
Sodium Hydroxide	NF			0.920 mg
Disodium Edetate (EDTA)	USP			0.20 mg
[redacted] Hydrochloric Acid[3]	NF/EP	pH adjustor		[redacted]
Water for Injection[3]	USP	[redacted]		

[redacted]

Comparison of composition: Proposed new formulation *vs* Approved Adrenalin® Injection

The proposed new formulation of Adrenalin® Injection, 30mL presentation contains the same active and inactive ingredients as the current formulation with the exception of three new inactive ingredients tartaric acid, sodium hydroxide, and EDTA.

Ingredient	New Formula Adrenalin 30mL Vial (mg/mL)	Current Formula Adrenalin 30mL Vial (mg/mL)
Epinephrine	(b) (4)	(b) (4)
Sodium Chloride	6.15 mg	9.0 mg
Chlorobutanol (b) (4) (b) (4)	(b) (4)	(b) (4)
Sodium Metabisulfite (b) (4)	(b) (4)	
Tartaric Acid	2.25 mg	
Sodium Hydroxide	0.920 mg	
Disodium Edetate (EDTA)	0.20 mg	
(b) (4) Hydrochloric Acid		
Water for Injection		

Quantitative Composition to FDA's IIG Database

Ingredient	New Formula Adrenalin 30mL Vial (mg/mL)	Concentration (% w/v)	Inactive Ingredients Guide Acceptable Levels*
Epinephrine	(b) (4)	(b) (4)	N/A
Sodium Chloride	6.15 mg		IM-IV-SC; Injection 0.9%
Chlorobutanol (b) (4) (b) (4)	(b) (4)		(b) (4)
Sodium Metabisulfite (b) (4)	(b) (4)		IM-IV-SC; Injection 0.15%
Tartaric Acid	2.25 mg		(b) (4)
Sodium Hydroxide	0.920 mg		
Disodium Edetate (EDTA)	0.20 mg		
(b) Hydrochloric Acid	(b) (4)		
Water for Injection	(b) (4)		

* FDA Inactive Ingredient Database at http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm

Type of container and closure used for dosage form: ***No change***

3.2.P.2 PHARMACEUTICAL DEVELOPMENT (for new formulation)

3.2.P.2.1 Components of the Drug Product

The table below lists all ingredients utilized in the new formulation of Adrenaline® Injection, the function of each ingredient, and the standard to which the ingredients complies.

Ingredient	Function	Standard
Epinephrine	Active	USP
Sodium Chloride	(b) (4)	USP
Chlorobutanol		NF
Sodium Metabisulfite		NF
Tartaric Acid		NF
Sodium Hydroxide		NF
Disodium Edetate Dihydrate (EDTA)		USP
Hydrochloric Acid	pH adjustor	NF/EP
Water for Injection	(b) (4)	USP

Epinephrine, USP is the drug substance in Adrenalin® Injection. The API sources remain same.

The drug substance is [redacted] during the drug product manufacturing process and is administered as a solution. The drug substance is [redacted]

It should be noted that ingredients Sodium Chloride, Chlorobutanol, and Sodium Metabisulfite are excipients currently present in the approved formulation.

Tartaric Acid is a new excipient utilized in the new formulation [redacted]. The purpose of this material is to [redacted]

Sodium Hydroxide is a new excipient utilized in the new formulation [redacted]. The purpose of this material is to [redacted]

Disodium Edetate Dihydrate (EDTA) is a new excipient utilized in the new formulation. [redacted] EDTA, is included for [redacted]

Hydrochloric acid is used to [redacted] adjust the pH of the drug product solution.

3.2.P.2.2 Drug Product

A hyperlink is provided to the following documents describing the details carried out as part of the various development studies for the new formulation of Adrenalin® 30mL.

Study	Document Number
[redacted]	

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- [redacted] (b) (4)

Labeling:
PI labeling looks fine. However, carton and package labeling need to be changed.
Remove the statement [redacted] (b) (4)

Deficiency Comments

1. [redacted] (b) (4)

2. **Remove the statement** [redacted] (b) (4) **from the carton and package labeling (to be in line with PI labeling).**

Following comments pertain to Biopharmaceutics:

3. **Submit a biowaiver request for your proposed drug formulation with justification that your proposed formulation changes of inactive ingredients/excipients will not affect the overall drug product performance, including bioavailability/safety/efficacy of your product compared to the currently approved drug product.**

4. **Submit comparative physicochemical property data such as osmolality of the proposed new formulation and the current formulation. The measurements should be done in triplicate for each lot tested.**

CONCLUSION AND RECOMMENDATION

Chemist recommends "Complete Response Action".

Chongho Kim -S

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Date: 2015.07.30 22:41:44 -04'00'

Ramesh Raghavachari -S

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Date: 2015.07.30 23:50:13 -04'00'

Initial Quality Assessment - OLDP Division of Post-Marketing Activities I

NDA: 204-640	**NME: Yes☐ No☒**	**Original NDA Approval Date: 12/18/13**
Supplement: 2	**Applicant: PAR STERILE PRODUCTS LLC**	**Product:** Adrenalin• (epinephrine injection, USP) 1 mg/mL
Clinical Division: DPARP		
Managed by: OND ☐ *Efficacy* ☐ *Labeling* ☐		**OPQ ☒**
Receipt Date: 3/31/15		**PDUFA Goal Date: 7/31/15**
Proposed changes: Drug Product reformulation as request by the FDA.		
Submitted as: Paper ☐ Electronic ☒	**Complete Response: Yes☐ No☒** **Previous Reviewer:**	
Submitted Category: CBE-0☐ CBE-30☐ PA☒		**Final Category: CBE-0☐ CBE-30☐ PA☒**
Expedited Review Requested: Yes☐ No☒	**Drug Shortage: Yes☐ No☒**	**Group Supplements: Yes☐ No ☒**

Facility Entry/Consults Needed:

Facility Entry: ☒	**Micro: ☒**	**Biopharm: ☐**	**Pharm/tox: ☐**
Statistics: ☐	**CDRH: ☐**	**OPF: ☐**	**DMEPA: ☒**

Other:

DMF Review: ☐

Comments:

The FDA had requested that the applicant attempt to reformulate the drug product. S-002 is the work of this investigation by the applicant.

On 5/29/15 Don requested the drug product site be uploaded into Panorama. Don will enter the profile code once the site is uploaded.

Micro should review the application.

As a result of the formulation some of the drug product Specifications Acceptance Criteria have been

[redacted] (b) (4)

QAL: Donald Klein	**Date: 5/29/15**
Assigned Reviewer: Chong Ho Kim	**RBPM: Yvonne Knight**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204640Orig1s002

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA CHEMISTRY CONSULTATION

Application number:	NDA 204640, Supplement 2 (CMC Supplement)
Supporting document/s:	41 (0020)
Applicant's letter date:	3/31/15
CDER stamp date:	3/31/15
Product:	Adrenalin® (epinephrine injection), 30 ml
Indication:	(b) (4)
Applicant:	Par Sterile Products, LLC (previously JHP Pharmaceuticals, LLC)
Review Division:	Division of Pulmonary, Allergy and Rheumatology Products
Reviewer:	Matthew Whittaker, Ph.D.
Supervisor/Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Carol Hill

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

NDA 204640 S-002, submitted on 3/31/15, is a Prior Approval Supplement which seeks to obtain approval for a change in formulation of the Adrenalin® (epinephrine injection, USP) 30 ml vial drug product (initial approval: 12/18/13). The new formulation includes the addition of the excipients tartaric acid and disodium EDTA dihydrate. Additionally, (b) (4) . The formulation change was made (b) (4) .

A Request for Consultation was received from Yvonne Knight from the Office of Pharmaceutical Quality (OPQ), Office of Program and Regulatory Operations (OPRO) on 7/27/15 to evaluate the safety profile of the impurities present in the new drug product formulation.

The drug product specification for the newly formulated 30 ml vial drug product (Product # 2002397) includes acceptance criteria of not more than (NMT) (b) (4) . The identification and qualification thresholds for degradants in drug products (b) (4) are (b) (4) *Impurities in New Drug Products,* July 2006*).* (b) (4)

The current review examines (1) support for the excipient levels in the new formulation and (2) the toxicologic effects of IV epinephrine plus Impurities A & B in male rats.

1.2 Brief Discussion of Nonclinical Findings

There are no concerns from the nonclinical perspective on the proposed formulation changes to the Adrenalin® 30 ml vial drug product.

The sponsor has investigated the toxicologic effects of two epinephrine-related impurities termed Impurity A and Impurity B in a 14 day repeat dose, intravenous study in male rats. The test article used in this study was a photo-degraded epinephrine solution which contained both impurities. 1/10 animals treated with the highest level of impurities (b) (4) died prematurely from consequences of urolithiasis. No adverse effects were observed in rats treated with epinephrine + Impurity A ((b) (4)) and Impurity B ((b) (4)). The results of this study provide supportive evidence for the proposed specification limit of NMT (b) (4) % for these impurities in the newly formulated Adrenalin® 30 ml drug product.

1.3 Recommendations

1.3.1 Approvability

The proposed formulation changes to the Adrenalin® 30 ml drug product are considered acceptable from the nonclinical perspective.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)
51-3-4

Generic Name
Epinephrine injection

Code Name
None

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

Molecular Formula/Molecular Weight
$C_9H_{19}NO_3$
MW: 183.20 (b) (4)

Structure or Biochemical Description

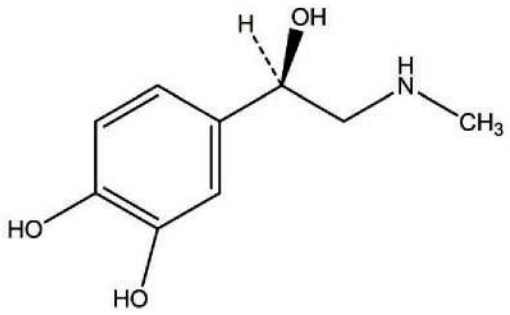

Figure 1. Chemical structure of epinephrine

Pharmacologic Class
Sympathomimetic catecholamine

2.2 Relevant INDs, NDAs, BLAs and DMFs

- NDA 204200, the 1 ml presentation of Adrenalin® from JHP Pharmaceuticals (approved 12/7/12)
- NDA 204640, the 30 ml presentation of Adrenalin® (approved 12/18/13)

2.3 Drug Formulation

Several changes to the Adrenalin 30 ml drug product formulation have been proposed including the reduction in concentration of 3 excipients and the addition of 3 new excipients (Table 1). They are as follows:

- (b) (4)
- (b) (4)
- (b) (4)
- Addition of tartaric acid at 2.25 mg/ml
- Addition of disodium edetate, dihydrate at 0.20 mg/ml
- Addition of sodium hydroxide at 0.92 mg/ml

Table 1. Comparison of drug product formulation of the currently approved Adrenalin drug product (Product # 2002288) and the proposed new formulation (Product # 2002397)

Ingredient	Current Approved Formulation		Proposed New Formulation	
	mg/mL	mM	(mg/mL)	(mM)
Epinephrine				
Sodium metabisulfite (b) (4)				
Chlorobutanol (b) (4) (b) (4)				
Sodium chloride	9.0	(b) (4)	6.15	(b) (4)
Tartaric acid				
Disodium edetate, dihydrate				
Hydrochloric acid (b) (4)				
Sodium hydroxide				
Water for Injection				

(b) (4).

It is noted that the container closure system has not changed from the one used with the currently approved drug product formulation.

2.4 Comments on Novel Excipients

Sodium metabisulfite, chlorobutanol, sodium chloride

(b) (4)

. Therefore there are no concerns from the nonclinical perspective regarding these changes.

Tartaric acid

(b) (4)

).

(b) (4)

. Therefore, the proposed tartaric acid concentration is considered acceptable.

Sodium hydroxide

(b) (4)

). The inclusion of sodium hydroxide in the formulation does not represent a toxicological concern from the nonclinical perspective.

Disodium edetate

(b) (4)

. Therefore the disodium edetate dose in a single injection of the approved morphine sulfate product exceeds the maximal exposure in the proposed new Adrenalin® formulation.

2.5 Comments on Impurities/Degradants of Concern

Par Sterile Products lists [redacted] impurities that are present in the new Adrenalin®, 30 ml DP formulation that are also present in the approved DP formulation (Table 2). These impurities include:

- [redacted]
- D-epinephrine
- Adrenalone

The specification limits for these impurities are equivalent to or lower than the limits established for the approved Adrenalin®, 30 ml DP formulation and are therefore considered to be acceptable from the nonclinical perspective.

The new Adrenalin®, 30 ml DP formulation also contains [redacted] degradants that are not present in the approved DP formulation. These degradants include:

[redacted]

The sponsor reports that [redacted] at a level of NMT [redacted]% in the original DP formulation, would be present in the form of [redacted] in the new DP formulation. The chemical structures for [redacted]

The drug product specification for the newly formulated DP includes acceptance criteria of NMT [redacted]% for [redacted] and NMT [redacted]% for [redacted]. The identification and qualification thresholds for degradants in the drug product with a maximum daily dose of < 10 mg is 1.0% (ICH Q3B(R2) *Impurities in New Drug Products,* July 2006). [redacted] Therefore, the established specification limits for each of these impurities are considered to be acceptable without further qualification given that they do not exceed the 1.0% threshold.

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(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The approved product label for Adrenalin® lists the recommended dosage as 0.3 – 0.5 mg IM or SC every 5 -10 minutes as necessary in adults. In children < 30 kg, the recommended dosage is up to 0.3 mg IM or SC every 5-10 minutes as necessary.

(b) (4)

2.7 Regulatory Background

Date	Event	Description
3/7/12	New NDA submission	NDA 204640 for Adrenalin®, 30 ml vial presentation
12/18/13	NDA Approval	
10/31/14	Prior approval supplement 001 submission	CMC supplement (b) (4)
3/31/15	Prior approval supplement 002 submission	CMC supplement for new DP formulation.

3 Studies Submitted

3.1 Studies Reviewed

Application	Submission date	Study #	Study title
NDA 204640	3/31/15	NA	Isolation and structure identification of two impurities in an epinephrine formulation
NDA 204640	3/31/15	284981	Evaluation of the safety profile of epinephrine (EP) impurities when administered intravenously to rats for 14 consecutive days

3.2 Studies Not Reviewed

Not applicable

3.3 Previous Reviews Referenced

Application	Product	Review date	Author
NDA 204200	Adrenalin® 1 ml vial	6/1/12	Jane Sohn, Ph.D.
NDA 204640	Adrenalin ® 30 ml vial	10/21/13	Matthew Whittaker, Ph.D.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Evaluation of the safety profile of epinephrine (EP) impurities when administered intravenously to rats for 14 consecutive days

(b) (4)

[redacted]

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/s/

MATTHEW T WHITTAKER
07/29/2015

TIMOTHY W ROBISON
07/29/2015
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204640Orig1s002

MICROBIOLOGY/VIROLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 17 August 2015

TO: File: NDA 204640

FROM: Jonathan G. Swoboda, PhD, RAC
Microbiology Reviewer
CDER/OPQ/OPF/Division of Microbiology Assessment

THROUGH: John W. Metcalfe, PhD
Quality Assessment Lead (Acting)
CDER/OPQ/OPF/Division of Microbiology Assessment

SUBJECT: Division of Microbiology Assessment's review of NDA-204640-SUPPL-2
Submission Date: 31 March 2015
Drug Product: Epinephrine Injection, USP (Adrenalin®)
Applicant: Par Sterile Products, LLC

Review Conclusion: The submission is recommended for approval from the standpoint of product quality microbiology.

This submission is a prior approval supplement assigned to the reviewer on 11 August 2015. The subject supplement pertains to a formulation change in the subject drug product. A table comparing the different formulations is reproduced below from page 3 of 3 (Section: 3.2.P.2; "32p23-mfg-proc-dev.pdf").

New Formula Adrenalin 30mL Vial (mg/mL)			Current Formula Adrenalin 30mL Vial (mg/mL)			
Ingredient	**Specification**	**Unit Formulation**	**Ingredient**	**Specification**	**Unit Formulation**	**Difference**
Epinephrine,	(b) (4)	(b) (4)	Epinephrine,	(b) (4)	(b) (4)	None
Sodium Chloride		6.15 mg	Sodium Chloride		9.0 mg	Reduction
Chlorobutanol (b) (4)		5.25 mg	Chlorobutanol (b) (4)		(b) (4	(b) (4)
Sodium Metabisulfite		0.457 mg	Sodium Metabisulfite		(b) (4	(b) (4)
Tartaric Acid		2.25 mg				New
Sodium Hydroxide		0.920 mg				New
Disodium Edetate (EDTA)		0.20 mg				New
(b)		(b) (4)	(b)			(b) (4)
Hydrochloric Acid*			Hydrochloric Acid		N/A	
Water for Injection*			Water for Injection		N/A	
		(b) (4)				

MEMORANDUM

The applicant has [redacted] (b) (4) A new antimicrobial effectiveness study was performed, and the results are provided in the document entitled, "mvm-0485.pdf" (Section: 3.2.P.2). The study was carried out per USP<51> using the new drug product formulation, which was formulated with [redacted] (b) (4) All concentrations complied with the requirements per USP<51>. The applicant indicates that [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

This approved specification is identical to what was previously reported in the original microbiology review dated 25 November 2013.

Verification of sterility testing

(b) (4). Sterility testing is conducted per USP<71>

(b) (4)

.

Acceptable

Reviewer's comment: The applicant has provided sufficient information demonstrating the sterility assurance of the manufacturing process used to produce the new drug product formulation per the Agency's requirements.

END

MEMORANDUM

Jonathan Swoboda -S

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John W. Metcalfe -A

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204640Orig1s002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 204640/S-002 Resubmission	**Biopharmaceutics Reviewer:** Mei Ou, Ph.D.	
Submission Date:	09/03/2015		
Division:	ODEII/Division of Pulmonary Allergy and Rheumatology Products	**Acting Biopharmaceutics Lead:** Kelly M. Kitchens, Ph.D.	
Applicant:	PAR STERILE PRODUCTS LLC	**Acting Supervisor:** Tapash Ghosh, Ph.D.	
Trade Name:	Adrenalin®	**Date Assigned:**	11/18/2015
Established Name:	Epinephrine Injection, USP	**Date of Review:**	12/1/2015
Indication:	Adrenalin® is a non-selective alpha and beta adrenergic agonist indicated for: • Emergency treatment of allergic reactions (Type 1), including anaphylaxis (Adrenalin® 1 mL and 30 mL vials) • Induction and maintenance of mydriasis during intraocular surgery (Adrenalin® 1 mL vial only)	**Type of Submission:** Prior Approval Supplement (PAS)-002 Resubmission	
Formulation/ strengths	Injection/1 mg/mL 1 mL single-use vial, 30 mL multi-dose vial		
Route of Administration	Intramuscularly (IM) or Subcutaneously (SC) Injection		
Type of Review:	Response to Complete Response Letter deficiencies for: • Biowaiver request • Comparative physicochemical property data		

SUMMARY:

Background: Par Sterile Products, LLC, originally submitted NDA 204640/Prior Approval Supplement (PAS)-002 on 03/31/2015 to seek the approval of a change in formulation for their drug product, Adrenalin® (Epinephrine Injection, USP, 1 mg/mL, 30 mL Vial), which was approved on 12/18/2013. The drug product Adrenalin® is designed for Intramuscular (IM) or Subcutaneous (SC) Injection into anterolateral aspect of the thigh to adults and children every 5 to 10 minutes as necessary.

The difference of inactive ingredients/excipient formulation between the proposed and the currently approved formulation include (b) (4) (tartaric acid and sodium hydroxide), disodium edetate, sodium chloride and sodium bisulfite. In the original submission, no changes in the drug substance specifications and analytical methods, no changes in the container/closure system, and no changes in the drug product stability program were stated by the Applicant.

However, the Agency issued a COMPLETE RESPONSE (CR) letter to the original submission of NDA 204640/S-002 on 07/31/2015 due to several deficiencies from Chemistry Manufacturing and Controls (CMC), Biopharmaceutics and Labeling perspectives.

The Biopharmaceutics deficiencies were:

- Submit comparative physicochemical property data such as osmolality of the proposed new

formulation and the current formulation. The measurements should be done in triplicate for each lot tested.

- Submit a biowaiver request for your proposed drug formulation with justification that your proposed formulation changes of inactive ingredients/excipients will not affect the overall drug product performance, including bioavailability/safety/efficacy of your product compared to the currently approved drug product.

Submission: On 09/03/2015, the Applicant re-submitted this NDA 204640/S-002 to the Agency, providing the full responses of the deficiencies issued in the CR letter to seek the approval of the proposed new formulation of drug product Adrenalin® Injection.

Review: For this resubmission of NDA 204640/S-002, the Division of Biopharmaceutics will focus on reviewing the responses for the two Biopharmaceutics deficiencies in the CR letter issued for the original submission.

RECOMMENDATION:

In this re-submitted supplement, the Applicant provided: (1) a biowaiver request for the in-vivo study requirements, and; (2) the comparative physicochemical property data, including the justification for the difference in osmolality, in order to support the proposed formulation changes of their drug product will not affect the overall drug product performance. The biowaiver request is granted, and the comparative physicochemical property data are adequate.

Therefore, from the Biopharmaceutics perspective, NDA 204640/S-002 for Adrenalin® (Epinephrine Injection, USP, 1 mg/mL, 30 mL Vial) is recommended for approval.

Signature

Mei Ou -S

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Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Signature

Kelly M. Kitchens -S

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Kelly M. Kitchens, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

cc. T.Ghosh; P.Seo

BIOPHARMACEUTICS ASSESSMENT

The Division of Biopharmaceutics reviewed the original submission of NDA 204640/S-002 (see Biopharmaceutics Review by Dr. Mei Ou in Panorama dated 7/30/2015), and issued two deficiencies from the Biopharmaceutics perspective in the Complete Response (CR) letter issued by FDA on 07/31/2015.

For this resubmission of NDA 204640/S-002 (submitted to FDA on 09/03/2015), Biopharmaceutics review team will focus on reviewing the responses for the two Biopharmaceutics deficiencies in the CR letter issued for the original submission.

1. Deficiency 1 (The deficiency #1 in Biopharmaceutics section in CR letter)
Submit a biowaiver request for your proposed drug formulation with justification that your proposed formulation changes of inactive ingredients/excipients will not affect the overall drug product performance, including bioavailability/safety/efficacy of your product compared to the currently approved drug product.

Applicant's Response for this deficiency:
As requested, a copy of our biowaiver request for the proposed drug formulation is provided in Module 1, Section 1.12.15.

Reviewer's comments:
The Applicant provided the biowaiver request for in-vivo study requirement and justification that the proposed formulation changes will not affect the drug product performance (See Appendix 1 of this review for details), which is considered acceptable by this reviewer.

2. Deficiency 2 (The deficiency #2 in Product Quality section in CR letter)
Submit comparative physicochemical property data such as osmolality of the proposed new formulation and the current formulation. The measurements should be done in triplicate for each lot tested.

Applicant's Response for this deficiency:
We acknowledge the agency's request to submit comparative physicochemical property data of the proposed new formulation (b) (4)) and the current commercial formulation (b) (4) . Par performed physicochemical testing that includes description, pH, color and clarity, osmolality and specific gravity for the proposed new formulation and current commercial formulation. The comparative physicochemical data is presented in Table 1. The description, color and clarity, and specific gravity of the proposed new formulation are comparable to the current commercial formulation. The pH results met the shelf-life acceptance criteria of 2.2-5.0 for both the formulations. The observed difference between lots for the current commercial formulation is attributed to (b) (4)

Based on the comparative evaluation of physicochemical properties, it is concluded that the proposed new formulation of Adrenalin® 30 mL multi-dose vials is comparable to the current commercial formulation with improvements made towards patient acceptability and to minimize the formation of degradation products during shelf-life.

Table 1: Comparative Physicochemical Data for Current Commercial Formulation vs. Proposed New Formulation of Adrenalin® 30 mL Multi-Dose Vials

Sample Name	Lot No.	Measurement #	Description	pH	Color and Clarity	Osmolality (mOsm/kg)	Specific Gravity
Test Procedure							
Adrenalin® 30 mL, current commercial batches, stock no. 2002288	807757F				Passes		
					Passes		
					Passes		
	789305				Passes		
					Passes		
					Passes		
	804508				Passes		
					Passes		
					Passes		
Proposed new formulation of Adrenalin® 30 mL Buffered, with 0.05% Bisulfite, and 0.02% EDTA, stock no. 2002397	RC3208				Passes		
					Passes		
					Passes		
	RC3210				Passes		
					Passes		
					Passes		
	RC3211				Passes		
					Passes		
					Passes		
Reference							

Reviewer's comments:

The Applicant provided the comparative physicochemical property data, including the justification for the difference in osmolality, for the proposed formulation and the currently approved drug formulation, which are considered acceptable by this reviewer.

OVERALL RECOMMENDATION:

In this re-submitted supplement, the Applicant provided: (1) a biowaiver request for the in-vivo study requirements, and; (2) the comparative physicochemical property data, including the justification for the difference in osmolality, in order to support the proposed formulation changes of their drug product will not affect the overall drug product performance. The biowaiver request is granted, and the comparative physicochemical property data are adequate.

Therefore, from the Biopharmaceutics perspective, NDA 204640/S-002 for Adrenalin® (Epinephrine Injection, USP, 1 mg/mL, 30 mL Vial) is recommended for approval.

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BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 204640/S-002	**Biopharmaceutics Reviewer:** Mei Ou, Ph.D.	
Submission Date:	03/31/2015		
Division:	ODEII/Division of Pulmonary Allergy and Rheumatology Products	**Acting Biopharmaceutics Lead:** Kelly M. Kitchens, Ph.D.	
Applicant:	PAR STERILE PRODUCTS LLC	**Acting Supervisor:** Tapash Ghosh, Ph.D.	
Trade Name:	Adrenalin®	**Date Assigned:**	07/22/2015
Established Name:	Epinephrine Injection, USP	**Date of Review:**	07/30/2015
Indication:	Adrenalin® is a non-selective alpha and beta adrenergic agonist indicated for: • Emergency treatment of allergic reactions (Type 1), including anaphylaxis (Adrenalin® 1 mL and 30 mL vials) • Induction and maintenance of mydriasis during intraocular surgery (Adrenalin® 1 mL vial only)	**Type of Submission:** CMC Prior Approval Supplement (PAS)-002	
Formulation/ strengths	Injection/1 mg/mL 1 mL single-use vial, 30 mL multi-dose vial		
Route of Administration	Intramuscularly (IM) or Subcutaneously (SC) Injection		
Type of Review:	The formulation change		

SUMMARY:

Background: Par Sterile Products, LLC, submitted an NDA 204640/Prior Approval Supplement (PAS)-002 on 03/31/2015 to seek the approval of a change in formulation for their drug product, Adrenalin® (Epinephrine Injection, USP, 1 mg/mL, 30 mL Vial), which was approved on 12/18/2013. The drug product Adrenalin® is designed for Intramuscular (IM) or Subcutaneous (SC) Injection into anterolateral aspect of the thigh to adults and children every 5 to 10 minutes as necessary.

The applicant agreed to a post-marketing commitment to evaluate formulation and process improvements to reduce levels of impurities in Adrenalin®. The Applicant submitted the current supplement to seek approval for a change in the drug product formulation. The difference of inactive ingredients/excipient formulation between the proposed and the currently approved formulation include [redacted] (b) (4) (tartaric acid and sodium hydroxide), disodium edetate, sodium chloride and sodium bisulfite. The applicant confirms there are no changes in the drug substance specifications and analytical methods, no changes in the container/closure system, and no changes in the drug product stability program.

Submission: The current supplement is submitted to seek approval of the proposed new formulation of Adrenalin® Injection. The compositions of the proposed new formulation and currently approved formulation are described in the table as below:

Ingredient	New Formula Adrenalin 30mL Vial (mg/mL)	Current Formula Adrenalin 30mL Vial (mg/mL)
Epinephrine	(b) (4)	(b) (4)
Sodium Chloride	6.15 mg	(b) (4)
Chlorobutanol (b) (4)	(b) (4)	
(b) (4)		
Sodium Metabisulfite (b) (4)		
Tartaric Acid	2.25 mg	
Sodium Hydroxide	0.920 mg	
Disodium Edetate (EDTA)	0.20 mg	
(b) (4) Hydrochloric Acid		
Water for Injection		

Review: The Division of Biopharmaceutics review will focus on the information submitted for supporting the changes in inactive ingredients/excipients in the final drug product composition. In this submission, the Applicant did not submit a biowaiver request with justification why they believe the change in their formulation will not affect the performance of their product.

This observation was communicated to the Clinical and CMC review team members. The agreement is that requiring a study to match the PK between the currently approved formulation and the proposed new formulation is irrelevant from a clinical perspective because treatment is titrated to effect and the absorption is different depending upon whether the dose is administered by the IM or the SC route. However, the Agency should ask the Applicant to submit a biowaiver request and provide justification for the formulation differences. The Division of Biopharmaceutics agrees with these points.

RECOMMENDATION:

In this supplement, the Applicant: (1) does not request a biowaiver for their newly proposed drug product with changes in the inactive ingredients/excipients of the formulation; (2) does not provide justification that the formulation changes will not affect the overall performance of their drug product.

Therefore, from the Division of Biopharmaceutics perspective, a **COMPLETE RESPONSE (CR)** is recommended for NDA 204640/S-002 for Adrenalin® (Epinephrine Injection, USP, 1 mg/mL, 30 mL Vial).

The following comments should be conveyed to the Applicant in the CR letter:

- Submit a biowaiver request for your proposed drug formulation with justification that your proposed formulation changes of inactive ingredients/excipients will not affect the overall drug product performance, including bioavailability/safety/efficacy of your product compared to the currently approved drug product.
- Submit comparative physicochemical property data such as osmolality of the proposed new formulation and the current formulation. The measurements should be done in triplicate for each lot tested.

Signature

Mei Ou -S

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Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Signature

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Kelly M. Kitchens, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

cc. T.Ghosh; P.Seo

BIOPHARMACEUTICS ASSESSMENT

The component and composition of inactive excipients changes for drug product
The Applicant provided the quantitative composition of new formulation and side-by-side comparison of proposed and the currently approved formulation of drug product shown in Table 1 and Table 2:

Table 1: Quantitative Composition of new formulation of Adrenalin® injection 1 mg/mL, 30 mL vial

Ingredient	Grade	Batch Quantity	Unit Formula	Function
Epinephrine	USP	(b) (4)	(b) (4)	Active
Sodium Chloride	USP		6.15 mg	(b) (4)
Chlorobutanol (b) (4) (b) (4)	NF		5.25 mg (b) (4)	
Sodium Metabisulfite (b) (4)	NF		(b) (4) 0.50 mg	
Tartaric Acid	NF		2.25 mg	
Sodium Hydroxide	NF		0.920 mg	
Disodium Edetate (EDTA) Dihydrate	USP		0.20 mg	
(b) (4) Hydrochloric Acid	NF/EP		(b) (4)	pH adjustor
Water for Injection	USP			(b) (4)

Table 2: The component and composition of formulation changes of Adrenalin®

	New Formula Adrenalin		Current Formula Adrenalin	
Ingredient	Batch Quantity	Unit Formula	Batch Quantity	Unit Formula
Epinephrine	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Chloride		6.15 mg		9.0 mg
Chlorobutanol (b) (4) (b) (4) (b) (4)		5.25 mg (b) (4)		(b) (4)
Sodium Metabisulfite (b) (4)		(b) (4) 0.50 mg		
Tartaric Acid		2.25 mg		
Sodium Hydroxide		0.920 mg		
Disodium Edetate (EDTA)		0.20 mg		
(b) (4) Hydrochloric Acid		(b) (4)		
Water for Injection				
		(b) (4)		

The proposed drug product specifications
The Applicant provided the In-Process, Release Testing and Shelf-Life (Stability) specification for drug product as Table 3, Table 4 and Table 5 below:

Table 3: The proposed specifications for the new formulation in-process testing

Test	In-process New Formulation 30mL	In-process Current Formulation 30mL
Description	Clear, colorless solution	N/A
		(b) (4)

Table 4: The proposed specifications for the new formulation drug release testing

Test	Release New Formulation 30mL	Release Current Formulation 30mL
Description	Clear, colorless solution essentially free from visible particulates	Clear, colorless solution
		(b) (4)

Table 5: The proposed specifications for the new formulation shelf-life (stability) testing

Test	Shelf-Life (stability) New Formulation 30mL	Shelf-Life (Stability) Current Formulation 30mL
Description	Clear, colorless to light yellow solution essentially free from visible particulates	Clear, colorless to light yellow solution
		(b) (4)

The proposed specification justification for drug product

The Applicant provided the justification of specification for drug product (at release and shelf-life) as Table 6 below:

Table 6: The release and shelf-life specification justification for drug product

Test	Acceptance Criteria		
	Release	Shelf-life	Justification
Description	Clear, colorless solution essentially free from visible particulates	Clear, colorless to light yellow solution essentially free from visible particulates	Visual observation to detect changes in color or particulates
[redacted]	[redacted]	[redacted]	[redacted]

(b) (4)

Reviewer's Comments:

- The release and stability specifications [redacted] (b) (4)
- The Applicant did not provide osmolality data for the current formulation.

RECOMMENDATIONS

In this supplement, the Applicant: (1) does not request a biowaiver for their newly proposed drug product with changes in the inactive ingredients/excipients of the formulation; (2) does not provide justification that the formulation changes will not affect the overall performance of their drug product.

Therefore, from the Division of Biopharmaceutics perspective, a **COMPLETE RESPONSE (CR)** is recommended for NDA 204640/S-002 for Adrenalin® (Epinephrine Injection, USP, 1 mg/mL, 30 mL Vial).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204640Orig1s002

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 24, 2015
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 204640/S-002
Product Name and Strength:	Adrenalin (Epinephrine Injection USP), 1 mg/mL
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	PAR Sterile Products, LLC
Submission Date:	September 3, 2015 and October 22, 2015
OSE RCM #:	2015-2345
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Kendra Worthy, PharmD

1 REASON FOR REVIEW

This review responds to a request from DPARP to evaluate the label and labeling and prescribing information for Adrenalin for areas of vulnerability that could lead to medication errors. The Applicant is seeking approval for a change in formulation to provide for a more stable product. On July 31, 2015, the Applicant received a Complete Response (CR) to the original supplement.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The purpose of the prior approval supplement (PAS) for Adrenalin is to provide changes to the label and labeling and to the prescribing information to reflect the change in formulation to provide for a more stable product. This supplement includes changes to the label and labeling based on the July 31, 2015 CR.

We performed a risk assessment of the proposed label and labeling and prescribing information to identify deficiencies that may lead to medication errors. Our FAERS search did not identify any reports relevant to label and labeling.

DMEPA finds the proposed label and labeling and prescribing information acceptable.

4 CONCLUSION

DMEPA concludes that the proposed changes to the label, labeling, and prescribing information are acceptable.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Adrenalin that Par Pharmaceuticals submitted on October 22, 2015.

Table 2. Relevant Product Information for Adrenalin	
Initial Approval Date	December 18, 2013
Active Ingredient	Epinephrine Injection
Indication	• Emergency treatment of allergic reactions (Type 1), including anaphylaxis (Adrenalin® 1 mL and 30 mL vials) • Induction and maintenance of mydriasis during intraocular surgery (Adrenalin® 1 mL vial only)
Route of Administration	Subcutaneous, intramuscular, intraocular, or intracameral
Dosage Form	Injection
Strength	1 mg/mL
Dose and Frequency	• Anaphylaxis (Adrenalin® 1 mL and 30 mL vials): o *Adults and Children 30 kg (66 lbs) or more*: 0.3 to 0.5 mg (0.3 to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2.1) o *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 • Intraocular surgery (Adrenalin® 1 mL vial only): Dilute 1 mL with 100 to 1000 mL of an ophthalmic irrigation fluid, for ophthalmic irrigation or intracameral injection
How Supplied	**Adrenalin® 1 mL Single-Use Vials:** Each carton contains 25 single-use vials containing 1 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL (1:1000) in a 3 mL clear glass vial. **Adrenalin® 30 mL Multi-Dose Vials:** Each carton contains either 1 multiple-dose vial or 10 multiple-dose vials containing 30 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL (1:1000) in a 36 mL amber glass vial
Storage	20° to 25°C (68° to 77°F) Epinephrine is light sensitive. Protect from light and freezing

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 10, 2015, we searched the L:drive using the terms, Adrenalin to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews[1], and we confirmed that our previous recommendations were considered and implemented.

[1] McMillan, Teresa. Label and Labeling Review for Adrenalin NDA 204640. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Nov 19. RCM No.:2013-2054

Owens, Lissa. Label and Labeling Review for Adrenalin NDA 204640, Silver Spring (MD); FDA, CDER, OSE, DMEPA (US): 2015 July 29 RCM No: 2015-1685

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on November 3, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[2]

Table 3: FAERS Search Strategy	
Date Range	**July 28, 2015 to November 3, 2015**
Product	**Adrenalin**
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

E.2 Results

Our search identified one case, but after further evaluation, we did not identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX G. LABELS AND LABELING

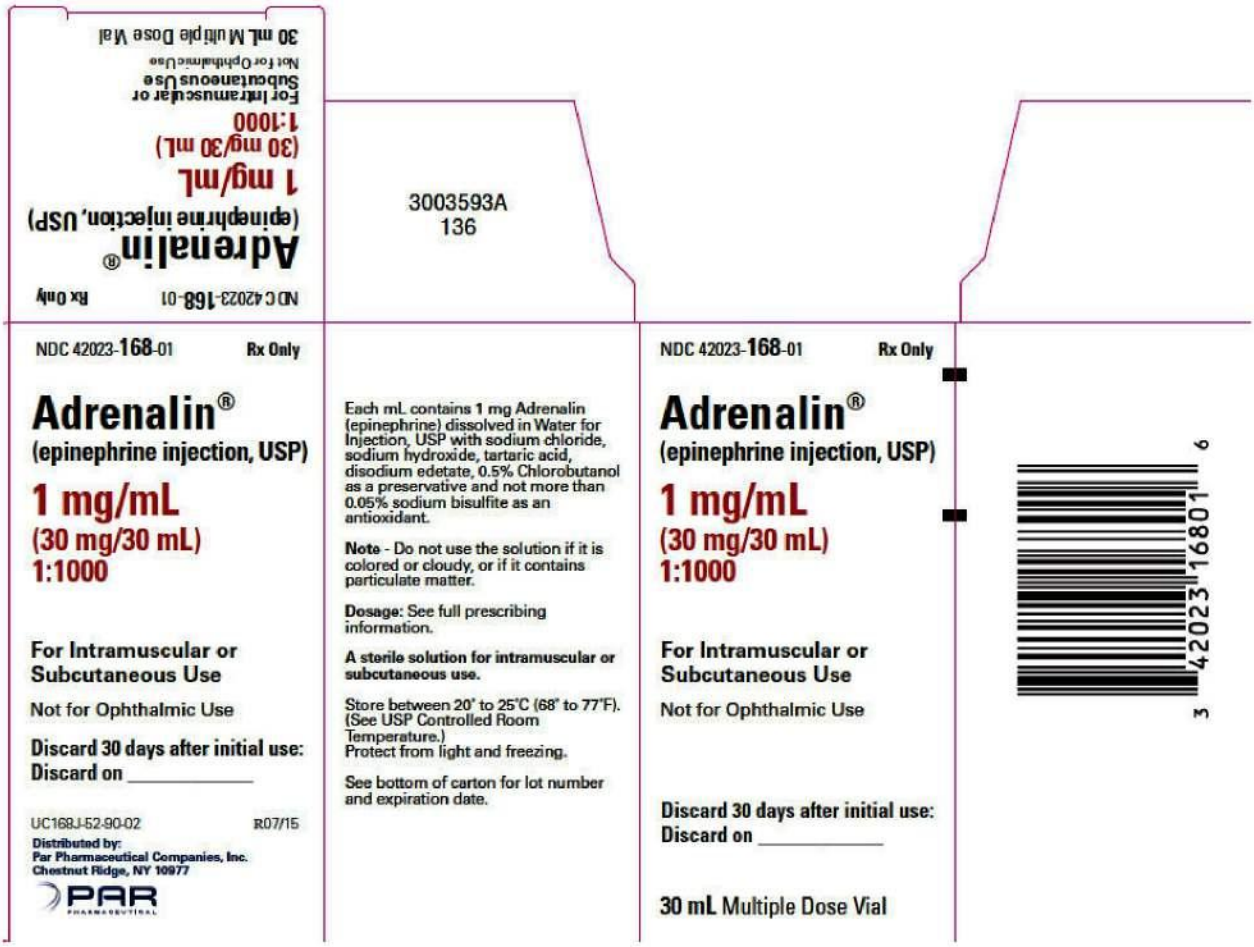
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Adrenalin labels and labeling submitted by Par Pharmaceuticals on September 3, 2015 and December 22, 2015.

- Container Label
- Carton Labeling
- Prescribing Information (no image)

G.2 Label and Labeling Images

[3] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.


NDC 42023-168-01 Rx Only
Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000
For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
30 mL Multiple Dose Vial
3003593A
136
NDC 42023-168-01 Rx Only
Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000
For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
Discard 30 days after initial use:
Discard on _____
UC168J-52-90-02 R07/15
Distributed by:
Par Pharmaceutical Companies, Inc.
Chestnut Ridge, NY 10977
PAR
Each mL contains 1 mg Adrenalin (epinephrine) dissolved in Water for Injection, USP with sodium chloride, sodium hydroxide, tartaric acid, disodium edetate, 0.5% Chlorobutanol as a preservative and not more than 0.05% sodium bisulfite as an antioxidant.
Note - Do not use the solution if it is colored or cloudy, or if it contains particulate matter.
Dosage: See full prescribing information.
A sterile solution for intramuscular or subcutaneous use.
Store between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)
Protect from light and freezing.
See bottom of carton for lot number and expiration date.
NDC 42023-168-01 Rx Only
Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000
For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
Discard 30 days after initial use:
Discard on _____
30 mL Multiple Dose Vial
3 42023 16801 6


(b) (4)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/s/

LISSA C OWENS
11/24/2015

KENDRA C WORTHY
11/24/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 29, 2015
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 204640/S-002
Product Name and Strength:	Adrenalin (Epinephrine Injection USP), 1 mg/mL
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	PAR Sterile Products, LLC
Submission Date:	March 31, 2015
OSE RCM #:	2015-1685
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Kendra Worthy, PharmD

1 REASON FOR REVIEW

This review responds to a request from DPARP to evaluate the label and labeling and prescribing information for Adrenalin for areas of vulnerability that could lead to medication errors. The Applicant is seeking approval for a change in formulation to provide for a more stable product.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The purpose of the prior approval supplement (PAS) for Adrenalin is to provide changes to the label and labeling and to the prescribing information to reflect the change in formulation to provide for a more stable product.

We performed a risk assessment of the proposed label and labeling and prescribing information to identify deficiencies that may lead to medication errors. Our FAERS search did not identify any reports relevant to label and labeling.

DMEPA finds the proposed label and labeling and prescribing information acceptable.

4 CONCLUSION

DMEPA concludes that the proposed changes to the label and labeling and prescribing information are acceptable.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Adrenalin that Par Pharmaceuticals submitted on March 31, 2015.

Table 2. Relevant Product Information for Adrenalin	
Initial Approval Date	December 18, 2013
Active Ingredient	Epinephrine Hydrochloride
Indication	• Emergency treatment of allergic reactions (Type 1), including anaphylaxis (Adrenalin® 1 mL and 30 mL vials) • Induction and maintenance of mydriasis during intraocular surgery (Adrenalin® 1 mL vial only)
Route of Administration	Subcutaneous, intramuscular, intraocular, or intracameral
Dosage Form	Injection
Strength	1 mg/mL
Dose and Frequency	• Anaphylaxis (Adrenalin• 1 mL and 30 mL vials): o *Adults and Children 30 kg (66 lbs) or more*: 0.3 to 0.5 mg (0.3 to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2.1) o *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 • Intraocular surgery (Adrenalin• 1 mL vial only): Dilute 1 mL with 100 to 1000 mL of an ophthalmic irrigation fluid, for ophthalmic irrigation or intracameral injection
How Supplied	**Adrenalin• 1 mL Single-Use Vials:** Each carton contains 25 single-use vials containing 1 mL Adrenalin• (epinephrine injection, USP) solution 1 mg/mL (1:1000) in a 3 mL clear glass vial. **Adrenalin• 30 mL Multi-Dose Vials:** Each carton contains either 1 multiple-dose vial or 10 multiple-dose vials containing 30 mL Adrenalin• (epinephrine injection, USP) solution 1 mg/mL (1:1000) in a 36 mL amber glass vial
Storage	20° to 25°C (68° to 77°F) Epinephrine is light sensitive. Protect from light and freezing

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 28, 2015, we searched the L:drive and AIMS using the terms, Adrenalin to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[1], and we confirmed that our previous recommendations were considered and implemented.

[1] McMillan, Teresa. Label and Labeling Review for Adrenalin NDA 204640. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Nov 19. RCM No.:2013-2054

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Table 3: FAERS Search Strategy	
Date Range	**November 13, 2013 to July 28, 2015**
Product	**Adrenalin**
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

E.2 Results

Our search identified thirteen cases, but after further evaluation, we did not identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded

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using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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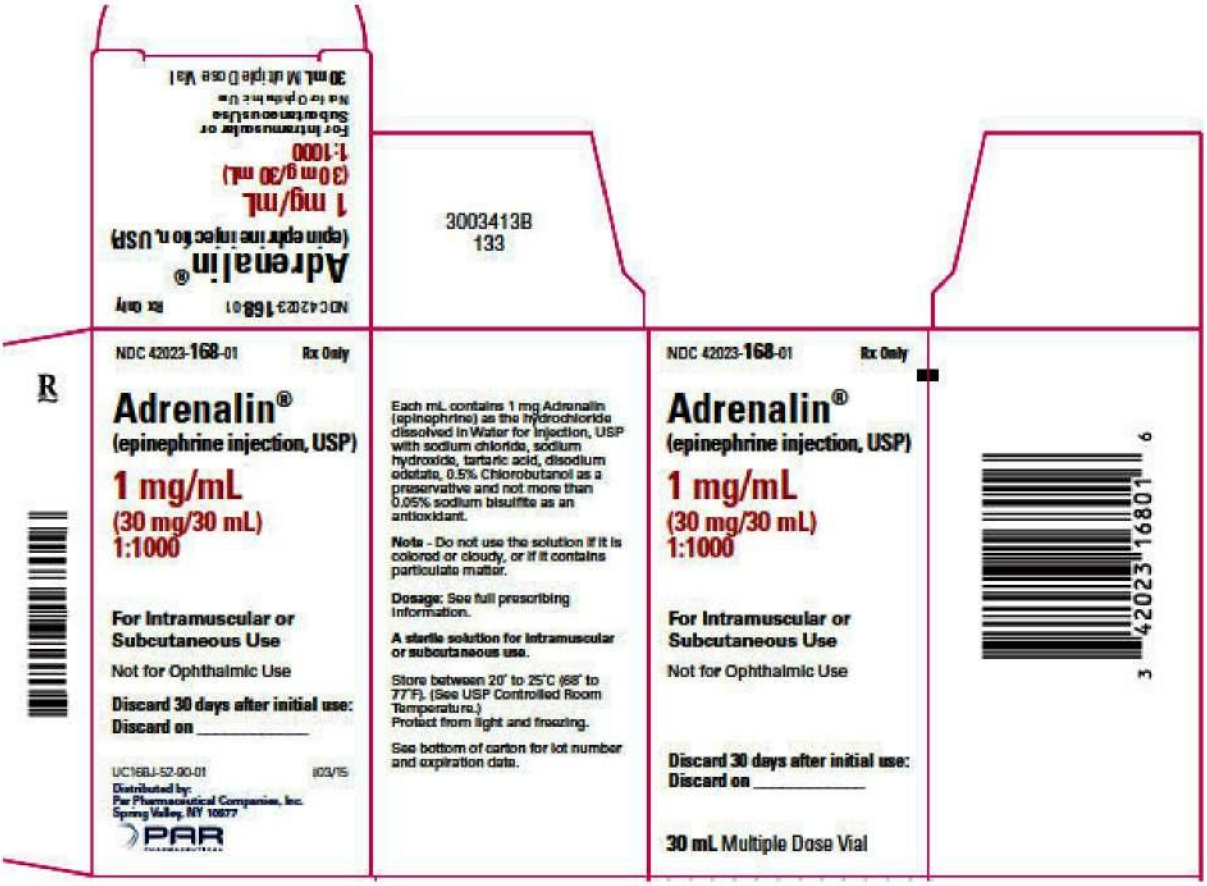
Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Adrenalin labels and labeling submitted by Par Pharmaceuticals on March 31, 2015.

- Container label
- Carton labeling
- Prescribing Information (no image)

G.2 Label and Labeling Images

[3] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.


NDC 42023-168-01 Rx Only
Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000
For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
Discard 30 days after initial use:
Discard on _____
UC16BJ-52-00-01 03/15
Distributed by:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977
PAR
3003413B
133
Each mL contains 1 mg Adrenalin (epinephrine) as the hydrochloride dissolved in Water for Injection, USP with sodium chloride, sodium hydroxide, tartaric acid, disodium edetate, 0.5% Chlorobutanol as a preservative and not more than 0.05% sodium bisulfite as an antioxidant.
Note - Do not use the solution if it is colored or cloudy, or if it contains particulate matter.
Dosage: See full prescribing information.
A sterile solution for intramuscular or subcutaneous use.
Store between 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Protect from light and freezing.
See bottom of carton for lot number and expiration date.
NDC 42023-168-01 Rx Only
Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(30 mg/30 mL)
1:1000
For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use
Discard 30 days after initial use:
Discard on _____
30 mL Multiple Dose Vial
3 42023 16801 6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/s/

LISSA C OWENS
07/29/2015

KENDRA C WORTHY
07/29/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204640Orig1s002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 204640/S-002

COMPLETE RESPONSE

Par Sterile Products, LLC
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Attention: Carla English
Manager, Regulatory Affairs

Dear Ms. English:

Please refer to your Supplemental New Drug Application (sNDA) dated March 31, 2015, received March 31, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adrenalin® (epinephrine injection, USP) 1 mg/mL, 30 mL vial.

We acknowledge receipt of your amendments dated July 22, and 27, 2015.

This supplemental new drug application proposes a change in formulation for the Adrenalin 30 mL vial presentation.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. (b) (4)

2.

BIOPHARMACEUTICS

1. Submit a biowaiver request for your proposed drug formulation with justification that your proposed formulation changes of inactive ingredients/excipients will not affect the overall drug product performance, including bioavailability/safety/efficacy of your product compared to the currently approved drug product.

LABELING

1, Remove the statement [redacted] (b) (4) from the carton and package labeling (to be consistent with the package insert labeling).

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Lydia Gilbert-McClain, M.D.
Deputy Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LYDIA I GILBERT MCCLAIN
07/31/2015
Acting Division Director